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Original Research

Rejection of Fecal Immunochemical Tests Within the Lower Gastrointestinal Diagnostic Pathway: A Cohort Study

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Abstract

Introduction/Objectives: The fecal immunochemical test (FIT) helps triage primary care patients at risk of colorectal cancer (CRC). Improving FIT returns has received recent attention, however uncertainty exists regarding the accurate completion of samples provided for laboratory analysis. This study aims to identify the rejection rate of returned FIT samples and determine rejection causes. **Methods:** FIT samples from symptomatic patients within South Yorkshire, Bassetlaw, and North Derbyshire are processed at a central laboratory. Tests requests are made from 225 GP practices, which serve an estimated 2 million population. This study describes a retrospective review of FIT samples received in the central laboratory between 01/09/19 and 31/12/22. Locally held data was interrogated in March 2023 to determine the number of FIT samples received and rejected during the study period. Documented reasons for rejection were explored to identify common themes. **Results:** Total FIT specimens received during the study period was 126 422. Of these, 5190 (4.1%) were rejected. Monthly rejection rates fell from 17.4% in September 2019 to 1.3% in December 2022 ($P < .001$). Sampling errors were the most frequent cause for FIT rejection (2151/5190), with other causes including: expired specimen; no sample collection date/ time, no request form, incomplete patient information and illegible handwriting. **Conclusions:** This is the first study exploring FIT rejection rates in symptomatic primary care patients, which shows improvements in rejection rates over time. Targeted interventions could improve rejection rates further, thereby reducing NHS resource use and costs and diagnostic delays.

Keywords

fecal immunochemical test, colorectal cancer, rejected specimen, diagnostic delays

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Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the UK. It is the second leading cause of cancer related deaths, with 16 800 deaths occurring annually.[1] An expedited diagnosis is recognized to improve survival for many cancers, with this evidence being strongest in bowel cancer.[1-3] Currently, only 39.4% of UK patients with bowel cancer are detected at the earliest stages (stage 1 or stage 2). This influences the likelihood of receiving curative therapies, with symptomatic individuals more likely to present with more advanced disease. Recent research has demonstrated that a 2-month diagnostic delay in CRC is associated with a >9% reduction in 10-year survival.[4] This emphasizes the importance in minimizing any diagnostic delays existing within the lower gastrointestinal diagnostic pathway.

The fecal immunochemical test (FIT) is now embedded within the 2-week wait (2WW) lower gastrointestinal (LGI) diagnostic pathway in England.[5] Its recognized advantages

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over symptoms in predicting CRC has seen FIT evolve from a diagnostic test to a key adjunct in triaging of referrals and the prioritization of investigations, which remain compromised following the COVID-19 pandemic.[6-8] Despite the increased adoption of FIT testing in symptomatic services, which involves patients completing samples at home, challenges persist in ensuring timely and consistent test returns.[9,10] This is particularly problematic in under-served populations.[11-13]

There is very limited work currently looking at the accurate completion of FIT specimens, which are returned to laboratories for processing. This largely unmeasured aspect of the lower gastrointestinal diagnostic pathway impacts its efficiency, as rejection rates may influence diagnostic delays, lead to potential test abandonment, and negatively influence NHS resource use and costs. In 2 bowel cancer screening studies from the USA (asymptomatic populations), the FIT specimen rejection rate ranged between 17% and 42%.[14,15] Our previous study examining FIT outcomes in a low-risk symptom population identified a 14.2% FIT rejection rate over a 3 month period (Oct-Dec 2019).[16] This incidental and potentially concerning finding led to this real-world study, which explores FIT rejection rates over a more prolonged period of time and determines why submitted samples were rejected.

Methods

Design and Setting

There are 225 primary care practices in South Yorkshire, Bassetlaw, and North Derbyshire, UK. These 225 practices serve an estimated population of 2 million people, with adult secondary care (including endoscopy services) provided by 8 hospitals. FIT has been used locally within these primary care practices since January 2018. This use of FIT followed National Institute for Health and Care Excellence Diagnostic Guidelines 30 (NICE DG30), which recommended the FIT to guide referral of patients with low-risk symptoms of CRC within primary care.[5] Patients eligible for FIT was extended in March 2021 following a NICE publication in November 2020.[9] This testing increased further following publication of national FIT guidelines in July 2022, which was later endorsed by NHS England.[10]

All FIT eligible patients were provided with a fecal sample collection device in primary care (OC-Sensor™ sample bottles; Eiken Chemical Company, Tokyo, Japan). Individuals were asked to sample their feces according to instructions, date the sampling device and return in the post to the designated laboratory within 7 days. A pre-paid return envelope was included with the provided FIT kits, alongside instructions on how to sample and return. This returns process ensured direct and timely delivery to the central laboratory, which is within the Department of Immunology and Protein Reference Unit (PRU) at Sheffield Teaching Hospitals, UK.

Returned FIT Samples

The PRU at Sheffield Teaching Hospitals routinely collects data of all FIT samples that it receives. This is used for monitoring as part of the UK NEQAS (National External Quality Assessment Services) scheme for Fecal Hemoglobin. Returned FIT samples are assessed by laboratory technicians and proceed to analysis if adequate FIT specimens are provided. The threshold for analysis is informed by predefined technical requirements, which includes provision of sufficient clinical information and considers adherence to test sampling instructions. When inadequate FIT samples are identified and rejected from analysis then the reason for test rejection is documented, and notification made to the referrer that an inadequate test has been provided through local electronic medical record systems.

Measures/Analysis

The primary outcome measure was the monthly rejection rate of FIT samples received by the central laboratory. This was determined by dividing the number of rejected samples by the total number of specimens received. Exploration of the reasons for rejection was conducted to identify common themes.

Statistical analysis was performed using SPSS Statistics, version 25 (IBM Corp), with significance level set at $P < .05$. Categorical variables are summarized using descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square or Fisher exact test. A Pearson correlation coefficient was computed to assess the linear relationship between FIT returns and rejections.

Ethics and study approval were granted from the UK Health Research Authority (REC reference—22/HRA/3889) and Sheffield Teaching Hospitals (STH22186).

Results

During the 40-month study period, the FIT rejection rate averaged 4.1% (5190 rejections/126 422 samples received). Figure 1 highlights the rejection rate breakdown by month, with rejection rates falling dramatically from 17.4% in September 2019 to 1.3% in December 2022 ($P < .001$). Figure 1 also demonstrates how samples received in the laboratory significantly increased following changes to FIT eligibility criteria in March 2021. This increased number of FIT samples returned in the region negatively correlated with FIT test monthly rejection rates ($r = -.780$, $n = 40$, $P \leq .001$).

The most frequent cause for FIT specimens being rejected were for sampling errors (41.4%, 2151/ 5190). This encompassed test specimens that had inadequate or excess fecal content, incorrect sample containers (eg, non-FIT fecal tests), or due to sample labeling errors. The

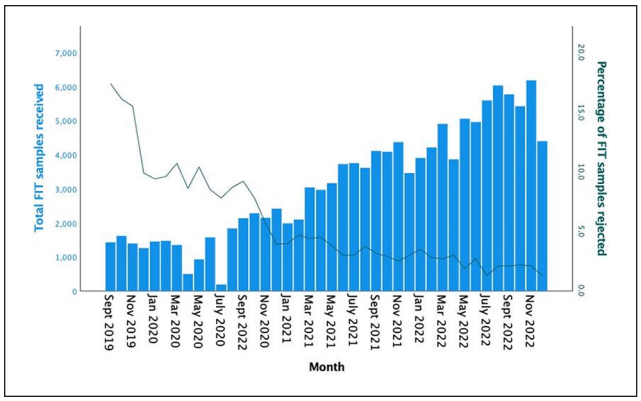

Figure 1. FIT samples received and rejected from symptomatic patients.

Table 1. FIT Rejection Causes Delineated by Patient and Non-patient Factors.

	N	%
Total	5190	100
Patient factors		
Sampling error	2151	41.4
No collection date/time	626	12.1
Expired sample submitted	11	0.2
Non-patient factors		
No request form	951	18.3
Combined patient and non-patient factors		
No/incomplete patient information	1367	26.3
Illegible handwriting	37	0.7
Other causes	47	0.9

breakdown of other rejection causes are demonstrated in Table 1. 0.9% (47/5190) of samples were rejected for other causes, which included leaked samples in transit, or when non-FIT investigations (eg, fecal calprotectin) had been requested by the GP. The frequency of these rejection events by month is shared in Figure 2.

Discussion

This is the first study examining FIT rejection rates in symptomatic patients managed within the lower GI diagnostic pathway. Our work demonstrates how FIT rejection rates have fallen significantly over time, with an overall rejection rate of 4.1% seen. This finding influences clinical decision-making in a time-dependent pathway, which may lead to CRC diagnostic delays and potential test abandonment. Rejected tests also significantly influence NHS resource use and costs. This work is pertinent to patients, clinicians, and commissioners of colorectal services. It also provides the foundations for designing future targeted interventions that reduce rejection rates, with both patient and non-patient factors requiring consideration. Maximizing the success of FIT testing, the efficiency of which is largely unmeasured, is pivotal in providing rapid access to diagnostics to those patients who most require it.

The large cohort and timeframe of review are strengths of this study. The data presented is also derived from English primary care, reflective of unselected real-world experience of FIT in symptomatic individuals. A limitation of this work is that patient-level or GP practice data was not collected. This could have helped determine whether sociodemographic variations were factors in samples being rejected. This has been shown in previous research to influence FIT returns, which may also be pertinent to its accurate completion.[11] Patient-level data may have also allowed exploration about whether samples were re-submitted for processing by patients after initial rejection.

Another limitation of this observational study is that uncertainty exists about what improved FIT rejection rates over time. The local Cancer Alliance delivered regular lower GI pathway updates to GP practices, provided educational events and gave patient information leaflets on stool collection (that included diagrams). These could all potentially explain improvements in the FIT rejection rate over the study period. Another plausible explanation is that GP and healthcare professionals became more familiar with FIT usage over time, which positively impacted the rejection rate. The reduction in the "no request form" outcome may reflect changes between 2019/2020, whereby local GPs started requesting FIT electronically, and were encouraged to print electronic labels and place them onto sampling containers at the time of requesting. The study period also covers the COVID-19 pandemic, where rapid and continuous changes to patterns of patient presentation and service delivery occurred in all parts of the NHS.

Previous research has shown that patient satisfaction with symptomatic FIT is high,[17] however a paucity of research exists examining the accurate completion of submitted FIT samples. Two previous studies from the USA showed FIT rejection rates between 17% and 42% in asymptomatic (screening) populations.[14,15] This high rejection rate may reflect differing national processes for administering FIT. It may also reflect variations in patients' motivations, with symptomatic individuals more likely to adhere to correct test performance when compared to asymptomatic individuals, having already exhibited health-seeking behavior by consulting with their GP. We have been unable to identify any published studies on FIT rejection rates in symptomatic populations. However, anecdotal experience from colleagues in other Cancer Alliances supports FIT rejection being a prevalent problem within the LGI diagnostic pathway. In London, previous unpublished research suggests FIT rejection rates were estimated to be 9%.[18] This has led to an initiative using a poster within GP practices, aimed at enhancing sampling adherence.

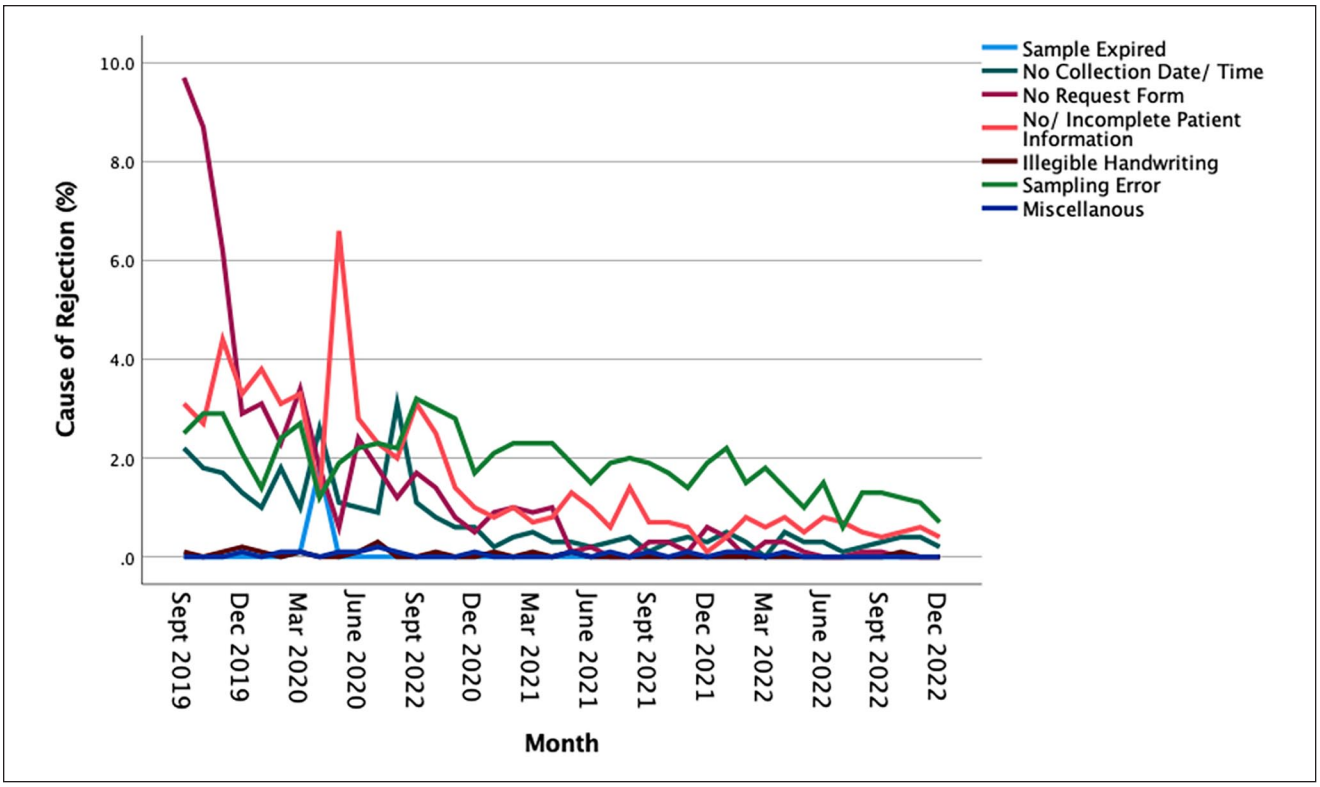

Figure 2. Percentage of FIT samples rejected by cause.

It is recognized from previous studies that diagnostic fecal tests can be challenging for patients, which influences test completion, return, and rejection rates.[19-21] Embarrassment, concerns around hygiene and contamination, discretion and privacy are all factors, which uniquely influence this method of diagnostic testing.[19] A recent systematic review and meta-analysis of blood specimen rejection rates demonstrated a pooled prevalence of 1.99% (16 118 499 specimens analyzed).[22] This finding is lower than our 4.1% FIT sample rejection rate, supporting differences between fecal and blood sampling for diagnostic purposes. Common to both testing modalities was the identification of missing patient's identification, inappropriate containers, labeling errors, and specimens not meeting predefined technical requirements (pre-analytic issues).[22] These pre-analytical phase errors have been identified in previous research to account for 70% of all blood sampling errors seen within the laboratory.[22,23]

Our study findings have implications to patients, clinicians, and commissioners of colorectal services. The rejection of FIT samples from the laboratory can lead to CRC diagnostic delays, which could adversely impact treatments. Prompt communication to patients and their GPs following test rejection could help to mitigate against these delays. Education within this communication could also increase the likelihood that a repeated sample is provided and adequate for processing. These findings need to also be considered in the context of non-return of FITs, which although not assessed in this study, has recently been shown to be 9.3% (3631/38 920 samples) within a neighboring region.[11] Targeted strategies to improve both FIT returns and their accurate completion would help support initiatives to enhance CRC case-detection.

Beyond the diagnostic delays is the consideration of costs. A FIT sample kit is estimated to cost £5.[24] NHS England data highlights how 565 534 2-week wait LGI referrals were made in 2022/2023.[25] Our previous study demonstrated how FIT performance in primary care was >5 times the number of patients being referred.[16] Using this metric, helps estimate that approximately 2.8 million FIT samples are being performed annually within England. Assuming a 1.5% FIT sample rejection rate would mean that an approximately 42 000 FIT samples are being rejected nationally. This equates to a £210 000 financial loss to the NHS through the submission of inadequate FIT samples. This figure is a conservative estimate as it excludes the cost of laboratory staff time, FIT processing costs, and health-related costs of having diagnostic delays. It also assumes rejection rates are comparable across the country.

These rejected FIT findings are unlikely to be unique to the symptomatic LGI pathway, but also prevalent within the national bowel cancer screening program that utilizes FIT.

Further research is therefore needed to determine rejection rates within other regions and within the asymptomatic population. Finally, our study has identified that both patient and non-patient factors are contributing to FIT sample rejection rates. We suggest that future targeted interventions consider these novel findings within their study design, alongside close engagement with relevant stakeholders.

Rapid diagnostic pathways require efficiency at all stages to ensure earlier and faster diagnosis for patients. This study demonstrates laboratory FIT rejection is common soon after its introduction but reduces over time. This is an under-recognized problem with the lower GI diagnostic pathway and our findings would support targeted interventions to address this important aspect, which could derive significant benefits to both patients and the NHS.

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Data Availability

The data that supports the findings from this study are available from the corresponding author (MK). This sharing of data would require agreement from the study sponsor (Sheffield Teaching Hospitals)and completion of a data sharing agreement.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

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