# NIHR CRSU

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# Diagnostic Test Accuracy (DTA) Meta-analysis

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# An example Diagnostic Test Accuracy Review

Review

Cerebrovascular Diseases

Cerebrovasc Dis 2013;35:493–501
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## Diagnostic Accuracy of CT Perfusion Imaging for Detecting Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

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# Methodology

- Bivariate approach simultaneously models the sensitivity and specificity from studies, thereby incorporating any correlation [at the study level] that might exist
- Random effects approach allows for heterogeneity beyond chance due to clinical and methodological differences between studies.
- Covariates were added to the bivariate model to examine whether sensitivity and/or specificity were different depending on specific study characteristics.

# Meta “ROC” plots

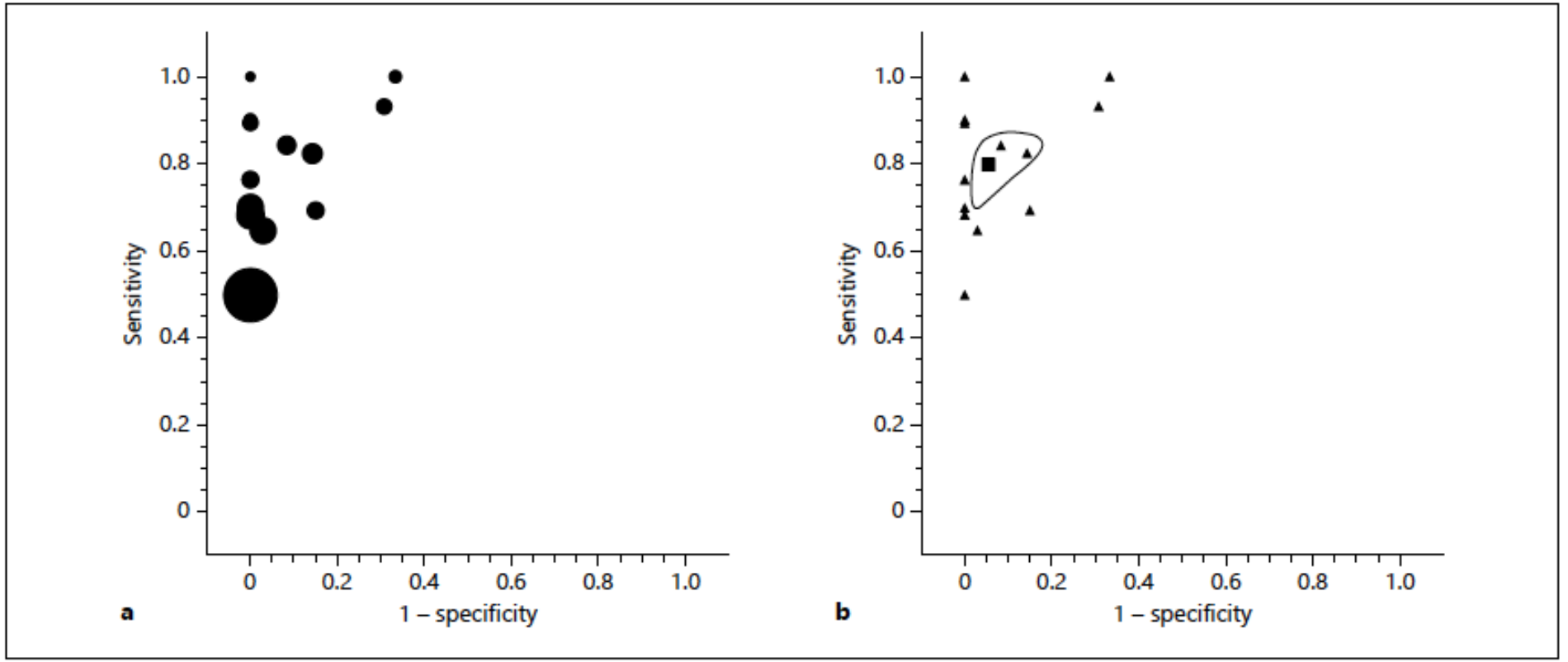



**Fig. 3. a** Diagnostic accuracy of the included studies for detecting ischemic stroke. The circle size represents the sample size of the corresponding study. **b** 95% confidence ellipse around mean sensitivity and specificity, which is represented by the square. The triangles represent the sensitivity and specificity of each included study.

# Conclusions

- CTP has a very high specificity and a high sensitivity for the diagnosis of ischemic stroke
- False negatives mainly occurred in cases of small lacunar infarcts. Other causes for false negatives were limited brain coverage and motion artifacts.
- The sensitivity of CTP varied considerably between studies, which is probably due to the heterogeneity in:
  - proportion of patients with lacunar infarcts varied between studies
  - maximum time between symptom onset and CTP scan acquisition varied between studies.
  - Proportion of patients with a confirmed diagnosis of ischemic stroke ranged from 37 to 100%,
  - coverage and temporal resolution of CTP imaging varied between studies
  - Post-processing of the raw CTP data

# Some questions

- What is an acceptable sensitivity and specificity?
- What can we conclude from the review about the sensitivity and specificity of the imaging test conducted by a given operator for a given patient?
- Does the review have value? Could it, either directly or indirectly, affect decision-making regarding the use of this imaging test?

# Different decision-makers may use and interpret evidence in difference ways

- Physicians
- Patients
- **HTA / reimbursement agencies**

NICE National Institute for Health and Care Excellence

NICE guidance

# Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel

Diagnostics guidance
Published: 2 October 2013
nice.org.uk/guidance/dg11

# Clinical Context

- Levels of faecal calprotectin can help distinguish between inflammatory bowel disease (IBD) and non-inflammatory bowel diseases.
- IBD is characterised by inflammation of the bowel, which is not seen in most patients with Irritable Bowel Syndrome (IBS).
- IBD is managed differently from IBS
- A range of laboratory and point of care diagnostics (POCT) were evaluated

# ‘Some’ of the tests included in the review

**Table 1 Technologies included in the assessment**

| Manufacturer | Test | Platform |
|---|---|---|
| Bühlmann | EK-CAL calprotectin ELISA test | ELISA – quantitative<br>Range: 10–600 micrograms/g |
| Bühlmann | EK-CAL calprotectin ELISA test | ELISA – quantitative<br>Range: 30–1800 micrograms/g |
| Bühlmann | LF-CAL25 Quantum Blue calprotectin test | Rapid test – Immunoassay designed for the quantitative determination of faecal calprotectin in combination with the BÜHLMANN Quantum Blue reader<br>Range: 30–300 micrograms/g |
| Bühlmann | LF-CHR 25 Quantum Blue calprotectin test | Rapid test – Immunoassay designed for the quantitative determination of faecal calprotectin in combination with the BÜHLMANN Quantum Blue reader<br>Range: 100–1800 micrograms/g |
| Phadia AB, part of Thermo Fisher Scientific | EliA Calprotectin | EliA – quantitative<br>Quantitative fluorescence enzyme immunoassay (FEIA) test<br>Range 15–3000 mg/kg |
| Preventis (sister company to Immundiagnostik) | KST11005 CalDetect Calprotectin Rapid test (version 1 – Caldetect) | POCT – immunochromatographic rapid test<br>A semi-quantitative test with 3 lines corresponding to: Calprotectin 'negative', Calprotectin≤15 micrograms/g, Calprotectin 16–60 micrograms/g and Calprotectin>60 micrograms/g stool |
| Preventis (sister company to Immundiagnostik) | CalDetect Calprotectin Rapid test (version 3 – CalScreen) | POCT – immunochromatographic rapid test<br>A yes/no test with only 1 test-line corresponding to the cut-off value of 50 micrograms/g stool (no inflammation=<50 micrograms/g and inflammation present=≥50 micrograms/g) |
| Abbreviations: ELISA, enzyme-linked immunosorbent assay; POCT, point-of-care test | | |

# Operation of tests

- the cut-offs for a POCT might be pre-specified in the design of the test.
- CalDetect reports 1 of 4 results when the test runs correctly: negative – faecal calprotectin is not detectable; negative – faecal calprotectin level is equal to or less than 15 micrograms/g; positive – faecal calprotectin level is 16–60 micrograms/g; and positive – faecal calprotectin level is more than 60 micrograms/g.
- Users might apply local cut-offs for interpreting the results of POCTs;

# Heterogeneity of evidence

- Seven studies compared **IBS and IBD**, at 8 cut-off levels ranging from 8–150 micrograms/g, all in adults in secondary care. All studies assessed enzyme-linked immunosorbent assay (ELISA) tests, and one also assessed the performance of the point-of-care test (POCT) CalDetect.
- Eleven studies reported **IBD compared with non-IBD**, at 8 cut-off levels. Eight studies were conducted in paediatrics and 3 in adults. All used ELISA tests, and one (Damms and Bischoff 2008) also assessed the Prevista POCT (not identified in the scope for the assessment).

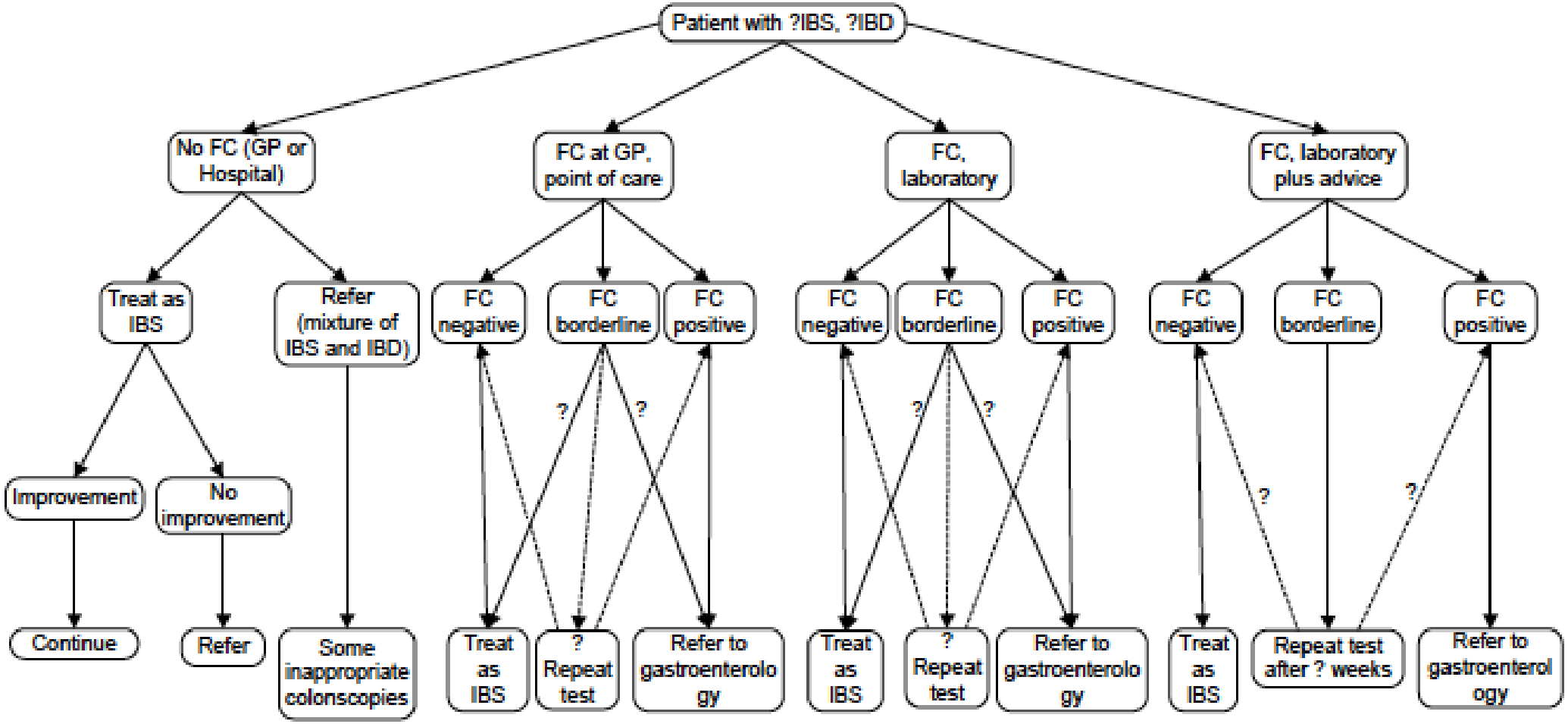
# Sensitivity and Specificity Data for Primary Care

| Test | GP current practice | CalDetect (POCT) | ELISA | Colonoscopy |
|---|---|---|---|---|
| **Cut-off** | – | 15 micrograms/g | 50 micrograms/g | – |
| **Sensitivity** | 100% | 100.0% (95% CI 85–100%) | 93.0% (95% CI 85–98%) | 95.0% |
| **Specificity** | 79% | 94.5% (95% CI 88–98%) | 94.0% (95% CI 76–100%) | 100.0% |
| **Test accuracy data source** | Primary care data from the NHS Technology Adoption Centre project | Secondary care data from Otten et al. (2008) | External Assessment Group meta-analysis of secondary care data | Expert opinion |

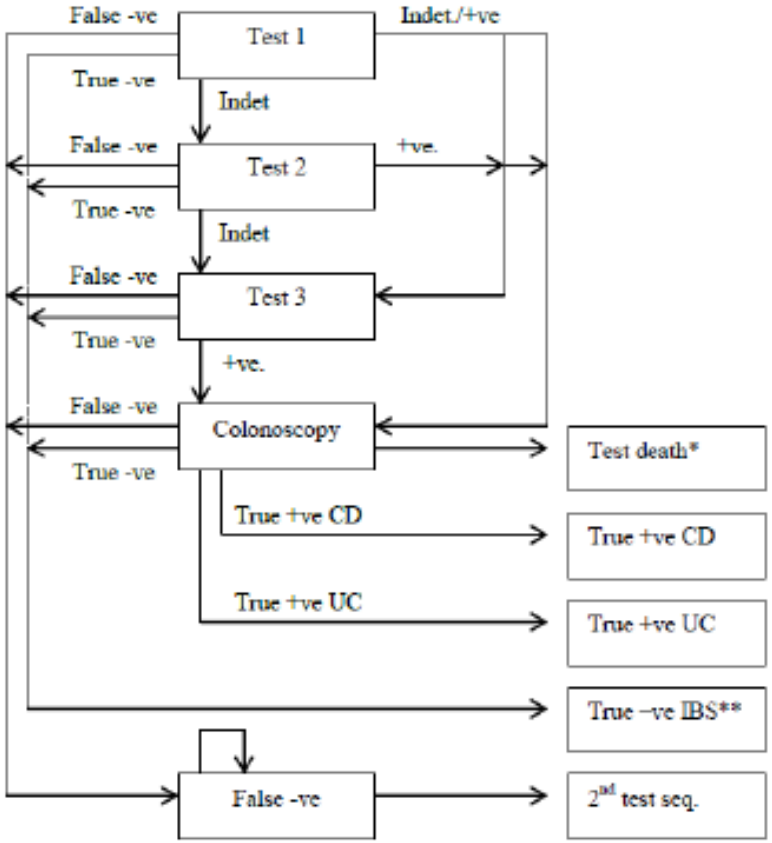
Abbreviations: CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; POCT, point-of-care test

[1] Confidence intervals used in the probabilistic sensitivity analysis, when reported, are given in brackets

# Modelled Clinical Pathway



# Decision-analytic modelling




*= death after colonoscopy

**= true negative = IBS

Figure 21. Model structure of initial test sequences

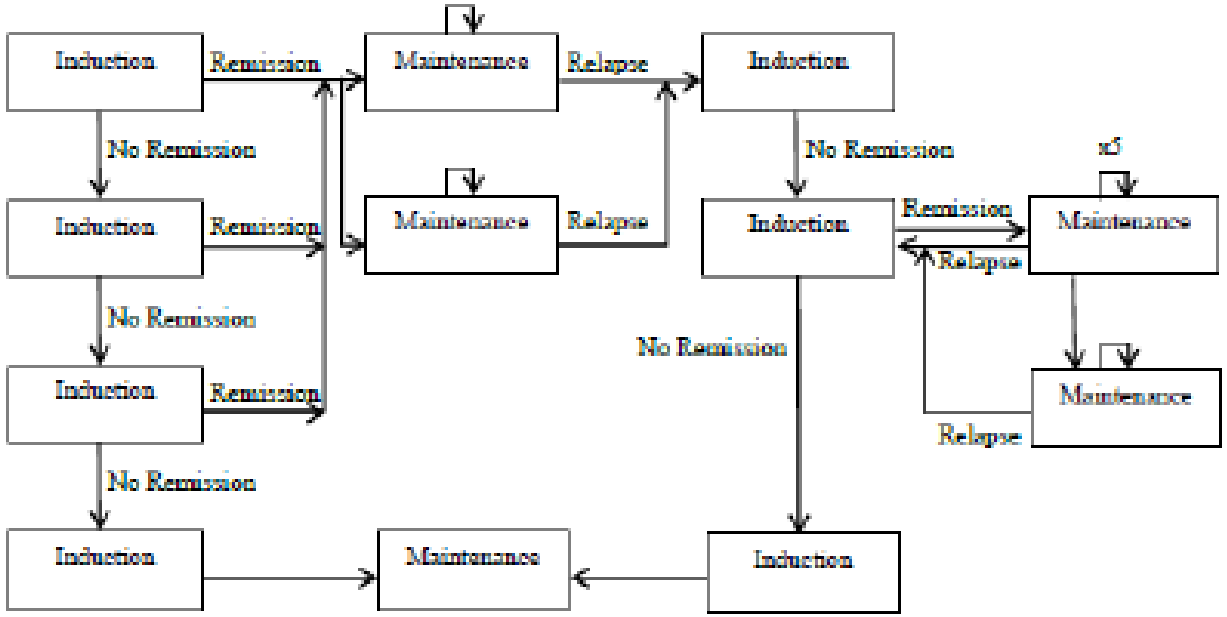



Figure 22. Model structure of Crohn's disease true positives

# Results of economic analysis

| Strategies | QALYs | Test costs | Other costs | Total costs |
|---|---|---|---|---|
| GP current practice (no faecal calprotectin testing) | | | | |
| Crohn's disease | 0.1832 | £22 | £493 | £515 |
| Ulcerative colitis | 0.2771 | £32 | £144 | £176 |
| IBS | 5.7682 | £202 | £2404 | £2606 |
| **Total** | **6.2285** | £257 | £3041 | **£3297** |
| Current practice plus POCT CalDetect (15 micrograms/g cut-off) | | | | |
| Crohn's disease | 0.1832 | £23 | £493 | £516 |
| Ulcerative colitis | 0.2771 | £33 | £144 | £177 |
| IBS | 5.7691 | £114 | £2408 | £2522 |
| **Total** | **6.2293** | £170 | £3044 | **£3214** |
| Current practice plus ELISA (50 micrograms/g cut-off) | | | | |
| Crohn's disease | 0.1831 | £23 | £492 | £515 |
| Ulcerative colitis | 0.2770 | £34 | £143 | £177 |
| IBS | 5.7690 | £116 | £2407 | £2524 |
| **Total** | **6.2291** | £173 | £3042 | **£3215** |

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IBS, irritable bowel syndrome; POCT, point-of-care test; QALYs, quality-adjusted life years

# “Real World Evidence”

- Implementation projects for faecal calprotectin testing in 2 Clinical Commissioning Groups were undertaken by the NHS Technology Adoption Centre.
- Patients diagnosed as having IBS and not referred for specialist investigation did not have colonoscopy, so it was not possible to completely exclude patients with false negative results (partial verification bias).

# Committee discussion

- The Committee was encouraged by the results of the assessment because it is likely that the use of faecal calprotectin testing will result in significant capacity being generated in colonoscopy departments
- The good diagnostic performance of faecal calprotectin has the ability to provide reassurance to both physicians and patients alike given the heterogeneous and overlapping symptoms in lower gastrointestinal disease.

# Recommendation

- Faecal calprotectin testing is recommended as an option to support clinicians with the differential diagnosis of inflammatory bowel disease (IBD) or irritable bowel syndrome (IBS) in adults with recent onset lower gastrointestinal symptoms for whom specialist assessment is being considered, if:
  - cancer is not suspected, having considered the risk factors (for example, age) described in the NICE guideline on suspected cancer and
  - appropriate quality assurance processes and locally agreed care pathways are in place for the testing.

# Questions

- How do we conduct useful diagnostic test research
  - How do tests perform?
    - Lack of gold standards
    - Sequential tests
    - “Real life” performance
  - How should physicians/patients , in principle, respond to test results?
  - How will physicians/patients actaully respond to tests in real-life?
- How do we commission and conduct “useful” reviews of diagnostic test evidence?

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Evaluation survey:

https://glasgow.onlinesurveys.ac.uk/nihr-crsu-cochrane-workshop-evaluation-survey-2019