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Abstract | Much time, effort and investment goes into the diagnosis of symptomatic cancer, with the expectation that this approach brings clinical benefits. This investment of resources has been particularly noticeable in the UK, which has, for several years, appeared near the bottom of international league tables for cancer survival in economically developed countries. This Review examines expedited diagnosis of cancer from four perspectives. The first examines the potential for benefits from expedited diagnosis of symptomatic cancer. Limited evidence from clinical trials is available, but the considerable observational evidence suggests benefits can be obtained from this approach. The second perspective considers how expedited diagnosis can be achieved. We concentrate on data from the UK, where extensive awareness campaigns have been conducted, and initiatives in primary care, including clinical decision support, have all occurred during a period of considerable national policy change. The third section considers the most appropriate patients for cancer investigations, and the possible community settings for this. UK national guidance for selection of patients for investigation is discussed. Finally, the health economics of the subject are reviewed, although few studies provide definitive evidence on this topic.

In all developed countries, much time, effort and finance is spent on the diagnosis of cancer.[1] This expenditure is based on the assumption that diagnosis of cancer and, in particular, early diagnosis of cancer, is beneficial. Cancer can be diagnosed before it generates symptoms. Early diagnosis is generally achieved using formal screening, or surveillance of those deemed to be at a high risk of

developing cancer, such as patients with longstanding inflammatory bowel disease or Barrett's oesophagus; although, some cancers are identified serendipitously when a suspicion of cancer is not the primary reason for the clinical examination. Screening and surveillance are not considered further in this Review, other than to remark that the successful promotion of screening programmes has strengthened public perception that the earlier that a cancer is diagnosed, the better the outcomes will be.

Before reviewing the evidence regarding how the diagnosis of symptomatic cancer can be improved, briefly reviewing why diagnosis of symptomatic cancer is necessary and should be improved is important. Only by being explicit about what we are hoping to achieve can we design services to meet our needs optimally. Thus, this review has four parts: the benefits of expedited symptomatic diagnosis (the 'why'); achieving expedited diagnosis of cancer (the 'how'); patient and population aspects of cancer diagnosis (the 'who and where'); and the health economics of expedited cancer diagnosis (the 'how much'). This review focusses largely on early diagnosis of symptomatic cancer in the UK, although, published data from studies conducted in other countries is referred to where relevant

[H1] Benefits of expedited symptomatic diagnosis

[H2] Types of evidence

The case for expedited diagnosis of cancer is built upon many individual pieces of largely observational evidence, with several potential biases (BOX 1). Few randomized trials have been conducted in this area, mainly because offering potential participants the possibility of an arm that appears to delay the diagnosis of cancer is difficult. The perception that rapid diagnosis of cancer is essential means that patients are unlikely to participate, making ethical approval difficult or impossible. However, trials comparing different diagnostic modalities can be performed. To date, these have mainly been conducted in the setting of secondary care: one example is provided by the SIGGAR trial, which was designed to compare the effectiveness of CT colonography versus that of colonoscopy in individuals with symptoms suggestive of colorectal cancer.[2] An alternative approach is to perform trials of cancer diagnostics in a community care setting, and a number of trials using this approach now have results available, or are in progress. These cover a variety of interventions: promoting earlier presentation of potential cancer symptoms[3-7]; the use of new technologies in the assessment of pigmented skin lesions[8]; the use of computerized decision-support tools in the diagnosis of cancer in primary care [9]; cancer-specific education for general practitioners (GPs)[5, 10];

direct access to low-dose CT for the early detection of lung cancer in primary care[11]; and lower symptom thresholds for urgent use of chest radiography[12]. Thus far, no trial has included a sufficiently large cohort to address the issue of whether or not expedited cancer diagnosis in primary care is beneficial, in terms of either mortality or morbidity.

[H2] Survival and diagnostic activity

Cancer survival provides the main rationale for expedited cancer diagnosis. This rationale is enshrined in numerous governmental publications internationally [13, 14] Among developed countries, the UK and Denmark have regularly appeared at the bottom of tables ranking the survival of patients with cancer.[15-18] These poor outcomes, relative to those of similar patients in other developed countries, are considered to arise in a large part from differences in the availability of, and willingness to use cancer diagnostic investigations, perhaps augmented by a decreased willingness of patients in England to seek medical care compared with those in Europe.[19] Investigators in one study reported an inverse relationship between cancer survival rates and the degree of separation of primary care from specialist care in health-care systems (the so-called 'gatekeeper role' of primary care, whereby access to specialist care requires a referral from primary care).[20] Gatekeeping is a common feature of health-care systems that deliver better overall population outcomes;[21] although, this counterintuitive finding of an association with poor cancer survival might be explained by the relative unwillingness of GPs to test for cancer when the risk of a hitherto undiagnosed cancer is small. This perception is supported by an international vignette study, across primary care physicians practicing in one of 12 different geographical areas, in which investigators asked GPs about their management of fictitious patients with clinical scenarios representing a small risk of cancer. This revealed a highly significant relationship between the willingness of the GP to investigate the possible cancer and higher national survival rates of patients with that cancer (P <0.05 for four of the five scenarios).[22] This relationship is also seen at a general practice level. In a study of upper gastrointestinal endoscopy rates in England, patients undergoing clinical examinations in general practices ranked in the highest third for endoscopy rates (mean of 12.9 procedures per 1,000 adults per year) had superior gastro-oesophageal cancer outcomes, including better overall survival (OR 1 versus 1.14, 95% CI 1.06–1.22; P <0.001) and fewer emergency admissions (OR 1 versus 1.53, 95% CI 1.42–1.65; P <0.001) than those undergoing examinations at practices in the lower third for endoscopy rates (mean of 4.4 procedures per 1000 adults per year) [23] Conversely, results of a study using electronic records of primary care data to investigate outcomes of patients with lung cancer revealed an association between higher general practice chest radiography rates and increased odds of early death from lung cancer when comparing the highest (≥5.34 chest examination per 100 of

population) and lowest (1–2.73 examination per 100 of population) quartiles for chest radiography (OR 0.85; 95% CI 0.75–0.97).[24] Despite this positive finding, authors of this study did not report survival figures, and the increased mortality might well reflect the presence of ascertainment bias (see BOX 1). However, a 2012 report from Leeds, following extensive campaigning to increase chest radiography rates, has shown a reduction in the percentage of patients with lung cancer presenting as an emergency from 33% in 2008–2010 to 28% in 2011 (P = 0.035), with a small improvement in 180-day mortality.[25]

Considerable variation exists in the use of cancer testing in the UK; for example, in 2012–2013 a 3.6-fold difference in CT use was observed between primary care trusts with the highest and lowest CT use, and a 3.1-fold difference in use of non-obstetric ultrasonography among these same trusts. Similar variations are seen for endoscopy procedures.[26] Considerable variations also exist between general practices in terms of referrals for suspected cancer, with a threefold difference in referral rates between practices in the lowest and highest deciles for referral rate.[27] In a study of 8,049 practices in England and 215,284 patients with cancer, those who were registered with general practices with the lowest use of the urgent cancer referral pathway had excess mortality, with a hazard ratio of 1.07 (95% confidence interval 1.05 to 1.08), when compared to the intermediate use group.[28] This difference equates to a clinically significant difference of 5–6 percentage points in cumulative cancer mortality at 4 years between patients registered with low-referring practices, compared with high-referring practices.

All of the observational studies described in this section support the hypothesis that increased use of cancer diagnostics increases the survival of patients with cancer,[29] and they underpinned one of the six recommendations of England's Independent Cancer Taskforce – reflective of a national ambition to achieve earlier diagnosis.[30] This report emphasised the need for both faster, and less restrictive investigative testing. The Task Force proposed that, by 2020, 95% of patients referred for further testing by a GP should receive a definitive investigation, and the result should be communicated to the patient within 4 weeks of the original consultation. However, patients with one of six common cancers who were offered initial diagnostic testing in primary care had a median time to referral of 16 days, compared with a median of zero days for those not offered primary care investigation. This data suggests that, if investigations of suspected cancer are to be extensively used by primary care physicians, then diagnostic services need to be more responsive than is currently the case.[31] Furthermore, delivery of cancer investigations has important safety, training, and quality components, which have to be maintained with any transfer of clinical responsibility for the patient.

[H2] Survival and time to diagnosis

The relationship between time to diagnosis and survival is complex and differs between cancer types. Time to diagnosis incorporates three elements: the patient interval, which begins when the patient first detects a bodily change; the primary care interval, which begins with first presentation to primary care; and the secondary care interval, which begins with referral to a specialist.[32, 33] The diagnostic interval is the sum of the latter two elements.

A clear relationship between times to diagnosis >3 months and worse survival, relative to those that are diagnosed within 3 months of initial presentation (OR 1.47; 95% CI 1.42–1.53) has been demonstrated in a landmark systematic review of 87 studies of patients with breast cancer.[34] This review did not separate the constituent parts of the time to diagnosis. Studies of the diagnostic interval and its association with survival in patients with colorectal cancer have shown a J-curve, with the most favourable 3-year survival observed in patients having a diagnostic interval of 28 days.[35, 36] This finding has been replicated using several international datasets.[37] After 28 days, the slope of the survival curve approximates to a 4% worsening of patients' survival outcomes per month of additional diagnostic interval.[35] Investigators in these studies measured survival from the date of diagnosis in order to eliminate lead-time bias (BOX 1). Patients with colorectal cancers diagnosed very rapidly have poor survival, either owing to aggressive disease presenting with obvious symptoms, thus making diagnosis easier relative to that of patients with less-aggressive disease, or because these patients are more likely to present as an emergency.[38] Survival also decreases as the diagnostic interval increases beyond 28 days owing to the growth of the tumour over time.[39] Patients with cancers located in other sites might well also have a J-shaped curve for the association between time to diagnosis and survival, but the number and methodological strength of reports available for any other form of cancer is substantially lower than that available on patients with colorectal cancer.[39, 40]

[H2] Morbidity and time to diagnosis

Reduced morbidity, and particularly improved symptom relief, is an important possible benefit of expedited diagnosis; although this aspect has received less attention than survival.[41] Diagnostic delay is assumed to cause distress, as suggested by data from a small study of 263 patients in Denmark, in which a significant association was observed between reported psychological distress and time to diagnostic delay (P <0.005), but this result has not been replicated.[42] Investigators in another study

reported no association between patient satisfaction and symptom duration in patients with colorectal cancer,[43] but elsewhere, data from a different study revealed longer total diagnostic intervals to be associated with poorer quality of life than that of patients whose disease was diagnosed after a shorter interval, as assessed using the EORTC-C30 scale in patients with endometrial (P <0.01) or ovarian cancers (P <0.04).[44] Separating the expected distress of receiving a diagnosis of cancer from that associated with any additional anxiety caused by diagnostic delay, whether perceived or real, is often difficult.[42, 45, 46] Initial distress, as measured on an emotional distress scale, resulting from the discovery of a symptom of breast cancer is negatively correlated with delay in presentation to the health-care system (correlation coefficient -0.29, P =0.01) .[47] This association might be complicated by the tendency of clinicians to investigate patients with anxiety or depression less rapidly than those without such symptoms, as has been demonstrated in patients with colorectal cancer.[48] In a Delphi technique based study published in 2015, the authors ranked the common cancers by how much benefit was to be expected from expedited diagnosis, with breast cancer ranked as the most likely, and pancreatic cancer the least.[41] Although this study focussed on survival benefits, the study also demonstrated that participants believed there to be a morbidity benefit of early diagnosis of all types of cancers. Reductions in morbidity from expedited diagnosis might also accrue owing to a reduction in the incidence of emergency admissions from cancer.

[H1] Achieving expedited diagnosis

[H2] Pre-presentation factors

For most cancers, the time between first noticing a potential cancer symptom and presenting to the health-care system is frequently the greatest proportion of the total time to diagnosis.[49] Pre-presentational times differ between cancers: in a study of 10,297 patients with cancer in England conducted between 2009–2010, patients with oropharyngeal (34%) or oesophageal cancers (39%) were most likely to present ≥15 days after noticing an initial symptom.[50] A study of 2,371 patients, with results published in 2014, defined delay as three months or longer and demonstrated that patients with prostate (44%) or rectal (37%) cancers are the most likely to delay consultation, although this study omitted data from patients with oesophageal cancers.[51] Another cohort study of 963 people in England recruited with symptoms of lung cancer before diagnosis showed that having multiple first symptoms is common (only 49.3% of the cohort had a single symptom), that symptoms evolve over time, and that people subsequently diagnosed with cancer and those diagnosed with non-malignant conditions present with similar symptoms.[52]

To expedite diagnosis of symptomatic cancer, understanding how patients recognize possible symptoms of cancer and the decisions they make regarding help-seeking is essential. The conceptual framework for the pre-presentational interval is now well established,[53, 54] and emphasizes the influence of patient, health-care system and disease-related factors. However, the precise barriers to, and facilitators of entry to health-care systems for each patient with symptoms of cancer are less well-understood. Some 'alarm' symptoms, such as a breast lump, are usually easily recognized as possible cancer, while recognition of other symptoms, such as fatigue, is less simple. Symptom appraisal can be influenced by: the 'normalization' of common symptoms (where they are perceived as an expected part of life, particularly during a liminal phase such as menopause[55]); the failure to interpret the symptom(s) as requiring medical attention; and the difficulties in recognizing new symptoms in the presence of other comorbidities.[56-58] Symptom appraisal and help-seeking are also influenced by psychosocial and cultural contexts, including a fear of stigma, cancer diagnosis and treatment, and fatalism, as well as practical barriers to help-seeking, such as a lack of access to healthcare and lack of sufficient time and/or transport to attend a consultation.[59]

[H2] Symptom awareness campaigns

Public campaigns aiming to raise awareness of the symptoms of cancer, and to promote help-seeking, might educate and empower people to hasten earlier presentation.[60] Some of these campaigns have shown promise, although few report long-term outcomes.[60] Public Health England's 'Be Clear on Cancer'[147] campaigns have led to increased public awareness of the headline symptoms of lung (recall of 'persistent cough' or 'hoarseness' by 18% versus 26% of patients in 2010 and 2012, respectively; P <0.001) and bowel cancer (change in 'bowel and/or bladder habits' increased from 21% to 43%; P <0.01),[61] increases in attendances for symptoms by those aged ≥50 years (29% and 63% increase versus the same weeks in 2011 for the bowel and lung campaigns, respectively,[62] and more cancers diagnosed (9.1% increase; P <0.001), with a small, but significant, increase in the proportion of lung cancers diagnosed at a stage amenable to surgical resection (stage I tumours from 14.1% to 17.3% of the cohort; P <0.001 and stage IV tumours from 52.9% to 49% of the cohort; P <0.001).[63] Considerable resources were expended in evaluating the outcomes of this campaign, although, to date, few peer-reviewed publications have resulted from this expenditure. Data from the 'I'll tackle it soon' UK study showed that a combined public awareness campaign and GP education programme for lung cancer led to increased chest X-ray referrals by 20%, and lung cancer diagnoses by 27%, although most of these additional cancers were of an advanced stage.[64 24]

The 'HeadSmart: Be Brain Tumour Aware'[148] charity campaign, launched in 2011 across the UK as a quality improvement strategy for expediting the diagnosis of brain tumours in children, employed

guidelines for professionals alongside public awareness campaigns. This campaign has been highly effective, with considerable reductions in total diagnostic interval (median 9.1 to 6.7 weeks) and in the median interval from first medical contact to CNS imaging (from 3.3 to 1.4 weeks; P <0.009).[65, 66] Whether raising awareness of individual symptoms, or symptom combinations, of other less common cancers will also promote more timely help-seeking currently remains unclear.[5] Cancer awareness campaigns also need to address their target audience's health literacy, with lower health literacy strongly associated with disadvantaged socio-economic and ethnic minority groups.[67] Linking information on awareness with other healthcare activities might improve patients' awareness: data from a trial that involved offering information about symptoms of breast cancer to women attending breast screening revealed an increase in the proportion of women who were breast cancer aware from 6%, to 21% (OR 8.1, 95% CI 2.7–25) when assessed two years later using a validated questionnaire.[7]

Few studies of interventions promoting earlier presentation to health-care systems, which specifically target individuals at an increased risk of cancer, have been conducted. Data from a Scottish trial with a cohort of people at a higher risk of lung cancer (smokers and former smokers) provides preliminary evidence of altered consulting patterns in this population, in response to an intervention comprising a single consultation session with a nurse and provision of a self-help manual on lung cancer symptoms;[4] interestingly, in order to improve patient engagement, smoking cessation was not mentioned. Evidence is now required on the effect of this intervention on clinical outcomes as well as consulting behaviour, and on the generalisability of similar interventions to other at-risk populations.

As well as formal awareness campaigns, information on all aspects of cancer is now freely available on the internet. Cancer-related searches for information increased during a breast cancer awareness campaign.[68] Potentially, improvements in diagnosis could be observed in a better-informed population, thus improving the survival of those diagnosed with a variety of different cancers.

[H2] In primary care

In most countries, symptomatic patients initially present to primary care, although some health-care systems allow direct access to specialist care. The clinician must first think of cancer as a possibility, and must then decide whether testing is required or not. The first stage of a diagnosis differs greatly between cancer types;[69] some are relatively simple, such as checking for the presence of a breast lump or a pigmented skin lesion. With these symptoms, the doctor, and usually the patient, will generally ensure cancer is explicitly addressed in the consultation. Other cancers are notoriously

difficult to diagnose conclusively, particularly when the symptoms are common features of benign conditions. For example, backache is the most frequent symptom of myeloma, although only one in a 1,000 adult patients reporting backache will transpire to have myeloma.[70] The risk of a brain tumour with new-onset headache is similar.[71] These 'difficult to diagnose' cancers are characterized by having three or more primary care attendances before diagnosis; from 10.1% of patients with breast cancer, to 50.6% of those with multiple myeloma,[72] with high proportions presenting as an emergency with a complication of their cancer (including 62% of patients with tumours of the CNS),[38, 72, 73] and poor outcomes. Counter-intuitively, continuity of primary care (that is, frequently consulting with the same clinician in a practice) has only a very small effect upon the rapidity of a cancer diagnosis.[74]

[H2] Clinical decision support

Insights into the epidemiology of cancer symptoms in primary care, including estimates of their positive predictive value, have enabled the development of risk models, notably Risk Assessment Tools and QCancer® (Clinrisk, Nottingham, UK), to predict the likelihood of an undiagnosed cancer in symptomatic primary care patients..[75-77, 78 , 79] A good level of evidence is available from systematic reviews indicating that clinical decision support improves physician performance and the ordering of diagnostic tests.[80, 81 82] These risk models have been formulated, mostly in the UK, as assessment tools for use by GPs.[83] The first evaluation of such a risk assessment tool, made available in a printed format for the assessment of patients with suspected lung or colorectal cancers, and found that its use resulted in an increase in 2-week referrals (by 31% and 26% compared with the 6 months immediately preceding the study period for lung and colorectal cancer, respectively) and increased use of chest radiography (by 4%) and colonoscopy (by 15%); these changes resulted in a 37% increase in the diagnosis of lung cancers, with an increased proportion of stage I or II cancers (localized and locally advanced), and a 76% increase in diagnosis of colorectal cancer .[84] Risk algorithms have been further developed into electronic tools that interact with the patient's individual clinical record. As a joint initiative between Macmillan Cancer Support, Cancer Research UK and the NHS, these tools were piloted in over 500 practices in the UK. They enable a doctor to enter symptoms and calculate risk, but also prompt the doctor to consider a cancer diagnosis when a patient presents features summating to a cancer risk of 2% or more are already recorded. In an evaluation funded by the three sponsoring organisations, 19% of urgent referrals for suspected cancer from participating GPs were prompted by use of the tool.[85] Such tools can, however, conflict with clinical judgement, making some GPs reluctant to use them in the consultation, and these tools are trusted less by more experienced GPs.[86] Furthermore, variation in interpretation of symptoms by

different clinicians can lead to substantial variations in risk assessment.[87] No studies in this area have examined the diagnostic utility of clinical judgement when combined with use of evidence-based tools, although guidance from the National Institute for Health and Clinical Excellence (NICE), published in 2015, explicitly allows clinicians to override the recommendations of decision support tools when a good reason to do so exists.[88] Evidence for the effect of clinical decision support on clinically important outcomes such as stage at diagnosis and survival remains lacking, however, and randomized controlled trials such as the Evaluation of a Computer aid for Assessing Stomach Symptoms (ECASS) trial are currently ongoing.[9] Current risk models are driven by simple algorithms; more sophisticated systems, driven by artificial intelligence, are currently in development and will likely reach the point of implementation in routine practice in the next few years.[83]

In the latest revision of NICE guidance for investigation of suspected cancer, conclusions from the papers underpinning the use of clinical decision support tools for the diagnosis of cancer were used to formulate the recommendations.[88] The tools themselves were not made the subject of a recommendation – either positive or negative – as these are regarded as a platform for delivery of information to clinicians. Seen in this light, the platforms *per se* had not been sufficiently studied to justify a recommendation.

[H2] Policy-driven initiatives

The recognition that more expeditious diagnosis of cancer could improve patients' outcomes is not new.[89] However, nearly a century passed, following an address to the British Medical Association in 1909, before national cancer policies recognized early diagnosis as a key element of cancer care. Early government intervention strategies designed to improve the outcomes of patients with cancer prioritised advances in treatment, as demonstrated by the 1971 National Cancer Act in the USA. By the early 2000s, however, some jurisdictions were seeking to expedite specialist referrals of patients with high-risk symptoms, and in the UK a 2-week target was set for the urgency with which patients suspected of having cancer should be seen.[13, 90] Guidance on selection of patients for urgent referral has become a feature of a growing number of health-care systems, notably those in which the GP acts as gatekeeper to specialist care.[91] Programmes of research aiming to determine the predictive value of symptoms have informed this, for example, patients with colorectal cancer often lack a single symptom defining high-risk disease, necessitating the introduction of a risk scoring system [75, 76] thus enabling guidance to be refined, and introducing the possibility of explicit risk thresholds for referral.[88]

The task of cancer diagnosis could, possibly, be extended beyond general medical practice to other providers of primary care. Dental practitioners and opticians identify the majority of oral and uveal

cancers, respectively.[92] The role of pharmacy practitioners is less clear. Patients with, for example, cough or epigastric pain, often present to pharmacies and not general practices. Therefore, training for pharmacists in cancer diagnosis was included as part of UK awareness campaigns. At present, apart from a small number of ongoing pilot studies,[93] pharmacists have no access to diagnostic testing, so have to refer symptomatic patients elsewhere – usually to general practice.

[H1] Patient and population aspects

Many risk factors for cancer have been identified. Increased age, gender-specific risks, a family history of close relatives affected at younger ages, obesity, ethnicity, co-morbidities, smoking and excess alcohol intake are among the most important.[94] However, the interplay between risk factors and symptoms is complex. The risk of cancer in a person with a particular symptom has been demonstrated to vary for three of these risk factors – age, sex, and cigarette smoking.[88] For the other risk factors, evidence of the association of different likelihoods of cancer with a particular symptom is very weak or absent.[88] In the QCancer® series of papers, risk factors and symptoms were retained in the same multivariable model; in situations in which a statistically significant association was observed between any risk factor and cancer, the odds ratio was generally much smaller than those for symptoms. [95-100] In these papers, which used patient's pre-existing medical records, doctors probably would have recorded the presence of risk factors more frequently in patients also presenting with symptoms of possible cancer. This approach generates ascertainment bias (BOX 1), which would inflate the apparent strength of associations between the presence of risk factors with development of cancer. Arguably, risk factors other than age, sex, and smoking should only be used in the selection of patients for screening programmes, and should be omitted from the clinical assessment of symptomatic patients.

Patients from ethnic minorities generally have worse cancer survival than the majority: this difference might reflect different biology,[101] but patients from ethnic minorities also experience more diagnostic delay.[102] Furthermore, black patients, compared with white patients, might be less willing to opt for clinical investigation of prostate cancer at any risk level, as shown in a vignette study of prostate cancer diagnosis.[103]

[H2] NICE guidance on patient selection

Almost all definitive testing for cancer requires biopsy, and thus specialist referral. A small number of cancer types can be diagnosed in primary care, such as chronic lymphocytic leukaemia, or myeloma.[104, 105] Some skin cancers can be identified when excision is performed in primary care – although, if cancer is suspected, specialist excision is generally recommended.[88, 106] Point-of-care

testing has been developed for myeloma, but the performance of this testing has yet to be evaluated in the primary care setting. For the remainder of cancer types, the likelihood of cancer at the time of referral varies considerably. In some referrals, cancer is highly likely such as when a very high lymphocyte count is identified in a blood test, or if an irregular, hard prostate is identified upon rectal examination.[107] Conversely, some necessary referrals are of the 'low-risk, but not no risk' patient, such as the patient presenting with persistent diarrhoea or unexplained abdominal pain, where the likelihood of cancer is only 1–2%.[108]

Selection of patients for investigation in the UK is largely guided by the NICE, although Scotland has its own guidance from the Scottish Intercollegiate Guidelines Network.[109] The 2015 version of the NICE guidance based its recommendations for investigation on an assessment of the likelihood that the patient's symptoms (sometimes supplemented by simple primary care tests) exceed a threshold risk of cancer of 3%.[88] Two broad exceptions to this figure were agreed. For children, the benefits of improved survival and/or reduced morbidity are experienced over a longer time, thus making investigations of suspected cancer in children at levels <3% risk a reasonable approach. Furthermore, very few symptom profiles of cancer in children – even the 'high risk' ones – represent risks >3%,[110-112] so using that figure would be extremely restrictive. The second exception was for cancers for which primary care testing is widely available, such as serum prostate specific antigen testing or chest X-ray. These tests, which are often inexpensive, refine the risk of cancer, such that patients with a positive test result have a revised risk of cancer >3%, and test-negative patients <3%.

Both NICE decisions, to use a risk threshold and the setting of the specific level, are contentious. Prior to this recommendation, no threshold had been explicitly used to structure any previous cancer guidance .[33] Several possible alternatives to using risk are available as the metric of choice. Priority (and by implication, extra resources) could have been given to investigating for cancers that are known to result in better patient outcomes from expedited diagnosis. If cost-effectiveness data had been available, this could have driven recommendations – indeed NICE recommendations are generally based on estimates of cost-effectiveness. This argument could have been reversed: types of cancer with poor survival could justifiably have been given priority in the hope that this would improve outcomes. Additionally, the availability of diagnostic resources could have influenced NICE's recommendations; some diagnostic services, notably those providing imaging and endoscopy, have seen considerable expansions in their level of use, and are struggling to meet current levels of demand, let alone offer additional ones.[113, 114]

The final decision to use positive predictive values (PPVs) for symptomatic cancer derived from primary care populations as a threshold has several advantages. This approach brings equity across

cancers, and could be adjusted if a lower (or higher) figure is later considered to be superior. Being numerical, PPVs are also amenable to being integrated into general practice software, thus enabling automated calculations of risk based upon symptoms and test results present in medical records, and prompting the GP to consider further investigations should this risk be above an agreed threshold level.[83] Finally, PPVs were available from primary care studies for nearly all of the common cancers, and several of the less common ones, as shown by the evidence review within the NICE guidance.[88] Primary care-derived PPVs differ from those for the referred population, owing to the referral selection process creating a population with a substantially higher prevalence of disease.[115] Thus, although the NICE guidance has strong face validity for primary care clinicians,[116] some specialists expressed concerns that the recommendations failed to match their personal experience of the symptomatology of cancer.[117]

[H2] Thresholds for cancer investigation

The final decision by NICE to recommend urgent investigation once a patient's risk of cancer exceeds 3% is a compromise between a liberalisation of previous guidance and a recognition that many members of the public would opt for cancer investigation at much lower levels of risk, even as low as 1%.[118] An additional issue relates to safety: some tests, such as colonoscopy, carry a small risk of harm.[119] The liberalisation to a 3% threshold for investigation (or lower if simple primary care testing is available) theoretically could lead to a major expansion in testing. In practice, much of this has already happened: imaging activity increased at 5.7% per annum between 2006–2015,[113] with similar increases in use of endoscopy also observed.[26] At the same time the number of urgent referrals made under the NHS 'two-week wait' system has risen every year, passing one million in 2012; this increase has been accompanied by a decrease in the percentage of patients in these clinics transpiring to have cancer (the 'conversion rate'), but an increase in the proportion of patients having their cancer detected by this route.[120] The driving force behind this expansion in the use of cancer diagnostics is currently not clear: it might reflect an increased awareness of cancer among patients, or GPs lowering their individual threshold for investigating, perhaps prompted by the major increase in research publications on the topic. At the same time as these attempts to expedite cancer diagnosis in the NHS, survival outcomes of patients with cancer in the UK have improved, and have narrowed the gap in outcomes relative to those of similar patients in other European countries – for some cancers at least.[121]

Internationally, new referral pathways have been developed to support guidelines allowing rapid assessment of patients with symptoms of concern. In the UK, Australia, and Canada, for example, patients referred using these pathways are seen by a specialist within 14 days. In Denmark, however,

a patient in a similar situation is seen within four working days and the whole diagnostic pathway through to treatment is accelerated.[122] These referral pathways reduce the time to diagnosis for many, but not all, cancers and have been criticised because their use is restricted to those patients with specific, generally high-risk symptoms.[123] For example, time to diagnosis in the UK fell more for those symptoms that already had the lowest times to diagnosis, and the best patient survival outcomes.[123, 124] However, giving preference to high-risk presentations excludes around half of all symptomatic patients and, consequently, in England only 34% of all cancers in 2013 were diagnosed in this way.[120] Health services in Scandinavia and the UK have, therefore, developed models of rapid assessment for patients with less-specific or lower-risk symptoms.[125]

{H2] Influence of diagnostic programmes

Any programme of investigation of symptoms will, as well as identifying patients with non-malignant conditions, identify two separate populations of patients with cancer. The first of these two populations is the obvious one, comprising patients in whom the cancer was causing the symptom. The second population consists of those patients who happened to have the relevant symptom but whose cancer was, in essence, an unrelated finding. Some of these 'unrelated' patients will have co-morbidities that explain their symptoms; for example, patients with chronic obstructive pulmonary disease are at a higher risk of lung cancer because of past smoking, and might well have cough and breathlessness, both also symptoms of lung cancer. The size of the 'unrelated' population is estimated at 27–48% of patients with lung cancer, and 12–32% for those with colorectal cancer.[126, 127] However, the data sources for these figures largely pre-date the increases in testing for cancer in the UK,[128, 129] and the proportion of unrelated cancers is now probably somewhat smaller.

[H2] Overdiagnosis

Overdiagnosis describes the diagnosis of disease in an asymptomatic person that does not result in a net benefit for that person.[130] Overdiagnosis is much more of a concern for screening programmes, but the expansion of diagnostic activity means that overdiagnosis is also possible for patients with symptomatic cancer.[130] Currently, thyroid cancer, prostate cancer, and melanoma are the most likely to be overdiagnosed. In South Korea, for example, the incidence of thyroid cancer rose 15-fold between 1993–2011, with no change in thyroid cancer mortality observed over the same time period.[131] A similar pattern has been reported in melanoma, with the considerable increase in incidence largely representing early stage disease, and also showing no overall change in mortality.[132] Prostate cancer is a further candidate. In the era where prostatectomy was the standard treatment of benign prostatic hyperplasia, incidental prostate cancers – almost certainly

unrelated to the patient's symptoms – were frequently identified. Overall, the evidence in this area is limited, we suspect that the risks of overdiagnosis from expediting symptomatic diagnosis are likely to be relatively small compared to the possible benefits..

[H1] Health economics

Health economic analyses of the costs versus benefits of expedited cancer diagnosis in symptomatic patients are much less advanced than analyses of the performance of cancer screening. The costs of diagnosis have been investigated in several studies, although the benefits much less so.[133] Diagnostic costs should include the costs of investigation in those whose results transpire to be negative, although these costs (which might be substantial) are often omitted.[134] Once these costs are included, the costs of diagnosis might exceed the costs of primary treatment, as has been estimated for patients with symptoms of possible colorectal cancer.[135] This finding reflects the high costs of colonoscopy relative to approaches used for the diagnosis of other forms of cancer, suggesting that costs for patients with other cancers also requiring a form of endoscopy for diagnosis might be similar.[136] The total annual cost of cancer diagnosis in the UK might be one billion pounds.[29]

Comparisons of the costs, per case, of alternative diagnostic strategies are possible. Such a comparison was included in the 2015 NICE guidance, whereby several possible testing strategies for potential patients with colorectal cancer (whose estimated risk of cancer was <3%) were compared.[88] Faecal occult blood testing was clearly the most cost-effective approach. However, data on the performance characteristics of cancer investigations in primary care populations are rarely available, and (debatable) assumptions have to be made that these are similar to reports from secondary care or screened populations. Similarly, little is known about adverse events from cancer investigation when conducted in primary care.[88]

Estimation of the benefits of expedited cancer diagnosis has been much more difficult than estimating the cost of implementing such strategies. As described earlier, evidence from clinical trials is insufficient. Establishing the costs of treatment for the various stages of cancer is possible, with patients with cancers of a less-advanced stage being cheaper to treat.[134] Accurate figures for survival, by cancer stage, are also available for most cancers. However, the timescale for transition between cancer stages and its relationship with symptomatology is much less well known.[137] Gaining this knowledge is a crucial step, as until we know what stage shift (if any) arises from the introduction of an intervention to expedite symptomatic cancer diagnosis, reliably estimating the benefits of such an approach will remain impossible.[138] Thus, reports of a small, but significant, stage

shift following a cancer awareness campaign are doubly welcome.[63] These might enable much more informative health-economic analyses.

[H1] Conclusions

The survival of patients with cancer is improving in all developed countries, including the UK, and the rate of these improvements shows no sign of slowing down. Some of these improvements are almost certainly a result of improved diagnostics. In the UK, times to cancer diagnosis have fallen,[123] and the proportion of patients presenting with cancer as an emergency has also fallen.[120] These improvements are contemporaneous with major reconfigurations and investment in cancer services and with a liberalization of the criteria for cancer investigation, coupled with better identification of those who are most at risk. These two themes likely reflect cause and effect – in part at least. We cannot yet know if attempts at early diagnosis have been cost-effective. These initiatives have certainly been costly – but at least we know we are getting something for the money.

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Author contributions

All authors made a substantial contribution to researching data for this article, discussions of content, writing the manuscript and reviewing and/or editing the manuscript prior to submission.

Competing interests

W.H. was the clinical lead for the recent NICE guidance on selection of patients for investigation for possible cancer, NG12. W.H. and G.R. have acted as consultants for Medx GmBh. The other authors declare no competing interests.

Review criteria

No overarching systematic review of the literature was performed, as the subject matter is considered too broad-ranging for such an approach. We had recently published a systematic review of the relationship between time-to-diagnosis and cancer outcomes,[2] in addition to several site-specific systematic reviews of the symptoms of cancer;[3-7] these were supplemented by the 70 systematic reviews underpinning the 2015 NICE guidance for suspected cancer.[8] The bibliographical databases of all of these reviews were used here, supplemented by our large personal databases of cancer-specific references. Specific literature searches were undertaken where required.

Key Points

Very few randomized controlled trials have investigated whether or not expediting the diagnosis of symptomatic cancer improves the outcomes of patients; however, observational evidence suggests benefit for some patients

Awareness campaigns often prompt earlier presentation to the health-care system, although the long-term effect of this earlier presentation is largely unknown

The provision of rapid access to specialist expertise, coupled with national guidance for selection of patients — and, subsequently, clinical decision support — might result in shorter times to diagnosis

Guidance from the UK National Institute of Health and Care Excellence use an explicit risk threshold of 3% for investigation of symptomatic cancer; this liberalisation will influence the spectrum of patients seen by specialists

The cost-effectiveness of initiatives to expedite diagnosis of symptomatic cancer is markedly under-researched

BOX 1. Common biases seen in observational diagnostic studies

Lead time bias: this bias is well recognized in screening studies. It arises when an intervention (such as screening or a diagnostic intervention) advances the date of diagnosis, but does not change the date of death. The interval between the date of diagnosis and death is longer, thus suggesting an illusory benefit of the intervention.

Ascertainment bias: this occurs when the population studied is unrepresentative of the whole population, usually having a higher risk of disease.[20] Testing of serum prostate specific antigen (PSA) levels in men with lower urinary tract symptoms provides an example of this type of bias. Despite no causal link between benign prostatic hyperplasia (BPH) and prostate cancer being established[21], men with symptoms of BPH are more likely to have their serum PSA levels measured, uncovering some incidental prostate cancers.

Verification bias: this occurs when patients with a positive test are more likely to receive definitive testing. PSA and prostate cancer provides another example. If two men with similar urinary symptoms both have PSA measured, then the man with a raised PSA is more likely to have definitive testing for prostate cancer (in this example, a biopsy) than the man with a normal PSA. This tends to inflate sensitivity estimates for the initial test (in this example, the PSA)..[22]

Recall bias: this affects studies in which information is collected after the outcome (diagnosis) is known. Patients with the outcome of interest, such as cancer, might be more willing to attribute pre-diagnostic symptoms to their cancer, and be more likely to report them.

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