

BJGP Commentary – commissioned - revision.

Title: “Testing times: the elusive diagnosis of cancer”

Authors: Nicholson BD¹, Perera R¹, Thompson MJ².

¹Nuffield Department of Primary Care Health Sciences, University of Oxford, UK OX2 6GG

Brian D Nicholson, Clinical Researcher, brian.nicholson@phc.ox.ac.uk

Rafael Perera, Professor of Medical Statistics, rafael.perera@phc.ox.ac.uk

²Department of Family Medicine, University of Washington, US

Matthew J Thompson, Professor of Family Medicine, mjt@uw.edu

Correspondence to: Dr Brian D Nicholson
University of Oxford,
Nuffield Department of Primary Care Health Sciences,
Radcliffe Observatory Quarter, Oxford, OX2 6GG.

e-mail: brian.nicholson@phc.ox.ac.uk

In this month's BJGP, Just and colleagues question PSA testing in men with lower urinary tract symptoms (LUTS) (Just Nov 2018 BJGP). Like others, they propose that the majority of cancers detected will be indolent and unrelated to the LUTS, basing their judgement on PSA screening trial data and general population LUTS surveys (1). Danish primary care data, not included by Just and colleagues, indicates that indolent prostate cancer detection increases as PSA testing increases without a corresponding change in advanced disease detection or mortality (2). Over half of UK hospitals now use multiparametric-MRI to protect men from the harms of unnecessary biopsy and treatment for indolent prostate cancer (3). The important question Just and colleagues raise is not *which* test should be performed once a patient is referred for suspected prostate cancer, but rather *should* patients with non-specific symptoms be tested in primary care and are there harms of testing them?

The myriad of urgent referral pathways, complex referral criteria, and regional variations in test and specialist access have created a complex bureaucracy for UK cancer diagnosis that has favoured patients with "alarm" symptoms. Within this context, cancers with non-specific symptom signatures such as myeloma and pancreatic cancer have become associated with longer intervals between presentation and diagnosis, they are less likely to be diagnosed via urgent GP referral and more likely to be diagnosed as an emergency (4, 5).

But general practice is dominated by common non-specific cancer symptoms such as LUTS, abdominal pain, back pain, and fatigue. Like cancer, these symptoms increase in incidence with age and comorbidity. Our conundrum as specialist generalists has always been how to efficiently differentiate benign or self-limiting causes from more serious diseases, such as cancer, without subjecting patients to the harms of unnecessary testing or overburdening secondary care. Given the high prevalence of non-specific symptoms and the low prevalence of cancer in primary care, different approaches are necessary for patients with these symptoms.

Ruling out cancer not ruling in cancer.

As GPs we are familiar with using tests to triage patients into further cancer investigation rather than away from it. Low haemoglobin, for example, rules-in patients for urgent colorectal investigation but a normal haemoglobin does not rule it out (6). Raised platelets are of interest to rule-in patients for investigation across a number of cancers, but normal

platelets do not rule-out cancer (7). There are surprisingly few simple triage tests or test combinations that GPs can use to rule-out cancer and avoid the need for further investigation, but the evidence is building.

The combination of normal inflammatory marker (ESR or Plasma Viscosity) and normal haemoglobin confidently rules-out myeloma in patients tested in primary care without necessitating the GP to think myeloma when requesting the test (8). FIT shows promise as a rule-out test for colorectal cancer in patients with non-specific abdominal symptoms, but access to FIT (a cheap and simple test) remains patchy in the UK, its suggested use as both a rule-in and rule-out test is confusing (von Wagner NOV 2018 BJGP), and the optimum analytical threshold to minimise false negatives in primary care is unclear (9).

Transferring testing strategies from settings with higher (secondary care) or lower (screening) cancer prevalence should be avoided as this leads to inaccurate predictions of test performance and (10). In cancer screening, for example, testing is calibrated to minimise referrals for false positive results rather than minimising false negatives. Continued analysis of primary care data should focus on identifying clusters of symptomatic and at-risk patients for whom a cancer rule-out strategy could be confidently employed. It is unlikely, though, that currently available blood tests will advance GP's rule-out ability significantly enough, and uncertainty for many cancers will remain.

Explaining symptoms not just ruling in cancer.

There is limited but increasing evidence for a move away from linear pathways to rule-in individual cancers, to more sophisticated multidisciplinary diagnostic centres (MDCs) equipped to explain the cause of non-specific symptoms. As complex healthcare interventions, MDCs intend to avoid multiple cancer site specific referrals for a heterogeneous group of patients. Reports from Danish MDCs show that cancer is diagnosed following 11% to 21% of referrals, exceeding the 8% achieved by the UK's 2-week-wait pathways, and serious other disease is diagnosed in 22% to 34% of patients (11).

A range of MDC models are under evaluation in the UK, some with stringent pre-referral triage testing (akin to the Danish MDCs), others with an MDC triage step following referral and prior to investigation, and some with up-front imaging then triage. MDCs have the potential to be a step beyond "one-stop-shop" clinics as multiple assessments and

investigations may occur in series over time and across multiple body sites, and serious or non-serious disease may be diagnosed (12). MDCs that retain responsibility for the patient until their symptoms are explained and managed are distinct from GP direct access (cancer) testing which leaves these actions to the GP (13).

After years of investment in cancer site-specific urgent referral pathways, this change in thinking appeals to generalists and specialists interested in explaining symptom causation and frustrated with subspecialist silos restricted to one cancer site. But for these MDCs to function, their positioning must become established within local healthcare systems and test access and patient flow must be liberated to allow cross-speciality referrals and shared multidisciplinary clinical responsibility. Ongoing evaluation of the optimal constellation of patient characteristics, symptoms, and pre-referral triage testing will facilitate adoption by ensuring that MDCs only accept patients who will benefit from intense investigation. One might also ask whether MDCs are filling a gap that GPs themselves could fill (given greater test access and more resources such as longer consultation times) by managing the diagnostic uncertainty inherent in primary care.

Reassuringly normal?

Overuse of diagnostic testing occurs when the potential harms of testing outweigh the potential benefits. This overuse is regarded a driver of overdiagnosis in primary care, but is difficult to quantify (14). In the LUTS example, more testing led to more men being diagnosed with indolent prostate cancer *and* more men being given the all clear. Unlike screening, a negative test in the presence of burdensome symptoms may be reassuring and reduce future primary care attendances. The counter to this is that a diagnosed cancer (that may otherwise have not caused problems) may lead to unnecessary treatment, further testing, and the psychological consequences of being given a disease label (15). We don't fully understand how these trade-offs play out in populations of symptomatic patients.

The bureaucracy that surrounds cancer diagnosis in the UK is unfamiliar to US Family Physicians (FPs). For cancers without a screening programme, FPs do not refer into cancer pathways but for a long time have had relatively liberal access to cancer investigations (particularly imaging), limited mainly by healthcare insurance coverage. In the largely fee for service model, subspecialists in the US have incentives to see patients and investigate.

However, diagnostic delays of patients with symptomatic cancer still occur. International comparisons between health systems with differing models of test access could help us to better understand where the line between over- and under-investigation lies, especially in relation to the many incidentally detected findings that modern imaging tests reveal when testing primary care patients with non-specific symptoms.

Getting the balance right.

You might ask, then, where does a GP's expertise in clinical reasoning and diagnosis fit into a healthcare system being slowly reconfigured into a tangled web of algorithmic guidelines of known risk factors and clinical features? Clearly, testing or referring every patient presenting with non-specific symptoms is not appropriate and we should feel justified to tolerate risk to differing extents. Without tests to hand, our clinical judgement (sometimes even a reassuring gut feeling) will mean we don't test, we watch-and-wait, or we test then monitor in primary care. These patients require appropriate and robust safety-netting but, as pressures of time and workload increase in primary care, GPs report selecting patients perceived to be at higher risk for closer follow-up (16). When safety-netting patients with non-specific symptoms we should be mindful to discuss the implications of our chosen testing strategy including, as Just and colleagues point out, the potential for overdiagnosis.

Funding

BDN is funded by National Institute for Health Research (NIHR) Doctoral Research Fellowship (DRF-2015-08-18). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health. MJT receives funding from the multi-institutional CanTest Research Collaborative funded by a Cancer Research UK Population Research Catalyst award (C8640/A23385).

References

1. Ostero IJJ, Brodersen J. Do men with lower urinary tract symptoms have an increased risk of advanced prostate cancer? *BMJ (Clinical research ed)*. 2018;361:k1202.
2. Hjertholm P, Fenger-Gron M, Vestergaard M, Christensen MB, Borre M, Moller H, et al. Variation in general practice prostate-specific antigen testing and prostate cancer outcomes: an ecological study. *International journal of cancer*. 2015;136(2):435-42.
3. Roland M, Neal D, Buckley R. What should doctors say to men asking for a PSA test? *BMJ (Clinical research ed)*. 2018;362:k3702.
4. Koo MM, Hamilton W, Walter FM, Rubin GP, Lyratzopoulos G. Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. *Neoplasia (New York, NY)*. 2018;20(2):165-74.
5. Zhou Y, Mendonca SC, Abel GA, Hamilton W, Walter FM, Johnson S, 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. *British journal of cancer*. 2018;118(1):24-31.
6. Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. *British journal of cancer*. 2008;98(2):323-7.
7. Bailey SE, Ukoumunne OC, Shephard EA, Hamilton W. Clinical relevance of thrombocytosis in primary care: a prospective cohort study of cancer incidence using English electronic medical records and cancer registry data. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2017;67(659):e405-e13.
8. Koshiaris C, Van den Bruel A, Oke JL, Nicholson BD, Shephard E, Braddick M, et al. Early detection of multiple myeloma in primary care using blood tests: a case-control study in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(674):e586-e93.
9. Juul JS, Hornung N, Andersen B, Laurberg S, Olesen F, Vedsted P. The value of using the faecal immunochemical test in general practice on patients presenting with non-alarm symptoms of colorectal cancer. *British journal of cancer*. 2018;119(4):471-9.
10. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *BMJ (Clinical research ed)*. 2016;353:i3139.
11. Forster AS, Renzi C, Lyratzopoulos G. Diagnosing cancer in patients with 'non-alarm' symptoms: Learning from diagnostic care innovations in Denmark. *Cancer epidemiology*. 2018;54:101-3.
12. Friedemann Smith C, Tompson A, Holtman GA, Bankhead C, Gleeson F, Lasserson D, et al. General practitioner referrals to one-stop clinics for symptoms that could be indicative of cancer: a systematic review of use and clinical outcomes. *Family practice*. 2018.
13. Smith CF, Tompson AC, Jones N, Brewin J, Spencer EA, Bankhead CR, et al. Direct access cancer testing in primary care: a systematic review of use and clinical outcomes. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(674):e594-e603.

14. Kale MS, Korenstein D. Overdiagnosis in primary care: framing the problem and finding solutions. *BMJ (Clinical research ed)*. 2018;362:k2820.
15. Nickel B, Moynihan R, Barratt A, Brito JP, McCaffery K. Renaming low risk conditions labelled as cancer. *BMJ (Clinical research ed)*. 2018;362:k3322.
16. Evans J, Ziebland S, MacArtney JJ, Bankhead CR, Rose PW, Nicholson BD. GPs' understanding and practice of safety netting for potential cancer presentations: a qualitative study in primary care. *The British journal of general practice : the journal of the Royal College of General Practitioners*. 2018;68(672):e505-e11.