Diagnostic performance of FOB Gold and HM-JACKarc in symptomatic primary care patients

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Introduction

The symptoms of colorectal cancer (CRC) are non-specific and overlap with other conditions. Survival rates for CRC are best when it is diagnosed at an early stage.[1] Faecal immunochemical tests (FIT) can be used to quantify levels of haemoglobin present in faeces.[2] FIT has replaced the guaiac test which is known to be less sensitive and specific for the detection of faecal haemoglobin.

A FIT result of ≥10 µgHb/g of faeces (µg/g) is recommended to refer symptomatic patients suspected CRC.[3] NICE NG12 also stipulates a target of 3% positive predictive value (PPV) for referrals onto suspected cancer pathways.[4]

FIT is not perfect as false positive and false negative results can occur.[1, 5] With these limitations in mind, FIT is best used as a screening test to help triage appropriate referrals for colonoscopy or contrast computed tomography.

FIT was available for primary care for Stockport and High Peak from March 2018 at Stepping Hill Hospital (SHH). Samples were sent to referral laboratories for testing using HM-JACKarc. Patients with faecal haemoglobin (f-Hb) ≥10 µg/g were offered a referral onto the 2-week-wait pathway (to rule out or diagnose cancer within 2 weeks) in line with NICE DG30.[6]

From June 2023, FIT was made available in-house using FOB Gold to improve turnaround times and process oversite of the service. By August 2023, NICE guidelines were updated, and FOB Gold (previously recommended) was graded as requiring "further research".[3] Following this change, an audit was planned to assess the diagnostic performance of both HM-JACKarc and FOB Gold. FIT assays are not harmonised, therefore bias is seen between assays.[7] This audit aims to assess if the difference in assays have an impact on patient outcomes.

Audit Criteria

The criteria set out for this audit were:

- The performance of FOB Gold should be comparable to a NICE recommended FIT assay (HM-JACKarc).
- The positive predictive value of FOB Gold should be at least 3% for CRC.
- Assess if the 10 µg/g cut-off is suitable for FOB Gold.

Methods

All FIT samples received between June 2021 and June 2024 from primary care were collected from the local laboratory information management system (Telepath). Patients age ≥18 years of age were included in this audit.

HM-JACKarc samples were received between 2nd June 2021 to 4th June 2024. The samples were analysed at University Hospital Monklands then Manchester Royal Infirmary and assayed on the HM-JACKarc analyser.

FOB Gold samples were received between 25th June 2023 to 4th June 2024. This third party, open platform assay (manufactured by Sentinel Diagnostics, distributed by Sysmex), was tested on a Siemens ADVIA Chemistry XPT analyser. Results of ≥10 µg/g are deemed positive for both assays.

Patient outcomes data was obtained by Cancer Services, using the Somerset cancer register (cancer database for tracking referrals to treatment) which categorises patients as either cancer or non-cancer. This data was paired with a FIT result within ±90 days of the patient's referral date. The final diagnosis was completed using colonoscopy or contrast computed tomography when the former was not suitable.

Multiple FIT results were obtained for the same patient in both cohorts. When there were multiple FIT results, we used:

- The FIT result which was paired with the referral.
- The most recent FIT result with latest referral (some patients were also referred multiple times).
- In patients without a referral the latest FIT result was used for analysis.

Negative FIT results with no follow-up for >6 months were assumed to be true negatives. This should allow time for safety netting (follow-up of patients with persistent symptoms who have a negative FIT result) which is promoted in the CRC pathway and encourages the GP to refer the patient based on symptoms, clinical suspicion and blood test results. This was applied to both cohorts.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated for both assays using Excel.

Results

HM-JACKarc

A total of 17,689 FIT requests were tested using HM-JACKarc over the 3-year period on 16,118 individual patients. The median age was 65 years (IQR 53-76), 56% were female and 44% male . For the results, please see Figure 1.

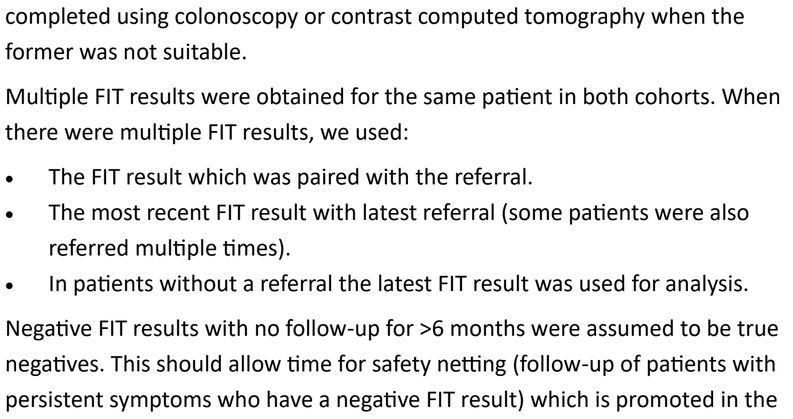

Figure 1: Flow diagram of patient results categorised by final outcomes for HM-JACKarc.

FOB Gold

A total of 13,776 FIT requests were tested using FOB Gold over the 12-month period on 13,043 individual patients. The median age was 67 years (IQR 50-76), 55% were female and 45% were male. For the results, please see Figure 2.

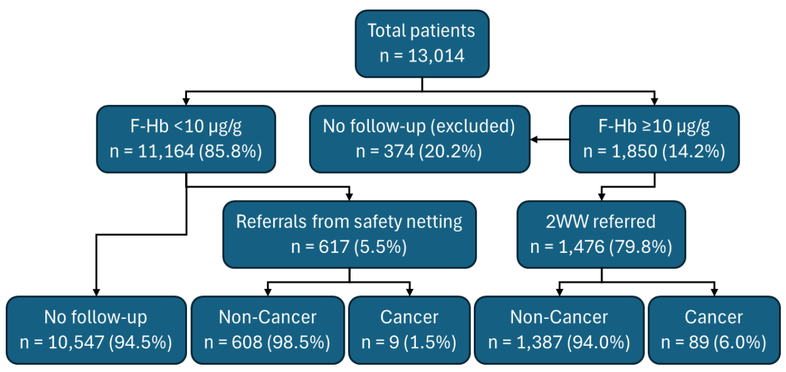

Figure 2: Flow diagram of patient results categorised by final outcomes for FOB Gold.

Some patients who had positive FIT results were not referred and were excluded because of unknown follow-up information. This could be due to referrals to other hospitals, referrals to non-CRC pathways or refusal for further testing.

Overall age range was 18-104 years between both cohorts. The median age of patients with CRC diagnosed was 75 years (IQR 65-81), ranging from 39-99 years.

HM-Jack			
F-Hb result (µg/g)	Number of results	CRC found	Proportion of total results (%)
<7	12,601	16	78.18
7.0 to 9.9	432	2	2.68
10.0 to 100.0	2,089	44	12.96
>100.0	996	88	6.18
Total:	16,118	150	

FOB Gold			
F-Hb result (µg/g)	Number of results	CRC found	Proportion of total results (%)
<4	10,410	8	79.99
4.0 to 9.9	754	1	5.79
10.0 to 100.0	1,073	24	8.24
>100.0	777	65	5.97
Total:	13,014	98	

Table 1: Distribution of results at different levels of faecal haemoglobin (f-Hb) for HM-JACKarc and FOB Gold.

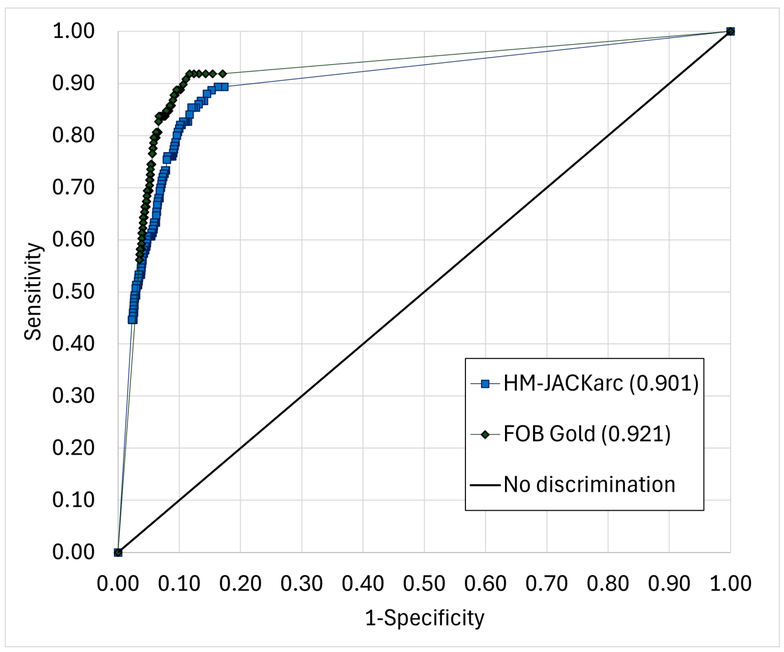

Figure 3: The Receiver Operating Characteristic curves for HM-JACKarc and FOB Gold. The area under the curves were 0.90 (0.78-0.93) and 0.92 (0.89-0.95) respectively.

	Cut-off (µg/g)	% Sensitivity (95% CI)	% Specificity (95% CI)	PPV % (95% CI)	NPV % (95% CI)
HM-JACKarc	7 (LLoQ)	89.3 (84.4-95.5)	82.6 (82.0-83.3)	4.8 (4.0-5.6)	99.9 (99.8-99.9)
	10	88.0 (82.8-94.4)	85.5 (84.9-86.1)	5.6 (4.7-6.6)	99.9 (99.8-99.9)
	100	58.7 (50.8-68.4)	95.5 (95.2-95.9)	11.4 (9.2-13.7)	99.6 (99.5-99.7)
FOB Gold	4 (LLoQ)	91.8 (86.4-97.3)	83.0 (82.3-83.6)	4.0 (3.2-4.9)	99.9 (99.9-100.0)
	10	90.8 (85.1-96.5)	88.9 (88.4-89.5)	6.0 (4.8-7.2)	99.9 (99.9-100.0)
	100	66.3 (57.0-75.7)	95.5 (95.1-95.8)	10.3 (7.9-12.6)	99.7 (99.6-99.8)

Table 2: Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the Lower Limit of Quantification (LLoQ), 10 and 100 µg/g for HM-JACKarc and FOB Gold.

The optimal cut-off was calculated using the Youden index (J = Sensitivity + Specificity - 1) for both assays for the detection of CRC. The optimum cut-off for HM-JACKarc 10 µg/g (J = 0.74) whereas FOB Gold optimum cut-off was at 9 µg/g (J = 0.80).

Discussion

The results from this audit show both assays are effective at identifying CRC at 10 µg/g. The calculated sensitivity and specificity of FOB Gold was numerically better than HM-JACKarc, but not statistically different by looking at overlapping confidence intervals. FOB Gold PPV for CRC was 6.0% which exceeds HM-JACKarc of 5.6%. Both assays exceeds the requirement of NICE NG12 which requires a PPV of at least 3%.[4]

The optimum cut-off differed slightly between both assays. If the cut-off was reduced to 9 µg/g for FOB Gold, this would have identified 1 CRC out of 76 referred patients (PPV 1.3%). However, the risk of CRC at this level does not meet the 3% PPV stimulated by NICE NG12.[4]

Both assays had a similar rate of false negative results. Only 2 out of 18 (11.1%) of these had quantifiable f-Hb for HM-JACKarc (at 8.0 and 9.9 µg/g). The same proportion of false negative results with detectable f-Hb (1 out of 9, 11.1%) was also seen for FOB Gold (at 9 µg/g). This shows both assays are affected by false negative results, with majority of the missed CRC cases having undetectable levels of f-Hb (88.9%).

There was a notable difference of screen positive rate observed with FOB Gold (14.2%) when compared to HM-JACKarc (19.1%). The positivity rate in other studies using HM-JACKarc and OC-Sensor ranged between 19.0-34.9%.[8] Studies involving FOB Gold tend to select medium or high risk of CRC with positivity rates ranging from 8.0-63.8%.[8] The selected populations in these studies do not reflect the symptomatic population in primary care. The reduced positivity rates between FOB Gold and HM-JACKarc translates to a reduction of endoscopy referrals by approximately 25% by changing assays.

Change in NICE guidelines and 2 week wait pathway

The change in NICE guidelines from (DG30 to DG56) stipulating the need of a positive FIT for referral for further investigations has reduced the number of referrals from 20.8% to 5.5% of patients with negative FIT results.

Collectively, between the use of updated guidelines and FOB Gold, a comparable number of CRC have been diagnosed despite a 43% decrease of referrals over a 2-year period (see Table 3). This has reduced the number of colonoscopies performed while detecting comparable number of CRC. This has optimised the use of endoscopy services by increasing the diagnostic rate for CRC. The changes have also increased the diagnostic accuracy of GP referrals for patients with negative FIT results (from 0.7% to 1.5%) by double. Previously, 53.5% of all referrals had a negative FIT. This has decreased to 29.5% following updated guidelines.

Time	GP 2WW referrals	Decrease in referrals	Decrease in referrals (%)	Number of CRC confirmed	CRC confirmed (%)
2022-2023	4,951	N/A	N/A	130	2.63
2023-2024	3,238	-1,713	-34.60	120	3.71
2024-2025	2,805	-433	-13.37	146	5.20

Table 3: Number of referrals by GPs for 2 week wait (2WW) for suspected CRC. The number of referrals have decreased by 43.3% over 2 years. The number of CRC confirm have remained stable (data from Cancer Services).

Limitations

A major limitation of this study was the assumption that negative FIT results without follow-up after 6 months were CRC negative. The risk of bias between cohorts was negated as both were processed in the same manner.

Both cohorts had a significant portion of positive results with no follow-up (20.2-24.0%). We were not able to confirm the outcomes for these patients, therefore this could impact the accuracy of the data. However, as the data was treated equally in both cohorts, this mitigates possible bias between both assays.

This audit was not able to assess the impact in detection of non-cancer intestinal pathologies as data was limited to identifying cancer or non-cancer. However, a new clinical pathway for cancer negative FIT positive patients has been established between Cancer Services and Gastroenterology which has increased the diagnosis and management of patients with inflammatory bowel disease and other significant pathologies.

Both cohorts followed different NICE guidelines, therefore the populations were not directly comparable. HM-JACKarc cohort followed NICE DG30 while FOB Gold followed NICE DG56. More safety netting occurred for HM-JACKarc as there was more of a focus on clinical symptoms rather than the use of FIT for referrals. This could lead to confirmation bias as a lower proportion of patients were safety netted for FOB Gold.

Conclusion

This audit has confirmed the diagnostic accuracy of FOB Gold exceeded a NICE recommended FIT assay (HM-JACKarc) using the 10 µg/g cut-off. The PPV of FOB Gold exceeded HM-JACKarc and the 3% stipulated by NICE NG12.[4] The use of FIT has helped reduced the number of endoscopy referrals by 43% without impacting cancer diagnostic rates.

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