

Direct access cancer testing in primary care: a systematic review of use and clinical outcomes.

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How this fits in

GP direct access testing for symptoms that could be indicative of cancer has previously been criticised for increasing testing and decreasing diagnostic yield. This systematic review did not support these concerns: no significant difference was found in the cancer conversion rate between GP direct access and specialist testing pathways. The time between test request and test performance was reduced and GP direct access testing achieved consistently higher GP and patient satisfaction. These findings are however limited by poor study quality: analysis of contemporary data is required to fully evaluate the effectiveness of direct access testing.

Abstract

Background. Direct access (DA) testing allows GPs to refer patients for investigation without consulting a specialist. The aim is to reduce waiting time for investigations and unnecessary appointments, enabling treatment to begin without delay.

Aim. To establish the proportion of patients diagnosed with cancer and other diseases through DA testing, time to diagnosis, and suitability of DA investigations.

Design and Setting. Systematic review assessing the effectiveness of GP DA testing in adults.

Methods. Medline, Embase, and the Cochrane Library were searched. Where possible, study data was pooled and analysed quantitatively. Where this was not possible the data is presented narratively.

Results. We identified 60 papers that met pre-specified inclusion criteria, most were carried out in the UK and were judged to be poor quality. We found no significant difference in the pooled cancer conversion rate between GP DA referrals and patients who first consulted a specialist for any test except gastroscopy. There were also no significant differences in the proportions of patients receiving any non-cancer diagnosis. Referrals for testing were deemed appropriate in 66.4% of those coming from GPs and 80.9% of those from consultants, this difference was not significant. The time from referral to testing was significantly shorter for patients referred for DA tests. Patient and GP satisfaction with DA testing was consistently high.

Conclusion. GP DA testing performs as well as, and on some measures better than, consultant triaged testing on measures of disease detection, appropriateness of referrals, interval from referral to testing, and patient and GP satisfaction.

Introduction

In the United Kingdom, general practitioners (GPs) have historically acted as gatekeepers to secondary care and specialist testing. Gatekeeping may cause diagnostic delay in three ways: 1) patients may be discouraged from presenting symptoms because they suspect the GP will not take action; 2) GPs may fail to investigate the presenting symptoms appropriately, sometimes because they have no access to the relevant diagnostic tests; 3) GPs may adopt, or be obligated by established clinical pathways to adopt, too high a risk threshold for referral, choosing to watch and wait inappropriately, and only acting on red-flag late-stage symptoms.¹⁻⁶ “Double gate-keeping” further lengthens delay when a GP must first refer the patient to a specialist who reviews the patient again before requesting further investigation.⁵

Direct access (DA) testing allows GPs to refer patients for diagnostic testing without referring to - or consulting with - a specialist first.⁷ It has the potential to reduce the number, cost and inconvenience of outpatient appointments and reduce the interval between a patient presenting to primary care and a diagnosis being reached (the diagnostic interval).^{8,9} This also has the potential to allow GPs a degree of freedom in which patients they refer for investigations, providing a route to investigation for patients whose symptoms may not trigger investigation as recommended by guideline criteria or about whom the GP has a ‘gut-feeling’ that investigation is warranted.¹⁰ Specialists, however, caution that capacity for secondary care investigation is limited and that DA leads to over-investigation without increased diagnostic yield.¹¹ Conversely GP reluctance to take on responsibility for investigation has been demonstrated in the contexts of knee imaging and infertility^{12,13} and GPs often fail to employ diagnostic tests for cancer despite having DA to them.¹⁴

The UK Department of Health invested £200m in 2012 to enhance GP access to four diagnostic tests for cancer as part of its commitment to save 10,000 lives lost due to late cancer diagnosis by 2015.¹⁵⁻
¹⁷ The tests chosen were non-obstetric ultrasound (ovarian cancer), flexible sigmoidoscopy (colorectal cancer) and magnetic resonance imaging (MRI) (brain cancer); it was also proposed to improve open-access to chest x-rays - where there were often significant reporting delays - to expedite diagnosis of lung cancer.^{15,18} In 2015, the National Institute for Health and Care Excellence (NICE) guidelines for suspected cancer recommended that GPs had direct and rapid access to laboratory tests (Ca125, faecal occult blood testing, full blood count), ultrasound and radiology (x-ray, computed tomography

(CT), MRI), and endoscopy of the gastro-intestinal (GI) tract for patients who do not meet the criteria for an urgent referral to a specialist but who do have symptoms warranting urgent investigation in specific clinical scenarios.¹⁹ At that time, a survey of GPs showed that investment was required to achieve DA to these tests across all English regions in order to reduce the intervals between request, testing, and reporting.²⁰ GPs reported good access to x-ray and laboratory investigations - apart from faecal occult blood testing and urine protein electrophoresis - whilst two thirds had DA to gastroscopy, half to CT, and one third to colonoscopy. Excluding x-ray, less than one fifth of GPs could access radiology and endoscopy within the timescales recommended by NICE.

We aimed to systematically review the evidence for DA testing of adults presenting to primary care, reporting the proportion of patients diagnosed with cancer or another diagnosis (the conversion rate), and where possible the indications for testing, time to testing, appropriateness and acceptability to GPs, specialists, and patients. Where reported, we include direct comparisons with outcomes in patients from the same population triaged by a specialist before testing. To our knowledge, there has been no published systematic review of this type to date.

Methods

Search

We registered the systematic review protocol with PROSPERO²¹ and conducted a comprehensive search of the following electronic databases: MEDLINE, Embase, and the Cochrane Library. The search strategy was adapted according to the requirements of the databases and is reported in Appendix 1. In brief, the key search terms were as follows:

- Direct, open, rapid, or one-stop diagnosis or investigations.
- Primary health care, general practitioner, general practice, family doctor, or specialist referral.
- Cancer, neoplasm, or carcinoma.

We included all study types except case studies and case series. We included adults (18yrs and older) attending primary care and undergoing DA testing where cancer could be an outcome. DA testing was defined as a test that a GP could access without consulting with a specialist first. Where reported we included data from "specialist" comparator groups. These patients either underwent specialist triage, where tests requested by a GP were first screened by a specialist to determine

whether the patient was appropriate for testing, or underwent specialist testing, where tests were requested by a specialist after they reviewed the patient in clinic. In addition to the database search, the reference lists of identified reviews and included studies were checked for additional papers meeting our inclusion criteria. Finally, a 'related articles' search was performed in PubMed on all included studies. No language or time limits were placed on the searches.

Data Extraction

The titles and abstracts of all retrieved articles were screened independently by two reviewers (BN and AT) and any disagreements were resolved through discussion. The full text of the remaining articles were read by two reviewers independently. Four initial screening questions were used for each paper: 1) Open/DA confirmed (Y/N) – if no, exclude; 2) Specialist triage of referrals (Y/N) – If yes, exclude; 3) GP DA referral outcome data reported separately? (Y/N) – if no, exclude; 4) Cancer diagnosis possible? (Y/N) – if no, exclude. Retained studies went on to full text review and data extraction by two independent reviewers. Data was extracted into a pre-prepared Excel spreadsheet, compared, and if necessary any disagreements were resolved by a third reviewer (CFS).

Quality assessment

The risk of bias and quality of the studies was assessed by two reviewers independently. Disagreements regarding the risk of bias in individual studies was resolved through discussion, with the involvement of a third reviewer if necessary. The Newcastle-Ottawa tool was used to review observational studies and the Cochrane Risk of Bias tool was used to assess the risk of bias in randomised controlled trials. The results of the quality assessment are used to provide an overall assessment of the quality of the included studies and no studies were excluded on quality alone.

Analysis

The primary outcome of interest was the number of cancers diagnosed by DA or specialist testing, recorded as the absolute number and expressed as the cancer conversion rate (CR). The CR is the number of cancer cases expressed as a proportion of all patients attending DA testing. Secondary outcomes of interest were non-cancer diagnoses (with corresponding CR), indications for testing, time to diagnosis, the appropriateness of referral determined by local, national or international guidelines, and measures of GP, specialist, and patient acceptability.

CRs were calculated for cancer and non-cancer diagnoses for each study, grouped by test type, and pooled to give a CR for each test. Pooled estimates were calculated in Stata where appropriate using the metaprop command, weighted using the Freeman-Tukey double arcsine transformation to allow for variation in sample sizes, for: the CR of each DA test; subgroups of studies reporting DA testing in relation to a specialist comparator group; and to summarise appropriateness.^{22,23} The Wilcoxon-Mann-Whitney test was used to investigate whether GP DA reduced the interval from referral to diagnostic test and referral to diagnosis. In addition, a narrative review of patient and GP satisfaction was conducted.

Results

The PRISMA flow diagram in Figure 1 outlines the selection of the 60 studies included in the review.

[Figure 1 about here]

Table 1 describes the papers included. There were 34 cross-sectional studies, 24 cohort studies, a randomised controlled trial, and a non-randomised trial. Gastroscopy was the most commonly studied DA test (27 studies),²⁴⁻⁵⁰ followed by lower GI endoscopy (proctoscopy, flexible sigmoidoscopy or colonoscopy, 15 studies),⁵¹⁻⁶⁵ CT (3 studies – 2x head, 1x chest),⁶⁶⁻⁶⁸ ultrasound (3 studies – 2x abdominal, 1x gynaecological),⁶⁹⁻⁷¹ MRI (3 studies),⁷²⁻⁷⁴ x-ray (2 studies),^{75,76} gastroscopy and lower endoscopy combined (2 studies),^{77,78} mammogram (1 study),⁷⁹ mammogram and ultrasound combined (1 study),⁸⁰ MRI and CT combined (1 study),^{81,82} transvaginal sonography (1 study),⁸³ and a range of radiological tests including MRI, CT and barium meal (1 study).⁸⁴ Fifty-seven studies (95%) reported DA testing performed in a hospital or specialist clinic setting, one utilised a DA test located in primary care²⁹ and two did not specify location.^{54,77}

[Table 1 about here]

Quality Assessment

The overall quality of the studies included in this review was poor. The majority (49, 82%) of studies included a representative sample of consecutive patients. However, thirty-nine studies (65%) demonstrated attrition of patients between inclusion and reporting outcomes without adequate explanation of why. Most (54, 90%) assessed patient outcomes through linked clinical records. Only one paper justified the sample size.³³ The vast majority of studies (56, 93%) presented a descriptive analysis without testing for significance between subgroups and nine studies (15%) justified the statistical method used.

Gastroscopy

Twenty-three studies reported data allowing cancer CR to be calculated for DA gastroscopy. Indication for testing was left to the GPs' discretion in 11 (41%) studies; five studies (19%) included only patients with dyspepsia; four required no previous gastroscopy (15%); one required no prior gastroenterological referral; one followed British Society of Gastroenterology gastroscopy guidance, and one stipulated specific alarm symptoms (Appendix 2).

The cancer CR ranged from 0% to 7.2% (pooled 1.7%, 95% confidence interval (CI) 1.2 to 2.2%, appendix 2) and the non-cancer CR ranged from 11.8 to 98.7% (56.9%, 95%CI 44.1 to 69.2%, appendix 3). When restricted to the eight studies including a specialist comparator group, the DA cancer CR ranged from 1.2 to 2.2% (pooled 1.6%, 95%CI 1.3 to 1.9%) and the specialist cancer CR ranged from 1.0% to 5.1 % (pooled 2.7%, 95% CI 1.8 to 3.7, p=0.03); the DA non-cancer CR ranged from 50.7% to 98.7% (pooled 66.6%, 95%CI 52.6 -79.3%) and the specialist testing non-cancer CR ranged from 44.2% to 99.0% (pooled 63.2%, 95%CI 51.6 – 74.0%, p=0.70).

Large bowel endoscopy.

Ten studies reported data allowing the calculation of cancer and other disease CR for large bowel endoscopy, the indication for testing was left to the GPs discretion in five studies (50%). The remainder specified a range of age and symptom criteria, most commonly rectal bleeding, anaemia, and change in bowel habit (Appendix 4).

The cancer CR ranged from 1.7% to 11.1% (pooled 4.5%, 95% CI 3.4 to 5.7%) and the non-cancer diagnosis CR ranged from 28.8% to 62.5% (pooled 46.5%, 95% CI 35.5% - 57.6%) (Appendix 4 and 5). When restricted to the four studies including a specialist comparator group, the DA cancer CR ranged from 3.6-10.8% (pooled 5.4%, 95% CI 3.5 to 7.6%) and the specialist cancer CR ranged from 0.9% to 7.0% (pooled 3.0%, 95% CI 1.6 to 4.6, p=0.06). The DA non-cancer CR in these four studies ranged from 40.3% to 62.5% (pooled 50.3%, 95% CI 40.0 -60.6%) and the specialist non-cancer CR ranged from 28.4 to 64.9% (pooled 47.5%, 95% CI 32.0 – 63.2%, p=0.77).

Other tests

Across the remaining 14 studies reporting data to allow the calculation of cancer and other diagnoses CR, the cancer CR ranged from 0.0% for transvaginal sonography for abnormal vaginal bleeding to 11.7% in a study reporting a wide range of DA tests used at the GPs' discretion (Appendix 6).^{83,84} The conversion rate for non-cancer diagnosis ranged from 4.2% for patients undergoing mammogram to 56.4% in a study reporting the use of DA x-ray used at the GPs' discretion (Appendix 7).^{76,79} As there were few studies reporting each test type, and test types were heterogeneous, results were not pooled. A summary of the cancer CR and non-cancer CR for all test types is in Table 2.

[Table 2 about here]

Appropriateness of referral

Nine studies reported the appropriateness of test requests using guidelines from the American Society for Gastrointestinal Endoscopy,^{25,59,77,78} the European Panel of the Appropriateness of Gastrointestinal Endoscopy,^{52,56} the British Society of Gastroenterology,²⁶ NICE,²⁷ and previously published work.²⁹ Overall, there was no significant difference between the appropriateness of GP DA referrals (mean pooled appropriateness 66.4%, 95% CI 41.2 – 87.4%) and specialist referrals (mean pooled appropriateness 80.9, 95% CI 73.9 – 87.1) ($p=0.24$).

Time to test and diagnosis

Specialist referrals resulted in a significantly longer interval between referral and testing (mean = 76.6 days, S.D. 48.0 days) compared to GP DA referrals (mean = 31.9 days, S.D. 20.5 days) ($z=2.0$, $p=0.03$, 9 studies). There was no significant difference, however, in the interval between GP DA (mean = 74.0 days, S.D. 15.6 days) and specialist referral (mean = 59.5 days, S.D. 21.9 days) and final diagnosis ($z=-0.78$, $p=0.44$, 2 studies).

Patient and GP satisfaction

Three studies reported patient satisfaction with DA endoscopy and sigmoidoscopy of over 90%.^{53,55,57} One study reported over 90% patient satisfaction with the time from referral to test and the test to receiving results, and the majority of patients felt that seeing a specialist first or receiving test results from a specialist was not necessary.⁵⁷

Two studies reported on GPs' satisfaction with DA testing. One study reported that over 90% of GPs found DA sigmoidoscopy "useful",³⁴ and the other that 72% of GPs who had referred patients for DA MRI felt that it was good value for money, including 84% of those who had thought that DA MRI involved extra cost.⁷²

Discussion

Summary

In this systematic review we aimed to summarise the current evidence for GP DA testing for symptoms related to cancer. Our results show that overall the DA CR ranged from 0-12% for cancer and 4-99% for non-cancer diagnoses, dependent on the type of DA test and the indications for

referral. Studies reporting a comparison between DA and patients seen by a specialist before testing showed a similar CR for both cancer and for non-cancer diagnoses and, when evaluated, no significant differences in the appropriateness of referrals.

GPs and patients reported high satisfaction with DA with only one study reporting a higher number of GPs preferring specialist over DA referral.⁵³ Concerns about DA testing related to the experience of the procedure itself, for example the discomfort of endoscopy, rather than the process of referral and testing. The small number of studies reporting measures of satisfaction, however, mean that these results should be viewed with caution.

DA reduced the time from GP referral to testing compared to specialist referral and this may have contributed to the high levels of patient satisfaction reported, although no data on patient satisfaction with specialist referral was reported for comparison. Despite the reduction in time to test with DA, there was no corresponding reduction in time to diagnosis. Previous reports confirm that expedited testing does not necessarily lead to quicker diagnosis due to waiting lists for further investigations, poor communication between specialties, and misunderstandings about who is responsible for arranging onward referral.⁸⁵

Strengths and limitations

We performed a comprehensive search and applied strict selection criteria to ensure we only included studies reporting GP DA testing. We retrieved 60 studies from 15 countries published between 1979 and 2015, making this the largest published review on DA cancer testing. However, the majority of studies were judged to be poor quality: most were observational, without a comparator group, using retrospective clinical record review, increasing the risk of bias and limiting the external validity of our findings. Reporting was of poor quality, for example, a justification of the methods used was often missing, and some authors did not comprehensively report diagnoses if focussing on other outcomes such as patient satisfaction which could be strongly influenced by the final diagnosis.

Studies reported a range of DA tests requested for a variety of clinical indications. Deriving pooled estimates from a heterogeneous group of studies has important limitations. For example, studies with different clinical indications for testing will have varying pre-test probabilities for cancer or non-cancer diagnoses. To minimise the effect of this limitation, we report the indications for testing and the CRs for each study individually. We also report CR ranges in addition to pooled estimates, stratify data by

test type, and report separate pooled estimates when studies report outcomes for both DA and specialist routes with the same clinical indications. Studies describing DA gastroscopy and large bowel endoscopy dominated, particularly in relation to the appropriateness and acceptability of DA testing, and so caution is advised in the generalisation of these findings to other test types.

The use of clinical guidelines to define the appropriateness of referral may present a further limitation. Guidelines, and their underpinning evidence, vary in quality and have been criticised for oversimplifying the complexity of primary care where undifferentiated symptoms are commonplace and associated with both minor illness and serious disease.^{86,87} They do, however, provide a standard of care, to improve service delivery and health outcomes against which to evaluate clinician action.⁸⁸

Comparison with literature

Two randomised controlled trials have investigated DA testing and were not included in this review as they were not investigations for cancer: MRI for knee symptoms (the DAMASK trial) and hysterosalpingography (HSG) for infertility (the OATS trial).^{12,13} Both studies found no difference in waiting times and patient outcomes between DA and specialist referral routes. Uptake of DA testing, however, was low in both studies. A qualitative assessment of OATS revealed that the main barriers to the uptake of DA HSG were the infrequency of patients presenting for infertility investigation, lack of clarity over the responsibility for follow-up, and lack of support and guidance.⁸⁹ DA tests to investigate symptoms that could indicate cancer will have greater uptake due to the higher prevalence of these symptoms in primary care, and since DA testing has been sanctioned by NICE in England and Wales, and incorporated into local referral pathways.³

Implications for research and practice

A common criticism of GP DA testing is that it could lead to an increase in inappropriate referrals, resulting in a decrease in the CR: our review suggests that these concerns are unsupported.⁷ Cancer CRs following DA testing were notably lower than the 10-11% CR reported following analysis of urgent (two-week-wait) cancer referrals in the UK.^{90,91} However, these early two-week-wait pathways, based on the 2005 NICE guidelines, were criticised for focussing on red-flag symptoms and being based on research derived from specialist care. As a result, patients with lower but not no risk symptoms were less likely to be referred urgently, experienced delays in diagnosis, and were more

likely to be diagnosed with cancer as an emergency.^{92,93} The move to improving access to diagnostic testing for lower risk symptoms in the 2015 NG12 NICE guidelines was based on emerging primary care research.⁹⁴ NG12 set a referral threshold of a 3% risk of cancer recommending combinations of clinical features for DA testing.⁹⁵ Our review suggests that a DA strategy may achieve a CR close to 3%, not only if the pathway entry criteria are evidence-based referral indications (similar to NG12), but also if the indication for referral is GP discretion alone. Detailed analysis of the outcomes of diagnostic pathways that have been developed in the UK to incorporate the NG12 DA criteria will greatly inform this debate, as will ongoing work on the investigations of non-specific cancer symptoms which, at present are less likely to be included as explicit guideline criteria.⁹⁶

This review has re-emphasised the importance of whole pathway redesign and the need to focus efforts to reduce diagnostic delay on all intervals between symptomatic presentation to GP and final diagnosis: DA may be successful in reducing the time to test but no difference was found in the total diagnostic interval.^{97,98} Post-testing delays could balance out gains made by a DA strategy in the pre-test period if resources are not also invested in reducing the time between testing, reporting, definitive diagnosis and treatment. Time spent waiting, whether for testing or treatment, has been identified as an important component in the satisfaction of cancer patients.^{3,99,100} Improving the pathway to diagnosis for patients with non-specific symptoms may be achieved by national programmes in the UK such as Accelerate Coordinate and Evaluate (ACE) and the Danish “three legged strategy” which are investigating the role of Multi-Diagnostic Centre based pathways for patients with non-specific symptoms of cancer that fall outside of current urgent referral pathways.¹⁰¹⁻¹⁰³

In conclusion, this study provides the first overview of the literature on GP DA testing for symptoms that could represent cancer. It suggests that DA testing at the discretion of the GP may not result in a significant decrease in the proportion of patients diagnosed with cancer or other non-cancer pathology. It supports the increase in DA testing included in the UKs 2015 NICE guidelines. Patients and GPs show high satisfaction with DA testing, but our results highlight the need for better quality contemporary evidence on the optimal DA testing strategy to ensure a balance is achieved between primary care testing and disease detection.

Declarations

As this paper is a systematic review of published literature, no ethical approval is required. The authors received no funding for the production of this review and declare no conflicts of interest. CFS is funded by a grant from Cancer Research UK. BDN, AT and CB designed the protocol for this review. AT, BDN, NJ, JB, and EAS carried out the screening of the papers, and extracted the data from the included papers. CFS provided a third opinion where there were discrepancies in the inclusion of paper and the extracted data, and carried out the statistical analyses. FDRH provided clinical expertise and interpretation. CFS wrote the first draft of the paper and BDN edited it. All authors reviewed and approved the final manuscript.

References

1. Hamilton W. Five misconceptions in cancer diagnosis. *Br J Gen Pract.* 2009;59(563):441-445.
2. Ott JJ, Ullrich A, Miller AB. The importance of early symptom recognition in the context of early detection and cancer survival. *Eur J Cancer.* 2009;45(16):2743-2748.
3. Richards MA. The size of the prize for earlier diagnosis of cancer in England. *Br J Cancer.* 2009;101 Suppl 2:S125-129.
4. Rubin G, Lyratzopoulos G, Abel G, Neal R, Walter F, Hamilton W. Cancer detection in primary care. *Lancet Oncol.* 2012;13(8):e325-e326.
5. Olesen F, Hansen RP, Vedsted P. Delay in diagnosis: the experience in Denmark. *Br J Cancer.* 2009;101 Suppl 2:S5-8.
6. Round T, Steed L, Shankleman J, Bourke L, Risi L. Primary care delays in diagnosing cancer: what is causing them and what can we do about them? *J R Soc Med.* 2013;106(11):437-440.
7. Sibbald B. Direct access to diagnostic services. *Br J Gen Pract.* 2009;59(562):e144-e145.
8. Walter F, Webster A, Scott S, Emery J. The Andersen Model of Total Patient Delay: A Systematic Review of Its Application in Cancer Diagnosis. *J Health Serv Res Policy.* 2012;17(2):110-118.
9. Rubin G, Berendsen A, Crawford SM, et al. The expanding role of primary care in cancer control. *Lancet Oncol.* 2015;16(12):1231-1272.
10. Stolper E, van Bokhoven M, Houben P, et al. The diagnostic role of gut feelings in general practice A focus group study of the concept and its determinants. *BMC Fam Pract.* 2009;10:17-17.
11. Birchall D. Primary care access to diagnostics: a paradigm shift. *Br J Radiol.* 2010;83(986):101-103.
12. Wilkes S, Murdoch A, Steen N, Wilsdon J, Rubin G. Open Access Tubal aSsessment for the initial management of infertility in general practice (the OATS trial): a pragmatic cluster randomised controlled trial. *Br J Gen Pract.* 2009;59(562):329-335.
13. DAMASK (Direct Access to Magnetic Resonance Imaging: Assessment for Suspect Knees) Trial Team. Effectiveness of GP access to magnetic resonance imaging of the knee: a randomised trial. *Br J Gen Pract.* 2008;58(556):e1-8; discussion 774.
14. Rubin GP, Saunders CL, Abel GA, McPhail S, Lyratzopoulos G, Neal RD. Impact of investigations in general practice on timeliness of referral for patients subsequently diagnosed with cancer: analysis of national primary care audit data. *Br J Cancer.* 2015;112:676.
15. Department of Health. *Improving Outcomes: A strategy for cancer.* London: Department of Health;2011.
16. Department of Health. *Direct Access to Diagnostic Tests for Cancer- Best Practice Referral Pathways for General Practitioners.* London: Department of Health;2012.
17. Richards MA. The National Awareness and Early Diagnosis Initiative in England: assembling the evidence. *Br J Cancer.* 2009;101(Suppl 2):S1-S4.
18. Hamilton W, Roobottom C. Early diagnosis of cancer by imaging: The primary care perspective. *Radiography.* 2012;18(1):5-8.
19. NICE. *Quality standard QS124 Suspected cancer.* National Institute for Health and Clinical Excellence; June 2016 2016.
20. Nicholson BD, Oke JL, Rose PW, Mant D. Variation in Direct Access to Tests to Investigate Cancer: A Survey of English General Practitioners. *PLoS ONE.* 2016;11(7):e0159725.
21. Nicholson BD, Tompson A, Jones N, et al. Direct access cancer testing in primary care: use and clinical outcomes. PROSPERO 2017 CRD42017056387. 2017; http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017056387.
22. *Stata Statistical Software: Release 14* [computer program]. College Station, TX: StataCorp LP; 2015.

23. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72(1):39.
24. Adang RP, Vismans JFJE, Talmon JL, Hasman A, Ambergen AW, Stockbrugger RW. The diagnostic outcome of upper gastrointestinal endoscopy: Are referral source and patient age determining factors? *Eur J Gastroenterol Hepatol*. 1994;6(4):329-335.
25. Aljebreen AM, Alswat K, Almadi MA. Appropriateness and diagnostic yield of upper gastrointestinal endoscopy in an open-access endoscopy system. *Saudi J Gastroenterol*. 2013;19(5):219-222.
26. Boulton-Jones JR, Follows MC, Mahmoud AA. Open-access endoscopy: Are age-based guidelines justified? An audit of experience of 1000 open-access endoscopies at a district general hospital. *Endoscopy*. 2003;35(1):68-73.
27. Broe M, Barry M, Patchett S, Hill ADK. Evaluating the clinical efficacy and cost effectiveness of direct access endoscopy. *Surgeon*. 2013;11(6):304-308.
28. Bytzer P, Hansen JM, Havelund T, Malchow-Moller A, Schaffalitzky de Muckadell OB. Predicting endoscopic diagnosis in the dyspeptic patient: the value of clinical judgement. *Eur J Gastroenterol Hepatol*. 1996;8(4):359-363.
29. Froehlich F, Burnand B, Pache I, et al. Overuse of upper gastrointestinal endoscopy in a country with open-access endoscopy: a prospective study in primary care. *Gastrointest Endosc*. 1997;45(1):13-19.
30. Gear MW, Barnes RJ. Endoscopic studies of dyspepsia in a general practice. *BMJ*. 1980;280(6223):1136-1137.
31. Gear MW, Wilkinson SP. Open-access upper alimentary endoscopy. *Br J Hosp Med*. 1989;41(5):438.
32. Goy JA, Herold E, Jenkins PJ, Colman JC, Russell DM. "Open-access" endoscopy for general practitioners. Experience of a private gastrointestinal clinic. *Med J Aust*. 1986;144(2):71-74.
33. Heaney A, Collins JS, Watson RG. Open access gastroscopy--3 year experience of a new service. *Ir J Med Sci*. 1998;167(3):136-137.
34. Holdstock G, Wiseman M, Loehry CA. Open-access endoscopy service for general practitioners. *BMJ*. 1979;1(6161):457-459.
35. Hungin AS. Use of an open-access gastroscopy service by a general practice: findings and subsequent specialist referral rate. *J R Coll Gen Pract*. 1987;37(297):170-171.
36. Johnston SD, Kirby J, Mackle E, Robinson TJ. A comparison of open access endoscopy and hospital-referred endoscopy in a district general hospital. *Ulster Med J*. 1999;68(2):73-78.
37. Jones R. Upper gastrointestinal endoscopy--a view from general practice. *J R Coll Gen Pract*. 1986;36(282):6-8.
38. Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut*. 2005;54(1):40-45.
39. Kerrigan DD, Brown SR, Hutchinson GH. Open access gastroscopy: too much to swallow? *BMJ*. 1990;300(6721):374-376.
40. Kolk H, Maarros H-I, Kull I, Labotkin K, Loivukene K, Mikelsaar M. Open access endoscopy in an epidemiological situation of high prevalence of *Helicobacter pylori* infection: applicability of the guidelines of the European Society for Primary Care Gastroenterology. *Fam Pract*. 2002;19(3):231-235.
41. Macintyre IMC. Open-access endoscopy for general practitioners. *Practitioner*. 1988;232(1445):348-351.
42. Mansi C, Mela GS, Savarino V, Mele MR, Valle F, Celle G. Open access endoscopy: a large-scale analysis of its use in dyspeptic patients. *J Clin Gastroenterol*. 1993;16(2):149-153; discussion 153-144.
43. O'Neill L, Quirke M, Hogan S, Eustace-Ryan AM, O'Regan P. Uncensored open access gastroscopy--limited resources--unlimited demand. *Ir J Med Sci*. 1998;167(2):89-91.

44. Oren R, Shulman-Manor O, Stalnikowicz R, Ackerman Z, Eliakim R. Open-access endoscopy of the upper gastrointestinal tract: is it indicated and efficient? Retrospective and prospective studies in an Israeli population. *Isr J Med Sci.* 1997;33(12):771-776.
45. Salo M, Collin P, Kyronpalo S, Rasmussen M, Huhtala H, Kaukinen K. Age, symptoms and upper gastrointestinal malignancy in primary care endoscopy. *Scand J Gastroenterol.* 2008;43(1):122-127.
46. Shah MY, Shah FY, Shah FY. Open access upper gastrointestinal endoscopy: a 2-year experience from 2001 to 2003. *Indian J Gastroenterol.* 2012;31(4):171-174.
47. Suvakovic Z, Bramble MG, Jones R, Wilson C, Idle N, Ryott J. Improving the detection rate of early gastric cancer requires more than open access gastroscopy: a five year study. *Gut.* 1997;41(3):308-313.
48. Tiwari I, Uddin W, Mazhar Z. Impact of open access endoscopy on early diagnosis, treatment and gastrointestinal radiology service. *Saudi J Gastroenterol.* 1997;3(3):130-132.
49. van Kerkhoven LAS, van Rijswijk SJ, van Rossum LGM, et al. Is there any association between referral indications for open-access upper gastrointestinal endoscopy and endoscopic findings? *Endoscopy.* 2007;39(6):502-506.
50. Wong BC, Chan CK, Wong KW, et al. Evaluation of a new referral system for the management of dyspepsia in Hong Kong: role of open-access upper endoscopy. *J Gastroenterol Hepatol.* 2000;15(11):1251-1256.
51. Arumugam PJ, Rao GN, West J, Foster ME, Haray PN. The impact of open access flexible sigmoidoscopy: a comparison of two services. *J R Coll of Surg Edinb.* 2000;45(6):366-368.
52. Balaguer F, Llach J, Castells A, et al. The European panel on the appropriateness of gastrointestinal endoscopy guidelines colonoscopy in an open-access endoscopy unit: a prospective study. *Aliment Pharmacol Ther.* 2005;21(5):609-613.
53. Basnyat PS, Gomez KF, West J, Davies PS, Foster ME. Nurse-led direct access endoscopy clinics: the future? *Surg Endosc.* 2002;16(1):166-169.
54. Donald IP, FitzGerald Frazer JS, Wilkinson SP. Sigmoidoscopy/proctoscopy service with open access to general practitioners. *BMJ.* 1985;290(6470):759-761.
55. Dougall A, Russell A, Rubin G, Ling J. Rethinking patient satisfaction: patient experiences of an open access flexible sigmoidoscopy service. *Soc Sci Med.* 2000;50(1):53-62.
56. Gimeno Garcia AZ, Gonzalez Y, Quintero E, et al. Clinical validation of the European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE) II criteria in an open-access unit: a prospective study. *Endoscopy.* 2012;44(1):32-37.
57. Hitchins CR, Lawn A, Whitehouse G, McFall MR. The straight to test endoscopy service for suspected colorectal cancer: meeting national targets but are we meeting our patients' expectations? *Int J Colorectal Dis.* 2014;16(8):616-619.
58. MacKenzie S, Norrie J, Vella M, et al. Randomized clinical trial comparing consultant-led or open access investigation for large bowel symptoms. *Br J Surg.* 2003;90(8):941-947.
59. Morini S, Hassan C, Meucci G, Toldi A, Zullo A, Minoli G. Diagnostic yield of open access colonoscopy according to appropriateness. *Gastrointest Endosc.* 2001;54(2):175-179.
60. Pullens HJM, Joosten M, Siersema PD, Brink MA. Open-access flexible sigmoidoscopy frequently leads to additional colonoscopy in symptomatic patients over 50 years. *J Gastrointest Liver Dis.* 2014;23(2):153-159.
61. Rainis T, Keren D, Goldstein O, Stermer E, Lavy A. Diagnostic yield and safety of colonoscopy in Israeli patients in an open access referral system. *J Clin Gastroenterol.* 2007;41(4):394-399.
62. Shakil AO, Ellis A, Faizallah R, Cochrane AM. Sigmoidoscopy service in a district general hospital: open-access versus hospital-referred. *Br J Clin Pract.* 1995;49(1):25-27.
63. Tate JJ, Royle GT. Open access colonoscopy for suspected colonic neoplasia. *Gut.* 1988;29(10):1322-1325.

64. Vellacott KD, Roe AM, Mortensen NJ. An evaluation of a direct access flexible fiberoptic sigmoidoscopy service. *Ann R Coll Surg Engl.* 1987;69(4):149-152.
65. Verma S, Gjaffer MH. Open-access versus hospital-initiated flexible sigmoidoscopy: a comparative audit of efficacy. *Eur J Gastroenterol Hepatol.* 2001;13(6):655-658.
66. Guldbrandt LM, Rasmussen TR, Rasmussen F, Vedsted P. Implementing direct access to low-dose computed tomography in general practice--method, adaption and outcome. *PLoS ONE.* 2014;9(11):e112162.
67. Simpson GC, Forbes K, Teasdale E, Tyagi A, Santosh C. Impact of GP direct-access computerised tomography for the investigation of chronic daily headache. *Br J Gen Pract.* 2010;60(581):897-901.
68. Thomas R, Cook A, Main G, Taylor T, Galizia Caruana E, Swingler R. Primary care access to computed tomography for chronic headache. *Br J Gen Pract.* 2010;60(575):426-430.
69. Connor SE, Banerjee AK. General practitioner requests for upper abdominal ultrasound: their effect on clinical outcome. *Br J Radiol.* 1998;71(850):1021-1025.
70. Ingeman ML, Ormstrup TE, Vedsted P. Direct-access to abdominal ultrasonic investigation from general practice-the role in earlier cancer diagnosis. *Fam Pract.* 2015;32(2):205-210.
71. Skillern LH, Pearce JM. An audit of general practitioner requests for pelvic ultrasound: analysis of referral patterns and outcome. *Br J Obstet Gynaecol.* 1993;100(12):1131-1135.
72. Apthorp LA, Daly CA, Morrison ID, Field S. Direct access MRI for general practitioners--influence on patient management. *Clin Radiol.* 1998;53(1):58-60.
73. Gough-Palmer AL, Burnett C, Gedroyc WM. Open access to MRI for general practitioners: 12 years' experience at one institution -- a retrospective analysis. *Br J Radiol.* 2009;82(980):687-690.
74. Taylor TR, Evangelou N, Porter H, Lenthall R. Primary care direct access MRI for the investigation of chronic headache. *Clin Radiol.* 2012;67(1):24-27.
75. Lim WS, Macfarlane JT, Deegan PC, Manhire A, Holmes WF, Baldwin DR. How do general practitioners respond to reports of abnormal chest X-rays? *J R Soc Med.* 1999;92(9):446-449.
76. Smith GL. An evaluation of direct access radiology in general practice. *J R Coll Gen Pract.* 1979;29(206):539-545.
77. Hughes-Anderson W, Rankin SL, House J, Aitken J, Heath D, House AK. Open access endoscopy in rural and remote Western Australia: does it work? *ANZ J Surg.* 2002;72(10):699-703.
78. Mahajan RJ, Barthel JS, Marshall JB. Appropriateness of referrals for open-access endoscopy. How do physicians in different medical specialties do? *Arch Intern Med.* 1996;156(18):2065-2069.
79. Curtin JJ, Sampson MA. Need for open access non-screening mammography in a hospital with a specialist breast clinic service. *BMJ.* 1992;304(6826):549-551.
80. Salih A, Webb WM, Bates T. Does open-access mammography and ultrasound delay the diagnosis of breast cancer? *Breast.* 1999;8(3):129-132.
81. White PM, Halliday-Pegg JC, Collie DA. Erratum: Open access neuroimaging for general practitioners - Diagnostic yield and influence, on patient management. *Br J Gen Pract.* 2002;52(477):331.
82. White PM, Halliday-Pegg JC, Collie DA. Open access neuroimaging for general practitioners--diagnostic yield and influence on patient management. *Br J Gen Pract.* 2002;52(474):33-35.
83. de Vries CJH, Wieringa-de Waard M, Bindels PJE, Ankum WM. Open-access transvaginal sonography in women of reproductive age with abnormal vaginal bleeding: a descriptive study in general practice. *Br J Gen Pract.* 2011;61(587):e340-346.
84. Barton E, Gallagher S, Flower CD, Hanka R, King RH, Sherwood T. Influence on patient management of general practitioner direct access to radiological services. *Br J Radiol.* 1987;60(717):893-896.

85. Eden B, Davies, A. *Primary Care Cancer Audit: Greater Midlands Cancer Network*. National Cancer Action Team and Royal College of General Practitioners;2010.
86. Cecamore C, Savino A, Salvatore R, et al. Clinical practice guidelines: what they are, why we need them and how they should be developed through rigorous evaluation. *Eur J Pediatr*. 2011;170(7):831-836.
87. O'Sullivan JW, Albasri A, Nicholson BD, et al. Overtesting and undertesting in primary care: a systematic review and meta-analysis. *BMJ Open*. 2018;8(2).
88. Nicholson BD, Mant D, Neal RD, et al. International variation in adherence to referral guidelines for suspected cancer: a secondary analysis of survey data. *Br J Gen Pract*. 2016;66(643):e106-113.
89. Wilkes S, Rubin G, Crosland A, Hall N, Murdoch A. Patient and professional views of open access hysterosalpingography for the initial management of infertility in primary care. *Br J Gen Pract*. 2009;59(562):336-342.
90. Meechan D, Gildea C, Hollingworth L, Richards MA, Riley D, Rubin G. Variation in use of the 2-week referral pathway for suspected cancer: a cross-sectional analysis. *Br J Gen Pract*. 2012;62(602):e590-597.
91. Donnelly C, Hart N, McCrorie AD, et al. Knowledge or noise? Making sense of General Practitioners' and Consultant use of 2-week-wait referrals for suspected cancer. *Br J Cancer*. 2017;117(5):597-603.
92. Zhou Y, Abel GA, Hamilton W, et al. Diagnosis of cancer as an emergency: a critical review of current evidence. *Nat Rev Clin Oncol*. 2017;14(1):45-56.
93. Zhou Y, Mendonca SC, Abel GA, et al. Variation in 'fast-track' referrals for suspected cancer by patient characteristic and cancer diagnosis: evidence from 670 000 patients with cancers of 35 different sites. *Br J Cancer*. 2018;118(1):24-31.
94. Hamilton W, Walter FM, Rubin G, Neal RD. Improving early diagnosis of symptomatic cancer. *Nat Rev Clin Oncol*. 2016;13(12):740-749.
95. NICE. *Suspected cancer: recognition and referral (NG12)*. National Institute for Health and Care Excellence;2015.
96. Koo MM, Hamilton W, Walter FM, Rubin GP, Lyratzopoulos G. Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. *Neoplasia*. 2018;20(2):165-174.
97. Weller D, Vedsted P, Rubin G, et al. The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer*. 2012;106(7):1262-1267.
98. Rubin GP, Saunders CL, Abel GA, McPhail S, Lyratzopoulos G, Neal RD. Impact of investigations in general practice on timeliness of referral for patients subsequently diagnosed with cancer: analysis of national primary care audit data. *Br J Cancer*. 2015;112(4):676-687.
99. Lis CG, Rodeghier M, Gupta D. Distribution and determinants of patient satisfaction in oncology: A review of the literature. *Patient Prefer Adherence*. 2009;3:287-304.
100. Gesell SB, Gregory N. Identifying priority actions for improving patient satisfaction with outpatient cancer care. *J Nurs Care Qual*. 2004;19(3):226-233.
101. Vedsted P, Olesen F. A differentiated approach to referrals from general practice to support early cancer diagnosis - the Danish three-legged strategy. *Br J Cancer*. 2015;112 Suppl 1:S65-69.
102. Nicholson BD, Oke J, Friedemann Smith C, et al. The Suspected CANcer (SCAN) pathway: protocol for evaluating a new standard of care for patients with non-specific symptoms of cancer. *BMJ Open*. 2018;8(1).
103. Fuller E, Fitzgerald K, Hiom S. Accelerate, Coordinate, Evaluate Programme: a new approach to cancer diagnosis. *Br J Gen Pract*. 2016;66(645):176-177.