Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 007 (February 2019)

Faecal immunochemical testing (FIT)-based prediction tools as triage for referral for colorectal cancer investigations

Why did Health Technology Wales (HTW) appraise this topic?

The majority of colorectal cancer cases are diagnosed through GP referral. NICE Diagnostics Guidance 30 recommends faecal immunochemical tests (FITs) to guide referral of symptomatic patients in primary care who do not meet the referral criteria for suspected cancer referral (NICE guideline 12). FIT-based prediction tools could help optimise referral for CRC investigations, reducing unnecessary colonoscopies.

HTW guidance: The evidence supports the adoption of FIT to guide the referral of patients with lower gastrointestinal symptoms for colonoscopy. The use of the FIT-based prediction tools FAST and COLONPREDICT shows promise but the incremental benefits as compared with FIT alone are uncertain from the evidence currently available.

HTW therefore supports the adoption of FIT as recommended by NICE Diagnostic Guidance 30 but proposes that a prospective and structured evaluation of the clinical and cost benefits of combining FIT with the prediction tools FAST and COLONPREDICT be incorporated into the implementation strategy in NHS Wales.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Appraisal Panel considerations

- For people presenting with lower abdominal symptoms who do not have high risk clinical markers for colorectal cancer (see the NICE Guideline 12 two-week referral criteria), NICE recommends the use of quantitative FIT to guide referral (diagnostics guidance 30). The Appraisal Panel agreed with the recommendations of DG30 and would support and promote their adoption in NHS Wales.
- The Panel were informed by clinical experts that FIT is currently not used in clinical practice in NHS Wales. The Panel concluded that the current evaluation and resulting HTW guidance provides an opportunity to promote optimal and evidence-based clinical practice in NHS Wales.
- The Panel were informed by experts working in primary and secondary care that there is currently considerable pressure on the diagnostic colonoscopy service in Wales. The Panel concluded that the use of FIT-based prediction tools may offer the opportunity to more effectively select patients who should and should not have colonoscopy, thereby leading to a reduction in referrals.
- The Panel concluded from the evidence currently available that while the use of FIT-based prediction tools (FAST and COLONPREDICT) shows promise, it is unclear the extent to which they offer incremental benefits over and above the use of FIT alone. The Panel noted that the acquisition of simple additional clinical and laboratory tests required for the prediction tools may add variably to consultation time and costs and that in this regard the use of the more simple FAST offers the potential for advantages as compared with COLONPREDICT. The extent to which this may be off-set by reduced diagnostic accuracy is, however, uncertain.
- The Panel concluded that the implementation of the recommendations of NICE DG30 in Wales provides an opportunity to evaluate the potential additional benefits of the use of FAST and COLONPREDICT. The Panel recommends a professionally led, prospective assessment in NHS Wales of FIT alone compared with FAST and COLONPREDICT, in guiding referrals for colonoscopy in primary care. The assessment should have defined clinical outcomes and follow-up that will allow the determination of positive and negative predictive value. The Panel concluded that such an assessment is particularly important, as an expert informed the Panel that the high levels of diagnostic sensitivity (up to 100%) that are reported in the published studies are unlikely to be achieved in 'real world' clinical practice. The Panel also noted that adequate follow-up is essential in such an evaluation, especially in patients with continued symptoms, to ensure that any missed pathologies are identified and an understanding of clinically important negative predictive accuracy is captured.

SUMMARY OF EVIDENCE APPRAISAL REPORT

Context

Colorectal cancer (CRC) is the 4th most common cancer in the UK, accounting for 12% of all new cancer cases. In 2015, there were 2,259 new cases of CRC in Wales, and 904 deaths. People with CRC are most commonly diagnosed through primary care referral for colonoscopy. NICE guideline NG12 (*Suspected cancer: recognition and referral*) recommends a referral within two weeks for people who meet any of the following criteria:

- ≥ 40 years or over with unexplained weight loss and abdominal pain
- ≥ 50 years or over with unexplained rectal bleeding
- ≥ 60 years and over with iron-deficiency anaemia or changes in their bowel habit
- Tests show occult blood in their faeces

For people presenting with lower abdominal symptoms who do not satisfy the NG12 two-week referral criteria (and are therefore considered low risk for CRC), NICE diagnostics guidance DG30 (*Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care*) recommends use of quantitative FIT to guide referral. There are four quantitative FITs available in the UK:

- HM-JACKarc system (Kyowa Medex/Alpha Laboratories Ltd)
- FOB Gold system (Sentinel/Sysmex, Sentinel Diagnostics)
- OC-Sensor (Eiken Chemical Co./ MAST Diagnostics)
- RIDASCREEN Hb and Hb/Hp test (R-Biopharm)

The OC Sensor, HM-JACKarc and FOB Gold tests were recommended for adoption under DG30; RIDASCREEN was not recommended due to lack of evidence at the time of assessment. FIT will be introduced into the colorectal cancer screening programme in Wales in phases from February 2019. As of February 2019, FIT is not yet used in Wales for the symptomatic population.

Demand for endoscopy services is set to increase due to a number of factors, including an aging population, increased awareness of symptoms and increased referrals following FIT screening. This can result in people who do not have CRC undergoing an unnecessary, invasive diagnostic procedure with associated risks like bowel perforation, bleeding, infection and abdominal pain. On the other hand, lack of referral risks a delayed diagnosis. Accurate prediction tools are required to triage patients who are designated low-risk but present with symptoms.

Evidence on clinical effectiveness, safety, economic analysis and patient issues

Two primary studies described the development and validation of risk scores to detect CRC in symptomatic patients: the COLONPREDICT score and the FAST score. The FAST score used FIT, age and sex; COLONPREDICT used FIT combined with multiple variables, including additional tests/examinations.

Both prediction tools included two threshold scores, established on 95% and 99% specificity for CRC detection. FAST threshold scores were ≥ 2.12 and ≥ 4.5; COLONPREDICT applied scores of ≥ 3.5 and ≥ 5.6. Sensitivity was similar between COLONPREDICT and FAST at the higher threshold score (87.1% and 89.3% sensitivity, respectively). When the lower threshold scores were applied FAST and COLONPREDICT reported 100% sensitivity, although specificity was greatly reduced compared to using the higher threshold. The majority of patients in both studies were analysed by OC-Sensor.

The FAST and COLONPREDICT studies also stratified patients into low-, intermediate-, and high-risk categories based on the score thresholds. Negative predictive values for the stratified populations were not reported; however, positive predictive values for the 'low-risk' group were 0.2% with COLONPREDICT and 0.0% with FAST. Use of these lower score thresholds may therefore be useful as a 'rule out' for CRC, avoiding unnecessary colonoscopies. Finally, both studies reported no difference between primary and secondary settings in post-hoc analyses.

Searches also identified one systematic review summarising studies that evaluated FIT combined with other markers, versus FIT alone. Sensitivity and specificity of FIT alone varied across the studies; sensitivity ranged from 52-95% and specificity ranged from 57-98%. Heterogeneity across the studies, including characteristics and FIT assays used, made comparative analysis difficult. Overall, the study authors reported sensitivity improved with FIT combined with DNA markers, but it did not appear to improve when combined with stool protein markers. Additionally, one further primary study developed a simple risk score for advanced neoplasia (described as advanced adenoma or invasive carcinoma). Specificity of this score for detecting advanced neoplasia was 88.1%.

No evidence on the cost effectiveness of FIT-based prediction tools was identified from the literature. This report includes a brief cost consequence analysis for FAST and COLONPREDICT as 'rule out' tests, based on the 'low-risk' stratification cohort for each tool. It should be noted that the analyses were based on the proportion of patients stratified into the low-risk group (18.8% for FAST and 39.5% for COLONPREDICT) within the validation cohort, and this may not be representative of the populations in primary care settings. The higher number of tests/variables required for COLONPREDICT results in a higher initial test cost, but this is partially offset by the higher reduction in colonoscopies. The analyses were not sensitive to whether the OC-Sensor or HM-JACKarc FIT analyser were used. Overall, the results of the cost consequence analysis suggests that FAST offers greater cost savings than those achieved through COLONPREDICT.

Organisational issues

Limited evidence on organisational issues was identified for FIT-based prediction tools in primary care. The authors of the FAST study noted that a more complex prediction tool (COLONPREDICT) may be limiting in practice, due to the number and type of variables included in the tool, such as anorectal examination and venous blood tests. One study surveyed GP attitudes towards the use of FIT in primary care as part of the two-week referral pathway. The survey identified that GP awareness of FIT, as both a rule-in and rule-out test, was low.

FIT to guide referral in primary care is currently being explored and planned in Wales, but the approach is inconsistent. As FIT is currently being introduced for asymptomatic screening, it is unlikely that a different analyser would be used for the symptomatic population.

Further research

Further studies to develop and validate FIT-based prediction tools for people presenting with lower abdominal symptoms in primary care, but who do not meet the two-week referral criteria, are recommended. Large, prospective, comparative multicentre studies are recommended to evaluate the comparative effectiveness of FIT-based prediction tools against FIT alone, other FIT-based predictions tools, and prediction tools that do not include FIT.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTWs evidence review methods and framework for producing its guidance are available from the HTW website.

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Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTWs Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.