The Peer-Reviewed Evidence Base for Use of the HM-JACKarc Faecal Immunochemical Test for Haemoglobin (FIT) Analytical System in Screening and Assessment of Symptomatic Patients

A Bibliography: September 2019

***HM-JACKarc* in Asymptomatic Screening**

Passamonti B, Malaspina M, Fraser CG, et al. A comparative effectiveness trial of two faecal immunochemical tests for haemoglobin (FIT). Assessment of test performance and adherence in a single round of a population-based screening programme for colorectal cancer. Gut 2018;67:485-96.

The aim was to: compare acceptability and diagnostic accuracy of a recently available faecal immunochemical test (FIT) system ***(HM-JACKarc***, Kyowa Medex Co., Ltd) with the FIT routinely used in an established screening programme (OC-Sensor, Eiken Chemical Co., Ltd). This was a randomised controlled trial within a population-based colorectal cancer (CRC) screening programme. Subjects eligible for invitation in the Umbria Region (Italy) programme were randomised (ratio 1:1) to be screened using one of the FIT systems.

Conclusion: Our results suggest that acceptability and diagnostic performance of HM-JACKarc and of OC-Sensor systems are similar in a screening setting.

Rubeca T, Cellai F, Confortini M, Fraser CG, Rapi S. Impact of pre-analytical factors on fecal immunochemical tests: need for new strategies in comparison of methods. Int J Biol Markers 2015;30:e269-74.

BACKGROUND: Harmonization of fecal immunochemical tests for hemoglobin (FIT-Hb) is crucial to compare clinical outcomes in screening programs. The lack of reference materials and standard procedures does not allow the use of usual protocols to compare methods. We propose 2 protocols, based on artificial biological samples (ABS), to discriminate pre-analytical and analytical variation and investigate clinical performances. The protocols were used to compare 2 FIT systems available on European markets: the OC-Sensor Diana (Eiken, Tokyo, Japan) and ***HM-JACKarc*** (Kyowa-Medex, Tokyo, Japan).

CONCLUSIONS: A good correlation was observed in comparing data generated using collection devices on the two systems. Manufacturers have developed different sample collection procedures for feces: therefore, data from different systems cannot easily be compared. Adoption of protocols to discriminate pre-analytical and analytical variation would be a significant contribution to harmonization of FIT, facilitating data comparison and information acquisition for sample collection strategy and effect of buffers on systems.

Results from the Scottish Bowel Screening Programme

Faecal immunochemical tests (FIT), using the HM-JACKarc analytical system, ware introduced on 20 November 2017, with the aim to increase participation in Scotland's bowel screening programme.

The report, from the Information Services Division, NHS National Services Scotland, contains comparisons of the new quantitative FIT and former test (guaiac faecal occult blood test/qualitative FIT two-tier reflex algorithm) for uptake (the percentage of those invited who returned a completed test kit) and positivity (the percentage of completed kits that were positive). The Key Performance Indicators reported over a two-year period summarise data from both the new and old tests. See the full details of the results of introduction of FIT as a first-line test at: https://www.isdscotland.org/Health-Topics/Cancer/Bowel-Screening/

A summary of the impressive findings is available at: https://www.isdscotland.org/Health-Topics/Cancer/Publications/2019-02-05/2019-02-05-Bowel-Screening-Publication-Summary.pdf

***HM-JACKarc* in Assessment of Symptomatic Patients**

Auge JM, Fraser CG, Rodriguez C, et al. Clinical utility of one versus two faecal immunochemical test samples in the detection of advanced colorectal neoplasia in symptomatic patients. Chem Lab Med 2016:54:125-32.

BACKGROUND: The utility of faecal immunochemical tests (FIT) in assessment of symptomatic patients with lower gastrointestinal symptoms has not been well explored. The aims of this study were to evaluate the diagnostic yield for advanced colorectal neoplasia (ACRN) in symptomatic patients using the first of two FIT samples (FIT/1) and the higher concentration of two FIT samples (FIT/max).

METHODS: Samples from two consecutive bowel motions from 208 symptomatic patients who required colonoscopy were analysed using the ***HM-JACKarc*** analyser. Patients were categorised into two groups: patients with any ACRN and individuals with other diagnoses or normal colonoscopy.

CONCLUSIONS: ***Undetectable FIT is a good strategy to rule-out ACRN in symptomatic patients. The diagnostic yield of collecting two samples for FIT can be achieved with one sample, but a lower faecal haemoglobin concentrations (f-Hb) cut-off is required.***

Godber IM, Todd LM, Fraser CG, MacDonald LR, Ben Younes H. Use of a faecal immunochemical test for haemoglobin can aid in the investigation of patients with lower abdominal symptoms. Clin Chem Lab Med 2016;54:595-602.

This study aimed to determine whether patients with lower abdominal symptoms can be investigated quickly using results of faecal haemoglobin concentration (f-Hb) measurements, and whether this test could form part of a diagnostic pathway for significant colorectal disease. 909 consecutive patients referred from primary care for colonoscopy were invited: 507 submitted samples for f-Hb measurement with a quantitative faecal immunochemical test for haemoglobin (FIT) (***HM-JACKarc***) and a diagnostic colonoscopy was completed in 484 patients.

The high NPV for significant colorectal diseases suggests that f-Hb could be used as a rule-out test in this context. Potential exists for using f-Hb measurements to investigate symptomatic patients and guide the use of colonoscopy resources: detailed algorithms for the introduction of f-Hb measurements requires further exploration.

Widlak MM, Thomas CL, Thomas MG, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther 2017;45:354-363

AIM: To assess using faecal immunochemical test for haemoglobin (FIT) or faecal calprotectin (FCP) to detect CRC and adenoma in symptomatic patients referred from primary care.

METHODS: A total of 799 referred for urgent lower gastrointestinal investigations were prospectively recruited. Of these, 430 completed colonic investigations and returned stool samples, and were included in the final statistical analysis. Faecal immunochemical test for haemoglobin was performed on ***HM-JACKarc analyser***, and FCP by the EliA Calprotectin immunoassay (Thermo Fisher Scientific, Waltham, United States).

RESULTS: The negative predictive value (NPV) using FIT alone or both markers (FIT and FCP) in combination was similar at 99% for CRC, with a sensitivity and specificity of 84% and 93%, respectively. FIT measurements were significantly higher in left-sided colonic lesions compared with the right side (713 vs. 94; P = 0.0203). For adenoma, the NPV using FIT alone, or both markers (FIT and FCP) in combination, was similar at 94% with a sensitivity and specificity of 69% and 56%, respectively.

CONCLUSIONS: Undetectable faecal immunochemical test for haemoglobin is sufficiently sensitive to exclude colorectal cancer, with higher values in left-sided lesions. FCP in combination does not appear to provide additional diagnostic information. Further studies to determine the health economic benefits of implementing faecal immunochemical test for haemoglobin in primary care are required.

Cubiella J, Digby J, Rodríguez-Alonso L, et al. The fecal hemoglobin concentration, age and sex test score: Development and external validation of a simple prediction tool for colorectal cancer detection in symptomatic patients. Int J Cancer 2017;140:2201-11.

Prediction models for colorectal cancer (CRC) detection in symptomatic patients, based on easily obtainable variables such as fecal haemoglobin concentration (f-Hb), age and sex, may simplify CRC diagnosis. We developed, and then externally validated, a multivariable prediction model, the FAST Score, with data from five diagnostic test accuracy studies that evaluated quantitative fecal immunochemical tests in symptomatic patients referred for colonoscopy (*including the 484 patient result database from the study by Godber et al. using* ***HM-JACKarc***). The diagnostic accuracy of the Score in derivation and validation cohorts was compared statistically with the area under the curve (AUC) and the Chi-square test. 1,572 and 3,976 patients were examined in these cohorts, respectively. The AUC for CRC detection was 0.88 (95% CI: 0.85-0.90) in the derivation and 0.91 (95% CI: 0.90-093; p = 0.005) in the validation cohort At the two Score thresholds with 90% (4.50) and 99%

(2.12) sensitivity for CRC, the Score had equivalent sensitivity, although the specificity was higher in the validation cohort ($p < 0.001$). Accordingly, the validation cohort was divided into three groups: high (21.4% of the cohort, positive predictive value - PPV: 21.7%), intermediate (59.8%, PPV: 0.9%) and low (18.8%, PPV: 0.0%) risk for CRC. The FAST Score is an easy to calculate prediction tool, highly accurate for CRC detection in symptomatic patients

The FAST Score is an easy to calculate prediction tool highly accurate for CRC detection in symptomatic patients and is independent of analytical FIT method used.

Quyn AJ, Steele RJ, Digby J, et al Application of NICE guideline NG12 to the initial assessment of patients with lower gastrointestinal symptoms: not FIT for purpose? Ann Clin Biochem. 2018;55:69-76.

Background: Our aim was to compare the utility of f-Hb as the initial investigation with the NICE NG12 symptom-based guidelines.

Methods: Data from three studies (one with ***HM-JACKarc***) were included. Patients had sex, age, symptoms, f-Hb and colonoscopy and histology data recorded. Sensitivity, specificity, positive (PPV) and negative predictive value (NPV) of f-Hb and NG12 were calculated for all significant colorectal disease (SCD: CRC, higher risk adenoma and inflammatory bowel disease). Overall diagnostic accuracy was also estimated by the area under the receiver operating characteristic curve (AUC).

Results: A total of 1514 patients were included. At a cut-off of ≥10 μg Hb/g faeces, the sensitivity of f-Hb for CRC was 93.3% with NPV of 99.7%.The sensitivity and NPV for SCD were 63.2% and 96.0% respectively. The NG12 sensitivity and NPV for SCD were 58.4% and 87.6% respectively.

Conclusion: f-Hb provides a good rule-out test for SCD and has significantly higher overall diagnostic accuracy than NG12

Widlak MM, Neal M, Daulton E, et al. Risk stratification of symptomatic patients suspected of colorectal cancer using faecal and urinary markers. Colorectal Dis 2018 2018;20:O335-42.

AIMS: A diagnostic accuracy study of colorectal cancer (CRC) was undertaken using a faecal immunochemical test for haemoglobin (FIT) with ***HM-JACKarc***, faecal calprotectin (FCP) and urinary volatile organic compounds (VOCs) in patients with lower gastrointestinal symptoms.

METHODS: 1016 symptomatic patients with suspected CRC referred by family physicians were recruited prospectively in accordance with national referring protocol. A total of 562 patients, who completed colonic investigations, in addition to providing faeces for FIT, FCP as well as urine samples for urinary VOC measurements, were included in the final outcome measures.

CONCLUSIONS: When applied to FIT negative group, urinary VOCs improves CRC detection (sensitivity rises from 0.80 to 0.97) thus showing promise as a second stage test to complement FIT in CRC detection.

Turvill J, Mellen S, Jeffery L, et al. Diagnostic accuracy of one or two faecal haemoglobin and calprotectin measurements in patients with suspected colorectal cancer. Scand J Gastroenterol 2018;53:1526-34.

Patients referred with suspected CRC provided two separate faecal samples each for faecal immunochemical testing (FIT) using the ***HM-JACKarc*** analytical system and faecal calprotectin (FC) prior to investigation. Diagnostic accuracy of FIT and FC were evaluated based on final diagnoses.

For two FIT, there was no advantage in their diagnostic accuracy compared with a single FIT. FC had a lower diagnostic accuracy for CRC than FIT, which was not improved by repeat FC. No benefit was identified with FIT-FC combined. For CRC, significant adenomatous polyps and organic enteric disease combined, FIT and FC performed similarly to each other but were poorer predictors (AUC 0.677 and 0.660). There was no uplift in diagnostic accuracy when the tests were repeated or combined.

It was concluded that this study supports using a single FIT at a cut-off close to that recommended by NICE DG30 to improve diagnostic accuracy for 'two-week wait' patients referred with suspected CRC.

Digby J, Steele RJ, Strachan JA, et al. Do other variables add value to assessment of the risk of colorectal disease using faecal immunochemical tests for haemoglobin? Ann Clin Biochem. 2019;56:472-9,

Faecal immunochemical test analysis has been a NHS Tayside investigation since December 2015. During the first year, 993 patients attending colonoscopy were invited to complete a detailed questionnaire on demographic background, symptoms, smoking status, alcohol use, dietary fibre, red and processed meat intake, physical activity, sitting time, dietary supplement use, family history of colorectal cancer, adenoma, inflammatory bowel disease and diabetes. Significant bowel disease was classified as colorectal cancer, advanced adenoma or inflammatory bowel disease. Unadjusted odds ratios for the presence of significant bowel disease compared with undetectable faecal haemoglobin, measdured using ***HM-JACKarc*** increased with increasing faecal haemoglobin. Rectal bleeding and family history of polyps were the only other variables with statistically significant odds ratios. Odds ratios adjusted for all other variables showed similar associations, but only faecal haemoglobin and family history of polyps had significant associations.

The conclusion was that haemoglobin is the most important factor to be considered when deciding which patients presenting in primary care with lower bowel symptoms would benefit most from referral for colonoscopy.

Mowat C, Digby J, Strachan JA, et al. Impact of introducing a faecal immunochemical test (FIT) for haemoglobin into primary care on the outcome of patients with new bowel symptoms: a prospective cohort study. BMJ Open Gastroenterol 2019;6:e000293.

This study assessed whether a FIT for faecal haemoglobin concentration (f-Hb) can be safely implemented in primary care as a rule-out test for significant bowel disease (SBD) (colorectal cancer (CRC), higher risk adenoma (HRA) and inflammatory bowel disease (IBD)) when used as an adjunct to the clinical assessment of new bowel symptoms: f-Hb was estimated using ***HM-JACKarc*** with a clinical cut-off of ≥10 µg Hb/g faeces

It was concluded that, in primary care, measurement of f-Hb, in conjunction with clinical assessment, can safely and objectively determine a patient's risk of SBD.

Nicholson BD, James T, East JE, et al. Experience of adopting faecal immunochemical testing to meet the NICE colorectal cancer referral criteria for low-risk symptomatic primary care patients in Oxfordshire, UK. Frontline Gastroenterology Published Online First: 09 October 2018. doi: 10.1136/flgastro-2018-101052

Faecal samples from routine primary care practice sent for faecal occult blood testing were analysed by a standard gFOBT method and the ***HM-JACKarc*** FIT between January and March 2016. Symptoms described on the test request were recorded. Patients were followed up over 21 months for evidence of serious gastrointestinal pathology including colorectal adenocarcinoma. The proportion of samples considered positive by FIT was considerably lower than gFOBT with the same rate of colorectal adenocarcinoma detection. One in three of those with positive FIT had a significant colorectal disease**.**

The conclusion was that the findings supported the National Institute of Health and Care Excellence recommendation (DG30) that FIT can be reliably used as a triage test in primary care without overburdening endoscopy resources.

Farrugia A, Widlak M, Evans C, et al. Frontline Gastroenterology [Epub ahead of print].

The aim of this study was to assess the use of FIT within the recent National Institute for Health and Care Excellence (NICE) NG12 and DG30 guidelines. FIT was performed in with ***HM-JACKarc*** and sensitivity, specificity, positive predictive value and negative predictive value, with 95% CI, for cancers and adenomas within each pathway (Two Week Wait, NG12 and DG30) were calculated.

It was concluded that use of FIT within NG12 NICE guidelines shows a high sensitivity and specificity and may be an effective triage tool when considering whether to perform investigations. However, there is still a miss rate. FIT within DG30 has excellent sensitivity and improved specificity; however, DG30 targets lower risk groups and accounts for only 13% of the entire referrals for suspected cancer. Therefore, managing the larger, higher risk NG12 group may require the addition of another test or marker to ensure that CRC is not missed.

National Guidelines

National Institute for Health and Clinical Excellence (NICE) Diagnostic Guidance DG30

- https://www.nice.org.uk/guidance/dg30 - Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care – states: The OC Sensor, ***HM-JACKarc*** and FOB Gold quantitative faecal immunochemical tests are recommended for adoption in primary care to guide referral for suspected colorectal cancer in people without rectal bleeding who have unexplained symptoms but do not meet the criteria for a suspected cancer pathway referral outlined in NICE's guideline on suspected cancer (NG12 - https://www.nice.org.uk/guidance/ng12) Results should be reported using a threshold of 10 micrograms of haemoglobin per gram of faeces.

Reviews

Westwood M, Corro Ramos I, Lang S, et al. Faecal immunochemical tests to triage patients with lower abdominal symptoms for suspected colorectal cancer referrals in primary care: a systematic review and cost-effectiveness analysis. Health Technol Assess 2017;21:1-234.

OBJECTIVES: To assess the effectiveness of FITs [OC-Sensor (Eiken Chemical Co./MAST Diagnostics, Tokyo, Japan), ***HM-JACKarc*** (Kyowa Medex/Alpha Laboratories Ltd, Tokyo, Japan), FOB Gold (Sentinel/Sysmex, Sentinel Diagnostics, Milan, Italy), RIDASCREEN Hb or RIDASCREEN Hb/Hp complex (R-Biopharm, Darmstadt, Germany)] for primary care triage of people with low-risk symptoms.

METHODS: Twenty-four resources were searched to March 2016. Review methods followed published guidelines.

RESULTS: Using a single sample and 10 μg Hb/g faeces threshold, sensitivity estimates for OC-Sensor [92.1%, 95% confidence interval (CI) 86.9% to 95.3%] and HM-JACKarc (100%, 95% CI 71.5% to 100%) indicated that both may be useful to rule out CRC. Specificity estimates were 85.8% (95% CI 78.3% to 91.0%) and 76.6% (95% CI 72.6% to 80.3%). Triage using FITs could rule out CRC and avoid colonoscopy in approximately 75% of symptomatic patients. Data from our systematic review suggest that 22.5-93% of patients with a positive FIT and no CRC have other significant bowel pathologies. Only one included study evaluated FIT in primary care; however, all of the other studies evaluated FIT at the point of referral. Further, validation data for the faecal haemoglobin, Age and Sex Test (FAST) score, which includes faecal immunochemical testing, showed no significant difference in performance between primary and secondary care. There were insufficient data to adequately assess FOB Gold, RIDASCREEN Hb or RIDASCREEN Hb/Hp complex.

CONCLUSIONS: Faecal immunochemical testing is likely to be a clinically effective and cost-effective strategy for triaging people who are presenting, in primary care settings, with lower abdominal symptoms and who are at low risk for CRC. Further research is required to confirm the effectiveness of faecal immunochemical testing in primary care practice and to compare the performance of different FIT assays

Westwood M, Lang S, Armstrong N, et al. Faecal immunochemical tests (FIT) can help to rule out colorectal cancer in patients presenting in primary care with lower abdominal symptoms: a systematic review conducted to inform new NICE DG30 diagnostic guidance. BMC Med 2017;15:189.

BACKGROUND: This study has attempted to assess the effectiveness of quantitative faecal immunochemical tests (FIT) for triage of people presenting with lower abdominal symptoms, where a referral to secondary care for investigation of suspected colorectal cancer (CRC) is being considered, particularly when the 2-week criteria are not met.

METHODS: We conducted a systematic review following published guidelines for systematic reviews of diagnostic tests. Twenty-one resources were searched up until March 2016.

RESULTS: Nine studies are included in this review. One additional study, included in our systematic review, was provided as 'academic in confidence' and cannot be described

herein. When FIT was based on a single faecal sample and a cut-off of 10 µg Hb/g faeces, sensitivity estimates indicated that a negative result using either the OC-Sensor or HM-***JACKarc*** may be adequate to rule out nearly all CRC; the summary estimate of sensitivity for the OC-Sensor was 92.1% (95% confidence interval, CI 86.9-95.3%), based on four studies (n = 4091 participants, 176 with CRC), and the only study of ***HM-JACKarc*** to assess the 10 µg Hb/g faeces cut-off (n = 507 participants, 11 with CRC) reported a sensitivity of 100% (95% CI 71.5-100%). The corresponding specificity estimates were 85.8% (95% CI 78.3-91.0%) and 76.6% (95% CI 72.6-80.3%), respectively.

CONCLUSIONS: There is evidence to suggest that triage using FIT at a cut-off around 10 µg Hb/g faeces has the potential to correctly rule out CRC and avoid colonoscopy in 75-80% of symptomatic patients.

Senore C, Haug U. Faecal immunochemical tests have the potential for correctly ruling out colorectal cancer in symptomatic patients. BMJ Evid Based Med 2018;23:113-4.

This article is a commentary on: Westwood M, et al. Faecal immunochemical tests (FIT) can help to rule out colorectal cancer in patients presenting in primary care with lower abdominal symptoms: a systematic review conducted to inform new NICE DG30 diagnostic guidance. BMC Med 2017;15:189, which recommends, inter alia, the use of ***HM-JACKarc.***

The NICE NG12 guidance recommends the adoption of FIT triage for adults without rectal bleeding, based on the evidence from this review. It was suggested that further research is needed to assess the value of this approach in different settings and in the actual target group suggested for FIT triage, namely, patients presenting in primary care with “low risk” symptoms.

It was concluded that NG12 urges audit of outcomes. It was also suggested that information about screening history (including faecal haemoglobin concentrations at previous screening FIT) might be valuable to optimise the use of FIT in triage of symptomatic patients.

Godber IM, Benton SC, Fraser CG. Setting up a service for a faecal immunochemical test for haemoglobin (FIT): a review of considerations, challenges and constraints. J Clin Pathol 2018;71:1041-5.

This review considers the application of the quantitative faecal immunochemical tests for haemoglobin (FIT) that have now been advocated by the National Institute for Care and Health Excellence (NICE: DG30) to assist in the triage of patients presenting with symptoms that suggest a low risk of colorectal (bowel) cancer. DG30 does advocate use of ***HM-JACKarc***, as repeated in this review. The review covers the following topics. Evidence is that FIT provides a good rule out test for significant bowel disease. However, a small number of cases will be missed, and robust safety-netting procedures are required to follow up some FIT-negative patients. A range of diagnostic pathways are possible, and there is no best approach at present. Introduction of FIT requires careful consideration of the logistics of supply of devices and information to requesting sites and of transport to the laboratory. A number of FIT analytical systems are available. Three are documented as appropriate for use in assessment of patients with symptoms. However, preanalytical, analytical and postanalytical challenges remain. The methods have different specimen collection devices.

The methods use polyclonal antibodies and there is no primary reference material or method to which FIT methods are standardised. Third-party internal quality control is lacking, and external quality assessment schemes have many difficulties in providing appropriate materials. Reporting of results should be done using µg Hb/g faeces units and with knowledge of the limit of detection and limit of quantitation of the analytical system used.

FIT can be used successfully in an agreed diagnostic pathway, along with other clinical and laboratory information: this requires a multidisciplinary approach, providing opportunities for professionals in laboratory medicine involvement.

Fraser CG. Faecal immunochemical tests for haemoglobin (FIT) in the assessment of patients with lower abdominal symptoms: current controversies. Gastroenterol Hepatol 2019;42:263-70.

This review considers controversies remains regarding FIT (including use of ***HM-JACKarc***) in assessment of patients with symptoms. These include whether and which qualitative and quantitative FIT can be used, which groups of patients would benefit most from FIT, whether FIT should be done in primary and/or secondary care, and how FIT should be incorporated into diagnostic pathways. Controversy was also said to exist as to the optimum cut-off used for referral for colonoscopy. It was suggested that a single sample of faeces may be sufficient. Reporting of results requires consideration. FIT provide a good rule in test for colorectal cancer and a good rule out test for significant bowel disease, but robust safety-netting is required for patients with negative results and ongoing symptoms. Risk scoring models have been developed, but their value is unclear as yet. It was suggested that further revaluation of these topics is required to inform good practice.

D'Souza N, Abulafi M. The faecal immunochemical test in low risk patients with suspected bowel cancer. Br J Hosp Med (Lond) 2019;80:22-6.

This review evaluated the evidence supporting the use of FIT in assessment of patients presenting in primary care at low risk of cancer (including those generated using ***HM-JACKarc***). It was noted that the data for the use of the faecal immunochemical test were extrapolated from all types of patients, including those at high risk. Data on low risk patients were said to be scarce and weak. It was stated that large national cohort studies are currently underway investigating the role of FIT test in the English population. The authors concluded that clear clinical pathways and rigorous safety netting are essential and should be part of implementing these guidelines to avoid missed cancers.

Pin Vieito N, Zarraquiños S, Cubiella J. High-risk symptoms and quantitative faecal immunochemical test accuracy: Systematic review and meta-analysis. World J Gastroenterol 2019;25:2383-2401.

The National Institute for Health and Care Excellence DG30 has recommended the adoption of FIT in low-risk symptomatic patients using a 10 µg Hb/g faeces threshold. Nevertheless, it is unknown whether the accuracy remains stable throughout the broad spectrum of possible symptoms. A systematic review and meta-analysis was performed to assess FIT accuracy (including that obtained with ***HM-JACKarc***) for CRC detection in different clinical settings.

It was concluded that the results of this meta-analysis confirmed that, regardless of CRC prevalence, quantitative FIT is highly sensitive for CRC detection. However, FIT ability to rule out CRC is higher in studies solely including symptomatic patients.

Conference report

Mole G, Withington J, Logan R. From FOBt to FIT: making it work for patients and populations. Clin Med (London) 2109;19: 196–9. Erratum in: Clin Med (Lond) 2019;19:360.

This conference report documents the presentations given at a meeting held at the Royal College of Physicians which addressed outstanding issues as to how to utilise FIT most effectively in the symptomatic population. The meeting contained sessions on clinical biochemical considerations and NICE guidance, implementing FIT in symptomatic populations: practice, learning and safety netting as a 'rule out' test, implementing FIT in primary care and evidence synthesis and next steps. Data from six 'FIT pioneer' sites shared data from formal research studies and service evaluations; the bulj of the data presented were generated with **HM-JACKarc**. In addition, FIT in primary care was discussed based on shared experience from three sites.

It was concluded that FIT is a highly accurate quantitative test for detecting 'occult' haemoglobin in faeces. Its implementation in the NHS Bowel Cancer Screening Programme will improve uptake particularly in those populations most at risk of CRC. Maximising its value in the symptomatic population, however, will depend on how it is implemented within secondary and primary care.

Book Chapter - Detailed Review of FIT in Assessment of the Symptomatic

Steele RJC and Fraser CG. Haemoglobin for Timely Assessment of Patients with Symptoms of Colorectal Disease in Olsen Timely Diagnosis of Colorectal Disease, Olson L, ed. Springer, 2018.

Abstract: Many patients present in primary healthcare with symptoms of serious colorectal disease (SCD), namely colorectal cancer (CRC), advanced adenoma and inflammatory bowel disease. However, SCD is present in only a small proportion. Colonoscopy is often a scarce resource and strategies to direct investigations to those who would benefit most would be advantageous. Guaiac-based faecal occult blood tests (gFOBT) have no role to play. However, there is now significant evidence that faecal immunochemical tests (FIT) for haemoglobin have many advantages. FIT are available in qualitative and quantitative test formats. Qualitative FIT could have some merits when used at home or in general practice or clinics: there is some evidence that these can be applied in both primary and secondary healthcare settings to detect CRC and rule-out most SCD, but they have many disadvantages. Quantitative FIT provide numerical estimates of faecal haemoglobin concentration (f-Hb). Studies (including three with ***HM-JACKarc***) have shown that, at low f-Hb cutoff, this test has high sensitivity for CRC and could be used as a rule-in test and prompt rapid referral for endoscopy. Perhaps more importantly, undetectable f-Hb provides

considerable reassurance that SCD is absent and further investigation may not be required. Using both point of care and quantitative methods, f-Hb has advantages over f-C in assessment of symptomatic patients. Risk-scoring models using f-Hb and other variables associated with SCD, especially age and sex, have been advocated. Although FIT have significant merits, no test is perfect and some cases of SCD will remain undetected; consequently safety-netting is required.

Evaluations of the *HM-JACKarc*

Itoh M, Fukada M, Nagai G. Evaluation of the Extel "Hemo Auto" HS and the Hemo Auto MC Feces Collection Container Using the HM-JACKarc Fully Automated Fecal Occult Human Hemoglobin Analyzer. J Clin Lab Inst Reagents 2011;34:387-92.

A detailed in-house evaluation of ***HM-JACKarc*** evaluating analytical sensitivity, within- and between-batch imprecision, linearity, recovery, potential interfering moieties, prozone effects, correlation with a predicate device and sample stability.

Carroll MRR, Piggott C, Pearson S, Seaman HE, Halloran SP. Evaluation of quantitative faecal immunochemical tests for haemoglobin. Guildford Medical Device Evaluation Centre (GMEC), Guildford, UK, 2013.

Evaluation of quantitative FIT products commenced in November 2012, at which time four products met essential criteria identified by BCSP. The Guildford Medical Device Evaluation Centre (GMEC) team commenced evaluation of the following four products; the ***HM-JACKarc****,* the NS-PLUS C15, the OC-SENSOR DIANA and the Sentinel FOB Gold NG for Hb analysed on the BioMajesty. The collection devices and analysers were recommended and provided by the manufacturers. The analysers were installed into the GMEC research laboratory at the University of Surrey by the suppliers and training was provided to two members of the GMEC team. Cascade training was then used to train a third member of the team. The practical evaluation work took place between December 2012 and August 2013**.**

Rapi S, Rubeca T, Fraser CG. How to improve the performances of Fecal Immunological Tests (FIT): Need for standardization of the sampling and pre-analytical phases and revision of the procedures for comparison of methods. Int J Biol Markers 2015;30(1):e127-31.

Lack of reference materials and standard procedures, on faecal tests leads to major problems in harmonisation of methods and do not allow the comparison of outcome data. In particular the absence of standardisation of pre-analytical characteristic was noted for faecal test methods for haemoglobin since different manufacturers have developed different sampling procedures and report units. Moreover the physical characteristics of the faecal specimen and the designs of specimen collection devices, *including that of the HM-JACKarc shown pictorially,* do not allow analysis of samples on different systems in consequence, faecal tests cannot be compared using standard evaluation protocols*.* ***The creation of specific protocols for the evaluation and comparison of analytical methods for analyse of faeces could lead to a significant improvement in the performance of methods and systems.***

Rapi S, Berardi M, Cellai F, et al. Effects of fecal sampling on preanalytical and analytical phases in quantitative fecal immunochemical tests for hemoglobin. Int J Biol Markers 2017;32:e261-6.

Four commercial sample collection devices for quantitative FIT-Hb measurements were investigated, *including HM-JACKarc devices*. The volume of interest (VOI) of the probes was measured from diameter and geometry. Quantitative measurements of the mass of feces were carried out by gravimetry. The amounts of collected materials are related to the design of probes. Three out four manufacturers (not Kyowa) declare the same target amount using different sampling volumes and obtain different amounts of collected materials. ***The introduction of a standard probes to reduce pre-analytical variability could be an useful step for fecal test harmonization and to fulfil the ISO 15189 requirements***

Fraser CG. Comparison of quantitative faecal immunochemical tests for haemoglobin (FIT) for asymptomatic population screening. Transl Cancer Res 2016;5 (Suppl 4):S916-9.

An editorial on methods available for the comparison of FIT analytical systems when used in asymptomatic screening which documents aspects of a comparison done in Florence with artificial biological samples.

Stability of faecal haemoglobin

Mellen S, de Ferrars M, Chapman CL, et al. Evaluation of sample stability for a quantitative faecal immunochemical test and comparison of two sample collection approaches. Ann Clin Biochem 2018;55: 657-64.

There are limited data on the effect of pre-analytical factors on faecal haemoglobin (f-Hb) when measured by FIT. The aim of this work was to evaluate the stability of f-Hb in faeces and to compare two methods of f-Hb sampling for FIT, namely specimen collection devices and traditional faecal pots: ***HM-JACKarc*** was used in this study. It was found that there is considerable heterogeneity in f-Hb sample stability therefore ***samples should be transferred rapidly into collection devices to prevent false negative results. Use of collection devices by patients can lead to false positive results compared to their use in a laboratory***.

Haemoglobin variants

Carroll MR, John C, Mantio D, Djedovic NK, Benton SC. An assessment of the effect of haemoglobin variants on detection by faecal immunochemical tests. Ann Clin Biochem 2018;55:706-9.

Lysates prepared from whole blood samples of patients with known variants were diluted in manufacturer-specific buffer to 10, 100 and 500 µg Hb/g faeces. These samples were

analysed on four FIT analysers (including ***HM-JACKarc***) and the results compared with samples with no known variant present (normal samples).

Of 20 common Hb variants studied, 17 did not affect detection of Hb by the FIT systems tested. Hb variants leading to a reduction in the presence of a globin chain caused a reduction in Hb detection; in such cases, cancers could be missed.

Sampling of faeces

Piggott C, John C, Bruce H, Benton SC. Does the mass of sample loaded affect faecal haemoglobin concentration using the faecal immunochemical test? Ann Clin Biochem 2018;55:702-5.

Faecal samples are typically collected by patients using a probe attached to the cap of a device which is inserted into a collection device into the preservative buffer, passing through a collar to remove excess sample: this process has potential for pre-analytical error. This study investigates whether faecal haemoglobin concentration (f-Hb) results are affected by the mass and method of sample collection. Methods Faecal samples with detectable f-Hb were loaded into collection devices from four manufacturers (including ***HM-JACKarc***) using increasing masses of sample. The f-Hb in the device buffer was measured using the relevant analyser. The results from the minimum recommended load were compared with results of 'sample overloading'.

***The mass of sample loaded onto the probe did not impact the f-Hb significantly using all four tested devices*.**

Faecal haemoglobin in adenoma

Mowat C, Digby J, Strachan JA, Steele RJC, Fraser CG. Low sensitivity of fecal immunochemical tests (FIT) for detection of sessile serrated adenomas/polyps confirmed over clinical setting, geography, and FIT system. Dig Dis Sci. 2019;64:3024-6.

This correspondence concerns the detection of sessile serrated adenoma/polyps (SSA/SSP). It was demonstrated that the data derived on patients presenting in primary care with lower bowel symptoms, in Scotland, with ***HM-JACKarc*** would add to the observations that, in comparison with adenomas, SSA are found less frequently at colonoscopy and may not be associated with significant f-Hb. Moreover, it was found that faecal haemoglobin concentration was less in SSA than in higher-risk adenoma and low-risk adenoma.

***In consequence, findings on FIT in detection of SSA/SSP are likely to be transferable between clinical settings, over geography, and with different FIT systems*.**

Faecal haemoglobin in ulcerative colitis – application of HM-JACKarc

Ryu DG, Kim HW, Park SB, Kang DH, Choi CW, Kim SJ, Nam HS. Clinical implications of fecal calprotectin and fecal immunochemical test on mucosal status in patients with ulcerative colitis. Medicine (Baltimore. 2019;98(36):e17080.

Although fecal calprotectin (Fcal) and the fecal immunochemical test (FIT) have been associated with endoscopic activity in ulcerative colitis (UC), the clinical implications of each marker depending on the mucosal status are not well known. A total of 174 results obtained from 128 patients with UC who simultaneously underwent colonoscopy and fecal tests were retrospectively evaluated: FIT was performed on the ***HM-JACKarc***. The correlation and predictability of fecal markers as a surrogate marker of endoscopic activity, and the sensitivity, specificity, and predictive value of fecal tests for mucosal healing were statistically evaluated. Both fecal tests showed a statistically significant correlation with Mayo Endoscopic Subscore (MES) Fcal was statistically superior to FIT in predictive accuracy for endoscopic activity FIT was superior to Fcal in sensitivity for mucosal healing Fcal and FIT were well correlated with endoscopic activity in UC and can be surrogate markers of mucosal inflammation.

Depending on mucosal status, Fcal was more accurate in predicting the endoscopic activity in active inflammation, whereas FIT (by HM-JACKarc) was more sensitive in predicting the achievement of mucosal healing,

Other publications

Allison JE, Fraser CG. The importance of comparing quantitative faecal immunochemical tests (FIT) before selecting one for a population-based colorectal cancer screening programme. J Lab Precis Med 2018;3:7.

This is a Guest Editorial on Gies A, Cuk K, Schrotz-King P, et al. Direct comparison of diagnostic performance of nine quantitative fecal immunochemical tests for colorectal cancer screening. Gastroenterology 2018;154:93-104. It makes the point that the authors have not evaluated one of the quantitative FIT systems widely used throughout Europe and Asia, namely ***HM-JACKarc***.