'A COMMON CONDITION: A RARE DIAGNOSIS?' WHAT IS THE SIGNIFICANCE OF DIAGNOSIS IN KLINEFELTER'S SYNDROME (47, XXY)?

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Abstract

Klinefelter's Syndrome (47,XXY) is a sporadic, non-inherited genetic condition occurring only in males where there is the presence of an additional X chromosome. Although not well known, Klinefelter's Syndrome is reported to be relatively common with an estimated incidence of between approximately 1/450 - 1/660 males (Radicioni & Lenzi 2010; Geschwind & Dykens, 2004). Few males are diagnosed, with only an estimated one quarter receiving a diagnosis and approximately 4 - 10% diagnosed before puberty.

Lack of diagnosis is reported to be a 'major problem' not least because of the array of significant health risks associated with the condition (Nieschlag, 2013; Bojensen & Gravholt, 2007). Low diagnosis rates are attributed in the literature to two factors: low awareness in general clinicians and variable phenotype. Despite the fact that low diagnosis rates are widely attributed in the literature to low awareness among general practitioners and variability in presentation of the syndrome making diagnosis difficult, there is a paucity of evidence to explore the veracity of these claims. This qualitative research examined the evidence for these assertions by exploring pathways to diagnosis and perceptions of the impact of diagnosis, or lack of it, from three different groups with different perspectives. These groups are: (a) affected individuals and their families (b) clinical specialists and (c) general practitioners.

What emerged was a picture of often long journeys for individuals and families as they struggled to find out ‘what was wrong’ with considerable impacts when diagnosis was not made until later in life. General practitioners appeared to have little or no knowledge of the syndrome, as did many clinical specialists. Lack of knowledge was compounded by a fractionated referral process and lack of clarity about who may be responsible for making a diagnosis. Recommendations for ways forward from the current impasse are proposed.

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CHAPTER 1

A COMMON CONDITION: A RARE DIAGNOSIS

1.1 Introduction

1.1.1 What is Klinefelter's Syndrome?

Klinefelter's Syndrome (47, XXY) is a common, but rarely diagnosed condition with approximate estimates of occurrence, with varied prevalence rates estimated between 1/450 (Bourke, Herlilhy, Snow, Metcalfe, & Amor, 2014; Radicioni & Lenzi, 2010) and 1/660 males (Verri, Cremante, Clerici, Destefani, & Radicioni, 2010; Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009), for example. Klinefelter's Syndrome is a sporadically occurring, non-inherited, genetic condition affecting only males where there is the presence of an additional X chromosome. The impact of the syndrome is lifelong and has biological, emotional and cognitive implications, causing an array of lifelong associated complex difficulties, including increased risks to health, education, social interaction and career. The syndrome is commonly reported by affected individuals and their families and echoed in the literature to have a negative impact on quality of life. Underlying full scale IQ is usually unaffected, but the impact of this systemic condition is frequently significant and often detrimental to the individual and to their family as almost all organ systems are reported to have been associated with a significant increased risk of morbidity and mortality in Klinefelter's Syndrome (Fruhmesser & Kotzot, 2011; Rocca et al., 2016; Stagi, et al., 2016; Zoller, Sundquist & Sundquist, 2016, for example). These risks include autoimmune diseases, diabetes type 1, hypothyroidism, respiratory problems, scoliosis, rheumatoid arthritis, osteoporosis, systemic lupus erythematosus and increased risk of cardio-metabolic complications. This constellation of increased risks to physical, neurological and psychological disorders have led to varied reports in the literature of estimated impacts on life expectancy below the general male population with reports of between 2.1 years (Bojensen, Juul, Birkebaek, & Gravholt, 2004) and 11.5 years (Nieschlag, 2013). Reasons for the differences in estimates have yet to be definitively established, with further research needed to identify if the increased risks are caused by the syndrome, or by other factors such as socioeconomic, which are, as yet, unknown (Bojensen et al., 2004). Research factors which may contribute to the discrepancy in estimated impacts on life expectancy in Klinefelter's may include the impact of the research base reporting on a variety of different co-morbidities in the literature and further, different

methodological approaches in the way the syndrome has been studied that may contribute to the variability in the literature (Boada et al., 2009). These include cancer (Swerdlow et al., 2005), socioeconomic factors (Bojensen, Stochholm, Juul & Gravholt, 2011) insulin resistance, metabolic syndrome and diabetes (Salzano et al., 2018) and epidemiological research studies describing mortality in Klinefelter's (Bojensen, Juul, Birkebaek, & Gravholt, 2004) which described increased mortality in Klinefelter's as attributed to a complex array of increased health problems such as infectious, neurological, circulatory and urinary tract diseases.

Understanding through further research to increase knowledge of potential impacts and implications of Klinefelter Syndrome for life expectancy is significant for affected individuals, families and the health professionals who care for them. Increasing knowledge in understanding morbidity and early mortality associated with Klinefelter's may be beneficial in terms of informing the implications for appropriate anticipatory approaches to care including screening, monitoring and timely treatments to potentially minimise emergence of increased health risks in Klinefelter patients. The complex factors and mechanisms influencing morbidity and mortality in Klinefelter's are acknowledged in the literature to be (as yet) unknown (Bojensen et al., 2004) and not completely understood (Salzano et al., 2018). This gap in the literature may account, at least in part, for the varied estimated impacts on life expectancy reported in the current literature.

1.1.2 Lack of diagnosis

"Nearly 70 years after its description, Klinefelter's Syndrome (47, XXY) remains a largely undiagnosed condition" (Radicioni et al., 2010).

The European Union defines rare diseases as those which affect less than 5 in 10,000 of the general population.[1] By this definition Klinefelter's Syndrome is not a rare disease (an incidence of 1/450 equates to 22 per 10,000, for example; Bourke et al., 2014) and is reported to be increasingly prevalent (Leggett, Jacobs, Nation, Scerif & Bishop, 2010). Nevertheless, diagnosis rates in Klinefelter's Syndrome are reported in the literature to be low, with 64%-75% remaining undiagnosed in their lifetime (Bojensen & Gravholt, 2010; Kebers, Janvier, Colin, Legros & Ansseau, 2002; Bourke et al., 2014; Gravholt et al., 2018; Kanakis &

[1] https://www.raredisease.org.uk/what-is-a-rare-disease

Nieschlag, 2018). Estimates made for the incidence of Klinefelter's Syndrome are based on older data (see Nieschlag, 2016) and the accuracy of claims that only 25% of patients are diagnosed and 75% remain undetected remains unclear, despite frequent contact with doctors by Klinefelter's individuals as a result of the increased health risks and conditions associated with the underlying syndrome and requiring medical attention (Nieschlag, 2013).

The literature presents a range of estimated prevalence rates for Klinefelter's Syndrome and a definitive rate of incidence appears inconclusive as yet. Reasons for this range of estimates are currently unclear, but there may be multi-factorial reasons for the varied reported estimates. As research interest has increased in Klinefelter's Syndrome in recent times, the estimated rates of prevalence in the literature has evolved seemingly in parallel with advances in research and the developing understanding and exploration of the syndrome. Current estimated rates of incidence reported in the literature range between 1/450 - 1/660 being the most commonly reported (Verri et al.,2010; Skakkebaek et al., 2018; van Rijn et al., 2008; Cordeiro, Tartaglia, Roeltgen, & Ross, 2010). Interestingly some recent research has appeared to move towards a broader estimated rate of prevalence which appears to encompass the broad range of estimated figures appearing in the literature over recent years (Akcan, Poyrazoglu, Bas, Bundak, & Darendeliler, 2018), for example with an estimate range of 1/500 - 1/1000.

Variation in the literature of the definition, or boundaries of exactly the precise definition of the diagnostic label of 'Klinefelter's Syndrome' seems to vary within the body of current literature with some researchers concentrating their definition exclusively on Klinefelter's as 47,XXY only. In contrast, some researchers extend their focus beyond the most common 47,XXY and beyond to include other sex chromosome aneuploidy (SCA) variations within their definition of the 'Klinefelter' label as in Sorensen, Nielsen, Jacobsen, & Rolle (1978) who include 48 XXYY, for example). Further, the varied definitions of 'Klinefelter Syndrome' extending this label beyond the conventional 47, XXY description and including any karyotype including a single Y chromosome and more than one X chromosome where the individual was listed as male is noted to be included in some Klinefelter studies (for example Herlilhy Halliday, Cock, & McLachlan, 2011). The inclusion of other variations may therefore affect estimated rates of prevalence being significantly less common (48,XXYY for example is estimated to occur in 1 in 18,000 males). As understanding and research expands understanding and informs clarity for the scope, or honing, of the Klinefelter definition, there

is the possibility that this lack of continuity in the literature may impact on estimates of prevalence. Further, as Klinefelter's Syndrome (47,XXY) is universally reported to be significantly under diagnosed, the definitive rates of prevalence remain unknown and therefore estimates based on population studies are currently the source of estimates reported in the literature.

In addition, there are consistent reports in the literature that, of the SCA's, Klinefelter's Syndrome (47,XXY) alone is increasing. Reasons for this increase are unclear and there is a need highlighted in the literature for further research to inform understanding for the reasons for this reported increase (Herlilhy et al., 2011). This suggested increase in incidence may further impact on estimated rates of prevalence and, as has been noted in the literature, Klinefelter's may be occurring more frequently than has been reported and there are frequent reports in the literature of the significant number of undiagnosed cases (Herlilhy et al., 2011).

When a diagnosis is made, this is often delayed beyond puberty into adulthood with only 10% of individuals thought to be diagnosed before puberty and only 4% before 10 years of age (Bojensen & Gravholt, 2007; Geschwind & Dykens, 2004). Variability of presentation (Bojensen & Gravholt, 2007; Leggett et al., 2010; Smyth, 1998; Tartaglia, Cordeiro, Howell, Wilson & Janusz, 2010) and low awareness in general practitioners (Nieschlag, 2013; Radicioni et al., 2010) are the two major reasons identified in the literature as the cause of under diagnosis (Bojensen, Host & Gravholt, 2009).

Lack of a diagnosis, or a later diagnosis, is reported to be a ‘major problem’ (Bojensen & Gravholt, 2007). Radicioni et al. and others report correlations between early diagnosis and quality of life (Nieschlag, 2013). Furthermore, the event of diagnosis is reported to be significant as this is anecdotally reported to be the key instigator, facilitating access to important preventative medical care and treatments (Radicioni et al., 2010; Groth, Skakkebaek, Host, Gravholt, & Bojensen, 2012). This is of clear significance given the increased necessity for hospital admissions of 70% (Bojensen & Gravholt, 2011) and the reported lower life expectancy below the general male population of those with Klinefelter’s Syndrome (Nieschlag, 2013).

It is apparent that research which explores and informs the factors involved in reaching a diagnosis is needed, not least to minimise the increased risks associated with the condition and to maximise opportunities for positive outcomes (Geschwind & Dykens, 2004) and

improve quality of life for Klinefelter's individuals (Nieschlag, 2013). However, reaching a diagnosis at birth is reported as unlikely as there are usually no obvious presenting clinical features (Bojensen & Gravholt, 2007; Tyler & Edman, 2004) and the lifespan physical phenotype is usually unremarkable to the casual observer (Geschwind & Dykens, 2004). The literature highlights the importance of educational support and targeted interventions and identification of strengths, as well as weaknesses, being important factors to establish for effective planning of psychosocial interventions (Verri et al., 2010; Rigamonti et al., 2016) but appropriate awareness and diagnosis of the condition appears to be lacking to enable appropriate support to take place. Similarly, despite the fact that behavioural and social profiles unique to Klinefelter's have been reported and are thought to provide important insight into treatment implications (Visootsak & Graham, 2009), such understanding may not have reached the practitioners likely to come into contact with Klinefelter's individuals. Furthermore, although the significance of the biological influences in Klinefelter's Syndrome has been shown to cause heightened sensitivities to psychological, educational, cultural and social factors (Verri et al., 2010), there is a paucity of research examining the impact socio-emotional and cognitive sequelae over the lifespan and efficacy of treatment and interventions has been noted (Geschwind & Dykens, 2004). Finally, calls for the recognition of the low diagnosis rates and recognition of the associated increased health risks in Klinefelter patients, although strongly advocated in current research (Wing, 2018; Wq, Eide, J, & Ym, 2018) may not yet have reached practitioners in the field. In sum, despite increased awareness in the literature of the importance of early diagnosis and effective treatment, the extent to which this information is reaching the practitioners who will affect the necessary changes is unclear.

1.1.3 Potential impact of better diagnosis

The notably high rates of misdiagnosis and no diagnosis in Klinefelter's Syndrome is accounted for, in part, in the literature by the confounding factor of the broad phenotype (and therefore lack of generally recognised 'typicality' of recognisable symptoms or presenting features of the syndrome). The broad spectrum of phenotypes presenting with Klinefelter's Syndrome is a notable hallmark of the syndrome and is well reported in the literature (Tartaglia et al., 2010; Rocca et al., 2016). However, the reasons for this variability are less clear, although the role of epigenetics in the wide phenotype and varied severity of symptoms in men with Klinefelter Syndrome has gained increasing momentum in recent research. Whilst recognised as a confounding diagnostic factor, this complex spectrum of phenotypic

descriptions could aid and inform a timely and accurate diagnosis if heightened awareness for this condition was achieved beyond specialised health professionals and into the wider medical community (research to date showing the variability in presentation of the Syndrome is reviewed in Chapter 2).

1.1.4 Multi-disciplinary and holistic treatment

Current research reflects the recent advances in understanding of the variability of the condition and increasingly advocates for a multi-disciplinary treatment approach for Klinefelter's patients from an early age (Rigamonti et al., 2016) reflecting the complexity and wide range of health challenges which frequently present with the syndrome. Recent research developments increasingly support the provision of clinics offering multi-disciplinary treatment for Klinefelter's males, due to the wide variation and impact of the condition (Chang, Skakkebaek, & Gravholt, 2015)

Recent advances in understanding of Klinefelter's Syndrome highlight an expanding understanding of the complexity and variability of the impact of the condition. A multi-disciplinary approach to care and diagnosis reflecting the complexity and variability of the condition is advocated as 'essential' in the care of Klinefelter boys and adults (Eberi et al., 2005). Additionally, Rigamonti et al. (2016) have pointed out the potential benefits of providing families with clinical and psychosocial information about the syndrome. It is recognised that timely diagnosis underpins appropriate management and interventions (Groth et al., 2012). Lack of, or delayed, diagnosis is reported as detrimental to individuals, their families and life outcomes although there is little formal evidence to support these claims. Anecdotally, clinical experts and families echo the importance of early diagnosis. Stanhope R. (2010), maintained that "diagnosis is important, making it early is even more important." Similarly, families anecdotally highlight the perceived positive difference of a timely diagnosis: "we were quite upset to think that a simple blood test could have saved years and years of misery" (Parent, personal communication, 2012).

1.1.5 Genetic advances enable early fertility intervention

The 47, XXY karyotype in Klinefelter's Syndrome causes infertility in almost all males with the condition. However, there has been recent progress in genetics advancing our understanding of the underlying physiology driving the mechanisms which result in infertility in almost all Klinefelter men (Winge et al., 2018). This has led to the recent unexpected

breakthrough which now provides Klinefelter males with the new possibility of early fertility intervention and of having children making diagnosis even more critical. Current research (Winge et al., 2018) proposes the notion that spermatozoa retrieval could be undertaken at the onset of puberty and before testosterone therapy. The opportunity for successful fertility treatment is time dependent and affected by the age of the patient as sperm extraction success decreases with age and, crucially, after testosterone therapy. Thus, developments in fertility possibilities renders age of diagnosis a critical factor in determining fertility in Klinefelter males, not only for affecting success of fertility treatment, but also in determining optimum testosterone treatment (TRT) due to effects of TRT on future possible fertility for the Klinefelter male.

1.1.6 Puberty and delayed diagnosis

In adolescence, puberty is closely aligned with adolescent experiences, observations have been reported that where passing through puberty is delayed or disrupted and a patient does not display signs of puberty at a similar age to his peer group there is a risk of becoming left behind or isolated from his peer group. These effects are reported to have not only physical, but social and emotional (Smith & Quinton, 2012) implications which may cause a barrier to positive emotional development. Further, these may impact early social interaction opportunities with negative implications for self-confidence and feelings of social isolation from peers. Similarly, general reassurances from general clinicians advising a 'wait and see' approach may have general, long term negative implications for psychological wellbeing (Bourke et al., 2014). Diagnosis has been reported as helpful for increasing understanding from others and beneficial for patients coming to terms with a diagnosis (Smith & Quinton, 2012).

1.1.7 Aims and objectives of this research

The primary aim of this qualitative research is to explore the significance of diagnosis in Klinefelter's Syndrome (47,XXY) and to obtain a rich picture of the lived experience of individuals and their families and the impact which diagnosis, early or late, had on their lives. As noted earlier, two reasons generally given for under-diagnosis of this syndrome (Bojensen et al., 2009) are a lack of awareness in general clinicians (Nieschlag, 2013; Radicioni et al., 2010) and variability of the syndrome (Bojensen & Gravholt, 2007; Leggett et al., 2010;

Smyth, 1998; Tartaglia et al., 2010). This study will explore the assertions in the literature that:

(i) diagnosis is significant to affected individuals

(ii) the condition is significantly under diagnosed due to (a) variability in symptom presentation and/or (b) low awareness in general practitioners.

Until relatively recently, behavioural research on males with Klinefelter's Syndrome had paid little attention to the whole person producing a somewhat 'lopsided' research history (Geschwind & Dykens, 2004) with a lack of a complete picture of Klinefelter's Syndrome. A qualitative approach will be adopted because of (a) the paucity of data available taking a 'whole person' approach and (b) the need for rich, detailed data examining pathways to diagnosis and differences in perspectives between those involved in that process. Emergent themes will inform the relevance of and pathways to diagnosis, the nature of provision and support available with and without a diagnosis. Perspectives from three different groups will be sought regarding the perceived importance of diagnosis for individuals with Klinefelter's Syndrome and their families in order to provide different perspectives and experiences. These groups are as follows:

(i) Individuals and families directly affected by Klinefelter's Syndrome

(ii) Medical specialists divided into (a) and (b) as follows:

(a) Experts: medical specialists with particular expertise in Klinefelter's Syndrome providing specialist services and treatment to patients with Klinefelter's Syndrome

(b) Specialists: medical specialists with expertise other than with Klinefelter's Syndrome but practising within areas of known increased risks in Klinefelter's males.

Both (a) and (b) provide specialist services and treatment to patients with Klinefelter's Syndrome.

(iii) General Practitioners who are often the first point of contact for general primary health care

This research is the first of its kind to investigate evidence to explore the perceived significance of diagnosis in Klinefelter's Syndrome in these three different groups and

provides information about the different perspectives regarding diagnosis, treatment and lived experiences (see Figure 1). Importantly, it may provide information about how diagnosis takes place: how families seek diagnosis and how general practitioners and specialists respond when presented with symptoms which may indicate Klinefelter's Syndrome. It will also examine awareness of the syndrome in GPs, consultants and specialists and effects of this on the diagnostic process.

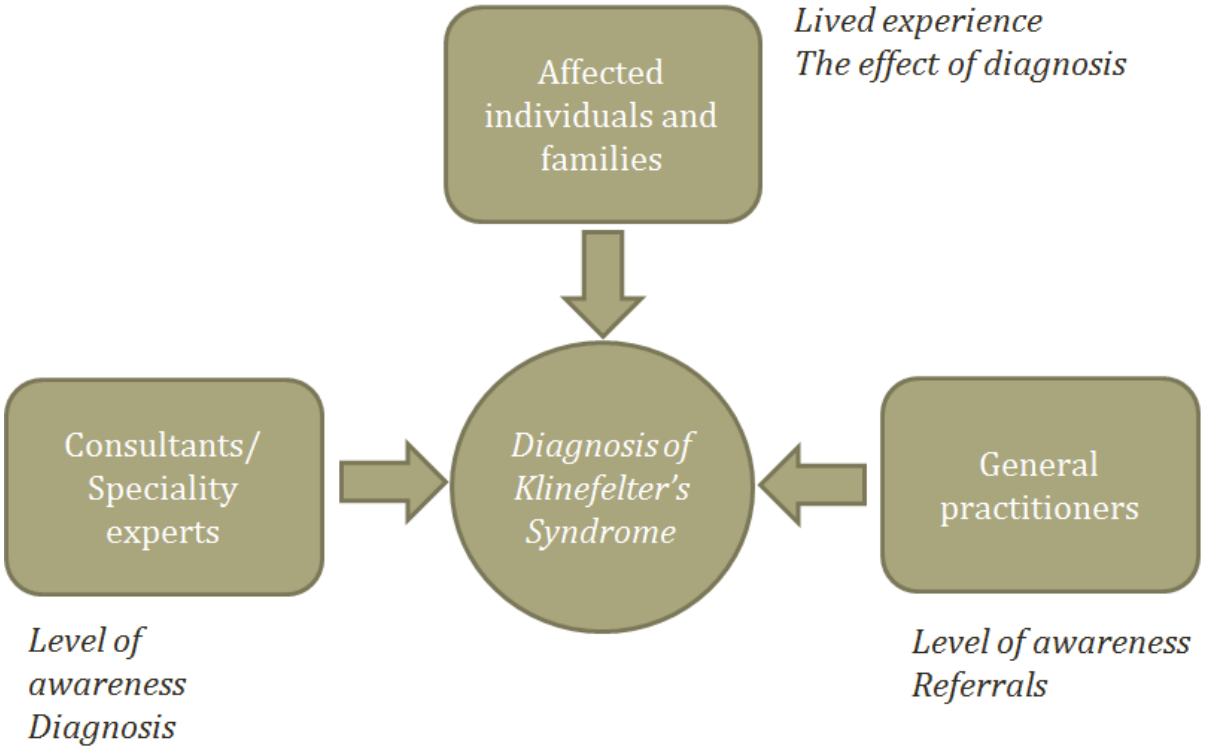


Figure 1: Possible perspective afforded by interviews with affected individuals and their families, consultants and specialty experts, and general practitioners.

1.1.8 Summary

Klinefelter's Syndrome is systemic condition carrying increased risks of morbidity and mortality across a spectrum encompassing a multiplicity of health, psychological, cognitive and emotional factors. Klinefelter's Syndrome is associated with a significantly increased mortality risk of 40% and increased risk of hospitalisation of 70% from an array of 78 over-represented co-morbidities including infertility, osteoporosis, the immune system, some cancers (Eberi et al, 2005) and infectious diseases.

Klinefelter's is not a rare disease, occurring in between an estimation of approximately 1/450 - 1/660 males, but remains significantly underdiagnosed with up to an estimated 75% of individuals never knowing they have the condition. This is thought to be due to a combination phenotypic variability and low general awareness of the condition. Furthermore, the frequently mild, presenting features often experienced in Klinefelter's Syndrome, particularly early subtle delays or differences in Klinefelter's Syndrome such as speech and language delay, or delay in reaching infant milestones, are not necessarily seen as other than insignificant delays of typical children and therefore paediatricians are not prompted to refer for genetic testing. The importance of early diagnosis has been highlighted in recent research which has shown that early diagnosis and hormonal treatment can act as mitigating factors, mediating favourable outcomes (Samango-Sprouse et al., 2018) and increased diagnostic vigilance is advocated in the literature as important for early recognition of significant effects of known increased risks to morbidities and mortality (Bojensen & Gravholt, 2011; Wq, Eide, J, & Ym., 2018). In short, the un-diagnosed individual is vulnerable to the increased risks associated with the condition and is not able to benefit from the preventative and beneficial measures increasingly advocated in recent research.

1.2 Contribution of Current Research to the Field

1.2.1 Exploring the reasons for lack of diagnosis

As noted earlier, it is estimated that only one quarter of all males with Klinefelter's Syndrome are diagnosed during their lifetime (Nieschlag, 2013). Lack of, or delayed, diagnosis is reported as detrimental to individuals, their families and life outcomes (Groth et al., 2012; Los & Ford, 2018; Lanfranco, Kamischke, Zitzmann, & Nieschlag, 2004; Radicioni et al., 2010). The importance of timely diagnosis is reported in the literature and echoed anecdotally by those affected (Radicioni et al, 2010). While there have been recent claims that the sensitivity and specificity to clinical indicators of Klinefelter's diagnoses have improved (Nieschlag, 2016), it is unclear how this conclusion was reached. By examining individual pathways to diagnosis, exploring how and when diagnoses were obtained, and the subsequent impact this had on Klinefelter's individuals and their families, it is hoped that the data generated by this study will contribute to the body of knowledge to our understanding of where and when lack of diagnosis arises and its perceived significance.

1.2.2 Why is early diagnosis important?

Stanhope (2010) maintained that "diagnosis is important, making it early is even more important." Klinefelter's Syndrome is associated with an increased risk of multiple morbidities and increased mortality, thus frequent contact with doctors (Nieschlag et al., 2016) can reasonably be anticipated. However, specific disorders are usually diagnosed and treated by specific specialists thus delivering a single disease treatment approach. This in contrast to the holistic approach increasingly advocated in recent literature and by experts in the condition (Nieschlag et al, 2016).

The importance of early recognition is needed to appropriately address the educational and therapeutic aspects of Klinefelter's Syndrome (Geschwind & Dykens, 2004; Herlilhy et al., 2011; Verri et al., 2010). The literature highlights the importance of educational support and targeted interventions and identification of strengths and weaknesses being important to establish for the effective planning of psychosocial interventions (Verri et al., 2010; Vizziello et al., 2016).

Research recognises the significant increase in mortality and morbidity in Klinefelter's Syndrome with an increased risk of mortality (Salzano et al., 2018) and a 70% increased risk

of hospital admission (Bojensen & Gravholt, 2011). Data from nation-wide epidemiological studies report these increased risks from a variety of different causes and the research to identify the underlying reasons in Klinefelter's Syndrome reports an interaction of contributory and causal factors including genetic, hormonal and socio-economic. Increased mortality has been described in a number of epidemiological studies and findings reported Klinefelter Syndrome was associated with an increased risk in mortality of 40% from diseases including infection, neurological, circulatory, pulmonary and urinary tract (Bojensen, Juul, Birkebaek, & Gravholt, 2004). As stated, further research is reported to be needed for clarity and providing a honed estimate for increased risks to morbidity and mortality for Klinefelter males. Further research reports a significant increase of 70% for risk of hospitalisation in Klinefelter patients. The reasons for admission included congenital malformations, psychiatric disorders, endocrine and metabolic disorders. Of particular note was the observation that the reported increase in hospital admissions was present before and after a diagnosis was made (Bojensen et al., 2006). The reasons for this are, as yet, unclear and research continues to explore contributory factors, but there is some agreement in the literature that contributory factors likely include a contribution of hypogonadism which is central to the syndrome and other unknown effects which seem to modify or impact on disease patterns. Other disorders directly linked to the underlying syndrome such as altered body composition, diabetes and cardiovascular disease and cognitive impairment are seen more frequently with further influences including socioeconomic factors (Chang, Skakkebaek, & Gravholt, 2015). The increased risk of earlier death in Klinefelter's Syndrome contributes to the urgency reported in the literature for early diagnosis and the need for an increase in the number of cases diagnosed.

Similarly, lack of diagnosis can deny the individual important health monitoring and screening for the known increased medical and health risks reported in Klinefelter's Syndrome such as psychiatric disorders, osteoporosis, excessive tiredness, diabetes type 2, autoimmune disorders, some cancers, immunological differences, syndrome specific testosterone level differences and arrested pubertal development (Kebers et al., 2002). It is evident that in many of these disorders, there is an urgency for early identification of increased risk to aid timely screening. This may be important in providing an opportunity for preventative measures and treatments to be put in place thus potentially minimising long-term health problems caused by lack of diagnosis leading to late intervention and an increased deleterious impact on health

and wellbeing. These increased risks may include conditions which may carry implications to longer term health if left untreated such as a delay in treatment with testosterone may cause a decrease in muscle and bone mass which is known to lead to increased risk of osteoporosis (Bojensen, Juul & Gravholt, 2003). Where diagnosis is made there may be a potential to avoid the emergence of some of the increased risks where early diagnosis informs prompt screening and anticipatory interventions.

Further, without diagnosis, difficulties with speech, language and social communication as well as potential behavioural difficulties cannot be addressed through appropriate interventions which modify teaching delivery and styles effectively to ameliorate the challenges Klinefelter's individuals often face (Ross et al., 2008). Whilst there is a recognised heterogeneity within Klinefelter's Syndrome, there are recognisable features of the condition which commonly present at key stages through the lifespan and which if correctly noticed, recognised and identified by general clinicians would result in increased diagnosis rates, appropriate care and improved quality of life (Nieschlag, 2013).

As stated, the importance of diagnosis and more significantly, early diagnosis, is now rendered with further urgency due to recent advances in fertility treatment. These advances make possible the unexpected option for some Klinefelter's males to become a genetic father. Until recent advances made this a possibility, Klinefelter's males were usually considered inevitably infertile with no possibility of the option to father their own offspring. Where a diagnosis has not been made prior to adulthood, men presenting for clinical attention for infertility may lead to a diagnosis for some individuals. Klinefelter's males account for 3% of all men evaluated for infertility (Los & Ford., 2018). The high prevalence of Klinefelter's men presenting for medical advice and treatments for infertility identifies fertility groups as a high-risk category group for diagnosing Klinefelter's Syndrome. These high-risk category groups may be appropriate to include in the 'diagnostic cluster' group (DCG) identified in this research. One benefit of identifying a high-risk cluster group is to provide an easily recognisable diagnostic 'prompt' or clusters of symptoms for use by general clinicians to aid consideration for patient referral for genetic testing and eventual diagnosis.

Recent breakthroughs in advanced reproductive technologies such as testicular sperm extraction (micro-TESE) has been successful in providing the opportunity for an estimated half of the men deemed infertile by reason of Klinefelter's Syndrome, to have the chance of

having a biological child (Los & Ford, 2018), although there are recent anecdotal reports that figures may currently be less than the early estimates.

Further diagnostic urgency is created by the significant role that timing of diagnosis plays in the success, or otherwise, of fertility treatments. Where a diagnosis is delayed, or achieved later in life, the chances of successful fertility treatment diminish (Los & Ford, 2018). This is due to a number of factors including the histopathology of the disease where the impact of syndrome causes an increasing progressive deficit of germ cell numbers through puberty with only infrequent pockets reported in adulthood (Los & Ford, 2018). Further, there are reports in the literature that fertility preservation in Klinefelter adolescents by means of sperm retrieval may be possible (Rives et al., 2018) for some. However, for this to be considered for the adolescent patient, not only is a correct diagnosis an essential outcome factor, but an early diagnosis has a critical role in affecting the outcome. The advances in fertility treatments have resulted in reports in the literature that precocious diagnosis and the timing diagnosis of Klinefelter's Syndrome is important as this may improve the possibility of fertility preservation, particularly after the onset of puberty. There are further reports that semen quality may decrease with age in Klinefelter's patients (Rives et al., 2018).

Further urgency for timely diagnosis is compounded by recent reports of the possibility that testosterone treatment has a detrimental impact on fertility. Not yet widely reported, there are early indicators that the uniformly prescribed testosterone treatment usually instigated around the time of puberty and required through the lifespan by Klinefelter patients may decrease the chances of fertility success in Klinefelter men (Rives et al., 2013). The case is made in the literature that sperm extraction may decrease with age and, crucially, decreases after the commencement of testosterone therapy (Rives at al., 2018). Therefore, support for the retrieval of spermatozoa at pubertal onset and before testosterone therapy is started to increase the chances of success is evident, time critical (Rives et al., 2013) and strongly advocated in recent research. These factors further emphasise the significance of not only diagnosis, but the time-critical nature of an early diagnosis for Klinefelter's males. Unexpected recent advances in fertility treatments now present options to Klinefelter patients that were previously not possible. However, as stated, the success of these fertility treatments is directly impacted by the clinical history of each patient through their lifespan and, crucially, include when diagnosis was made in each patient and which treatments may have been administered (such as testosterone). These factors which have dynamic impact on the outcomes throughout the

lifespan of the Klinefelter males affecting the health, wellbeing, risk to morbidity and increased mortality risks and quality of life of each Klinefelter's individual. Additionally, the opportunity to father their own biological child is now a possibility for some, but this potential opportunity is significantly impacted by previous diagnostic and treatment factors in each patient. Thus, the interplay of factors impacting on opportunities, life choices and quality of life for Klinefelter's males, including diagnosis, treatment and clinical interventions heighten the urgency of increasing awareness among general clinicians and the wider community.

1.2.3 Multi-disciplinary research and treatment

Much previous research has taken a piecemeal approach to Klinefelter's Syndrome, leaving it unclear where and when difficulties arise and often focusing on particular health risks reflecting the specialisms of those conducting the research. This approach has inevitably resulted in a fractionated body of research which did not describe the multi-dimensional impact of the syndrome for patients and associated implications to their lifelong health and wellbeing.

A more comprehensive and cohesive research body has recently emerged in the field leading to a broader and deeper identification and description of the whole of life impact and implications of the disease. Recent work in the United States (Tartaglia et al., 2015) has begun developing multidisciplinary clinics with integrated services for Klinefelter's patients and a wider body of research has emerged in recent times with a current focus on the importance of a multi-disciplinary treatment approach for Klinefelter's males (Gravholt et al., 2018). Reported benefits included providing infants, children and adolescents becoming adults who matured confident and self-aware of their condition. Economic benefits were also reported to the health and mental health system as the need for support services was expected to decrease as services became more efficiently integrated. Referral routes for individuals with a diagnosis to multi-disciplinary clinics has not been specified.

Strengthening the case for improved diagnostic practices is the reported increasing prevalence of Klinefelter's Syndrome (Leggett et al., 2010; Morris et al., 2008; Bruining, Swaab, Kas, & van Engleland, 2008; Bojensen et al., 2003). Although the reason for the reported increase has not yet been identified, the literature reports that Klinefelter's Syndrome alone in the sex chromosome trisomies (SCT)'s is increasing. In their study of 2008, Morris et al. reported

findings of an increase in prevalence of Klinefelter's Syndrome since the six surveys of unselected new-borns in research carried out in the 1960's and 1970's. These findings were echoed in the reported findings in the study by Davis et al. (2016) and hypothesised that increasing prevalence and significantly increasing ascertainment rates made possible by advances in non-invasive pre-natal testing (NIPT), there is a likelihood that more paediatricians will have increased referrals for children with a known diagnosis of Klinefelter's Syndrome (Davis et al., 2016).

As stated, an estimated two-thirds of males with Klinefelter's Syndrome may go undiagnosed. The literature identifies the reasons for this under-diagnosis to be hindered by the variable phenotype commonly reported for this condition (Los & Ford, 2018) and the low awareness of the disease among health professionals (Radicioni et al., 2010). While more widespread and more effective screening has been recommended to increase diagnosis rates (Verri et al., 2010; Rogol, 2016; Gravholt et al., 2018), given the variability in the presentation of the syndrome there is a lack of evidence to determine when and how this might be most productively done. Recent advances in prenatal testing have resulted in increasing numbers of conditions diagnosed before birth. The general appearance of most Klinefelter's males are unremarkable to the casual observer (Geschwind & Dykens, 2004) and is a significantly underdiagnosed population reportedly due to the variable phenotypes and low general awareness. Research estimates that perhaps a quarter of Klinefelter patients have no discernible diagnostic features either by their history or on examination (Los & Ford, 2018). However, there is increasing speculation in the literature that, despite frequently presenting with subtle findings and the commonly reported general low awareness both of which act as confounding factors to diagnosis, the increase of non-invasive prenatal testing (NIPT) will cause an increase of prenatal diagnosis. Estimates currently cite the expected diagnosis rate for Klinefelter's infants being a tenfold increase should NIPT be introduced as standard screening for all pregnancies (Davis et al., 2016). Thus a 'sharp' increase of diagnosis in prenatal and neonatal births is anticipated over the coming ten years (Davis et al., 2016). A future increase in the number of diagnosed Klinefelter's children presenting at their general practitioner for healthcare advice is therefore anticipated. In parallel with the anticipated rise in prenatal identification of Klinefelter's Syndrome due to the increasing practice of NIPT, there may be a similar increase in the need for appropriate genetic counselling for parents.

Thus, the significant advances in recent times across several scientific disciplines including fertility treatments, prenatal testing and genetics have rapidly informed and changed our understanding and knowledge of Klinefelter's Syndrome. The reported increasing prevalence of Klinefelter's Syndrome, combined with the anticipated ten-fold rise in diagnosis rates within the coming ten years, has clear implications for a pressing need for further research. This is needed to inform appropriate management for patients such as enhancing health professionals' understanding of necessary screening, preventative measures and provision of treatments. The increasing diagnosis rates and increasing awareness would also necessitate an equal increased need for provision of early diagnosis management by health care professionals (Los & Ford, 2018).

As stated, the lack of, and under diagnosis of, Klinefelter's Syndrome is universally reported in the literature. Further to this, lack of diagnosis is reported as being of significance for the possibility of fertility preservation after the onset of puberty.

Additionally, diagnosis is universally reported as having significance for the medical care and the quality of life of Klinefelter patients (Rives et al., 2018; Salzaon et al., 2018).

Thus, the imperative of achieving diagnosis and, crucially, early diagnosis is highlighted in the literature and identified as a critical factor for beneficial quality of life and includes protecting possible fertility opportunities for Klinefelter patients. The advances for treatment for infertility has meant that the previous anticipated irrevocable and actual infertility of most Klinefelter's men is now not necessarily the case and the impact of these advances now provide the hope to Klinefelter's men they may genetically father their own child.

1.2.4 Aims of this research

This qualitative research will explore and investigate if diagnosis is perceived as an essential gateway to improving quality of life or provides access to interventions that can cause negative symptoms to diminish. Further, if there may be an 'infant core' of identifiable symptoms which may be beneficial as a prompt for early screening. This research explores the veracity of these assertions through individual narratives and investigates how diagnosis and age at diagnosis impacted on individuals' subsequent life paths. The objective is to inform the wider picture through describing individual narratives with particular reference to the impact of diagnosis. Further, research commonly reports that lack of, or later, diagnosis is attributed to lack of awareness in general clinicians.

Emergent themes from the three participating groups may inform understanding of the relevance of diagnosis, provision, support and variation of presentation that is reported in the literature. No studies have evaluated the economic impact of increased morbidity and mortality in Klinefelter's Syndrome and if it is possible that early diagnosis and treatment may have a positive effect on health care systems (Maggi, Schulmann, Quinton, Langham, & Uhl-Horhuraeher, 2007). Geschwind & Dykens (2004) report that further research into how socio-emotional and cognitive features interact over the lifespan and efficacy of treatment is helpful. Increasing understanding of these factors may be beneficial to broaden knowledge and enrich information regarding importance of timely diagnosis, preventative screening, intervention and support.

1.2.5 Importance of preventative screening and early treatment

As previously noted, lack of diagnosis, or later diagnosis, is reported to be 'a major problem' (Bojensen & Gravholt, 2007). Radicioni et al (2010) and others, report correlations between early diagnosis and quality of life (Nieschlag, 2013) as well as access to important preventative medical care (Radicioni et al., 2010; Groth et al., 2012).

A more widespread screening is advocated to increase diagnosis rates (Verri et al., 2010), but how and when to implement this is still unclear (Nieschlag et al., 2016). The frequent requirement for medical advice and treatment sought by Klinefelter's patients (who may still be undiagnosed) due to concomitant diseases (Groth et al., 2013) may provide multiple diagnosis opportunities. It may be that the groups of disease of known increased risks may present effective diagnostic clusters for targeted screening for Klinefelter's Syndrome. These are presented for consideration as Diagnostic Cluster Groups (DCG) later in this study (Chapter 8).

The importance of screening and early treatment is further highlighted in a follow up study of Klinefelter males. This 20 year follow up study found that initially at 27 years, the Klinefelter males were considerably impaired in several domains including below average school performance, immaturity, few friends, mental illness, little energy and initiative, few hobbies or interests and working in unskilled roles. In contrast, the follow up at age 37 noted considerable improvement in conditions such as mental health, social adjustment, relationships with others and activity levels (Nielsen & Pelsen, 1987). The subsequent follow up at age 47 showed further improvements such that the single point of difference was a

higher proportion of Klinefelter males were single than in the control group of 46, XY males. The significance of the Nielsen findings proposed that, had diagnosis been made in childhood, the results of the examinations conducted at age 27 would have been markedly improved had an earlier diagnosis been afforded to the patients involved with subsequent provision of information, counselling, support and treatment. The findings of the Nielsen study highlighted the importance of making available information about the positive aspects of the development of Klinefelter's males. This is the context particularly of the high proportion of selective terminations in Denmark where this condition had been prenatally diagnosed.

A multi-disciplinary approach to diagnosis and care is advocated as 'essential' in the care of Klinefelter's boys and to support their family to enable the development of their child (Rigamonti et al., 2016). Providing lifespan healthcare and education is underpinned by timely diagnosis, appropriate management and interventions can be put in place (Groth et al., 2012). Physicians should be attentive to the increased risks of medical conditions (Tyler & Edman, 2004; Groth et al., 2013) as this would provide opportunities for earlier screening and treatment. Lack of diagnosis can deny the important monitoring and screening for increased medical risks associated with Klinefelter's Syndrome and the timely provision of preventative treatments and support. Examples of such increased risks and concomitant screening and preventative measures advocated in the literature are summarised in Table 1 at the end of Chapter 2 (page 48).

CHAPTER 2

INCREASED HEALTH RISKS

2.1 Introduction

Over 70 years after its description, Klinefelter's Syndrome (47,XXY) remains a condition which is commonly overlooked by health professionals and frequently remains a 'dormant' diagnosis, often until the individual has cause to seek medical advice in adulthood for fertility problems (Radicioni et al., 2010). As already noted, one of the major reasons why Klinefelter's Syndrome is difficult to diagnose - and is often misdiagnosed - is reported to be because it presents with a broad range of phenotypes. Research commonly attributes this to be a confounding factor in diagnosis (Bojensen & Gravholt, 2007).

The reasons for this reported variability are yet to be definitively proven but a number of possible contributing factors have been postulated and are widely reported as significant. These include parental origin of the supernumerary X chromosome, gene dosage effects and the genetic properties of the supernumerary X chromosome (Disteche & Berletch, 2015; Nieschlag et al., 2016). Recent research suggests possible X linked factors (including copy number variations and duplications) (Zitzmann, Gromoll, & Nieschlag, 2004) which may contribute to the variable clinical phenotype (Rocca et al., 2016).

Klinefelter's Syndrome is known to be associated with a significant number of increased health risks which are the causes of the reported reduction in life expectancy estimated to be between 2 - 11 years (Bourke et al., 2014; Nieschlag, 2013). The most frequently associated categories of medical disorders include motor, cognitive, behaviour dysfunction; tumours; vascular disease; endocrine/metabolic and autoimmune diseases (Stagi et al., 2016). Increased health risks include autoimmune diseases (diabetes type 1, multiple sclerosis, hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus (sle) (Seminog, Seminog, Yeates, & Goldacre, 2014) and cardio-metabolic complications (Radicioni et al., 2010).

Recent advances in genetics has prompted some speculation in the literature regarding the merits, or otherwise, of population based genetic screening (Herlilhy et al., 2014). There is some discussion in the literature regarding the benefits of such wider spread screening and particularly for genetic conditions with variable phenotypes (Herlilhy, Halliday, McLachlan, Cock & Gilliam, 2010). Although it is well recognised that Klinefelter's Syndrome carries

increased significant risk to physical morbidity and mortality, it is less widely accepted that there is sufficient corpus of evidence to support the notion that diagnosis affects outcomes related to quality of life (QOL). This is perhaps inevitable as the extremely variable phenotype results in widely varied life experiences and outcomes.

Recent evidence suggests that, in addition to the additional X chromosome, familial learning disabilities (FLD) may play a further contributory factor to the hallmark variability noted for Klinefelter's Syndrome (Samango-Sprouse et al., 2014). Recent research foci identify specific areas of neurodevelopmental differences in Klinefelter's offspring of families with learning disabilities. These areas of differences were noted to include IQ evaluation, fine and gross motor skills, speech and language (Samango-Sprouse et al., 2014). If the presence of family learning disabilities were to affect the phenotype of the Klinefelter's family member, this may suggest that the hallmark variability of the condition may be attributable to factors in addition to the presence of an extra X chromosome.

Further difficulty in identifying a diagnosable profile of symptoms may arise because across the lifespan increased risk factors interact and influence adult outcomes making it difficult to identify and treat the difficulties which arise as a result of the syndrome (Tartaglia et al., 2010). The increased need for hospital admission and treatment reported for Klinefelter's Syndrome patients results in disproportionate frequency of hospital treatment (Bojensen & Gravholt, 2011). However, Nieschlag (2013) reports that primary care physicians had not knowingly seen any Klinefelter's patients in recent times and postulated this may be an indication of the low awareness reported for this condition among clinicians.

Current evidence underscores the need for increased awareness and identification of the health risks in Klinefelter males in order to provide screening, rather than simply waiting for severe clinical symptoms to present (Tartaglia et al., 2010). This need becomes ever more apparent from nationwide epidemiological studies conducted in Denmark and Britain which showed a significant increase in mortality and morbidity arising from the variety of different health risks experienced by Klinefelter patients. In one study mortality was reported to increase by 50% and the risk of being admitted to hospital with any diagnosis was increased by 70% (Bojensen & Gravholt, 2011). Several case studies report that Klinefelter's Syndrome has been associated with higher prevalence of certain diseases although this alone does not explain the reported lower quality of life reported by many Klinefelter's patients. Further, findings from research indicate that Klinefelter's men are more likely to experience a lower

psychological and sense of social well-being which cannot be explained alone by their frequently reported physical ailments and discomforts (de Ronde, de Haan, & Drent, 2009).

The plethora of increased risks to health and reported variability in presentation of the syndrome is apparent from a review of the relevant research literature in which a diverse range of additional health risks is described. The review is significant for setting the context of the need for frequent contact with health professionals for individuals with Klinefelter's Syndrome and to describe the array of increased risks to health and wellbeing. Taken together, these factors suggest Klinefelter's individuals are a vulnerable group requiring monitoring, screening and timely treatment for which appropriate provision is dependent on diagnosis. Further, the possibility that identification of groups of characteristic symptoms may be beneficial to aid diagnosis is explored by identifying known areas of increased risk and utilising these in a novel model of diagnostic cluster groups.

The following section indicates examples of the array of increased health risks reported for Klinefelter's males. This indicates a plethora of health problems which they may experience and for which they may need to seek treatment from health professionals. The constellation of risks provides an insight into potential significance of diagnosis in prevention, or early intervention where these symptoms present.

2.2 Physical sequelae and increased health risks

2.2.1 Testosterone deficiency, infertility and hypogonadism

Endocrinological abnormalities are caused by the extra X chromosome sometimes resulting in lower testosterone levels from puberty, small testes, androgen deficiency and deficient sperm production usually resulting in infertility (Geschwind & Dykens, 2004). Hypogonadism is the result of androgen deficiency and can result in changes in body composition, type 2 diabetes and risk of developing metabolic syndrome (Groth et al., 2012). Hypogonadism also results in a progressive testicular failure and this failure begins during pubertal development (Stagi et al., 2016).

Testosterone deficiency and infertility is anticipated in Klinefelter’s Syndrome but varies between individuals. Infertility is usually expected and reported in most individuals with Klinefelter’s Syndrome. Many boys with the Syndrome pass through puberty spontaneously with mild symptoms, but it is not uncommon for puberty to be disrupted or delayed by the

presence of the additional X chromosome (Verri et al., 2010). Many men report decreasing libido from 25 years onwards (Lanfranco et al., 2004; Bojensen & Gravholt, 2007) and problems with fertility may lead to advice begin sought in adult years, not infrequently resulting in diagnosis of the underlying condition.

Klinefelter's patients are routinely treated with lifelong testosterone substitution commencing at puberty, but the optimal programme remains to be established. Evidence for the benefits of this treatment to date remains inconclusive not least because there have been no randomised, placebo- controlled trials on the effects of testosterone-replacement therapy (TRT; see Bojensen Gravholt, 2004, for a discussion of this 'glaring omission' which creates a significant gap in the research regarding the efficacy of the effects and potential benefits of testosterone treatment). Other research findings, from studies not employing randomised control trials (RCT) methodology are mixed. Some research reports improved physical and psychological benefits for those on testosterone replacement therapy (TRT) programmes, whereas in contrast, others anecdotally report increased mood swings and aggressive tendencies with the onset of testosterone treatment. Startlingly, recent research exploring the effects of TRT treatment on mood and wellbeing report quality of life may be reduced in Klinefelter's patients treated with TRT (de Ronde et al.,2009). This research contrasts with the traditionally held notion that TRT aids self-esteem and fatigue (Herlilhy et al., 2014).

These mixed findings, along with reports in the literature, advocates for further research to determine appropriate testosterone treatment in adolescence as well as optimal testosterone replacement and sperm retrieval in adolescents and young adults. This is not least because both appear to be ‘age critical’ as sperm extraction success is now believed to decrease with age and after testosterone therapy (Rives et al., 2013).

2.2.2 Metabolic disorders, the heart and vascular system

Defects in systems relating to the endocrine system are reported to cause or control many common human disorders, including cancer, neurodegenerative diseases and cardiovascular disease. Numerous studies report an increased risk of cardiovascular problems In Klinefelter's Syndrome and suggest that there is a need for cardiovascular screening in Klinefelter’s individuals (Host et al., 2014; Sawalha, Harley, & Scofield, 2009; Seminoq, Seminoq, Yeates, & Goldacre, 2014; Walter, Guiseppe, & Claudio, 2007). Klinefelter's Syndrome predisposes affected individuals to metabolic syndrome, metabolic disorders which carry metabolic

consequences with cardiovascular sequelae and contributes to the increased mortality risk to Klinefelter patients (Nieschlag, Werler, Wisturba, & Zitzmann, 2014; Gies, Unuane, Velkeniers, & De Schepper, 2014).

Other research highlights increased risk of thrombosis and embolisms (Byung-Soo-Kang et al., 2012; Fruhmesser & Kotzot, 2011; Groth, Skakkebaek, Host, Gravholt, & Bojensen, 2013; Murray, 1988; Zhang, 2009; Zoller, Sundquist & Sundquist, 2016), and chronic obstructive airway disease (Ueki et al., 2014). Finally, evidence for increased mortality from cardiac related problems are reported for Klinefelter's males with particular risk of sudden death caused by mitral valve prolapse and cardiovascular disease.

2.2.3 Bone mineral, osteological risks, Vitamin D deficiency

Klinefelter's Syndrome has known long-term consequences for bone health with impaired bone mineral status and impaired bone metabolism that begins in early life (Stagi et al., 2016). Testosterone deficiency is considered the major risk factor for early osteoporosis and altered body composition (Stagi et al., 2016) as testosterone is fundamental for bone maturation to be reached by the time of the end of puberty and to be maintained though adult life with implications for regulation of important metabolic systems. Deficiencies of Vitamin D are reported in Klinefelter males (Groth et al., 2012). This is important as it is well recognised that Vitamin D plays an important role in bone metabolism and further, that a deficiency in Vitamin D may have a role to play in worsening bone mass (Stagi et al., 2016). A number of studies have reported reduced bone mass and formation, this can lead to osteoporosis, a condition which tends to be under recognised and undertreated in men (Host et al., 2014). This adds considerably to fracture risk (Haider et al., 2014; Rocca et al., 2016) and can lead to back pain and musculoskeletal problems (Groth et al., 2013). The potential long-term sequelae of poor bone health in this group has led to a recommendation for monitoring and follow up to screen for and prescribe treatment for management of bone mineral status (Stagi et al., 2016).

2.2.4 Autoimmune systems

Immunological differences in Klinefelter males has led to Klinefelter's Syndrome being labelled 'an immunological disorder' (Merchant & Shahani, 1989). Links between Klinefelter's Syndrome and autoimmune diseases include increased risk of progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE) and connective tissue diseases

were reported (Ishihara, Yosimura, Nakao, Kanakura, & Matsuzawa, 1999; Kobayashi, Shimamoto, Taniguchi, Hashimoto, & Hirose, 1991; McDonald, Fam, Paton, & Semm, 1988; Sawalha, Harley & Scofield, 2009; Host et al., 2014). Gies et al. (2014) report increased risk of thyroid dysfunction and Rocca et al. (2016) report greater likelihood of metabolic syndrome, and autoimmune disorders (see also Smyth & Bremer, 1998). Furthermore, inflammatory diseases such as rheumatic arthritis and systemic sclerosis are also reported to occur more frequently in those with Klinefelter's Syndrome (Rovensky et al., 2010). Additional risk factors are reported for Raynaud's disease (also known as Raynaud's phenomenon) in Klinefelter patients where the condition can occur in isolation, but also emerge as a secondary disorder usually associated with the immune system disorders such as rheumatoid arthritis, lupus, and T cell abnormalities reported to carry implications for the development of autoimmune disease (Ishihara et al., 1994). Later studies have found significant increased risks of Klinefelter patients to autoimmune diseases including Addison's disease, diabetes mellitus type 1, rheumatoid arthritis, Sjogren's syndrome, acquired hypothyroidism, multiple sclerosis and systemic lupus erythematosus (Seminoq et al., 2014; Scofield et al., 2008). Screening for auto-immune diseases is advocated as an integrated approach particularly during transition of medical care during late adolescence and beyond (Gies et al., 2014).

2.2.5 Diabetes and obesity

Obesity and diabetes are not unrelated to metabolic difficulties and Rocca et al. (2016) also report increased risk of obesity and diabetes along with a higher likelihood of metabolic dysfunction. Other researchers have also noted an increased tendency towards Type 2 diabetes and given that Type 2 diabetes primarily occurs as a result of obesity this dovetails with Rocca et al.'s reports (see Stagi et al., 2016; Ueki et al., 2014). Klinefelter Syndrome is also associated with hypergonadic hypogonadism and carries an increased risk of cardiovascular disease although there is not a clear understanding of the mechanisms underlying these elevated risks. However, there is recognition that there is a complex relationship between Klinefelter Syndrome, metabolic syndrome and the increased cardiovascular risk (Salzano et al., 2018). Despite an absence of a clear understanding of the underlying reasons for the increase, there is no lack of evidence in the research that insulin resistance, metabolic syndrome and type 2 diabetes are more frequently diagnosed in Klinefelter's Syndrome than in the general population and the accompanying increased risk to cardiovascular disease

(CVD). Klinefelter's Syndrome patients are a recognised high-risk population for mortality caused by metabolic abnormalities and related conditions such as CVD. An early diagnosis and tailored drug interventions are reported to be important in reducing the known risks carried with the underlying condition. (Salzano et al., 2018).

2.2.6 The brain

The additional X chromosome and the resulting hormonal changes are reported to have a wide and complex effect on brain structures (Skuse et al., 1997; Rose et al., 2004). These include differences in structural brain development (Peper et al., 2009) with subsequent impact on the regulation of brain structure and function during early and adult life (Vadakkadath, Meethal, & Atwood, 2005). Grey matter reductions in Klinefelter males are also reported in the insula, temporal gyri, amygdala, hippocampus and cingulate areas (Giedd et al., 2006). Neuroimaging studies have shown that the presence of an additional X chromosome is associated with abnormal structure and function of frontal areas of the brain which are areas are associated with executive function, frontal lobe differences for regulating thinking, emotions and behaviour (van Rijn & Swaab, 2015).

Differences in brain structure in Klinefelter patients may account for some differences in stress reactivity (Rose et al., 2004) and smaller amygdala volumes and smaller hippocampus volumes were reported. The widespread and complex affect hormones and sex chromosomes have on stress reactivity has been acknowledged. Other differences in the brain caused by hormone differences in Klinefelter's Syndrome are reported to cause numerous affects in relation to development, maintenance and cognitive functions and impact on regulation of brain structure and function during early and adult life (Vadakkadath et al., 2005) and structural brain development (Peper et al., 2009).

The X chromosome has been found to play a role in intelligence (Verri et al., 2010). While full-scale IQ is usually unaffected, pervasive learning difficulties are commonly reported in Klinefelter's Syndrome (Geschwind & Dykens, 2004). Although variability is commonly reported, there are some shared cognitive features common to many of the Klinefelter's group (Verri et al., 2010). Reading difficulties may emerge as a result of underlying phonological processing skill deficits (Geschwind & Dykens, 2004). Expressive and receptive language problems (Geschwind & Dykens, 2004; Bender, 1989) may be result of difficulties with audiological processing and associated poor reading, dyslexia and verbal memory, deficits in

frontal systems, attentional learning difficulties, phonological processing and verbal reasoning (Graham, Bashir, & Stark, 1988). These factors are likely to contribute to the increased risk of academic under achievement, early school leaver rates and occupational under achievement compared to family members. Evidence suggests these deficits continue into adult life (Boone, Swerdloff, Miler, Razanui & Lee, 2000) with a reportedly more complex profile presenting in adults than in Klinefelter's children (Geschwind & Dykens, 2004).

2.2.7 Other

A number of researchers suggested an increased risk of cancerous tumours, but these have not been substantiated in later reports and evidence to support these claims remains limited as yet. Increased risks of some cancers have been reported (Eberl et al., 2005; Salwalha et al., 2009) including breast cancer and leukaemia and lymphoma (Keung, Buss, Chauvenet, & Pettenati, 2002; Gies et al., 2014). An increased risk of leukaemia and lymphoma has been described (Keung et al., 2002).

Other associated sequelae that have been reported to be associated with Klinefelter's Syndrome include increased susceptibility to infection and recurrent pneumonia (Scheibel, Rosenfeldt, Marquart, Valerius, & Garred, 2009) and skin disorders such as dermatitis (Vreeburg et al., 2013), varicose veins and epilepsy (Nieschlag, 2013). Thyroid dysfunction is known to be an increased risk in Klinefelter's Syndrome and routine screening for thyroid dysfunction is recommended as part of a holistic care plan (Gies et al., 2014).

Furthermore, Cederlof et al. (2014) report increased risk of psychosis, autism (six times higher risk) and ADHD in Klinefelter patients with treatment implications for patients. Similarly, Bruining et al. (2009) and Seminoq et al. (2014) have reported higher rates of attention hyperactivity disorder (ADHD), and autism spectrum disorder (ASD), as well as emotional symptoms including anxiety disorders and depressive disorders (see also Cordeiro, Tartaglia, Roeltgen, & Ross, 2012).

2.2.8 Cognitive and behavioural difficulties

Cognitive and behavioural difficulties have received less attention relative to the physical and health challenges and risks which face individuals with Klinefelter's Syndrome (van Rijn et al., 2008). This may, in and of itself, contribute to under diagnosis since physical manifestations tend to present later in life after early diagnostic opportunities have passed.

As noted in Section 2.1.1.6, Males with Klinefelter's Syndrome frequently experience a complex constellation of cognitive difficulties (Verri et al., 2010) including delayed developmental levels, difficulties with speech, language and social communication as well as behavioural difficulties (Rigamonti et al., 2016; Visootsak & Graham, 2009). Cognitive difficulties usually in occur the presence of unaffected underlying IQ (Geschwind & Dykens, 2004) although some researchers have indicated that some individuals may have learning disabilities (Host et al., 2014).

It is well recognised that children with Klinefelter's Syndrome are at increased risk for neurodevelopmental disorders and subsequent effect on language, although a lack of research to date makes it difficult to identify the risk accurately. Difficulties with speech and language in Klinefelter's Syndrome are well reported as frequently evident from the earliest years.

Research consistently reports findings showing significantly higher rates of educational difficulty in the Klinefelter's children, with 28% in special classes or schools, 32% having special educational needs (SEN) and 47% having received speech and language therapy (SLT) (Bishop et al, 2009). Although most cognitive deficits are generally mild with many Klinefelter's boys performing in the normal or superior range and attending mainstream schools, there is an increased risk of educational difficulties especially in those areas affected by language (Bishop et al., 2009).

The language difficulties which Klinefelter's individuals seem more likely to encounter (Bishop et al., 2009) appear to be fundamental; these include an increased risk of auditory processing difficulties (Geschwind & Dykens, 2004; Klinefelter's Syndrome Support Group UK survey 1999) and poor phonological skills (Bishop, Barry & Hardiman, 2012). Deficits in phonological skills are known to be strongly associated with poor reading and dyslexia (Melby-Lervag, Lyster & Hulme, 2012) and therefore it is not surprising that reading difficulties may be a concomitant of Klinefelter's syndrome (Tartaglia et al., 2010). Language based and attentional learning disabilities and dyslexia are commonly reported with deficits in phonological processing, verbal memory and social skills (Geschwind et al, 2000; Graham, Bashir, Stark, Silbert & Walzer, 1988; Geschwind & Dykens, 2004). Although variability is reported, there are some shared cognitive features common to many of the Klinefelter's group (Verri et al., 2010). Reading difficulties may emerge as a result of underlying phonological processing skill deficits (Geschwind & Dykens, 2004).

Language difficulties experienced alongside difficulties in social cognitive processing form a theme in the research literature (Visootsak & Graham, 2009; van Rijn et al., 2006; Bishop et al., 2009). Differences in brain structures that may influence vulnerability to stress are reported (Rose et al., 2004) and higher prevalence of psychiatric disorders (de Ronde et al., 2009). The heightened emotional experiences of Klinefelter's individuals, in parallel with their decreased abilities to identify and verbalise these (van Rijn, Swaab, Aleman & Kahn, 2008; de Ronde et al., 2009), the deficits they experience with correctly interpreting tone of voice (van Rijn et al, 2008), interpretation of facial cues such as anger (van Rijn, Swaab, Aleman & Kahn, 2006), in addition to the frequently reported social communication difficulties in Klinefelter's Syndrome (Rigamoni et al., 2016) may contribute to the emotional outbursts and behavioural difficulties experienced by individuals (Tartaglia et al., 2010). Moreover, Grace (2004) noted that the high school drop-out rate reported for Klinefelter's boys is closely linked to difficulties they commonly experience with integration into their peer group resulting from these difficulties.

Research reports high rates of prevalence of language and communication problems in Klinefelter's and an increased risk (11%) of a diagnosis of autism spectrum conditions (ASC). The additional X chromosome has links with depressed pragmatic language skills and increased autistic traits (Lee et al., 2012). Further, where a diagnosis of ASC had not been made, profiles indicating mild autistic features in Klinefelter individuals are reportedly not uncommon. Findings in the literature indicate that the rate of ASC is likely to be significantly higher in Klinefelter's Syndrome (Bishop et al., 2009) with an association for autistic features in individuals with Klinefelter's Syndrome of a 10-20 fold increase over the general population. Difficulties with emotion regulation and self-regulation are not uncommon in Klinefelter's Syndrome (van Rijn et al., 2006). Self-regulation has been linked with the pre-frontal cortex, the amygdala, the central nervous system (CNS) and the autonomic nervous system (ANS) (Segerstrok & Nes, 2007; Malik & Camm, 1995; Kamanth et al., 2013). Differences in these brain structures are reported in Klinefelter's males and these differences may contribute to the reported increased risks and vulnerabilities often experienced in the Klinefelter population.

Less well appreciated are the deficits reported for Klinefelter's males with social attention, affective arousal and empathy. Research has shown that the Klinefelter's population frequently experience reduced empathic understanding and decreased empathic skills

(understanding of own and others' emotions) in the presence of decreased affective arousal (van Rijn, Barendse, van Goozen & Swaab, 2014). This may help to explain reports of difficulty in managing social situations and building friendships for those with Klinefelter's Syndrome (van Rijn, Swaab, & Aleman, 2008).

As the array of increased risks to health reported to be linked to Klinefelter's Syndrome, awareness of these is beneficial for early recognition and interventions.

2.3 The impact of Klinefelter's Syndrome, quality of life and wellbeing

The definition of quality of life (QOL) is defined by the World Health Organisation (WHO) as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment."[2] Klinefelter's Syndrome is associated with a complex array of clinical treatment approaches and support resulting from the constellation of physical, neurocognitive and psychosocial aspects not uncommonly experienced in the syndrome (Close, Talboy, & Fennoy, 2017). Further, quality of life has been reported to be adversely affected in those with Klinefelter's Syndrome (Turriff, Macnamara, Levy, & Biesecker, 2017; Close, Fennoy, Smaldone, & Reame, 2015). Understanding factors that influence QOL in Klinefelter's Syndrome are therefore of interest and may be helpful in informing health professionals regarding treatments, therapies and interventions to improve health related quality of life.

The potentially complex consequences of living with Klinefelter's Syndrome present significant challenges for daily life and further burdens prospects of positive participation in society. These difficulties are exacerbated by lack of knowledge about the condition and lack of holistic perspective of service providers making the need for dissemination pressing. It has been demonstrated that early diagnosis of Klinefelter's Syndrome affects and improves quality of life and provides the opportunity for better medical treatment (Herlihy et al., 2010; Nieschlag, 2013; Radicioni et al., 2010). Research has reported the medical and cognitive aspects of Klinefelter's Syndrome and, increasingly, research has explored the possible

[2] https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/

impacts on quality of life. The personal impact of Klinefelter's Syndrome and factors which contribute to quality of life are increasingly recognised to include diagnostic history such as age at diagnosis, clinical, social and demographic aspects (Herlihy, Halliday, Cock, & McLachlan, 2011). Patients diagnosed at younger ages reported many similar symptoms and difficulties as those individuals diagnosed later in life indicating that earlier diagnosis and intervention would be beneficial. Further, Klinefelter males reported much poorer outcomes for their quality of life than the general male population (Herlihy et al., 2011).

Evidence of diminished quality of life (de Ronde, et al., 2009) and the experience of needs not met are reported to affect ability to participate in daily life including education, work, sleep and health care (Jaegar, Rojvik & Berglund, 2014). Research exploring factors affecting quality of life (QOL) as perceived by Klinefelter patients identify an association between lower levels of educational achievement and lower quality of life. Interestingly, Klinefelter males with higher education qualifications reported significantly higher quality of life scores compared with those who attained lower or mid-education (de Ronde et al., 2009). These reported perceptions of educational attainment having links with quality of life are interesting, prompting a series of further contemplations concerning what, or how, resilience to some of the sequelae of Klinefelter's Syndrome may be conferred. In one study, Klinefelter patients with a bachelor or masters' degree reportedly attained scores for quality of life similar to the control group of non-Klinefelter's males (de Ronde et al., 2009), particularly for vitality and general health.

Negative consequences of Klinefelter's Syndrome were reported to include infertility, psychological impacts, and differences in appearance (Turriff, Levy, & Biesecker, 2014). These factors appeared to impact on adaptation and were further affected by coping strategies. Where interventions were available and utilised for improving coping strategies for negative perceptions, an improvement in adaptation was anticipated (Turriff et al., 2014). Diagnosis and subsequent support and interventions would offer opportunities for patients to better manage the challenges of living with Klinefelter's Syndrome and may beneficially affect negative perceptions and increase effective coping thus improving adaptation (Turriff et al., 2014).

Social communication problems and reported difficulty with social integration and consequently a higher risk of social isolation is reported in Klinefelter's Syndrome. Social

coherence is achieved where the members of a social group are in accord and are attuned to the group and where the group displays a shared regard and regulation of agreed norms.

A lack of social coherence is reported to have a direct bearing on the health and wellbeing of an individual. Studies have reported an engagement of physiological processes caused by the experience of negative social situations, such as social isolation and further that physiological factors underlie behavioural, social and cognitive function (Tartaglia, et al., 2010; van Rijn et al., 2012). These negative consequences are reported to be detrimental to health including bestowing an increased susceptibility to disease and social withdrawal (Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010). Further risks associated with social isolation are reported to exceed the combined risks for heart disease, smoking, obesity and alcohol (Lynch, 2000).

Observations that de-personalisation can be a genesis for social isolation strengthens the reported requirement for speech and language therapy (SLT). The intervention of SLT is reported to be beneficial in supporting the social communication problems often reported in Klinefelter's Syndrome. Conversely the value of close meaningful relationships as conferring a protective resilience has been described and findings around social motivation in Klinefelter's males is reported to indicate the importance of social interaction to Klinefelter individuals, whilst commonly experiencing deficits in social cognition, social communication and overall social difficulties (van Rijn et al., 2012).

Circumstances of familiarity and perceived safety in a familiar social environment mean the brain is less vigilant for threat and requires less emotional energy.

The section of increased health risks in Klinefelter's Syndrome indicates the kaleidoscopic variety of symptoms with which an individual with Klinefelter's Syndrome may present. These, however, have traditionally been researched and treated in isolation reactively as symptoms present. Diagnosis, specifically early diagnosis may have a valuable role as a gateway to anticipatory pro-active screening and monitoring through the lifespan for preventative and early treatment provision is a recurrent theme with respect to individual presenting sequelae.

This research suggests that Klinefelter's may be seen and treated as a series of individual presenting symptoms with consequences for diagnosis and the day to day experience of the Klinefelter individual and their families. This will be investigated by exploring the diagnostic

process and how and why this may be perceived to affect life span health, wellbeing and quality of life.

2.4 Holistic care: background and context

Research that informs through a whole person approach may be beneficial to reveal factors significant to promote wellbeing for Klinefelter's males (Gies et al., 2014). Understanding factors in Klinefelter's Syndrome that may contribute to effective management of increased risks to health with potential detrimental consequences for duration of, and quality of, life would be beneficial.

Studies report that a focus on the 'whole person' is needed to assist in optimising the wellbeing and positive life paths for Klinefelter males (Geschwind & Dykens, 2004). There is a reported propensity for those with the condition to internalise problems which can lead to negative implications for their mental health. Evidence frequently highlights the important vulnerabilities and health problems associated with the syndrome. There are, however, some studies with a focus on reported strengths that may characterise some Klinefelter individuals. Research findings report Klinefelter's males to be highly motivated by curiosity, learning new skills and having a kind spirited nature. Additionally, despite experiencing significant social problems, Klinefelter's boys and men are reported to be motivated to interact with others and forming meaningful relationships and close family ties are reported as a strong motivator for the group as a whole.

Lifespan adaptation and motivation findings reported anxiety, depression and increased risk of internalising symptoms leading to significant problem. Feelings linked with sadness, loss and being exploited by others were reported in parallel with demonstrating empathy for others.

Research with a focus on the emotional functioning of Klinefelter's males report that this group would find lifespan, developmental support that extended into adult years beneficial (Geschwind & Dykens, 2004).

There appears to be some discord in the current research where findings into the benefits of androgen treatment appear contradictory in some areas de Ronde et al. (2009) report findings that quality of life is *reduced* in Klinefelter patients who are on androgen treatment and experienced to a greater degree in those using gel patch application for testosterone treatment

(TRT). This could be described as a revolutionary finding and extremely significant not least because the overwhelming majority of males who are diagnosed with Klinefelter's are invariably, prescribed testosterone treatment. In contrast, there are a significant number of studies advocating for the efficacy of testosterone replacement therapy (TRT) with reports of positive effects on health and quality of life (Bourke et al., 2014). Despite the lack of a single randomised trial of the benefits of testosterone therapy (Nieschlag, 2013) TRT remains a commonly recommended and prescribed therapy.

As stated, although TRT is the universal standard treatment prescribed by endocrinologists for the treatment of Klinefelter's Syndrome, the efficacy and characteristics of the treatment have yet to be studied and defined (Nieschlag, 2013). The finding that TRT affects QOL taken in parallel with the under researched benefits or otherwise of TRT is a startling finding.

2.5 Physical sequelae, making a difference: early diagnosis summary

As stated, Klinefelter's Syndrome is known to be a common genetic disorder in males with an estimated 1/450 - 1/660 males with this condition. When taken together, the literature identifying and expanding on the multiplicity of increased risks known to challenge an unhindered lifespan of health and wellbeing to those with Klinefelter's Syndrome. Well documented are the myriad of risks the diagnosis carries and the literature universally recognises the role of diagnosis, and importantly, an early diagnosis. This makes it possible to anticipate known, increased and significant risks which may characterise the life path of individuals with this condition with possible implications for their wellbeing and place in society, their family and the impact on the family unit, also with societal impact with associated increased and multiple demands on health and educational resources where no correct diagnosis is made. Findings from evaluations have resulted in reports that a multi-disciplinary model is 'essential' for the care of Klinefelter's boys and their families to facilitate the children's development and growth and to assist the families with current clinical and psychosocial information about the condition (Rigamonti et al., 2016).

Recognised cognitive and social difficulties underscore the need for early diagnosis to enable early educational intervention and transitional support through into adult life with support for social functioning and daily adaptive living skills in Klinefelter’s males.

2.6 Summary

Thus, Klinefelter's Syndrome carries increased risks to a multiplicity of diseases and vulnerabilities. These include infertility, metabolic syndrome, type 2 diabetes, osteoporosis, scoliosis, reduced bone mineral density, fractures, increased risk of mortality from hip fractures, increased cardiac risk factors, mortality from cardiovascular diseases, sudden death caused by mitral valve prolapse, restrictive lung defects, morality from pulmonary embolism, hypothyroidism and immunological differences. In children, learning disabilities are common with delayed speech, psychosocial and behavioural difficulties, educational difficulties persisting throughout the school years and into adulthood.

There is additional potential societal impact to national health care systems, particularly the cost implications of treating preventable, secondary diseases resulting from lack of screening and preventative measures.

Diagnosis, specifically early diagnosis and pro-active screening through the lifespan for preventative and early treatment provision is a recurrent theme with respect to individual presenting sequelae. Diagnosis is thought to be beneficial in aiding the anticipation of increased risks, identifying problems early and providing necessary support and treatment to minimise the emergence of the known increased health risks carried within the condition.

Table 1: Screening and preventative measures

Screening/Preventative Measures in Klinefelter's Syndrome	**Examples of Increased Risks in Klinefelter's Syndrome**
pre-natal parental genetic counselling; caution about inaccurate internet information;	Impacts/outcomes affected by environmental factors, individual gene differences affect outcomes
	Developmental delays
endocrine differences, testosterone levels, testosterone treatment if required, assessment of timely and pre-instigation of TRT treatment, fertility preservation opportunities, counselling and information for parents (if pre-pubertal)/individual, timely testicular sperm extraction considered	endocrinological abnormalities, infertility, small testes, lowered testosterone levels
cardiovascular screening (preventing endocarditis), heart disease (e.g. timely operative repair minimises loss of ventricular function), cardiovascular malformation, screening for venous thromboembolism	heart and vascular: thrombosis, embolisms, mitral valve prolapse, vascular disease, pulmonary embolisms, varicose veins
recurrent infections (screening for immunodeficiency), respiratory chronic obstructive airways disease Immune differences	Significant increased susceptibility to infection, recurrent pneumonia, chronic bronchitis, restrictive lung defects, asthma variable immunodeficiency, Allergies
screening for lowered bone density, bone mineral status	Long-term consequences on bone health, osteoporosis, reduced bone mass, back pain, mortality from bone fractures, musculosketal problems
screening for autoimmune diseases, inflammatory diseases, type 2 diabetes, T cell differences complete pituitary hormonal screening and conventional pituitary MRI 'essential' for Klinefelter's patients for pituitary tumour early diagnosis of Klinefelter's Syndrome for attention to the course of the disease of connective tissue is emphasised	metabolic and autoimmune differences: type 2 diabetes, autoimmune diseases, Raynaud's Syndrome/disease; progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), connective tissue disease (14-fold increase), antiphospholipid syndrome, anklylosing spondylitis, juvenile idiopathic arthritis, psoriatic arthritis, polymyositis/dermatomyositis, immune differences, metabolic syndrome, rheumatic diseases, rheumatoid arthritis, obesity, T cell differences

	(conferring increased risk to autoimmune diseases), Addisions' disease, diabetes mellitus type 1, Sjogren's syndrome, pituitary tumour
screening for diminished thyroid levels	
Cancers	cancers: including breast cancer, leukaemia, lymphoma, germ cell tumours
motor functions	Chewing difficulty/reluctance for textured food in infants, muscle tonus, dyspraxia, back pain and problems, flat feet, fine motor skills, gross motor skills
screening for psychiatric disorders cognitive risks (complex cognitive) daily living functioning screening and timely treatments for emotional difficulties	depression, anxiety, schizophrenia cognitive risks: attentional problems, ADD/ADHD, emotional and behavioural disorders significant increased risk: shyness, social withdrawal, language deficits, social difficulties, executive function impairments, working memory, relational reasoning, difficulty in encoding verbal information into working memory internalising distress, self-esteem, daily functioning, adaptability, social skills, activities of daily living, leadership, depressed adaptive skills (particularly in the communication domain)
screening in autism spectrum conditions	ASC, ADHD, ADD, social communication difficulties
Other Screening for ASC disorders (higher risk of ASC in XXY)	speech and language delay/disorder, impaired verbal ability, auditory processing disorder, disrupted sleep, hereditary skin disorders and/or diseases, syndromes involving the skin, excessive fatigue, obesity, dyslexia, educational difficulties such as literacy, sensory sensitivities: auditory, touch and textures, colour, visual over stimulation; difficulties in social cognition including interpretation of tone of voice, facial expressions causing difficulties with non-verbal cues for social language

	and interaction, dental cavities, social isolation, stress related problems, anxiety, low self-esteem, social difficulties motivated and have an interest in social interaction, in presence of social difficulties due to autistic type behaviours and deficits in social cognition
Daily living functioning: additional risks: professional awareness important Classroom concerns: poor motivation, slow worker, disorganised are concerns that should alert educators to the need for further assessment Neuropsychological assessment/screening recommended for young XXY children in early school years to screen for learning disabilities, ADHD, executive function Referral to psychology: concerns for anxiety, depression, social withdrawal	Learning difficulties: reading disabilities, verbal cognition and language impairments Daily living: immature daily functioning, (affects compliance and ability to follow up with educational and therapeutic care, may not display age appropriate skills) Academic difficulties (found in 60-85% of Klinefelter individuals), language-based learning difficulties
Digestive disorders, early data suggests gluten free diet may be beneficial Possible associations with hypercoagulable state	Gastroenterology: chronic symptoms of malabsorption, celiac disease, digestive disorders Mesenteric vein thrombosis associated with Klinefelter's Syndrome
Preventable causes of increased mortality and morbidity: osteoporosis, chronic obstructive airway disease, type 2 diabetes, should screened for Weight reduction programmes if overweight	

2.7 Making sense of variability?

Despite the fact that a great deal of research has been done which, when taken together, shows variability in the way that Klinefelter's Syndrome presents, remarkably little research has examined the nature of the reported variability. This is important also because the variability of Klinefelter's Syndrome is reported to contribute to its under diagnosis.

As a result of taking a 'whole person' approach (Geschwind & Dykens, 2004) this study may be able to examine, to some extent at least, whether or not the syndrome is as variable as reported, or if the apparent disparate descriptions of the syndrome may be drawn together into a cohesive kernel of identifiable similarities that may be beneficial to contribute to increasing timely and accurate diagnostic statistics. One particularly intriguing possibility is that similarities may be more apparent between individuals in infancy and childhood with variability becoming increasing apparent as the sequelae resulting from lack of diagnosis and individual circumstances materialise. A further possibility is the possibility that the syndrome is not intrinsically as variable as reported, but that timing of diagnosis may have a role in the impact of the condition and the way it presents.

In sum, much of the research to date has tended to treat the multiplicity of symptoms exhibited by those with Klinefelter's Syndrome in relative isolation and with little consideration about where and when these difficulties unfold across the lifespan. This has resulted in a literature which is somewhat fragmented in that it lacks explanatory power that would be derived from a wider multi-disciplinary lifespan approach. Most stark of all is the lack of knowledge and understanding of what this means for the lived experiences of individuals affected by Klinefelter's Syndrome and the impact which has on them and their families. There is not yet evidence that different treatment options are efficient and reduce morbidity, mortality and improve outcome (Nieschlag et al., 2016). Further, there is a lack of evidence that early diagnosis and treatment is of advantage (Gravholt, 2016) and formal proof of improved long-term adult outcomes is lacking (Nieschlag et al., 2016).

By taking a qualitative 'whole person' approach, this research explored these lacunae in the literature with a view to providing important data to underpin later experimental work. Importantly, it will examine the timescale of diagnoses and impact from the perspective, not only of individuals and families, but from those involved at different levels of the diagnostic process, i.e. the general practitioners and medical specialists to whom they might be referred.

CHAPTER 3

METHODS

3.1 Introduction

This chapter reviews the methodological approach adopted in this research and explains the way in which Interpretative Phenomenological Analysis (IPA) and Thematic Analysis (TA) were used in this study. Section 3.2 discusses and explains the rationale for the use of a combination of Interpretative Phenomenological Analysis (IPA) and Thematic Analysis (TA). Section 3.3 provides details about participant groups and their recruitment Section 3.4 explains the methods used to conduct interviews and 3.5 explains how the rich data obtained from interviews was analysed given the use of either TA or IPA.

This research takes a qualitative approach, the aim of which was to explore perceptions of the significance of diagnosis in Klinefelter's Syndrome (47,XXY) of different groups potentially involved in the diagnostic process. The qualitative interviews conducted were primarily unguided to allow the participants to express their views freely and unencumbered by prior assumptions. It was thought this approach would be more inclined to elicit novel, or unanticipated responses which would be of value to explore and enrich the research purpose.

The aim was to elicit a '360 degree' insight from different perspectives from each group (see Figure 1, p. 21). Using this '360 degree' approach also made it possible to examine the impact that reported lack of diagnosis may have on the lives of affected individuals and their families and to explore the two reasons reported in the literature for the significant under diagnosis of Klinefelter's Syndrome namely:

- low awareness of the syndrome in general clinicians
- variability of presentation of the syndrome acting as a confounding diagnostic factor

Despite the reports that these factors cause the reported low diagnosis rates, there is a paucity of evidence for the veracity of these claims. Responding to this apparent gap in the literature, this research therefore sought to explore:

- levels of awareness of Klinefelter's Syndrome in health professionals involved in the diagnostic process, with particular focus on perspectives of general practitioner

- perceptions of the syndrome with particular reference to diagnostic significance from health professionals who may be involved in the diagnostic process
- perceptions about the diagnostic process and the perceived significance of diagnosis for affected families
- perceptions about the effect of late, or later, diagnosis compared to timely diagnosis individuals and families

Emphasis on the lived experience of individuals and their families was important because no studies to date have examined the extent to which diagnosis may be important in (a) determining the wellbeing of individuals and their families and (b) allowing access to appropriate medical treatment and other support. Similarly, little is known about the diagnostic role of medical experts who come into contact with Klinefelter's Syndrome individuals as a result of referrals for any one of the range of 'risk factors' with which they may present to the healthcare system as a result of the variability in the symptom presentation associated with the syndrome. These included a range of individuals with potentially differing expertise with respect to the syndrome ranging from speech therapists to consultant urologists and paediatricians to those dealing primarily endocrine or genetic disorders. Each group was identified as having an important perspective on the issue of diagnosis. Their participation and contributions were recognised as important to elicit and understand as fully as possible to describe, inform and enrich understanding about the meaning of diagnosis for those with the syndrome, those involved in the diagnostic process.

3.2 Qualitative approaches adopted in this research

This research uses a combination of two qualitative methodologies: Interpretative Phenomenological Analysis (IPA; Smith, 1996, 2003, 2015) for the Family Group and Thematic Analysis (TA: Boyatzis, 1998; Roulston, 2001; Braun & Clarke, 2006) for the Expert, Specialist and General Practitioner Groups. The rationale for this dual approach is given below as each type of approach is described and discussed.

3.2.1 Interpretative Phenomenological Analysis (IPA)

Interpretative Phenomenological Analysis 'provides psychologists the opportunity to learn from the insights of the experts - research participants themselves.' (Smith, 2003, 2015). For this reason, IPA provides an important platform for the research process undertaken with the

Family Group in this study. IPA asks and seeks information to inform our understanding and illuminate individual perspectives of the phenomenon of the impact of one condition, Klinefelter's Syndrome, asking of the individual: 'what is it like to have that experience?' In this important respect, IPA is a methodological approach which matches well with the need to examine the lived experiences of individuals living with Klinefelter's Syndrome and their families and in particular to examine the nature of their experience with respect to diagnosis or the lack thereof.

IPA provides opportunity to take an idiographic approach and gain an insight into the 'lived experiences' of each participant, told in their own words. This methodology affords an insight into the complexities of individual life experiences and how these are perceived by each of the individuals who share their story. Importantly, for this research, providing accounts in the individuals own words was prioritised to provide each participant with their own platform unencumbered by interruption from other sources, to allow their own individual thoughts and experiences to shine through. IPA explicitly sets aside prior assumptions and does not test hypotheses, prioritising instead the revealing of each unique life story in rich detail through the application of the research approach. Use of IPA for the Family Group therefore ensured that insights from this group would inform the key question this research sets out to explore: What is the significance of diagnosis in Klinefelter's Syndrome?

To enlarge, IPA is described as an “examination of how people make sense of their major life experiences” (Smith, 2003, p.2) or, exploring experience in its own terms. Researchers using this approach are particularly interested in what happens when everyday lived experience takes on a particular significance, or an event of some importance occurs which has larger impact for a participant. The aim of IPA is immersed in the purposeful understanding people’s everyday experience of reality, in detail in order to gain an understanding of the phenomenon in question (McLeod, 2011). Significantly for this study, an IPA study may explore similarities and differences between individuals, whilst being possible also to consider general claims. This is a choice available to the researcher in IPA and contrasts with the requirement in qualitative approaches (Grounded Theory, for example) for the development of theoretical models. IPA is also seen as a flexible approach, particularly suited to examining new topics where little data – let alone theory - is available to drive the data collection process. Smith (2003) maintained that “it should be recognised that (in IPA)

there is no definitive way to do IPA" (p.53) and there is the flexibility to adapt the method to "your own way of working and the particular topic you are investigating."

It was expected that a holistic, data rich methodology may be beneficial to shed light on the fragmented literature which until relatively recently tended to examine individual symptoms medically as they are presented to specialists without examining the possible impact on individuals and their families. Interpretative Phenomenological Analysis (Smith, 1995, 1996) and Thematic Analysis (TA) (Braun & Clarke, 2006) approaches combined to provide narrative, individual accounts of living with Klinefelter's Syndrome. IPA was of particular value given that it is based on the premise that "participants are experts in their own experiences and can offer …an understanding of their thoughts, commitments and feelings through telling their own stories, in their own words, and in as much detail as possible" (Reid, Flowers, & Larkin, 2005).

3.2.2 IPA and health psychology

IPA has been identified as a beneficial methodology for exploring subjects which are 'complex, ambiguous and emotionally laden and as an effective methodology for exploration of topics of a complex, ambiguous and sensitive nature (Smith & Osborn, 2015). Further, IPA gives primacy to understanding people's everyday experience of reality (Holloway & Todres, 2003). Klinefelter's Syndrome can be reasonably considered as one such condition, with a complex array of health implications and impacts, some being of a sensitive and personal nature requiring a delicate and careful research approach. Aspects of Klinefelter's Syndrome involve psycho-somatic relationships and may be difficult to verbalise or comfortably explain for participants. A sympathetic methodological approach applied with sensitivity and a respectful insight into distressing associations was recognised to require vigilance during interviews.

The utility of the flexibility of style and approach adopted in IPA has been widely recognised and used by clinical and health psychological researchers. Recent reviews report the increasing use of IPA since 1996, with a noted increase within the field of psychology: particularly in the fields of health and clinical psychology. This increase is in part attributed to the value placed on experiences which are detailed and context-rich accounts and has the potential for contributing to informing biopsychosocial perceptions (Reid, Flowers & Larkin, 2005). Topics where IPA has been used highlight the utility for health and psychological

fields, including chronic illness (Osborn & Smith, 1998), pain (Smith & Osborn, 2015) and quality of life (Holmes et al., 1997). The use of IPA makes it possible to explore Klinefelter's Syndrome for individuals affected and their families from a 'whole person' perspective. Of particular interest was the importance (or otherwise) of diagnosis on the lived experience of Family Group. This study explored the extent to which this (a) emerges in the descriptions given by a group of individuals and families and (b) the extent to which this is borne out by those with different perspectives in the medical specialist and general practitioner groups. It is to these latter groups which we now turn.

3.2.3 Thematic Analysis

The study provided a direct voice to GPs, experts and specialists by focusing on and exploring their perceptions of diagnosis in this syndrome and the impact they perceive this may have. The perceptions of medical experts were sought to better understand the significance of diagnosis from those professionals who provide treatment and support to affected individuals and their families. Further, to explore factors which may determine timely diagnosis was seen as valuable in contributing to increasing understanding how, when and why diagnosis may be delayed and the potential impact this may have for those affected. The perceptions of general practitioners were also sought to inform claims in the literature that low awareness in general clinicians is one of only two given reasons for the reported significant under diagnosis. For these groups, Thematic Analysis rather than IPA was used as an approach because, in contrast to the family group, exploring the lived experience of the GPs, experts and specialists was not a focus for this study. Instead, the perspectives of these health professionals were sought to explore the diagnostic process.

Despite being widely used, there is a lack of agreement in the literature about the precise nature of thematic analysis. Braun and Clarke (2006) describe thematic analysis as a method 'for identifying, analysing and reporting patterns within data'. As described, this study is primarily exploratory in nature. The TA methodological approach is an effective method of exploration for discussion with the healthcare professionals, enabling the conversations to reveal themes and concepts embedded throughout the interviews (Rubin & Rubin, 1995, p. 226). Thematic analysis provides the opportunity for explorations of rich descriptions in thematic terms across the data corpus. As described, this study explores data from a '360

degree' perspective, therefore a methodological approach facilitating the gathering and analysis from these different perceptions was sought.

Thematic analysis has been recognised in the literature as beneficial when exploring an under researched area, or when the views of participants are not well known. In both these regards, this study explores an area not previously one of focus and with participants whose perspectives on this topic have not previously been sought. In both these areas, this study took a novel approach to answer a question identified in the literature as significant, but not, as yet, explored.

TA has been reported as a flexible approach to analysing qualitative data commonly taken in psychological research. There has been discussion in the literature concerning the application of TA and the application and theory behind thematic analysis. Braun and Clarke (2006) argue that TA is a method in its own right. Benefits of TA are recognised to be the flexibility and independence from theory this approach provides, which can nevertheless yield rich, detailed and complex data. Themes are patterns across data that are important to the description of a phenomenon and are associated to a particular research question. The themes are subsequently analysed having been developed into categories and analysis is conducted. Themes are developed by means of identifying significant parts of the data. Interpretation can include identifying theme frequency of occurrence and highlighting relationships between themes. The researcher decides which themes are most crucial. These are not necessarily the themes which occur most frequently. Themes provide an accurate understanding of the big picture and attempt to identify the meaning of the data.

Thematic analysis has its genesis in grounded theory where assertions are supported from within the data and generated theories evolve from the data. In both approaches data from interviews are transcribed and themes identified from the reading of these. Similarities and differences are compared, and theoretical models may be developed.

3.2.4 Theme identification in Thematic Analysis

A 'theme' in terms of thematic analysis is defined as capturing something important about the data and is in relation to the research question. The theme identifies a pattern in the narrative, or an identifiable folio of messages which have resonance and value in the context of the research question.

Importantly, relevance and value of themes are not necessarily determined by the number of times, or prevalence of themes are mentioned. It may be possible that a theme may be identified, despite minimal mentions in a transcript, a significant finding may be captured, for example. In this sense, there is a judgement, a choice exercised by the researcher.

Alternatively, a single theme may be identified across different speakers. This raises the important possibility that, in this study, themes may appear either only across individuals within participant groups or, alternatively, be held in common by individuals across different groups. This makes it possible to compare and contrast emergent themes arising from different group perspectives.

3.2.5 Latent themes

Of further interest was the documented opportunity afforded by the thematic analysis approach was the opportunity for more subtle, nuanced themes to be revealed as well as more explicit themes. These, less obvious themes are sometime referred to as 'latent' themes (Clarke & Kitzinger, 2004) which, for completeness of exploration were valuable to explore should these present themselves through the narratives. In this study, themes were revealed and identified from the data, thus patterns were inductive in derivation. Perhaps reflecting the unguided nature of some of the transcripts, some of the themes seemed, at first, unrelated to the immediate research question. However, on concentrated analysis, some nuanced and fleeting comments revealed fragile, but nevertheless significant and valuable links to fundamental concepts apparently driving underlying meanings or beliefs of participants. In these examples particularly, taking a conscious data-driven approach with a lack of pre-existing coding frames was valuable, exposing these 'hidden themes'. For both the explicit and the 'latent' themes, the data were described and, within the context of thematic analysis, interpreted to offer theories and broader implications of these meanings where this was of significance. There were also instances where 'latent' themes touched on ideas and concepts which affected the patterns, or meanings of the data. This was seen as valuable in revealing some broader structures and processes which were identified as significant in the diagnostic process and affected or influenced beliefs or perceptions as they were expressed in some of the narratives.

In common with IPA, Thematic Analysis can be beneficial for reporting experiences, meanings and the realities described by participants (Braun & Clarke, 2006). Relevant to this

study also is the provision of this approach through which the 'reality' of participants is made clear thus illuminating the context for perceptions of diagnosis in the groups of health care professionals.

For these reasons IPA was identified as appropriate as an explorative approach for the Family group and Thematic Analysis was identified as a beneficial, appropriate and effective methodological approach to explore perceptions within and across the Expert, Specialist and GP Groups in this study.

3.2.6 IPA and Thematic Analysis

The results of an IPA study compared to a study using TA can be very similar. While there are some differences of procedure between IPA and TA, but both emphasise the flexibility and scope for the researcher to take a creative approach as neither IPA nor TA needs to be followed prescriptively (Smith, 2003, 2015). Not infrequently, IPA is used when the participant size is smaller due to the idiographic nature and focus of many IPA studies.

This study engaged an approach using IPA for the Family group and TA for the Specialist/Expert and GP groups. The idiographic aspect of IPA provided a particularly appropriate framework for examining the data obtained from interviews with Klinefelter's individuals and their families when exploring the unique characteristics of individual participants in a rich narrative style. IPA has a dual focus on unique characteristics of individuals and also for identifying patterns of meaning across participants in all participant groups. In contrast, TA has a focus primarily on patterns of meaning across group participants (Braun & Clark, 2012) which was recognised as an effective approach for the medical specialists and general practitioners' groups. This approach provided a context for analysis for data patterns across both individuals within groups and across participant groups and provided further diagnostic context and information to support and complement the detailed life narratives explored with and described by Klinefelter family participants.

In contrast to thematic analysis, IPA coding occurs across the first data item and subsequently develops themes for each individual interview, developing each stage of analysis for each data item before progressing to the next. Due to the importance of the nuances and detail likely in each individual narrative, the opportunity to explore and analyse each interview as a separate entity was identified as beneficial.

Importantly, both IPA and Thematic Analysis may seek patterns in the data. Smith (2003) highlights the flexibility of IPA in that guidelines are seen as flexible recommendations, rather than prescriptive and the process can be tailored and honed by the researcher. Similarly, Braun and Clarke (2012) report Thematic Analysis also has the same characteristics of flexibility with a lack of constraints and limitations and as key advantages of this method. These characteristics were seen by the researcher as beneficial exploratory devices, allowing flexibility of approach and style devolving providing the freedom to follow the direction of the participants conversational flow, in contrast to a more prescriptive and rigid approach. These approaches were chosen to provide an environment more likely to provide each participant to tell their own story, in their own way thus eliciting individual accounts, each representing each individual in their own words.

3.3 Participant Groups

To achieve the aims of this study three groups of participants will be recruited each with different perspectives and experiences as follows:

Individuals and family members:
The views of this group are sought because of their lived experience with the syndrome. The Family Group reveals individual perceptions, thoughts and feelings of individuals and family members about diagnosis. Individuals, parents and siblings were included in the Family Group. All family members were invited to participate.

Medical specialists: this group is differentiated into 2 sub-groups:
i) Experts: Those with expertise in Klinefelter's syndrome
ii) Specialists: Those with no specific specialist knowledge of Klinefelter's syndrome but with expertise in areas of increased risk in Klinefelter's Syndrome. Their views are sought to examine their perceptions of the significance of diagnosis to affected individuals and to compare their perspective to other participant groups.

General practitioners:
This group is included in order to begin exploring levels of awareness in GPs of the syndrome and, where GPs are aware, their perceptions of the significance of diagnosis to individuals and their families. This perspective is important since GPs often act as 'gatekeepers' when accessing relevant medical expertise.

This qualitative research is the first of its kind to investigate evidence in three different groups for the reported perceived significance of diagnosis. Membership of each group is summarised in Table 2 (page 61).

3.3.1 Consideration of sample size in qualitative research

Qualitative samples must be large enough to assure that most or all of the perceptions that might be important are uncovered by avoid repetitiveness (e.g. Glaser & Strauss, 1967). When Guest et al. (2006) examined their data from 60 participants they suggested that as few as 6 interviews might be sufficient to ensure discovery of meaningful themes and useful interpretations and that further interviews may simply lead to repetition. In a review, Mason (2010) reported that a sample size of 25-30 participants was typical, depending on the analysis methods used.

The emphasis on the idiographic and the hallmark detail-rich accounts sought in IPA contribute to the characteristically smaller number of participants associated with IPA studies. With ten participants reported to be at the higher end of most recommendations for sample sizes (Smith et al., 1999), this study is beyond the higher recommended number for IPA, having eleven family participants in the Family Group.

Table 2: Summary of participants in each group

Participant Group	**Families**	**Healthcare Specialists**		**General Practitioners**
		Experts	**Specialists**	
Nature of participants	Individual Mother Father Sibling	Endocrinologists, Fertility Urologist	Gastroenterologist Dietitian Speech and Language Therapist Physiotherapist	
Location of interview	At convenience of family: home address/other	At convenience of expert: Hospital/clinic	At convenience of expert: Hospital/clinic	At convenience of GP: home address/other
Total participants	11	4	4	7

Table 3: Age at diagnosis and participant information.

Green highlighting indicates those who were interviewed, varying from 1-4 family members.

Age at diagnosis	**Current Age**	**Individual**	**Family members**			**Recruitment via**
			Mother	**Father**	**Sibling**	
0	20	P1				Clinical centre of excellence
6	25	P2				Previously known
16	21	P3				Higher education
18	26	P4				Higher education
27	35+	P5				GP referral via Fertility expert
35+	40	P6				Support group

Table 4: Specialists' experience with Klinefelter's Syndrome

Specialism	Primary	Secondary	Specialists' experience with Klinefelter's Syndrome		
			Increased risks	With diagnostic experience	With treatment experience
Endocrinology					
Urology					
Fertility					
Gastroenterology					
Physiotherapy					
Dietician					
Speech Therapist					

Specialist and Expert participants		Secondary; preventative		Increased risks in Klinefelter's	

3.4 Recruitment of Participants

3.4.1 General considerations

Recruitment was carefully considered for all groups with the aim of maximising opportunities to recruit as broad and representative sample as possible. The use of personal contacts is often used where reaching participants might otherwise be difficult (e.g. Sadler et al., 2010). Anecdotally, the recruitment of Klinefelter's Syndrome participants has been reportedly challenging due in part to the low diagnosis rates. Ascertainment bias was a further significant consideration for this research with previous studies recruiting from support groups or clinical groups, which have been noted for their potential lack of representative presentation or experiences. With this in mind, this study sought to recruit as wide a range of participants as possible to try and minimise a bias towards one particular participant profile.

The recruitment was purposeful in that the researcher aimed to interview families who had been diagnosed at different times in their lifespan with the aim of exploring their views about the process and timing of diagnosis and their perceptions of how the timing of diagnosis affected their life experiences and outcomes.

All family members were invited to take part as it was recognised that each family member may have a different but significant story to tell about the impact of diagnosis on not only the diagnosed individual, but also a significant impact on the family. Further, the sensitivity of the diagnosis of Klinefelter's Syndrome was recognised and therefore it was anticipated that not all of the individuals with the diagnosis would feel comfortable taking part. Further, the experiences of diagnosis during childhood and the efforts to gain a diagnosis may not have been an experience the affected individuals remembered and therefore the views and experiences of the parents were considered important to elicit the diagnosis experience from parents. Finally, the experiences of the siblings were sought to enrich and further illuminate the narratives of the potential impact of the syndrome on the family as a unit and any siblings of that family. The research into the impact of the syndrome on siblings is scarce although anecdotally the impact of the condition, diagnosis and necessary treatment was perceived to be significant for the lives of siblings. Their perceptions were sought to provide a more complete picture of the familial impact of this rarely diagnosed condition. Brief details of the time and reasons for diagnosis for each individual are given below.

3.4.2 The Family Group

Family 1: I1 was diagnosed by amniocentesis and therefore was diagnosed before birth. This family were the earliest to be diagnosed of all the family group as the diagnosis was made during pregnancy. His mother is interviewed.

Family 2: I2 was diagnosed at age 6 years old and was the result of enquiries made by the mother following perceived developmental delays.

Family 3: I3 was diagnosed at age 16 due to hospital investigations for an unrelated condition. The son, mother, father and sibling are interviewed.

Family 4: I4 was diagnosed at age 18. This was catalysed because of bullying at boarding school caused by his lack of pubertal progression and consequent physical differences. A private referral out of the NHS system was made at the request of the individual and his mother. P4 was interviewed.

Family 5: I5's diagnosis was made in the late twenties following frequent referrals for problems throughout childhood and beyond, the after physical differences were described by the individual which led to diagnosis by a urologist. His mother was interviewed.

Family 6: I6 was diagnosed in his late thirties following frequent health problems. His mother was interviewed.

3.4.3 Specialists and Medical Experts

Recruitment for this group were drawn from the contact groups shown in Table 4 (page 63). Existing contacts and relationships built by the researcher were contacted to ask for assistance in recruiting or participating as identified in the table above followed by snowballing once these contacts had been made. The expert and specialist group were further divided into two subgroups: one group were identified as experts in Klinefelter's Syndrome and the second subgroup were identified as specialists in conditions other than Klinefelter's Syndrome, but in which there is an increased risk of occurrence in Klinefelter's patients. Participants in these groups were invited to participate to elicit their views about the process and place of diagnosis of the condition within their own experience of caring and treating their patients. Further, it was hoped that their perceptions and experience in the health system

may illuminate reasons for the reported underdiagnosis, thereby expanding knowledge and our understanding of pertinent factors.

Table 5: Expert and Specialist Interviewed Groups Two (a) and (b)

Specialist	Diagnosis	Treatment/ intervention	Screening	Monitoring (ongoing care)	Preventative/ongoing (consultant has personal KF treatment experience)	Reason/Symptoms
Endocrinologist						Timely treatment Thyroid screening Bone density
Urologist						
Fertility						TESE options
Gastroenterologist						IBS symptoms Quality of life Prevent hospital admission
Physiotherapist						Back pain Muscle tone Prevent hospital admission
Dietitian						Minimise IBS symptoms Quality of life
Speech Therapist						Specific SLT Educational input Social communication support
Underpinned by psychological support						

Key:

Yes	If required	Specialist recommends ongoing input

3.4.4 General practitioners

As stated, the literature reports low awareness in general clinicians as one of the two reasons for low diagnosis rates of Klinefelter's Syndrome. These reports, however, did not expand on these claims or the context in which these claims were made. This research therefore sought to explore these reports and sought to provide accounts which may illuminate the perceptions of general practitioners regarding Klinefelter's Syndrome with particular relevance to the diagnostic process. This was in an attempt to begin to uncover factors which may have a bearing on the reported low diagnosis rates. Recruitment of general practitioners were drawn via personal contacts and building networks with general practitioners. The recruitment of general practitioners was the most challenging of the groups to recruit among a high number of general practitioners who declined the invitation to participate. The GP group therefore was the most challenging of the groups to recruit.

Table 6: GP recruitment

GP	**Contacted via**
GP1	Personal
GP2 **GP3**	Personal referral
GP4	Referred by another GP
GP5	Recommended by third party
GP6	Recommended by third party
GP7	Recommended by third party

3.5 Materials and apparatus

A list of questions for each group was prepared in advance. The purpose of the questions was as an aide memoire for the researcher, rather than as a script. The purpose of the interviews was envisaged to elicit as far as possible the thoughts and perceptions of each group with as little prompting as possible. The questions were also prepared to have available should this prove beneficial to aid the conversational flow. In practice, questions were not

referred to in interviews, but formed an important part of the preparation prior to the interviews taking place. A copy of the questions is included in Appendix 7 (page 331).

Each interview was audiotaped using 2 digital recorders:
1.Sony IC Recorder ICD-BX140
2. Sony IC Recorder ICD-240
Each audio recorder was fitted with additional microphones, both being identical models:
2 x Olympus Compact Zoom Microphone ME34

3.6 Interviews and discussions

Unstructured interviews were conducted with the participants and interviews lasted for the duration the participant wished the interview to last. Length of each interview varied according to the time each participant had available and wished to talk for. The Family group interviews varied between approximately 40 minutes and two and a half hours. The Expert and Specialist groups, as for the Family group, talked for as long as they wished, or their time allowed, and again, this varied between each participant. Each discussion lasted between approximately one hour to two and a half hours. This pattern was repeated for the GP group who, as with the Experts and Specialists, spoke for as long as they chose to do so and for approximately between 45 minutes and 2 hours. Questions were prepared as an informal checklist for the researcher and were used as an aide memoir for the researcher during preparation. The participants were told that the research was exploring perceptions and ideas about Klinefelter's Syndrome and were invited to ask any questions they may have about the study before, during and after the interviews. If the participant did not raise the topic of diagnosis, the intention was this would have been asked by the researcher, but in the event, the participants raised this during the course of their discussion.

Participant information sheets had been prepared and these were offered before and after the interviews. Consent forms were prepared and signed by the participants. Copies of these documents are included in Appendix 8 (page 332); Appendix 9 (page 336). Documents were tailored to be relevant to the participant (a Family Group Participant Information Sheet, was prepared for example and a tailored version for health professionals). The interviews were conducted to elicit the thoughts of the participants with the aim of creating conditions for respondents to discuss their views freely. The role of the researcher was to follow the conversational patterns of the participant and to allow flexibility for exploring the issues

raised. Interviews for each of the three groups were qualitative but the themes and questions explored differed in accordance with the perspective and knowledge of each group. Where information was requested by the participant during the interview, this was freely given where possible and in this sense, some of the interviews were more reciprocal than was anticipated by the researcher. Earlier work had shown that unstructured exploratory discussions can provide the freedom for participants to guide the topics discussed, previously leading to significant and novel information being revealed by participants. Emergent themes and individual narratives, driven by the participants, provide a 'whole person' study approach was anticipated to inform a more complex picture of functioning from infancy through to adulthood and may reveal insights, significant for medical, cognitive and psychosocial sequelae in this holistic impact, systemic condition.

The interviews were taped, digitally recorded and, as required by IPA and Thematic Analysis transcribed verbatim and analysed. Interviews are analysed on two levels using IPA: the descriptive and the interpretative. Each transcript was read and annotated for descriptions and experiences, before being read again to identify and record associations and explanations. The themes identified in and from the transcripts were read, discussed and verified independently, also noting words and themes. Within an IPA methodology the researcher is encouraged to reflect upon their own preconceptions about the data and attempts to suspend these in order to focus on grasping the experiential world of the participant.

3.7 Specific techniques and procedures

Results from participant discussions were detailed, organised into themes and transcribed for each participant. Each transcript was analysed, and key thoughts were identified with annotations made through the manuscripts, identifying key thoughts and ideas. Further, each transcript was summarised by theme for each participant to distil the narrative of the participants. These annotated transcripts were further examined and organised into themes for each participant. Further analysis examined identified themes and ideas of significance within and across the groups. Each transcript was further summarised by theme for each participant to compliment the narrative of the participants.

During discussions involving family members their role within the family was identified on the transcript (for example, the use of M to indicate the mother of a participant or F to indicate the contribution of the participant's father, S to indicate a sibling and I to indicate an

individual with Klinefelter's). Further, the family participants are identified by the order in which diagnosis was made, for example: M1 indicates the mother of the Klinefelter's individual who was first in the family group to be diagnosed.

The primary concern was to protect the confidentiality of all the participants.

3.8 Validation

The assistance of individuals with experience of qualitative analysis but who were independent from the research were sought to verify the validity of themes and data messages. The themes were discussed and corroborated. As IPA methodology suggests, specific instantiations of the themes are reported directly from the transcripts reflecting the issues and experiences of the participants and in their own words. This to maintain as much of the authenticity of the conversational flow and spontaneity of the conversation with ideas and thoughts expressed as they happened in that moment.

3.9 Ethical, health & safety

Ethics approval was sought and obtained from the University of Bournemouth Ethics Panel and from NHS England, with the latter being obtained in February 2016 via the Exeter NHS Trust (IRAS ID 172427).

Informed consent was sought from the participants and all were clear that they were able to withdraw at any time from the study without prejudice. All participants were assured of confidentiality and that participant identity would be protected when including information from interviews by appropriate anonymization and editing of transcripts and quotations. Written notes, transcripts and tapes from interviews were anonymised and kept in a locked unit at Bournemouth University and computer files containing data were password protected.

There was a potential for some participants to find discussions during the interview upsetting. The researcher did not seek to ask questions that the participant may find upsetting. However, it was recognised that the participant may themselves raise topics during the discussion that may be difficult or sensitive or may prompt difficult memories. If this happened, the researcher paused the interview and asked if the participant wished to terminate the discussion. If the participant declined and wished to continue, the discussion would only proceed if and when the participant suggested they were ready and wished to so do. Any

interview would be terminated immediately should there be any grounds to believe this is appropriate.

Earlier research undertaken by the researcher and carried out with participants outside the aegis of the NHS suggested that individuals and family members may find the opportunity to talk through their experiences to be beneficial, but also at times, potentially upsetting. If participants had become upset the interviews would have resumed only if the participant wished. The researcher did not seek to ask questions that the participant may find upsetting. However it was recognised that the participant may themselves have raised topics that may be difficult or may prompt difficult memories. Were this to have happened, the researcher would have paused the interview immediately and asked if the participant wished to resume the discussion. The discussion would have proceeded if the participant stated this was their wish and suggested they were ready to do so. No interviews were terminated before the discussion was completed and there were no grounds to believe this was appropriate. The researcher remained conscious of the time the participants were generous enough to provide for the interviews.

For the medical experts and GP groups, time pressures were recognised as a common problem and care was taken to ensure that interviews were tailored to the time the participants had available. The researcher also needed to be mindful of personal safety and in all cases, the researcher informed another individual where the interview was being held, the time the interview was arranged for and contacted the other individual when the interview was completed.

3.10 Data analysis

The data collection phase did not set out to test hypotheses, but rather, to explore and uncover new information by revealing experiences and perceptions and this stance was maintained in data analysis. Analysis of each of the group findings were divided into chapters for each of the groups (as described in Chapter 1, page 20) with the medical specialists being sub-divided into two separate groups (Experts and Specialists). The Experts group were medical professionals who had particular expertise in Klinefelter's Syndrome, the Specialists group were medical professionals who had particular expertise in conditions reported to be of increased risk in Klinefelter's Syndrome, but not primarily with expertise in Klinefelter's. During data analysis, significant differences between the two groups (Experts and Specialists)

emerged. Due to this, presenting the findings in separate, distinct chapters was identified as beneficial and therefore the medical specialists remained separated in two distinct groups and each in distinct chapters.

(ii) Medical specialists divided into (a) and (b) as follows:

(a) Experts: medical specialists with particular expertise in Klinefelter's Syndrome providing specialist services and treatment to patients with Klinefelter's Syndrome

(b) Specialists: medical specialists with expertise other than with Klinefelter's Syndrome but practising within areas of known increased risks in Klinefelter's males.

Interviews were recorded and transcribed. Each was analysed for themes identified through the rigour of detailed familiarisation of the transcripts, reading and re-reading, becoming immersed in the detail of the data to bring to conscious notice, thereby identifying common and divergent patterns, explicit and latent themes. The process of data analysis followed the procedure in the diagram below:

Table 7: Procedure taken for analysis

Stage	Process
1	Audio tapes transcribed verbatim (portrait layout)
2	Transcripts typed as narrative conversation
3	Transcripts prepared for analysis: landscape layout with three columns for notes
4	Transcripts notes in margins for initial comments
5	Transcripts re-read for thorough identification of comments of note and initial themes
6	Transcripts re-read and initial colour coding of identified key points and themes
7	Transcripts re-read and further notes added
8	Transcripts re-read and first themes identified by participant
9	Transcripts re-read and detailed review, analysis and summary written for each individual participant (portrait)
10	Transcripts examined by each Group and initial themes across each group identified and noted
11	Transcripts examined by each Group and colour coded
12	Document written for each group detailing themes within each group
13	Document written for all groups detailing themes for all groups
14	Themes (explicit and latent) drawn into cohesive, consolidated whole for cross-group perceptions.
15	Data corpus analysis completed.

The interviews explored the individuals' perceptions of, and around, the topic of diagnosis in Klinefelter's Syndrome and how, if at all, these were shaped or informed. An interview schedule was prepared, with informal guidance from practitioners in the field, which would address the research questions, should these not have been raised by the participant during the natural flow of the conversation. These were deliberately open, allowing each participant to tell their own story without interference (Smith, 1996, 2015).

With permission from the participant, each interview was recorded and transcribed verbatim having been anonymised several times through the process of transcription and analysis to render the identity of each participant anonymous. Particular care has been taken for all the groups to provide anonymity. For families, Klinefelter's is a sensitive diagnosis and in the arena of health care professionals, particularly in specific areas of expertise, there is clearly professional networking and contact between professionals. Therefore, care has been taken to remove information which may jeopardise confidentiality. For example, hospitals are not named, and locations are kept to wide geographic regions in the UK (Central/Southern England, for example).

Each text for the Family Group was examined with IPA (Smith, 1996). The tapes were listened to, transcripts made and read many times. Themes and messages of significance to each participant and/or to the research question and aims were identified from the transcripts.

Each tape for the Expert, Specialist and General Practitioner Groups were examined using Thematic Analysis and, as with the Family Group, were listened to, transcripts made verbatim and read many times. As with the Family Group, themes, messages and views were identified from each of the transcripts and were noted.

The Family Group were examined using IPA as the research sought to explore the research questions through hearing the lived experience of the Families. In contrast, the Expert, Specialist and General Practitioner Groups were interviewed not to elicit their lived experiences, but to elicit their perceptions about the diagnosis of Klinefelter's Syndrome. For this reason, Thematic Analysis was chosen as an appropriate methodology.

The interviews were conducted at the place of choice of each participant, to minimise any inconvenience to the participants and to conduct the interviews in surroundings where individuals would feel most at ease.

Interviews were carried out with individuals living with and directly affected by Klinefelter's Syndrome either as an individual with the condition, or as a family member where a family individual has a diagnosis of Klinefelter's Syndrome (Group One). The interviews were carried out to examine whether or not they perceived diagnosis to be of significance to them and how this may have affected their subsequent life events.

Interviews were also carried out with two further groups: a group of medical experts who have primary expertise in Klinefelter's Syndrome, a group of medical experts who had primary medical expertise in conditions of the known increased risks associated with Klinefelter's Syndrome (Group Two) and a group of general clinicians who have expertise in the areas of general medical practice and who provide primary health care for the general community and are usually the first health care professionals to see individuals who are seeking general healthcare advice (Group Three).

A qualitative approach was also chosen to elicit different perspectives from different stances to the diagnosis of Klinefelter's Syndrome and the recognition that an in-depth focus on the topic would be best met through a qualitative approach. This approach was selected to provide the most open and flexible approach for providing the setting for each participant to speak freely to elicit individual views and this was a key factor in the design.

The information sought was the exploration of the different perspectives of different groups to the explore significance of diagnosis. It was felt that questionnaires and structured questions may limit views potentially revealed by the participants and may restrict the conversation thereby preventing the full exploration of the topic. Pre-determined scripts or questionnaires were felt to be restrictive, requiring assumptions or 'second guessing' by the researcher. Further, this approach may limit the potential for novel, as yet unreported factors which unguided conversations may reveal.

The interviews were in-depth to elicit detailed, data rich accounts and perspectives regarding diagnosis and how this may impact the lives of individuals and families affected. Analysis sought to identify themes and perspectives of importance to each participant, to explore the perceived implications of these perspectives to the diagnosis of the syndrome in the context of the family, the health professionals involved in the diagnostic process and to the wider societal implication. The study also sought to inform the current literature by enrichment

through detailed narratives and descriptions the reported reasons in the literature given for the under diagnosis of this syndrome.

A detailed and rich exploration was aimed for to provide as much context, description as possible to gain a thorough and rich understanding of the perspective of each group.

CHAPTER 4

RESULTS: EXPERT GROUP

4.1 Introduction

The two main reasons cited in the literature for lack of diagnosis in Klinefelter's Syndrome are the variability in presentation of the syndrome and poor awareness of the syndrome in general practitioners, who are the gatekeepers for access to consultants with greater expertise. What has not yet been examined are the perceptions of Expert likely to see individuals with Klinefelter's Syndrome for diagnosis and/or treatment. The Expert group in this study is a specialist group who are experts in the field of endocrinology. The Expert group are sufficiently aware of the variety of symptoms and issues with which Klinefelter's patients present in order to catalyse a diagnosis on the basis of the symptoms they see or for which the patient has been referred. For this reason, the Expert group have particular expertise in Endocrinology and were interviewed to ascertain their perceptions of diagnostic significance in Klinefelter's Syndrome. These perceptions were examined in a series of interviews with Experts.

As noted in Chapter 3, a schedule of questions was prepared in advance as a memory prompt for the researcher, rather than as a script. The interviews were designed to be conversational in style, with an open and flexible style, driven in content by the participant. This style was adopted to minimise the role of the researcher to maintain the flow of the interview and probing points raised by the Expert. The aim was to elicit as much data rich detail in the narratives as possible to provide a rich and full insight into the perspectives of the Expert group. This was to provide sufficient commonality to allow comparisons across the participant groups. A qualitative exploration of perceptions was chosen to provide a detailed narrative, thus providing a rich picture of how Experts responded to possible Klinefelter's symptomatology and how this was shaped by their awareness of the syndrome and their ongoing contact with Klinefelter's patients.

Section 2 of this chapter provides details about how themes were extracted from these interviews and provides the basis for the narrative analysis which follows in Section 3.

4.2 Examining themes from interviews

As described, the themes were identified through analysis of each interview transcript and agreed through discussions with 2 colleagues; one of whom had particular expertise in conducting qualitative research. Prior to discussions, anonymised transcripts with all comments made by the researcher on the transcripts were removed to ensure no influence from the researcher's thoughts were imposed on colleagues. Transcripts were read, discussed and themes agreed.

The following themes were identified from the transcripts as follows:

Table 8: Experts table of themes

Theme	**Sub-theme(s)**
'A common condition, a rare diagnosis'	low awareness in general clinicians
'The clues are there': variability, subtlety and 'a lifetime of clues'	Variability in presentation of the syndrome? Subtlety in presentation A lifetime of clues How and when diagnosis was made Diagnosis "makes things better" The costs of lack of diagnosis Societal implications, NHS and wider health systems

4.3 Analysis of interview themes

4.3.1 A common condition, a rare diagnosis

All the Experts opened their narratives with observations about awareness and the influence on diagnosis:

E1: *"Many are below the radar"*

E2: *"Yes, it's a lack of awareness, I think that's right, people don't think about it"*

E1: *"Klinefelter's could not be described as a rare condition"*

E1: *"increasingly … the chromosomes are done for some other reason and then they're sent to us"*

A consistent strand throughout the narratives of the Expert group was setting the clinical context for diagnosis. The interviews with Experts revealed the extent to which there was very little of awareness of the syndrome among specialists who, in the course of referrals for presenting symptoms, might be likely to encounter individuals with undiagnosed Klinefelter's Syndrome. They felt that, among their professional colleagues in different medical specialisms or in general practice, this was a condition that simply fell 'below the radar' since it was regarded as a rare condition and there was agreement that a general low awareness about Klinefelter's Syndrome currently exists in the medical and health communities:

E2: *"So it's much commoner than anybody thinks ok, but actually there are figures out there in the literature, it's actually 3 or 4 times as common in terms of diagnosed cases, so it's clear we're all missing cases"*

E2: *"it's never the GP… I think GPs haven't got that level of awareness generally"*

E1: *"GPs … generally they've heard about it, they don't know what it is"*

E3: *"probably the vast majority of XXY boys are born without anybody knowing"*

For those among the Experts group who had existing specialised knowledge of Klinefelter's syndrome, there was a view that poor awareness of Klinefelter's among general medical professionals is a significant problem for families seeking diagnosis. Difficulties in getting a diagnosis are reported to be experienced by families despite the reported importance of diagnosis, with estimated rates of incidence currently being between 1/450 - 1/660 males. Thus the Expert group were in accord with the existing literature in reporting that a lack of awareness contributes to low diagnosis figures (Verri et al., 2010). The Experts' narratives made it clear that 'not knowing what you didn't know' meant there was no motivation for clinicians to increase their knowledge. This was despite the fact that estimates of prevalence appeared to be increasing rather than decreasing:

E3: *"it's is dropping, becoming more common, maybe, maybe dropping down to 1/500"*

The story unravelled through the Experts narratives therefore is of a common syndrome, increasing in prevalence that, contrarily, currently appears to be invisible in the health system and to many medical professionals, thus contributing to continued low diagnosis rates.

General practitioners' lack of awareness of the syndrome emerged as an issue along with the need to increase general levels of awareness through education and dissemination:

E2: *"it's raising awareness and education really in GP's … that's exactly it, yes, and that's exactly the problem"*

Importantly, lack of knowledge about the syndrome can cause, or contribute to, poor information being given to families at the time of diagnosis. These concerns were voiced clearly by the Experts, along with the need to find individuals with sufficient expertise to provide appropriate support for affected individuals and their families:

E3: *"then … it's how people are informed of the diagnosis, that's the tricky thing. Often people will turn around, to parents and say: 'ok your sons' got Klinefelter's, but we don't know very much about it'"*

E3: *"so that's the challenge we know a little bit, not a lot, they want to find someone who knows about it."*

4.3.2 'The clues are there': variability, subtlety and a lifetime of clues

Despite the frequently reported variation of the syndrome, there seems a possibility of a shared 'Klinefelter story' through a 'lifetime of clues'. However, the clues were not always in clear sight because of a combination of variability and subtlety in presentation:

E2: *"there's as much variation in an XXY boy as there is in an XY boy"*

4.3.2.1 Variability in presentation of the syndrome

Despite the frequent references to variability of the syndrome in the literature, there appears a paucity of data on the extent, or nature, of the variability between individuals. In accord with the literature, Expert narratives regarding low awareness continued, with the group consensus that variability influences diagnosis rates downwards; variation of the syndrome was seen as a further barrier to diagnosis:

E2: *"the most likely thing is the phenotype of the condition is so variable"*

E1: *"why is the condition so varied … there is an enormous spectrum of variability some only have a few problems, whereas others have enormous problems, skeletal, autoimmune, social, educational"*

E2: *"there's as much variation in an XXY boy as there is in an XY boy"*

The possibility is raised that the variation mentioned as a 'confounding' diagnostic factor may be, in part, a normal expression of natural differences that exists between all individuals and this natural individual variation between all individuals may be the cause of the frequently reported 'variability', rather than a variability resulting from the syndrome. It is interesting to consider, therefore, if there may be a case to be made here for the variability factor being a diagnostic distraction away from the characteristic commonalities which may be *shared.*

4.3.2.2 Subtlety in presentation

Geschwind (2004) stated that 'the phenotype is usually unremarkable to the casual observer'. The apparent lack of visible differences, or signs of any disorder, contribute to lack of diagnosis for and contributes to the reported low diagnosis rates. The narrative of the Expert group begins to set a context for low and late diagnosis rates and reasons why Klinefelter's may remain undetected by many general clinicians, unless health professionals are aware of the subtle presentations often associated with this syndrome. Of note were the Expert comments concerning the possible implications for many Klinefelter's males who reportedly have subtle impacts and/or no discernible physical indicators which would prompt for diagnosis, not least because many individuals have the appearance of a typically developing male. The point reinforced by the Expert group was a picture of a syndrome which may become apparent through the lifespan at different ages and in varying ways for each individual. The lack of awareness of general health professionals and lack of recognition of the significance of these lifespan 'indicators' were highlighted through the Experts accounts when describing these shared commonalities:

E3: *"the majority are just the same as everybody else, there are subtle differences, they might be a bit slower, or dyspraxia, less confidence … when they get to puberty I will step in with testosterone if needs be"*

E2: *"it's the milder ones ... the whole thing about the condition is it's variability and I think that's the key to it and I think there are children who start off in puberty and I think they've got normal hormones early on … so I think there is that cohort and much more difficult to diagnose"*

Diagnosis was perceived as less likely for those with subtle, or absence of, discernible differences. However, diagnosis was perceived to be as important for those with subtle presentations as for those with more obvious characteristics. Diagnosis was directly linked by the Experts to accessing important help and support (at school, for example) and for optimising lifespan health through monitoring, screening and timely treatment. The difficulties experienced by those with subtle presentations was highlighted in several key areas by the Experts, including being identified as the group most vulnerable to not having a diagnosis. The Experts point out that where a child has more pronounced problems, support is more readily available, but in the case of subtle impacts, parents are less likely to secure a diagnosis and access appropriate help and support:

E3: *"it's tricky, it's a very tricky one … if the boy has subtle learning issues then it's very difficult to get support, if they've got major learning difficulties then the whole system rolls out, special schools but if it's just subtle … then it's very difficult really, the system doesn't work that well."*

The Experts make clear that access to support depends on both severity and clarity of presentation. This is likely to have implications for those with a combination of mild and subtle symptomatology.

The issue of balancing out the need for care whilst avoiding over diagnosis or treatment is one which practitioners consider and is particularly likely to arise for the practitioner when Klinefelter's Syndrome is diagnosed, but presentation is 'mild':

E2: *"there's two ways of thinking about that (under diagnosis) one is that we're not picking up something we ought to pick up to help, the other approach is, well, if it's still so relatively mild do you need to identify it in the first place?"*

There was consideration of a balance between under versus over diagnosis, under treatment versus over treatment. It was interesting that the notion that diagnosis may be of less value where symptoms were medically perceived to be 'so mild' was raised by one of the Expert Group. This thought was one also mentioned in the GP group:

GP4: *"the amount of problems that they have is so variable that in fact maybe only 1 in 2,000 perhaps have that need … has a problem to be diagnosed, or we don't know really, do we?"*

In contrast, it was interesting to note a striking difference to the idea that diagnosis may be of less value where the symptoms were 'milder'. This was not true for any of the Family group, all of whom, despite the variety of effects of the syndrome (differences attributed to timing of diagnosis) for each family, described diagnosis as essential:

M6: *"Basically I think everyone should be entitled to an early diagnosis. I think it's vital to have a diagnosis, certainly"*

I4: *"I wish I'd got told at birth. It's kind of hard … I wish I'd got told earlier. Knowing was 100%. You need to know"*

Although this was a consideration made when dealing with Klinefelter's individuals, it was not clear whether or not there were instances when Klinefelter's was 'picked up' but was not diagnosed because the mildness of the presentation suggested that this might not be helpful. However, at a later stage in the interview, there were thoughts from the Expert group which note the need for early diagnosis in order to facilitate effective and appropriate intervention for the benefit of the affected individual:

E2: *"if you're seeing a young man and treating him appropriately you will do bone density scans … you need to ensure the boys do physically develop, or go through puberty"*

Similar concerns were also expressed by E1, who points out that opportunities for educational development may be missed if diagnosis was not made:

E1: *"Yes, I think they are … puberty may not be such an issue, but you know they may have missed out on some educational opportunities you know, nobody's thought: 'oh, they've got learning difficulties and there's a reason behind it'"*

To summarise, these narratives suggest that lack of diagnosis may occur where the presentation is subtle and there are no, or few, observable physical indicators of any problem or condition. A subtle profile is not unusual for Klinefelter's males because there is no evidence of any condition at 'first glance'. This resonates with Geschwind's (2004) assertion that 'the physical phenotype is usually unremarkable to the casual observer'. Evidence from the Expert group suggests that the subtle indicators of Klinefelter's Syndrome are frequently missed not only by 'the casual observer', but also by many health professionals, including general clinicians and paediatricians. The Experts link diagnosis to support and interventions

which are seen as significant throughout their narrative and describing how even for those with 'subtle' difficulties, intervention may be important, and diagnosis is the route to providing this.

4.3.2.3 A lifetime of clues

Despite few observable symptoms, or outwardly obvious signs of the syndrome, the Experts identified co-morbid conditions which may have been identified as increased in Klinefelter's Syndrome, and some of these are considered below. It was interesting to note that these shared commonalities represented clusters of shared similarities, rather than differences, which was an interesting notion given the frequently reported 'hallmark' variability of Klinefelter's:

E2: *"any children with mild learning difficulties, autism, should have a chromosome straightaway"*

E2: *"especially if he's got learning difficulties you've got to think about Klinefelter's"*

It may be that these may be beneficial to prompt for chromosome testing where there is awareness in the clinician of the importance of making this referral, for example, in autism:

E2: *"I just think young people with Klinefelter's are much more likely to get autism traits and you know with a lot of chromosome abnormalities, that's the case"*

The Expert group also acknowledged there may be confusion caused at various life stages as the levels of knowledge in general clinicians may not extend to the possible physical differences, which may characterise different ways the syndrome may manifest. This may be particularly evident during adolescent years and how this may differ between individuals:

E2: *"a lot of people aren't aware that they can start off in puberty normally, so they get confused by that"*

E2: *"if they've got signs that are failing, voice doesn't change etc. and so on they should be referred at that point. I think GP's haven't got that level of awareness generally"*

Importantly, examination of what the Experts considered as important clues for diagnosis appeared to reveal a chronology of 'diagnostic clues', which they describe as characteristics which may be helpful for diagnostic indicators. This suggests that there may be a ‘lifetime of clues’, a series of lifetime points where there may be diagnostic opportunities if practitioners were sufficiently aware. The group narratives in this research describe these diagnostic clues, which have been identified and organised into a group indicative of diagnostic 'clues'. These are referred to, for the first time in this study, as the 'Diagnostic Cluster Group' (DCG). The DCG is formulated from data from each of the groups and identifies symptoms of increased incidence in Klinefelter's Syndrome and the life points at which the clues likely emerge. The data revealed through the narratives of the groups in this study reveal the importance of identifying and subsequently recognising these lifetime clues, or cues, as relevant to a diagnosis, and thereby lead to recognition of the underlying condition. It is hoped the DCG may be beneficial to contribute to raising awareness in those medical areas of increased risk for Klinefelter's patients, thereby increasing diagnosis rates in these areas of medical speciality.

The 'lifetime of clues' are a series of 'clusters' identified through the narratives of each group in this study as potentially indicative, and/or characteristic of, Klinefelter's Syndrome. As stated (Chapter 2), there is an array of increased health risks for Klinefelter's individuals and early identification and awareness of these increased risks may be beneficial for screening, monitoring and early interventions.

In this research, the groups identified and described varying constellations which they felt were significant in Klinefelter's. These were identified in this study as a series of Diagnostic Cluster Groups (DCG), each with unique characteristics described by each group. These have been included at the end of each of the relevant chapters: Figure 2, (Chapter 4, page 100); Figure 4, (Chapter 6, page 154); Figure 5, (Chapter 7, page 221); Figure 8, (Chapter 8, page 264); Table 17 (Chapter 7, page 226).

Further, each of the diagnostic 'clusters' appeared to emerge at anticipated moments in time through the lifetime of the Klinefelter's individual. Therefore, it was hoped that these 'Klinefelter clusters' may be beneficial to provide a 'lifetime of clues' with the purpose of aiding diagnosis and for raising awareness in specific areas of health specialisms of the

increased risks of Klinefelter patients and thereby increase vigilance in the wider health community.

Having considered significant factors for diagnosis and setting the context for the place of diagnosis in life experiences of individuals and their families, the Experts moved on in their narratives to describe the process and examples of impacts of having a diagnosis. It is this pattern of conversation that the Experts moved on to consider.

4.3.2.4 How and when diagnosis is made

The Experts moved on in their narratives to describe how and when diagnosis is made. They did not necessarily expect to make a diagnosis of Klinefelter's, with the expectation that this would have been made before referral to them. Further, the group perception was the Klinefelter's diagnosis was often made in the course of testing for something else, rather than a primary testing for Klinefelter's. In many instances, the diagnosis was made as incidental to the original referral. This process of diagnosing whilst testing for something other than Klinefelter's was not uncommon in the Family group in this study. This 'accidental' Klinefelter pathway to diagnosis may provide a context for the apparently 'symptom driven' approach to treatment and diagnosis and for the reported 'haphazard' routes to diagnosis experienced by the patients who were not referred for testing for suspected Klinefelter's, but an array of various other conditions, during the course of which the underlying Klinefelter's Syndrome was made:

E2: *"increasingly we're getting them from the genealogists because the chromosomes are done for some other reason and then they're sent to us"*

Referrals through private health care were also discussed, with this being reported as a factor in diagnosis and often resulting from perceptions of dismissive approach to parental concerns and feelings of frustration at no diagnosis having been made, despite the multiple hospital referrals. In these cases, having pursued a number of referrals, with parents describing no satisfactory outcome, private referrals had been sought:

E2: *"Right, presumably no one was listening to the parents … they get frustrated"*

E1: *"or psychosocially, absolutely they feel differently, and they may feel very frustrated but, yes, I think that's very important to pick up"*

Where a diagnosis has been made, how this diagnosis was made is raised by the Expert group. Individuals with obvious physical differences were said to be the most likely to be diagnosed, but this group are in the minority, with many more having few, subtle or no discernible physical signs which may prompt health professionals to think of referring for chromosomal testing. Despite few observable symptoms or outwardly obvious signs of the syndrome, the Expert group identified a chronology of 'diagnostic clues', which they describe as characteristics which may be helpful for diagnostic indicators.

The Expert group recognised the challenge often experienced by families to get a diagnosis, and this was apparent in their narratives. It was clear from the Experts' comments that, for many families, there was an instinctive sense of knowing there was a problem, sometimes for years, but, for many, diagnoses remained elusive. Such experiences were not uncommon, and this was acknowledged by the Expert group and evident in their perspectives of the effect of this on the families. The frustration felt by families was acknowledged by the Experts who recognised there may have been barriers and multiple referrals before diagnosis was made:

E2: *"often I think families are very frustrated, often they know something's not quite right, but they can't put a name on it and obviously often they get shrugged off by other health professionals"*

E1: *"some people it's a complete surprise, others haven't felt right all the way they've felt slightly different and that they knew they were not quite the same one way or another"*

Here the Experts have highlighted key factors that provide a context for the diagnostic challenges experienced by Klinefelter's families and the implications of this.

4.3.2.5 Diagnosis “makes things better”

Experts narratives in interviews also revealed the considerable benefits when diagnosis was made. Not least was the feeling of acknowledgement and understanding for Experts and families alike:

E2: *"then everything fell into place, his learning difficulties which had always been very frustrating for him and not knowing why"*

There was also the view that diagnosis provides understanding and insight for those supporting or working with individuals. Providing a definitive diagnosis is seen by the Experts to provide a context within which those who support Klinefelter's individuals are better informed to provide not just support, but appropriate support:

E2: *"if you then make a genetic diagnosis it is very clear to people that, yes, there is a very good reason and suddenly a lot of other possibilities are opened up"*

The Expert group also clarify how diagnosis not only acts to 'make sense' of the worries of the family that something was wrong before diagnosis, but also empowers families with knowledge and insight into the syndrome. This bestows understanding and empowers parents to make more informed decisions (choice of school, for example):

E2: *"that's one area where early diagnosis can help you manage things better, but education is a big thing"*

E1: *"it's looking out, really and help the boy develop in confidence, socially, things like that, promote activities really that are going to, if they tend to be a bit solitary try to get them out doing you know, social things, really"*

The Experts narrative highlights the place of preventative approaches which may confer resilience which become possible with a diagnosis:

E2: *"also I think so people will take the learning and the behaviour much more seriously and I think that's important"*

The perception that diagnosis is seen as not only significant to individuals, but also to their family and the health systems which support them is a powerful theme which resonates throughout the Expert narrative. There is a strong feeling that the Experts share the frustration they acknowledge the families experience of diagnostic difficulties such as low general awareness, which contribute to this:

E2: *"so sometimes you make that diagnosis and actually you wish it had been done earlier and that's why I think anyone with learning difficulties should at least get their chromosome checked because this is the sort of thing you might find"*

4.3.2.6 The cost of lack of diagnosis

Experts acknowledge that there were also health implications and increased risks for an array of problems. First, the narratives highlighted why Experts thought that diagnosis was important, not least because it informs professional judgement about treatment approaches and informs clinical management:

E1: *"screening is important for educational and motor interventions"*

E2: *"the important thing is that the puberty side gets looked at earlier and if the child needs pubertal induction, if they don't start on their own, then you can start them in a timely manner"*

The importance of timely treatment is a theme of significance in the Expert group and it is clear that this is an important consideration in the management and treatment of individuals with the syndrome.

Not only was early diagnosis linked with time critical treatment, but importantly also with an array of minimising other known increased health risks and optimising effective interventions and support:

E2: *"I think at various points it makes things better for the kids basically"*

E1: *"Lack of a diagnosis is important, making it early is even more important"*

E2: *"I think it's very helpful"*

The health implications of no diagnosis to the family, to the health professionals and wider health systems also became apparent from Experts' narratives:

E2: *"I think particularly at a time like this when resources are very limited it's important to make a diagnosis like this"*

E2: *"I think that will probably have important impacts later on the development of their bones etc. because testosterone is extremely important for normal bone health and also then you're monitoring them very carefully and if they start puberty then you're watching very carefully ready to start the testosterone when the time is right"*

The Expert descriptions indicate that effective management of the syndrome is dependent on diagnosis being made. Numerous important health and wellbeing considerations were identified by the Expert group and where diagnosis has not been made, this was seen as deleterious to health, wellbeing and significantly, to later outcomes:

E2: *"so I think that overall testosterone we know is very important for your metabolism, it's important for your bone health, so I think that all these factors are very important"*

E2: *"if you then make a genetic diagnosis it is very clear to people that, yes, there is a very good reason and suddenly a lot of other possibilities are opened up"*

In addition to physical health, diagnosis was also seen as a gateway to support educational needs and making the most of educational opportunities:

E2: *"the child may not get all the help that they need in terms of education etc."*

E2: *"they may have missed out on some educational opportunities, you know"*

E1: *"it's developmental problems, developmental delay, speech delay or perhaps behavioural in the older boy, behavioural problems, autistic spectrum tendencies … puberty problems and later on in life, fertility problems"*

E1: *"there is a percentage who need educational support, I think about two thirds need speech therapy"*

Experts saw the time around puberty may be when emerging differences may become evident and this had important psychosocial impacts for Klinefelter's individuals:

E2: *"I think we talked about the lack of puberty … they get teased by other boys"*

E2: *"the lack of puberty … they look a bit more feminine and the voice and the breasts they get well that in itself is a real sort of psychological burden, you know I've known boys who don't go swimming etc. because they'll know that these will be noticed, and they don't want to do that…"*

Other physical differences may also become increasingly important (as well as having long-term health implications):

E1: *"they can put on weight very easily … and they get what we call insulin insensitivity which makes you more likely to get cardiovascular disease, particularly aschemic heart disease in the long term"*

E1: *"there will be some … I think there might be a slight increase looking at the morbidity figures, I think hip fractures … a higher risk of osteoporosis"*

The narrative of the Expert group clarifies the critical importance of awareness to increased risks and, therefore, the importance of taking a proactive stance. One such example being the important strategy of watching and careful monitoring as an integral part of the management of the syndrome. The importance of this management approach by the Experts for anticipating and providing timely treatment is clear throughout their narratives. Equally, it is made clear that this opportunity is bestowed to them only by a diagnosis having been made. The significance of timely treatment also highlights the long-term health problems which can result from lack of diagnosis, including long term damage to bone health and complications from abnormal pubertal progression.

4.3.2.7 Societal implications, the NHS and wider health systems

Closely linked to the costs to the individual of lack of diagnosis, Experts' narratives revealed awareness of wider costs and implications. Experts emphasised diagnosis provides the opportunity to practise preventatively and there is, therefore, awareness that the individual is at increased risk of a constellation of health problems with immediate implications, which also carry increased risks for developing health problems later in life. Conferring resilience is possible where the underlying diagnosis has been made and anticipatory guidance provides ongoing screening, monitoring and timely treatment:

E2: *"yes, in the greater scheme of things I think the gains are huge if you make a diagnosis you might actually prevent a lot of health problems in the future"*

E2: *"In the long term there's fracture etc., so there's economic importance to the Nation as well"*

Conversely, where no diagnosis has been made, a preventative approach is not possible as the increased risks to health and wellbeing are not recognised. Treatment is therefore inevitably symptom led, taking a reactive, passive approach which does not minimise the probability of emerging threats to health:

E1: *"screening is important for educational and motor interventions"*

E2: *"yes, and I think the main thing is the autoimmune ... some of the boys have hypothyroidism which would then be picked up because again once the diagnosis is made, you screen them yearly for the thyroid they're more prone to, things like metabolic problems"*

Importantly, the Experts describe how diagnosis not only provides a context for management of Klinefelter's patients, but also provides health professionals with essential information to enable them to take an anticipatory approach to treating the condition. This provides an opportunity to not only prevent problems, but also put treatment approaches in place to optimise health and wellbeing:

E2: *"you know I'd worry about a 38-year-old, a diagnosis that late they may have lost out significantly on their bone development which makes it more likely to get fractures"*

Thus diagnosis opens up a new treatment pathway where health professionals are able to take a proactive, protective approach to treatment, as well as reacting to symptoms if and when they present. In other words, the Expert testimony reveals diagnosis is a gateway for professionals, as well as the families, to provide a more informed, effective, proactive treatment approach:

E2: *"so again you have to try and optimise their health in other ways and make sure you're on top of things like that, … the markers of cardiovascular disease, blood pressure that sort of thing"*

E2: *"bone health is also very, very important"*

The importance of diagnosis for Klinefelter patients was described by the Expert group and the significance not only for the individual and their family, but also the wider societal impact.

4.3.2.8 Ways forward

Through the course of interviews with Experts' it became apparent that there was a variety of ways in which diagnosis and treatment of individuals with Klinefelter's Syndrome could move forward, and these are now examined below.

(i) Increasing awareness through training

The key to important change was seen as a seemingly straightforward process of raising awareness, especially among health professionals who are in the position of making the critical referral for chromosome testing; currently not often seen in mainstream health care practice as frequently as Experts consider it should:

E2: *"it all comes down to … the education of health professionals to think about these … not so rare, conditions"*

E2: *"the education of professionals, that's the top thing"*

E2: *"yes, in the greater scheme of things I think the gains are huge if you make a diagnosis you might actually prevent a lot of health problems in the future"*

(ii) Identifying commonalities

There was agreement within the Expert group that if commonalities can be identified, from which evidence-based recommendations can be produced, this may contribute to reducing missed diagnoses and reduce lack of treatment for affected individuals.

Important treatments and management are identified through the Expert narratives, with a broad range of necessary interventions and holistic provision identified as important:

E2: *"the optimal treatments, I think they need educational support, they need psychosocial support, of course and at the time of puberty you may need to think about giving them testosterone if they need it, potentially"*

This 'triangle of support': educational, psychosocial support and testosterone where needed was identified as part of an appropriate, overall management approach which includes, in parallel, a programme of monitoring and screening. Of note, was the importance the Expert group placed on the critical place of monitoring and screening as part and parcel of optimal care for Klinefelter's males. Where this is not provided, there is significant risk to an array of health threats which, undetected or treated, are significantly detrimental to developing life threatening disease and health problems. The significance of the treatment approach was described to optimise health and, importantly, to act as a preventative series of measures to reduce the known increased risks to health and wellbeing bestowed by the syndrome. These necessary, routine checks and screening programme included checking for increased risks:

E2: *"yes, things like complications, metabolic syndrome, looking at their cardiovascular markers, looking at their blood pressure, looking at the weight, looking for autoimmune diseases like hypothyroidism and treating that. Because that's the other thing, you've got to treat that, or they feel quite lousy. You know hypothyroidism may go undiagnosed as well for ages"*

Research was seen as very important for the immediate way forward, to inform and illuminate important and identify significant factors in Klinefelter Syndrome. An urgent need for both qualitative and quantitative data was identified to inform diagnosis and treatments, particularly longer-term data exploring issues such as:

E2: *"their quality of life, what happens to their weight as they get older, um, and bone health, what are their bones like in the long term? What's the fracture risk? All of these questions need to be answered"*

That Klinefelter's Syndrome may raise as many questions as more is revealed about the relevance of this condition to affected families is described by the Expert group who comment on the lack of longer-term data, information and knowledge:

E3: *"we don't really know what the outcomes will be, we don't really know what difference that whole effect has on functioning in life … it's very difficult to know"*

E2: *"and what sort of life-style effects their lives? How do they feel on a day to day basis? And I suspect that many of them not getting the appropriate hormone replacement feel pretty horrible. Because the other thing about testosterone is it gives you energy. Without that your energy levels fail. You just don't feel like doing anything."*

E2: *"Yes, I think quality of life is key"*

E2: *"I think at various points it makes things better for the kids basically"*

The Expert group were in accord that diagnosis is significant and important for the individual Klinefelter patient and their family. Further, that diagnosis provides important information for health professionals involved in their care. The over-arching theme was the opportunity to provide a better quality of life through timely diagnosis and effective care resulting from that.

(iii) Diagnostic tools: appropriate screening and a diagnostic model

Currently there is an absence of a screening criteria for Klinefelter's and this was identified as a barrier to screening for the syndrome at birth. However, there were observations that wider screening for earlier identification may be beneficial to inform management and timely intervention:

E3: *"should we screen everybody at birth in terms of the true nature of what screening means? ... Then it's not really anything you're going to put right by identifying first - it doesn't really fit into the clear screening criteria"*

E1: *"psychological assessments are useful for early school, speech, co-ordination and dyslexia, also to monitor for abnormal puberty"*

The lack of recognition of symptoms for Klinefelter's, or low awareness of the condition, is again referred to as a factor, even where referral is made to paediatricians:

E2: *"I think most paediatricians ... again they probably need clues and I don't think they'll think about it with someone with learning difficulties"*

The Experts felt that a model, such as the proposed model (Chapter 8, page 248) to aid diagnosis would be worthwhile and may contribute to identifying individuals currently diagnostically missed. The Expert group concurred that there are 'a high instance of constellations by three or four years of age' which, if recognised when seen by general practitioners, for example, would be of assistance in increasing diagnosis rates. The differences in the Family group were variations which appeared to have their genesis in the late diagnosis, emerging as secondary problems only later in life. This seems an interesting notion, particularly in the context of the frequently reported variability between individuals with Klinefelter's Syndrome:

E1: *"I think a model could be very worthwhile ... if you can produce firm recommendations based on evidence this would stop a lot being missed and therefore having no treatment"*

E1: *"there are a high instance of constellations and signs by 3 or 4 years of age"*

(iv) Greater understanding of chromosomal underpinnings

Klinefelter's Syndrome could be described as a 'new' diagnosis, not made possible until advances revealed the underlying chromosomal difference in 47, XXY. It may be reasonable to suggest that current healthcare systems were designed primarily to provide and treat reactively diseases and symptoms. With recent advances, practising proactively with prevention in symbiosis with treatment now provides a preventative approach to patient care. However, current healthcare systems may not yet be structured around the new model that is informed by such medical advances:

E2: *"we don't know is the correct answer. There may be something in there (Xp vs Xq influences on height). There are some genes on the X chromosome that we know are responsible for growth hormone problems in boys, but we know about very few of them"*

Similarly, reasons for some of the physical variabilities are yet to be identified but influences of differences on the extra X chromosome have been proposed as possible factors. It seems possible that the increased tallness in some Klinefelter individuals may be caused by X chromosome variance for example (such as Xp or Xq), and several factors have been suggested as likely contributing to or causing physical variances between Klinefelter males. As suggested by one of the Expert Group, many of these factors and their influence remain unclear as yet. That progress is being made with understanding and revealing more about the interplay and significance of genetic differences is made clear. In the meantime, that there are unanswered questions is clear in the Experts' discussions:

E2: *"at the moment we're coming up with new players slowly but surely"*

This sense of unknowing, or gaps in knowledge, being of significance in a Klinefelter's diagnosis in general, and specifically in having a diagnosis, was a subtle themed message which ran throughout the narratives as an implied thread of significance.

The narratives provided an insight into the perceptions of Experts who have particular expertise in treating Klinefelter's patients. Their perspectives echoed the literature in highlighting the diagnostic problems for Klinefelter families and the challenges this presents to important monitoring, screening and timely treatments which are available and important for health and wellbeing in Klinefelter's individuals. As the Expert testimony emphasises, this

is possible only where diagnosis has been made. Therefore, the importance of making a diagnosis early resonates throughout the Experts' narratives.

Figure 2: Diagnostic Cluster Group (DCG): Experts 1

Developmental Diagnostic Clues:
'A Lifetime of Clues'

Ante-Natal, Early Infant Clues	
Ante-natal diagnosis	E3: "it's never the GP - ante-natal diagnosis, maternal age or if they're over 35 as they're looking for Downs and they find XXY then that's a surprise to lots of people" E2: "it's never the GP, antenatal diagnosis or CVS - maternal age or if over 35 they're looking for Downs and they find XXY" E2: "the boys I see … antenatal diagnosis … sometimes the genetics team would have picked it up antenatally" E2: "one alerts someone to the diagnosis it can be made in a number of ways … it can be made through amniocentesis … you have under masculinisation of the baby… but that's a very small number of cases really"
Abnormalities at birth	E2: "just after birth if they've got abnormalities of the genitalia … that's very rare"

↓

Childhood Clues	
Developmental delays	E2: "if it's missed then, then the next stage might be incidence of learning difficulties, or developmental delay as the child's growing up" E3: "some we have come through behavioural problems … early childhood, developmental delay which may be 1 - 2 years of age, slow to walk slow to talk" E2: "early childhood developmental problems, developmental delay which may well be 1-2 years of age … slow to walk, slow to talk" E2: "they might be a bit slower, or dyspraxic, less confidence"

Learning difficulties	E2: “about two thirds need speech therapy … about two thirds will need educational support” E2: “anyone with learning difficulties may have that, so you may pick it up at that stage and if you don’t you might miss it until possibly the time of puberty but again, a small proportion” E3: “any child with mild learning difficulties, autism should have a chromosome straightaway” E3: “education is a big thing … I think anyone with learning difficulties should at least get their chromosomes done”
Behavioural/ physical problems	E2: “then mostly after that it’s developmental problems, developmental delay, speech delay or perhaps problems behavioural in the older boy, behavioural problems, autistic spectrum tendencies” E2: “some we have come through behavioural problems, early childhood, some with physical problems”
Tall stature	E2: “then later on probably later childhood, if there’s a very tall stature which is a rare thing in XXY anyway”
	E3: “something’s not quite right”

Clues at Puberty	
Lack of puberty	E3: “the next time is at the time of puberty … the lack of puberty” E3: “pubertal induction, if they don’t start on their own … (or) just not seem to go through puberty in the right way”
Start puberty, but then stop	E2: “probably quite a significant proportion of patients so start off in puberty initially so you may not even pick it up at that point … they go into puberty spontaneously yes, some of them will start off, but they fail during the course of puberty … so that would be a clue”

	E3: “there are children who start off in puberty and I think they’ve got normal hormones early on … a lot of people aren’t aware they can start off in puberty normally, so they get confused by that. If they’ve got the signs that things are failing, voice doesn’t change, and so on they should be referred at that point”
Breast tissue	E3: “if a boy doesn’t progress through puberty or they develop a lot of breast tissue that would be a reason or there’s an unusual pattern of puberty” E2: “during puberty years with the teenage years if a boy doesn’t progress through puberty well or they develop a lot of breast tissue or there’s an unusual pattern of puberty”
Natural pubertal progression	E2: “you need to ensure the boys do physically develop … go through puberty, but quite often they do” E2: “others may go all the way through puberty and gradually the testes don’t function very well and eventually you end up on testosterone as a result”
Testes	E2: “after the onset of puberty … is small testes”
Lack of testosterone	E3: “testosterone gives you energy, without that your energy levels fail, you just don’t feel like doing anything”
Increased risks	E3: “increased risks, yes, cardiovascular problems, autoimmune – some of the boys have hypothyroidism, they’re more prone to metabolic problems” E3: “hypothyroidism may go undiagnosed as well for ages”
Psychosocial	E3: “psychosocially absolutely they feel differently, and they may feel very frustrated … yes I think that’s very important to pick up”

Post puberty/adult	
Testes	E3: “others may go all the way through puberty and gradually the testes don’t function very well and eventually you end up on testosterone as a result”

Abnormal genitals	E3: “urology is the other way to go because of genital abnormality”
Physical and fertility problems	E2: “some with physical problems … then later on in life fertility problems”
Risks	E3: “putting on weight more easily makes you more likely to get cardiovascular diseases in the long term” E2: “I think hip fractures … low testosterone … managing osteoporosis” E3: “in the long term there’s fracture etc.”
	E2 concluded: “it’s often a question of time really.”
General Stages of Diagnosis	
Antenatally	E2: “some of those are picked up incidentally and antenatally”
General	E2: “they may have had a chromosome test for some reason, they may have had an amniocentesis has picked it up, or the genitalia may not be normal, but actually the most common reasons are learning difficulties and autism or something like that, … but tall stature may not be….”
Private referral	E3: “private referrals … presumably no-one is listening to the parents, they get frustrated”

E3: “the clues are there”

E3: “you know, Klinefelter’s could not be described as a rare condition”

Experts	
Stature	E3: “tall stature may not be an issue for quite a lot of people, they may end up at quite a normal height for the family and they’re even some children who are small with Klinefelter’s”

	E3: “it’s not unusual to see a Klinefelter’s boy who’s completely normal in terms of height”
Benefits of early diagnosis	E3: “at various points it makes things better for the kids, basically … early diagnosis can help you manage things better”

CHAPTER 5

RESULTS: GENERAL PRACTITIONERS

5.1. Introduction

The literature gives two reasons for the under-diagnosis of Klinefelter's Syndrome: variability of the syndrome and low awareness in general practitioners. However, there appears a striking paucity of evidence regarding awareness levels or the reported low awareness. For this reason, awareness and perceptions of Klinefelter's Syndrome in general practitioners were explored in this study with the aim of revealing insights into awareness and the possible role this may play in diagnosis, or under diagnosis, of the syndrome. Perceptions of general clinicians were identified as an important diagnostic factor by families (see Chapter 7) and are reported in the literature as having a key role in the diagnostic process.

A pattern of diagnostic difficulties was consistently reported by individuals and families for whom, despite experiencing frequent medical referrals for a constellation of medical problems, diagnosis of the underlying chromosomal condition eluded them. This caused not inconsiderable distress in a number of cases where later diagnosis was seen as unnecessarily delayed and this was seen as detrimental to the affected families (Chapter 7). General Practitioners are acknowledged as the initial gatekeepers for referral and treatment, being the first point of contact for most individuals or families when health or medical problems or queries arise. Therefore exploring the experiences and perceptions of General Practitioners was considered an important factor in understanding the context of when, how and why diagnosis may, or may not, occur in Klinefelter's Syndrome and if there was any evidence to support if this may have any bearing on the reported low awareness among general clinicians.

A qualitative approach was taken to explore the way in which GPs went about diagnosis and it was felt important to provide a freedom to express their views, avoiding building on current assumptions. Thus a list of questions was prepared in advance of discussions, the purpose of which was as an 'aide memoir' for the researcher, rather than as a script. The intention and subsequent approach was to provide the participants the freedom to control and direct the conversation. This was to elicit their views with minimum intervention from the researcher and to ensure continuity of key conversational topics, should these not be raised by the participant. This was done with the hope of providing an environment which may elicit the

views of the participants in their own words, un-swayed or encumbered by the researcher. Thus a flexible approach was taken to the interviews, whilst preparation was made to raise specific questions if these remained unaddressed by the participant in the natural course of the conversation; the emphasis was taken to encourage the participant to lead the conversation. A survey, or more structured interview approach, would have required second guessing what the reasons may be.

The General Practitioners were located in different regions, including the South of England, London and Wales.

5.2. Examining themes from interviews

Transcripts from interviews with GPs were analysed and five themes were identified from the transcripts as follows:

Table 9: GP themes

Theme	**Sub-theme(s)**
'A common condition, a rare diagnosis?'	Diagnostic challenges and awareness
‘It’s not my role’	Referral system Who diagnoses?
The System (Part 1)	Barriers to diagnosis
Getting diagnosed: how and why	Luck, persistence and private health insurance The System (Part 2): the value of diagnosis
The theme with no name	

5.3. Analysis of Interview Themes

5.3.1 ‘A common condition, a rare diagnosis’

There was strong evidence from the opening of the GP discussions that Klinefelter's Syndrome is simply, in their own words, 'not on a GPs radar':

GP4: *"It's very much under the radar, yes it is"*

GP2: *"it's not on our radar"*

Furthermore, when mentioned, Klinefelter's was unanimously thought to be a rare condition by the GPs. All the GPs reported that, if a condition is considered rare, this perceived rarity will further contribute to under diagnosis by reducing the possibility of a GP considering this during differential diagnosis:

GP4: *"I have never ever had a Klinefelter's patient"*

GP1: *"I think it's not something that's on my radar. Really. It's not on my radar"*

GP6: *"I've never had a Klinefelter's patient"*

GP5: *"well certainly from the perspective of diagnosing it, erm, it would have to be done, you'd have to have suspected it for starters, which would not be easy necessarily to do"*

In a sense, this misconception may cause a 'Catch 22' situation where a condition is not considered because it is thought to be rare, this subsequently contributes to under diagnosis as the GP does not think of it, which in turn perpetuates the perception that it is rare:

GP1: *"I don't think I've ever had a person with Klinefelter's that I know of and it's certainly not that common"*

GP5: *"I've not had a patient with this and it's not common"*

GP1: *"I think because it's actually quite rare I don't think it's up there on our differentials, to be honest"*

Logically following this perception of rarity was the perception, reported by all the GPs (with one exception), that they had not seen a Klinefelter's patient:

GP5: *"I have not had a case in my career"*

GP1: *"I don't think I've ever come across a patient with Klinefelter's in my career"*

NHS England report that 'the number of patients looked after by a GP varies but the average is around 1,800'. Given the reported incidence of Klinefelter's Syndrome is estimated to be between 1/450-1/660 (Verri et al., 2010) this seems unlikely. [3]

[3] https://www.healthcareers.nhs.uk/explore-roles/doctors/roles-doctors/general-practice-gp/working-life

On the contrary, statistically it would be likely that there would be between 5-10 Klinefelter's patients associated with the average GP practice at any one time.

When GPs were told during the course of the interview about incidence rates, they uniformly expressed surprise that it was far more common than they anticipated:

GP2: *"Well, it's relatively common then isn't it?"*

GP1: *"I'll be honest, that number surprises me"*

GP4: *"I was going to say which does sound far more common than I had sort of had a perception of and certainly that would mean I expect that I would have expected to have at least one or two patients in my career"*

GP5: *"I would have expected to meet one and I don't believe I did, which probably means I didn't recognise it when I did"*

GP7: *"I'm in a practice of 14,500 patients. I recall I had one patient with a diagnosis of Klinefelter's probably over 20 years ago … I'm not aware we have one now, I'm sure we probably do but I'm not aware of them"*

GP4: *"Wow"*

The GP reaction to the reported estimates in the literature of 64-75% being undiagnosed in their lifetime and 4% being diagnosed before the age of 10 years was a similar reaction of surprise:

GP1: *"4% is pretty poor isn't it, to get to puberty with only 4% diagnosed"*

The lack of awareness and extent of the knowledge of the GP group is apparent in their narratives when describing their understanding and contact with the syndrome, with several describing their 'contact' with Klinefelter's reduced to a question on a multiple-choice paper whilst at medical school:

GP4: *"it probably turned up on an MCQ question ... I'm sure Klinefelter's turned up under an MCQ question somewhere at med school"*

GP4: *"I'm sure if I had a patient come in who had already been diagnosed with it, I'd be quickly Googling it"*

GP6: *"Klinefelter's is something you vaguely hear about at med school … it's not something you usually hear about"*

There was one exception to the latter point with one GP reporting they had missed making the diagnosis in one patient and subsequently found out that the diagnosis was made by a colleague some 6 years later. The lack of GP awareness prompted the GP who described regret at missing the diagnosis of Klinefelter's in a patient:

GP5: *"well I, er, do have a regret, yes well you do regret if something isn't diagnosed … I regret that I haven't been able to change things at a stage that would have made somebody's quality of life better"*

The missed diagnosis was subsequently diagnosed 6 years later, leading the GP to ponder the how low awareness of Klinefelter's contributed to the missed diagnosis:

GP5: *"I don't know maybe if I had thought more about it as a potential condition, a serious potential condition for that young man then maybe I would have researched more and then maybe I would have pushed more."*

The response from the GPs was noticeable from initial responses and in the unanimous perception that:

(a) Klinefelter's Syndrome is rare

(b) A GP would not think of it as a diagnosis

(c) GPs reported they had never had a Klinefelter's patient, despite the fact that statistically it was highly likely that there would be a handful of Klinefelter's patients associated with most GP practices

(d) The combination of (a)-(c) created a Catch 22 situation which made diagnosis, especially early diagnosis, unlikely.

This striking consistency of opinion appears to confirm the accuracy of the reported low awareness in general clinicians in the literature.

The dominant and most significant theme in the GP group was low awareness, which echoed the low awareness reported in the literature. The low awareness set a context for the under-diagnosis universally reported for Klinefelter's by providing further insight into the process of

diagnosis, from initial differential diagnosis by the GP, through to the effect of the referral process, how and why a referral is made (or not) and what barriers exist to delay or prevent a diagnosis. All the factors involved in the process of diagnosis were significantly illuminated and informed by the perceptions of the GP group and set a context for the estimated rates that only 3/10 males with Klinefelter's are diagnosed in their lifetime and 4% diagnosed below the age of 10 years.

All the GPs reported they had not had a Klinefelter patient, although this seems improbable if the reported incidence of 1/450 - 1/600 is correct. This would appear to strengthen the case for significant under-diagnosis of Klinefelter's, as reported in the literature. All the GPs had been in general practice for many years (two having recently retired) which precludes newly qualified, or new to general practice, being a reason for lack of awareness of Klinefelter patients in their practice. The GP group agreed that they had not (knowingly) had a Klinefelter's patient. Their perceived lack of contact with Klinefelter's appeared to contribute to the condition not occurring to them when considering differential diagnosis, thus perpetuating the misconception that Klinefelter's is rare and, ironically, making the condition less likely to be diagnosed as the GP does not think of it.

5.3.2 'It's not my role'

GP3: *"you know there are a lot of conditions unfortunately that GPs, that we expect someone else to make that diagnosis"*

Having ascertained awareness of the GP group of Klinefelter's and the unanimous perception that this is a rare condition and unlikely to occur to a GP when considering a diagnosis, the discussion moved to think about when, or how, the GP thought diagnosis may occur. The GP group highlighted that to diagnose a condition, a GP must first think of it:

GP1: *"you must think of it to diagnose it"*

GP2: *"I'm wondering with Klinefelter's if just our radars' are not tuned to it"*

GP5: *"well certainly from the perspective of diagnosing it, erm, it would have to be done, you'd have to have suspected it for starters, which would not be easy necessarily to do"*

GP3: *"It's just unrecognised"*

GP5: *"would a GP think of it? I would think on average, no. I would have said no"*

These comments resonate strongly across the GP group: a GP simply does not think of Klinefelter's as a possible diagnosis at all. Moreover, the view of the GP was that this is not a condition they perceived as their role to diagnose, even if they were to think of it:

GP5: *"certainly diagnosis would not have been easy as a GP"*

GP4: *"no, it's not on my radar, so I think, I'd like to think that the people I'm referring to, it's on their radar"*

GP4: *"they would be diagnosed in secondary care, so I think that these type of people would be referred anyway"*

GP4: *"I think unless we're doing blood tests we're not specialised enough in primary care to decide whose got Klinefelter's and who hasn't"*

There is, it would seem from the testimony of this GP group, a low chance that general practitioners will recognise, or expect to diagnose, Klinefelter's Syndrome. For those health professionals who will diagnose the condition, the chances of an individual actually being referred to an appropriate expert is minimal. An appropriate GP referral for Klinefelter's Syndrome would be to a geneticist or an endocrinologist. However, as the GP narrative reveals, this referral would be unlikely to be made by the GP as they would have to think of Klinefelter's as a possible diagnosis to prompt them to refer to an endocrine or genetic team:

GP2: *"There's no point, you know, only a geneticist or an endocrinologist knowing about it because most people don't see an endocrinologist or a geneticist"*

This observation seems to strike at the heart of one of the diagnostic problems:

GP3: *"if you don't know about it, so we can't diagnose it"*

GP3: *"we're just not tuned to seeing it and because of under diagnosis we don't see it, we just don't see what's in front of us, really"*

Strikingly, this perspective is similarly expressed by the Specialist group, thus presenting an insight into diagnosis being unlikely to be made in either group.

The dialogue moved on from thinking about awareness to consider aspects of GPs as clinicians and how they perceived aspects of their role may further affect their patients. It was interesting that the GPs perceptions were that diagnosing a condition such as Klinefelter's is not a part of their remit, or role:

GP2: *"I'm guessing again it's something the paediatricians [would do] once we'd referred - then do a DNA testing"*

GP4: *"I think that you have to accept that you're a jack of all trades and that's what you're there for"*

It was interesting to note, however, that GPs may work, and respond differently, when presented with better-known conditions such as autism, where they felt significantly more confident about recognition and referral:

GP1: *"certainly if I thought it was autism, I might say it. I think I might feel more comfortable with that as a diagnosis whereas I don't feel certain with it, it's not something I'm familiar with, I would definitely go on the basis of referring for symptoms or features rather than necessarily the diagnosis itself"*

Taken together, the GPs perception of their role in the diagnostic process suggests that they feel that it is not their role to make a diagnosis of Klinefelter's Syndrome, particularly given that they perceive this to be a 'rare' condition which they have 'never encountered'. For diagnosis to be made depended on the referring practitioner in primary care to be sufficiently aware to make appropriate referrals for a Klinefelter's diagnosis. However, as the narratives of the GP group demonstrate, this is unlikely due to low awareness of the syndrome in primary care. This created a 'pass the parcel' mentality alongside the previously noted 'Catch 22' situation which resulted from lack of awareness of the condition; the combination of these two phenomena made diagnosis even less likely.

5.3.3 The System (Part 1): Barriers to Diagnosis

Perceived barriers to diagnosis notably included the health care system itself. This was revealed through a picture emerging from the GP descriptions when describing how the referral system in the NHS is structured and perceived demands placed upon a service under financial pressure.

5.3.3.1 Protecting over-stretched colleagues in secondary care

A significant factor for some in the GP group was the pressure they perceived they, as primary health care professionals, were under, including restrictive government budgets, increasing demand in terms of number of patients, less time per patient appointment and an increasingly system driven system with less personal autonomy. This latter perception contributed to a picture painted of an embattled service with increasing national demands from the government, healthcare systems and patients in parallel with decreasing health care budgets and increasingly restrictive practice with less perceived GP autonomy.

There was also a feeling of pressure described by the GPs and experienced across different aspects of their working life as an unspoken work factor, but significant to their decision making when considering a referral to specialist colleagues to minimise the demands on clinics and specialist centres. There was an expression of a duty to protect resources and over-stretched colleagues in secondary care:

GP4: *"we're like, they call GPs the policemen of the NHS in that we don't refer every single person to secondary care, we just wheedle out the ones that need to be"*

GP4: *"obviously the place to refer them would be to an endocrinologist but what the endocrinologists don't want is a load of people who potentially have got autism or ADHD or learning difficulties turning up at their endocrine clinics"*

5.3.3.2 Diagnosis – if not related to medical illness - is lost in the system

The role of the GP within the health service and how the GP group perceived their place in the system was revealing in identifying how the referral system works and the gaps they perceive are created by a fragmented and fractionated system of referral and patient care. This theme is explored further by looking at the GP descriptions and perceptions of existing barriers to diagnosis and begins to reveal a context for Klinefelter's as a diagnosis 'lost' in the system and invisible to the medical profession:

GP5: *"it's a very interesting thought that children who have been referred for speech and language or for this that and the other, erm, I think often that kind of diagnosis tended to get lost"*

GP5: *"it's lots of different things: one it's developmental and it's not illness and it tended to get lost and it was down the health visitors' side and not the GPs' side who might not have records of this"*

5.3.3.3 Variability or subtlety in presentation reduce the likelihood of diagnosis

"The phenotype is often unremarkable to the casual observer" (Geschwind & Dykens, 2004)

Geschwind's observation that Klinefelter's symptoms may be difficult to spot was borne out by the GPs in their narratives:

GP: *"Klinefelter's - you think there's nothing wrong - but there is"*

This echoes the feeling voiced by parents and their families that they feel 'something is wrong' but it is not recognised and they are not quite sure what it is that is wrong. It seems possible, therefore, that a lack of any obvious physical problems may be a significant factor in the lack of a GP recognising the possibility of an underlying condition:

GP1: *"I think things people think about, chromosomal things, disorders, depends slightly on presentation - they normally end up with some sort of visible abnormality as well"*

This comment from GP1 highlights GP expectations which may affect timely diagnosis as frequently the physical phenotype for a Klinefelter's male may be subtle in presentation. This, in parallel with lack of knowledge about the characteristic clues of Klinefelter's, may result in the GP missing the diagnostic opportunity:

GP2: *"a spectrum with subtle symptoms is unlikely to be diagnosed"*

In the first instance, often due to subtle presentation, the GP assessing the presenting problems which would likely be dismissed as over-anxious parental concerns, or lack of symptoms resulting in no recognition of any underlying condition. These assumptions resulted in a GP taking a 'wait and see' approach. The GPs described how they would wait for significant periods before taking any action:

GP1: *"if you are going to diagnose it as a GP you're not going to do it until they're quite a bit older … perhaps you know, you've already had quite a few problems by the time you start thinking about it, it's not going to be 'til 17, 18*

because you're going to earlier on be thinking 'oh well, it's a natural variant of normal'"

In some cases, GPs mentioned that there was a perceived value in waiting to see if problems resolved without referral or intervention. In the case of a diagnosis where presentation was subtle, this could result in a considerable diagnostic delay as alarming symptoms failed to emerge, with presentations explained away as a 'natural variant of normal' with a strategy to 'wait and see', letting nature 'take its' course'. These decisions may further delay referral:

GP5: *"even if things were getting towards a bit abnormal now, I still wouldn't say you know, let's wait until they're 16 and see how they are when they're 16 and be natural"*

As described by the only GP who had knowingly encountered a Klinefelter's patient resulting in a missed diagnosis, the oversight and delays, although justified by the GPs, was reported by the family as significantly prolonging the stress of coping without treatment caused by lack of diagnosis. In the case of the family described by the GP, diagnosis was delayed by 6 years, from first presentation at approximately 13 and eventually diagnosed at 19. This led to lack of treatment throughout the teenage years and abnormal puberty with associated psychosocial problems. The only GP in the group to have knowingly seen a Klinefelter's patient with this encounter resulted in the GP missing the diagnosis. The diagnosis was made by a colleague over 6 years later:

GP6: *"I had one patient with Klinefelter's … it was sat on and sat on by me for a while … yes sometimes that can happen … then he was referred on erm, nothing came of it and I think he was diagnosed after I retired … so it was a delayed diagnosis … He was diagnosed at 19, but he probably presented at about 13, 14, between 13 and 15 somewhere along those lines"*

To compound the delay, GPs stated that, even where a referral is made to secondary care, their belief is that the patient will be likely referred back to the GP with no diagnosis. This is perceived by the GP as a poor reflection on their professional judgement and, as commented is likely to deter the GP making the same referral again due to lack of confidence or professional pride:

GP6: *"even when you do refer on, they're likely to say, 'well you know this is normal', or, 'we're in the range of normal here'"*

GP4: *"which is why the GP won't refer because they'll just get shoved back at them which'll make them look incompetent"*

GP4: *"you would put the natural delay on, you would not actually refer to start with until you know, you were happy they were going to take it on, on the whole unless you had very pushy parents or perhaps private insurers or something like that"*

There seems to be an emerging pattern for some individuals where symptoms are sufficient for families to seek medical advice, but sufficiently subtle, or mild, that general practitioners describe they are likely to consider these symptoms 'normal' and within acceptable bands of normal development and therefore it is easy to see how no further action is taken at that stage. Despite multiple visits, the GPs describe they may conclude the family fall into the 'worried well' category, or the GP may refer on but is reluctant to do so where there is a lack of medical symptoms, or illness.

The lack of obvious 'out of the normal range' of symptoms were an example of how diagnosis can be delayed because presentation is noticed, but not considered of sufficient concern by health professionals to refer for chromosome testing. The GP group have an expectation of observable symptoms or illness, rather than something which may be difficult to discern. This combined with their own observations about their lack of knowledge and their misconception that the syndrome is rare, consequently not on their 'radar', makes diagnosis increasingly unlikely.

5.3.3.4 The importance of ‘being ill’

Where referral was made to paediatricians, this would not be considered an illness, rather, as developmental or behavioural and would likely be referred back to the GP (see Fractionation 1 pathway in Figure 4). Compounding the diagnostic conundrum in this instance would be the perception of the GP that this was a developmental problem, putting the problem out of the remit of their role:

GP5: *"I think as a GP.. a GP doesn’t do development"*

GP5: *"no they wouldn't diagnose, no they wouldn't, none of them, the GP would consider none of that anything to do with them, because, no of course they wouldn't because it's not an illness as such, it's different, you know it could be considered developmental"*

GP4: *"it wouldn't be my job to diagnose something like Klinefelter's. I think you have to have the suspicion, but you wouldn't be the person making the diagnosis"*

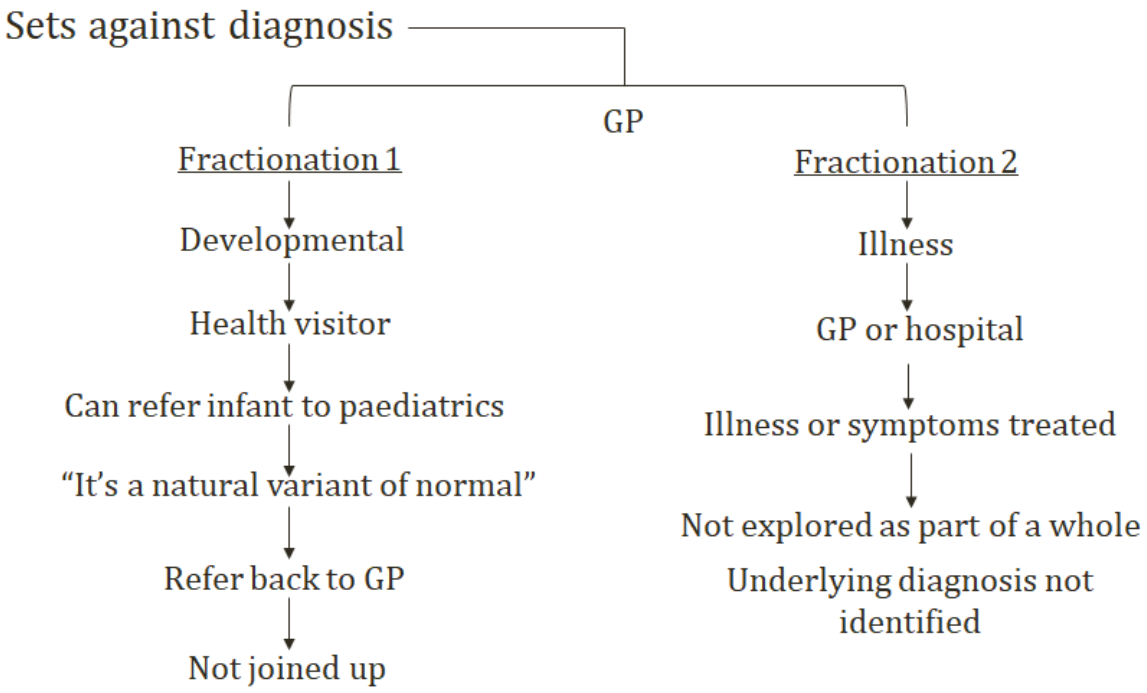
GP5: *"they may send them off to a psychologist, refer to family therapy or elsewhere"*

This process of referring on when the GP perceives the problems to be developmental or family issues rather than illness or medical is illuminating in identifying barriers to diagnosis. The decision of the GP to refer perceived behavioural or developmental problems away from a medical referral, choosing instead alternative, non-medical pathways would likely decrease the diagnosis being made as Klinefelter's is not an inherently developmental problem, but a systemic chromosomal disease. In other words, the likely presenting characteristics of a child with Klinefelter's Syndrome will not likely be recognised as symptomatic of an underlying medical condition. Rather, the presenting developmental or behavioural symptoms lead to subsequent referral away and out from the medical system, thus reducing the likelihood of a diagnosis being made.

This perhaps is part of the genesis of the lack of diagnosis in Klinefelter's, beginning, perhaps, with the first appointment contact with the GP:

GP7: *"er, yes, now, I think the thing to remember is that if somebody came to see me with a whole load of symptoms that might be Klinefelter's, I wouldn't even think of it"*

Figure 3: Difficult pathways and barriers to diagnosis when symptoms are presented to general practitioners



5.3.3.5 The System Structure and Diagnosis

The interviews with the GPs revealed the surprising situation where it would appear that often nobody will take responsibility for a patients' particular condition or diagnosis. The fractionated approach to diagnosis seems replicated in other medical settings and was important in revealing how the system seems to work in practice:

> GP1: *"it's extraordinary sometimes when you have a patient who's ill, you end up batting back and between one person and another to try and get somebody admitted … because the surgeons say that's a medical problem and the medical people say 'oh no that's a surgical problem' and you've got a patient who's ill and you're going backwards and forwards because nobody will take responsibility for a patient's particular condition"*

The influence of the system on diagnosis and how it is structured began to emerge and make sense of reasons why diagnosis may prove challenging, in addition to the low awareness of the GP. In terms of diagnosing Klinefelter's Syndrome, the conversations with the GP group

highlighted a context which describes a system that, due to the fractionated structure of the referral system, seems to work against a diagnosis being made.

5.3.3.6 Professional Confidence in Making Referrals

GP1: *"however, the mother came back and a referral was made to paediatricians … yes, that would have been a paediatrician, yes … said 'ok we'll ask somebody to see what they think' and they didn't think anything of it, either, they said: 'you know he's growing and he's an adolescent and that's what you might expect', yes, that would have been a paediatrician yes"*

Where referral is made and results in no diagnosis, the specialist was reported to refer back to the GP. The GP group reported this would make them significantly less likely to refer on again for a second opinion. Further there were reports by the GPs of their concerns that this may adversely affect their professional reputation:

GP6: *"I've had other conditions where I've been convinced that something's happening and I've been told 'oh don't be silly, dear'"*

GP4: *"I think with certain problems if you're pushed back once and told that 'no there's nothing to worry about' whatever it happens to be, then you're probably less inclined to present again, because, you know, you're a bit of a wimp"*

GP5: *"which is why the GP won't refer because they'll just get shoved back at them which'll make them look incompetent"*

The GP group made the point that there is no recognised referral pathway for Klinefelter's Syndrome and this is perceived to contribute to a missed diagnosis:

GP5: *"it's almost a hot potato and you're just chucking it somewhere else and hoping that will sort it"*

As the narratives of the GP group highlight, the lack of a recognised referral and care pathway negatively affects the diagnostic process in parallel with a change to the system. On referring to a consultant in the past, the consultant would refer on to the next step, if this was appropriate. However, where diagnosis is unclear or not made, the NHS now required that the specialist refer back to the GP. This change to the referral process is seen as unhelpful:

GP3: *"the system is geared to prevent, delay diagnosis"*

This again reinforces the view expressed by the Expert Group that, unless the presentation is obvious, there are minimal chances of Klinefelter's being correctly picked up. The GP group describe factors which may affect their reluctance to refer, such as parental persistence, picked up through chance, luck or if the family have private health cover. This view puts into context the experiences of the Family Group and provides a context for the low diagnosis rates.

The challenges to diagnosing Klinefelter's Syndrome described within the GP narratives appear to be exacerbated by the system structure, which is driven by referring for illness, medical symptoms and reacting to medical problems. The experiences of the GP group who work within the system highlight some of the ways the system itself can work against the diagnosis of Klinefelter's. The GP experiences and working approaches to the referral system brings into focus the context for which diagnosis can be easily overlooked.

Several factors and experiences of the way the system works were identified by the GP group, which they perceive may affect the diagnosis of Klinefelter's Syndrome.

These factors are summarised in the table below:

Table 10: Factors: diagnosis delay

Reason Number	Reason for Diagnosis Delay
1	Lack of awareness
2	Lack of recognition: No recognised physical signs Behavioural, not physical Subtle Not an illness Variation
3	"A natural variation of normal" Professional pride 'Wait and see'
4	Referral system Specialist will refer back to GP with no diagnosis GP anxieties: to be sure of symptoms and potential diagnosis before referring
5	NHS system: sets against diagnosis

Having explored some of the systemic factors affecting diagnosis, the discussions moved to think about getting diagnosed and how diagnosis, when it is made, may come about.

5.3.4 Getting Diagnosed: How and Why

5.3.4.1 Luck, persistence and private health insurance

GP2: *"Klinefelter's - you think there's nothing wrong - but there is"*

The GP Group agreed that where there are subtle, or non-specific symptoms, as is frequently reported to be the case with Klinefelter's, there is less chance of action being taken. The GP Group were in accord that a subtle presentation would be unlikely to be a cause for GP concern, and less likely to be referred and diagnosed:

GP3: *"if a subtle spectrum, non-specific symptoms, is more unlikely to be diagnosed ... if not observable"*

It was interesting that all described factors which may influence their reluctance to refer and result in a referral which otherwise would not have been made at that time. There were three

factors mentioned by the GP group which they identified would reduce their reluctance to refer. These factors were:

i). diagnosis through lucky happenstance where diagnosis of Klinefelter's was identified in the course of investigations for other symptoms.

ii). 'pushy parents'. There was agreement in the group narratives that, where parents were actively advocating for further testing, this would make the GP more likely to refer, than if the parents were not actively requesting referral.

iii). private health cover

These factors are explored in greater depth below.

Luck

GP6: *"I suspect more often than not, it comes out through luck really, not through any particular skills and yes, a co-incidental sort of something; it's on the periphery"*

Persistence

GP5: *"if a subtle spectrum - non-specific symptoms - is more unlikely to be diagnosed unless parents push for diagnosis, if it's not observable"*

GP4: *"I suspect … it's not the easiest thing to discuss … a child's long-term condition, unless the parents are almost particularly forceful there's something wrong"*

GP5: *"the parent would have to be quite insistent"*

Private Health Insurance

GP5: *"you would not actually refer to start with until you were happy they were going to take it on unless you had very pushy parents or perhaps private health insurance"*

Putting this into wider context, it was striking to note that the Family Group in this study reported luck, persistence and private health cover had been a factor in all the Family Group diagnoses made. In other words, for none of the families in this study was a referral made to

test for Klinefelter's. All were diagnosed in the course of referrals made for conditions and/or symptoms other than Klinefelter's. In the course of the investigations for other conditions, the Klinefelter's was found.

5.3.4.2. The System (Part 2): The value of diagnosis

Further discussion with the GP group elicited their thoughts and suggestions for changing perspectives in general practice in ways they suggested would be helpful in facilitating diagnosis. The group expressed ideas which supported and developed practical changes which may increase Klinefelter's diagnosis, having considered aspects of diagnostic benefits. These included the increasing use, and ease of, chromosomal testing.

The point was made by the GP group that a diagnosis of Klinefelter's has only recently been made possible through recent technological and medical advances. Before chromosomal testing was introduced, it would not have been a diagnosis which could have been possible. In this sense, Klinefelter's is a recent, a 'new' condition; before the advent of chromosomal testing, GPs would not be expected to diagnose this:

> GP5: *"nobody could ever find out in the past of course because there would never be any chromosomal tests"*

The system described by the GP Group highlights a system designed to react to symptoms and to cure illness. The advent of diagnostic discoveries, such as a 'new' condition as Klinefelter's, provides opportunities for preventative practice where the increased risks are known and can be screened for, providing the chance of timely treatment. To counter these opportunities, the GP Group have highlighted how the current system is not designed with these pro-active measures in mind. However, the GP group suggested ways in which they felt a diagnosis can be beneficial, transformative and how this may be increased in Klinefelter's:

> GP7: *"it's like all these things if you do have an underlying diagnosis it makes you more aware of the potential conditions that can occur … then, yes, one gets into screening and so on, on a regular basis"*

> GP2: *"All doctors love to practice preventative medicine. I mean, that's the goal"*

Conversely, lack of diagnosis was perceived as a limitation to the care the GP can offer as the underlying condition is not known:

GP7: *"quite a few GPs who say you shouldn't make a diagnosis, what you do is create a differential, but you don't actually hone in any further … the problem with that is if you don't make a diagnosis and you don't hone in any further, you can't set up a proper treatment plan"*

GPs felt that diagnosis could better inform their management and treatment of a patient, providing them with a context from which to plan for a preventative approach:

GP7: *"yes, you look at the conditions they're prone to and you say 'we can alter this and then you look at the things you can alter … maybe doing yearly screening for their thyroid and, you know, doing hormone checks and the like because that may make a difference"*

GP7: *"what you have to do is learn to manage it, now certainly, if Klinefelter's has medical implications so they are much more prone to certain disease entities then actually the knowledge of that is important because what you can then do is counsel 'look, you are more likely to get this and this and we need to do everything we can to help you manage not to get it or to deal with it'"*

This proactive, preventative approach was advocated by the GP group to maximise quality of life, not only through early planned medical screening and intervention, but they were also advocating diagnosis as an effective empowering conduit for the patient through self-knowledge and encouraging personal responsibility:

GP1: *"Men don't want to see a doctor, having a diagnosis means they are more likely to see a doctor or take their health seriously and understand their condition"*

GP7: *"I … I suppose it ultimately goes down to the sort of thoughts of life and the whole of life is a calculated risk and it's up to each individual to lower their risk as much as possible"*

GP7: *"where does diagnosis sit in this? Does it aid the individual to self-manage their own health and wellbeing better? Does lack of diagnosis deny this?"*

GP7: *"does knowledge of diagnosis enable individuals to take more personal responsibility for health and wellbeing?"*

There were contrasting perceptions about the value of diagnosis and there were suggestions that help and support would be forthcoming without a diagnosis and questioning what benefit diagnosis would offer:

GP4: *"I suppose it depends on what we do with the information, I mean if we diagnose somebody with Klinefelter's where do they go? Is there – I'm asking you now – is there treatment?"*

GP4: *"yes the diagnosis is important once they get to puberty, but that's relevant to them but up to that point I guess it's just help and stuff, then there's so much available now"*

There was also a perceptible anxiety about defensive medicine where missing a diagnosis may have legal implications for a GP or loss of patient trust as a result of missed diagnosis:

GP4: *"I think definitely, yes, particularly as we're in an age of where everybody is looking to sue you for something or other if you missed"*

GP5: *"I can imagine that it would be quite difficult because if they've had to fight, you know, could see a lot of doctors who perhaps poo-pooed their concerns, by the time they get a diagnosis they're probably quite angry about the whole thing and are very, quite distrustful of doctors and professionals by that time which would certainly not help them or the child in the future even if it's a perfectly valid perception"*

However, there was unequivocal support for finding ways to change the Klinefelter's diagnostic status quo and an interest across the GP Group to access more information. There was also recognition for emotional or underlying, less tangible patient benefits:

GP5: *"and having a diagnosis can give reassurance"*

There was a feeling mentioned in different ways, and linked to different themes, that there was a GP perception that the service was compromised and the possible implications to costs of diagnosis and treatment:

GP1: *"due to struggling budget and the need to reduce expenditure"*

GP5: *"if you can diagnose people earlier quite honestly in the end you will probably save money rather than spend money in the end"*

GP7: *"a factor whether or not you would diagnose something early is whether it is treatable whether it is preventable and how much it would cost to do, what benefit you would get from the diagnosis"*

New ways of thinking and new approaches were topics raised by all the GP Group, with the observation that, as health professionals, they are the only group to receive all the patients' letters and the implications this may have for addressing diagnosis:

GP2: *"no one else gets all the letters, the GP is the only person who sees every letter"*

GP3: *"The big picture is our job, our jobs as a GP to practice holistically and perhaps we're fairly well placed to be co-ordinating things like this, like we do with other illnesses as well"*

GP2: *"if you think, this person has had all those symptoms, could it be Klinefelter's ... quite often it's the GP that's seen all of the letters from the referrals and puts them all together"*

For the GP group who revealed these ideas, and the implications of the GP being uniquely placed to take a joined up, holistic perspective for treatment and diagnosis gave the GP the opportunity to perceive a patient differently, taking a holistic perspective by reading through the medical background as one life, rather than a series of unrelated symptoms. This was seen as a potential way forward, rather than the traditional approach:

GP1: *"I would definitely go on the basis I was of referring for symptoms or features rather than necessarily the diagnosis itself ... you would refer by symptoms than by what you thought the condition was everyone gets triaged by them"*

5.3.5 An intrinsic value? “The theme with no name”

There were interesting hints through some of the narratives which wove through the GP conversations suggesting more fundamental benefits of diagnosis. On closer analysis, these

tendrils had shared underlying thoughts and feelings. The notion that diagnosis may have an intrinsic importance was implied by GP suggestions that diagnosis may impact on the individual by affecting their understanding of themselves, providing insights, or answers, to affected individuals. In other words, even where there were subtle symptoms, there was acknowledgement from the GP group that the value in diagnosis lay in information which may provide answers for affected individuals and their families, greater insight, understanding or self-knowledge and were of a more abstract nature. These thoughts are hinted at through the narratives:

GP7: *"I suppose it ultimately goes down to the sort of thoughts of life and the whole of life is a calculated risk and it's up to each individual to lower their risk as much as possible"*

5.3.6 Ways forward

A limitation of the current system was identified to be an absence of screening prompts and the benefits of screening the whole population was not thought to be workable at the current time. That there are identifiable characteristics which may be helpful for diagnosis was welcomed by the GP group. There was interest in diagnostic 'prompts' or tools and a consensus that a diagnostic prompt would be useful. The advantage of a model, or diagnostic prompt, was also thought to be helpful in providing an appropriate screening prompt as it distinguishes a population for testing, drawn together by shared core prompts:

GP5: *"well I would have thought that would have been the kind of time where you could have had a blood test done relatively easily because now you've got a select population, rather than the whole population"*

GP4: *"A prompt would be useful, a tool, like anything to prompt you to think about it"*

GP5: *"now you've got a select population"*

The GP group also highlighted current diagnostic routes, currently either a referral for symptoms or illness, often to a paediatrician. For developmental referrals, these are ordinarily made to the health visitor, which is a non-diagnostic referral. The explanation of the structure of the healthcare system made sense of some of the diagnostic difficulties reported in the literature and by families:

GP3: *"yes but you think of Klinefelter's you think of an adult mainly because we think of most medical issues as thinking of adults unless they are paediatric conditions"*

GP3: *"All the DoH, PCT want to know is: 'if I were to pay an extra amount for this test would it make' - ultimately the end game - 'would it make a difference to this person's life if this person had a diagnosis of Klinefelter's, would it change anything?'"*

There was a striking accord within the GP group on issues around perceptions of Klinefelter's being rare and there was evidence for the GP group in this study that their knowledge of Klinefelter's was low. The GPs suggested ways to increase awareness, with education and training mentioned by all the group:

GP4: *"a training case or an article or something that just brings it to the forefront of people's minds … if it's in the forefront of your mind then people will diagnose it"*

GP6: *"I think probably it would be a good thing to have as a part of just general GP education I mean it should be … it should come up in the undergraduate course as something to consider and perhaps to put in a slightly stronger light"*

The GP group agreed that increasing awareness was important and made several suggestions they felt may be helpful to increase diagnosis. There was also consensus that taking a holistic perspective would be valuable:

GP1: *"I think it's short sighted to see everything as just individual problems … you need somebody who's looking at the overall thing ... with children it's usually the parents with gut instinct that something's not right"*

GP1: *"what people need is a co-ordinator who says 'well hang on a minute, this isn't quite right' … Somebody as the co-ordinator as somebody who is looking at the overall dynamics"*

GP2: *"The big picture is our job, our jobs as a GP to practice holistically and perhaps we're fairly well placed to be co-ordinating things like this, like we do with other illnesses as well"*

GP3: *"if you think, this person has had all those symptoms, could it be Klinefelter's ... quite often it's the GP that's seen all of the letters from the referrals and puts them all together"*

Other suggestions included on-line prompts such as drop-down boxes, or system prompts for reference when diagnosing:

GP1: *"something that prompts the GP when GPs type in 'developmental delay'"*

5.4. Summary

In summary, the GP Group were unanimous at the opening of their narratives that Klinefelter's Syndrome is a rare condition which would not occur to them when diagnosing a patient. Further, they did not consider it their role to diagnose Klinefelter's, considering it rather the role of the specialist in secondary care. The subtle 'unremarkable phenotype' commonly expressed in Klinefelter's males was observed to cause the GP Group to not recognise there was a problem, partly due to the subtle indicators, and partly due to the system structure, which is designed primarily to be reactive and symptom driven.

If presented with a Klinefelter male, the GP group expressed the view that delays would be common with a referral not a likely outcome. Anxious parents or individuals were frequently reassured by the GP that their symptoms were not indicative of any diagnosis, being told:

GP5: *"we're in the range of normal here"*

GP6: *"Mum had been worrying about every little thing and had been all along ever since they were sort of, that high, and so the gynocomastia was something that you initially say 'you don't need to worry about that'"*

The GP group were surprised by the estimated rates of incidence which they felt were much higher than they believed. Ways of supporting GPs in increasing diagnosis were discussed and there was uniform support for increased training and awareness for GPs and medical students. Other ways to support GPs in diagnosing were suggestions for online prompts and a model, or diagnostic protocol.

The value of a diagnosis was discussed from various facets and these included diagnosis as benefits the treatment of the patient through anticipatory management, a holistic approach through new ways of approaching care and raising awareness. The GP group made the point that, as generalists, they are uniquely placed to take a holistic view, being the only health professionals to see all the letters from other health professionals. This gives them, in their view, a powerful insight into the 'whole person' in patient care and diagnosis:

GP2: *"The big picture is our job, our jobs as a GP to practice holistically and perhaps we're fairly well placed to be co-ordinating things like this, like we do with other illnesses as well"*

Diagnosis was seen as beneficial on a wider societal scale, as well as beneficial to the individual:

GP6: *"on the whole money is a factor and if you can prevent something by diagnosing it early then it is worth doing, as well as for the suffering and everything else, it's clearly worth doing"*

GP3: *"if you can diagnose earlier quite honestly in the end you will probably save money rather than spend money in the end because you're going to save trouble in certain areas - more social saving and health spending"*

Despite having to accept the limitations of their role, the GP group felt this may also be a strength in providing an important holistic insight into patient care and diagnosis. The closing thought was echoed in different words by all the GP group about the need to raise awareness of Klinefelter's Syndrome in GPs and, in this sense, the group provided a compelling insight into the low awareness of general clinicians reported in the literature.

GP2: *"I think the first thing before you even start to educate the public would be to educate the doctors"*

CHAPTER 6

RESULTS: SPECIALISTS

6.1 Introduction

The Expert and Specialist group were interviewed to explore their perceptions and awareness of Klinefelter's. Referral mechanisms were explored with a particular focus on the processes and factors affecting diagnosis of Klinefelter's beyond primary care.

Klinefelter's males are reported to experience increased hospital admission rates of an estimated 70% in parallel with frequent contact with health professionals for an array of health and medical conditions. Each of these conditions has the potential to result in a referral to the relevant specialist for the health problem arising. If this is the case, this would suggest multiple opportunities for health professionals, specialising across a range of disciplines, who are likely to come into contact with Klinefelter's males.

As consistently reported, a Klinefelter's diagnosis remains, for most, unidentified through the patients' lifespan. This study sought to explore possible reasons for this with a group of specialists who were interviewed and were health professionals in specialities more likely to see Klinefelter patients resulting from primary referrals to treat an array of symptoms, irrespective of the underlying Klinefelter's Syndrome being diagnosed. Exploring factors influencing the possible diagnosis of Klinefelter's Syndrome, following a referral from primary care, was expected to provide insights into how and when Klinefelter's may be diagnosed beyond primary care. Low awareness in general clinicians is universally reported in the literature to significantly contribute to low diagnosis rates (Bourke et al., 2014). Following on from these claims, anecdotal reports from affected families claim diagnostic difficulties, sometimes causing significant delays to receiving diagnosis. For these reasons, an exploration of perspectives with a group of specialists was felt to be particularly valuable in the context of the research question.

All the Specialists are experts in a variety of the increased risk areas more likely to be experienced by Klinefelter males compared to non-Klinefelter males. These areas are categorised in a 'cluster' of health problems (the Expert DCG 1) which Klinefelter's males are reported to be at increased risk.

A number of the specialist areas can be reasonably expected to have expertise in treating Klinefelter patients as these are known to be areas of referral for a patient with the diagnosis (fertility, for example).

Table 11: Specialists' in this study experienced in a multi-disciplinary treatment approach for Klinefelter's patients

Specialist	**Abbreviation**	**Experience with treating Klinefelter's patient**
Dietician	DIT	✓
Fertility	FRT	
Gastroenterologist	GST	✓
Physiotherapist	PHY	✓
Speech and Language Therapist	SLT	✓
Urologist	URL	

6.2 Themes from Interviews

As previously, themes for interviews were extracted using thematic analysis. Five themes emerged from the interviews with the Specialist Group. Some of these were commonly held with other groups (Theme 1: resonated with the GP and Specialist groups; Theme 2 with the GP group). The themes were as follows:

Table 12: Table of themes from participant specialists

Theme	Sub-themes
'A common condition: a rare diagnosis.'	Awareness and diagnosis The Invisible Syndrome: "it doesn't really exist as a speciality"
The System (Part 2)'It's Not My Role'	Getting diagnosed: how and why
Lack of a diagnostic pathway	The need for a Klinefelter's pathway; a holistic approach
The Self	

6.3 Analysis of Interview Themes

Each theme identified in Section 2 is discussed in further detail below.

6.3.1 'A common condition, a rare diagnosis'

"It doesn't really exist as a speciality"

The Specialist and GP Groups had a shared response when asked about their perceptions of Klinefelter's Syndrome. Both groups felt that the condition was not one they were familiar:

PHY: *"I must admit I'd never heard of it before"*

GST: *"I'm sure that some of my colleagues have never seen, or don't think they've seen, Klinefelter's patients in the past"*

SLT: *"I don't think Klinefelter's would be one that would ring many bells with us"*

SLT: *"It's not well known, I doubt it would have a lot of time spent on it as a difficulty, as opposed to other diagnosis"*

The Specialist Group's perceptions also echoed the GP Group who highlighted the idea that certain conditions are of more current interest and are consequently more likely to receive attention for professional development and training. In contrast, conditions which are not of current interest are identified as being less likely to be recognised by health professionals:

SLT: *"we as a profession forget about that diagnosis [Klinefelter's Syndrome] because it's got a low profile currently, so I suppose it's not in our consciousness in the same way we might be looking at other things … I think we're all primed these days to think about autism and ADHD, very primed for that, it's front of our minds … it's just not on our radar"*

Speech and language problems are not uncommon in Klinefelter's males and intervention by a speech and language therapist is regarded to be beneficial for some. A revealing comment was made by the speech and language therapist who suggested that another reason why Klinefelter's may not be diagnosed is because it may be confused with other conditions which are considered to be common, such as Autism (ASD) and ADHD. The Speech Therapist suggested an incorrect diagnosis such as Autism may be made for Klinefelter's. This 'masking' of the correct diagnosis by another, better known condition was felt to be a possible factor in confounding diagnosis:

SLT: *"I don't think we'd probably pick up on the different pieces or we might mistake it for ASD … I could see a lot of false positives with ASD arising … that one diagnosis (ASD) could hide others or it could be an erroneous diagnosis and masking what was actually something else … so the whole physical thing is missed"*

The suggestion is that this diminished attention may impact on recognition, not being 'front of mind', and consequently, diagnosis. Perceptions of low awareness of the condition and low knowledge about the phenotype and potential impacts were also held in common between Specialists and GPs.

There was also interest in knowing more information around the impact of Klinefelter's from some in the Specialist Group where specific questions around their own understanding or recollections were asked:

FRT: *"do many patients with Klinefelter's have learning disorders?"*

FRT: *"they're more likely to be bigger build, aren't they?"*

FRT: *"is there something about prisons?"*

Similarly, there was a shared Specialist Group perception with the GPs that Klinefelter's is a rare condition. As with the GP group, the condition was not only thought to be rare, but there was again surprise at the reported prevalence:

DIT: *"I thought it would be more like 1/5,000"*

Similarly, there was a shared perception that the Specialists would not expect to see, or have seen, many Klinefelter's patient's, which is reflected in their comments when describing their contact:

GST: *"we tend to only have a few per clinic, so it is not many I would see"*

DIT: *"very little that I know but I've got very little direct experience in the field"*

SLT: *"I think that my profession would very rarely be aware of a diagnosis"*

PHY: *"if I hear of a random condition (like Klinefelter's) I'll do a bit of reading"*

Surprisingly the Specialist Group did not expect that they would be made aware of a diagnosis of Klinefelter's Syndrome when they are treating a patient where the diagnosis had been made. Further, the Group were clear, that for all, except the fertility expert, there would be no expectation that they would make the diagnosis, even in the rare circumstance where they may suspect it. In that instance, they may (perhaps) refer back to the GP.

Within the Specialist Group there was agreement that the Specialists were symptom, or illness, driven. There was consensus that diagnosis of underlying conditions such as Klinefelter's was not considered to be within the remit of their area of speciality. The diagnosis, or not, of Klinefelter's was regarded to be of no importance:

GST: *"it's a wholly incidental thing"*

That the Klinefelter's diagnosis is seen as not of relevance to the Specialist Group was surprising and indicates that there may be a perception that the diagnosis does not have a more generalised impact which may be relevant to treatment and care of a Klinefelter's patient, which was in contrast with the opinions expressed by individuals and families (Chapter 7, page 155).

At other points during the interviews this viewpoint was tempered by a recognition that there is poor understanding of how Klinefelter's may cause or interact with different conditions or symptoms. This was felt to be an important oversight:

GST: *"it's very important, because I think if there's no realisation there's any increased risk of issues then people will not deal with them or recognise them"*

GST: *"I think one important question is what's my impression of the knowledge of Klinefelter's in gastroenterology consultants … ? ... basically zero"*

The need for a more joined up approach, making connections between individual symptoms and Klinefelter's Syndrome, was expressed where Specialists had previous, or current, experience of treating Klinefelter's patients:

GST: *"I still come back to what I said originally which is that it's the understanding first as a gastroenterologist, because some of my colleagues don't understand this connection … you need understanding on both sides because I'm sure that some of my colleagues have never seen, or don't think they've seen, any Klinefelter's patients in the past"*

Their awareness of the syndrome was identified as significant to informing their treatment approach which was driven by not treating symptoms in isolation for Klinefelter patients.

A comment made by the Speech and Language Therapist highlighted the reliance on waiting for symptoms and difficulties to emerge, rather than early preventative screening, increased the time taken to arrive at a diagnosis which was seen as the main opportunity to put support and treatments in place in a timely fashion, rather than waiting for symptoms to appear:

SLT: *"they're always on the back foot everyone's on the back foot because everything's post diagnostic isn't it, rather than people being on the look-out for that being present and then putting in measures to support everything's on the back foot because it's sort of waiting for the child to have a difficulty and for that difficulty to be noticed by the right person … it's all loaded to be missed isn't it"*

Where Klinefelter indicators go unrecognised, this means that opportunities for support, particularly early preventative care, are often missed.

To summarise, the Specialist Group were in accord with the views expressed by General Practitioners that low awareness contributes to low diagnosis which, in turn, reinforces the misapprehension that Klinefelter's is rare. This perpetuates the under diagnosis as the diagnosis is rarely made and therefore is not thought of by those well placed to diagnose the condition. This, again, seems to perpetuate the 'Catch 22' diagnostic challenge described by the GP group:

URL: *"the primary issues … is having it in your mind in the first place … it's probably the case for diagnosis like Klinefelter's gradually slip to the back of your mind until you see someone with it and then it comes to the front again"*

Taken together, these issues suggest a 'whole person' approach to treatment would be beneficial, rather than seeing Klinefelter's Syndrome as something which was incidental to the primary focus on treating referred symptoms.

6.3.2 'It's not my role': Pass the parcel

SLT: *"well, it's all loaded to be missed isn't it"*

The Specialists generally agreed that someone other than the Specialist would diagnose:

URL: *"it wouldn't be a terribly common diagnosis for a urologist to make um, I've been a consultant 10 years, have I made any new diagnosis that haven't been diagnosed by a health professional previously - maybe once or twice"*

The Specialist Group reported also that diagnosis of a medical condition, such as Klinefelter's, would not be a condition they would expect to diagnose:

SLT: *"I suppose maybe there's an aspect of assuming that medically it would have been spotted … because there is quite an array of physical needs and so I suppose we'd sort of think that signs of symptoms would have presented and that would have been one of the things that was looked at and so our medical colleagues somewhere would have already been dealing with that"*

There were differing views about expecting Klinefelter's referrals, with some expecting referrals for Klinefelter's patients, but others not anticipating a link between Klinefelter's and their area of expertise:

URL: *"there wouldn't normally be a referral reason for a referral to a urologist" (for Klinefelter's).*

URL: *"It wouldn't be my primary responsibility to make that diagnosis"*

PHY: *"that's part of the problem, it's not ignorance, it's more what can I do about it? ... I guess I could go back and report back to the GP and say 'by the way so and so has got those symptoms, these correlate with symptoms such as this. If you want to consider something further, go for it"*

From the narratives of the Specialists, there was an expectation that a diagnosis would have been made before referral. This was surprising within the context of the GP Group who also perceive that making a diagnosis is not their role either. The question therefore of considering who is responsible for making a diagnosis seems unavoidable. It would appear that both the GP and the Specialist Groups work on the basis that a diagnosis (if there is one) would have been made by someone other than them. This perhaps contributes to the Klinefelter's diagnostic conundrum:

SLT: *"I suppose maybe we'd just expect something like that might have come up already and if it hasn't there's an aspect of assuming that medically it would have been spotted"*

URL: *"I think to myself I'm recognising something here, but this is not my primary responsibility then I would put that in my letter for the GP to deal with"*

If the Specialist did suspect an undiagnosed condition, they were likely to refer this back to the GP who, from the narratives in the GP group, explain that diagnosis is not a role of a general practitioner, or primary health care. This 'pass the parcel' approach was apparent through the narrative descriptions of diagnosis where a diagnosis was assumed to have been made before seeing each particular Specialist, but the diagnosis was not considered to be the role of the Specialist either. Similarly, the GP does not expect to make this diagnosis in primary care and, in the event of the Specialist referring back to primary care with no diagnosis, the GPs state they assume there is no diagnosis to be made. In this climate of a diagnostic 'pass the parcel', low diagnosis rates or delayed diagnosis seem inevitable for many. Taken in the context of the frequent contact with medical professionals reported by Klinefelter families and their surprise the diagnosis was not made during the course of one of

those referrals, the Specialist narratives are helpful in understanding how and why, despite multiple referrals, diagnosis was not made.

6.3.3 Lack of a diagnostic pathway for Klinefelter's Syndrome

6.3.3.1 The need for a pathway to avoid a fragmented approach

The problematic conundrum of who exactly would diagnose Klinefelter's was explored further in the narratives of the GPs in parallel with the Specialist observation that a lack of formalised pathway played a significant part in diagnostic 'cul-de-sacs':

> URL: *"diagnosis is fragmented … because presentation is non streamlined … there's huge variance, there's no standardisation of the diagnostic process"*

The Specialist group describe the fractionated approach where each specialism is treated in isolation, rather than taking a 'joined up' approach:

> GST: *"a lot of doctors would then go into their sub-speciality and won't be thinking about that there could be any cross over with their speciality, so gastroenterology is definitely one of them"*

Without a clear or formalised pathway for diagnosis or treatment, and an expectation among the Specialist and GP Groups that diagnosis was not their role, there appeared to be a lack of diagnostic clarity or diagnostic ownership, with the lack of a formal diagnostic pathway, which was compounded by the lack of recognition of a specialism to which Klinefelter's individuals may be referred:

> GST: *"there don't tend to be individuals with an expertise in Klinefelter's … it doesn't really exist as a speciality"*

No one perceived themselves to be responsible for making a Klinefelter's diagnosis. Furthermore, even those who know of the condition consider that somebody else will have made the diagnosis, if there is a diagnosis to be made. This approach seems to provide a context for the frequent contact with health professionals and multiple referrals described by the Family Group and sets a context revealing why diagnosis was not made as a result of these multiple referrals. Indeed, some recognised the fractionated approach as being systemic, part of the structure of health care in the NHS:

PHY: *"the NHS was designed on a medicinal approach and that's why we have such separate entities … I've seen so many people in the past, they've seen this person, this person but trying to collaborate that isn't possible, you need to get to the pathways so in a way you're trying to create a pathway for Klinefelter's"*

It is interesting to note that Klinefelter's Syndrome, where it is diagnosed, may be diagnosed in adult years due to infertility usually caused by the syndrome. Infertility, unlike Klinefelter's Syndrome, follows a conventional medical referral pathway, being referred to secondary care as a medical, symptom-driven problem. Infertility is well reported to be a problem for the majority of Klinefelter males and fertility problems are reported to be the main reason to prompt adult diagnosis. For these reasons, awareness of, and diagnosis of, Klinefelter's by a fertility expert is to be anticipated. Notably, the fertility expert was one of the experts who expressed familiarity with Klinefelter's and was the only Specialist who expected to make diagnoses of the condition in the course of his role:

FRT: *"mainly because we're doing chromosomes for fertility issues. Not in any way that we're suspicious of it but it's more the certain types of fertility investigations that we would do a chromosome analysis"*

Fertility is the only discipline which routinely tests chromosomes; the remaining Specialists do not necessarily conduct the testing which would reveal the underlying condition. Therefore, symptoms are treated without making the diagnosis of Klinefelter's Syndrome:

GST: *"some of my colleagues don't understand this connection … you need understanding on both sides because I'm sure that some of my colleagues have never seen, or don't think they've seen, any Klinefelter's patients in the past."*

6.3.4 The value of diagnosis

FRT: *"a lot of people get frustrated when we can't come up with a diagnosis"*

Some Specialists recognised the frustration which both individuals and families felt when they were not able to make a diagnosis. Specialists who had, or were, treating Klinefelter's patients more regularly felt that diagnosis, and specifically early diagnosis, was important:

SLT: *"absolutely I think this needs to be diagnosed earlier … my profession yes, would have a huge amount to contribute … it would be those type of augmentative alternative communication systems"*

Diagnosis was, as with the Expert and GP Groups, perceived to be valuable in providing an understanding for patients and a context for other symptoms. There was a suggestion that this was seen as beneficial in providing reassurance to patients:

GST: *"for the patient themselves to understand the connection that this isn't all in their heads, this is something associated with their condition because then they can deal with that … with the knowledge that some of these symptoms that they suffer can be associated with the underlying chromosomal disorder"*

There was recognition that diagnosis may cause feelings of losses and gains, with a constellation of conflicting emotions resulting from the diagnosis. This mixture of feelings was aptly described by the fertility specialist:

FRT: *"they need to talk it through, um yes, some there is quite a shock because it's an absolute, it's quite black and white … I tend to see them only once, they may be referred on"*

FRT: *"some people may have relief we've diagnosed something um, surprised … I think most people have never heard of it so therefore again you are telling them something which is going out of one's territory … so it's true to say surprised, but lack of understanding of it"*

The frustration felt at a lack of diagnosis may be followed by a feeling of shock, not least at the definitive nature of a diagnosis following a long period of uncertainty and lack of knowing, but also of surprise and a lack of understanding of a condition they are very unlikely to have heard of.

This initial mixture of feelings may be followed by a feeling of relief, which the Family Group refer to this either directly or indirectly in their narratives. It is interesting to consider that, on closer consideration, this may appear a contradictory reaction to a diagnosis which confers the possibility of significant impacts, and the potential for negative impacts on daily life, for the individual and their family, and the question: 'Why would anyone be relieved at being diagnosed with Klinefelter's Syndrome?'. One way of understanding this may be that

for individuals and families it provides a reason for 'the way things are' and provides a context for some aspects of the patients' life. Diagnosis can bring feelings of relief and validation to family suspicions that something was 'not quite right':

PHY: *"you get some people who strive for answers you can't get it because it's an unknown entity and so they get more and more frustrated and it can actually make the condition worse … so it's having a basis and an understanding of what's wrong and having that diagnosis can be very beneficial"*

In this context, diagnosis may be perceived as sense making, or a vindication for instinctive concerns that there is a problem which can now be addressed and explained:

GST: *"it's a question of saying well these things are associated, they're not going to shorten your life … but I can understand they can have a significant effect on morbidity, on your quality of life and therefore we need to pay attention as best we can"*

The contribution of diagnosis beyond providing preventative medical interventions, such as screening and treatment, was also described by those Specialists who had personal experience of providing this treatment approach for Klinefelter's patients:

GST: *"the most important intervention from my point of view is that someone with Klinefelter's has more … control and more ownership of the symptoms that they don't panic about things that happen and they understand that there are things that can be done … the symptoms can be managed and they can be associated with having Klinefelter's in the first place"*

Specialists also realised that the relief individuals and families felt at diagnosis came from a sense of validation at having pursued a diagnosis and that they were being taken seriously:

FRT: *"I suppose seeing a fertility expert saying … It's not just some endocrinologist saying … poo pooing it - it's taking it seriously … we're validating it"*

The Specialists, as with the GP Group, acknowledge that, for some, diagnosis is significant for conferring a sense of identity and the 'self':

SLT: *"you're supporting social interaction, you're supporting understanding of self"*

Even more nuanced appreciations of the impact of diagnosis were apparent where the complex interaction of the personality of the individual, their presenting symptoms and their diagnosis was considered:

SLT: *"and personality, I think in both situations (ASD and Klinefelter's) both diagnosis it's the interplay between personality of the individual and the ASD so what the effect of the ASD on the individual and what effect of the individual is on the diagnosis for ASD, I'm sure there's just as complicated a relationship with Klinefelter's so there's the effect of the Klinefelter's on the individual and there's the effect of the individual on the presentation of the Klinefelter's"*

Some specialists felt that, when an early diagnosis was made, parents had the opportunity to provide better support for their children and that this often had an impact on their sense of 'self':

SLT: *"what his mother did from early on, she'd found an effective way to communicate with the little figurines so he actively had input to avoid a huge amount of frustration where adaptive behaviours could have built up barriers - that didn't happen because his mother implemented really effective things when he was tiny and she gave him a voice"*

SLT: *"she found an effective communication channel and so she averted a whole load of frustration and helped him develop a sense of self, so he was able to be an effective communicating agent in the environment, so if you speak to educational psychologists or child psychiatrists they will tell you what she did was she supported him … facilitated a sense of self at a very young age that could not have developed like that and I think that's a really important area"*

The importance of diagnosis, and its impact beyond the individual, were also important. These were particularly marked when considering the effect of lack of fertility on others. Diagnosis results from a fertility referral were reported as often made with the individual and their partner. The diagnosis therefore impacts directly on both individuals:

FRT: *"oh most of them come with their partner and … a huge impact on fertility"*

This aspect of Klinefelter's Syndrome revisits the theme of Klinefelter's being a family, or shared, diagnosis: for those diagnosed in childhood, there were implications for parents and siblings as well as for the individual with implications for all stages of life. For those diagnosed as adults the diagnosis affected future choices for building their own biological family. In this sense, it is commonly a shared diagnosis, whatever the age at diagnosis:

FRT: *"the implications on fertility and have they talked it through? Now you can't talk it through with a 10 year old … and things change. They may say 'oh yes I'm quite happy to think about donor sperm' but there's two people in the discussion and their partner may not be. Do they tell their partner? When do they tell their partner?"*

The Family Group also raised the issues around fertility and how to manage their own, and any future partner's, feelings around this. There was recognition that this was a sensitive and potentially difficult area to cope with and there seems currently little or no support for this aspect of the syndrome. The value, or benefit, of having professional support for matters of fertility integrated into holistic care to provide counselling together with up to date factual, medical advice was discussed alongside who would be best placed to provide this:

FRT: *"all fertility, it's the five issues: it's easy: it's the medical, the ethical, the emotional, the financial and the legal. And the family."*

Despite the complexity of these issues for the individual and their family, the lack of counselling or onward support after diagnosis was described:

FRT: *"I diagnose it and it goes out of my territory"*

Clearly diagnosis is something with costs and benefits which needs to be dealt with by the individual and their families. This arose from the step change in access to treatment and support which diagnosis catalysed. The opportunity diagnosis offers to aid timely treatments, obviating potential risks to health problems through screening and monitoring and beginning treatment in a timely fashion was noted:

URL: *"that strengthens the case for diagnosis because for something that is totally objectively demonstrable like autoimmune, thyroid problems, for example … of earlier diagnosis to autoimmune and thyroid disease enables you to intervene*

earlier and change the clinical course of the disease then that would be a very valuable thing"

Diagnosis was seen as the gateway to providing timely and preventative professional services to minimise known areas of increased risk emerging. As stated, there was the value of diagnosis in providing validation for families' long quest (as evident in their testimonies) for answers where a difference has been long recognised, but with no label or recognition from health professionals. In this sense, as stated, there are links between emotional and psychological benefits and diagnosis, in addition to the monitoring, treatment and support resulting from diagnosis:

PHY: *"symptoms are anxiety and isolation … it's the whole person, absolutely, completely … it's understanding why they've come in the first place"*

There is a sense in which diagnosis places individual symptoms in context and allows for a different, more holistic, approach to treatment. This will now be explored further.

6.3.5 The need for a holistic approach

There is acknowledgement in the specialist group that holistic treatment is a 'gold standard' to aim for and there was universal support for this approach in principle, but in practice the Specialists reported they essentially worked in isolation, determined by symptoms:

FRT: *"we use the term 'integrated' I think it should be called something like 'togetherness' … you've got so many issues you've got endocrine, potentially social issues, you've got potentially educational issues, relationship issues, you've got so many other issues that need to be addressed, and any form of integrated care is better or joined up thinking, whatever you want to call it but I've had no practical experience of it at all"*

GST: *"I think that for all the other reasons - the holistic approach, you know - the increase in anxiety and other concerns about health etc. that the Klinefelter's may or may not have, but may have, you know … that needs dealing with … certainly in the initial consultation to make sure they're aware that this can be associated with their condition"*

The notion of holistic care was not only about providing better support for individuals, but also for a need to treat the whole person:

PHY: *"symptoms are anxiety and isolation … it's the whole person, absolutely, completely … it's understanding why they've come in the first place"*

This relates to the earlier narrative in Section 3.4 regarding the individual's ability to make sense of their diagnosis and to make better sense of themselves as a result. To repeat a quotation used in Section 3.4:

GST: *"it's a question of saying well these things are associated, they're not going to shorten your life … but I can understand they can have a significant effect on morbidity, on your quality of life and therefore we need to pay attention as best we can"*

Awareness among Specialists of the need for 'joined up' care became apparent, though less obviously so, from comments where the importance of linking up individual symptoms were stressed, and it became apparent that those with Klinefelter's present with a constellation of different symptoms:

DIT: *"if someone's very, very, anxious then they call it visceral hypersensitivity so certain chemicals will be released … basically the nerves reaching the gut are over-sensitised … people who are maybe stressed and anxious … that's what they mean by the gut/brain axis that what you are thinking and feeling can directly affect the gut"*

SLT: *"obviously a big factor in Klinefelter's is anxiety because if you're anxious you're suppressing processing and that's obviously another difficulty so if you can address the anxiety levels then everything else is going to benefit"*

SLT: *"it's not owned by our profession, but I think we perhaps understand more than other professions that anxiety is catastrophic for well-being, for learning, for memory, … all learning is about perception and memory and functioning and if anxiety is too high then it's going to wreck everything else"*

SLT: *"because you've got normal cognitive ability the frustration's going to be there"*

These narratives show a complex interaction between anxiety, stress, wellbeing, learning and memory. A multi-disciplinary approach was advocated to deal with the potential interaction of symptomatology:

DIT: *"a multi system approach … if somebody's very stressed and anxious, diet may help to some extent, but it's not going to get rid of the stress and the anxiety so an ideal service would be providing both, so they would be seeing a psychologist to manage the stress and anxiety - it may be they're struggling to deal with day to day life - but it might be the food and the impact the food is having, is causing the stress and anxiety because these foods cause them to rush to the loo all the time and they don't want to leave the house"*

FRT: *"what is the future, that is the prognosis, what is …and then piece it all together and then I could put my little piece of the jigsaw"*

The case for holistic care was reinforced by the Specialist descriptions of the ongoing challenges experienced by some Klinefelter's patients. Relationships and challenges of managing the complexities of independent living caused observations about the specific difficulties these can present to the Klinefelter's individual. These were seen as a lifelong problem:

SLT: *"relationships as well as social relationships and the expectation to self-manage those things become more complicated the older you are because obviously you're going to be more and more independent so as life gets more complicated they need the same amount of input to help them with the more complicated curriculum"*

SLT: *"the demands of everyday life become more complicated don't they as you're accessing higher education you're having to deal with unstructured time, masses of unstructured time uncertainty, having to navigate your own pathway through the day … you're encountering really sophisticated young people … and that all ramps up so that all…. yes you've probably had tons of input but you're going to need it more than ever … because the demands get more sophisticated"*

There were noticeable differences between those specialists who practised in isolation, rather than a holistic, preventative, approach. Where specialists had not had experience of treating patients holistically, they were less likely to advocate the advantages of ‘joined up’ care.

6.3.6 Future developments

Some of the Specialist Group felt that advances in medicine would change the nature and timing of diagnosis. One specialist also highlighted the need to identify affected individuals so that, when developments in treatment become available, they could be offered appropriate treatment. Thus, diagnosis was seen as a kind of 'future proofing':

> URL: *"things change in medicine and the fact you can't do anything now doesn't mean you won't be able to do anything about it in the future … If you don't identify the affected individuals, then you can't know whether you are going to be able to make a difference in the future … There may be multiple reasons why earlier diagnosis might be a good idea"*

Diagnosis and subsequent provision were seen as an important factor in conferring resilience to known increased risks. The Specialist Group highlight treatments and strategies which are instrumental in preventing or diminishing emerging problems which were broad ranging:

> URL: *"there is a broader reason for diagnosis here which allows assessment and monitoring"*

Until recently, infertility was expected in almost all Klinefelter's males. Infertility is reported by the family group as one of the most difficult aspects of the condition to come to terms with. The hope offered by the recent developments to assist some Klinefelter’s males to have their own biological children is likely to have a significant impact in diminishing the emotional burden of the condition treatment advances include a surgical technique where retrieval of sperm is attempted. This prospect is a recent advance, with treatment in its infancy, and not a treatment which works for all. Although in its infancy, reportedly, for greatest chances of success, there may be an optimum time to offer TESE treatment, currently estimated to be before aged 30-35 years (Bourke et al., 2014).

Currently this awareness seems limited in the UK to a small circle of experts in specialist fertility centres and endocrinologists. The Specialist Group for this study were not aware of the fertility advances and the potential impact for individuals and their partners of possible

treatment. This knowledge is important, not least because some Specialists questioned the value of diagnosis if there was little that could be done to improve the lot of those affected. The Specialist Group also raises a question explored with each of the groups as part of this study:

URL: *"is there value in making a diagnosis in medicine if you're diagnosing something you can't do anything about?"*

URL: *"so if you take a man in his 60's with Klinefelter's who looks back on his life and says 'I'm sad that my wife and I weren't able to have children', would it have been beneficial to him to have known in his 20's that he was XXY and likely to be sub-fertile? - that is my philosophical question"*

As we have already seen in Section 3.4, however, the value of diagnosis appears to be not only in the possibility of helping with infertility, but in helping individuals and families with sense-making of their feeling that ‘something was wrong’ and providing a ‘recognition gateway’ to further treatment and support for a range of symptoms.

An increasing role of a diagnosis potentially saving the NHS money and preventing later problems was recognised:

URL: *"in England in a single night if you could knock off one of those future patient hospital admissions because they knew of the diagnosis of Klinefelter's then you'd save £350.00 … so every single night in hospital even if nothing is done costs the NHS £350.00"*

Back pain and problems are not uncommon in Klinefelter's Syndrome and can disrupt sleep as well as day to day activities. The physiotherapist described the place of back problems as a societal problem generally and the savings to the NHS if this were dealt with early and effectively:

PHY: *"if we were to take away the whole condition itself and just think about backpain the general we know that it's one of the biggest, one of the most expensive problems in the western world because everyone seems to get back pain … There are a lot of studies out there that say preventative classes are fantastic … if you can have 2 or 3 sessions as a preventative based route,*

you're going to save a lot of money so looking at it from an economical point of view, it's fantastic"

The increasing role, and benefits of prevention, were also recognised as part of this approach:

PHY: *"preventative based therapies are a real buzz word now because it's all about cost … preventative based therapies is really important, we know that fear avoidance is one of the biggest problems in back patients … now, we know with Klinefelter's you have lower tone as it is … we know that when they have weeks of rest that's probably causing more problems in the long term"*

One specialist recognised the role of early diagnosis in averting some of the behavioural problems which have been associated with Klinefelter's. Emotion regulation has been reported to be an area of difficulty for Klinefelter's males, with studies reporting deficits in neural systems involved in emotion regulation and accompanying anxiety and stress which may result from this. Support and targeted strategies to better understand and manage related situations for this known increased risk can be provided, where a diagnosis has been made. Speech and language therapy can include programmes of support to target and ameliorate deficits:

SLT: *"I think for anybody with Klinefelter's or whatever you're helping with management of emotion, you're helping with organisational skills, you're helping with self-regulation, you're helping with the reflection of social outcome, the dynamics of social interaction, the outcomes and understanding them"*

SLT: *"I think we should be just be more mindful that school is a very, very, stressful place and I think a whole load of children without any diagnosis find it a very unnatural stressful place to be so how much worse to be there with additional levels of anxiety and misunderstandings of what your role is"*

These stressors were likely to lead to the development of behavioural responses which, while initially 'protective' for the child, were problematic in the longer term:

SLT: *"that's what, what they need is a voice and if they're not given a voice then that group that I see a lot of … those complicating barriers which have become functional behaviours for them so the withdrawing or using*

inappropriate means to get attention, all those they go on like layers of an onion and they go one like boom, boom, boom, boom, and they're there and once they're there that's when you've got real problems and she stopped all that … all of those layers going on"

The speech therapist described the difference the efforts of a mother made in obtaining an earlier diagnosis:

SLT: *"I think it was doing that so young that she (the mother) averted a whole load of problems"*

A recurring theme among Specialists, when asked about future treatment, emphasised the theme of the need for holistic care. A number of specialists emphasised the need for large teams, centres of excellence and multi-disciplinary care:

SLT: *"you have a group of professionals, a centre of excellence so you have the very high numbers so they're learning from them and they're seeing the extent of the variants … that aspect of care should be considered as being centres of excellence that way you're getting the research as well."*

URL: *"in big centres I'm guessing they would probably have access to psychological support"*

PHY: *"gold standard … I think straightaway it should be collaborative, so it should be a multi-disciplinary team working together, communicating together how to look at what the needs of the individual is, that ultimately is the key thing."*

When considering the future gold standard for treatment of Klinefelter's Syndrome, the Specialists also considered potential barriers to future developments. Perceived barriers primarily highlighted the systemic limitations of the NHS and a symptom-driven model which may be out of date. A symptom driven model acts to divide the symptoms of Klinefelter's into referrals for individual problems, thus dividing the syndrome into a series of separate treatment pathways. These contribute to reducing the chance of diagnosis of the underlying chromosomal condition because of a 'pass the parcel' approach (see Section 3.2):

PHY: *"the NHS was designed on this medicinal [symptom-driven] approach and that's why we have such separate entities. … they see this person this person,*

but trying to collaborate this isn't possible, you need to get to the pathways so in a way, you're just trying to create a pathway for Klinefelter's."

The funding barriers in the NHS were identified by all Specialists who recognised the need for further funding, while recognising the budgetary constraints this need places on an already strained NHS system:

PHY: *"the NHS … it's been strangled because of funding … it's become bloated in areas and compressed in areas it shouldn't be … and ultimately until it becomes organised it's still designed for a 1940's, 1950's UK"*

This perspective seems to particularly resonate as a shared underlying concern about the NHS system, and perhaps particularly highlights the challenge this presents for a condition such as Klinefelter's; a 'new' diagnosis identifying the underlying cause for a constellation of problems, all individually requiring management, whilst maintaining an important need to also recognise and treat the condition as one, underlying, systemic condition. This Specialist perspective of a mismatch between the system, the specialist referral system and the way the condition presents is thus a key perspective to understanding a key factor in under diagnosis.

6.4 Summary

To summarise, diagnosis was seen as the gateway to providing timely and preventative professional services to minimise known areas of increased risk emerging. Specialists saw the value of diagnosis in providing validation for individuals and families, allowing them to make sense of the things they had felt were wrong, usually for a very long time. In an echo of the Expert Group perception of diagnosis, there was a recognition that a diagnosis can bring feelings of relief and validation to family suspicions that something was 'not quite right'. They were also aware of the power of diagnosis to transform care and act as a gateway for treatment and that the 'label' would help in gaining recognition from health professionals. Diagnosis would also be a pre-requisite for a more holistic health care plan recommended by the Experts and Specialists with experience of treating a Klinefelter's patient.

This leads to the Specialist pondering the question raised by one of the Experts: that diagnosis can cause worry and anxiety. This needs to be balanced against losses and gains of diagnosis. It was notable that the Family Group, at whatever age the diagnosis was made, were unanimous in their support for not only a diagnosis being made but being made early. In

this respect, the family group reported diagnosis were different experiences for each family. Where diagnosis was made earlier, there were opportunities for preventative approaches, for example:

> SLT: *"because what you'd be doing is taking a proactive stance against anxiety, providing additional clarity and the two go together … it's the source of the unknown that's the anxiety so you're externalising systems"*

Despite this balancing act, and the pros and cons which inevitably come with diagnosis, all agreed that diagnosis was a critical turning point in the lifelong experience of living with Klinefelter's Syndrome:

> SLT: *"I think it's always valuable"*

Figure 4: Diagnostic Cluster Group (DCG): Specialists 2: "it doesn't really exist as a speciality"

Developmental Diagnostic Clues:
'A Lifetime of Clues'

Symptom/prompt for diagnosis	
Developmental delay	URL: "if you're diagnosed at the age of 5 because of dyspraxia or other aspects of developmental delay"
Learning difficulties	SLT: "the literacy aspect, with dyspraxia and dyslexia" SLT: "difficulties with organisation … auditory processing … slightly different empathy levels, a warmer empathy that you see typically with ASD"
Autism	SLT: "we might mistake it for ASD … I could see a lot of false positives with ASD arising"
Anxiety	GST: "the increase in anxiety and other concerns about health that Klinefelter's may have that needs dealing with" PHY: "symptoms are anxiety and isolation … it's the whole person" SLT: "a big factor in Klinefelter's is anxiety … if you're anxious you're suppressing processing … anxiety is catastrophic for well-being"
Relationships and emotion	SLT: "for anybody with Klinefelter's you're helping with management of emotion … relationships, as well as social relationships" SLT: "it was the speech and language problems that caused the emotional behaviour"
Autoimmune problems	GST: "I would not be surprised to see an associated immune related condition" URL: "autoimmune, thyroid problems"

Hospitalisation	GST: "I think they would be far more likely to present themselves to hospital in general, certainly hospital services earlier on than later"
Back problems	PHY: "back problems … we know with Klinefelter's you have lower tone … lower tone hypermobility"
Fertility	FRT: "we're doing chromosomes for fertility issues"

FRT: "you've got endocrine, potentially social issues, educational issues, relationships issues and any form of integrated care is better"

Specialists

GST: "this is a common condition … that has associated morbidity which a lot of us specialists see in isolation but actually they are all connected"

CHAPTER 7

AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS OF PERCEPTIONS OF FAMILIES AFFECTED BY KLINEFELTER'S SYNDROME (47, XXY)

7.1 Introduction

This section presents the themes that were identified from discussions with families who have a family member diagnosed with Klinefelter's Syndrome. Themes were identified and a summary of these are provided in Table 13 below. Following this, the themes are considered in greater detail and quotes are used to provide examples of each theme and how they related to each of the families.

Eleven discussions were held with family members who have a family member with a diagnosis of Klinefelter's Syndrome. Discussions lasted between 1 hour and 2.5 hours and were driven by opening the discussion with an open question about diagnosis and if this had significance for their family. This was to set the context with the participants to aid and prompt conversational flow, where this was helpful. As far as possible the discussions were unguided and the role of the researcher was to follow the conversational patterns of the participants, allowing flexibility and expansion of the discussion for further exploration of issues raised. There are reports in the literature that diagnosis is important for access to treatment and support, which are significant to outcomes. The perceived significance of diagnosis for Klinefelter's Syndrome, and the experience of the diagnostic process for Families, was identified as being important to explore in addition to the GP, Specialist and Expert Groups. To ascertain as complete a picture as possible for the families, interviews with parents and siblings were explored in addition to individuals with Klinefelter's Syndrome. Perceptions from parents was thought potentially to be informative regarding formative years or may have recollections which the individuals with Klinefelter's may not remember, particularly from their childhood years.

Families echo the importance of diagnosis, all agreeing that early diagnosis is even more important; in this, the literature, expert perceptions and families are in agreement that diagnosis is highly significant for not only the individual, but also the family. Equally, diagnosis remains elusive for most, with a reported 64-75% remaining undiagnosed through their lifetime and only 4% diagnosed before the age of 10.

As IPA methodology describes, specific themes are reported from the transcripts reflecting the lived experiences of the participants in their own words. Results from the conversations were analysed and summarised as experiences or outcomes for each participant family. To protect the anonymity of each family, each family is identified in the transcripts and reported data as F1 (Family 1); F2 (Family 2), for example. Family members are identified as I (indicating an individual with Klinefelter's), M (indicating a mother of a participant), F (indicating a father) or S (indicating a sibling). |Families are numbered in order in which they were diagnosed: M1 denotes the Mother of the individual to be diagnosed at the youngest age in this study, M2 denotes the Mother of the individual to be diagnosed second in the group. This numbering system is used to identify all the Family members; therefore, I4 indicates an individual with Klinefelter's who was fourth in the group to be diagnosed, for example.

The ages at which each of the families were given a diagnosis is shown in Table 13.

Table 13: Age at diagnosis and the diagnostic pathway of each family.

Participant	**Age at Diagnosis**	**Diagnostic Pathway**
F1	0	Amniocentesis
F2	6	Private referral for Fragile X
F3	16	Marfens/ Raynauds Syndrome
F4	18	Private referral for disrupted puberty
F5	26+	Urological
F6	35+	Hypothyroidism

Table 1 Participants age at diagnosis

All the families in this study were affected by having a family member diagnosed with Klinefelter's Syndrome. The family group in this study were diagnosed with Klinefelter's Syndrome during pregnancy, at 6 years of age, 16 years, 18 years, 26+ years and 35+ years of age respectively.

As stated, Klinefelter's Syndrome is estimated to affect between 1/500 - 1/600 males and prevalence is reported to be increasing. Despite these figures indicating that Klinefelter's is relatively common, the condition is generally perceived to be rare with low levels of knowledge and awareness reported to contribute to low diagnosis rates. The literature

consistently reports the under diagnosis of the syndrome with an estimated 64-75% remaining unaware of their diagnosis through their lifetimes and fewer than 4% being diagnosed under the age of ten years.

In this climate of low diagnosis rates and with a backdrop of reported misconceptions in medical generalists that Klinefelter's is rare, this study explored the perceptions of medical experts, general practitioners and affected families. The reason for choosing these groups was to explore the claims in the literature that the causes of the under diagnosis of Klinefelter's are variability of the condition and a low awareness of the condition in general practitioners. Although these claims are frequently reported in the literature, there is a paucity of evidence to substantiate these. Further, this study explored perceptions of the significance of diagnosis within the groups. Anecdotal evidence from family experiences appear to support the claims that diagnosis can be difficult to achieve, despite multiple referrals and reported increased contact with health professionals.

Given the relative commonality of the syndrome and the relative perceived 'rareness' of diagnosis, this study sought to explore the veracity of these claims and factors which may contribute to the reported low diagnosis rates.

This study also explored the perceptions of the groups involved in the Klinefelter's diagnostic process and their perceptions of the significance of diagnosis. This was undertaken to elicit awareness, perceptions and diagnosis to provide insights into diagnosis of Klinefelter's Syndrome from the groups involved.

This chapter reports the results from the family group who shared their experiences of Klinefelter's Syndrome. Diagnosis and family perceptions around diagnosis were discussed and revealed through the family narratives. The analysis of these discussions revealed perceptions from the family group which were subsequently identified and arranged into themes, which are reported and explored below.

7.2 Themes from interviews

Table 14: Table of themes from participant families

Theme	Sub-theme
Diagnostic difficulties	Early parental concerns: 'something's not quite right' 'The clues were there': diagnostic opportunities
Finding out: a complete picture	First reactions; later reactions: 'on reflection'; losses and gains
Moving on	Care and Support; the value of diagnosis; delayed diagnosis
Cost of adult diagnosis **A shared diagnosis** **The 'Self'**	Emerging variability Family The right to know

7.3 Analysis of interview themes

7.3.1 Introduction

The following section explores the family experiences and perceptions of diagnosis. Parents described their concerns for their son caused by problems they first noticed in infancy. Despite seeking early medical advice, and having frequent contact with health professionals, they described shared difficulties in getting a diagnosis. For one family, diagnosis resulted from amniocentesis and were, therefore, aware of the diagnosis from the beginning. For the remaining families, one was diagnosed in childhood, two were diagnosed in the teenage years, and for two families' diagnosis was delayed until adult life.

After diagnosis, reflecting on their diagnostic experiences, the families shared a perception that a lifetime of Klinefelter's 'clues' were evident from infancy, and saw these as diagnostic opportunities missed due to lack of recognition by medical professionals. The families revealed a shared conviction, from the earliest years, that the concerns they shared with health practitioners were justified.

The family group described an identifiable pattern of problems, for which they sought medical advice from the infancy of their son, but parental concerns were not shared by the health professionals. They describe how, despite frequent contact with health professionals,

the characteristic symptomology of Klinefelter's Syndrome was not recognised, causing diagnostic delays of up to 30 years.

The parents reveal their feelings and frustrations at the difficulties to get a diagnosis and the perceived missed diagnostic opportunities. The families described the felt symptoms indicative of Klinefelter's Syndrome were apparent from infancy into adult life. These perceptions caused the families to reflect on these clusters of symptoms as multiple missed diagnostic opportunities through the lifetime. When diagnosis was made, the simplicity of making the diagnosis caused bewilderment at the delay.

Reflecting on their diagnostic experiences took the narratives of the family recollections back to the beginning: to infancy and a shared perception that 'the clues were there'. This was the genesis of the search for diagnosis and it is from these beginnings that the following section explores the diagnostic experiences of the family group.

7.3.2 Diagnostic difficulties: Early parental concerns

M3: *"as a parent you know something's not quite right"*

The narratives of the Family Group revealed an early awareness, or instinctive feeling, for the families that 'something was wrong' from the beginning, in infancy. These were described as feelings of unease that 'something was not quite right'. Repeated reassurances from clinicians caused family frustration and, despite assurances from health professionals, these feelings of concern endured and were, for some, later recognised as the genesis of the diagnostic pursuit.

The family descriptions highlighted the frequency of contact resulting from parental concerns and a shared perception of problems identified by the family in the early years and continued until diagnosis was made:

M3: *"I always felt that there was something different and I just couldn't put my finger on it, just late development"*

M3: *"I always felt that something was not quite right and that he was slower in development, he had problems in every aspect of talking, walking, crawling, all the normal … even though I know every individual is different ... he was very slow"*

M2: *"I knew something was not right. I just knew from the beginning. There were little signs that didn't add up ... I read up on things like autism, but although some ticked some of the boxes, none were really right ..."*

It was interesting to note that, where diagnosis was made later into teenage years, there was a developing awareness in the individuals around their own development. These echoed the parental concerns in earlier childhood that all was not well:

I4: *"I probably would have asked my Mum more and more times 'we need to go and see someone' ... I asked her about a year before ... then she started to have a few concerns as well and she was like, 'yes we should probably go and see someone'"*

I4: *"deep down I'm thinking 'is there something wrong with me?'"*

M6: *"he would always say 'what is wrong with me' why don't I have any motivation? What is the matter?' ... that was a repeated refrain"*

Despite ongoing worries about their son and multiple health contacts, families describe persistent worries that there were problems and how their pursuit of a diagnosis and the challenge of becoming diagnosed: for some, considerably delayed. Their perceptions and experiences in the diagnostic process are explored in the following section.

Table 15: Infant Milestones and Infant Referrals

Infant Milestones	**Early Prompts for Early Diagnosis?**
M3: "I know he was late to crawl, late to walk, late to speak, speech was quite late.."	M6: "audiology he was referred, speech he was referred - he had big problems there - co-ordination, reading and writing definitely…"

7.3.2.1 Diagnostic difficulties: 'the clues were there' (Part 1)

Early family concerns led to frequent medical appointments from infancy, arising from parental concerns around a shared pattern of infant delays: developmental delay, delays in reaching infant milestones and a pattern of early referrals for speech, audiology and motor

development. These appeared to be presenting as a kernel, or 'core' pattern of early symptoms. These early 'core' indicators of the underlying syndrome were not recognised as such, but dismissed as idiosyncratic developmental delay, not considered as indicative of any medical issue. Although referrals were made from primary care for speech, audiology and motor delays, these were not considered holistically but referred to separate specialists who considered each area of referral in isolation:

M2: *"he was referred by the health visitor for all his early checks, he didn't speak at all and he failed all the health visitor checks … when he was referred they said he was fine … and not to worry"*

M3: *"late development, he had problems in every aspect, he was late to crawl, late to walk, late to speak, speech was quite late"*

M3: *"when his brother came along he couldn't say his name, so pronunciation, yes"*

Thus this early 'infant core' of developmental delay and infant referrals for speech, motor and audiological delay was not recognised as symptomatic of any underlying condition and thus was overlooked as a diagnostic prompt for a medical condition.

The Family group described how contact with health professionals continued to be frequent and driven by specific health and development concerns for their son. This pattern of medical appointments and referral continued from infancy, through childhood and beyond:

M3: *"learning to ride a bike was impossible, doing shoelaces, button through button-holes, he struggled kicking a ball, catching a ball, he struggled"*

Despite this shared profile of multiple medical appointments, diagnosis was not made in the early years, despite the shared insistence of parents that they felt there were problems:

M6: *"nobody could ever get to the bottom of it ... you just know, as a parent you know something's not quite right"*

The families described a shared pattern of contact with health professionals and referrals from primary care through the infant and childhood years:

M2: *"I took him to the GP so many times - he was referred to audiology, speech therapy, paediatricians, educational psychologists… they just kept saying he was a bit slow they just didn't recognise it"*

M6: *"audiology he was referred, speech he was referred - he had big problems there - co-ordination"*

M1: *"a lot of GPs haven't heard of the condition and didn't really have any up to date information"*

7.3.2.2 Diagnostic difficulties: Low awareness, subtle presentation, other diagnosis made, absence of illness

M5: *"We've seen all these experts since the age of 2 … from the age of 2 we took him to all these specialists, paediatricians … and he's been to his GP with problems over the years – no one said 'there's something going on here'"*

The Family group echoed the views of the GP and Specialists Group in describing the effect of the subtle delays which, later, the families felt were indicative from an early age of Klinefelter's Syndrome. Reflecting on these early delays, the family group shared the view that if there was increased awareness of Klinefelter's in the doctors they saw from early childhood, these indicators could have resulted in earlier diagnosis:

M6: *"I'd never heard of it, nobody's ever heard of it"*

M6: *"the doctors don't seem to know much about it, or even know about it"*

The families described how their concerns persisted and the differences and delays they observed in their son were indicative of a more pervasive problem which justified seeking medical advice, despite assurances from health professionals to the contrary.

Although the underlying condition was not diagnosed in early life, other diagnoses were made for some in the group and this led to families querying why diagnosis was not made as a result of these referrals.

For the family group, there were conditions diagnosed, but not the underlying condition, and this oversight led to concerns that a fractionated, or skewed provision approach may be taken, resulting in an incomplete approach to the management of the Klinefelter's profile:

M2: *"they thought he had ADHD … he was diagnosed with dyslexia … dyspraxia … no one ever even mentioned Klinefelter's"*

M5: *"he's Asperger's ... he's definitely got Asperger's"*

M5: *"he was having speech therapy I do wonder then if the speech therapist had said 'he may have this'"*

In this context, it was interesting to consider the perspective of the speech therapist (Specialist Group) and the GP group who attributed possible diagnostic errors or omissions to low awareness of Klinefelter's, compared to conditions which currently have a higher public profile, such as autism or ADHD. There were suggestions that this may have been the case for diagnostic delay in some of the referrals for our Family group. Despite the Families having early concerns and seeking medical advice from health professionals resulting from these, diagnosis was not made as a result of any of these early endeavours.

Instead, the families perceived they were dismissed as over-anxious, or unreasonably persistent parents, and subtle presentation led to reassurances that these were 'normal' delays which would resolve naturally:

M2: *"I wrote a 7-page document about my son for the paediatrician to read, it had all my concerns with examples on it. All he had to do was put the heading 'Klinefelter's Syndrome', but he just said he was a 'normal' boy"*

M2: *"the paediatrician - despite saying there was no problem with my son - suggested he could go on Ritalin … I said 'no' … why prescribe something when you have just said there is no problem … ? It seemed to me he offered it because I was persistent"*

The family experiences of diagnostic difficulties were resonant of some of the barriers to diagnosis identified by the GP and Specialist Groups, including the perception that a lack of immediately 'discernible' illness or symptoms and low awareness of Klinefelter's contribute to diagnostic delay:

M1: *"you know, with Klinefelter's Syndrome, there is the problem that you can just appear perfectly normal"*

The life place of diagnosis seemed to be highlighted by the parental view that lack of a visible problem or appearing 'perfectly normal' was seen as a problem. At first this seemed an unusual observation, prompting the question: why would lack of discernible differences be seen as 'a problem'? However, when taking this perspective in the context of the difficulties caused by late diagnosis, this perception would seem to underscore the importance parents placed on a diagnosis being made. This view echoes Geschwind (2007) reporting that 'the phenotype is usually unremarkable to the casual observer' and resonated with the GP group perspective that some indicators of Klinefelter's may be mistaken for a 'normal' presentation and interpreted as a 'natural variant of normal', resulting in delay to diagnosis or missed diagnosis:

M3: *"the doctors don't seem to know much about it … maybe if I'd taken him back to the doctors all the time … I just felt somethings not right. He wasn't ill. He wasn't ill"*

M2: *"the GP's just kept telling me that there was nothing wrong, he was just a bit slow … looking back, he wasn't 'just slow,' ... there was a diagnosis to be made … they just didn't spot it"*

M5: *"that needs to change, it's educating the people, these children are seen consistently with these problems, GP's are the first people they go to"*

It was interesting to reflect that the family group experiences mirrored the perspectives of the GP and Specialists groups who described reasons for a Klinefelter's diagnosis being missed. The family felt these symptoms were identified from an early age and, further, were indicative of Klinefelter's Syndrome, but were overlooked. The family group perceived that the symptoms evident from infancy were unrecognised as early signals of Klinefelter's, thus resulting in missed diagnostic opportunities. The perception of the families when diagnosis was subsequently made was that these early contacts were seen as missed diagnostic opportunities which could, and should, have been picked up at the time:

M6: *"unfortunately we didn't know he was suffering from this … he was not diagnosed until he was 26,27 which we felt very let down by, actually because we'd seen speech therapists, educational psychologists, psychiatrists"*

7.3.2.3 Diagnostic opportunities: Multiple health appointments: 'the clues were there?' (Part 2)

M5: *"no one tested for anything, it's unbelievable isn't it, when I think of the people we've taken him to over the years"*

In addition to the early delays in infancy, which continued into childhood, the family group described multiple referrals for an array of symptoms. These referrals were a shared pattern within the family group and were a genesis of family perceptions that the referrals, in addition to the early (unrecognised) 'signals' were diagnostic opportunities which, as with the earlier GP encounters, could have resulted in the Klinefelter's diagnosis.

Where referrals were made from primary care, lack of diagnosis as a result of referrals to specialists were reported to be for similar reasons to those in primary care. These delays were perceived to be a lack of, or low, awareness and knowledge of Klinefelter's, lack of recognition of subtle presentation, parental over-anxiety, or diagnosis of specific impacts of the syndrome, rather than diagnosing the underlying condition:

M2: *"we saw the GPs, then we saw the paediatricians ... they did a very simple assessment … and said there was no problem"*

M6: *"he was just lacking in confidence … by some points his visits to the doctor were frequent and his confidence was dropping … in the first year the school nurse came in for a physical check ... how much would it cost them? … the GP didn't do a physical exam"*

The challenge of getting a diagnosis was reported by all the Family group with consistent descriptions in their narratives revealing a pattern of multiple contact with medical professionals. There was synergy between the family testimony and the reports in the literature of increased risk to psychosocial and health problems, with a reported 70% increased risk of hospital admissions. There were descriptions of health problems in the family group narratives which identified frequent contact with health professionals with shared health problems appearing to be in 'clusters' of symptoms:

I4: *"chest infections - I've had quite a few of them … before I even got diagnosed with asthma … I got a chest infection that went on for months … I think that was Year 7 to 8 - I had a chest infection"*

M2: *"he had two episodes of pneumonia within 18 months when he was 10 ... the first was really serious with complications … and he missed nearly a year of school"*

The history of hospital admissions and diagnosis of other conditions prompted queries for the Klinefelter's diagnosis not being made as a result of these:

I3: *"I was quite poorly when I was 8 or 9 years old and I was in hospital quite a bit … I was just not eating anything and was just wasting away … I can't remember why I was in hospital on a drip - so why didn't they find it then?"*

I4: *"I used to see the doctor quite a lot … I was really out of breath … I was about 9. The doctor confirmed I had asthma … I wish I'd been told - I'd gone for a blood test when I found out that I had asthma … so it would be nice if I'd found out then"*

A constellations of health problems were described, including digestive related problems, allergies and back problems, some requiring hospital admission and further referrals:

M2: *"he has had ongoing gastroenterology problems and been hospitalised 3 times as an emergency just for that … he now has regular appointments with a gastroenterologist, and he has done much better since being monitored and managed … he also sees a dietician which has helped with the symptoms a lot"*

I3: *"I think I'm allergic to penicillin and something, I get asthma and hay fever … I've had all those upset tummies"*

In addition to the symptoms requiring hospital treatment, there was a pattern of health problems which impacted on daily life:

I4: *"back pain that's quite common, that's the worst pain"*

I3: *"I struggle with my sleep, anger issues, stress and sleep"*

I3: *"I don't have breakfast in the morning I find it too hard to digest anything"*

I4: *"and allergies, yes, a weird one - plasters - I get all scratchy and it swells up"*

M6: *"it's a kind of allergy it flares up, his hands have been in a terrible state... so we had real problems with his hands"*

It was interesting to note these symptoms and health problems are in areas identified as of increased risk in the literature in Klinefelter's:

M2: *"he's always had allergy problems - all his immunisations he had to be given in hospital - they said he had some differences in his T-cells … lots of food intolerances and odd allergies … he's doing better on a gluten free diet now"*

M2: *"they also said he has completely absent folate, but no one has found out why that is yet"*

Therefore the family narratives present the conundrum that having a diagnosis was perceived as difficult and effortful, with the system placing diagnostic barriers in the way of timely diagnosis. The perspective of the family group emphasises the importance they place on the value of early diagnosis with suggestions for screening:

I3: *"you think they should test all baby boys when they're born to see if they've got it … they can test to see if they've got other things wrong with them when they're born, so why can't they find out they've got Klinefelter's Syndrome? Then they can get the treatment they need and the support they need when they're at school"*

These testimonies taken together provided a powerful insight into how the perceived diagnostic barriers affected the families. These perceptions resonate with the Specialist Group who, from their perspective, concur with the Family that despite multiple contact with medical professionals, diagnosis of an underlying condition is not necessarily their focus:

GST: *"1/600 is common and that has associated morbidity which a lot of us specialists see in isolation but actually they are all connected, and I don't think that many of my colleagues would even know that"*

The experiences of multiple visits to doctors and health professionals was a common thread across the narratives. Where diagnosis was not made until later, these were perceived, in retrospect, to have been indicative of an underlying problem:

M5: *"unfortunately we didn't know he was suffering from this. He was not diagnosed until he was 26,27 which we felt very let down by, actually because we'd seen speech therapists, educational psychologists, psychiatrists…he'd seen a urologist 5,6 years before he was diagnosed, that is (pause) unbelievable… none of them picked it up"*

7.3.2.4 Diagnostic opportunities: Education and School: 'the clues were there' (Part 3).

M2: *"the noise from the big girls' shoes outside the classroom makes me scribble"*

In addition to the pattern of early problems with developmental delay, infant and childhood milestones, a pattern of referrals for late speech, motor skills, audiology and a shared story of referrals to specialists for a constellation of medical and health problems, there were shared descriptions of learning difficulties. Interestingly, as with the infant years which revealed shared 'core' problems and delays in the infant years, there was also a shared pattern of core difficulties from the earliest school years. Problems presented from nursery age and early school years, continuing through their school years and beyond into adult life. Learning difficulties were described by all the families and continued, regardless of support:

M6: *"speech he was referred - he had big problems there - co-ordination, reading and writing definitely"*

M3: *"he couldn't do any sport either - his co-ordination … he was the quiet one, who if you were picking the teams he'd always be the last one"*

M2: *"when I first started reading with him - he just couldn't remember even 3 sounds - couldn't even remember 'T-O-M' for example … by the time we got to 'M' he'd forgotten the 'T' … he was found to have profound auditory processing problems over 10 years later"*

In addition to the early school 'core' problems of learning difficulties, there were experiences of other problems affecting school life including distractibility in the classroom and heightened sensory awareness:

M2: *"I did notice from early years a specific, but subtle, difficulty with some pronunciation of words, he missed out sounds from words and bits of words -*

like 'puter' for computer. … he spelt 'erosion' - 'ear ion.' He was later found to have profound auditory processing problems"

M1: *"at junior school … we began to notice at that stage he did have more difficulty sort of writing and he might miss out words"*

These problems were evident in the early years such as distractibility, heightened sensory awareness and friendship problems:

M2: *"he was trying to explain that he couldn't concentrate in class - he said: 'the noise from the big girls' shoes outside the classroom makes me scribble' … he meant the sound of shoes of pupils walking outside the classroom distracted him … Actually he still chooses shoes based on the noise they make"*

I3: *"distractions, you know, everyone talking all around you, even the noise they make"*

M5: *"he lacks concentration, he's been diagnosed with ADHD actually"*

I2: *"sometimes with remembering information that many friends have told me, and I ask the same question again and again and they say 'well you asked that 5 minutes ago - that sort of thing"*

The similarities described in infancy and early school years appeared in contrast to the variability reported for Klinefelter's males. The early years for the families revealed an identifiable shared 'core' of infant similarities which burgeoned into a shared pattern of similarities of core learning difficulties from the early school years.

It was interesting that the 'core' learning difficulties of spelling, dyslexia and dyspraxia continued through into adult life:

I2: *"um, the reading and writing was quite challenging… my brain is not very good at remembering things … um, the hyper flexible bones…"*

M5: *"he's definitely got dyslexia … his writing's not what you would call 'grown up' writing … it's the writing and the spelling"*

M6: *"his reading … he was not an auditory learner - he was very visual so within 3 or 4 sentences everything's gone"*

The learning difficulties caused parental concern and assessments by educationalists and paediatricians were undertaken. Although these referrals identified specific problems with learning, such as dyslexia and motor skills, these referrals did not prompt referral for chromosomal testing:

> M2: *"I took him to an educational psychologist … she was very impatient with him … he couldn't understand her instructions. She just upset him … her report was very general, mentioned nothing at all of value and was very unhelpful"*

The early years for the families revealed a shared profile of an identifiable shared 'core' of similarities from infancy which evolved into a shared core of problems evident in the early school years. These appeared to evolve into a complex and diverse array developing only in later life where secondary problems were reported by the families where support and treatment had not been forthcoming, with the delay to diagnosis attributed by the families to be the cause. Variability only appeared to evolve by emerging as an increasingly complex and diverse array in later life where secondary problems were reported by the families who were still undiagnosed at 26 and 36 and continued lack of diagnosis mean that support and treatment had not been forthcoming.

Learning difficulties and problems at school such as dyslexia, dyspraxia and friendship problems were, as described by the GP and Specialist groups, unlikely to lead to any chromosomal testing because these were not considered as indicative of a medical problem, or illness. This medical approach appeared to be evident in the experiences of the families:

> M2: *"we saw so many doctors before he was diagnosed - GPs, paediatricians, speech therapists, educational psychologists … they all said he was a lovely little boy, just a bit slow. I felt my concerns were dismissed ... I had to try not to worry about what they thought of me and just carry on trying to find an answer."*

Parental concern persisted, with shared descriptions of health and educational referrals for an array of problems and symptoms. As the undiagnosed boys in the family group were all now of nursey age or above, they had moved on to start school and away from the umbrella of health visitor checks and the monitoring of early years. Having started school, in addition to the learning difficulties they experienced, there were further problems, including socialising and friendships with peers:

M6: *"from the first day at school he had extreme anxiety … he had to be prised off me which upset us both"*

I3: *"socialising … I think with me you do struggle with social environments … the interacting was hard … having conversations with people, that's something I struggled with"*

F3: *"I'd say possibly general build, he was always not very well developed he never had that, it was the way he saw things, very black and white, never got jokes … he can't see the nuances, he's so black and white"*

The narratives revealed a shared profile of clusters of symptoms evident from the early years and emerging as distinct and characteristic clusters from infancy through childhood. This shared 'Klinefelter's core' of infant and childhood problems was evident from birth until the pubertal years. Here, the characteristic core seemed to evolve and at this time, physical differences and variabilities began to emerge.

The significance of the core of infant and childhood problems indicated that, for our families at least, there was a shared, identifiable set of core characteristics indicative of Klinefelter's Syndrome. If this were correct, there is a possibility that increasing awareness of this may be beneficial for increasing diagnosis rates.

The family group perceived their shared problems in the early years provided sufficient clues for the Klinefelter's diagnosis to have been made at that time:

M6: *"he feels a number of symptoms and signs in his early teens that could have been picked up, if not at birth … he describes himself with features fairly typical of the syndrome like feelings of never really fitting in and finding it hard to relate socially"*

7.3.2.5 Diagnostic opportunities: Teenage years: 'the clues were there' (Part 4)

As the family group moved into the teenage years, 4 families remained undiagnosed. For these families, disruption to puberty and problems with peers and bullying caused significant problems and disruptions at school, with the additional burden of negative effects on self-esteem, confidence and wellbeing during their teenage years:

M3: *"he was an easy target - they weren't the sort of friends you'd want for him, taking advantage of him an easy target without a doubt"*

M6: *"he didn't have a very happy time at school - he was bullied, he was marginalised … he had a group of friends, they wouldn't let him play, they used to spend most of lunchtimes jumping on his back, they called him names and they were horrible names"*

M5: *"a group of boys - every time they saw him they'd push him down the stairs or kick him… they'd even pushed him down the stairs. They made his life hell. Isn't that awful. He hadn't done anything it was just he was a bit different - an easy target"*

For two of the families, diagnosis was made in the teenage years at 16 and 18. For both boys, there were descriptions of physical impacts of the syndrome, with disrupted puberty in addition to the infant and learning difficulties which had manifested from the early years and continued to affect their school days:

F3: *"just struggling with his schoolwork, his writing wasn't very good and really, spelling, he'd just get words wrong … he thought it was the other way around"*

I4: *"I struggled a bit at school, always struggled quite a bit like writing and mental processing"*

I3: *"I think it was the learning aspect I always struggled with, taking in information and then turning it around so it was in an easier language … everything was just quite hard to understand"*

Although the families had pursued diagnosis in childhood, these concerns did not result in diagnosis. The resulting delay to diagnosis and how this affected their teenage years was described by the two individuals:

I4: *"the voice not dropped yet, no facial hair, um, my chest area er, I was just a bit like 'oh well' and then before I thought: 'oh well there's something wrong with me', like the Adam's apple"*

I4: *"obviously I would have loved my voice to drop … at the time I wanted it like so badly - like the most thing I've ever wanted … like to drop, to be normal … like everyone else and a bit sad I couldn't have that"*

In addition to the learning difficulties they had always experienced, and which continued throughout the teenage years, these physical differences, which became increasingly apparent through the teenage years, were revealed to cause loss of confidence, self-esteem and isolation from their peers:

I4: *"Year 11 - 13 I had quite chubby legs … I don't know why I just couldn't lose the weight off my legs (laughs) my name was, like, 'sausage' (laughs) and all the younger years used to call me it. It was really embarrassing - horrible, yeah. … they used to take the mickey about my voice a bit - I was self-conscious about it"*

The narratives described the difficulties their son faced at school and the increasingly difficult school days where physical manifestations of Klinefelter's Syndrome began to affect puberty. This caused significant distress to the boys who were bullied and isolated and caused later reflections that early diagnosis and timely treatment with testosterone would have ameliorated the array of physical, emotional and psychosocial problems which characterised their teenage years. In this sense, lack of diagnosis was seen as an expensive oversight by the families still undiagnosed:

I3: *"you need confidence at school, or they just feed on you"*

The following section explores the family experiences of finding out the diagnosis of Klinefelter's.

7.3.3 Diagnosis – finding out: a complete picture

Getting a diagnosis, how diagnosis was made; First reactions: 'I suppose I was very lucky"; Later perceptions: On reflection; losses and gains 'it's just a simple blood test'

As described, the lives of the family group had been overshadowed to an extent by the lack of the Klinefelter's diagnosis. In this section, the route to diagnosis is described by the families.

The family diagnosed first was made by amniocentesis and therefore, for this family, there was not the distinguishing problematic search for diagnosis experienced by the other families:

M1: *"amniocentesis was offered, and I had one done previously … so I was fairly comfortable with the idea"*

For the remaining families, diagnosis had been difficult, characterised by ongoing contact with medical professionals over many years. Increasing worries or specific motivation, despite repeated medical assurances, pressed some of the families to persist in seeking answers:

M2: *"I took him to the GP so many times - he was referred to audiology, speech therapy, paediatricians, educational psychologists… NHS and eventually private. No-one recognised anything, they just kept saying he was a bit slow, but he wasn't 'just a bit slow' he had a problem - they just didn't recognise it"*

For the families diagnosed in their teen years, there was also the shared life experiences of effortful diagnostic challenges, with diagnosis made at ages 16 and 18, having been considerably delayed after their first concerns were raised. For the family diagnosed at age 16, diagnosis was made when investigating other health problems and this was seen as a diagnosis made due to fortuitous circumstances:

M3: *"he was diagnosed at 16, he wasn't referred for Klinefelter's, he had white fingers, his hands were really cold, I can't remember the name of it, Raynauds? ... They wanted more tests done they thought Marfens Syndrome then we saw a lady doctor … She was genetics, she referred for a blood test"*

For the fourth family, diagnosed at 18, persistent visits to primary care and eventual request for a private referral was described:

I4: *"I was persistent asking my Mum, so we went and saw a doctor… for about 2 years I thought 'it'll do it eventually' ... but I was about 18 - persisting and going to the GP a few times - the stick I got pushed that one"*

Echoing the GP accounts of infant years when diagnosis was not made, the families diagnosed at 16 and 18 describe the experience of initial reassurance from medical practitioners in their teenage years that nothing was wrong and being advised a 'wait and see' approach. It was striking that similar anxieties of parental instinctive feelings that something was wrong in the early years were also experienced by some of the individuals diagnosed in

their teens. For some, these feelings were strong enough to motivate persisting, regardless of previous medical reassurances:

I4: *"then I went again to the GP it was like 'if you're really feeling this we can go and refer you to someone' and I was like 'yes please'"*

Unlike the family diagnosed at 16, who were diagnosed whilst undergoing tests for other conditions, disrupted puberty was the motivation behind the persistence of the family diagnosed at 18, who described repeated visits to his GP resulting in an eventual private referral to an endocrinologist who made the diagnosis:

I4: *"Yes, it was like BUPA or something, yeah it was all private, I got lucky there"*

For four of the families, therefore, diagnosis had been made by age 18, following a series of significantly different diagnostic routes. The narratives reveal none of the diagnoses were made as a result of referral for Klinefelter's and there was a feeling that diagnosis was made either through luck, family persistence or having private health insurance. For these families, diagnosis was seen as an unnecessarily effortful and stressful endeavour, which they felt could, and should, have been made previously during the frequent contact with health professionals.

For the last two families, the diagnosis remained elusive for a further 10 - 20 years:

M5: *"we've seen all these experts since the age of 2 … from the age of 2 we took him to all these specialists, paediatricians ... and he's been to his GP with problems over the years - no one said 'there's something going on here'"*

M6 (reading): *"much of his motivation and social difficulties seem to have been attributed to him being a normal teenager and, now in his 30's, living at home and unemployed he feels very frustrated and disenchanted"*

M5: *"unfortunately we didn't know he was suffering from this. He was not diagnosed until he was 26,27 which we felt very let down by, actually because we'd seen speech therapists, educational psychologists, psychiatrists…he'd seen a urologist 5,6 years before he was diagnosed, that is (pause) unbelievable… none of them picked it up"*

For the four families now diagnosed before age 20, the experience of diagnosis and feelings about finding out the diagnosis is explored in the following section.

M1: *"I was very lucky because … I found out before he was born"*

When diagnosis was made, the family feelings and challenges around the diagnostic experience were a focus in the narratives. The reactions to diagnosis were described in the context of what had come before diagnosis and was linked, for some families, to how and why the diagnosis was made. The family narratives reveal the first reactions to the diagnosis and the consequent emotions following the initial reaction. Differences in diagnostic perceptions for the family group were distinguished by the lengthy and effortful challenge to be diagnosed.

For the earliest, diagnosis was made by amniocentesis and therefore the family had a different diagnostic experience as the only family not to experience diagnostic delay:

M1: *"well I suppose I was very lucky because you know I found out before he was born … amniocentesis was offered"*

The timing of this diagnosis brought its own challenges and anxieties and the initial reaction to the diagnosis reflected the stress of being offered the choice of termination, presented to them by the consultant at the hospital, having had the results:

M1: *"it was obviously rather depressing … it did cause a lot of anxiety … I also remember on one of the forms that we had to fill in for some reason at the hospital … they were already offering the choice of having a termination which makes you think of this as … is a really serious condition"*

Diagnosis at this early stage carried the burden of significant anxiety and worry with the anxiety compounded by difficulties accessing accurate information:

M1: *"we didn't know anything about the condition at the time and even the consultant who told us about the result of the amniocentesis didn't know a great deal about it … we felt as if we were in the dark initially and this consultant did give us some very outdated literature which was based on an American prison population"*

For the second family diagnosed at 6, the diagnosis process had been more challenging, with multiple referrals with reassurances being given from general practitioners that there was no cause for concern. Having pressed for referral, the second family were referred to a psychiatrist who made the diagnosis in the course of testing for Fragile X:

M2: *"I persisted and went back to the GP and against his advice made a written request for a private referral out of the local NHS system to a London paediatric psychiatrist. We had a one-hour appointment, he read my document about my son, he sent us for a blood test … I thought 'good, now I know' … that was the start"*

7.3.3.1 Finding out: First reactions

The experience of diagnosis was different for the family group; for some the diagnosis was delayed for over 20 years. For the family to be diagnosed earliest, the diagnosis was seen as timely and valuable. All the families experienced the route to diagnosis, or the experience of diagnosis, to be difficult and burdensome

Initial reactions to the diagnosis varied and depending primarily on the timing of diagnosis: for some was relief that diagnosis had finally been made, for others the initial reaction was shock. Each diagnosis was seen as conferring its own burden, with the earliest diagnosis presenting the family with an immediate decision. Amniocentesis presented the shock of a diagnosis being made, followed by the stress and pressure of deciding the immediate future:

M1: *"it's kind of tough when you learn about this sort of thing, you know in the middle of your pregnancy and you're suddenly faced with all these difficult choices"*

The urgency of diagnosis presented some families with the challenge of accessing accurate information. Outdated or lack of information was described as contributing to the stress of diagnosis:

I3: *"Mum and Dad had some leaflets they were like, 'well we've got some leaflets here so you can read up about it'. It was quite hard to understand"*

For those diagnosed in their teens, the initial shock of diagnosis was also received with conflicting feelings of losses and gains, with emotional aspects of the impacts of diagnosis (such as infertility) to try and come to terms with:

I4: *"when they told me I was a bit shocked I was like 'oh, ok' and then he told me all about it - the infertility and stuff. It didn't feel great"*

There were feelings of sadness on hearing the diagnosis, with feelings of loss as well as recognition:

I4: *"yeah, I was like I remember crying with my Mum in the lift on the way down. I didn't know what to do at first, to be honest when he told me… then that was for a few days … I was really shocked and a bit 'oh I've got Klinefelter's' - everything matched to be honest"*

There was a feeling of finality at diagnosis for those who had sought an answer to concerns over the years. There was also the feeling that parental confidence had been adversely affected by feeling dismissed by doctors over the years. Diagnosis being made was restorative for parents:

M3: *"I was glad we did have a diagnosis. I just thought 'hooray - eventually' I just knew something wasn't right"*

For others, diagnosis was a vindication of their concerns and anxieties over the years and a validation of their instinctive feelings, which were perceived as incorrectly dismissed by health professionals over the years during the family efforts to seek answers.

For the parents and family, the initial reaction to diagnosis was a sense of relief that, after the years of worry, a diagnosis had been made. There were also feelings of recognition on finding out more about the symptoms of Klinefelter's:

I4: *"the voice not dropped yet, no facial hair, um my chest area, er I was just a bit like 'oh well' and then before I thought ' oh well there's something wrong with it, like the Adam's apple' and then when he told me I was like 'oh it all makes sense now'"*

For the latest diagnosed, in addition to the shock of the diagnosis, there were additional burdens of strongly expressed feelings of parental regret and felt they had some responsibility for the delay to diagnosis:

M5: *"unfortunately we didn't know he was suffering from this. He was not diagnosed until he was 26, 27 which we felt very let down by, actually because we'd seen speech therapists, educational psychologists, psychiatrists … he'd seen a urologist 5, 6 years before he was diagnosed, that is (pause) unbelievable … none of them picked it up"*

M6: *"'why didn't I know this before?' you'll always ask yourself that, won't you … I do wonder now - he was having speech therapy, I do wonder if the speech therapist had said to me … maybe if I'd persevered and thought 'why is he having speech therapy?'"*

M6: *"we had no idea … well I feel that I've let him down as well"*

The impact of the diagnosis and feelings that the struggles of the previous years could have been avoided by earlier diagnosis was the over-riding reaction from the families diagnosed last. Their narratives reveal a sense of loss of opportunity which earlier diagnosis was perceived to provide.

Diagnosis carried a complex range of feelings with significant effect on the families' lives. Despite the complex effects of diagnosis and subsequent emotions, the perception of the family group was united that diagnosis is important. After the initial shock of diagnosis, the families describe the experience and life effects of coming to terms with what diagnosis meant for them.

7.3.3.2 Finding out: later reflections: losses and gains

Having been diagnosed, the first reaction the families described was shock. This, however, for some, was tempered after the initial shock of diagnosis, with a range of reactions and responses experienced. Where there had been physical disruptions to puberty, the feelings of relief that treatment would now be available were strongly expressed:

I4: *"literally I was like the first two weeks I was like, oh great … as soon as the treatment kicked in I was like 'bring it on'"*

These feelings were evident in those who had experienced disrupted puberty resulting in teasing and bullying at school due to the physical differences to their peers. For some families the shock and sadness of diagnosis was replaced by the promise of a change for the better where pubertal disruption had caused problems with peers at school:

I4: *"Like it didn't feel great, to be fair, but it felt like 'I've got it, now I can get treatment for it now so … so it was a shock and at first it was: 'oh no this isn't good' and then when I saw him a few weeks later I realised 'this is good because now I can get treatment and fix it'"*

The impact of the undiagnosed syndrome during teenage years was significant and difficult to cope with feelings of loss of self-esteem, confidence and isolation from peers. Despite the initial sadness of the diagnosis, this was followed by the relief of treatment. The feelings of relief were due to anticipation of onset of treatment, being seen and experienced as a way forward with hope for transformational changes to 'put right' the physical problems caused by the syndrome. In this context, diagnosis was experienced as a balancing of losses and gains: despite the difficulty of diagnosis, which carried the burden of knowing of the infertility experienced in Klinefelter's males, there was relief and sense of 'returning' to how they felt before the syndrome 'interrupted' development:

I4: *"big time ... 'cos like 'I can develop now'"*

I3: *"I think it did both mentally and physically, I think it did make a difference … and I just started becoming more confident, yes I think I gained in confidence"*

7.3.3.3 Relief, sense making, 'we knew'

Access to experts with knowledge of the condition was identified by the Families as beneficial, particularly so at and around the time of diagnosis. Feelings of relief and recognition were experienced alongside a sadness that diagnosis had been delayed, with the problems this had caused for some, and with the knowledge of problems with fertility and what that may mean for them:

I4: *"no matter how bad the information like the infertility - that would be the worst one to know ... I had a problem with my mouth, er voice, and all the muscles, I kind of knew there was a problem, but I'm glad I could get that sorted"*

M2: *"My initial reaction was I was glad he didn't have something worse … then I was glad because I could plan for providing for him properly. Without diagnosis I would have been trying to provide for something I didn't know about and that's not possible"*

There was a feeling of finality at diagnosis, relief of finally knowing and having answers for concerns over the years:

I4: *"very surprised, like I couldn't believe it, like I had Klinefelter's and it was like I didn't really know what it was until he explained it and then it all made sense after that"*

The families' response to diagnosis revealed significant lifetime differences which resulted from diagnosis. For all, there were descriptions that diagnosis provided a sense of validation to their concerns over the years.

The importance of having an early diagnosis was, for all the families, set in the context of the elusiveness of diagnosis, experienced within family recollections of 'knowing' something was wrong and their efforts to uncover the answer provided a backdrop for these:

M3: *"it was a relief to get a diagnosis and know"*

M2: *"it just made so much sense … I knew from the beginning there was something not making sense, just little things"*

F3: *"diagnosis answered a lot of questions on our minds"*

I3: *"it's a lot to take in, it was quite hard to understand ... it was quite tiring, so it took its' toll on me in the end … it was quite stressful, but obviously it was a relief"*

Following the initial reaction to the diagnosis, there were shared thoughts: the value of the information diagnosis provides, relief that a diagnosis was made after a long search, a vindication of their earlier concerns and a sense that this was a beginning:

M2: *"I thought good now I know … now we can start … diagnosis gives you a complete picture … you know what you're dealing with"*

M3: *"I was glad we did have a diagnosis, I just thought 'hooray - eventually'"*

The thought that diagnosis was important, but that early diagnosis even more important was emphasised by the earliest of the family group who was diagnosed by amniocentesis:

M1: *"if you know what you're dealing with you can get help … and I think really obviously the earlier you know the better"*

M1: *"well I suppose I was very lucky because I found out before he was born"*

Where diagnosis had not been made in time to prevent failure of puberty and associated damage to confidence and self-esteem, diagnosis was seen as transformational, although 'better late than never' with the knowledge that diagnosis and treatment were a gateway to change and to 'return' to his peer group and re-gain his sense of self identity. The place of diagnosis in the lives of the four families diagnosed before 20 years of age was articulated in strong and positive terms:

I4: *"yeah, yeah - I feel really positive … if somebody doesn't know they've got it, I remember it was just horrible … Year 11, Year 12 was just crap, sorry, it was like, awful - everyone would just laugh, take the mickey out of your appearance and how you spoke and deep down I'm thinking: 'is there something wrong with me?' and then I went and found out there was and I was, like, 'great, so at least I can get it sorted out' … Knowing was 100% … you have to know"*

The family narratives are a strong testament to the importance diagnosis had for them and the family unit. Their testimonies reveal the challenge of the search for diagnosis and the place diagnosis had for each of the family. When eventual diagnosis was made, the perceptions of the importance of diagnosis was emphasised in the reactions of the families and the differences diagnosis made to their lives.

Having had a diagnosis, the value of diagnosis is explored through the perspectives of the families in the following section.

7.3.3.4 Finding out: 'on reflection'; losses and gains

Although diagnosis was made for different reasons, at different times in their lives, diagnosis was seen as transforming for the first four families to be diagnosed. After the initial reactions to the diagnosis, feelings around diagnosis evolved and diagnosis was subsequently described

in terms of losses and gains. This section explores perceptions of the value of diagnosis with the families now aware of the diagnosis with a subsequent section considering the longer term perceptions of the families with a later diagnosis.

For the four families diagnosed before age 20, diagnosis was experienced as beneficial, although the delay to diagnosis was perceived to be detrimental. The diagnostic challenges experienced by the family group were now considered in the impact of diagnosis on the family life. The sense of losses and gains was threaded throughout the narratives:

I4: *"no matter how bad the information like the infertility - that would be the worst one to know ... I had a problem with my, er voice, and all the muscles, I kind of knew there was a problem, but I'm glad I could get that sorted"*

I2: *"I don't really let Klinefelter's hinder my life or try and think about it as me having a condition. I try and think I'm a normal person with anyone else, but with a few problems"*

7.3.3.5 Information and adjustment

The family accounts emphasised how diagnosis conferred important information to parents which allowed them to adjust their thinking. This was seen as valuable in facilitating a change in parenting approach with an adjustment to their expectations and informing their decision making for their sons:

M3: *"diagnosis, yes, yes, yes, ... it makes you much more accepting"*

M2: *"diagnosis meant I could properly help my son with tailored provision in light of the understanding of the impact of the syndrome. I put in one to one support from the start for things he found difficult and for his strengths to boost his confidence and sense of achievement"*

The Family participants reported the experience of diagnosis was stressful and difficult, regardless of age at diagnosis. Each family experienced diagnosis in different ways, due in part to their experiences before diagnosis was made:

M2: *"without diagnosis you haven't the insight into the whole person, you're just addressing pieces of the jigsaw, haphazardly on what you can see, or as problems come up. You're not addressing the fundamental whole person …*

being proactive and putting things in place to prevent problems … you can't do that without a diagnosis"

M2: *"I think diagnosis gives you a complete picture which I think is really helpful with Klinefelter's Syndrome … you know what you're dealing with"*

7.3.3.6 Getting the experts on board

The families diagnosed earliest describe life differences made by having timely knowledge of the condition. The families described beneficial impacts, such as access to timely expert support, monitoring, and screening, which facilitated timely treatment, if needed. The two earliest to be diagnosed described the timely support they were able to co-ordinate for their son with the advantage of assessment and access to the experts:

M1: *"that was an advantage to be able to get that sort of thing set up at a fairly early stage so that he could be monitored and seen by a paediatrician"*

M1: *"it was good for us to know because we, as soon as he was born, we were able to set up the wheels rolling for arranging to see the appropriate consultants in the meantime, endocrinologists whatever and particularly at Great Ormond Street, so that was an advantage to get that set up at a fairly early stage so that he could be monitored and seen"*

M2: *"as soon as the diagnosis was made we were referred to Great Ormond Street, endocrinology, psychology … that expertise was a crucial part of his development and for me as a parent from 6 years right through and into his adult years."*

I2: *"I think my health dips in and out … I (am looked after) by great doctors in London I can't remember them all off the top of my head, there's a gastroenterologist, dietician I see and someone about my absent folate… I value their expertise …"*

There were descriptions through the narratives revealing the impact of Klinefelter's on the individual and their sense of self.

7.3.4 The Right to Know; 'getting myself back'

M5: *"basically I think everyone is entitled to an early diagnosis"*

Central to perceptions of diagnosis was a sense of lack of diagnosis causing loss of self-esteem, confidence, and, for some, a sense of loss of identity. The sense of diagnosis belonging to identity and understanding of the self was also suggested:

I3: *"I don't know, does the condition actually affect a person's personality? Or not? Does it make their personality different? If I didn't have it, if I were the same person, no me, but didn't have the condition, would my personality be different?"*

There were family hints of these emerging behaviours where diagnosis was delayed:

M2: *"when he was starting at nursery his behaviour started to cause problems, he would get really upset and have tantrums ... I thought it was frustration. I found ways to communicate with him like using visual things and little toys, when he felt more in control and realised he was understood, he seemed to calm down and his behaviour changed back to his normal self ... I think he just felt panicked and knowing he was able to make himself understood calmed him back down"*

SLT: *"that's what ... what they need is a voice, and if they're not given a voice then that group that I see a lot of ... those complicating barriers which have become functional behaviours for them, so the withdrawing or using inappropriate means to get attention, all those, they go on like layers of an onion and they go on like, boom, boom, boom, boom and they're there and once they're there that's when you've got real problems"*

M2: *"one day I saw when he realised what communication was ... we had a wall hanging with little pockets with things in numbered one to twenty ... he pointed to one pocket and I gave him what was in it. His face lit up - literally lit up - when I gave him what was in the pocket. That's when he realised what dialogue was and that's when I realised I had to find a way to communicate with him that wasn't using language - not then, not until later anyway - that was one of the most important days of his early years - he realised he wasn't trapped inside himself, I think"*

Central to perceptions of diagnosis was a sense of lack of diagnosis causing loss of self-esteem, confidence, and, for some, a sense of loss of identity. Diagnosed at 18, the effect of untreated, disrupted puberty caused bullying and teasing at school. The narrative describes how he had been happy at school and popular with friendships:

I4: *"when I was younger like Year 8 and stuff, I had friends … when I grew up and got to about Years 9, 11 I had really good friends … then I moved schools"*

Diagnosed at 18, the effect of untreated, disrupted puberty caused bullying and teasing at school. The narrative describes how he had been happy at school and popular with friendships, but this changed when he became the subject of teasing and isolation from his peers:

I4: *"then I moved schools - that was quite hard - 'cos that was when my voice hadn't dropped and everyone else's had so I didn't make friends in Year 11, 12 … it was tough … joining in was tough"*

His lack of diagnosis and treatment was described as becoming a barrier to integrating, joining in and expressing himself in his peer group. This later changed as a result of diagnosis and onset of treatment and his testimony was interesting in the way he talked about the changes wrought by onset of treatment, with the feelings that he could now return to being himself, back to the self he was and could once again 'felt like just myself…be myself':

I4: *"it boosted my confidence a bit more, that's for sure … voice hadn't dropped, confidence went down to an all-time low, just felt like crap about everything … then when I came back (after diagnosis) … I felt, like, great … then I came back to uni and felt even better, felt on top of the game, no, but felt like just myself … yeah, just be myself. Be myself"*

In contrast, the family diagnosed at 6 had provided a tailored programme of education and support underpinned by prioritising self-esteem and social relationships:

I2: *"I remember my school days very fondly and I really liked my school days um, I had a timetable filled with lessons that I enjoyed but also helped me to do classes that were a struggle, I was struggling at.. and join in with my tutors and my peers and, just join in really"*

The value of early diagnosis was described by the families and their descriptions of the provision they were able to facilitate. One parent reveals how an early piece of advice underpinned the provision she chose for her son which prioritised protecting and building confidence:

M2: *"the psychiatrist who diagnosed him told me his priorities were his confidence and his social relationships - that was a fantastic piece of advice that underpinned everything I did after that - for example, I turned down the place in the dyslexia base and kept him in the small prep school where there was a rounded education and he was already very happy there, with friends.."*

The family read out the comments of a clinical psychologist who supported the family following the diagnosis. This was seen as a testament to the significance of early diagnosis and the insight for parents this confers into providing appropriate and informed provision which, importantly, protected and nurtured a sense of self:

M2: *"the ongoing thoughtful and flexible approach has provided him with an environment which has prompted his development in all areas of his life and allowed him to flourish … this … has not only enabled him to progress in his education, but also to gain in confidence and develop a positive sense of himself"*

This highlighted the place of diagnosis as facilitating provision of a protective folio for the development of the self with provision of anticipatory, protective treatment and support. Further, this provides important information for the family regarding the development of the individual.

This risk to the healthy development of self was alluded to in the Specialist group by the speech therapist who described the consequences of lack of diagnosis and appropriate support causing 'layers' of defensive behaviours. These behaviours were attributed to the developing of protective behaviours resulting from frustration, including withdrawing and self- isolation from problems with peers of bullying.

This resonated with the importance of facilitating understanding explained by the Specialist group:

SLT: *"you're supporting social interaction you're supporting understanding of self"*

The effectiveness of such timely interventions from specialists was evident in the positive experiences described by a family diagnosed at 6 and, despite the struggle academically and social anxiety reveals a positive approach to problems:

I2: *"I think I fit in with everyone else as best I can um, I socialise - I do get nervous sometimes socialising - but when I'm in there and I start getting to know people then I'm not so nervous… that's because of all the hard work and time that I put in .. to have speech therapy lessons"*

The implications to the 'self' are hinted at in the Family narratives and underlines the less tangible, but significant, role diagnosis may play beyond educational and medical implications. Where diagnosis was not made, the perception was that diagnosis confers understanding which is significant to the development of the individual self and, in that sense diagnosis was seen as important.

There were also instances where diagnosis had informed parent choices about sharing information and their efforts to protect their son from information which may have had a worrying effect on his self-perception:

M1: *"we didn't tell him he had this condition about the full story until he was about 18 ... we thought it might just overload him ... how that would affect his image of himself"*

In this sense, the links made by the families between diagnosis, the ability to 'be yourself' and develop a sense of self are highlighted and the distress this caused where this is impeded. It is interesting to consider that this may be a causal platform, or offer an insight into, the increasingly variable problems of those diagnosed later. There were also expressions that families are entitled to diagnosis and this raises their view that there is a 'right to know':

M5: *"basically I think everyone is entitled to an early diagnosis"*

In the following section, perceptions reveal the cost to families of delay to diagnosis.

7.3.5 Moving on: the value of diagnosis: care and support; cost of late diagnosis

M1: *"being forewarned, we were forearmed, as well"*

Early, timely diagnosis was described to be important by all the families. For those diagnosed before they were aged 20, diagnosis was described to facilitate a positive change to their lives. Despite acknowledging the diagnostic challenges, of whom both were positive about diagnosis being important for informing parental choices and the resulting lifelong support:

M1: *"it's kind of tough when you learn about this sort of thing, you know in the middle of your pregnancy and you're suddenly faced with all these difficult choices, but in the end it was good for us to know"*

The transformation diagnosis afforded the families was seen as multifactorial but important for the positive changes the knowledge of the diagnosis made possible:

M1: *"I suppose we felt we just had to go for it and deal with the problems as we went along, but being forewarned, we were forearmed as well"*

Diagnosis was perceived to be necessary to the successful parenting of a child with Klinefelter's Syndrome and provided important insights into how to support and provide for their son.

For those diagnosed latest at post 25 years of age, the perceptions around diagnosis were perceived differently to earlier diagnosed families. The feelings of relief and anticipation of positive changes were absent from their narratives, which were dominated by descriptions of regret and loss of opportunity to benefit from diagnosis.

Without knowledge of the diagnosis, parents felt this was to the detriment of their son and the family unit:

F3: *"yes so it would have helped, it probably affects his quality of life"*

M6: *"much of his motivation and social difficulties seem to have been attributed to him being a normal teenager and, now in his 30's, living at home and unemployed he feels very frustrated and disenchanted"*

The following section explores how the family group perceived diagnosis affected the family.

7.3.5.1 Care and Support

M1: *"and just generally paying attention to those little details"*

For families diagnosed in the teens, diagnosis was associated with onset of treatment which could be started to address their pubertal disruption This was seen as relieving and an end to loss of self-esteem and confidence brought about by the isolation from peers. Teenage diagnosis was perceived as 'too late,' but was nevertheless seen in positive terms as making sense of parental concerns and a gateway to educational provision and support.

For other families, early diagnosis meant access to information to make informed choices for their son, schools for example, access to experts, monitoring and screening for early intervention, should these be required. Beneficial impacts following from diagnosis were identified by those diagnosed earliest, making clear how the knowledge of the condition changed their parenting style and informed their decisions significantly:

M1: *"although it was hard at the time, it was probably very good for us that we found out when we did … it enabled us to make decisions well in advance, about his schooling and that sort of thing"*

Both families describe how the diagnosis helped guide their choice of school and affected their priorities for their son:

M1: *"I did go around and look at these schools beforehand … the class sizes were much smaller and there was a much more structured approach"*

I2: *"I remember my school days very fondly and I really liked my school days um I had my own timetable filled with lessons that I enjoyed but also helped me to do classes that were a struggle, I was struggling at and join in with my tutors and my peers and just join in really"*

I2: *"It was very helpful I think I had a personalised timetable up until I got to university so the personalised timetable was very good… you need to make those younger years more enjoyable but also so you have to work on the things that are not fun and they become easier over time"*

Diagnosis meant that parents were aware of the value of being sensitive to nuances as early indicators of potential difficulties and enabled early intervention. Parents also described the value of adjusting and managing expectations of their son:

M1: *"when he started to go to kindergarten … it was a nice playgroup but we felt that he perhaps wouldn't get the kind of attention that he needed … I'd noticed when I went to pick him up he wasn't interacting so much with the other children he just wanted to stand on the side lines … so we decided to send him to a Montessori school where they had a different set up"*

Parents narratives described how having a diagnosis not only shaped their approach to parenting and informed choices about education and choice of school, for example, but also changed their decisions in the light of knowledge about the syndrome:

M2: *"I had been pressing for a place at the local dyslexia base, but when we got the diagnosis I turned the place in the base down … as the base was specialising in dyslexia … Great Ormond Street had advised I prioritise his self-esteem and social relationships - that was a really important piece of advice … it meant I approached his needs in a holistic way"*

Reports and expert assessments were also identified as important to inform parental choices and guide educational strengths and weaknesses:

I2: *I did things with my hands instead of using my brain to read or write… I think I read my first sentence to my class using symbols above the words…I built, like learning a part of history through making it in a box and um that helped a lot, that was really helpful in visual…"*

Interestingly these strategies in early school days were still useful through into adult life:

I2: *"I'm better with visuals than writing something… we did many things like that… that helped towards me - to this day - thinking about words through sometimes imagery"*

7.3.5.1.1 Not just help, the right sort of help

Early diagnosis was seen to have given the opportunity for parents to inform themselves as best they could, which they found helpful and beneficial for planning and choosing school and setting extra help in place and before problems arose and provide an informed insight into help and support that would be appropriate:

M1: *"we had read things about … perhaps having more difficulties than other pupils … the way they process information … they might have difficulty learning to read and write and slower learning"*

M1: *"we used to pay for him to have an hour or two extra reading every week and I think that helped … I think we already began to notice writing and his spelling"*

M2: *"he went to school part time to join in and for the rest of the week he had one to one support for literacy, speech and language, cooking, drums, and things he was good at"*

Significantly, the boys to be diagnosed earliest were both reported to have enjoyed school, in contrast to the later diagnosed families, the parents describe how diagnosis affected their choice of school for their son and that diagnosis alerted them to make prompt changes where early signs indicated this may be beneficial:

M1: *"so we decided to send him to a Montessori school where they had a different set up … only 3 or 4 in her little group … just paying attention to those little details you might not get in a normal playgroup … he was quite happy there"*

M2: *"I kept him in his small prep school where he was very happy and had friends and put in a timetable of tailored support to provide the expert one to one help he needed - he really flourished"*

The provision resulting from diagnosis was perceived to have conferred a resilience against known risks in Klinefelter's Syndrome. The early diagnosis was seen as being the key to facilitating an informed and appropriately different parental approach.

The education of both boys diagnosed earliest was described to have been a positive experience and both were said to be happy at their school. Both had extra provision, small classes and one to one specialised help at school, and one of the boys having a personalised tailored education, with attending school part time with out of school tutored support:

M2: *"I put in place a tailored education of one to one support for his strengths and weaknesses … he had a personalised symbol driven system to facilitate the idea of reading and to get over his auditory processing problems ... we drove*

hundreds of miles a week to his lessons - that was good too as he could have naps to give him energy for his next lesson"

Significantly, protecting self-esteem drove parental choices for the two youngest boys to be diagnosed. School was a positive experience and despite academic struggles, both chose to study at undergraduate and post graduate levels:

I2: *"well the symbols were easier than reading the word straight from the page, the symbols helped me picture the words that were difficult for me to read and drew a picture that would remind me what that word was and then I could read a paragraph, a sentence… yes, I think the symbols bump started - jump started - my brain to reading words over a certain length of years of doing it"*

Early diagnosis was also described as facilitating a thoughtful and conscious parental approach to aspects of the condition as well as influencing educational decisions:

M1: *"and just generally paying attention to those little details which you might not get in a normal playgroup ….. he was quite happy there, actually… they took a bit more time and trouble with children, particularly if they knew they were shy or had a bit of a problem…."*

M1: *"and also I think in two stages, he was about 7 or 8 and later when he was about 10 or 11 they did various psychological tests, they produced reports which we could then hand on to the school which was quite useful"*

The diagnosis also provided a context for health professionals to be vigilant and refer sooner rather than later if differences or difficulties seemed to be emerging.

Further care and remedial treatment were felt to benefit from early diagnosis and regular monitoring. Where there had been health problems parents found that the process of referral was more streamlined, with referral directly to an appropriate specialist, rather than back to the GP causing further delays:

M1: *"if you get a good paediatrician who knows about the condition that that can be a great help because he then in turn can refer you on to somebody else … for example, that's what we did when he had some skin problems and the Expert suggested he see a colleague of his … that was quite helpful really, so I*

didn't have to go back to my GP and go through the whole referral rigmarole again"

The mention of referrals was an interesting reference particularly when reflecting on the comments of the Specialist Group and the potential place these specialisms may play in vigilance for Klinefelter's diagnosis:

M1: *"once we'd been assigned a particular consultant at Great Ormond Street then you would have a regular assessment from about the age of three, so we did have regular appointments"*

Thus, diagnosis was seen as the gateway to early monitoring and intervention and was important for the family to know there was the expert guidance and screening, which was perceived as beneficial for the well-being of the family and reduction in anxiety and stress:

M1: *"I was just aware that once they started seeing children at Great Ormond Street it would be a good idea to get him on the ladder there then just began to follow his physical development really"*

M1: *"it was so helpful definitely because it was so reassuring to see a paediatrician who was familiar with the condition and knew what to look for, obviously and what tests might be needed in the future"*

M1: *"as they get older that's why it's good to have a good endocrinologist just to be aware of certain problems that might occur like osteoporosis and he's had one or two bone scans already … it's good to be aware of that too and knowing if they need to take any extra vitamins, vitamin D"*

The discussion with the earliest two families to be diagnosed echoes the observations of the Expert group that timely diagnosis makes monitoring and early intervention possible, thus avoiding or preventing problems. These perspectives were voiced by the families who also emphasised the value of intervening early where new or secondary problems were evident:

M1: *"and the clinical psychologist was very helpful, at one stage … he started pulling his hair out, I think it was an anxiety thing I think … and we went through a couple of stages with that … they came up with sort of various suggestions about how he could deal with that"*

M2: *"there was a time when we had indications of frustration and behavioural problems … we had psychological support at Great Ormond Street which was so important … and …the behaviour stopped"*

It was interesting that neither of the boys diagnosed earliest required testosterone treatment and went through puberty with no need for any intervention and this remained the case to date.

Early diagnosis allowed parental preparation to manage the fertility problems which Klinefelter's almost inevitably carries. The news of infertility was described by all the group as difficult. For those diagnosed earliest, there were opportunities to manage this news and provide time to absorb what this meant:

M2: *"I actively thought about looking out for his self-esteem and tried to set up his expectations in terms of what was possible for him…from the beginning, I never said 'when you have a family' because I knew that may not be an option for him .."*

Recent advances in medicine have resulted in progress being made in the fertility treatment, offering the opportunity in some cases of becoming a biological father. The hope that this development offers was important to the family group who knew about this development:

M1: *"the very fact that there may be a small chance is, is good and at least they have the option to, to have this procedure to identify any viable sperm and then have that sperm frozen for future use … it is immense"*

For the two families diagnosed before the age of 10, there were powerful testimonies to their perceptions of the importance of early diagnosis to their family:

M2: *"I told him about the diagnosis in small incremental ways, like I told him he had something different about him that meant he found some things a bit difficult, like reading and writing … so I told him over time in bits and pieces, so he came to know over time"*

M2: *"without diagnosis you have not the insight into the whole person, you're just addressing pieces of the jigsaw, haphazardly or as problems come up. You're*

not being proactive and putting things in place to prevent problems … you can't do that without a diagnosis"

M1: *"if you know what you're dealing with you can get help … and I think really obviously the earlier you know the better"*

In addition, both early diagnosed families described the reassurance and importance of their ongoing access to experts in the field:

M1: *"we've been very fortunate … you've got a lot of top people working who are at the forefront of research"*

Further, other important, non-medical support and input was described and, importantly, identified by the parents as a decision-making influence on education and choice of school. The families valued the assessments undertaken as a part of a cohesive 'whole person' approach to their sons' support which provided not only medical assessment, but to provide assessments of cognitive strengths and weaknesses. These were valued for the information this provided parents and informed their decision making. Taking a 'whole person' approach was felt to be significant to wellbeing and quality of life:

M2: *"the psychiatrist who diagnosed him advised I prioritise his self-esteem and social relationships and this underpinned all my choices for him from the age of 6 - one to one support for his strengths, as well as his weaknesses so he could experience success as well, not just be always struggling at things"*

The value of diagnosis and the array of medical, educational and psychosocial treatment and support which was provided to the families after a diagnosis had been made was extensive and transforming:

I2: *"my advice would be, it's just persistence and take every day as it comes… the school days were fun, but very very difficult … it's always good to be positive about a negative… life flows more smoothly if you are positive all the time, or try to be, than negative… keep a positive mental attitude throughout your school years…."*

For families diagnosed earliest, there were lifetime benefits from an early age, including a proactive and preventative management approach, holistic in style and delivery. This also

meant, that if it were necessary, monitoring of testosterone levels meant treatment could be started at the optimum time.

Thus, diagnosis was seen to confer a protective approach as well as an anticipatory approach before difficulties or problems emerge. Where problems do become apparent, these can be treated quickly, thus avoiding cumulative behavioural problems if left un-recognised.

Where diagnosis had been made earliest, secondary problems were not experienced and, where there had been indications of emerging secondary problems (behavioural, for example) these stopped and did not recur with specialist input and support. For those diagnosed the earliest (before birth and aged 6 years) the difficulties were contained to the initial 'core' problems

7.3.5.1.2 Care and Support: Later diagnosis

M3: *"it's a simple blood test, why couldn't it have been picked up years ago when he was a child … ?"*

For those diagnosed in their teens (aged 16, aged 18) the 'core' difficulties remained, but further problems emerged into their teenage years. These were caused by their lack of pubertal progression and the consequent physical differences this caused.

The regret later diagnosis caused was evident in the narratives and reflections of the later diagnosed families: different phrases and expressions were used when speaking of later diagnosis with 'if only' evident in their narrative:

I3: *"I think they found out too late, I think if they'd found out before I even hit my teenage years it would have helped"*

I4: *"if I'd had the treatment earlier, I'd probably have been on the same level as everyone else"*

Where abnormal puberty was the prompt which led to diagnosis, the treatment was seen as an immediate relief which would start pubertal progression and restore a sense of normality to life:

I3: *"if they found out before I hit puberty that would have helped obviously with the treatment and me going through my puberty, I think it might have helped*

me gained confidence and be better at socialising and maybe be better at taking information"

Despite some of the negative impacts of the syndrome, there were expressions of acceptance and relief that diagnosis, where delayed, had been made and not delayed further. The delay to diagnosis was seen as a barrier to timely treatment and the cause of the ensuing problems which timely diagnosis would have avoided through provision and treatment:

I4: *"at least I found out before I'm 20 … I'm one of the lucky ones … phew"*

I4: *"Diagnosis. yeah … I don't know what I'd do if I didn't know now. Obviously I'm grateful I found out, but it would've been nice to find out before that"*

There were also feelings of lost opportunity to provide appropriate educational support and extra help at school. Diagnosis was seen as the gateway to providing help at school which was noted to make a positive difference:

M1: *"so they could've possibly missed out on extra help at school and if you're not picked up until you're a teenager, again there's all sorts of implications because of the testosterone levels and all the rest of it"*

For the families diagnosed in the teenage years, diagnosis was also seen as positive, although these were experienced along with feelings of regret the diagnosis was not made earlier, with a perception that diagnosis could have been made earlier, but was missed:

I3: *"I think they found out too late, I think if they'd found out before I even hit my puberty years it would have helped - that would have helped obviously with the treatment and me going through my puberty"*

There was a sense of incongruity when feelings of relief and happiness were included in the family reactions: relief diagnosis was finally made, there was sadness that it had been delayed:

M3: *"I just thought 'oh hooray… eventually!'"*

These reactions may appear incongruous as a response to being told of a diagnosis which includes difficult implications such as infertility and may include coping with learning

difficulties and physical differences needing lifelong treatment, but was indicative of the value diagnosis was perceived to signify:

M3: *"getting the extra help at college … I thought 'oh it's a brilliant time now because he's getting extra support"*

M3: *"he really really struggled … he was just leaving school when he found out, when he went to college he had his own LSA - that's why for him I wish we'd known before … then he did get that extra input and he did really well at college - really well"*

I3: *"I always wanted to come to university, but if I hadn't had the help and support I had I don't think I'd be where I am today"*

As for the earlier diagnosed families, the teenage diagnosis was valued in providing parents with an understanding of the impact of the condition and enabled them to adjust their thinking:

M3: *"diagnosis, yes, yes, yes, … makes you much more accepting"*

F3: *"had he had the support he had at university, at school I think it would have made a great deal of difference, he struggled when he was at school, he just struggles, I think it might have made a difference … I think it was a bit late when we got it … unfortunately he was about 16"*

Where puberty was disrupted, this caused significant distress and resulted in bullying, feelings of difference, withdrawal and isolation. There was agreement that diagnosis in teenage years was 'too late', but treatment was seen as redemptive for the difficulties of their school years caused by the differences caused by their disrupted and lack of pubertal progress. Puberty was seen as a particularly sensitive time, with lack of diagnosis and treatment problematic. Reflecting on earlier feelings of sadness and isolation before diagnosis were tempered by post diagnosis relief that diagnosis had been made, treatment was forthcoming, and these were experienced as positive, transformational events:

I4: *"obviously I would love my voice to drop … at the time I wanted it so badly … like the most thing I've ever wanted … to be normal like everyone else and a*

bit sad I couldn't have that. But now I've got the treatment it's changed all that"

7.3.5.1.3 Diagnosis, treatment and transforming: 'it's a brilliant time'

For those diagnosed before 20, diagnosis was seen as a solution, the beginning of the chance for transformation and change with multiple positive consequences now a possibility:

I4: *"going on the treatment boosted … I was feeling a lot better about myself, yes confidence is the main thing"*

M3: *"diagnosis got him the extra help at college otherwise I don't think he would have got through…he really struggled. I thought 'oh it's a brilliant time, because now he's getting extra support"*

I4: *"I was getting on a bit better making friends, it boosted my confidence a bit more that's for sure. I went from Year 9 to Year 11 I was like pretty high confidence, got along. Then as soon as I got into the new school voice hadn't dropped, confidence went down to an all-time low, just felt like crap about everything … then when I came back half-way through that year, I felt like, great. And then I came to uni and felt even better … felt on top of the game. No, but felt like just myself. Yeah. Just be myself, Be myself"*

There were descriptions how their lived experiences were changed by the event of diagnosis. Despite the stress, and following on from the initial shock of diagnosis, diagnosis was seen as positive for them all:

I4: *"yeah I was a bit self-conscious of myself and I was a bit … had low confidence in my body and then I went and … got diagnosed … when I got diagnosed I felt it was just a bit of a relief"*

There was also a further recognition when reading about the symptoms and a clarity was felt to be achievable through diagnosis for providing an answer which made sense to them contributing to their sense of self; part of a cohesive whole person:

I4: *"yeah, I was yes most of the symptoms on the Klinefelter list, that's what I've got and the I read up on the treatment and it speeds everything up and I thought 'yeah! I can't wait to get started!'"*

Diagnosis is described in positive language and style, in contrast to the evident strain when describing diagnostic difficulties. Strikingly, there was evident relief and, perhaps, unexpectedly joyful reactions to the diagnosis which, despite the negative impact of the diagnosis, illuminated how important this was seen to be by those affected by diagnostic delay:

I4: *"Diagnosis was very good I was on the phone to my friend he was like 'your voice is deeper, you've changed a lot' (smiles) … yeah that made me feel so good about myself and the treatment"*

There was a noticeable change to expressions and tone of voice when the family group were describing the impact of diagnosis on their lived experience. These expressions were in contrast to previous sections of narratives with stronger, positive tone of voice evident, smiles during the recalling of the feelings around diagnosis, reinforced by positive language and relaxing of body tension.

Diagnosis was seen as important to every family group and early diagnosis was seen as even more important. The significance of diagnosis was such that life experiences were talked about in terms of before or after diagnosis, signifying the place of importance diagnosis was perceived to have in their lives:

I4: *"I was like, 'great, nice to get this sorted and then soon as I got diagnosed I was like really eager to get the treatment started. I knew and it has made a lot of difference"*

I4: *"I realised you can get treatment for it so it was like 'cool,' big time 'cos like 'I can develop now"*

I3: *"I didn't get any help before diagnosis … after, support made a lot of difference"*

I4: *"no matter how bad the information, like the infertility that would be the worst one to know I had a problem with my voice, and all the muscles I kind of knew there was a problem, but I'm glad I could get that sorted"*

The two families with the earliest diagnosis both explain how they chose private schools for their sons, on the basis of smaller class sizes which they recognised would be appropriate.

This decision led to the observation that the diagnosis had, for both these families, considerable financial burdens in providing for their sons and educational provision was seen as a significant factor for the family finances:

M1: *"we moved him into a private school for all the extra help, that's why we went down that route, actually"*

The sacrifices of time and money were added burdens for the family: time to arrange, co-ordinate and travel to medical appointments and money to fund support such as private speech therapy, private school fees and extra lessons. Although the financial burden was significant and reported by all the families to have caused them to make family sacrifices in order to fund the extra support, this was seen as essential to provide for their sons:

M1: *"we did go and get some extra help for him when he was in school … When he was in junior school we used to pay for him to have an hour or two extra every week and I think that helped"*

The perceived lack of standardised care pathway and regional differences were seen as significant factors to the care each family received. The family group clearly described throughout their narratives the proactive, ongoing intervention they perceived was necessary by the family:

M1: *"I think if I hadn't known what I wanted if I hadn't known about Great Ormond Street and paediatricians there … I don't quite know where I would have ended up, maybe I would have ended up at the local hospital with somebody who wasn't very knowledgeable about the condition and could've been a whole different story"*

This active and engaged parenting was perceived as necessary and all had concerns about their son as greater independence from the family home became inevitable. There were also evident strains and demands on the family to facilitate and co-ordinate diagnosis and subsequent provision:

M2: *"it seems people get diagnosed in a sort of haphazard way … for things like asthma there is a proper route to get diagnosed from when you first see your GP … I don't think that exists for Klinefelter's, or for treatment … which there*

should be for both - I was lucky I found out about going to Great Ormond Street and then UCLH"

The earlier to be diagnosed families describe that a lack of care pathway also puts parents in the driving seat, this is seen as simultaneously advantageous and disadvantageous. Parents noted the difficulty caused by the lack of a formal pathway. The families who were diagnosed the earliest underline that there is currently no standardised pathway of care. Treatment can be fragmented, can vary from region to region and the knowledge of the family can have a significant effect on the treatment they receive.

The family descriptions of the positive feelings about diagnosis, in contrast to those not having a diagnosis, highlights the importance and value of knowing:

M3: *"I just thought 'oh eventually, there IS something that's not quite right ... I just thought, 'it's been 16 years, it's a simple blood test, why couldn't it have been picked up years ago when he was a child … then he could have had a lot more help"*

I4: *"Yeah, yeah I feel really positive. If somebody doesn't know they've got it … 'cos I remember it was just horrible. Year 11, Year 12 was just crap, sorry, it was just, like felt awful - everyone would just laugh, take the mickey out of your appearance and how you spoke and deep down I'm thinking 'is there something wrong with me?' and then I went and found out there is - and I was, like, 'great so at least it can get sorted out'. Knowing was 100%. You have to know."*

The family narratives emphasise their feelings around diagnosis and how these were affected by the different timing of each diagnosis. For the earliest diagnoses, made before age 10, there was appreciation of the beneficial effects of diagnosis.

For those diagnosed later, in the teenage years, there was relief that a diagnosis had been made and regret for the lost opportunities they perceived resulted from lack of diagnosis. To balance these feelings, there were positive feelings that diagnosis, although delayed was not 'too late', being made in time for positive transformational life impacts. The following section has a focus on the family narratives of the two families diagnosed last: at 26+ and 35+ years of age.

7.3.6 Cost of adult diagnosis: emerging variability

M5: *"We were quite upset actually to think he'd gone through all that and a simple blood test could have saved him years and years of misery"*

In the families where diagnosis was delayed beyond into adult life and diagnosed at 26 and 35, there were different experiences of diagnosis and there were feelings, for the latest to be diagnosed, that it came 'too late'. Diagnosis remained elusive and therefore too late for them to experience the benefits of diagnosis described by the earlier diagnosed families:

M5: *"maybe if I'd persevered and thought 'why is he having speech therapy?' we knew something was wrong - you can't always know what's wrong, you just don't know"*

In contrast to the families diagnosed earlier, there were also descriptions of difficulties which were perceived to have increased over the years. This is unlike the earlier diagnosed families, all of whom experienced diminishing of problems and a perception that diagnosis had brought beneficial changes. Strikingly, the families perceived that, where diagnosis was delayed, this had the effect of causing significant secondary problems and an increase in intensity of primary problems. Where diagnosis was delayed into adult life, this was seen as significantly detrimental:

M5: *"oh very, yes, very bad anxiety, been a problem for a very long time, I'd say it's got worse"*

As with the other families, there had been early parental concerns, but despite medical referrals and repeated attempts to find the diagnosis, this had not resulted in earlier diagnosis. This was experienced as an expensive oversight. For those diagnosed last at ages 26 and 35, there was a contrast between reactions of the families diagnosed earlier. Other families, even where diagnosis was delayed into the late teens, there were positive feelings around diagnosis, as well as shock that diagnosis was not made earlier. For both of the families diagnosed into their twenties and thirties, there were none of the positive feelings linked to diagnosis, in contrast to the earlier diagnosed families.

Despite the efforts they had made over the years to have a diagnosis, their narratives told of a sadness for their son and difficulties which they attributed to lack of diagnosis. There were

also descriptions of difficulties which they perceived had increased over the years in contrast to the other families who all perceived diagnosis had brought beneficial changes:

M5: *"oh very, yes, very bad anxiety, been a problem for a very long time… I'd say it's got worse…"*

M5: *"not only that, you get on to other problems, it's all to do with this isn't it ... terrible depression at times, really bad"*

M6: *"a degree of irritability, low mood and general anxiety"*

The theme of multiple health referrals was referred back to for the latest to be diagnosed who shared a similar pattern of repeated medical referrals, but not resulting in diagnosis until adult life. In this context, the families found the lack of diagnosis particularly hard to accept:

M6: *"not one person had ever diagnosed this condition, which is unbelievable isn't it, really. He's seen a urologist 5, 6 years ago that is … (pause) unbelievable … none of them picked it up"*

Diagnosis was perceived to provide answers and make sense of family worries and questions which, until diagnosis, remained un-answered:

M5: *"having a name for something helps a lot, because when he was at school we could have said 'this is what he's suffering from', then people could go and find out all about it and it would give them a greater understanding of what the child is going through"*

For those who had the latest diagnosis, there were parental feelings of guilt and having let their son down, alongside the regret that diagnosis had come so late:

M6: *"we had no idea … well I feel that I've let him down as well … we've seen all these experts since the age of two and he's been to his GP with problems over the years … no-one said 'there's something going on here' from the age of two we took him to all these specialists, paediatricians"*

The family group also described the importance of diagnosis in providing parents with important information about support and provision for their son and, where diagnosis was not made until the adult years, there was a realisation that they had been denied this information:

M5: *"Basically I think everyone should be entitled to an early diagnosis, I think"*

And the eventual diagnosis was described in more negative terms, while also expressing feelings of regret and remorse for the diagnostic delay:

M6: *"we had a shock I'd never heard of it. It was a terrible shock. We were quite upset actually to think he'd gone through all that and a simple blood test could have saved him years and years of misery"*

M5: *"I think he just sort of gave up really"*

7.3.6.1 Diagnostic delay

All of the family group advocated strongly for early diagnosis in all Klinefelter's individuals no matter how subtle, or otherwise, the presentation appeared to be:

M1: *"it does make a massive difference rather than you're in the dark… it's that fear of the unknown, what the future holds and how things might change as well "*

M1: *"if you know what you're dealing with you can get help"*

For the two boys diagnosed earliest (antenatally and at 6 years old), there were no pubertal problems, and neither were on testosterone treatment, despite being in their twenties. It was interesting that the two diagnosed youngest did not require treatment during puberty. Having been diagnosed, they were both monitored for their pubertal progression and, had treatment been necessary, intervention would have been prompt and timely. They were also reported to enjoy school and had tailored support and small class sizes.

For two of the families, diagnosis came at the end of their teenage years: one at 16, one at 18. Both had sought medical advice for similar problems for general poor health worries over the years and latterly with concerns over pubertal differences.

The later diagnosis was considered late but seen positively and associated with the benefits of diagnosis: help in the latter educational years after the diagnosis was made. There were feelings of regret support was not provided earlier and feelings, expressed by all the family group that the process of diagnosis was seen as essentially a straightforward blood test. This

heightened feelings that with this simplicity of testing, diagnosis should be forthcoming earlier.

For the individuals diagnosed as a result of abnormal puberty, testosterone treatment was seen as positive and there was relief that treatment was available to resolve the numerous problems and distress this caused:

I3: *"I think it did both mentally and physically, I think it did make a difference … and I just started becoming more confident, yes I think I gained in confidence"*

For the families diagnosed at 26 and 35, the descriptions from both families mirror their shock. This seemed related to the lateness of the diagnosis as well as the shock of the diagnosis itself: For the two families diagnosed last the impact on both families was described in more negative terms while also expressing feelings of regret and remorse for the diagnostic delay. For both families who were diagnosed in later years (post 26), there were accounts of hardship and struggle which were attributed to the untreated Klinefelter's Syndrome, caused by the lack of diagnosis:

M6: *"he had a fairly tough time and was bullied in his secondary school"*

M5: *"much of his motivation and social difficulties seem to have been attributed to him being a normal teenager and now in his 30's, living at home and unemployed he feels very frustrated and disenchanted"*

Implications of the syndrome were perceived to be problems which have become worse over time with social contact, anxiety and depression, with one family describing significant unhappiness:

M6: *"having been diagnosed at that late age he needed a long time to come to terms with it and he needed a lot of counselling"*

The two oldest to be diagnosed were felt to have fared worse than if they had been diagnosed earlier, with secondary problems developing with increasingly problematic impact:

M5: *"he got a summer job … I dropped him off, my car was parked in the car park with my shopping. He was sat crying on the footstep - how sad is that? He said 'I've walked out … I just couldn't cope with the people and everything.' He was*

- he couldn't cope. I was quite shocked, really. He can't cope with people. It's a socialising thing."

M5: *"he's in a terrible state, he just can't cope he's in a terrible state, he's shaking. He shakes you see, if we went into a bank and then asked him to sign something he shakes"*

M5: *"I think that's why he took that overdose … it was desperation they gave him charcoal, he would have died if it had gone to his liver … thank god I was there, it doesn't bear thinking about, the ambulance man said: 'lad nothing in life is ever worth doing that for' it's true isn't it … they don't think like that"*

7.3.7 A shared diagnosis: family and diagnosis

Taking the narratives as whole, it was clear that although the focus was the family member with Klinefelter's, their testimony made clear how profound was the effect on the families:

S2: *"I do think (diagnosis) is important, it gave my brother access to the help he needs, and it confirmed my mother was right"*

S2: *"diagnosis opens a lot of doors to help at school and … psychological help … I don't think he would have got that support without a diagnosis"*

The value placed on diagnosis was evident through the narratives, with 'struggles' and implications described for all the family. There were different accounts of how the impact was experienced, or perceived, but the accounts make it clear that, although differently experienced, all did feel the profound impacts of the syndrome. In this respect, diagnosis had an impact on the family:

M6: *"I think it would have helped him a lot, I think it would have helped the family a lot … you have a lot more understanding"*

M6: *"your patience does wear thinly at times … yes, fortunately his brothers are very good with him, I can see at times they find it a bit trying"*

The idea that diagnosis offered a context was described by the siblings, as well as parents, and was thought to be helpful in providing answers and making adjustments to expectations:

S3: *"I couldn't understand why he couldn't catch a ball and he'd be all over the place … um I think that's what I found frustrating 'come on catch the ball, it's not that hard' (laughs) and then when Mum told me I thought 'oh that makes sense… that's why'"*

In this respect, diagnosis was a shared diagnosis and demands were perceived to result from the syndrome with family implications:

S2: *"I think people tend to focus on the diagnosed one, rather than the ones who care for them … their family is the one who had to guide and protect them through all the nuances and difficulties of life"*

F3: *"I think it might have helped (the family) earlier, yes, I think it might have made a difference, I think it was a bit late when we got it, unfortunately I think he was about sixteen…yes, so it would have helped"*

Diagnosis was perceived by all the families as important and carrying significance to the life of the individual and the family who support them:

S2: *"I think psychological support is very helpful for the family"*

The siblings' narrative described the significant impacts the diagnosis was perceived to make, with accounts of siblings changing their behaviour and getting themselves into trouble at school by 'standing up for' their sibling, who they perceived as unable to assert themselves with their peers, highlighting perceived vulnerabilities:

S3: *"so I sort of found myself maybe sticking up for him and looking out for him"*

S2: *"my brother is very trusting and gullible, and that's a dangerous combination"*

The siblings' narrative described the significant impacts the diagnosis was perceived to make to their lives, with accounts of siblings changing their behaviour to compensate or protect their brother, who was seen as vulnerable, or taking a parenting role:

S3: *"I think it we're in a public setting I do try and make sure I'm more well behaved so that he doesn't … I try and set a good example"*

S3: *"I'm like 'Mum I'm the one saying something why don't you say something?'"*

Thoughts from the family group for family support included the opportunity for psychological support to increase understanding for the syndrome and the impacts on the family as a group as well as for individuals:

S3: *"I think maybe … sitting down with the siblings explaining it to them … maybe someone within the field … so they're more knowledgeable and understanding I think that's missed in a way I do think that's an important part of it, to be aware how to deal with it"*

S3: *"a sibling group … yeah that would definitely be helpful to know more people who deal with the situations, just exchanging stories and talking about it … just give them more knowledge, that's the main point, a bit more of an understanding"*

S2: *"I think it would be a good idea for the boy to see a psychologist and maybe have a few sessions as a family"*

S3: *"of course it is (diagnosis is helpful) if something's found at an early age of course it's helpful um I don't think he would ever have gone to uni and done some of the things he's done if he wasn't diagnosed … the earlier you find out, the better"*

There was consensus that the diagnosis was shared lived experience within the family. There were shared perceptions about the diagnostic experiences within the group and an emphasis of the significance of the diagnosis and the impact on the family:

I2: *"they are the ones helping you and supporting you and being there for you 100% so they're the ones you need to keep by your side"*

Families diagnosed before adult life perceived diagnosis as a facilitator of positive change, affecting their parenting:

M2: *"diagnosis was the beginning of knowing what was needed… but trying to provide this carried a huge commitment of time and money to provide the support and education he needed … as well as one to one support is hard - you have to find and co-ordinate everything yourself … everything is just fragmented"*

Thus diagnosis was seen as a positive beginning with access to information and expert assessment to provide appropriate support, but conversely, finding where and how to provide this was difficult.

For the family group, the later the diagnosis, the less beneficial effects were reported. For the final ruminations of the group, their thoughts turned to the future and it is this final theme which is considered in the final section:

M2: *"I have learned to try to not look too far ahead"*

There were impacts on the family resulting from later diagnosis and this was experienced particularly negatively where diagnosis was delayed beyond the teenage years, where no beneficial effects were described:

F3: *"I suppose it can be difficult to come to terms with as a family … I think it would have helped to have a diagnosis earlier, but we have to live with that and go from there"*

M6: *"we had no idea … well I feel that I've let him down as well … we've seen all these experts since the age of two and he's been to his GP with problems over the years … no-one said 'there's something going on here' from the age of two we took him to all these specialists, paediatricians"*

M5: *"I think then we would have found out everything about it, what help he would have needed and in the future about the hormone treatment"*

M3: *"I just thought 'oh eventually … there IS something that's not quite right' … I just thought 'it's been 16 years, it's a simple blood test, why couldn't it be picked up years ago when he was a child? … then he could have had a lot more help"*

7.3.7.1 Fertility

Recent advances have meant that there is now treatment offered to males with Klinefelter's Syndrome which offers the hope for some becoming biological fathers. This treatment has only become available over the past ten years or so; previously there had been no realistic prospect of this for the majority of Klinefelter's males. The treatment lends a particular, and further, impetus to diagnosis. However as treatment is reported to be time dependent, with

optimum treatment time recommended during the twenties. This advance represents significant hope, but is clearly also dependent on a diagnosis having been made:

M1: *"you don't know when things might change and I mean the very biggest thing is, or one of the biggest things is the fertility thing, which is obviously very sad and you know some of the boys it's very important, well I suppose for all of them with this condition"*

M6: *"knowing he will not have children. I think he finds that difficult"*

Anxieties around, and associated with, infertility such as self-esteem, how and when to disclose to a partner were seen as a further burden. Infertility was seen as a life defining and difficult aspect of the condition:

I4: *"sometimes I do think about it a little bit like if I marry someone I've got to probably break it you know about the infertility thing before I marry them. You know, sometimes I think will they say 'no I don't want that to happen' kind of comes into my mind, yeah, but if the person I'm going to marry one day, she will know that, she will do that for me"*

The advances in fertility treatment has implications for the urgency of diagnosis and having the opportunity to have fertility treatment. Further urgency is lent to having a timely diagnosis as early research indicates that success of the fertility treatment is time dependent, and therefore the window of opportunity for treatment may be missed by a later diagnosis and success rates likely diminished:

M1: *"it is immense and unless you are in that position you can't imagine quite how they feel … that can make you feel very depressed … so I suppose now maybe there is a glimmer … it's got to be a good thing"*

7.3.7.2 Holistic support

Increased awareness in increased risk groups was felt to be important: 'diagnostic cluster group' (DCG)

M5: *"a speech therapist should be looking out for this how many speech therapists are looking out for this from day one … he has apparently got all the physical manifestations and signs of this"*

There are also manifestations which were identified by some in the Family Group affecting wider settings such as work and employment prospects.

The family group agreed that a multi-disciplinary informed centre of excellence offering lifespan specialist support is needed. The impact of the syndrome was perceived to affect quality of life by all the family group. Diagnosis was perceived to be the start of a process by which the negative impacts could be ameliorated through treatment and support. Late diagnosis was seen as denying the family the chance to provide an appropriate home environment for their son:

I4: *"might be helpful (psychological support) 'cos like getting the news, getting the injections having these random mood swings it's a bit like full-on, it's a bit weird as well, so maybe … maybe … you also feel a bit down at times, depressed maybe. You feel like down in the dumps a bit"*

M6: *"it's the social aspect that's hard… the anxiety"*

I4: *"the sleep is still screwed up … I just don't understand what's going on"*

M5: *"the worst thing is this night thing his sleep is awful, awful"*

M6: *"he has significantly disrupted sleep, that is still a problem"*

I4: *"I think my parents just forgot I had mood swings … That's the only downside of it (the testosterone treatment) … it does improve but gradually, the first 3 or 4 years you have mood swings"*

I4: *"a few months ago like I was going to a party, I was getting ready. I just felt so angry, I just felt so tense for no reason"*

I4: *"just chill out in my room, just not speaking to anyone really, it's a bit anti-social, but it works, or going for a nap or something"*

These angry feelings were upsetting and disturbing for the individuals who found it difficult to understand and cope with and also for their family, who were not infrequently affected by the mood swings and, trying to be understanding, could also find these difficult to manage at times. Therefore, psychological support was identified as being helpful for the families, were it offered. The stress of managing the 'big feelings' experienced by the group, was evident:

I4: *"I was in my room and just chilled in there … yeah now it's alright I get the odd mood swing here and there, but it's usually when I go home as well (laughs)"*

There were also perceptions that support for social interaction and relationships may be beneficial as there were accounts of these being sources of difficulty.

7.3.8 The future: a vulnerable group

The feelings of needing to protect from vulnerability was a common anxiety for all the family groups who all described their perceptions that Klinefelter's Syndrome increases vulnerabilities to illness, poor health and expose them to individuals who would seek to take advantage of them. As with all the families, there was considerable anxiety and concern for the future as their sons moved into adulthood:

M1: *"but as they get older that becomes more difficult … once they're over 18 there's this confidentiality even with the doctor and they … so it gets harder to … trying to protect them and push their case forward"*

There was recognition and some frustration that increasing in age meant increased societal pressure and expectations. The message was of anxiety for their sons, seen as naïve to the wider world and beyond the safety net of home and family. In this sense, the gap between a Klinefelter's male and a male who does not have the condition widens, rather than diminishes, over time:

M1: *"you feel more because it's expected of them in the adult world, but particularly when they go to university … they just don't know how to deal with certain sorts of situations because they quite often lead quite a sheltered life really, they go to school and parents protect things with them and they're not really street wise"*

The importance of social awareness, the ability to empathise and have an understanding of others and different views are seen as potential problem areas:

M1: *"particularly with relationships and things like this where one has to be terribly careful, I think it's very hard for young people now in a way … the whole social thing, it's tricky"*

In thinking about the social implications, there was a shared concern, with the greatest fragility noted was the naivety of their sons and the risks they perceived this exposed them to:

M1: *"they take people at their word, really"*

F3: *"I'm more concerned about how it affects him and his future and his interactions with other people because he can be a little black and white … the problems I think he is going to have in the future and it worries me in that respect more than anything else, really"*

M1: *"you have to learn to let them learn, sort of experience the world for themselves … just learn to be more independent … you worry whether someone like him will be taken advantage of in life"*

M6: *"it's the social aspect that's hard, the anxiety"*

The dilemma for them all was the awareness of the decreasing opportunities to protect their son or sibling from vulnerable situations:

M1: *"well you can't be with them all the time in every situation can you so that's quite difficult to come to terms with isn't it really because you're always sort of fearing that something (laughs) could go badly wrong"*

There was consensus that psychological support, workshops and help would be beneficial for the family as well as specifically for their son, particularly with a focus on vulnerabilities.

In conclusion, the family narratives illuminated a shared family sense of struggle caused by the impact of Klinefelter's Syndrome. To ease the struggles, an early diagnosis was perceived as not only significant, but essential.

Table 16: Summary of Help

From Parents	Medical	From Education	Other	For Family
Paying attention to details - early intervention	Input from experts from early years: monitoring and screening	Extra one to one support: reading, writing, literacy, extra sessions to revise lessons	Social opportunities, support for socialising at school and beyond	Access to expert information; support for parents, carers and siblings
	Psychological support for emotional and psychosocial input; quality of life	Speech therapy input	Career help: cv, interviews, job applications	
	GP: informed and optimising good health		Hobbies: something to be good at, one to one lessons for hobby's ensure understanding and to keep on task	

7.3.8.1 Diagnostic Cluster Group (DCG) Family (DCG Part 3)

There was a clear message from the earlier to be diagnosed that diagnosis empowers parents' decision making and, for those diagnosed in their late teens, diagnosis provided an answer.

Due to the significantly increased risks, these have been included in the Diagnostic Cluster Group (DCG), as proposed earlier in this study, as a summary checklist for potential diagnostic purposes. The DCG is intended for use to aid and inform potential diagnosis through identification 'clusters' of recognised health risks for those with Klinefelter's Syndrome. It is hoped these may be beneficial in providing targeted select groups for referral for chromosome testing, such as asthma and allergies.

From descriptions and lived experiences of the Family group, diagnosis (or the lack of it) seemed to have a potential to impact differently on the same individual, depending on the treatment and support provided to that individual. Intriguingly, in those to be diagnosed at a younger age, the impact of the condition appeared to remain contained to the few, but significant, deficits reported in infant males: a 'core' set of difficulties. When diagnosed later, increasingly complex profiles, troubled life experiences, emotional fragility and emergence of

patterns of social withdrawal, isolation, anxiety, depression, under-achievement and medical problems were recorded. Is it possible, therefore, that timing of diagnosis may have a part to play in the hallmark variability that is universally reported for the syndrome? Variability in the literature perhaps contributing to the perception that Klinefelter's is variable but is in fact a reflection of the fragmentation in the literature.

There are reports in the literature that diagnosis is important for access to treatment and support which are significant to outcomes. The perceived significance of diagnosis for Klinefelter's Syndrome and the experience of the diagnostic process was important to explore in addition to the GP, Specialist and Expert Groups. To ascertain as complete a picture as possible for the families, interviews with parents and siblings were explored in addition to individuals with Klinefelter's Syndrome.

7.4 Summary

The Family group created a powerful shared narrative emphasising the importance of the diagnosis of Klinefelter's. All reported that diagnosis had significance to their lives, regardless of timing of diagnosis. Diagnostic challenges were described by all the families and was seen as an essential gateway to important services, treatment and support to manage the life 'struggles' caused by the underlying syndrome. Diagnosis was also seen to be a major contributing factor to outcomes and, where this was delayed, this was seen as unnecessary and detrimental to the wellbeing of their son, or brother:

M3: *"I struggle with it all"*

I3: *"yes, you do have to struggle a lot more in life"*

There was also unison for the need for a diagnostic pathway to provide a streamlined diagnostic process to assist with avoiding diagnostic delays, increased awareness of health professionals and provision of a holistic programme of care to address the complex array of health problems, maximise potential for wellbeing and minimise emergence of secondary problems. For this group, there seemed striking commonalities, with the reported hallmark variability emerging only when diagnosis was considerably delayed. This delay was perceived to result in a later emerging array of complex problems:

M5: *"we were quite upset actually to think he's gone through all that and a simple blood test could have saved years and years of misery"*

For the closing Family group thoughts, there were considerations for the future, with anxiety and worries for the welfare of their sons. There was agreement that this was a vulnerable group open to being taken advantage of by others:

M1: *"they just don't know how to deal with certain sorts of situations … they quite often lead quite a sheltered life really … they're not really street wise"*

The need for a specialist clinic delivering holistic care and support was advocated for by all the Family group due to the constellation of impacts of the syndrome and the lifetime effects and need for monitoring, care and guidance:

M5: *"a centre, multi-disciplinary … who can advise on the whole … someone from the team should be able to go to school encourage them … the expert team consistent throughout their life"*

There was also unison for the need for a diagnostic pathway to provide a streamlined diagnostic process and provision of a holistic programme of care to address the complex array of health problems, maximise potential for wellbeing and minimise emergence of secondary problems:

M1: *"I think if I hadn't known what I wanted, if I hadn't known about Great Ormond Street and paediatricians there I don't know where I would have ended up, maybe I would have ended up at the local hospital with somebody who wasn't very knowledgeable about the condition and it could have been a whole different story"*

For this group, there seemed striking commonalities, with the reported hallmark variability emerging only when diagnosis was considerably delayed. This delay was perceived to result in a later emerging array of complex problems for those diagnosed latest and there was regret for the lost diagnosis and the protective support this facilitates:

M5: *"we were quite upset actually to think he's gone through all that and a simple blood test could have saved years and years of misery"*

The Family group created a powerful shared narrative emphasising the importance of the diagnosis of Klinefelter's. All reported that diagnosis had great significance to their lives, regardless of timing of diagnosis. Finally, the diagnosis was experienced as a shared, family

diagnosis with significant impacts for the family unit. In sharing their narratives, the Family were united in their advocacy of not only having a diagnosis, but having an early diagnosis:

M5: *"basically I think everyone is entitled to an early diagnosis"*

I4: *"Knowing is 100%. You need to know"*

Figure 5: Diagnostic Cluster Group (DCG) Families (DCG 3)

Developmental Diagnostic Clues:
'A Lifetime of Clues'

Antenatal, Early Infant Clues	(Family 1 diagnosed amniocentesis)
Diagnosed antenatally	M1: "I was very lucky because I found out before he was born... amniocentesis"
Late development	M3: "I always felt that there was something different and I just couldn't put my finger on it, just late development… I always felt that something was not quite right" M3: "he was late to crawl, late to walk, late to speak, speech was quite late, he had problems in every aspect of walking, talking crawling, all the normal… he was very slow, slower in development" M6: "the paediatrician said 'he's coming on, he's just a bit slow, they do everything at their own pace, just a bit slow"
Referrals	M2: "he was referred for late speech, late to walk, audiology, all his milestones" M6: "audiology he was referred, speech he was referred, he had big problems there, co-ordination, reading and writing definitely"

↓

Childhood Clues	(Family 2 diagnosed age 6)
School	M1: "when he started to go to kindergarten, I noticed he wasn't interacting so much with the other children, he wanted to stand on the side lines" M6: "from the first day at school he had extreme anxiety" M3: "pronunciation" M1: "at junior school we began to notice… he did have more difficulty writing and he might miss out words" M6: "he's definitely got dyslexia" M6: "learning to rise a bike was impossible… doing shoelaces, button through button-holes, he struggled kicking a ball, catching a ball" I3: "distractions, everyone talking all around you, even the noise they make" M6: "we thought he had hearing problems, he had a test at school"

Health	M1: “some skin problems” M2: “immunology – immunisations T cells” M2: “chest” I4: “chest infections I’ve had quite a few of them, before I even got diagnosed with asthma… I got a chest infection that went on for months” I3: “I get asthma and hay fever” M2: “he had lots of allergies, he was allergic to all his childhood immunisations and had to have them as a day patient in hospital, he was referred to a specialists and immunology with off T-cell results” M2: “the GP’s missed his chest infection… then he was diagnosed with serious pneumonia with serious complications… he was off school for nearly a year… then he got it again only not with the same complication… everyone was very vigilant after that” M2: “after his pneumonias he had real problems with food and his weight was falling… he had real problems with his tummy, eating and it affected his quality of life… he was admitted at least 3 times as an emergency... now he sees a specialist and is on a gluten free diet which has really helped… seeing a dietician and being monitored by experts has kept him well since… and able to manage his symptoms” I3: “I’ve had all these upset tummies and backache… I struggle with my sleep, anger issues, stress and upset” I3: “I was quite poorly when I was 8 or 9 years old and I was in hospital quite a lot… I was just not eating anything and was just wasting away I can’t remember why I was in hospital on a drip” M2: “flat feet”

Clues at Puberty	(Family 3 and 4 diagnosed at ages 16 and 18)
Health	M3: “he was diagnosed at 16, he wasn’t referred for Klinefelter’s, he had white fingers, his hands were really cold, Raynaulds? They wanted tests done, they thought Marfens” M1: “he started pulling his hair out… I think it was an anxiety thing” F3: “I’d say possibly general build he was always not very well developed… just struggling with his schoolwork” M6: “he was lacking in confidence, his visits to the doctor were frequent and his confidence was dropping”

School	I4: "I struggled a bit at school. Always struggled quite a bit like writing and mental processing" I3: "I think it was the learning aspect I struggled with" M6: "he didn't have a happy time at school he was bullied he was marginalised… they called him names and they were horrible names… I thought it had stopped but in sixth form it was continuing"
Puberty	I4: "I went a few times to the GP and they went 'oh it'll develop' and I was like 'my voice hasn't dropped yet is there a problem here?' And they were like 'no it'll develop' I was persistent asking my Mum... I was about 18… had a private referral and then when he told me I was like 'oh well it all makes sense now" I4: "like… the voice not dropped yet, no facial hair… and I wanted to get it sorted 'cos I was like getting a bit of stick for it as well" I4: "I was quite shy… when my voice hadn't dropped… I didn't make many friends… it was really tough… joining in was really tough, it was horrible"
Other	I3: "I was a bit shy. I suppose back then I didn't know I had the condition, so I just through I'm not confident enough" M6: "in the school playground… he came… a group of boys every time they saw him they kicked him… punched him. pushed him down the stairs... they made his life hell… he was just a bit different, he was an easy target" I3: "socialising I think with me you do struggle with social environments… the interacting was hard… having conversations with people that's something I struggled with"

Post Puberty/Adult Clues	(Family 5 and 6 diagnosed at 26 and 35+)
Health	I4: "I used to see the doctor quite a lot" M2: "absent folate haematology" I3: "I try not to eat anything with cream in it, it's a bit sickly… I don't have breakfast in the morning I find it too hard to digest anything" M6: "it's a kind of allergy, it flares up, his hands have been in a terrible state with blistery stuff, we had real problems with his hands" I3: "I think I'm allergic to medicine, penicillin" I4: "and allergies yes, a weird one – plasters… I got all scratchy and it wells up and goes all yellow"

	I4: “back pain, that’s quite common, it’s the worst pain” I4: “the sleep is still screwed up” M6: “the worst thing is this night thing his sleep is awful, awful” I4: “it affects other stuff as well… muscles, bones as well, the back pain… mood swings, stress from the testosterone, muscle problems dyslexia and dyspraxia…” M6: “they also think he’s got hearing problems” M6: “we had no idea… well I feel that I’ve let him down as well… we’ve seen all these experts since the age of 2 and he’s been to his GP with problems over the years – no one said ‘there’s something going on here’ from the age of two we took him to all these specialists, paediatricians” M6: “no one tested for anything it’s unbelievable isn’t it when I think of the people we’ve taken him to over the years”
Puberty	I4: “voice hadn’t dropped, confidence went down to an all time low, just felt like crap about everything”
Other	M6: “it’s the writing and the spelling, he’s definitely got dyslexia” M6: “he’s definitely got Asperger’s” M6: “he can’t cope with people, it’s a socialising thing... he just can’t cope, he’s in a terrible state, he’s shaking, he shakes you see” M6: “very bad anxiety, very bad been a problem for a long time, I’d say it’s got worse” M6: “motivation and social difficulties… living at home unemployed” M6: “you get onto other problems… terrible depression at times, really bad” M6: “motivation and social difficulties… living at home unemployed” M6: “I do wonder now, he was having speech therapy, I do wonder then if the speech therapist had said ‘he may have this’… may be if I’d persevered and through ‘why is he having speech therapy?’ we knew something was wrong, you can’t always know that’s wrong”

Group strengths	
Puzzles	M5: “he was excellent at doing puzzles unbelievable… when he saw the psychologist she actually said she’d never seen anyone put the pieces together as quickly as he did”

Navigation	F3: “if you’re at an airport and you’re looking around you say ‘where do we go?’ and he says ‘down there, it says so on that sign’ that’s the way he is in some situations he doesn’t miss a trick, very, very observant, he’s very good like that” F3: “wayfinding, navigating is excellent… he doesn’t need a satnav, I’d say excellent at map reading, I’d say he was unusually good”
Visual detail	M5: “he was good at puzzles and good at wayfinding… visual detail yes, he said: ‘do you know you’ve got 17 lamps in this room?’

Table 17: School Diagnostic Cluster Group (DCG 4)

Distractibility	I2: "the big girls' shoes outside (the classroom) makes me scribble" I4: "distractions, you know, everyone talking all around you, even the noise they make"
Anxiety	M6: "from the first day at school he had extreme anxiety"
Writing and Spelling	F3: " just struggling with his schoolwork, his writing wasn't very good and really, spelling, he'd just get words wrong… he thought it was the other way round, little tell-tale signs of things not quite right" I4: "I struggled a bit at school. Always struggled quite a bit like writing and mental processing" M6: "His spelling is… he's definitely got Dyslexia….his writing's not what you would call grown up writing …..it's the writing and the spelling
Understanding	I3: "I think it was the learning aspect I always struggled with, taking in information and then turning it around so it was in an easier language….obviously I never got that kind of help when I was at school - everything was just quite hard to understand
Socialising	I3: "socialising….I think with me you do struggle with social environments…. the interacting was hard…. having conversations with people, that's something I struggled with"
Asperger's	M6: "I wonder if it's part of his syndrome, there's no doubt that he's Asperger's, he's definitely got Asperger's"
General	F3: "I'd say possibly general build, he was always not very well developed he never had that, it was the way he saw things, very black and white, never got jokes…. he can't see the nuances, he's so black and white"

CHAPTER 8

ALL GROUPS

8.1 Introduction

The two main reasons cited in the literature for lack of diagnosis are variability in the syndrome and low awareness of the syndrome in General Practitioners. The perceptions of three groups possibly involved in the diagnostic process of Klinefelter's Syndrome were explored.

Five themes from different perspectives were identified across all the groups narratives.

Table 18: Table of themes from All Groups

Theme	**Theme Heading**
Theme 1	A Common Condition: A Rare Diagnosis
Theme 2	'A Lifetime of Clues': Similarities - 'Klinefelter's Clusters'
Theme 3	The System
Theme 4	Diagnosis: similarities and (later) variability links to later diagnosis
Theme 5	Ways Forward

8.2 Analysis of themes

8.2.1 'A common condition, a rare diagnosis'

E1: *"Klinefelter's could not be described as a rare condition"*

The Expert Group opened their narratives with their views around the under diagnosis of the syndrome and reasons for this. Unlike the other groups, the Experts resonated with the reports in the literature that Klinefelter's Syndrome is not rare, but common and increasing in prevalence. Further, that the under diagnosis is caused by low awareness and knowledge in General Practitioners and specialists:

E2: *"GPs …generally they've not heard about it, they don't know what it is"*

GP4: *"I have never, ever had a Klinefelter's patient"*

GP1: *"I think it's not something that's on my radar. Really. It's not on my radar"*

PHY: *"I must admit I'd never heard of it before"*

The Expert Group echoed the literature when discussing estimated rates of incidence and emphasised that Klinefelter's is reported to be increasing in prevalence:

E2: *"it's dropping, becoming more common, maybe, maybe dropping down to 1/500"*

In contrast to this, the perception in wider medical professionals was that Klinefelter's is rare:

DIT: *"I thought it would be more like 1/5000"*

GP5: *"I've not had a patient with Klinefelter's that I know of and it's certainly not that common"*

Interestingly the GP Group shared this perception with the Specialists who also perceived Klinefelter's to be rare:

GST: *"it's the understanding first as a gastroenterologist because some of my colleagues don't understand this condition … I'm sure that some of my colleagues have never seen, or don't think they've seen any Klinefelter's patients in the past"*

It was interesting that these perspectives were echoed in the GP and Specialist narratives who shared the perceptions of the Experts that there was low awareness of Klinefelter's:

GST: *"it doesn't really exist as a speciality"*

The responses of the general health professionals were surprise when told of the estimated rates of prevalence:

GP5: *"well it's relatively common then, isn't it"*

GP1: *"I'll be honest, that number surprises me"*

GP7: *"I'm in a practice of 14,500 patients. I recall I had one patient with a diagnosis of Klinefelter's probably over 20 years ago… I'm not aware we have one now…I'm sure we probably do, but I'm not aware of them"*

Reasons for the low diagnosis were perceived to be linked to early medical training and the current focus on conditions other than Klinefelter's for ongoing professional development:

GP4: *"it probably turned up on a multiple-choice question somewhere at med school"*

SLT: *"I think we're all primed these days to think about autism and ADHD, very primed for that, it's front of our minds…. it's just not on our radar"*

This striking consistency of opinion appears to confirm the accuracy of the reported low awareness in general clinicians in the literature. The low awareness set a context for the under diagnosis universally reported for Klinefelter's.

The Expert view was to recommend raising awareness and knowledge in the wider community and with a particular focus on general clinicians:

E2: *"it's raising awareness and education really in GPs… and that's exactly the problem"*

The lived experiences of the Family Group emphasised the impact on diagnosis the low awareness caused and how this resulted in diagnostic delay:

M3: *"the doctors don't seem to know much about it, or even know about it"*

M6: *"no one tested for anything, it's unbelievable isn't it, when I think of the people we've taken him to over the years"*

I4: *"I was persistent asking my Mum so we went and saw a doctor for about 2 years… I thought 'it'll do it eventually', but I was about 18 - persisting and going to the GP…"*

M2: *"I took him to the GP so many times.. he was referred to audiology, speech therapy, paediatricians, educational psychologists… they all said he was normal and just a bit slow. Eventually I gave up with the system and went to*

London to a private child psychiatrist… after a one hour appointment he arranged the blood test"

Reported as a further problem caused by low awareness and noted by the Expert Group initially, is the difficulty families experience in accessing accurate and up to date information when they are diagnosed. This was seen as problematic by the Experts:

E2: *"then it's how people are informed of the diagnosis… often people will turn around to parents and say 'ok your sons' got Klinefelter's but we don't know very much about it"*

This resonated with the Family experiences who also describe the problems of finding access to information about Klinefelter's which was seen as unhelpful and stressful at a difficult time:

I3: *"Mum and Dad had some leaflets, they were like, 'well, we've got some leaflets here so you can read up about it.. it was quite hard to understand"*

The families gave an insight into the how they experienced the lack of information and the impact trying to access accurate information about Klinefelter's affected them on finding out the diagnosis:

M1: *"we didn't know anything about the condition at the time and even the consultant who told us about the result of the amniocentesis didn't know a great deal about it… we felt as if we were in the dark initially and this consultant did give us some very outdated literature which was based on an American prison population"*

The importance of recognition for symptoms and increased health risks in Klinefelter's was noted by the Experts and by those in the Specialist group who had experience of treating Klinefelter's patients and were aware of some of the health risks associated with their area of expertise. It was interesting to note that there were different perceptions about Klinefelter's between the Specialists who had, and had not, treated Klinefelter patients preventatively:

GST: *"I think if there's no realisation there's any increased risk of issues, then people will not deal with them or recognise them"*

Lack of recognition was evident in the GP and Specialist groups who described how other conditions are better recognised due to higher levels of general awareness and this may result in a diagnosis of other conditions in a Klinefelter's male, but the diagnosis of Klinefelter's remaining invisible:

SLT: *"we might mistake it for ASD .. I could see a lot of false positives with ASD … that .. could hide others or it could be masking what was actually something else - so the whole physical thing is missed"*

M2: *"they thought he had ADHD … he was diagnosed with dyslexia, dyspraxia… no one ever mentioned Klinefelter's…."*

The perception that diminished attention may impact on recognition and therefore diagnosis was evident in the GP and Specialists groups. The referral mechanisms of the family group perhaps were an example of how this worked in practice. The referrals for the family group when diagnosed with Klinefelter's were for amniocentesis (Family 1); Fragile X (Family2); Marfens and Raynauds Syndromes (Family 3); Disrupted puberty (Family 4); Urology related (Family 5); Hypothyroidism (Family 6).

The combined factors of low awareness in health professionals beyond the endocrinology experts, the misconception that Klinefelter's is rare and thus not a diagnosis that occurs to the GP or specialist groups and the expectation that, even if there were an underlying diagnosis, this is not relevant to the symptoms for which the patient has been referred. This 'Catch 22' situation is evident in the perceptions of the specialist group.

Taken together, a clear picture is painted through the insights of the shared narratives for the under diagnosis of Klinefelter's and the diagnostic difficulties experienced by our families:

GST: *"I think one important question is what's my impression of the knowledge of Klinefelter's in gastroenterology consultants……. … basically zero"*

GP7: *"…er, yes, now, I think the thing to remember is that if somebody came to see me with a whole load of symptoms that might be Klinefelter's, I wouldn't even think of it"*

The Expert group and the Family group were united in echoing the importance of increasing awareness in health professionals beyond endocrinologists and affected families:

E1: *"it all comes down to the education of health professionals to think about these not so rare conditions"*

M5: *"we've seen all these experts since the age of 2… from the age of 2 we took him to all these specialists, paediatricians… and he's been to his GP with problems over the years - no one said 'there's something going on here"*

8.2.2 A Lifetime of Clues: 'Klinefelter's Clusters'

Despite the variability frequently reported for the syndrome, there seemed for the families in this study, the suggestion of a shared pattern of clues through the lifetime: 'a lifetime of clues.' However, there seemed the possibility that a combination of subtlety of presentation, the low awareness of general clinicians and a natural variability contributed to delays in diagnosis. Despite frequent references to variability in the literature, there seems a paucity of data on the nature of the variability. Echoing the literature, the Experts suggested variability has a downward effect on diagnosis rates:

E1: *"The most likely thing is the phenotype of the condition is so variable"*

Interestingly a counter point to this is raised by one of the Experts suggesting a different reason for the variability:

E2: *"there's as much variation in an XXY boy as there is in an XY boy"*

In expressing this perspective around variability, raises the interesting possibility that the variation referred to as a confounding diagnostic factor may be a normal expression of natural differences that exists between all individuals and not a variability arising from the syndrome. For the Families in this study there was a pattern of shared characteristics evident from early childhood. In this, there may be a case for the variability being a natural variation between individuals and a diagnostic distraction away from the commonalities that may be shared.

This characteristic, shared commonalities described by the families in this study are referred to as a 'Klinefelter core' and are explored as a potential early diagnostic facilitator (Figure 6, page 248), the Core Deficit: Multi-Dimensional Diagnostic Model.

Exploring the notion of variability, for the families in this study, it was later in life, when diagnosis was delayed for two families into adult life, were there variabilities evident and were attributed by the families to be caused by the late diagnosis:

M6: *"much of his motivation and social difficulties seem to have been attributed to him being a 'normal' teenager and, now in his 30's, living at home and unemployed, he feels very frustrated and disenchanted"*

M5: *"very, yes, very bad anxiety, been a problem for a very long time… I'd say it's got worse"*

M5: *"unfortunately we didn't know he was suffering from this. He was not diagnosed until he was 26,27 which we felt very let down by, actually, because we'd seen speech therapists, educational psychologists, psychiatrists… he'd seen a urologist 5, 6 years before he was diagnosed…. that is (pause)… unbelievable… none of them picked it up"*

M5: *"I think he just sort of gave up really"*

Lack of illness, or visible symptoms were additionally thought to cause under diagnosis as health professionals were not generally aware of the often subtle indications of the underlying syndrome. This was reinforced by the Expert group who described a picture of the syndrome presenting in different, but anticipatory, ways through the lifespan. For example, for two of the families, puberty was not disrupted, and testosterone treatment was not required. For four of the families, puberty was disrupted, and, for the two teenage diagnoses, treatment was begun to progress through puberty. Although variable in how puberty progressed between each boy varied, there are known increased risks and differences between an XY boy and a Klinefelter boy and one of these is the possibility of disruption to puberty. Diagnosis is the only factor that will alert the physician to this and thus allow monitoring to inform timely treatment, if required:

E1: *"there are subtle differences…. when they get to puberty I will step in with testosterone if needs be"*

The cost of a later diagnosis will result in lack of treatment, the implications of which can affect the lived experience of the teenage years, sometimes for all of the teenage years. This anticipatory, preventative approach to the syndrome was identified by the Experts, but was not recognised or mentioned by the other medical groups:

E1: *"if you're seeing a young man and treating him appropriately, you will do bone density scans.. you need to ensure the boys do physically develop .. or go through puberty"*

In accord with the Experts, however, the Family group were united in emphasising the importance of holistic care. This, in contrast to the fractionated care four of the six families described. Two of the families had themselves facilitated and co-ordinated a 'joined up' approach, but this was the result of family efforts and negotiated on a case by case basis with Experts in centres of excellence:

I2: *"I think my health dips in and out - I have had health problems and I have been looked after by great doctors in London… I can't remember them all - there's gastroenterology, a dietician, someone about my low folate .. Yes, I think it makes a lot of difference… I value their expertise… their (expertise brings) confidence in me and reassures me that I am fine and everything's going well and they keep a close eye on me"*

The lack of a coherent pathway to diagnosis and treatment led to perceptions in the families that care was delivered in a fractionated approach:

There were accounts of the impact of lack of diagnosis and treatment in the lived experiences of the Family group:

I4: *"if somebody doesn't know they've got it…'cos I remember it was just horrible. Year 11, Year 12 was just crap… it just felt awful, everyone would just laugh, take the mickey out of your appearance and how you spoke and deep down I'm thinking 'is there something wrong with me?"*

Similarly, there was synergy between the Experts description of the care and treatment they provide, if diagnosis has been made and a boy or young man is under their care, and descriptions of opportunities and treatment missed where diagnosis has not been made:

E2: *"puberty may not be such an issue, but you know they may have missed out on some educational opportunities … nobody's thought: 'oh they've got learning difficulties and there's a reason behind it'"*

M3: *"I just thought 'oh eventually, there IS something that's not quite right. I just thought 'it's been 16 years, it's a simple blood test, why couldn't it have been picked up years ago when he was a child … then he could have had a lot more help"*

The group narratives identified a 'Klinefelter cluster' of a lifetime of clues which were described by the Expert group and evident in the lived experience of all the Family group. This shared profile seemed to potentially be beneficial for prompting diagnosis, were there a raised awareness of the condition and these characteristic 'clues.' The shared pattern of similarity also raised interesting ruminations regarding the reported variability in Klinefelter's as the narratives of our families resonated with the pattern of similarities described by the Experts. There was also the conundrum that existence of shared, predictable likely characteristics in Klinefelter's were evident in the earliest to be diagnosed who described one of the benefits of early diagnosis was the insight this provides into likely issues to be anticipated and thus early warning for anticipatory support:

I4: *"..I didn't really know what it was until he* (the endocrinologist*) explained it and it all made sense after that"*

This insight was only possible because of the 'sameness' of the condition which made anticipating the characteristic Klinefelter signals possible:

E2: *"any child with mild learning difficulties, autism, should have a chromosome straightaway"*

E1: *"if they've got signs that are failing, voice doesn't change etc. and so on, they should be referred at that point. I think GPs haven't got that level of awareness generally"*

This lifetime of clues was described in the narratives of the Experts and raised the notion that these important clues may be helpful as diagnostic clues evident as a series of points where if practitioners were sufficiently aware, may be diagnostic opportunities:

GST: *"it's a question of saying well these things are associated they're not going to shorten your life, but I can understand they can have a significant effect on morbidity on your quality of life, and therefore we need to pay attention as best we can"*

FRT: *"you've got so many issues, you've got endocrine, potentially social issues… educational issues, relationship issues…"*

The group narratives in this research describe these clues which were organised into a group of lifetime diagnostic clues. These are referred to for the first time in this study as the Diagnostic Cluster Group (DCG). This is formulated from data from each group and identifies symptoms and clusters of symptoms, of likely increased incidence in Klinefelter's and the life points at which vigilance for these may be beneficial.

The earliest cluster of clues were described from infancy and formed a pattern of parents seeking medical advice for a developmental delay and infant referrals for late milestones:

F3: *"I always felt that something was not quite right and that he was slower in development, he had problems in every aspect of talking, walking, crawling…"*

M2: *"he was referred by the health visitor for all the early checks, he didn't really speak and he failed all the health visitor checks - speech, motor, audiology he was referred… they said he was fine, not to worry"*

M3: *"when his brother came along he couldn't say his name… so pronunciation"*

M3: *"learning to ride a bike was impossible, doing shoelaces, button through button-holes, he struggled kicking a ball, catching a ball… he struggled"*

I2: *"the reading and writing quite challenging, um my brain is not very good at remembering things .. um the hyperflexible bones and the not allowed to have kids because of the problems there .. but I try not to let Klinefelter's hinder my life"*

For those not diagnosed by the teenage years, pubertal disruption caused bullying and isolation throughout the teenage years at school. It is also hoped that the DCG may be beneficial to contribute to raising awareness in areas of medical speciality thereby increasing diagnosis rates in these areas of medical speciality.

It was interesting to note that despite the frequently reported variability of the syndrome, for the families in this study, there were shared patterns from infancy through childhood. For this group, there were commonalities, rather than variability These descriptions of a shared profile were early developmental delay, childhood referrals, learning difficulties at school

and, for some, disruption to puberty. Multiple referrals for shared health problems were also a shared experience.

That there are descriptions of Klinefelter's which were recognised by the families when they read about the syndrome when recently diagnosed seems to suggest identifiable characteristics are reported for the syndrome. If this were correct and there is an identifiable 'Klinefelter's profile, this would seem to further underline that early diagnosis can alert parents and health professionals not only to the existence of the underlying syndrome, but also provide anticipatory guidance. This would only have meaning or value if there is a shared Klinefelter profile and for our families, when diagnosed, there was recognition of the 'typical' Klinefelter hallmarks:

M5: *"... he has apparently got all the physical manifestations and signs of this"*

I4: *"I didn't really know what it was until he (the endocrinologist) explained it and then it all made sense after that"*

I4: *"I was, yes, most of the symptoms on the Klinefelter's list… that's what I've got"*

8.2.2.1 The Invisible Syndrome: The need for a Klinefelter Pathway: a lifetime of clues

Interestingly apparent contradictions appeared to emerge from within the Klinefelter's diagnostic story: despite the reported variability of the syndrome, there appeared for the group in this study, a shared cluster of characteristics. These shared, or 'core' characteristics appeared to remain as a 'core' of deficits in the Klinefelter infant and remain through their developing years, into adult life. It was interesting to consider that these may be beneficial prompts for diagnosis: a cluster of diagnostic prompts.

A limitation of the current system was identified to be an absence of screening prompts. The place of GPs in the ongoing care of Klinefelter's patients was identified to be made more difficult by the lack of a diagnostic or treatment pathway. That there are identifiable characteristics which may be helpful for diagnosis was welcomed by the GP group. There was an interest in diagnostic 'prompts' or tools and a consensus that these would be useful. The advantage of a diagnostic model was also thought to be helpful in providing a screening prompt by distinguishing a population for testing drawn together by shared core prompts.

For this study these are identified as a series of Diagnostic Cluster Groups (DCG) emerging from the narratives of each group in this study. Taken together, a DCG across all the groups narratives was produced.

It is hoped that this may contribute in providing a cluster of diagnostic 'clues' for diagnostic purposes. The DCG may also be beneficial in the planning of treatment by identifying clusters of increased risk for early, proactive intervention.

There were also thoughts that the GPs may have a beneficial role in diagnosing Klinefelter's, particularly referring to the Diagnostic Cluster Groups (DCGs 1 - 4) where referral clusters in higher risk health categories for Klinefelter's may be beneficial as part of the 'lifetime of clues' and thus prompt for chromosomal testing:

> GP3: *"if you think, this person has had all those symptoms, could it be Klinefelter's… quite often it's the GP that's seen all of the letters from the referrals and puts them all together"*

These suggestions were beneficial as positive steps GPs suggested may be valuable to positively affect the under diagnosis of Klinefelter's.

The lack of a diagnostic and treatment pathway was seen as detrimental to increasing diagnosis and providing a holistic approach to care:

> URL: *"diagnosis is fragmented .. because presentation is non-streamlined .. there's huge variance, there' s no standardisation of the diagnostic process"*

This was seen to have resulted in the symptom led approach:

> GST: *"a lot of doctors would then go into their sub-speciality and won't be thinking about that there could be any cross over with their speciality…"*

Without a formalised pathway for diagnosis and treatment, with the perception in the GP and Specialist groups that diagnosis was not their role, there appears to be a lack of clarity, or diagnostic ownership. This lack of pathway seemed compounded by the lack of recognition of the specialisms to the relevance of the Klinefelter's diagnosis:

> GST: *"there don't tend to be individuals with an expertise in Klinefelter's - it doesn't really exist as a speciality"*

The need for a pathway to change the current fragmented approach was thought to be helpful.

8.2.3 The System

The group narratives moved forward to share thoughts regarding the process of diagnosis and how this works within the framework of the healthcare system. This was also a significant aspect of the conversations with the GP and Specialist groups whose insights presented a different perspective which, along with the insights from the Experts contributed to a rounded picture of the diagnostic process which was valuable in contributing to revealing how this may affect diagnosis in Klinefelter's Syndrome.

The narratives of the way the health care system is structured suggested that the lack of diagnostic pathway contributes to low diagnosis and similarly there were perceptions that the fractionated approach was systemic, part of the structure of the health care system. However there was recognition that times have changed, and 'new' diagnoses are now made possible which struggle for diagnostic recognition and appropriate care as the system has yet to 'catch up:'

> PHY: *"the NHS was designed on a medicinal approach and that's why we have such separate entities … I've seen so many people in the past, they've seen this person, this person, but trying to collaborate that isn't possible, you need to get to the pathways… so in a way you're trying to create a pathway for Klinefelter's"*

The lack of a care pathway and a system structured to respond to illness and as symptom driven was seen to further contribute to the low recognition of Klinefelter's within the system:

> PHY: *"the NHS … ultimately until it becomes organised its' still designed for a 1940's, 1950's UK"*

This perspective particularly seemed to resonate as a shared underlying concern about the NHS and particularly illuminated the challenge this structure presents for a condition such as Klinefelter's: a 'new' diagnosis owning one underlying cause with an accompanying constellation of problems, each of which carrying its own individual management needs whilst maintaining the need to recognise the syndrome is one, systemic condition. The insights of the Expert and Specialist groups provided an understanding of a mismatch

between the system, the referral system and the way Klinefelter's presents and thus provides a key understanding for under diagnosis and relevance for treatment approaches.

8.2.3.1 Owning the diagnostic role

The GP and Specialist groups indicate reasons for delayed diagnosis had its' genesis in the structure of the system and how the referral system works. There were shared perceptions between the GP and Specialist groups that diagnosis of Klinefelter's was not their role. Further the agreed view was that the underlying diagnosis was not widely recognised to be of any significance and the symptoms for which a patient was referred was approached in treatment terms as an isolated symptom. Therefore, the existence of, or the diagnosis of, an underlying condition was seen as beyond the role of the GP and the Specialist. The GP group believe it is the role of the Specialist to diagnose and the Specialist will treat or diagnose only that symptom for which they specialise. The underlying Klinefelter's was seen as:

GST: *"it's a wholly incidental thing"*

The perception that the Klinefelter's diagnosis is of irrelevance was tempered by a recognition that there is poor understanding of how Klinefelter's may interact, or cause an array of symptoms or conditions which should prompt a holistic approach:

GST: *"it's very important because I think if there's no realisation there's any increased risk of issues, then people will not deal with them or recognise them"*

Revealingly, the GP group expected the referral from primary care to a Specialist would result in diagnosis. In contrast, the Specialist group expected the GP to have made the diagnosis, or if not, the perception of their own role was to treat the symptoms for which the patient was referred and only those symptoms:

URL: *"it wouldn't be my primary responsibility to make that diagnosis"*

PHY: *"I guess I could go back and report to the GP and say 'by the way, so and so has got those symptoms, these correlate with symptoms such as this… if you want to consider something further, go for it"*

Linked to the low awareness of Klinefelter's was a resulting lack of recognition of the 'lifetime of Klinefelter clues.' The GP group describe how these can be diagnostically

overlooked either because there is a lack of identifiable illness or as being a 'natural variant of normal':

GP5: *"it's lots of things, one it's developmental and it's not illness and it tends to get lost and it is down the health visitors' side and not the GPs side… I think often that kind of diagnosis tended to get lost"*

GP5: *"if you're going to diagnose it as a GP you're not going to do it until they're quite a bit older... perhaps you know, you've already had quite a few problems by the time you start thinking about it… it's not going to be 'til 17,18 because you're going to - earlier on - be thinking 'oh well, it's natural variant of normal'"*

There was a unity between the GP and Specialist perspectives of how the system works and potential impact of this on diagnosis. Neither group considered it was their role to diagnose Klinefelter's. Perhaps reflecting the symptom driven structure of the referral system, there was also a reluctance of the GP group to refer to the Specialist Group where there was perceived to be an absence of 'illness':

GP5: *"no they wouldn't diagnose, no they wouldn't - none of them - the GP would consider none of that anything to do with them because, no , of course they wouldn't because it's not an illness as such, it's different, you know, it would be considered developmental"*

GP4: *"even when you do refer on, they're likely to say 'well you know, this is normal, or 'we're in the range of normal here'"*

This fractionated approach to referral perhaps sets the context for the lived family experience which they described as a pattern of medical referrals, none of which resulted in the Klinefelter diagnosis. This contact with health professionals was seen later by the families as missed diagnostic opportunities:

The narratives of the health professional groups highlight the lack of recognised referral and care pathway negatively effects the diagnostic process. The diagnostic challenges appear to be exacerbated by the system structure which is driven by illness and reacting to medical symptoms:

GP: *"the system is geared to prevent, delay diagnosis"*

The Expert group led the perceptions in describing how Klinefelter's is frequently diagnosed incidentally in the course of testing for other conditions. In a sense the misconception may cause a 'Catch 22' situation where Klinefelter's is not considered because it is thought to be rare, which subsequently contributes to under diagnosis as the GP and Specialists do not think of it, which in turn perpetuates the perception that it is rare. Resulting from this diagnostic conundrum, the Expert group of endocrinologists to whom a referral would be appropriate, describe that referrals are made to them as a result of testing for conditions other than Klinefelter's. The lived experiences of the family group provided insights into how this translates into the practical experience of trying to get a diagnosis is illuminated by the observation that the appropriate referral is unlikely to be made:

E2: *"increasingly we're getting them from the genealogists because the chromosomes are done for some other reason and then they're sent to us"*

GP3: *"there's no point, you know, only a geneticist or an endocrinologist knowing about it, because most people don't see an endocrinologist or a geneticist"*

The low referral for Klinefelter's testing was indicated in both the GP and Specialist narratives where there was agreement that neither group considered diagnosis was their role. There was the expectation therefore, that, if there were a diagnosis to be made there was the assumption that the diagnosis would be made elsewhere:

GP2: *"you know, there are a lot of conditions unfortunately that GPs, that we expect someone else to make that diagnosis"*

SLT: *"because there is quite an array of physical needs and so I suppose we'd sort of think that signs of symptoms would have presented and… our medical colleagues somewhere would have already been dealing with that"*

GP4: *"no, it's not on my radar, so I think.. I'd like to think that people I'm referring to - it's on their radar"*

GP7: *"would a GP think of it? I would think on average, no. I would have said, no"*

The narratives of the Expert, GP and Specialist groups presented a compelling picture of how the diagnostic process may impact on the efficient diagnosis of Klinefelter's and provided a

context for the families' frustration and feelings of regret when diagnosis had been delayed into adult life:

M5: *"why didn't I know this before? You'll always ask yourself that, won't you?... we had no idea… well I feel that I've let him down as well…"*

Thus, the way the healthcare and referral systems are structured was reflected in the lived experiences of the family group all of whom described their diagnostic experiences as made through luck, persistence, or having private health insurance. The Expert group acknowledged the frustrations of families:

E2: *"right presumably no one was listening to the parents, they get frustrated"*

The family group highlighted the frustration they felt at suspecting there was a problem, but feeling dismissed by health professionals when no diagnosis was made and their eventual frustration when diagnosis was made, but for some, considerably delayed:

I4: *"..I didn't really know what it was until he (the endocrinologist) explained it and it all made sense after that"*

This frustration and feelings of 'something not being quite right' created concerns in the families, but the lack of diagnosis meant answers which would help to provide a context for these concerns and answers for these feelings and were not forthcoming, was acknowledged by the Experts:

E2: *"or psychosocially… they feel differently, and they may feel very frustrated but, yes, I think that's very important to pick up"*

There was a resonance between the Family and Expert Groups whose narratives focused on similar messages and perceptions but often expressed and experienced from different perspectives.

This was again evident in the subsequent theme of diagnosis and how this is perceived by the groups.

8.2.3.2 Diagnosis: timing of diagnosis; importance of early diagnosis

The Experts open their thoughts on diagnosis with a recognition of the diagnostic challenge not uncommonly experienced for Klinefelter's patients and their family. There was

recognition also that diagnosis frequently was made after family concerns, often for many years before diagnosis was made:

E1: *"often they know something's not quite right, but they can't put a name to it and obviously they get shrugged off by other health professionals"*

The value of diagnosis shone through the narrative of the Experts and was strongly resonate with the Family perceptions:

E1: *"I think at various points it makes things better for the kids, basically"*

Where diagnosis had been delayed, or lost, the Expert Group provided insights into the cost of the delay and the family group enhanced this further with vivid insights into the difference to the lived experience diagnosis, or lack of diagnosis:

M5: *"we had a shock. I'd never heard of it. It was a terrible shock. We were quite upset to think he'd gone through all that and a simple blood test could have saved years and years of misery"*

The value of diagnosis conferring other benefits such as providing answers and a reason for the family concerns:

E1: *"then everything fell into place - his learning difficulties which had always been very frustrating for him and not knowing why"*

E2: *"it's looking out, really and help the boy develop in confidence, socially, things like that"*

GP7: *"it's like all these things, if you do have an underlying diagnosis it makes you more aware of the potential conditions that can occur … then, yes one gets into screening and so on.. on a regular basis"*

I2: *"I think my health dips in and out but I (am looked after) by great doctors in London .. I can't remember them all.. there's gastroenterology, dietician, I see someone about my low folate….I think it makes a lot of difference ..brings confidence in me and reassures me that I am fine"*

The Family group had a shared, but also different perspectives around diagnosis and this seemed significantly determined by the timing of diagnosis. There was a frequent surprise or shock at the diagnosis.

Thereafter, different family perspectives became evident. For families diagnosed earliest, before age 10, their experiences reflected the beneficial reasons of diagnosis identified by the Experts.

Where diagnosis was made early, diagnosis was seen as empowering with insight into what was needed:

M1: *"being forewarned we were forearmed, as well"*

M2: *"with diagnosis you can care and provide for your son… without diagnosis you can still care just the same, but you are denied the opportunity to know how to provide for specific needs - Great Ormond Street assessments showed that …. educational programme of tailored one to one provision for his strengths, as well as his weaknesses"*

I2: *"I remember my schooldays very fondly and I really liked my school days - I had my own timetable filled with lessons that I enjoyed but also helped me to do classes that were a struggle, I was struggling at and join in with my tutors and my peers and um just join in, really"*

For the family diagnosed in their teen years, there was a mixture of relief and frustration the diagnosis was not made before:

I4: *"going on the treatment boosted my… I was feeling a lot better about myself, yes, confidence is the main thing"*

M3: *"diagnosis got him the extra help at college otherwise I don't think he would have got through"*

For the families diagnosed into adult years in the mid-twenties and beyond there was shock at the diagnosis and anger that this had not been made before, particularly when recollecting the multiple health referrals made over the years:

M5: *"it was a shock, a terrible shock…"*

The Expert Group highlighted specific Klinefelter vulnerabilities and how diagnosis would impact on this from a professional judgement about treatment approaches and informs clinical management in health, educational provision, emotional and psychological vulnerabilities and the implications of these to quality of life if left unheeded:

E1: *"screening is important for educational and motor interventions"*

E2: *"the important thing is the puberty side gets looked at earlier and if the child needs pubertal induction…. you can start them in a timely manner"*

E2: *"I think that will probably have important impacts later on the development of their bones etc because testosterone is extremely important for normal bone health and also then you're monitoring them very carefully"*

E1: *"yes and I think the main thing are the autoimmune… some of the boys have hypothyroidism which would then be picked up because again, once the diagnosis is made, you screen them yearly for the thyroid they're more prone to, like metabolic problems…"*

As the lived experience of the families, the impact of diagnosis and the implications of no, or late diagnosis are also described by the Expert Group:

E1: *"it's developmental problems, developmental delay, speech delay or perhaps behavioural in the older boy, autistic spectrum tendencies .. puberty problems and later in life, fertility problems"*

E2: *"the child may not get all the help they need in terms of education etc, they may have missed out on educational opportunities"*

E1: *"the lack of puberty .. they get teased by other boys"*

The lived experience of our family group provided an insight into the prescient words of the Expert group about the cost of late diagnosis:

I4: *"obviously I would have loved my voice to drop …at the time I wanted it so badly… like the most thing I've ever wanted … to be normal… like everyone else and a bit sad I couldn't have that"*

E1: *"there is a percentage who need educational support, I think about two thirds need speech therapy"*

As in evident in the lived experience of the later diagnosed in the Family group, delayed diagnosis was described to carry negative implications by the Experts:

E2: *"so sometimes you make that diagnosis and actually you wish it had been done earlier and that's why I think anyone with learning difficulties should at least get their chromosomes checked because this is the sort of thing you might find"*

The Family and Expert Groups were in striking accord in their emphasis on the important difference diagnosis, and crucially, timing of diagnosis makes:

E2: *"I think at various points it makes things better for the kids, basically"*

M6: *"we were quite upset actually to think he's gone through all that and a simple blood test could have saved years and years of misery"*

The societal importance of diagnosis in Klinefelter's Syndrome was observed to be considerable, particularly practising preventative medicine and minimising or preventing known health risks, made possible through diagnosis:

E2: *"you have to try and optimise their health and make sure you're on top of things like that… the markers of cardiovascular disease, blood pressure…"*

E1: *"in the long term there's fracture etc so there's economic importance to the nation as well"*

It was striking that that, when the GP and Specialist Groups were made aware of rates of incidence and some of the implications of diagnosis, the place of diagnosis in health and wellbeing was of interest to both groups. Diagnosis as the gateway to preventative treatment approaches was seen to be important for delivering appropriate patient care:

GP7: *"you look at the conditions they're prone to and you say 'we can alter this and then you look at the things you can alter … maybe doing yearly screening for their thyroid and you know, doing hormone checks and the like, because that may make a difference"*

The Specialist and GP Groups, having accessed further information about Klinefelter's described their perceptions of the value of a 'dynamic' diagnosis which provides a context for management of Klinefelter patients and enables health professionals to take an anticipatory approach to patient care and deliver a differential approach to treatment:

GP7: *"quite a few GPs who say you shouldn't make a diagnosis, what you do is create a differential, but you don't actually hone in any further… the problems with that is if you don't make a diagnosis and you don't hone in any further, you can't set up a proper treatment plan"*

E2: *"in the greater scheme of things I think the gains are huge if you make a diagnosis you might actually prevent health problems in the future"*

8.2.4 Ways Forward

8.2.4.1 A new early diagnostic model

There is a current absence of screening criteria for Klinefelter's and this was noted as a diagnostic barrier from birth. There was agreement that wider screening to prompt for earlier diagnosis may be beneficial:

E2: *"should we screen everybody at birth in terms of the true nature of what screening means, then it's not really anything you're going to put right by identifying it first, it doesn't really fit into the clear screening criteria"*

The Experts felt that a model, such as the proposed model to aid diagnosis would be worthwhile and may assist with identifying individuals currently diagnostically missed. The Expert group concurred that high instance of constellations evident by 3 years of age would be helpful in raising diagnosis rates, where these were recognised by general practitioners:

E1: *"I think a model could be very worthwhile, if you can produce firm recommendations based on evidence this would stop a lot being missed and therefore having no treatment"*

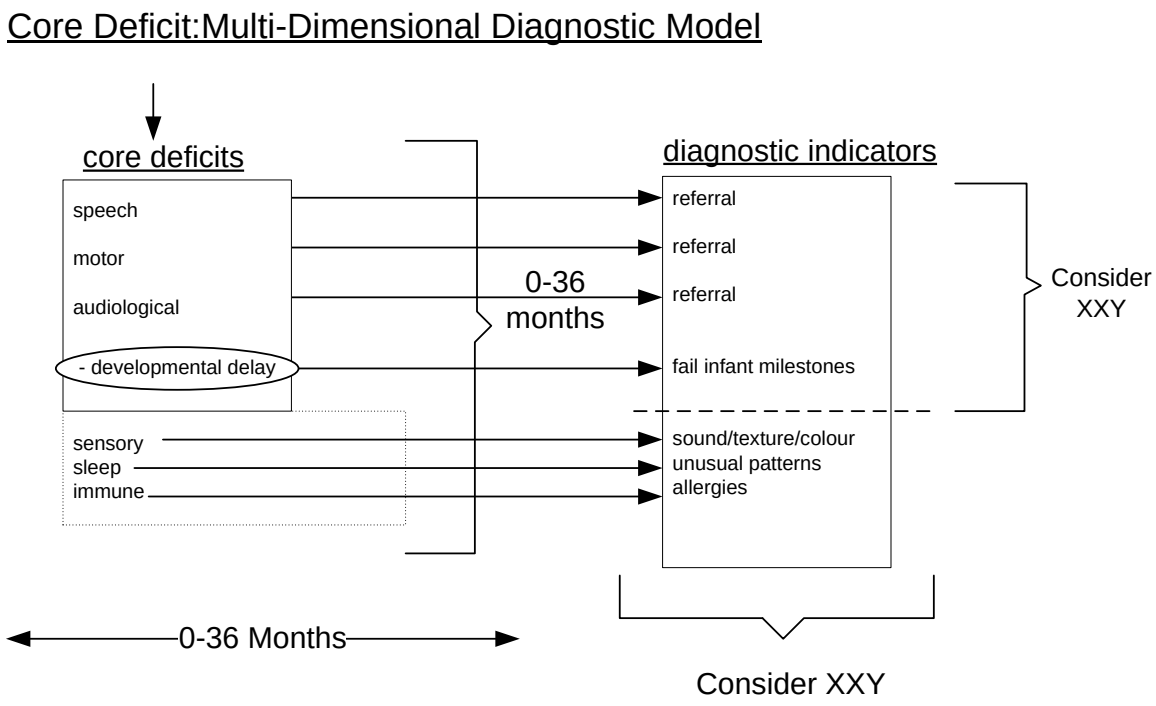
GP5: *"well I would have thought that would have been the kind of time where you could have had a blood test done relatively easily because now you've got a select population, rather than the whole population"*

GP4: *"a prompt would be useful, a tool, like anything to prompt you to think about it"*

A model was developed from data from earlier research has been further developed and is presented for consideration below. The Infant Core is a model which utilises the information gathered by standard infant checks currently undertaken routinely by health visitors. The family group reported a shared pattern of a 'core' of infant characteristics which have been used to design the model below. The model is designed as an early prompt for GPs, through prompts identified in the health visitor checks, to consider referring for chromosomal testing. The Infant Core model suggests that a certain pattern of infant referrals could be used as a prompt to screen those male infants for Klinefelter's and is designed for use between birth and 36 months of age, thus increasing diagnosis and optimising chances for early diagnosis:

GP5: *"well, now you've got select population"*

Figure 6: Core Deficit: Multi-Dimensional Diagnostic Model (Faithfull-Lloyd, 2011/12)



E1: *"I think most paediatricians … again they probably need clues and I don't think they'll think about it with someone with learning difficulties"*

8.2.4.2 A new approach for a 'new' diagnosis: Holistic care; a new model

Taking a holistic approach to care with a 'whole person' approach for Klinefelter's as a systemic condition was seen as the optimum treatment and was particularly emphasised by the health professionals who had experience of treating a Klinefelter's patient and taking a preventative stance:

PHY: *"it's the whole person absolutely, completely"*

Diagnosis was seen as the gateway to providing timely and preventative professional services to minimise known areas of increased risk emerging. Further links were made between emotional and psychological benefits and diagnosis in addition to the monitoring, treatment and support resulting from diagnosis:

PHY: *"symptoms are anxiety and isolation…it's the whole person, absolutely completely,… its understanding why they've come in the first place"*

There is a sense that diagnosis places individual symptoms in context and allows for a change to provide a more holistic approach to treatment. There is acknowledgement across the groups that holistic care is the 'gold standard', but their reality was to practice essentially in isolation in their areas of expertise:

GST: *"1/600 is common and that has associated morbidity which a lot of us specialists see in isolation, but actually they are all connected, and I don't think that many of my colleagues would even know that"*

There was recognition in the specialists who had experience of treating a Klinefelter's patient preventatively and this was evident in the striking difference between those who had this experience and those who had not. Those with prior experience of treating a Klinefelter's patient, taking a preventative approach, described the place of diagnosis to make possible the differential treatment they provided for Klinefelter patients:

GST: *"I think that for all the other reasons - the holistic approach you know, the increase in anxiety and other concerns etc that the Klinefelter's may or may not have but may have…. that needs dealing with … certainly in the initial consultation to make sure they're aware this can be associated with this condition"*

This was interesting in providing an insight into ways diagnosis can inform nuances of delivery of treatment and how this can not only empower the individual through knowledge of the condition, but also inform the health professionals who care for them and instigate a holistic approach. There is a role of early diagnosis in averting other problems, behavioural problems and emotion regulation for example which have been associated with Klinefelter's. Studies have reported deficits in neural systems involved in emotions regulation and accompanying anxiety and stress which may result. Active support and strategies to assist with managing these vulnerabilities and building confidence to better understand and ameliorate these increased risks can be provided where diagnosis has been made:

SLT: *"I think for anybody with Klinefelter's.. you're helping with the management of emotion, you're helping with organisational skills, you're helping with self-regulation, you're helping with the reflection of social outcomes, the dynamics of social interaction, the outcomes and understanding of them…"*

Klinefelter's is a systemic condition and there were united group perceptions of the value of a holistic approach. The Expert and Specialist groups gave an insight into elements of a holistic approach which would be beneficial to support and protect the well-being of the whole person:

SLT: *"you have a group of professionals, a centre of excellence so you have the very high numbers so they're learning from them and seeing the extent of the variants… that aspect of care should be considered as being centres of excellence, that way you're getting the research as well"*

PHY: *"gold standard… I think straightway it should be collaborative, so it should be a multi-disciplinary team working together, communicating together how to look at what the needs of the individual is, that ultimately is the key thing"*

E2: *"things like complications, metabolic syndrome, looking at their cardiovascular markers, looking at their blood pressure, looking at the weight, looking for autoimmune diseases like hypothyroidism and treating that .. because that's the other thing, you've got to treat that, or they feel quite lousy,.. you know hypothyroidism may go undiagnosed as well, for ages"*

E1: *"the optimal treatments, I think they need educational support, they need psychosocial support… and at the time of puberty you may need to think about giving them testosterone if they need it"*

As seen, there are an anticipated array of problems for Klinefelter males, back pain is not uncommon, with disruption to sleep and day to day activities:

M2: *"he's been hospitalised for digestive problems several times and his back has been an ongoing problem….since he's had a programme with the physiotherapist to improve his back and muscle health.. he's not been admitted….actually the same is true for his appointments with a gastroenterologist…he's able to manage the symptoms and he's not so anxious.."*

There were also perceptions within the groups that increasing diagnosis and putting preventative practises in place would be beneficial in saving the NHS money and preventing the emergence of later problems:

URL: *"in England in a single night if you could knock off one of those future patient hospital admissions because they knew of the diagnosis of Klinefelter's then you'd save £350.00 … so every singly night in hospital even if nothing is done, costs the NHS £350.00…"*

PHY: *"preventative based therapies are a real buzz word because it's all about cost.. preventative based therapies are really important, we know that fear avoidance is one of the biggest problems in back patients… now we know with Klinefelter's you have lower tone as it is… we know that when they have weeks of rest that's probably causing more problems in the long term"*

GP5: *"if you can diagnose people earlier quite honestly in the end you will probably save money rather than spend money, in the end"*

The physiotherapist commented on the role of prevention in managing back pain:

PHY: *"back pain .. is one of the most expensive problems in the western world … there are a lot of studies out there that say preventative classes are fantastic… if you can have 2 or 3 sessions as a preventative based route, you're going to*

save a lot of money so looking at it from an economical point of view, it's fantastic"

Similarly, the family group were united in advocating for a holistic centre offering a whole person approach:

M5: *"a centre, multi-disciplinary, who can advise on the whole… someone from the team should be able to go into school, encourage them… the expert team, consistent throughout their life"*

The need for a more 'joined up' approach - making connections between individual symptoms and Klinefelter's Syndrome was made where specialists had previous, or current experience of treating Klinefelter's patients. The narratives also emphasised the importance of diagnosis and the shared nature of the diagnosis of Klinefelter's beyond the individual and into the family:

FRT: *"most of them come with their partner … a huge impact on fertility"*

FRT: *"all fertility, it's the five issues, it's easy: it's the medical, the ethical, the emotional, the financial and the legal. And the family"*

This aspect of Klinefelter's revisits the notion that where diagnosis is made in childhood, the knowledge of the diagnosis and implications for fertility are carried by the family. Fertility was one aspect of a childhood diagnosis with implications for the family as a lifespan diagnosis for all life stages. For those diagnosed later the diagnosis affected their future choices for building their own biological family with implications for their future partner. Through all these life stages and for the wider family unit, Klinefelter's was perceived and experienced as a shared diagnosis.

GST: *"I still come back to what I said … which is that it's the understanding first as a gastroenterologist, because some of my colleagues don't understand this connection … you need understanding on both sides, because I'm sure that some of my colleagues have never seen, or don't think they've seen, any Klinefelter's patients"*

The need for a 'whole person approach' and the constellation of increased health risks, taken together with the clusters of likely impacts, presents a challenge for individuals and their

family alike. The need for a holistic approach was identified and emphasised by all the groups, through their own, different perceptions as specialists. A striking difference within one group was the different perceptions between those specialists who had experience providing a holistic approach to at least one Klinefelter patient (Gastroenterologist, Speech Therapist, Dietician, Physiotherapist) and those who had not (Urologist, Fertility). This suggested that those who had personal contact with delivering a multi-disciplinary approach were able to evaluate the success of this approach.

An example of an individually tailored multi-disciplinary holistic care plan devised for one Klinefelter's individual is included in the Appendices of this study.

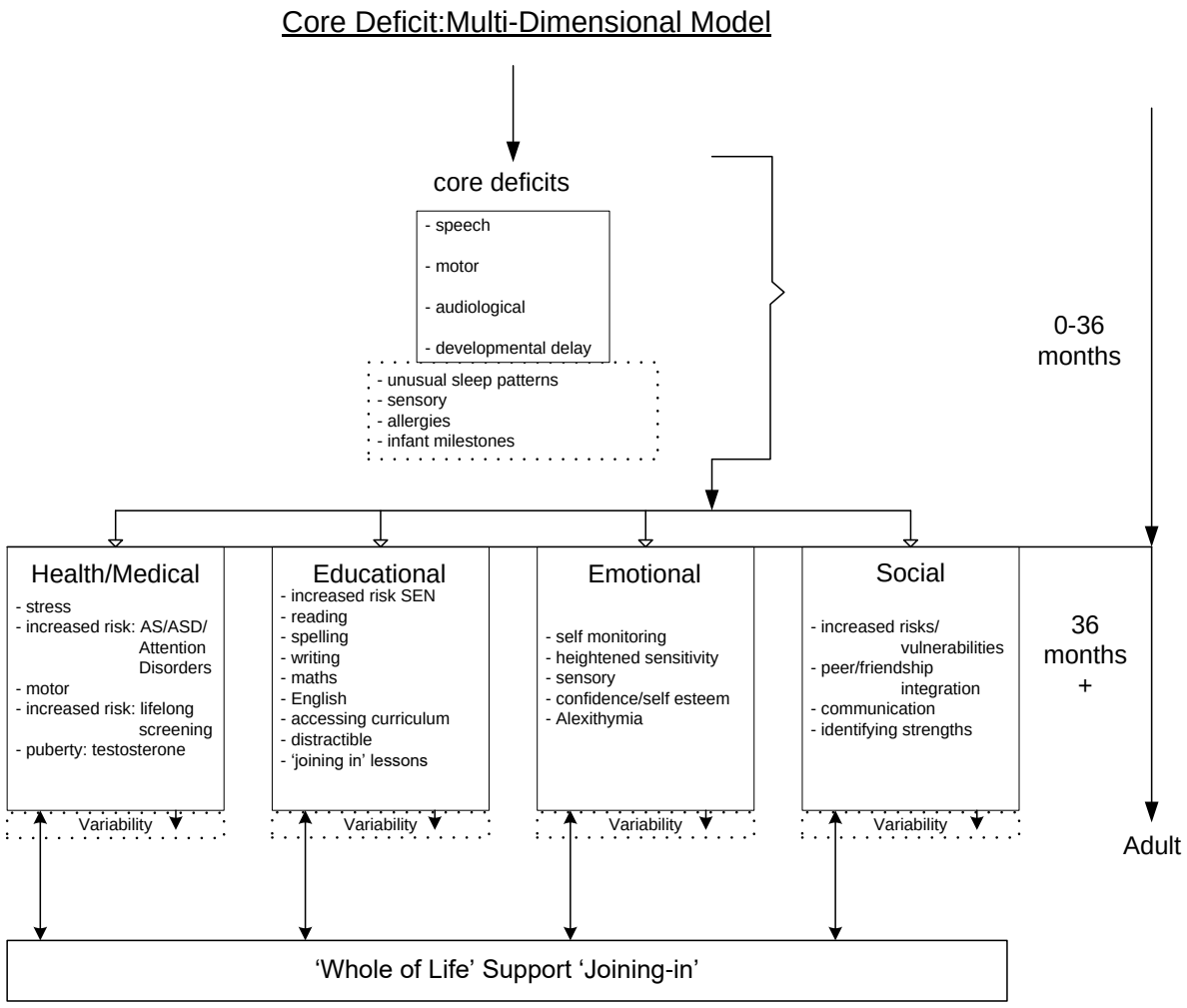
SLT: *"it's not owned by our profession, but I think we perhaps understand more than other professions that anxiety is catastrophic for well-being, for learning, for memory… if anxiety is too high, then it's going to wreck everything else"*

DIT: *"a multi-system approach… if somebody's very stressed and anxious.. they call it visceral hypersensitivity so certain chemicals will be released.. basically the nerves reaching the gut are over sensitised.. that's what they mean by the gut/brain axis what you are thinking, and feeling can directly affect the gut ..diet may help to some extent, but it's not going to get rid of the stress and the anxiety"*

FRT: *"what is the future, what is the prognosis… and then piece it all together and then I could put my little piece of the jigsaw"*

A model designed from earlier data and enriched by the narratives in this study, is proposed upon to assist in the delivery of a holistic approach: The Core-Deficit, Multi-Dimensional Model (Figure 7, page 254).

Figure 7: Core Deficit: Multi-Dimensional Model (Faithfull-Lloyd, 2012)



PHY: *"it's the whole person absolutely, completely"*

The value of providing a holistic approach to care was also recognised within the GP group. The GP group raised the interesting notion that GPs are the only medical professionals who see all the letters for each patient, thus their perception was this provides the GP with unique insight into the needs of each patient. This was felt to be an opportunity to positively impact on their Klinefelter patients:

GP3: *"no-one else gets all the letters, the GP is the only person who sees every letter"*

GP2: *"the big picture is our job, our jobs as a GP is to practice holistically and perhaps we're fairly well placed to be co-ordinating things like this, like we do with other illnesses as well"*

The Specialists, in unison with the Experts, reinforced the need for holistic care in the face of the ongoing challenges of Klinefelter's patients. The transition into adult life was seen as increasingly demanding with managing the complexities of independent living and the increasing difficulties and lifelong problems these present to the Klinefelter's individual:

SLT: *"the demands of everyday life become more complicated…. relationships, as well as social relationships and the expectation to self-manage those things become more complicated the older you are…"*

I2: *"well my advice would be there's hard times coming ahead… but stick at it, they're going to get angry, they're going to get upset.. its going to get hard for both the family and the son and it's just persistence and take every day as it comes and it will get better… I can speak for myself the school days were fun, but very very difficult.. those school days I worked my hardest"*

Diagnosis was seen as proving insights into Klinefelter hallmarks, also seen as beneficial to inform provision and support for parents. Educational provision and understanding the reasons for learning difficulties was seen as an important benefit of early diagnosis:

M2: *"diagnosis gives you a complete picture… you know what you're dealing with"*

Differential, sometimes lateral, approaches to education and school provision was described by one Klinefelter's individual diagnosed at age 6 who described the personalised timetable put into place:

I2: *"It was very helpful.. I think I had a personalised timetable up until I got to university, um, so .. very good putting in things you may enjoy and are easy to you, you need to stretch your mind and make those younger years more enjoyable but also to work on the things that are not fun… I did cooking and things I did with my hands instead of using my brain to read or write"*

Reading and writing were described by the families as challenging and school was described as a struggle. Diagnosis and access to specialised assessments provided parents with insights into how to teach through areas of strength and provide understanding that these were not problems which would change. The success of taking different, sometimes lateral approaches

during educational years were described when thinking about successes with the curriculum, reading and writing:

I2: *"well, the symbols were easier than reading the words straight from the page - the symbols helped me picture the words that were difficult for me to read and draw the picture that would remind me what that word was and then I could read a paragraph a sentence…I read my first sentence to my class using symbols above the words.. "*

I2: *"building, er learning a certain part of history in a box um that helped a lot and was really helpful in visual because I'm better with visuals.. we did many things like that - that helped towards me - to this day - thinking about words through sometimes imagery"*

It was interesting to have an insight into how understanding areas of strength were beneficial to inform lateral approaches:

I2: *"yes, I think the symbols 'bump started - jump started' - my brain to reading words over a certain length of years of doing it"*

Diagnosis would seem to have less value if there was not a shared profile. This profile appeared to change significantly only where diagnosis was made in adult life where emerging variability was described. This prompted an interesting notion that, perhaps Klinefelter's is not intrinsically variable, but marked by identifiable 'clusters' through the lifetime with variability emerging only later in life. This would suggest the possibility of variability being linked to timing of diagnosis:

M5: *"oh yes very, yes very bad anxiety been a problem for a very long time.. I'd say it's got worse"*

M5: *"I'd say that's why he took that overdose, it was desperation"*

M6: *"having been diagnosed at that late age he needed a long time to come to terms with it and he needed a lot of counselling"*

Medicine was seen as dynamic and evolving and the implications for this and the meaning of diagnosis was highlighted through the narratives. One such example is the advent of micro-TESE treatment, where sperm are sought by a surgical procedure, offering the hope to some

Klinefelter's males of becoming biological fathers. Until recently, infertility was seen as almost inevitable in Klinefelter's males. Infertility is reported by the family group as one of the most difficult aspects of the syndrome to come to terms with:

M1: *"the very biggest thing is, or one of the biggest things is the fertility thing which is obviously very sad and you know, some of the boys it's very important, well I suppose for all of them with this condition"*

I4: *"sometimes I do think about it a little bit like if I marry someone I've got to probably break it, you know, about the infertility thing before I marry them…. sometimes I think they will say 'no, I don't want that to happen' kind of comes into my mind…"*

The hope offered by the recent developments to assist some Klinefelter males to have their own biological children is likely to have a meaningful impact in diminishing the emotional burden of the condition to Klinefelter males and potentially, their partners:

I4: *"knowing how deep it was, you know, I've got this life thing"*

Early indications suggest that success of the procedure may be linked to age of the patient. For this procedure to be an option, diagnosis of Klinefelter's is a pre-requisite emphasising the essential contribution diagnosis makes to the potential quality of everyday life:

URL: *"things change in medicine and the fact you can't do anything now doesn't mean you won't be able to do anything about it in the future… if you don't identify the affected individuals, then you can't know whether you are going to be able to make a difference in the future… there may be multiple reasons why earlier diagnosis might be a good idea"*

The advent of chromosomal testing, resulting from recent medical advances appear, from the narratives across the groups, to have superseded the symptom driven, illness treatment approach on which current health care systems are based. The opportunities presented by medical advances which make diagnosis of Klinefelter's Syndrome possible, seem to present as a dawn of opportunity for new, proactive approaches to patient care and treatment. Identification of Klinefelter's as a systemic condition with an array of implications to health and wellbeing empowers the physician and family with the necessary knowledge to anticipate, minimise and prevent known health risks, informs parental decisions and parental

choices for their son and the opportunity to take a proactive, dynamic treatment approach to optimise healthy and improved quality of life for Klinefelter's families. The theme of a shared diagnosis indicates the importance of continued family support which resonates with the suggestions in the family group that support and information for the families may be beneficial:

I2: *"they are the ones helping you and supporting you and being there for you 100% so they're the ones you need to keep by your side for rest of your life"*

8.2.5 The Self

M5: *"basically I think everyone is entitled to an early diagnosis"*

There were interesting hints through some of the narratives which wove through the GP conversations suggesting more fundamental benefits of diagnosis. On closer analysis these ideas were linked by an underlying recognition that knowledge of a diagnosis has a relationship with understanding the 'self.' A number of observations suggest that diagnosis may impact on the individual by affecting their understanding of themselves. In other words, even where symptoms were subtle there were suggestions across the groups and echoed in the family testimonies, that diagnosis has significance beyond medical and health with implications for bestowing greater understanding, or self-knowledge that has meaning and significance beyond the medical:

I3: *"I don't know, does the condition affect a person's personality? Or not? Does it make their personality different? If I didn't have it, if I were the same person, me, but didn't have the condition would my personality be different?"*

Intriguingly, diagnosis was suggested as importantly fundamental to know and of intrinsic value to becoming 'oneself'. Diagnosis was seen therefore, as essential information to know, to protect from this potential 'dis-connect' from the self:

M6: *"he would always say 'what is wrong with me? Why don't I have any motivation? What is the matter? … that was a repeated refrain.."*

The narratives across the groups also provided insights into significance of diagnosis beyond making possible the provision of medical intervention and treatments and highlighted the importance of diagnosis for conferring a sense of identity and the 'self:'

SLT: *"you're supporting social interaction.. you're supporting understanding of self…"*

Further nuanced recognitions of the impact of diagnosis were described where the interaction of individual personality and their underlying condition was considered:

SLT: *"and personality… I'm sure it's just as complicated a relationship with Klinefelter's… so there's the effect of the Klinefelter's on the individual and there's the effect of the individual on the presentation of the Klinefelter's"*

There were perspectives that an early diagnosis gave parents, as well as health professionals, the opportunity to consider specific ways to support their son, with potential implications on their developing sense of self:

SLT: *"his mother … found an effective way to communicate with him with the little figurines.. he actively had input to avoid a huge amount of frustration where adaptive behaviours could have built up barriers - that didn't happen because his mother implemented really effective things when he was tiny and she gave him a voice"*

SLT: *"she found an effective communication channel and so she averted a whole load of frustration and helped him develop a sense of self, so he was able to be an effective communicating agent in the environment, so if you speak to educational psychologists or child psychiatrists, they will tell you what she did was she supported him … facilitated a sense of self at a very young age that could not have developed like that and I think that's a really important area"*

The idea of self and the place diagnosis has within this was continued with the suggestions across the groups that linked diagnosis with empowerment and the individual taking control of their diagnosis:

GP7: *"what you have to do is learn to manage it, now certainly, if Klinefelter's has medical implications so they are much more prone to certain disease entities then actually the knowledge of that is important because what you can then do is counsel: 'look you are more likely to get this and this and we need to do everything we can to help you manage not to get it, or deal with it"*

GST: *"I think that for all the other reasons - the holistic approach you know, the increase in anxiety and other concerns etc that the Klinefelter's may or may not have but may have…. that needs dealing with … certainly in the initial consultation to make sure they're aware this can be associated with this condition"*

GP7: *"I suppose it ultimately goes down to the sort of thoughts of life and the whole of life is a calculated risk and its' up to each individual to lower their risk as much as possible…where does diagnosis sit in this? Does it aid the individual to self-manage their own health and wellbeing better? Does lack of diagnosis deny this"*

GP7: *"does knowledge of diagnosis enable individuals to take more personal responsibility for health and wellbeing?"*

One family read from a document from a clinical psychologist with particular expertise in endocrinology who highlighted the significance of diagnosis and provision to the developing self:

M2: *"his family.. have provided him with an environment which has allowed him to flourish…. this … has enabled him .. also to gain in confidence and develop a positive sense of himself"*

In this sense, diagnosis was seen as transforming, allowing the individual to feel they can 'be themselves.' Where diagnosis interrupted their development, this seemed to lead to suggestions of feelings of being unable to be them 'self.' There were descriptions of developing defensive and adaptive behaviours as protection from the isolation they were experiencing. The onset of treatment, precipitated by diagnosis was seen as the gateway and a chance to return to their 'self:'

I4: *"when I was younger like Year 8 and stuff, I had friends… when I grew up and got to about Years 9,11….I had really good friends … I went from Year 9 to Year 11 was like, pretty high confidence, got along… then … new school… voice hadn't dropped, confidence went down to an all-time low, just felt like crap about everything… then when I came back half-way through that year (after diagnosis and treatment started) … I felt great, and then I came to uni*

and felt even better… felt on top of my game. No, but felt like just myself. Yeah. Just be myself. Be myself"

8.2.6 Research and awareness

There were suggestions from all the groups that increasing awareness in general clinicians would be beneficial and ways to achieve this were proposed by the groups:

GP4: *"a training case of an article of something that just brings it to the forefront of people's minds … if it's in the forefront of your mind then people will diagnose it"*

GP3: *"I think probably it would be a good thing to have as part of just general GP education, I mean it should be, it should come up in the undergraduate course as something to consider and perhaps to put in a slightly stronger light"*

Further qualitative and quantitative research was seen as a priority to provide much needed insight and information to inform diagnosis and treatments, particularly longer-term data:

E1: *"their quality of life, what happens to their weight as they get older, um and bone health, what are their bones like in the long term? What's the fracture risk? What sort of lifestyle affects their lives? How do they feel on a day to day basis?.. all of these questions need to be answered …"*

E2: *"we don't really know what the outcomes will be, we don't really know what difference that whole effect has on functioning in life … it's very difficult to know"*

As already seen in the narratives of the groups, diagnosis is seen to confer multi factorial benefits, not only as a gateway to preventative care and treatments which significantly affect quality of life, but also in helping individuals and families with sense making of their feelings that something was wrong and providing a recognition gateway to proactive, preventative treatment and support for a range of symptoms.

8.3 The End Game

Klinefelter's Syndrome could be described as a new diagnosis, made possible only recently through advances revealing the underlying chromosomal differences:

GP5: *"nobody could ever find out in the past of course because there would never be any chromosomal tests"*

Healthcare systems may reasonably be suggested to have been designed to provide a symptom driven, reactive approach to treat illness and symptoms. The recent advances make proactive treatment approaches and preventative interventions possible for patient care and there was shared recognition of the potential these advances present:

GP2: *"all doctors love to practice preventative medicine, I mean, that's the goal"*

However, the structure of current health care systems may not yet be designed to respond to the advances in care made possible by recent advances as highlighted through the narratives and lived experiences of the families in this study and perspectives of the Expert Group:

E2: *"yes I think quality of life is key"*

The links between diagnosis, treatment and empowering families and health professionals to support Klinefelter's individuals were evident through the family testimonies and the importance of knowing to prioritise and build confidence:

I2: *"It's always good to be positive about a negative…life flows more smoothly if you are positive all the time.. or try to be…."*

The overarching perception shared across the groups was to provide a healthier, happier life was directly linked to early diagnosis.

This study sought to explore perceptions of the significance of diagnosis in Klinefelter's Syndrome. The narratives elicited from three groups involved in the diagnosis and treatment of Klinefelter's Syndrome revealed that, for this group, diagnosis was perceived as not simply significant, but essential:

I4: *"Knowing is 100%. You need to know"*

Figure 8: Diagnostic Cluster Group: All Groups

E3: “the clues are there…”

Ante natal, early infant clues	
Experts	E2: “the boys I see .. antenatal diagnosis … sometimes the genetics team would have picked it up antenatally”
Families	M1: “I was very lucky because I found out before he was born…amniocentesis” M2: “he was referred for late speech, late to walk, audiology, all his milestones” M3: “he was late to crawl, late to walk, late to speak, speech was quite late, he had problems in every aspect of walking, talking crawling, all the normal ..he was very slow, slower in development” M6: “audiology he was referred, speech he was referred, he had big problems there, co-ordination, reading and writing definitely”

Childhood clues	
Experts	E2: “then mostly after that it’s developmental problems, developmental delay, speech delay or perhaps problems behavioural in the older boy, behavioural problems, autistic spectrum tendencies” E2: “early childhood developmental problems, developmental delay which may well be 1-2 years of age.. slow to walk, slow to talk” E2: “about two thirds need speech therapy.. about two thirds will need educational support” E3: “education is a big thing… I think anyone with learning difficulties should at least get their chromosomes done” E3: “any child with mild learning difficulties, autism should have a chromosome straightaway” E2: “they might be a bit slower, or dyspraxic, less confidence” E3: “something’s not quite right”
Families	M1: “when he started to go to kindergarten, I noticed he wasn’t interacting so much with the other children, he wanted to stand on the side lines” M7: “from the first day at school he had extreme anxiety” M1: “some skin problems”

	M2: “immunology – immunisations T cells” M3: “pronunciation” M6: “learning to ride a bike was impossible… doing shoelaces, button through button-holes, he struggled kicking a ball, catching a ball” M1: “at junior school we began to notice .. he did have more difficulty writing and he might miss out words” I3: “distractions, everyone talking all around you even the noise they make” M6: “he’s definitely got dyslexia” M2: “flat feet” I4: “chest infections I’ve had quite a few of them, before I even got diagnosed with asthma… I got a chest infection that went on for months” M2: “he had lots of allergies, he was allergic to all his childhood immunisations and had to have them as a day patient in hospital, he was referred to a specialist and immunology with odd T-cell results” I3: “I’ve had all these upset tummies and backache… I struggle with my sleep, anger issues, stress and upset” I3: “I was quite poorly when I was 8 or 9 years old and I was in hospital quite a lot … I was just not eating anything and was just wasting away I can’t remember why I was in hospital on a drip” I2: “classes were a struggle, I was struggling and joining in with my peers” I2: “I think I read my first sentence to my class using symbols above the words” I2: “it was really helpful in visual … because I’m better with visuals than writing so … that helped towards me – to this day – thinking about words through imagery”

Clues at puberty	
Experts	E3: “the next time is at the time of puberty .. the lack of puberty..” E3: “pubertal induction, if they don’t start on their own… (or) just not seem to go through puberty in the right way” E3: “there are children who start off in puberty and I think they’ve got normal hormones early on….a lot of people aren’t aware they can start off in puberty normally, so they get confused by that. If they’ve got the signs that things are failing, voice doesn’t change, and so on they should be referred at that point”#

	E3: “increased risks, yes, cardiovascular problems, autoimmune – some of the boys have hypothyroidism, they’re more prone to metabolic problems” E3: “psychosocially absolutely they feel differently, and they may feel very frustrated.. yes I think that’s very important to pick up” E3: “hypothyroidism may go undiagnosed as well for ages” E3: “testosterone gives you energy, without that your energy levels fail, you just don’t; feel like doing anything”
Families	M3: “he was diagnosed at 16, he wasn’t referred for Klinefelter’s, he had white fingers, his hands were really cold, Raynaulds? They wanted tests done, they thought Marfens” I4: “I went a few times to the GP and they went ‘oh it’ll develop’ I was like ‘my voice hasn’t dropped yet is there a problem here?’ and they were like ‘no it’ll develop’ I was persistent asking my Mum … I was about 18.. had a private referral and then when he told me I was like ‘oh well it all makes sense now” I4: “like .. the voice not dropped yet, no facial hair…and I wanted to get it sorted ‘cos I was like getting a bit of stick for it as well” F3: “I’d say possibly general build he was always not very well developed… just struggling with his schoolwork” I4: “I struggled a bit at school. Always struggled quite a bit like writing and mental processing” I3: “I think it was the learning aspect I struggled with” I3: “I was a bit shy. I suppose back then I didn’t know I had the condition, so I just thought I’m not confident enough” M7: “he was lacking in confidence, his visits to the doctor were frequent and his confidence was dropping” I3: “socialising I think with me you do struggle with social environments .. the interacting was hard …having conversations with people that’s something I struggled with” I2: “I struggle with attention span my attention span is not great”

↓

Post puberty/adult clues	
Experts	E3: “others may go all the way through puberty and gradually the testes don’t function very well and eventually you end up on testosterone as a result” E2: “some with physical problems … then later on in life fertility problems” E3: “urology is the other way to go because of genital abnormality”

Families	I4: “voice hadn’t dropped, confidence went down to an all time low, just felt like crap about everything” M6: “it’s the writing and the spelling, he’s definitely got dyslexia” M6: “he’s definitely got Asperger’s” I4: “I used to see the doctor quite a lot” I3: “I try not to eat anything with cream in it, it’s a bit sickly.. I don’t have breakfast in the morning I find it too hard to digest anything” M6: “it’s a kind of allergy, it flares up, his hands have been in a terrible state with blistery stuff, we had real problems with his hands” I4: “back pain, that’s quite common, it’s the worst pain” I4: “sleep is still screwed up” I4: “it affects other stuff as well .. muscles, bones as well, the back pain… mood swings, stress from the testosterone, muscle problems dyslexia and dyspraxia..” M6: “he can’t cope with people, it’s a socialising thing.. he just can’t cope, he’s in a terrible state, he’s shaking, he shakes you see” M6: “very bad anxiety, very bad been a problem for a long time, I’d say it’s got worse” M6: “motivation and social difficulties… living at home unemployed” M6: “I do wonder now, he was having speech therapy, I do wonder then if the speech therapist had said ‘he may have this’ … may be if I’d persevered and thought ‘why is he having speech therapy?’ we knew something was wrong, you can’t always know what’s wrong’ M6: “you get onto other problems .. terrible depression at times, really bad” M6: “no one tested for anything it’s unbelievable isn’t it when I think of the people we’ve taken him to over the years”

Symptoms and medical	
Families	I4: "chest infections - I've had quite a few of them…. before I even got diagnosed with asthma…. I got a chest infection that went on for months….I think that was Year 7 to 8 - I had a chest infection" M2: "he had two episodes of pneumonia within 18 months when he was 10 .. the first was really serious with complications …and he missed nearly a year of school" I4: "I used to see the doctor quite a lot… I was really out of breath…. I was about 9. The doctor confirmed I had asthma….I wish I'd been told - I'd gone for a blood test when I found out that I had asthma… so it would be nice if I'd found out then" I3: "I was quite poorly when I was 8 or 9 years old and I was in hospital quite a bit… I was just not eating anything and was just wasting away… I can't remember why I was in hospital on a drip - so why didn't they find it then?" M2: "he has had ongoing gastroenterology problems and been hospitalised 3 times as an emergency just for that … he now has regular appointments with a gastroenterologist, and he has done much better since being monitored and managed …he also sees a dietician which has helped with the symptoms a lot" I3: "I don't have breakfast in the morning I find it too hard to digest anything" M2: "he's always had allergy problems - all his immunisations he had to be given in hospital - they said he had some differences in his T-cells… lots of food intolerances and odd allergies… he's doing better on a gluten free diet now" I3: "I think I'm allergic to penicillin and something, I get asthma and hay fever… I've had all those upset tummies…" I4: "and allergies, yes, a weird one - plasters - I get all scratchy and it swells up…" M6: "it's a kind of allergy it flares up, his hands have been in a terrible state with ..so we had real problems with his hands" I4: "back pain that's quite common, that's the worst pain" I3: "I struggle with my sleep, anger issues, stress and sleep" M2: "they also said he has completely absent folate, but no one has found out why that is yet.. " I2: "I think my health dips in and out"
Specialists	SLT: "we might mistake it for ASD .. I could see a lot of false positives with ASD arising" GST: "there appears to be an increased risk and definitely what we would call functional problems, constipation, bloating, discomfort, slow transit … we see that across Klinefelter's patients"

	GST: “I would not be surprised to see an associated immune related condition” DIT: “it’s quite a complex condition that there’s thought to be quite a strong gut/brain axis so quite a lot of people who suffer with stress, anxiety or depression are more likely to develop irritable bowel syndrome… what you are thinking and feeling can directly affect the gut” GST: “we see inflammatory bowled disease .. I would not be surprised to see a functional problem so discomfort or symptoms that are significant enough to affect quality of life” URL: “if you’re diagnosed at the age of 5 because of dyspraxia or other aspects of developmental delay” FRT: “we’re doing chromosomes for fertility issues” URL: “autoimmune, thyroid problems” SLT: “difficulties with organisation…auditory processing …slightly different empathy levels, a warmer empathy than you see typically with ASD” SLT: “it was the speech and language problems that caused the emotional behaviour” SLT: “the literacy aspect, with dyspraxia and dyslexia” PHY: “back problems… we know with Klinefelter’s you have lower tone.. lower tone hypermobility” GST: “I think they would be far more likely to present themselves to hospital in general, certainly hospital services earlier on than later”

Experts

E3: “at various points it makes things better for the kids, basically …early diagnosis can help you manage things better”

Specialists

GST: “this is a common condition …that has associated morbidity which a lot of us specialists see in isolation but actually they are all connected”

Families

I4: “Knowing is 100%. You need to know”

CHAPTER 9

CONCLUSIONS AND FUTURE RESEARCH

Klinefelter's Syndrome is a common condition, with a rate of prevalence estimated to affect between 1/500 - 1/660 males (Verri et al., 2010). Few males are diagnosed with only one quarter diagnosed during their lifetime with a reported 64 - 75% remaining undiagnosed (Bojensen & Gravholt, 2010; Radicioni et al., 2010; Gravholt et al., 2018). Lack of diagnosis of Klinefelter's Syndrome is reported to be a 'major problem' (Bojensen & Gravholt, 2007). The literature attributes this under diagnosis to low awareness in general clinicians and variability of the syndrome (Nieschlag, 2004).

Klinefelter's is reported to have increased risks to morbidity and to affect life expectancy with mortality reportedly earlier than in the general male population. Although the reasons for this are not as yet clear, early diagnosis is seen as a significant factor in protecting against known risks to health and well-being through timely diagnosis and subsequent screening, monitoring and treatment (Bojensen & Gravholt, 2004; Bojensen et al., 2011).

This study examined the significance of diagnosis in Klinefelter's Syndrome for individuals affected and their families and the reasons why, despite its frequency of occurrence, diagnosis rates are so low. This chapter summarises key findings and critically evaluates the research carried out in order to examine possible next steps with this work.

9.1 Summary of the findings from each group

This study took a qualitative approach, examining the perceived significance of diagnosis, not only of individuals and families, but also experts in Klinefelter's Syndrome (endocrinologists), specialists in conditions other than Klinefelter's Syndrome and general practitioners. This is thought to be the first study undertaken which has taken this '360-degree' approach in order to investigate how diagnosis is perceived and affected by practitioners' experiences as well as those directly affected. The aim of this approach was to examine how the combination of practitioners' knowledge and perceptions of Klinefelter's may impact on the diagnostic process and the perceived impact this had on affected individuals and families. This approach proved uniquely revealing showing the difficulties and real struggle experienced by families receiving late diagnosis of the syndrome and the

systemic factors around diagnostic procedures and referral which resulted in the poor diagnosis rates currently observed.

9.1.1 The Family Group

Individuals with Klinefelter's, parents, and siblings were interviewed, providing important insights into the effects of the syndrome on the family as a unit. What emerged was the extent to which Klinefelter's Syndrome is a diagnosis experienced and shared by the family unit. This is significant in highlighting the need to provide support for the family as well as the Klinefelter individual.

In contrast to the conventional perspective, for the families in this study, parents revealed a consistent and intriguing pattern of shared commonalities in symptoms, rather than variability, from the earliest years. The assumption of variability in clinicians echoing the reported variability in the literature is in contrast to the consistent 'core' of symptoms reported by the Family group. This contrast may be explained, in part, by a variability in the literature (Boada et al., 2009), where individual symptoms – rather than a holistic picture based on the totality of individuals' experiences – tend to be emphasised. Where variability did emerge, this was in the adulthood of those diagnosed latest in adult life: their narratives revealed emerging secondary problems including increasing anxiety, social isolation and depression, the genesis of which was attributed by the families to be a late diagnosis, made beyond age 25.

The Family group were united in describing diagnosis as significant and, particularly, early diagnosis as important:

M5: *"basically, I think everyone is entitled to an early diagnosis"*

I4: *"Knowing is 100%. You need to know"*

M1: *"I suppose I was lucky because I found out before he was born….being forewarned, we were forearmed"*

Without a timely diagnosis, a 'lifetime of clues' were seen to have been missed and along with this the opportunity to receive appropriate treatment and support:

M5: *"we were quite upset actually to think that he'd gone through all that and a simple blood test could have saved years and years of misery"*

Lack of diagnosis was perceived to leave individuals vulnerable and at increased risk of developing a kaleidoscope of secondary and emerging problems later in life with considerable detrimental impacts on their quality of life. Conversely, early diagnosis was

perceived as providing the opportunity for timely preventative support giving Experts with the information needed to provide monitoring and screening of the syndrome's sequelae (testosterone levels, bone density and hypothyroidism, for example). In this way diagnosis may confer a protective factor against secondary problems which can result from lack of timely intervention:

E2: *"I'd worry about a 38-year old, a diagnosis that late…."*

Early diagnosis may also help to avoid problems such as bullying at school, increased risks of depression, social isolation and under achievement at school and ensure important provision at school where special educational needs may require specialist support and intervention in the classroom and with social interaction with peers. The risks of bullying and isolation in school were summed up by one parent:

M5: *"They made his life hell"*

Families who were diagnosed earliest felt diagnosis meant they were better equipped to provide for their son and provided important insight to informing better decision making (choice of school, for example). In light of the diagnosis and the insights this provided, parents described how they were able to facilitate a holistic style approach to their son's care.

However, the lack of formalised Klinefelter's pathway for diagnosis and treatment meant that co-ordinating this care was a responsibility taken by parents and negotiated on a case by case basis with the medical professionals involved, perceived as a considerable and stressful burden of significant time and money for the families.

These valuable insights into early years and beyond catalysed the genesis of the models presented in this study for early diagnosis prompts during the first 36 months of life: 'the Core Deficit Multi-Dimensional Diagnostic Model' (Figure 6, page 249) and a model designed as a basis for a holistic approach to care: 'the Core Deficit Multi-Dimensional Model' (see Figure 7, page 255). The need to examine further these possible 'core' set of symptoms and referrals reported by the parents in early life and which might arise prior to later variation was apparent.

9.1.2 Experts

The Experts echoed the literature and the lived experience of the Family group in advocating for early diagnosis:

E2: "*I think the gains are huge if you make a diagnosis, you might actually prevent a lot of health problems in the future"*

Diagnosis was also perceived as important for providing answers as well as providing a context for the problems that had been noticed by the families: preventative screening, monitoring and providing opportunities for informed decision making (parents choosing educational settings, for example):

E2: *"I think at various points it makes things better for the kids, basically"*

Importantly, one of the Experts echoed the views expressed by the Family group, stating that the variation Klinefelter's symptomatology was no greater than might be found in a variety of symptoms expressed in the general population:

E2: *"There's as much variation in an XXY boy as there is in an XY boy"*

Again, the need to examine a possible 'core' set of symptoms which might arise prior to later variation became even more apparent.

9.1.3 The GP and Specialist groups and a 'new' diagnosis

Both the GP and Specialist groups revealed a startlingly low awareness of Klinefelter's Syndrome, with a very low knowledge base with respect to Klinefelter's Syndrome even given the oft reported, but poorly substantiated, low awareness in general practitioners frequently reported in the literature (Herlihy et al., 2011):

GP5: *"I've not had a patient with Klinefelter's that I know of and it's certainly not that common."*

GP4: *"It probably turned up on a multiple-choice question somewhere at med school"*

GP2: *"It's not on our radar."*

GP7: *"I'm in a practice of 14,500 patients and I've had one Klinefelter's patient in 20-25 years"*

GST: *"I think one important question is what's my impression of the knowledge of Klinefelter's in gastroenterology consultants - basically zero*"

GP and Specialist narratives identified a lack of clarity in the system around 'owning' the diagnostic role, for example:

GP5: *"it's developmental, and it's not illness, a GP doesn't do development*"

Lack of ownership appeared to emerge from a fragmented and disconnected approach to diagnosis:

GST: *"1/600 is common and has associated morbidity which a lot of us specialists see in isolation but actually they're all connected, and I don't think that many of my colleagues would even know that"*

Moreover, Specialists often felt they were responsible only for diagnosing within their specialism creating even more fragmentation in the process:

URL: *"this is not my primary responsibility… I would put that in my letter for the GP to deal with"*

This 'pass the parcel' approach to diagnosis alongside the very low awareness of the syndrome and poor diagnosis rates indicate the urgency of establishing a Klinefelter pathway for diagnosis and treatment:

PHY: *"the NHS was designed on a medicinal approach and that's why we have such separate entities…. you need to get to the pathways,… so in a way, you're trying to create a pathway for Klinefelter's"*

Creation of a diagnostic pathway would not only provide clear guidance for both GPs and specialists but would crucially serve to increase awareness in clinicians and help to create a 'big picture' in which Klinefelter's Syndrome was seen more holistically rather than as a series of individual, disparate, symptoms. This could also dovetail with advances in detection of Klinefelter's Syndrome and simplicity of diagnosis made possible through chromosome testing, as described by a parent: *"it's a simple blood test, why couldn't it be picked up years ago when he was a child?"* (M3)

9.2 Key findings

A number of insights were illuminated through the novel 360-degree approach taken in this study which revealed experiences and perceptions of those involved with, and around, diagnosis of Klinefelter's Syndrome. They revealed why diagnosis is important and the reasons for under-diagnosis as well as the possibility of seeing Klinefelter's as a condition rather than a syndrome (i.e. a collection of symptoms) which has the potential for a clear pathway to diagnosis and care. Findings regarding lack of diagnosis and the lack of a joined up perspective for subsequent care should serve as 'beacons' for physicians and the National Health Service, shining a light on, and acting as a warning signal, for fundamental issues which need to be addressed. Key findings are listed below:

9.2.1 Diagnosis is important

Insights shared through exploring perspectives of the Experts and the lived experiences of the Families revealed a united perception that diagnosis is not only significant, but timing of diagnosis is important and significant. A proactive approach, engendered by early diagnosis, avoids later difficulties. Diagnosis is important because it allows families

and practitioners alike to think and act proactively to prevent difficulties which might arise from the medical sequelae of Klinefelter's and make more effective management and support decision making. This proactive approach may also help to prevent difficulties arising from learning difficulties and bullying in school, enhancing the wellbeing of the individual. Importantly, effective early diagnosis and support may save the National Health Service money in the long term arising from multiple contacts with GPs and specialists and through awareness of increased risks, preventative practice and timely treatment may prevent emergence of known vulnerabilities to health and wellbeing.

The advent of medical advances in fertility now provide the possibility for some Klinefelter males to father their own biological children. The advent of the success of this procedure of surgical sperm retrieval is reported to be affected by factors such as age of the individual (Rives et al., 2013; Herlihy & McLachlan, 2015) and timing of earlier intervention with testosterone treatment (Rives, et al., 2018). Given that outcomes may be affected by such factors, this aspect of diagnosis and management of Klinefelter's further increases the significance and urgency of early diagnosis.

9.2.2 Diagnosis is a family experience

This study revealed the extent to which Klinefelter's Syndrome is a diagnosis experienced and shared by the family unit (see 7.3.7, page 209). This is significant in highlighting the need for providing support for the family as well as a focus on the Klinefelter individual.

9.2.3. Reasons for under-diagnosis

The narratives of the GP and Specialist groups were significant in revealing factors which delay, or may prevent, diagnosis. These factors were partly indicative of the changes and advances in medicine which created a mismatch with the current healthcare system revealing it is not designed or equipped to deal with 'new' diagnoses and the different approaches these advances demand.

(i) Lack of awareness

The narratives of the GP study resonated with the reports in the literature of a low awareness of general clinicians. Surprisingly, the Specialist group generally appeared to have very little knowledge, or experience of, Klinefelter's. For both groups this was best summed up by the phrase *'it's not on our radar.'*

(ii) Fragmented approach and lack of ownership of diagnosis

Diagnosis appeared to be extremely fragmented with individual specialists treating individual symptoms. Currently there was perceived to be no standardisation of the diagnostic process (and an absence of screening prompts) which contributed to a lack of clarity about the referral and diagnostic process and led to lack of diagnostic ownership creating a 'Catch 22' situation where neither GP nor Specialist perceived the diagnosis of Klinefelter's to be their role and thus contributing to late, or missed, diagnosis. This seemed to provide the genesis for the family perceptions that despite multiple contact with health professionals, diagnostic opportunities were perceived to have been missed and delayed despite 'a lifetime of clues': Diagnostic Cluster Groups (Figure 2 page 100; Figure 4 page 154; Figure 5 page 221; Figure 8, page 264); 4.3.2 (page 82); 7.3.2.3 (page 166); 7.3.2.4 (page 169); 7.3.2.5 (page 172); 7.3.2.1 (page 161); 8.2.2 (page 232).

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9.2.4. New perspectives on Klinefelter's Syndrome

Interestingly, for the groups in this study, the narratives revealed shared patterns of commonality attributed to the syndrome, in contrast to the hallmark reported variability. Emergent narratives revealed novel insights into the variation commonly reported in the literature: *"there's as much variation in an XXY boy as there is in an XY boy"* (E2) and reveals early hints of commonality rather than variability in this study.

These commonalities are presented as the Diagnostic Cluster Groups and additionally reflected in the novel models presented for consideration for early diagnosis: the 'Core Deficit: Multi-Dimensional Diagnostic Model', (see Figure 6 on page 249) and a 'blueprint' model for holistic care: the 'Core Deficit: Multi-Dimensional Model': see Figure 7 (page 255).

9.2.5 Increasing diagnosis

The need to increase diagnosis in Klinefelter's as advocated in the literature (Herlihy et al., 2011; Herlihy & McLachlan, 2015) is echoed by the groups in this study. Ways forward which were identified to address issues currently resulting in under-diagnosis are listed below:

(i) Education

It is clear that both GPs and Specialists were unaware of Klinefelter's Syndrome and that little information had been given to them either during the course of their training or since training had been completed as part of professional development. Ways to address this have been proposed in this study with suggestions from the GP group for an increase in the

Klinefelter profile through medical school and beyond into professional training such as seminars and professional development opportunities:

GP4: *"a training case, or an article, or something that just brings it to the forefront of people's minds…"*

GP6: *"it would be a good thing to have as a part of just general GP education … it should be.. it should come up in the undergraduate course"*

A conference is planned in the near future to begin this process.

(ii) Creation of a Diagnostic Pathway

Diagnostic Pathways provide clear guidance on the nature of a condition, its aetiology and symptomatology and often include the optimal timeline for diagnosis with practical recommendations about how this might be implemented in practice. The pathway is made accessible to practitioners via summary documentation which can be made readily available on-line. A diagnostic pathway for Klinefelter's Syndrome would serve multiple functions: it would educate clinicians about Klinefelter's, making them aware that this is not a rare condition. It would indicate key symptomatology, especially where commonality in symptoms is apparent (i.e. what are the key clues) and would indicate where diagnostic clusters of symptoms arise. Finally, it would indicate appropriate testing and clarify diagnostic and referral routes.

(iii) Creating a model for understanding Klinefelter's Syndrome

Both (i) and (ii) above beg the question of whether or not there is a model which brings together current understanding of Klinefelter's. While a very limited number of experts in the UK and abroad may have a comprehensive understanding of the Syndrome, it is safe to say that this knowledge resides with them and takes the form of accreted experience and knowledge gleaned from research over many years. In Chapter 8, a model is proposed which brings this research and lived experience to create a model for treatment: the 'Core Deficit: Multi-Dimensional Model', (see Figure 7, page 255). A simplified model is summarised in (Section 9.4, page 278; Figure 9, page 280).

9.3 Limitations of the study

This study took a qualitative approach to explore detailed accounts and perceptions from each group to elicit as much detail as possible to inform the research question. The limitations of this mean that the groups in this study were relatively small to elicit detailed, data rich accounts. While the findings of the current study suggest that such an approach can

reveal the dynamics of diagnosis in a way that would not be possible in a study involving large numbers, there is the possibility that those interviewed may not be representative of groups they represent. While this possibility is ameliorated to some extent by the use of a multiple group approach which provides some 'cross-validation' of findings, it is clear that future research needs to examine larger groups. Recent research used larger sample sizes and different methods to examine the experience of those with Klinefelter's Syndrome reporting a higher risk for anxiety and depression, (Skakkebaek et al., 2018), for example, but the scope of the research included Klinefelter's participants only, thus missing the wider picture of family impact, missed diagnostic clues, lack of ownership of diagnosis and the paucity of understanding among both general and specialists clinicians which became apparent in this study.

Using multiple groups also helped to avoid the potentially 'self-fulfilling' nature of qualitative studies in which existing hypotheses are more easily confirmed. However, it is clear that ideally those conducting interviews with participants are blind to the hypotheses of the study, although careful thought would be required about how effective qualitative interviewing might be carried out in this manner.

A fundamental question of establishing the incidence of Klinefelter's Syndrome, particularly in the UK, remains unclear. While some epidemiological studies have taken place in the UK, Denmark and Australia (Herlihy et al., 2011), it is clear that incidence levels are yet to be definitively established, particularly given the rapid changes in chromosome testing. Future research examining data from these studies would therefore be beneficial.

9.4 Multi-disciplinary, individualised care in Klinefelter's

This final section summarised the possibility for new forms of care which have resulted from this research. The need for a holistic approach to care for Klinefelter's as a systemic condition was highlighted by the group narratives. Informed by the 'Diagnostic Cluster Groups' and the 'Core Deficit - Multi-Dimensional Model' (Figure 7, page 255), a suggested model for delivering an individual holistic care plan is proposed by the 'Individual Holistic Care Plan' shown in Figure 9 (page 280).

As noted earlier, this study revealed underlying reasons for the under diagnosis reported in the literature and, in contrast to the reported hallmark variability of the syndrome, revealed descriptions of shared commonalities. These commonalities contributed to the 'lifetime of clues' identified at the end of the Expert, Specialist and Family chapters as

'Diagnostic Cluster Groups' and are dealt with in some detail at: 8.2.2, page 232; Figure 2, page 100; Figure 4, page 154; Figure 5, page 221; Table 17, page 226; Figure 8, page 264 Table 21, page 324; Table 15, page 161).

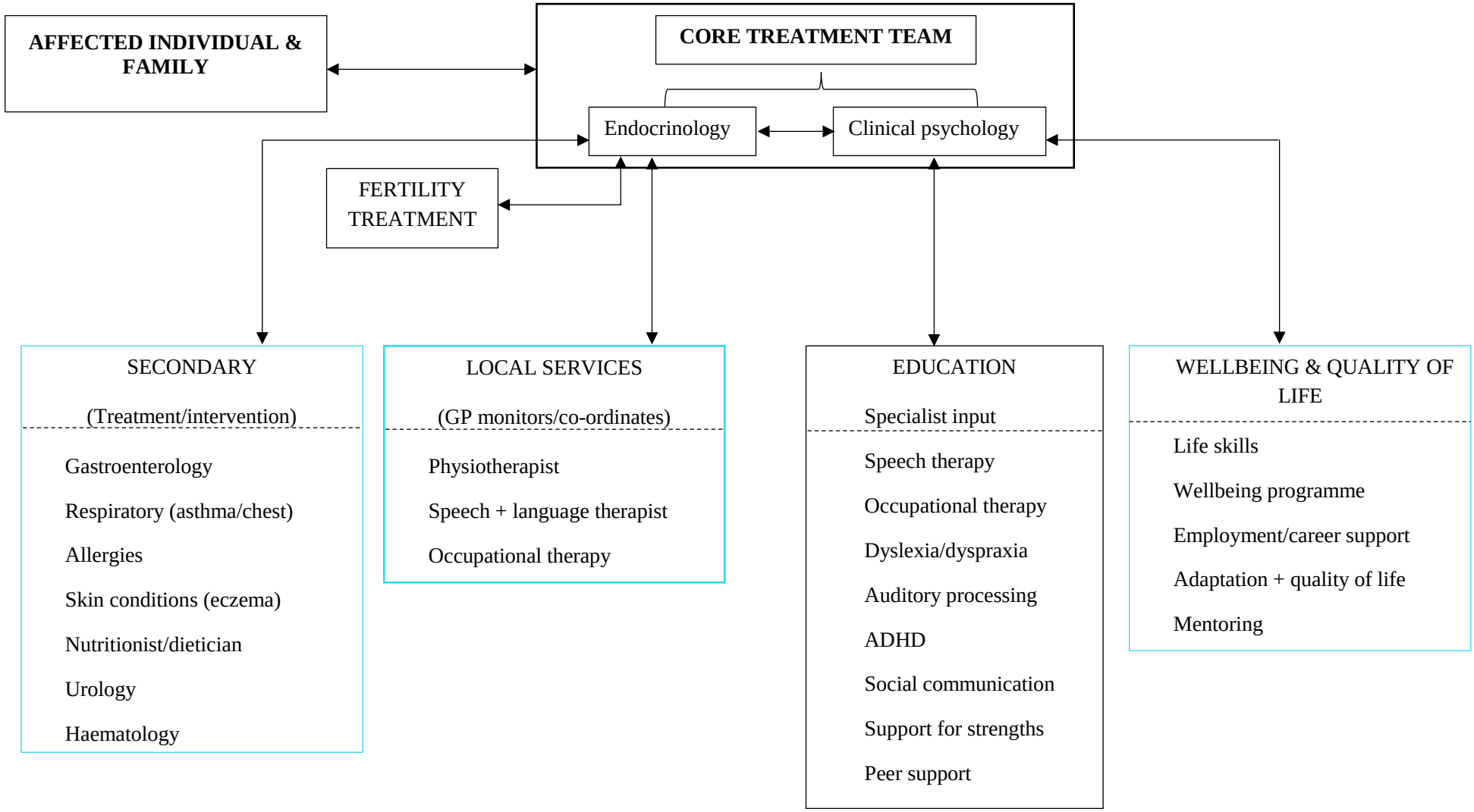
The Individual Holistic Care Plan (IHCP) (Figure 9, page 280) provides a simplified version of the care plan (discussed in Chapter 9 in this concluding section), in combination with the 'Core Deficit: Multi-Dimensional Model' (Figure 7, page 255) by proactively supporting known areas of increased health risk and by providing a personalised approach through delivering a 'tiered' system of care, offering treatment for existing health problems or symptoms (where required), screening and monitoring for increased risks and preventative care to optimise health and wellbeing.

By providing this 'whole person' approach it is hoped this will have a beneficial effect on quality of life and wellbeing as well as reducing the need for hospital admissions where known health risks are minimised through practising a preventative approach through pro-active, careful, managed monitoring and care. Research currently under way is examining the implementation and efficacy of this approach in a clinical setting in collaboration with University College London Hospital.

Figure 9 (page 280) shows how individual care plans based on a holistic view of Klinefelter's Syndrome might work. At the heart of this model is the interaction between the affected individual and their family and the 'Core Treatment' team. The Core Treatment team consists of an Endocrinologist with expertise in Klinefelter's Syndrome (and their team) who addresses medical issues and the Clinical Psychology team who address wellbeing and additional education needs. The individual and family receive care and liaise closely with the Core Treatment team to receive both support and information in relation to endocrinology, general health, education and wellbeing.

Again, with close liaison and mutual information at the heart of the care plan, the Endocrinology Team ensure that appropriate fertility treatment is given and, where necessary that appropriate treatment is received for secondary sequelae arising from the syndrome. The Endocrinology Team also liaise with the GP who monitors and co-ordinates local services. The Clinical Psychology Team provides psychological input and support, provides assessments to examine educational strengths and weaknesses and referring to additional learning needs specialists as required. Support for wellbeing may also be accessed and, particularly for those in secondary and tertiary education, mentoring and life skills support is provided.

Figure 9: Individual Holistic Care Plan (IHCP)



The GP group highlighted they are well placed to hold a diagnostic and co-ordination role with Klinefelter patients:

GP3: *"we're fairly well placed to be co-ordinating things"*

The GP group identified that their role could contribute positively to increasing diagnosis through their having oversight of all patient letters which may alert a pattern of referrals identified in the Diagnostic Cluster Groups, thus prompting a referral for Klinefelter's testing:

GP2: *"no one else gets all the letters, the GP is the only person who sees every letter"*

GP2: *"if you think 'this person has all the symptoms, could it be Klinefelter's?'... quite often it's the GP who sees all of the letters from the referrals and puts them all together"*

To assist with this, raising awareness and the provision of a diagnostic pathway was felt by the GP group to be helpful as a focus for GP training from medical school and continued into professional development:

GP2: *"all doctors love to practice preventative medicine, I mean, that's the goal*"

The GP, working under the guidance of the Experts, may therefore be well placed to take an active role in the implementation of part of the model under the guidance of the Expert 'Core Team' as suggested in this model. In this way, GPS may act as a 'first tier' of support. A second 'tier' provided through referral to Specialists in specific medical disciplines to treat specific symptoms and/or subsequently monitor the increased risk categories identified in the DCG's (gastroenterology for example). The third tier is provided through recommendation for treatment from the core team to the GP and has a focus on promoting, preventing and maintaining health and wellbeing via referral to local services from the GP under the guidance of the core team: physiotherapy, occupational therapy, speech and language therapy and a dietician to focus on nutrition, for example. Alternatively, the model may be flexibly implemented and is designed to be delivered on a case by case basis, so that any part(s) of the model may be provided directly through, or by, the Core Team, rather than locally, should this prove beneficial.

9.5 Diagnosis Matters

The Family and Expert groups revealed that diagnosis is significant and early diagnosis even more significant. Incidence rates are reported to be increasing, in parallel with the advent of non-invasive prenatal testing (NIPT) resulting in cases being identified earlier. This is predicted to result in an increase in cases being identified earlier, thus causing an

increase in numbers presenting to general clinicians for advice and treatment. Research which informs and illuminates knowledge and understanding relating to the place that diagnosis has in life experiences and quality of life is important. This research reveals insights from those directly involved in the diagnostic process of Klinefelter's Syndrome (47,XXY) whose narratives present a united advocacy for early diagnosis and subsequent informed, holistic approach to care, resulting in beneficial impacts on quality of life. Insights from the combined group narratives illuminate the positive difference that timely diagnosis was perceived to make to individuals, their family, health care systems and wider society:

E2: "*I think quality of life is key*"

I2: *"It's always good to be positive about a negative… or try to be…"*

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APPENDIX

Appendix 1

Table 19: Variability? – commonalities in strengths

Navigation	F3 "if you're at an airport and you're looking around you say 'where do we go?' and he says 'down there, it says so on that sign, that's the way' he is in some situations he doesn't miss a trick very, very, observant, he'll not gloss over things he's very good like that" M5: "oh fantastic at navigation, brilliant, absolutely brilliant, in his pushchair he'd go 'eeeee, (laughs), brilliant, in the car he'd say: 'this is the way, that is the way" M2: "I've actually got very lazy about remembering routes and directions… I know if I need to know the way to anywhere he will find it ….like magic. Give him a map of anywhere he will take you there.. amazing" F3: "wayfinding, navigating is excellent… he doesn't need a sat nav, I'd say excellent at map reading, I'd say he was unusually good"
Visual Detail	M5: "He was good at puzzles, and good at wayfinding…. visual detail, yes actually he said 'do you know you've got 17 lamps in this room', not tactful I suppose, then he said 'you've got an awful lot of cobwebs all around the home, so yes visual details' good"
Puzzles	M5: "he was excellent at doing puzzles, unbelievable… when he saw the educational psychologist she actually said she'd never seen anyone put the pieces together as quickly as he did" M2: "he saw so many people for assessments from when he was very young. I knew, knew, there was something that had to be known about him…he saw an educational psychologist….he saw several actually… one gave him a test and said: 'oh he couldn't have done that so quickly, he must have just guessed'. But then she checked - he hadn't guessed, he'd just done them all really quickly. And he'd got them all right. She didn't know what to say…. I've got used to that happening"
Work Ethic	M6: "once he got involved in something he would stick at it, he would work through the night if something needed doing and even today he's the same, he could if he wanted to do it he can really focus on something"

Appendix 2

Table 20: Holistic Support: Teen to Adult

Provision	
Psychological and Mood	I4 "might be helpful (psychological support) 'cos like getting the news, getting the injections having these random mood swings it's a bit like full-on, it's a bit weird as well, so maybe.. maybe….you also feel a bit down at times, depressed maybe. You feel like down in the dumps a bit" I4: "I think my parents just forgot I had mood swings …. That's the only downside of it (the testosterone treatment)…..it does improve but gradually, the first 3 or 4 years you have mood swings" I4: "a few months ago like I was going to a party, I was getting ready. I just felt so angry, I just felt so tense for no reason" I4: "just chill out in my room, just not speaking to anyone really, it's a bit anti- social, but it works, or going for a nap or something" I4: "I was in my room and just chilled in there… yeah now it's alright I get the odd mood swing here and there, but it's usually when I do home as well (laughs)"
Sleep	I4 "the sleep is still screwed up …. I just don't understand what's going on" M5: "the worst thing is this night thing his sleep is awful, awful" M6: "he has significantly disrupted sleep, that is still a problem" I3: "I still get very tired now …I don't think it make any difference to that"
Anxiety	M6: "it's the social aspect that's hard… the anxiety"
Speech Therapy	M6: "a speech therapist should be looking out for this how many speech therapists are looking out for this from day one… he has apparently got all the physical manifestations and signs of this…."

Appendix 3

Table 21: Health Problems, School and Hospital

Health Problems	Allergies: I3: "I think I'm allergic to medicine penicillin and something…. I get asthma and hay fever… I've had all those upset tummies and backache… I struggle with my sleep anger issues, stress and upset" I4: "and allergies yes a weird one - plasters….I go all scratchy and it swells up and goes all yellow….." M6: "it's a kind of allergy.. it flares up, his hands have been in a terrible state with blistery stuff, we had a real problem with his hands….. he had seen a specialist who couldn't do anything so he can't always play golf, he's good at badminton, it's the social aspect that's hard" Chest: I4: "chest infections I 've had quite a few of them um, before I even got diagnosed with asthma I had this inhaler because I got a chest infection that went on for months…. I think that was Year 7 to 8 I had a chest infection….. " Digestion: I3: "I try not to eat anything with cream in it it's a bit sickly, I don't have breakfast in the morning, I find it too hard to digest anything…" Back: I4: "back pain that's quite common… it's the worst pain" General: M5: "he seems to get more colds" I4: "the endocrinologist sees me for just the hormones… it affects other stuff as well… like muscles, bone as well the back pain must be from something… it's all a bit together obviously like the mood swings, stress from the testosterone, muscle problems and the back …. Dyslexia, dyspraxia 'cos I've always had learning problems and I never knew I had Klinefelter's until two years ago so, yeah…" M5: "they also think he's got hearing problems…we thought he had a hearing problem…. he had a test at school"
School	M5: "it's obviously affected us greatly over the years with schooling and everything"
Hospital	I3: "I was quite poorly when I was 8 or 9 years old and I was in hospital quite a bit… I was just not eating anything and was just wasting away… I can't remember why I was in hospital on a drip… so why didn't they find it then?..... "

Mood	M5: "not only that, you get on to other problems, it's all to do with this isn't it.. terrible depression at times, really bad" M6: "he can't cope with people, it's a socialising thing... he just can't cope, he's in a terrible state, he's shaking, he shakes you see"

Appendix 4

Table 22: Adult Life: Independence, Vulnerabilities and Variability

Vulnerability	M1: "but as they get older that becomes more difficult … once they're over 18 there's this confidentiality even with the doctor and they … so it gets harder to …. trying to protect them and push their case forward" M1: "you feel more because it's expected of them in the adult world, but particularly when they go to university … they just don't know how to deal with certain sorts of situations because they quite often lead quite a sheltered life really, they go to school and parents protect things with them and they're not really street wise" M1: "well you can't be with them all the time in every situation can you so that's quite difficult to come to terms with isn't it really because you're always sort of fearing that something (laughs) could go badly wrong …. " M1: "particularly with relationships and things like this where one has to be terribly careful, I think it's very hard for young people now in a way….. the whole social thing, it's tricky" M1: "they take people at their word, really" F3: "I'm more concerned about how it affects him and his future and his interactions with other people because he can be a little black and white … the problems I think he is going to have in the future and it worries me in that respect more than anything else, really" M1: "you have to learn to let them learn, sort of experience the world for themselves … just learn to be more independent …. you worry whether someone like him will be taken advantage of in life" I4: "a few months ago like I was going to a party, I was getting ready. I just felt so angry, I just felt so tense for no reason"
Variability	M6: "it's the social aspect that's hard, the anxiety…."

Appendix 5

Table 23: Family Holistic Support Table: From Diagnosis

Provision	E1: "it's looking out really"
Holistic	M1: "it probably ideally it probably it is the holistic approach would be the best option… " M1: "ideally probably the holistic approach would be the best option" M5: "a centre, multi-disciplinary… an expert who can advise on the whole, don't you think…" M5: "there should be a special clinic, it should be all geared up, don't you think" M5: "what and how are endocrinologists doing to have a stronger say in writing to GP's and increasing diagnosis figures? It must cost much more to provide all the support later on and after things have gone wrong, to put them right, than to put support in place earlier"
Emotional	M5: "possibly emotional support.. I think they would need a lot of emotional support, they need a lot of back up with this… they can become aggressive, it's everything, really, relationships - that's vital as they get older, that's a huge thing as they get older they get married they can't have children they would need a bit of psychology from that point of view. They are very different actually" I3: "yes, a good way of getting rid of anger"
Education	I3: "a good care plan that shows teachers how to support a young lad with this condition, one to one support with the teacher so they can get the extra support they need, so they can get through school….." M5: "it would help the teacher: 'this is what they need' I think it would help a lot" M5 "someone from the team should be able to go to school encourage them to… the expert team consistent throughout their life, yes"
Employment	M5: "like job applications, interviews, which is a shame because I'm sure the majority of them have a lot to offer but they may be keep it quiet …. they need to be nurtured more and have a good mentor in the workplace"
Socialising	I3: "they'd have support groups, um groups where people could get together, meet up and make friends that way, friends clubs"
Ways forward	M1: "it all goes back to the diagnosis and the fact we're lucky enough to live in an area where you have some really good consultants who specialise …."

Appendix 6

Table 24: Variability: Adult Diagnosis

Symptom	
Mood/Psychology/ Socialising	I4: “voice hadn’t dropped, confidence went down to an all time low, just felt like crap about everything” M6: “you get onto other problems… terrible depression at times, really bad” M6: “he can’t cope with people, it’s a socialising thing... he just can’t cope, he’s in a terrible state, he’s shaking, he shakes you see” M6: “very bad anxiety, very bad been a problem for a long time, I’d say it’s got worse” M6: “motivation and social difficulties… living at home unemployed” I4 "might be helpful (psychological support) 'cos like getting the news, getting the injections having these random mood swings it’s a bit like full-on, it’s a bit weird as well, so maybe.. maybe….you also feel a bit down at times, depressed maybe. You feel like down in the dumps a bit" I4: "I think my parents just forgot I had mood swings …. That's the only downside of it (the testosterone treatment)…..it does improve but gradually, the first 3 or 4 years you have mood swings" I4: "a few months ago like I was going to a party, I was getting ready. I just felt so angry, I just felt so tense for no reason" I4: "just chill out in my room, just not speaking to anyone really, it’s a bit anti- social, but it works, or going for a nap or something" I4: "I was in my room and just chilled in there… yeah now it’s alright I get the odd mood swing here and there, but it’s usually when I do home as well (laughs)"

	M6: "it's the social aspect that's hard… the anxiety" M5: "not only that, you get on to other problems, it's all to do with this isn't it.. terrible depression at times, really bad"
Dyslexia	M6: "it's the writing and the spelling, he's definitely got dyslexia"
Speech Therapy and Audiology	M6: "I do wonder now, he was having speech therapy, I do wonder then if the speech therapist had said 'he may have this'… may be if I'd persevered and through 'why is he having speech therapy?' we knew something was wrong, you can't always know that's wrong" M5: "a speech therapist should be looking out for this how many speech therapists are looking out for this from day one… he has apparently got all the physical manifestations and signs of this…." M6: "they also think he's got hearing problems"
Autism/ Asperger's	M6: "he's definitely got Asperger's"
Medical	I4: "I used to see the doctor quite a lot" M2: "absent folate haematology" M6: "no one tested for anything it's unbelievable isn't it when I think of the people we've taken him to over the years" M6: "we had no idea… well I feel that I've let him down as well… we've seen all these experts since the age of 2 and he's been to his GP with problems over the years – no one said 'there's something going on here' from the age of two we took him to all these specialists, paediatricians"
Digestion	I3: "I try not to eat anything with cream in it, it's a bit sickly… I don't have breakfast in the morning I find it too hard to digest anything"
Allergies	M6: "it's a kind of allergy, it flares up, his hands have been in a terrible state with blistery stuff, we had real problems with his hands"

	I3: “I think I’m allergic to medicine, penicillin” I4: “and allergies yes, a weird one – plasters… I got all scratchy and it wells up and goes all yellow”
Back pain	I4: “back pain, that’s quite common, it’s the worst pain”
Sleep	I4: “the sleep is still screwed up” M6: “the worst thing is this night thing his sleep is awful, awful” M6: "he has significantly disrupted sleep, that is still a problem" I3: "I still get very tired now …I don’t think it make any difference to that"
Overall	I4: “it affects other stuff as well… muscles, bones as well, the back pain… mood swings, stress from the testosterone, muscle problems dyslexia and dyspraxia…”

Appendix 7

Aide memoire questions used by the researcher for each participant group

Group One: Individuals and Families

1. What made you concerned? When did you become concerned?
2. What difference, if any, did having a diagnosis make?
3. What choices or decisions did you make that were affected by diagnosis?
4. How did you get a diagnosis (route)?
5. How did you feel about the diagnosis?
6. Would support at school have been helpful? If so, what would have helped at school?
7. What support would have been helpful out of school?
8. What did you find most difficult?
9. What do you think may have helped?
10. What treatment/support did you receive before and after diagnosis?
11. What difference did the treatment and support make?
12. Do you think there were opportunities when a diagnosis has been made earlier?
13. How important or not do you think diagnosis was?
14. How do you feel about quality of life? Can you describe the positives and negatives?
15. Do you think this is affected by having Klinefelter's Syndrome?
16. What would help?
17. What referrals, if any, were made in infancy?
18. What you think it is like to have Klinefelter's Syndrome?
19. What are the key factors in outcomes in Klinefelter's Syndrome?
20. What would be the 'gold standard' of treatment?

Group Two a) and b): Medical Experts and Specialists and Three: General Practitioners

1. What difference, if any, does having a diagnosis make in Klinefelter's Syndrome?
2. What are the increased risks, if any, of not having a diagnosis?
3. Is the timing (age) at diagnosis important? How does timing/age of diagnosis impact on phenotype?
4. Are there any early indicators that may be useful to prompt for genetic screening?
5. What are the key management factors for individuals with Klinefelter's Syndrome?
6. Are there preventable conditions in Klinefelter's Syndrome? Is prevention linked to diagnosis in Klinefelter's?
7. Do you consider Klinefelter's to be a rare condition? What is the rate of incidence in Klinefelter's Syndrome?
8. What are the key factors in outcomes in Klinefelter's?
9. What would be the 'gold standard' of treatment?
10. What would be the optimum route to diagnosis in Klinefelter's Syndrome?

Version Number: 4

Date 19.6.2015

Appendix 8

Participant Information Sheets (Family group)

INFORMATION ABOUT THE RESEARCH

"A Common Condition: A Rare Diagnosis?" What is the significance of diagnosis in Klinefelter's Syndrome?

Understanding the impact, if any, of diagnosis in Klinefelter's Syndrome.

We would like to invite you to take part in an interview that forms part of a PhD research study. Before you decide, we would like to let you know some information about the research, why it is being done and what it would involve for you to take part.

We hope the information provided below will be helpful. Please contact us if you would like to ask about any of the information.

Thank you for taking part in this research discussion and for making time to speak with me. Your time and contribution is very much valued.

Part 1 tells you the purpose of this study about what it will involve for you. Part 2 gives you more detailed information about how the research will be carried out.

Please ask us if there is anything that is not clear, or if you would like more information.

Part 1 What is the purpose of the study?

The purpose of the study is to explore the significance of a diagnosis of Klinefelter's Syndrome to individuals and their family. It is hoped that this may contribute to understanding how increasing diagnosis rates may be achieved, particularly at an early age.

Why have I been invited?

You have been invited to take part because you are a family member of an individual with Klinefelter's Syndrome.

Do I have to take part?

It is entirely up to you to decide if you wish to participate. You will have received an information sheet to help give you time to decide. You are very welcome to contact the researcher before to ask any questions you may have about the research. On the day of the interview, the researcher will describe the study and answer any further questions you may

have. If you are happy to take part in the study, the researcher will then ask you to sign a consent form to say you are happy to take part in the study.

You are free to withdraw from the research at any time should you wish to.

This will not have any effect on any care or treatment you may receive.

What will happen if I take part?

You are invited to take part in a face to face interview with a PhD researcher from Bournemouth University talking about topics related to diagnosis and subsequent care and provision you or your family may have received following this. There may be some specific topics to discuss, but there is flexibility to discuss any areas of interest. The interviews may be audio taped to aid the accurate recollection of the researcher. Your recording is completely confidential and all the information regarding identity will be anonymised and only the research team will have access. Interviews will take place at a time and place that is convenient with you. The length of the interview will depend on your answers, or the time you have available.

What are the possible disadvantages and risks of taking part?

The interview will be approached in a way that gives the direction and control of the content to you only topics that you feel you wish to discuss will be raised. The researcher will not be seeking to ask any questions that are of a particularly sensitive nature.

If you do wish to stop the interview, you may choose to do so at any time.

What are the possible benefits of taking part?

Many parents and individuals welcome and benefit from the opportunity to talk about their experiences. This research will provide an opportunity for those taking part to voice their opinions and experiences about diagnosis and subsequent care, potentially helping other families in this situation.

Will my taking part in the study be kept confidential?

We follow ethical and legal practice and all information will be handled completely confidentially. The details are included in Part 2

This completes Part 1. If you are interested in taking part, please read the information in Part 2.

Part 2.

What will happen if I choose to withdraw from the research?

You are free to withdraw from the research at any point. Any information or data already collected will be destroyed. It will not be possible to remove it once it has been included as part of a thesis or publication, once the data has been collected from the interviews.

What is there is a problem?

If you have a concern about any aspect of the research, please ask to speak to Jennie Faithfull-Lloyd on (01202 – number). You may also if you wish, speak formally to Professor Sine McDougall (Lead Supervisor on 01202 - 961722).

Will my taking part in this research be kept confidential?

Yes, your taking part in this study will be kept confidential. Your interview will be recorded and will then be transcribed into text. At this point all personal details that may identify you such as name and specific location data will be anonymised to maintain confidentiality. In accordance with data protection laws and Bournemouth University policy all your personal information and interview data will be physically locked in a secure filing cabinet at the University. Any personal information such as your name, or address will be destroyed after the interview has taken place. If you wish to be informed of results, a method of contact will be kept for longer in a secure location.

What will happen to the results of the research study?

Results will be analysed and discussed in a PhD thesis at Bournemouth University. It is also intended that the results be published in a scientific publication. Direct quotations may be used, but at no point will it be possible to identify the participant. If you wish to have access to the general results once the study has completed, please tell the interviewer.

What is organising the research?

The research has been undertaken as part of a PhD through Bournemouth University and under the guidance of a supervisory team experienced in working with individuals and families who may have had a diagnosis of Klinefelter's Syndrome and in carrying out psychological research.

Who has reviewed the research?

This research has been looked at by an independent group of people called a Research Ethics Committee to protect your wellbeing, safety and rights.

Thank you for taking time to read through this information sheet. If you have any questions regarding the research or wish to take part, please contact Jennie Faithfull-Lloyd (Lead Researcher) at jfaithfull-lloyd@bournemouth.ac.uk. An interview time and location that is convenient with you will be arranged.

Thank you for taking the time to read this information sheet.

Version Number: 3

Date: 19.6.2015

Appendix 9

Participant Information Sheets (Expert, Specialist, General Practitioner groups)

INFORMATION ABOUT THE RESEARCH

Study Title:

"A Common Condition: A Rare Diagnosis?" What is the significance of diagnosis in Klinefelter's Syndrome?

Understanding the impact, if any, of diagnosis in Klinefelter's Syndrome.

We would like to invite you to take part in an interview that forms part of a PhD research study. Before you decide, we would like to let you know some information about the research, why it is being done and what it would involve for you to take part.

We hope the information provided below will be helpful. Please contact us if you would like to ask about any of the information.

Thank you for taking part in this research discussion and for making time to speak with me. Your time and contribution is very much valued.

Part 1 tells you the purpose of this study about what it will involve for you. Part 2 gives you more detailed information about how the research will be carried out.

Please ask us if there is anything that is not clear, or if you would like more information.

Part 1

What is the purpose of the study?

The purpose of the study is to explore the significance of a diagnosis of Klinefelter's Syndrome. It is hoped that this may contribute to understanding how increasing diagnosis rates may be achieved, particularly at an early age.

Why have I been invited?

You have been invited to take part because you are either a medical clinician with expertise in Klinefelter's Syndrome, a medical clinician in conditions with reported associated increased risks with Klinefelter's Syndrome, or a medical clinician in general practice.

Do I have to take part?

It is entirely up to you to decide if you wish to participate. You are very welcome to contact the researcher before to ask any questions you may have about the research. On the day of the interview, the researcher will describe the study and answer any further questions you may have. If you are happy to take part in the study, the researcher will then ask you to sign a consent form to say you are happy to take part in the study.

You are free to withdraw from the research at any time should you wish to.

What will happen if I take part?

You are invited to take part in an interview with a PhD researcher from Bournemouth University. The discussion will focus on diagnosis and care associated with Klinefelter's Syndrome. There may be some specific topics raised, but there is flexibility to discuss any areas of interest. The interview may be face to face, by email or over the telephone depending on your preference. It is anticipated that it will take no longer than 25 minutes. The interview will be audio taped to aid the accurate recollection of the researcher. Your recording is completely confidential and all the information regarding identity will be anonymised and only the research team will have access. The audio tape will be kept in a locked drawer in a secure area for up to 3 years after which it will be destroyed. The researcher will anonymise the data which will then be transcribed. Interviews will take place at a time and place that is convenient with you. The length of the interview will depend on how long you wish the discussion to continue, your answers, or the time you have available.

The interview will take place at a time and place convenient with you in a confidential setting where the discussion cannot be overheard.

What are the possible disadvantages and risks of taking part?

The length of the interview will be kept to the minimum of time required and this is anticipated to not exceed 25 minutes.

If you do wish to stop the interview, you may choose to do so at any time.

What are the possible benefits of taking part?

This research seeks to explore perceptions of the significance of diagnosis in Klinefelter’s Syndrome between different groups.

Will my taking part in the study be kept confidential?

We follow ethical and legal practice and all information will be handled completely confidentially. There is further information in Part 2. It is not possible to safeguard confidentiality where the safety of others or the participants themselves appear to be at serious risk. If information comes to light during the interview that has significance for the safety of

the participant this will be divulged to the appropriate medical professional (their GP, for example).

This completes Part 1. If you are interested in taking part, please read the information in Part 2.

Part 2.

What will happen if I choose to withdraw from the research?

You are free to withdraw from the research at any point. Any information or data already collected will be destroyed. It will not be possible to remove it once it has been included as part of a thesis or publication, once the data has been collected from the interviews.

What if there is a problem?

If you have a concern about any aspect of the research, please ask to speak to Jennie Faithfull-Lloyd on (01202 - 961722). You may also if you wish to speak formally to Professor Sine McDougall (Lead Supervisor on 02102 - 961722).

Will my taking part in this research be kept confidential?

Yes, your taking part in this study will be kept confidential. Your interview will be recorded and will then be transcribed into text. At this point all personal details that may identify you such as name and specific location data will be anonymised to maintain confidentiality. In accordance with data protection laws and Bournemouth University policy all your personal information and interview data will be physically locked in a secure filing cabinet at the University. Any personal information such as your name, or address will be destroyed after the interview has taken place. If you wish to be informed of results, a method of contact will be kept for longer and locked in a secure location at the university.

It is not possible to safeguard confidentiality where the safety of others or the participants themselves appears to be at serious risk. In this case, an appropriate medical professional will be informed.

What will happen to the results of the research study?

Results will be analysed and discussed in a PhD thesis at Bournemouth University. It is also intended that the results be published in a scientific publication. Direct quotations which have been anonymised may be used in publications, but at no point will it be possible to identify the participant. A copy of the results will be provided to you should you wish.

Who is organising the research?

The research has been undertaken as part of a PhD through Bournemouth University and under the guidance of a supervisory team experienced in working with individuals and

families who may have had a diagnosis of Klinefelter's Syndrome and in carrying out psychological research.

The contact details for the Deputy Dean are: Professor Matt Bentley, Deputy Dean Faculty of Science and Technology. Bournemouth University. Fern Barrow, Poole, Dorset. BH12 5BB.

Who has reviewed the research?

This research has been looked at by an independent group of people called a Research Ethics Committee: "South West – Exeter Research Ethics Committee" to protect your wellbeing, safety and rights.

Thank you for taking time to read through this information sheet. If you have any questions regarding the research or wish to take part, please contact Jennie Faithfull-Lloyd (Lead Researcher) at jfaithfull-lloyd@bournemough.ac.uk. An interview time and location that is convenient with you will be arranged.

Thank you for taking the time to read this information sheet.

Version: 5

12.2.16

Appendix 10

Consent Form

Interview Number:

Participant Identification for this interview:

Centre/Hospital Number

CONSENT FORM

Title of Project: “A Common Condition: A Rare Diagnosis?” What is the significance of diagnosis in Klinefelter’s Syndrome?

Name of Researcher: Jennie Faithfull-Lloyd

I confirm have been given the information sheet for the study named above. I have had the opportunity to consider the information about the research, ask any questions I may have and am happy that these have been answered.

Please initial against each box.

1. I understand that my participation is voluntary and that I am free to withdraw at any time. ☐
2. I understand that I am taking part in an interview and that any information gathered will be anonymised and kept confidential. I also understand that the interview will be audio taped but this information will also be anonymised and kept securely at all times. ☐
3. I understand that relevant sections of my data collected during my study may be looked at by individuals of the research team from Bournemouth University but will not be available to others. ☐
4. I agree to participate in the study. ☐

Name of Participant:

Date

Signed

Name of Researcher

Date

Signed