Original Article

Modelling the episodes of care for iron deficiency anemia patients in a secondary-care center using continuous-time multistate Markov chain

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Abstract

Background: Despite the high prevalence of gastro-intestinal (GI) cancer in iron deficiency anemia (IDA), some IDA patients do not complete all the necessary GI investigations at the initial referral. As a result, existing cancers are diagnosed at a later referral with worse prognosis. The potential to detect GI cancer early depends on minimizing the delay time spent between the two consecutive referrals, where a patient did not complete investigations at the first referral, but at the second is diagnosed with positive GI cancer. This retrospective longitudinal study aims to highlight the proper methods to model these referrals.

Methods: Using anonymized data of 168 episodes of care for IDA patients at an IDA clinic in a secondary care setting, continuous-time multi-state Markov chain is employed to determine the transition rates among three observed states for IDA patients at the IDA clinic, "incomplete investigations," "negative GI cancer," and "positive GI cancer" and to estimate the delay time.

Results: Once in the state of incomplete investigations, an estimated mean delay time of 3.1 years (95% CI: 1.2, 5) is spent before being diagnosed with positive GI cancer. The probability that a "positive GI diagnosis" is next after the state of "incomplete investigation" is 17%, compared with 11% when it is followed in the state of negative GI cancer. Defining the survival as the event of not being in the state of "positive GI cancer," the survival rate of IDA patients with negative GI cancer is always higher than those with incomplete investigations. Finally, being diagnosed with positive GI cancer is always preceded by the prediction of being considered "very high risk" at the earlier visit.

Conclusion: A baseline model was proposed to represent episodes of care for IDA patients at a secondary care center. Preliminary results highlight the importance of completing the GI investigations, especially in IDA patients, who are at high risk of GI cancer and fit to go through the investigations.

Keywords: Endoscopy, episodes of care, gastrointestinal cancer, iron deficiency anemia, secondary care

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INTRODUCTION

The early detection of gastro-intestinal (GI) cancer could lead to improve its prognosis. However, newly developed malignant tumors and some types of advanced cancers (right-side colorectal cancer) are asymptomatic or difficult to be picked up by the usual population screening

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programme (sigmoidoscopy, Fit test).[1] Accordingly, opt-in clinical investigations that target the 'at high-risk' population are necessary to detect these new or silent-type cancers. Due to the strong association between iron deficiency anaemia (IDA) and GI cancer,[2-6] and with the aim of managing IDA and investigating whether GI cancer is the underlying cause of any confirmed iron deficiency, a dedicated IDA nurse-led clinic was established under the supervision of the Gastroenterology Department at Poole General Hospital, UK, in 2004.[4,7] The diagnosis of GI cancer is established by standard clinical investigations including gastroscopy, colonoscopy, computed tomography (CT) scanning, and biopsy.[4]

Despite the high prevalence of GI cancer in IDA (8-10%),[8] and being a major trigger for urgent GI investigations,[9-14] due to informed patient preference, concurrent illness, or major co-morbidity including frailty, some IDA patients do not complete all the necessary GI investigations.[4] Consequently, cancers that already existed during the time the patients did not complete their investigations are diagnosed at later referrals with worse prognosis. Many factors may influence patient's re-referral to the clinic such as new symptoms including rectal bleeding, weight loss, stomach pain, and being a recurrent IDA patient who is willing and fit enough to undergo the GI investigations.

The time spent by a confirmed IDA patient between two consecutive referrals to the clinic, where, at the first episode of care the required GI investigations were not completed, and at the second the patient is diagnosed with positive GI cancer is referred to as the 'delay time'. The potential to detect GI cancer early depends on minimizing this delay time. To predict the risk of GI cancer in patients with confirmed IDA, a binary multivariable logistic model was previously built and internally/externally validated based on four simple variables: age, sex, hemoglobin concentration (Hb), and mean cell volume (MCV)– the IDIOM model (Iron Deficiency as an Indicator of Malignancy).[4,15] Based on the predicted cancer risks that were derived from this model, IDA patients were stratified into five risk groups in which the lowest risk group (ultra-low risk) represents the lower half of the first quarter of positive predictive values, with negative predictive values = 100%, and the highest risk group (very-high risk) represents the fourth quarter of positive predictive values.

Due to the small size of the available multi-state data, in which only 168 episodes of care were found in the admission history at the IDA clinic for 83 patients, with only four positive GI cancer cases at the subsequent episodes of care, the leading focus of this study is on gaining insights into the proper methods of modelling the episodes of care for IDA patients at the IDA clinic, and not on making inference from the preliminary results of applying these proposed methods on such small sample size. Therefore, when enough data becomes available in the future from a subsequent temporal period at the same clinic and/or from other similar secondary-care centers, a large-scale study can make use of the suggested methodology in this study to estimate the delay time, and to examine whether being stratified in ultra-low risk or very-high risk group by the IDIOM score at the earlier episode of care could lead to being diagnosed with positive GI cancer at the following episode of care.

METHODS

Study population

A total of 2788 patients with no other neoplasm, and with confirmed iron deficiency were referred to Poole hospital IDA clinic during the period of 2004-2018. Confirmed iron deficiency was defined by transferrin saturation <15% and/or serum ferritin less than the lower laboratory limit of normal at the time of the analysis. The anonymized secondary data for each referral, per patient, included:

- Patient ID
- Sex
- Age
- Blood hemoglobin concentration (Hb)
- Mean cell volume (MCV)
- Iron studies (transferrin saturation and serum ferritin)
- Date of the visit(s) to the IDA clinic
- The outcome of the GI investigation (positive/negative GI cancer)
- Indicator of the GI investigations' completion

GI Investigations were considered "complete" if the upper GI tract had been examined by gastroscopy, and the colon had been fully imaged either by colonoscopy or CT colonography.[4]

Statistical analysis

Usually patients are seen at intermittent referral visits in the IDA clinic, at which admission information is collected, but information from the periods between visits is not available. The admission history (or the outcomes of episodes of care), for any IDA patient, comprises being observed either in the state of incomplete investigations, in the state of positive GI cancer, or in the state of negative GI cancer but never in any more than one state at one time; these states are finite disjoints states. Because the durations between the consecutive admissions to the clinic are irregularly spaced, a continuous-time multi-state Markov chain was appropriate

to model these states, to determine the transitions rates between states, and to estimate the delay time.

Due to their ability to represent repetitive events, and time, Markov chains have been used intensively to model transition rates in clinical settings. In particular, Markov chains are frequently used to model disease progression.[16] Markov models are often developed to represent random processes that evolve over time.[17] These random processes satisfy the Markov property of "memorylessness".[18] That is, the state of the process at a future time, given the previous history of the process up to the present time, depends only on the present-time state. These models assume that an entity is always in one of a finite number of discrete states, called Markov states, and all events are represented as transitions.[19] IDIOM score was used to predict the GI cancer risk for each patient and to stratify the patient per visit in the different risk groups based on the threshold proposed in Almilaji, *et al*.[15]

Specifying the baseline model

The patient clinic admission history was modelled in a three-states continuous-time Markov model [Figure 1], through which the IDA patient can be moved in. These observed states are: S1) incomplete investigations, S2) negative GI cancer, and S3) positive GI cancer. "Death" state was not included in the model due to the totally missing information about this event, and because the time spent in states S1 or S2 is independent of any transition after S3. The time of observation refers to the last time the patient is seen at the clinic per referral and is used as surrogate time for the diagnosis time. Time interval between any pair of consecutive visits per patient is measured in years.

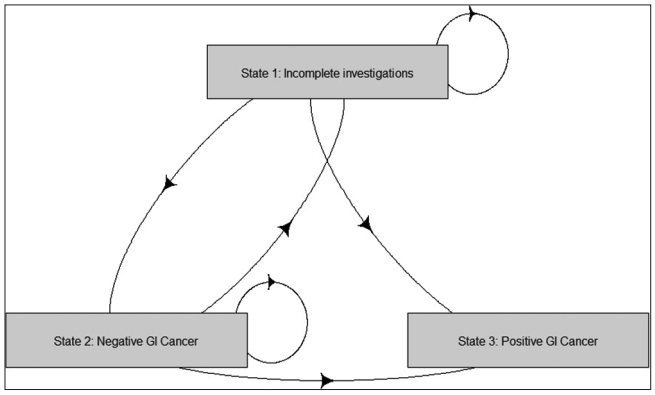

Figure 1: Markov-state diagram. The rectangles represent states, arrow represent transitions between states. Arrows leading from a state to itself indicate that the patient remains in that state in consecutive cycles

Model assumptions

- For each instant of time t, for each pair of states the probability of an event at time t + 1 depends exclusively on the actual state of the process and not on the previous states (Markov property).
- Transition probabilities only depend on the difference t between s and s + t and not on the actual times (s, s + t) that is the Markov model is homogeneous.
- As any clinical diagnosis is based on complete investigations, positive and negative GI cancer are assumed to be 100% accurate. So, no misclassification is proposed in this model.
- Positive GI cancer stage is an absorbing state as the patient cannot go back to the other states once it enters this absorbing stage. Once a patient is diagnosed with positive GI cancer, he/she will be transferred from the IDA clinic to another specialist clinic to start receiving cancer treatment.
- Though some patients might totally avoid the GI investigations, in this analysis, "non-investigations" is regarded as a subset of incomplete investigations.
- The observation times vary either randomly and independently of the current outcome of the investigations, or according to primary care policies in which IDA patients with new signs of GI cancer are re-referred to the clinic. Hence, observation times are assumed to be non-informative sampling times.[20]

Intensity matrix

The tendency of a patient to make a transition from one state to another is described by the rate of transition (transition intensity). Transition rates (q_{ij}) are elements of an intensity matrix Q, in which at time $t > 0$, it is given by:

$$Q = \begin{bmatrix} -(q_{12} + q_{13}) & q_{12} & q_{13} \\ q_{21} & -(q_{21} + q_{23}) & q_{23} \\ 0 & 0 & 0 \end{bmatrix}$$

The proposed model is governed by this transition intensity matrix. The transition rate represents the number of occurrences of an event for a given number of patients per unit of time and is similar to an instantaneous velocity. It can take any value in the range $[0, \infty]$. The rows sum, in this matrix, to 0. The diagonal entries are defined as minus the sum of all the other entries in the row. It is important to remember that the data are assumed to represent snapshots of the process at arbitrary times and fitting the model is a process of finding values of the four unknown transition intensities: q12, q13, q21, and q23, which maximize the likelihood. Transition probabilities for any time t, calculated by taking the matrix exponential of the scaled transition intensity matrix

$$P(t) = e^{tQ}$$

The final row is all zeroes in this Q matrix because positive GI cancer is an absorbing state and there are no transitions back to the other states. Inevitably, when insufficient data is used, the parameters of the proposed model (transition intensities) cannot be identified. Hence, given the small size of the data, the proposed model in this study was built as a simple model with no covariates.

As this study was a retrospective analysis of anonymized secondary data, no patient was involved. R (version 3.6.1), RStudio (version 1.2.5001), and msm package were used to run the statistical analyses and to produce the graphs. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[21] were used to ensure the reporting of this study.

RESULTS

Patients

Patients started to be re-referred to the clinic in 2008 because of which the number of returning visits started to increase gradually. The median time between any two consecutive referrals for all patients at the clinic was about 3 years. The median age of the 83 patients' cohort was 70 years (IQR: 60–77). Despite the four positive GI cancer cases at the subsequent episodes of care being all male IDA patients, female patients were more likely to re-visit the clinic than male patients (Female/Male sex ratio: 2.5 (=59/24)), as can be seen from Figure 2.

During the study period, there were 2873 episodes of care. About 2788 of these represent the first episodes of care for every patient, in which, 393 patients had incomplete investigations, 2194 diagnosed with negative GI cancer, and 201 diagnosed with positive GI cancer. Of the patients who had negative GI cancer or incomplete investigations, 83 had been re-referred to the clinic for the second time. About 18 of these patients did not complete investigations, 62 were negative GI cancer, and three were positive GI cancer. Two of these 83 patients whose previous diagnoses were negative had been re-referred to the IDA clinic for the third time in which one was diagnosed with positive GI cancer and one with negative GI cancer, as can be seen from the following patients' flow chart [Figure 3].

To summarize the multi-state data in this study, a frequency table of pairs of consecutive states that counts for all patients, the number of times a patient had an observation of one state followed by an observation of another state is presented [Table 1]. Thus, out of the four GI positive cases, two came from state 1 (incomplete investigations),

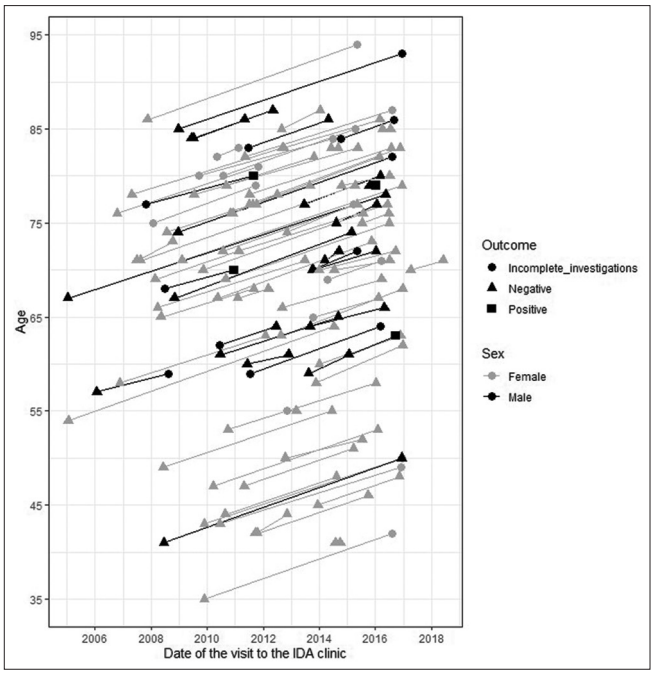

Figure 2: Patients' admission history to the IDA clinic during the study period 2004–2018

and two from state 2 (negative GI cancer), as can be seen from Table 1.

Transition intensities estimates and 95% confidence intervals (CI)

The maximum likelihood estimates of the unknown parameters and 95% confidence intervals (CI) is given in Table 2.

From the estimated intensities of the fitted model in Table 1, it can be seen that the rate of moving from "incomplete investigations" to "positive GI diagnosis" (0.031) is higher than that of moving from "negative GI diagnosis" to "positive GI diagnosis" (0.008). Patients are five times (0.153/0.031) more likely to be diagnosed negative GI cancer than positive GI cancer at a later visit to the clinic (transitions from state 1). After being diagnosed with negative GI cancer moving into the state of being not investigated state is eight times (0.066/0.008) more likely than the progression into positive GI cancer.

Once in the state of negative GI diagnosis, an estimated mean of 13.4 years (95% CI: 6.8, 26.2) is spent in the state of negative GI diagnosis before being diagnosed with positive GI cancer, or moved into the state of being with incomplete investigations. And the probability that "positive GI cancer" is next after the state of "negative GI cancer" is 11%. Once in the state of incomplete investigations, an estimated mean of 5.4 years (95% CI:

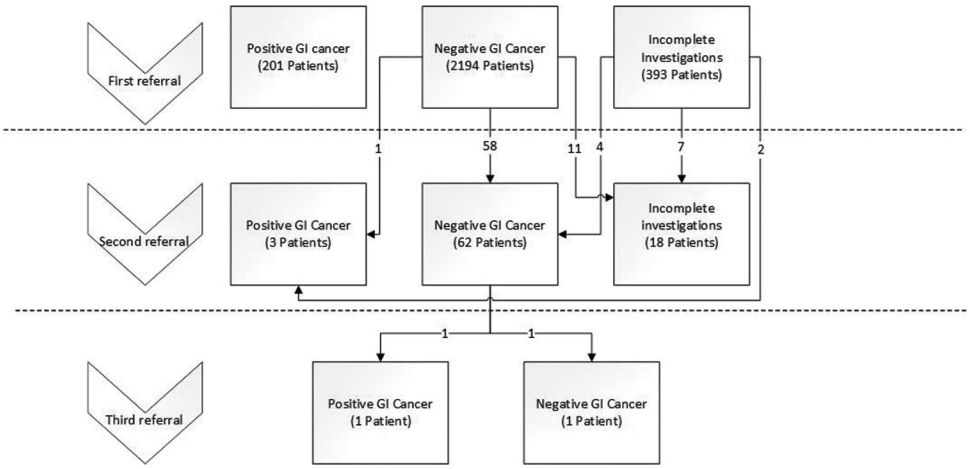

Figure 3: Flow chart of patient' states at the IDA clinic during the study period 2004–2018

2.2, 13.4) is spent in the state of incomplete investigations before being diagnosed with negative or positive GI cancer. The estimated mean delay time was 3.1 years (95% CI: 1.2, 5). And the probability that the "positive GI diagnosis" is next after the state of "incomplete investigation" is 17%.

Survival plot

Defining survival as the event of not being in the state of "positive GI cancer," the 10-year survival probability for IDA patients with negative GI diagnosis is approximately 0.87, as opposed to 0.79 with incomplete investigations. Accordingly, the survival of IDA patients with negative GI diagnosis is always higher than those with incomplete investigations, as can be seen from Figure 4.

IDIOM risk groups

At the following visits, for all patients who have completed their investigations, no difference was found between the observed GI cancer risk that was 6% (4/67) and the 8% predicted risk by IDIOM. A preliminary conclusion could be that that recurrent IDA is not a risk factor for GI cancer. Interestingly, the four patients who have been diagnosed with positive GI cancer were predicted by IDIOM score to be in the very-high risk group at the earlier visits. Also, all the patients who were predicted to be in the lowest risk group at the earliest visits and completed their investigations at the follow-up visits, were diagnosed with negative GI cancer.

Table 1: Frequency table of consecutive states pairs

	To		
	Incomplete investigations	Negative GI cancer	Positive GI cancer
From			
Incomplete investigations	7	4	2
Negative GI cancer	11	59	2

DISCUSSION

About 14% of the patients who were referred to the IDA clinic did not complete their investigations at the first referral to the clinic, compared with 79% diagnosed with negative GI cancer and 7% with positive GI cancer at the same first referral. About 21% did not complete their investigations at their subsequent referrals to the clinic compared with 74% diagnosed with negative GI cancer and 5% with positive GI cancer at the following referrals.

Applying the proposed methods on the available data showed that the transition rate of moving to positive GI cancer is higher when patients are observed in incomplete investigations state than negative GI cancer. The average delay time in "incomplete investigations" for IDA patients is about 3 years, and the probability that a positive GI cancer is followed by the state of incomplete investigations was 17% compared with 11% when it is followed by the state of negative GI cancer. Another finding was that the survival of IDA patients with incomplete investigations was always lower than those with negative GI cancer despite the fact that the waiting time in the state of "negative GI cancer" was about double the time of the delay time. Finally, being diagnosed with positive GI cancer always preceded by the prediction—according to IDIOM score—of being considered very high risk at the earlier visit. Nevertheless, as mentioned earlier, these former findings are preliminary

Table 2: Estimated transition Intensities

Transition Intensities	Estimates (95% CI)
State 1-State 1	-0.184 (-0.46, -0.07)
State 1-State 2	0.153 (0.05, 0.45)
State 1-State 3	0.031 (0.01, 0.14)
State 2-State 1	0.066 (0.03, 0.14)
State 2-State 2	-0.075 (-0.15, -0.04)
State 2-State 3	0.008 (0.002, 0.03)

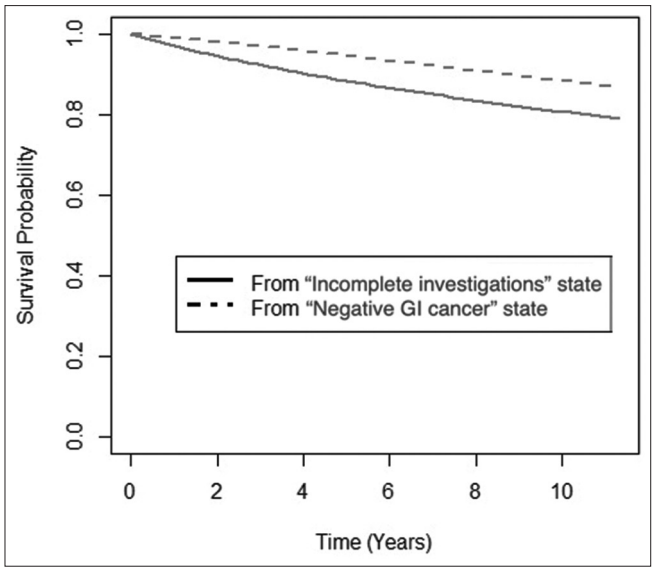

Figure 4: Survival plot. Survival is defined as not being in the state of "positive GI cancer"

results only and should always be reported within the context of the available small-size data and interpreted with caution especially that only two patients developed cancer from the group of incomplete investigations and the other two developed from previously negative diagnosis group. The small numbers of patients have resulted in wide confidence intervals for the estimates.

The limitations of this study include the inability to increase the size of the sample, and accordingly restricting the analysis to a baseline model of the transitions between consecutive admissions. However, for any future large-scale studies using the methodology proposed in this study, we should take into consideration the following issues that became apparent while developing the model:

1. Transition rates might be dependent on patient-related variables such as sex, age, and other pathologies including inflammatory disease, celiac disease, adenoma, and so on. For any future model to be accurate, the effects of these covariates on the transition rates should be addressed by using a proportional intensities model.
2. In the developed baseline model, there was no differentiation between the events of "incomplete investigations" and "no investigations". A question about whether being observed with partial or no investigations could affect the transition rates to the positive GI cancer state differently must be answered. If a variance is found, a separation between these two states should be adopted in any future model.
3. One of the assumptions in this study was that a negative GI cancer is always accurate because it is based on full clinical investigations, and thus there was no account for any misdiagnosis margin. A future comprehensive model must investigate and support this claim.
4. This study implicitly assumed that in those patients who were diagnosed with positive GI cancer at the subsequent referral to the clinic, after not completing the investigations at earlier referral, the GI cancer had already existed at the time of the first referral. However, high-grade aggressive GI cancer could have an onset time between the consecutive referrals. One way to compensate for this fact is to include the GI cancer grade and stage in the analysis and examine whether at the succeeding visits, positive GI cancers tend to be diagnosed at late stages/more aggressive grades indeed.
5. One of the developed model assumptions in this study was that detecting GI cancer early depends on minimizing the delay time. However, considering the former point—the possibility for more aggressive GI cancer to be initiated in the time interval between two referrals—leads to the conclusion that detecting GI cancer early depends also on the frequency of the investigations. The effect of investigations frequency on the transition rates should be assessed as well.
6. Though a normal progressive disease model will end up with "death" state, death state was not included in the developed model. Adding death state to the model could help to examine the over-diagnosis of nonprogressive or very slow-growing GI cancers.
7. Most importantly, in the developed model, "incomplete investigation" state was presumed as a mutually exclusive state from positive and negative GI cancer states, as only the "observed" states in the patients' admission history were considered. However, a patient who is observed in the state of incomplete investigation might be healthy (negative GI cancer) or have a hidden GI cancer that can be diagnosed by clinical investigations. Accordingly, to incorporate this possible misclassification, a hidden Markov model should be fitted to distinguish between the observed states and the truly underlying states of the IDA patients' admissions as proposed in the diagram [Figure 5].

The strengths of this study are that it represents the first study that demonstrates the appropriate methods to model the IDA patients' episodes of care at a secondary-care center. It also raises the awareness of the importance of completing the GI investigations, especially in IDA patients who are at high risk of GI cancer but physically fit to do the investigations-. The estimation of the transition

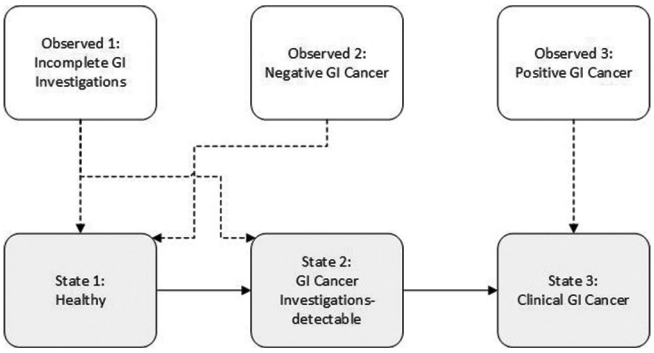

Figure 5: Markov three-state diagram: the white boxes are the observed states and the gray boxes are the true underlying state. The solid lines are the transitions between true states. Observation of incomplete investigations could be truly healthy or misclassification of an investigations-detectable GI cancer

rates and length of delay time in the state of incomplete investigations in future large-studies can help policy makers to establish what is the maximum delay time a confirmed IDA patient should not be allowed to stay in before being investigated, and what are the measures that could be put in place to reduce or minimize this time.

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Ethical approval

Retrospective analysis of anonymised secondary data, external ethics approval was not required. Bournemouth University ethics approval was attained on 22/02/2018, reference id: 19925.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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