Editorials

The elusive diagnosis of cancer:

testing times

In this issue of the *BJGP*, Just and colleagues question PSA testing in men with lower urinary tract symptoms (LUTS).[1] 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.[2] 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.[3] Over half of UK hospitals now use multiparametric-MRI to protect men from the harms of unnecessary biopsy and treatment for indolent prostate cancer.[4] 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.[5,6]

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.[7] Raised platelets are of interest to rule-in patients for investigation across a number of cancers, but normal platelets do not rule-out cancer.[8] 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.

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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.[9] Faecal immunochemical testing (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,[10] and the optimum analytical threshold to minimise false negatives in primary care is unclear.[11]

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.[12] 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 laboratory tests will advance GPs' 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 referral pathways, and serious other disease is diagnosed in 22% to 34% of patients.[13]

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.[14] 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.[15]

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 as a driver of overdiagnosis in primary care, but is difficult to quantify.[16] 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.[17] 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 including 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.[18] 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[1] point out, the potential for overdiagnosis.

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