**Supplementary data**

**Figure S1 Strobe diagram of recruited patients**



Table S1. Test comparison information given to primary care practices for the focus group interviews.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Test** | **Sensitivity**  **TP/TP+FN** | **Specificity**  **TN/FP+TN** | **PPV**  **TP/TP+FP** | **NPV**  **TN/TN+FN** | **Limitations** |
| USC pathway1 | 80.4% | 47.2% | 3.5% | 99.0% | low no’s of confirmed CRC  AUC=0.65 |
| Raman-CRC blood test\* | 85.7% | 68% | 14% | 98.7% | fasted state required |
| FIT faecal test | 93.3% | 77.3% | 11.2% | 99.7% | rectal bleeding |
| CT colonogram2 | 89% | 75% | n/a | 99.9% | small polyps (PPV 80%), 30% need colonoscopy too |
| Colonoscopy# | 95% | 90% | 2-11% (depends on symptoms) | 99.4% | capacity,invasive, bowel prep, completion rate 57%3 |

\*Preliminary figures based on analysis of first 110 pt’s

# Colonoscopy has 5% miss rate for cancer, CTC 3.4% miss rate

1.Simpkins, SJ, Pinto-Sanchez, MI, Moayyedi, P et al. (2017) Poor predictive value of lower gastrointestinal alarm features in the diagnosis of colorectal cancer in 1981 patients in secondary care. Alimentary Pharmacology and Therapeutics, 45 (1). pp. 91-99. https://doi.org/10.1111/apt.13846

2. Lung PF, Burling D, Kallarackel L, et al. Implementation of a new CT colonography service: 5 year experience. Clin Radiol. 2014; 69(6): 597-605. doi: 10.1016/j.crad.2014.01.007.

3. Bowles CJ, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut 2004; 53: 277-283.

Box S1. GP focus group questions.

1) Can you describe the current colorectal cancer USC referral pathway?

What are your perceptions of it?

(Prompt: memorised or need to refer to it, makes secondary care the gatekeeper for tests, NICE criteria, timeliness, capacity, reassurance to have a guideline to follow, ignores GP’s ‘instinct’)

2) Experience of the timeframe from referral to colonoscopy/CTC? How do you manage patient’s expectation? Frequency of repeat consultations between referral and test being done?

(Prompt: 37 days average)

3) Do you consider your personal volume of USC pathway referrals to be just right, too few, or too many?

(Prompt: how much does knowledge of waiting times and resource capacity affect your likelihood to refer a patient?

4). If resources weren’t a problem and if you could wave a magic wand tomorrow what do you think we should do about improving outcomes from CRC? What do you perceive are the barriers to early diagnosis of CRC?

(Prompt: Wales is 22nd of 28 in the European league table of CRC survival, screening problems, resources, effective tests, patient choice, patient education). Perception of need for better access to diagnostics in primary care (invasive and non-invasive)

5). Which situation would the Raman-CRC blood test be of most value to a GP:

-non-specific symptoms? eg constipation, abdominal pain

-younger age group below USC age?

-all USC patients? What would a USC pathway look like with Raman-CRC embedded?

-should it be a secondary care tool ie decision to perform colonoscopy or not: help with triage/prioritisation of referral in secondary care

6). Given the Raman-CRC test performance described (on vignette sheet) would you have confidence to use it?

If not, what sens/spec/PPV/NPV would it need to have?

(Prompt: to seek to understand what is most important for a GP, ability to exclude (NPV) or to correctly identify cancer (PPV))

7).What additional clinical trials would you like to see with the blood test before implementation?

Further observational work with larger numbers/centres/situations?

Release test for use and observe outcomes?

RCT test v no test?

Comparison with FIT?

NICE guidance?

**VIGNETTES**

Assumptions: Colonoscopy/CTC capacity is the same as present

Raman-CRC blood test is routinely available under local guidelines.

Raman-CRC test performance is 85.7% sensitivity, 68% specificity, 14% PPV, 98.7% NPV, based on interim analysis of 120 cases and controls.

1. 60 y.o. male presents with tiredness. His wife (also in the practice) diagnosed with breast cancer a year ago and just completing adjuvant chemotherapy. He has had time off work himself when she has been ill with side effects. On deeper questioning he describes 6 weeks of increased stool frequency (usually once/day, now 3 times per day). No history of rectal bleeding or mucous, abdominal pain or weight loss. Doesn’t smoke. Abdominal and rectal examinations are normal. Simple diagnostics show he is not anaemic and a stool culture is negative.

a) Refer to secondary care on USC pathway without further testing

b) Request Raman-CRC blood test to risk stratify

c) Involve patient in decision making? Explore patient expectations/underlying concerns....

d) Other?

2. A 50 year old patient who is a frequent attender describes three or four episodes of rectal bleeding. This is fresh blood, noticed in the toilet water. No anal pain or itching. No change on bowel habit. Appetite and weight stable. On citalopram for anxiety. No relevant family history. Abdominal examination: appendicectomy scar, nil else. Rectal exam: small skin tags, no masses felt, no blood on glove, no proctoscope available. FBC normal.

Action?

3. 45 year old female patient, complains of tiredness and self limiting looser stools for 3 weeks, but does have a FH of bowel cancer. Examination normal.

Decision made to perform a Raman-CRC blood test. The test returns positive 2 days later.

How would you go about discussing this with the patient in the follow up consultation?

Box S2. GP focus group vignettes.

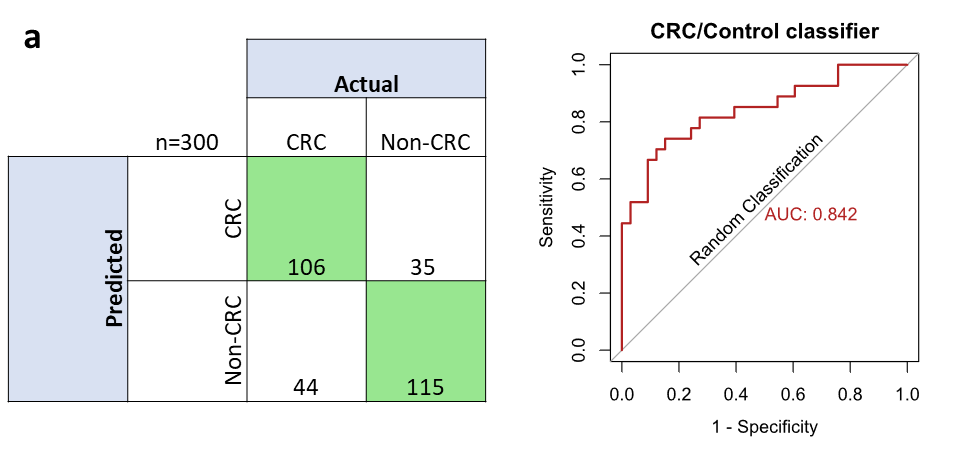
Table S2. Initial themes and categories of focus group interviews.

|  |  |
| --- | --- |
| **Initial themes** | **Initial categories** |
| Reflecting on the existing referral pathway | Care taken to use pathways appropriately |
|  | Difficulty in referring outside of the criteria |
|  | system pressure to get early diagnosis |
|  | ‘Shoehorning’ |
|  | Getting timely referrals |
|  |  |
| Acceptability of test | Reducing patient anxiety |
|  | Convenient for patient |
|  | GP need for longer term reliability |
|  | Need for GP confidence in test |
|  | Need for HB support and governance |
|  |  |
| Utility of the test as a triage tool | Managing the ‘grey’ areas |
|  | Building an evidence base |
|  | Providing GP reassurance |
|  | Managing patient expectations of the test |
|  | Assessing risk |
|  | Potential resource and cost implications |
|  | GP education required |
|  | Meeting early diagnosis targets |
|  |  |
| Utility of the test as a diagnostic tool | Specificity of the test |
|  | Diagnosing in non-invasive testing populations |

**Raman-CRC model retrospective cohort**

Table S3: Retrospective model training cohort demographics. SD: standard deviation

|  |  |  |  |
| --- | --- | --- | --- |
|  | Colorectal cancer | Control |  |
| Total patients | 150 | 150 |  |
| Mean Age (years), (SD) | 67 (11) | 65 (13) |  |
| Female | 66 | 81 |  |
| Male | 84 | 69 |  |



**Figure S2** Confusion matrix and ROC curve analysis of the model training for control and colorectal cancer (CRC). All data refer to resampled and averaged test set predictions.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Tumour location | Initial diagnostic test | | Total |
| Colonoscopy | CT colonogram |
| Colorectal cancers | | | |  |
|  | Right side | 6 | 2 | 8 |
|  | Left side | 7 | 1 | 8 |
|  | Rectal | 10 | 3 | 13 |
| Non-colorectal cancers | | | | |
|  | Pancreatic | 1 | 3 | 4 |
|  | Prostate | 2 | 1 | 3 |
|  | Lung | 1 | 2 | 3 |
|  | Bladder | 1 | 1 | 2 |
|  | Renal | 0 | 1 | 1 |
|  | Peritoneal/ovarian | 0 | 1 | 1 |
|  | Breast | 1 | 1 | 2 |
|  | Hepatocellular | 0 | 1 | 1 |
|  | NET | 0 | 1 | 1 |
|  | Anal SCC | 1 | 1 | 2 |
| Non-malignant disease | | | | |
|  | Colorectal polyps | 90 | 12 | 102 |
|  | Colitis | 4 | 0 | 4 |
|  | Ovarian Cyst | 1 | 0 | 1 |
| Controls |  | 225 | 151 | 376 |
|  | | | **Total** | **532** |

Table S4: Prospective primary care cohort with final diagnosis breakdown. NET: neuroendocrine tumour; SCC: squamous cell carcinoma

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | CRC diagnosis | Non-CRC diagnosis |
|  | Participants, n | 29 | 503 |
| Sex | Male | 23 | 240 |
|  | Female | 6 | 263 |
|  | Median age (range) | 71 (51-87) | 70 (50-92) |
| Presenting symptom: | |  |  |
|  | rectal bleeding | 15 (52) | 162 (32) |
|  | change in bowel habit | 19 (66) | 412 (82) |
|  | loose stool | 11 (36) | 280 (56) |
|  | increased frequency | 13 (45) | 216 (43) |
|  | urgency | 4 (13) | 82 (16) |
|  | incomplete emptying | 4 (14) | 84 (17) |
|  | constipation | 6 (20) | 161 (32) |
|  | abdominal pain | 9 (30) | 193 (39) |
|  | anal pain | 2 (7) | 23 (5) |
|  | abdominal mass | 1 (3) | 20 (4) |
|  | rectal mass | 3 (10) | 16 (3) |
|  | anal mass | 1 (3) | 12 (2) |
|  | loss of appetite | 3 (10) | 58 (12) |
|  | weight loss | 10 (33) | 151 (30) |
|  |  |  |  |
|  | Haemoglobin (median;range) | 125(71-161) | 133 (63-207) |
|  | Ferritin (median;range) | 30 (6-617) | 75 (4-2427) |
|  | CEA (median;range) | 6 (1-2385) | 2 (1-1149) |
|  |  |  |  |

Table S5: Prospective cohort information with presenting symptoms and blood test parameters

Values are n (%) unless otherwise stated. CEA: carcinoembryonic antigen

Table S6. List of participating practices and practice demographics.1

|  |  |  |  |
| --- | --- | --- | --- |
| **GP practice** | **Assigned practice number** | **Urban or Rural** | **Registered Practice population (2016)** |
| Dulais Valley Primary Care Centre | 1 | Rural | 6016 |
| Oak Tree Surgery , Brackla | 2 | Urban | 18018 |
| Portway Surgery, Porthcawl | 3 | Urban | 13854 |
| Strawberry Place Surgery | 4 | Urban | 6734 |
| Uplands Surgery | 5 | Rural | 9534 |
| Vale of Neath Practice | 6 | Urban | 9266 |

**GP practise selection criteria**

GPs practices with a known research interest as part of a research network were invited to take part. 6 practices agreed to participate, 5 of the 6 practices had been involved in patient recruitment to the study and 1 practice had not been involved with patient recruitment for the study. 24 general practitioners were interviewed as part of the focus groups. 2 practice managers, 1 advanced nurse practitioner and 1 health care assistant nurse also attended but did not provide any verbal input to the interviews.

**Interviewer information**

DAH is a colorectal consultant who has postgraduate training in research methods, previous experience of qualitative research, clinical experience from treating patients with CRC and is the chief investigator of the study. His involvment and roles within the study was explained to all focus participants at the start of each focus group.

Information given to GP focus groups.

* Serum based colorectal cancer biomarker
* 72 hour turnaround time
* Cost low ~ £10 per test
* Test output either ‘normal’ or ‘abnormal’

|  |  |  |  |
| --- | --- | --- | --- |
| **Theme** | **Focus Group Response** | **Subtheme** | **Evidence** |
| Perceptions of current USC pathway |  | Care taken to use pathways appropriately  Difficulty in referring patients who do not fit criteria.  System pressure for early diagnosis | “I do think the 2 weeks wait with the USC has helped things. If we go back to the dark ages we did have, even for urgent referrals they could be waiting weeks and weeks and weeks before seeing anybody or got listed for a colonoscopy. So I think USC have certainly bought things forward a bit.” (GP 2, practice 2)  “The biggest problem [with current referral process] is if they don't meet the criteria and you have some concerns about them/…/then there is a long wait there to be seen.” (GP 4, practice 2)  “I think they [secondary care] are being quite criteria based on everything… I do think they are ignoring concern at times. I‘ve had a couple of cases where you try and communicate that clinical concern, that gut instinct/./And you will get criteria-based rejection.” (GP 2, practice 5)  “It doesn't allow for atypical presentations does it? Sometimes you do just have that gut feeling when you see someone and there is no leeway to get that through.” (GP 1 & 2, practice 4)  “I think we GPs are frightened/criticized for referring as USC not urgent, but the waiting time for urgent, that’s the one that we are concerned about. It’s not 6 weeks or 12 weeks its can be 24 weeks, so if we are dithering as to whether this is USC or not we will refer USC, partly because we have covered ourselves [and] partly because urgent isn’t urgent.” (GP 1, practice 3)  “If I think a back 5-10years, I was not referring as freely as I refer now. There probably is the same resource issue now but the message you are getting is refer, refer, refer, do not delay, we do not want people having cancer and us missing it because we need to get those survival rates up and time from symptoms to diagnosis needs to be better.” (GP 1, practice 1) |
| Utility of Raman-CRC as a triage tool |  | Managing the ‘grey’ areas.  Provides reassurance to patient and GP  Help to meet early diagnosis targets | “It’s another tool in your box. If you think its barn door then it doesn't matter what a blood test shows does it, but for those nebulous areas [it’s useful].” (GP 1, practice 2)  “It’s very good at saying you haven't got cancer so you can be reassured.” (GP 2, practice 1)  “Sometimes it's difficult to reassure people because they are worried about it; without any further tests being done. So if there was a test like the Raman test and they are available it would add that reassurance. Not only to the public but also to us as well.” (GP 2, practice 2)  at that point [less than 6 weeks of symptoms] you wouldn’t be thinking about a USC but Raman may change your referral.” (GP 1, practice 3) |
| Utility of Raman-CRC as a diagnostic tool |  | Specificity of the test  Potential as a non-invasive diagnostic tool. | “Its [specificity] could do with being a bit better… Its fine, but any improvement would be a bonus… It’s better than what we have got.” (GP 1, practice 4)  “I think it will quite useful in the context of elderly population who diagnosis is largely academic, but does help in terms of advanced planning. They are the ones that cause quite a tricky situation, what to do, where to go next.” (GP1, practice 5)  “It is less invasive where people lack capacity, i.e. people in care homes with significant mental illness, it would be a good test. Where usually to decide if they need a colonoscopy you need to get an advocate to decide, so there is benefit there as well.” (GP 2, practice 5) |
| Acceptability of Raman-CRC test in practice |  | Reducing patient anxiety  Convenient for patient  More evidence needed | Sometimes it's difficult to reassure people because they are worried about [cancer]; without any further tests being done. So if there was a test like the Raman test and they are available it would add that reassurance. Not only to the public but also to us as well… You may not need to do any further investigations.” (GP 2, practice 2)  “If you’ve got a negative [Raman] test result whilst awaiting the colonoscopy, you can say ‘look there’s a 98% chance it’s not going to be cancer’. How relieving it that whilst waiting for it. You could say look for now it’s not the mainstay of investigations we will still go down the NICE guideline route but I don’t think it’s likely, it would be a huge weight off his mind and reduce a lot of patient anxiety.” (GP 3, practice 5)  “The test would have to be validated someway and in the pathway rather than just assuming we could go down this route and ignore the established guidelines. (GP 1, practice 5) |

**Table S7. Evidence summary for key primary care interview themes.**