Comorbid chronic diseases and the diagnosis of cancer:

A review of disease-specific effects and underlying mechanisms

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Contributions

CR and GL designed the study. CR and AK researched data and evaluated the evidence for this article. CR wrote the draft manuscript with additional input from GL. All authors made substantial contributions to the interpretation, discussion and presentation of the findings and reviewed the manuscript before submission.

Competing interests

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Abstract

Early diagnosis of cancer is a key strategy for improving cancer outcomes. However, achieving this goal can be challenging, particularly for the growing number of people with chronic conditions (comorbidity/multi-morbidity). This is because pre-existing diseases may impact patient participation in cancer screening, help-seeking for new/changing symptoms and clinicians' decision-making on use of diagnostic investigations. Evidence suggests that pre-existing neurological, pulmonary, cardiac and psychiatric conditions are associated with longer patient and diagnostic intervals and advanced cancer stage. In contrast, hypertension and some gastrointestinal and musculoskeletal conditions may be associated with prompt help-seeking and timely cancer diagnosis. We propose a comprehensive framework that encompasses how disease, patient and healthcare factors may influence the diagnostic process in cancer patients with pre-existing chronic illness. Previously postulated aetiological mechanisms (including the 'alternative explanations', 'competing demands' and 'surveillance effect' hypotheses) are integrated with newly identified mechanisms, including false reassurance by investigations performed for chronic disease monitoring or patient worry of appearing hypochondriac (due to repeated consultation for chronic diseases or co-existing mental health conditions). By considering the specific effects of chronic diseases on the diagnostic process, tailored early diagnosis initiatives can be developed to improve health outcomes for the large proportion of cancer patients with pre-existing chronic conditions.

Key messages

- Many individuals with possible cancer symptoms have pre-existing chronic diseases (comorbidity, multi-morbidity), which can impact diagnostic timeliness and cancer stage.
- There is evidence that neurological, pulmonary, cardiac and psychiatric disorders are associated with longer intervals before cancer diagnosis and more advanced stage at diagnosis.
- Effects seem to vary in direction and size according to pre-existing disease type and the nature of presenting symptoms.
- Targeted interventions to expedite cancer diagnosis and improve cancer outcomes may be possible by considering the effects of chronic diseases on participation in cancer screening, patient help-seeking for cancer symptoms, and doctor's decision-making about the use of investigations.

Early diagnosis of cancer is a key strategy for cancer control[1] and for improving cancer outcomes. However, many cancer cases arise in patients with pre-existing chronic conditions, and how to achieve early diagnosis among this growing patient group remains unclear. Approximately three out of four cancer patients have at least one pre-existing chronic disease[2 3]. The relationship between cancer and other chronic conditions has different dimensions[4]: many conditions share common risk factors with cancer (for example, chronic obstructive pulmonary disease (COPD) and lung cancer are both associated with tobacco smoking); some conditions (such as diabetes) and their treatments can influence the risk of developing cancer and its prognosis[5]. Lastly, chronic conditions can affect timely cancer diagnosis by influencing the diagnostic process[6-8].

Herein, we focus on the influence of chronic conditions on the diagnostic process and their impact on two prognostically important diagnostic outcomes: stage at diagnosis, and emergency presentation status. Motivated by the limitations in current evidence[9-12], we also examine whether the impact varies for specific chronic diseases and cancer types. To elucidate mechanisms through which chronic diseases may influence the diagnosis of cancer, we review the evidence on disease-specific effects on various process measures that characterise the diagnostic pathway: participation in cancer screening; patients' help-seeking for cancer symptoms; clinicians' decision-making regarding use of investigations; and time from symptom onset to diagnosis.

By considering previously described and newly identified mechanisms arising from the reviewed quantitative and qualitative literature, we propose a comprehensive framework, which can guide the development of targeted interventions for expediting cancer diagnosis.

Variability of measures for defining chronic diseases

In Box 1 we have provided definitions of commonly used terms. There is considerable variability in terminology and methods used to measure morbidity. Studies often rely on coded patient record entries for episodes of care preceding the diagnosis of cancer. Composite comorbidity measures such as the Charlson comorbidity index are used frequently, without detail on specific morbidities. However, many studies also include information on specific chronic diseases (as opposed to composite morbidity measures), identified through case note reviews and patient or healthcare provider reports (Figure 1 and Supplementary Table 1).

Most evidence refers to patients who have been diagnosed with a few common cancers (colorectal, lung, breast); some research refers to symptomatic individuals not yet diagnosed with cancer (Supplementary Table 1).

Box 1: Key Terminology

Diagnostic pathway: sequence of events and related actions leading to cancer diagnosis. It includes events taking place from the onset of possible cancer symptoms or first cancer-related investigation (including screening tests) up to when the cancer is diagnosed. *Given the variability of prior definitions[13] this definition considers the Model of Pathways to Treatment[6,8], the Routes to Diagnosis[14] and NICE pathways guidance[15].*

Multimorbidity: co-existence of several conditions (two or more) in an individual, where none can be deemed to require attention above the others. Both non-communicable diseases and chronic infectious diseases (HIV, hepatitis C) are encompassed. *Definition in line with recommendations from the UK Academy of Medical Sciences[16].*

Comorbidity or chronic diseases in the context of cancer: one or more chronic conditions in a patient with cancer or under investigation for a possible cancer. *Definitions and time-windows pre-cancer vary[17] (for example, 5 years or 3 months pre-cancer; or at hospital admission when cancer is diagnosed). Measures include aggregate comorbidity scores based on secondary care records (for example, Charlson comorbidity index), specific comorbidities identified through case note reviews of primary or secondary care records or patient-reports.*

Diagnostic time or diagnostic interval: time from first symptomatic presentation in primary care to the cancer diagnosis. *Definition in line with the Aarhus statement[18]. Some studies only report 'diagnostic delay' with various definitions (for example, >3 months or >6 months). The term diagnostic interval is preferable to 'delay', as the latter relies on subjective judgement which may have poor reproducibility[8].*

Patient or help-seeking interval: time from when a patient first notices a symptom to the first medical visit for that symptom. It can relate to actual experience or intended help-seeking behaviour. *Definition in line with the Aarhus statement[18]. Some studies only report 'patient delay' with various definitions (>3 weeks, >3 months or median time longer compared to a reference group). Evaluating the patient interval rather than 'delay' is preferable to avoid subjective judgements[8].*

IMPACT ON DIAGNOSTIC OUTCOMES

Cancer stage at diagnosis

The evidence on the effects of chronic diseases on cancer stage is mixed, with some studies indicating an association with advanced stage[19-31], others showing no effect[32-34] and some reporting a reduced risk of advanced stage[19,22,25,28,31,34,35] for patients with chronic diseases (Figure 1). Hereafter we report estimates only if statistically significant.

A large New Zealand study of 14,096 patients with different cancers found that most of 42 examined chronic diseases were associated with increased risk of advanced stage[19]. The risk was particularly high for dementia, neurological, pulmonary, cardiac and major psychiatric disorders, with odds ratios (OR) ranging between 1.27 and 6.26. Psychiatric conditions were also associated with more advanced cancer stage in other studies[22,23] (e.g. advanced breast cancer: OR=1.27[22]; advanced oesophageal cancer occurring in 37% versus 18% of patients with and without psychiatric illness[23]). One small study reported contrasting effects by type of psychiatric morbidity: major depression increased the risk of advanced breast cancer, while phobia decreased the risk[27]. Information on consultation frequency was not available.

As reported by a US study on 11,312 patients, those with alcohol and tobacco-related chronic conditions have a higher risk of advanced stage head and neck cancers, while non-comorbid patients are at lower risk (39% versus 6%), irrespective of consultation frequency[30].

Contrasting effects on the stage at diagnosis of prostate and breast cancer have been reported for different chronic diseases[22,25,28]. For example, the risk of advanced stage was increased by severe renal disease, substance abuse and vascular conditions among prostate cancer patients[28], and by diabetes, haematological and psychiatric morbidities among breast cancer patients[22] (ORs between 1.15 and 2.06). In contrast, a lower risk of advanced stage was reported for prostate cancer patients with hypertension, dyslipidemia and coronary artery disease (ORs between 0.67 and 0.84)[28] and for breast cancer patients with benign breast, gastrointestinal, musculoskeletal and cardiovascular diseases (ORs between 0.62 and 0.87)[22]. Another large study on prostate cancer[36] also found that chronic conditions reduced the risk of advanced stage.

Diabetes might have different effects, depending on its severity[24]: poorly controlled diabetes was associated with advanced colorectal cancer (OR=2.1), while this was not the case for well-controlled diabetes. Disease-specific effects might also be modified by patient factors (for example, age),

healthcare factors and tumour characteristics (symptom 'signature' of the cancer), but the evidence on possible effect modification is scant.

Diagnosis of cancer as an emergency

Across various countries, a substantial minority of cancer patients are diagnosed in an emergency context[11]. Efforts to prevent emergency presentations are justified because such diagnoses are associated with worse clinical outcomes and patient experience[14,37,38]. The majority of evidence suggests that patients affected by chronic conditions have a higher risk of diagnosis of cancer as an emergency[31,37,39-50] (Figure 1). An English study on emergency diagnosis of any cancer reported a 1.3 risk ratio for patients with Charlson comorbidity score of 1 versus 0[49]. Similarly, the risk of emergency colorectal cancer diagnosis was higher for patients with one versus no comorbidity (OR=1.5) and even higher for 3+ versus no comorbidity (OR=2.0)[37]. This is in agreement with an American study showing higher risks of emergency presentations for colorectal and lung cancer (OR=1.89 and OR=3.79, respectively) among patients with one versus no chronic disease[31].

Only a few studies examined the effect of specific conditions on emergency cancer diagnoses[43,51-54], but some conditions appear to be associated with particularly high risks, including dementia, cardiac and neurological diseases[43] (dementia OR=2.46; congestive heart failure OR=1.49). Obesity has also been associated with emergency presentations[53].

In contrast, a Swedish study described a possible 'protective' effect of certain conditions, as it found a higher prevalence of hypertension among non-emergency colon cancer patients compared to those diagnosed as an emergency[52].

In summary, the evidence suggests that chronic diseases can be associated with cancer stage and emergency cancer diagnosis, but effects vary by disease. Some conditions, such as dementia, neurological, pulmonary, cardiac and major psychiatric disorders are associated with an increased risk of advance stage and emergency diagnosis across cancer types. In contrast, hypertension, dyslipidemia, benign gastrointestinal and musculoskeletal conditions, are associated with a lower risk of advanced stage, across cancers. Widely used aggregate measures of chronic conditions can lead to biased results when some diseases increase and others decrease the risk of advanced cancer.

IMPACT ON THE DIAGNOSTIC PROCESS

Herein, we examine the evidence on disease-specific effects on various process measures characterising the diagnostic pathway.

Participation in cancer screening

Participation in breast cancer screening is higher in women with a chronic condition compared to those with none (OR=1.3) or two or more conditions (OR=1.2)[55]. However, women with severe disability are less likely to participate in breast screening compared with those with moderate (OR=0.72) or no disability (OR=0.88)[55]. Similarly, women with a chronic condition are more likely than those without to have cervical cancer screening (OR=1.13)[56]. On the other hand, increasing Charlson comorbidity scores are associated with a lower probability of breast and cervical screening, possibly because physicians are less prone to recommend screening in patients with worse overall health status and/or patients refusing screening[57]. Further, participation in colorectal cancer screening decreases with increasing levels of comorbidity (88% of 65-69 year old individuals underwent screening if Charlson score=0 versus 82% if score$\geq$4)[58].

Considering specific chronic conditions, women with diabetes[59,60] have lower probability of participation in breast cancer screening compared to non-diabetic women (66% versus 60%; OR=0.79, after adjustment for socio-economic status and overall comorbidity)[59]. Similarly, there was lower participation in breast cancer screening in women with HIV infection (50% versus 63%)[61], depression (46% versus 62%; adjusted OR=0.63)[62] or obesity (64% versus 69%)[63]. Obesity is also associated with a lower participation in breast[64] and cervical[65] screening, after adjustment for socio-demographic factors and health care access, general health status, other comorbidities or health-seeking behaviour.

In contrast to diabetes, musculoskeletal conditions are associated with a higher probability of breast screening (75% versus 63% in women with and without musculoskeletal conditions; adjusted OR=1.46)[63].

In summary, individuals with a chronic disease are more likely to participate in breast and cervical cancer screening, but only if there is no associated disability. Regarding specific conditions, heterogeneous effects have been reported, with diabetes, HIV infection, depression and obesity being associated with a lower probability of cancer screening and musculoskeletal conditions with higher probability.

Help-seeking for possible cancer symptoms

Chronic diseases can influence help-seeking behavior in the context of new or changing symptoms. They can have variable effects[51,66-70], with some diseases being associated with shorter[71] and others with longer patient intervals[72-76], while some studies[77-79] found no such effects (Figure 1).

A study of patients with lung cancer[75] showed that those with COPD took twice as long to consult with lung cancer symptoms (mean help-seeking interval 166 versus 81 days), while those with a history of renal failure had significantly shorter patient intervals than non-comorbid patients (mean of 53 versus 102 days, respectively). A survey on help-seeking for various cancer symptoms[74] highlighted how pre-existing cardiac conditions were associated with a lower likelihood of help-seeking for change in bowel habit (OR=0.4); in contrast, hypertension increased help-seeking for persistent cough (OR=2.0) or abdominal bloating (OR=2.3) and chronic urinary diseases increasing help-seeking for rectal bleeding (OR=5.8).

Diagnostic events post-presentation

Beyond their effect on patient help-seeking, chronic diseases can also influence healthcare providers' decision-making (sometimes in combination with patient factors) regarding diagnostic reasoning and referrals for specialist investigations or use of diagnostic tests.

Diagnostic process, referrals and use of investigations. Some studies[47,78,80-82] only examined the overall effect of any disease (rather than specific diseases) on the diagnostic process (Figure 1). Having any chronic disease versus none had no effect on specialist referrals for gynaecological cancers[78] or on gastroscopy rates among oesophago-gastric cancer patients[47].

On the other hand evidence on the effects of specific chronic diseases is provided by several studies[2,46,66,69,70,72,73,79,82-85]. In particular, congestive heart failure or coronary artery disease can lead to missed opportunities to refer patients promptly for endoscopic examination[84], despite symptoms of colorectal cancer. Psychiatric illness was also associated with prolonged pre-referral intervals to a specialist or colonoscopy (with referral occurring after 60 days or more) in a study on colorectal cancer (OR=4.0)[69].

Diagnostic interval (from first presentation to diagnosis). Some studies examined disease-specific effects on the diagnostic interval[23,46,66,67,69,70,72,79,83,86,87]; others only examined the overall effect of any chronic disease[68,78,81,82,85,88-93] (Figure 1). Overall, having any pre-existing disease is strongly

associated with a longer diagnostic intervals, according to two large studies on leukemia and myeloma[91,92] and one on lymphoma[81]. For example, chronic lymphocytic leukemia patients with a pre-existing condition (versus none) had OR=2.83 for a prolonged diagnostic interval (defined as longer than the average time of 63 days between first symptomatic presentation and diagnosis)[92]. A longer diagnostic interval was also reported among upper aero-digestive tract cancer patients with a pre-existing disease versus none (OR=2.84)[88] and for oral cancers[68]. Among laryngeal cancer patients[88], 42% experienced a diagnostic interval of more than one year if Charlson comorbidity score$\geq$3, compared to 7% if comorbidity score 0-2.

A study on colorectal cancer[86] showed that specific diseases were associated with longer intervals before the cancer diagnosis: the longest being 26 days for inflammatory bowel disease (OR=1.33); coronary heart disease (OR=1.20), anxiety/depression (OR=1.12) and diverticular disease (OR=1.18) were also associated with longer diagnostic intervals. Effects of pre-existing diseases were stronger among individuals aged 80 or more. Similarly, mental health problems and gastro-intestinal conditions were associated with longer diagnostic intervals in a large study on colorectal cancer[79]. Psychiatric illness was also associated with a longer diagnostic interval for oesophageal cancer (median 90 days in comorbid versus 35 days in non-comorbid patients)[23].

Performance of investigations. The evidence on the effects of chronic diseases on performance of investigations is scant. No difference in false-positive rates by Charlson comorbidity score[94] has been reported in older women undergoing breast cancer screening. A higher risk of colorectal cancers after a previous negative colonoscopy has been reported for patients with chronic diseases (OR=1.16)[80]. Such occurrences are thought to primarily reflect missed lesions or incomplete polypectomy at the index colonoscopy[95]. Pre-existing diseases might lead to difficulties with bowel preparation[96] and/or increased technical difficulties for the endoscopist[97,98] or reduced patient tolerance during the examination, interfering with the endoscopic examination and possibly increasing the risk of missed lesions.

MECHANISMS OF INFLUENCE

While quantitative research has allowed to document associations with diagnostic outcomes, details on possible mechanisms by which chronic diseases might influence the cancer diagnosis (Box 2) are mainly provided by qualitative research (Supplementary Tables 2-3).

Box 2: Mechanisms by which chronic diseases might influence the cancer diagnosis	Examples of pairs of chronic disease/treatment and cancer
MECHANISMS INTERFERING WITH TIMELY CANCER DIAGNOSIS	
Pre-existing theories	
• **Alternative explanation**: Cancer symptoms are attributed by patients and/or doctors to a pre-existing condition or its treatment. Particularly relevant when symptoms of cancer and of the chronic condition overlap.[12,22,28,86]	COPD and lung cancer IBS and colon/ovarian cancer ACE-inhibitor induced cough and lung cancer
• **Competing demands**: Chronic conditions that are complex to manage or are perceived to be of particular gravity can distract the patient and/or doctor from appraising and investigating new vague symptoms that might be due to cancer.[99]	Cardiac condition and variety of cancers
• **Pathological hypothesis**: Some chronic conditions or their treatments interact with cancer pathogenesis, influencing cancer aggressiveness at the cellular or physiological level.[22,100]	Diabetes and colorectal cancer
Novel theories emerging from the current review	
• **Over-reassurance (of patient and/or doctor) from diagnostic tests** performed for chronic disease monitoring.	Ultrasound for gynaecological condition and colon cancer
• **Worry/anxiety to be seen as hypochondriac** due to frequent consultations for chronic diseases or co-exisiting mental health conditions. This might influence patients' reporting of symptoms. Frequent consultations can also influence doctors' interpretation of symptoms in light of anxiety disorders.	Mental health condition and variety of cancers
• **Fatalism** (due of morbidity-related poor health) leading to reluctance to undergo investigations.	Multi-morbidity and variety of cancers
• **Communication problems** due to specific chronic conditions.	Dementia, mental health, hearing problems and variety of cancers
MECHANISMS FACILITATING TIMELY CANCER DIAGNOSIS	
Pre-existing theories	
• **Surveillance effect/Opportunities**: Frequent consultations for monitoring or treatment can offer patients opportunities to mention possible cancer symptoms or healthcare providers might notice new sign/symptoms.[101]	Hypertension or musculoskeletal conditions and variety of cancers
Novel theories emerging from the current review	
• **Self-efficacy** due to familiarity with the healthcare system. This can influence patients and indirectly also healthcare providers' decisions on diagnostic strategies.	Variety of chronic diseases and cancers
• **Positive expectations** due to previous experiences with chronic disease management.	Variety of chronic diseases and cancers
• **Priorities** with respect to diagnosing cancer early or facilitating access to health services for patients with specific conditions.	Diabetes or COPD 'management programs' and variety of cancers

Notes: COPD Chronic Obstructive Pulmonary Disease; IBS Irritable bowel syndrome.

Alternative explanation mechanism

Influencing help-seeking for cancer symptoms. Patients may attribute cancer symptoms to pre-existing diseases (or to treatments for pre-existing diseases[72,102]) as offering alternative explanations for their symptoms. Previous reports most frequently relate to chronic respiratory diseases (COPD and asthma) and gastro-intestinal conditions interfering with help-seeking for lung cancer and colorectal cancer symptoms, respectively[51,66,72,75]. Supplementary Table 2 illustrates this with examples from qualitative studies.

Influencing the diagnostic interval. Chronic diseases can lead to longer diagnostic intervals and emergency cancer diagnosis due to missed opportunities[46 66] when symptoms are attributed by the doctor to a pre-existing disease or its treatments, despite repeated symptomatic presentations[51]. Alternative explanations can also be reinforced by doctor-patient interactions[72 67] (Supplementary Table 3). Interviews with GPs[85] indicate that chronic diseases can lead to a longer primary care interval in 23% of cancer patients, most frequently because of alternative explanations: in 90% of comorbid lung cancer patients with longer primary care intervals, symptoms were ascribed to a pre-existing disease. In a study on colorectal cancer[86] chronic conditions classified as representing 'alternative explanations' increased the diagnostic interval (by an average of 9 days; inflammatory bowel disease was associated with the largest increase, i.e. average 26 days). Reviews of GP free text notes[70] and significant event audits[46] highlighted missed diagnostic opportunities in patients with a history of diverticulitis or gynaecological conditions, with both GPs and specialists initially attributing colorectal or ovarian cancer symptoms to these conditions or related medications.

Competing demands mechanism

Influencing help-seeking for cancer symptoms. Some chronic diseases may lead to a prolonged patient interval if they are perceived to be of particular gravity (e.g. heart disease), diverting attention from new symptoms, especially if vague. For example, a survey[74] highlighted how having a cardiac condition decreased the likelihood of prompt help-seeking for change in bowel habit.

Influencing the diagnostic interval. Doctors can prioritise the treatment of pre-existing diseases or worry about a patient's poor health status due to chronic diseases, leading to longer intervals before

investigations involving invasive procedures[73]. For example patients with congestive heart failure or coronary artery disease, might not be referred promptly for endoscopic investigation of possible colorectal cancer symptoms[84]. Another study[86] showed that a single 'competing demand' condition (for example, coronary heart disease) increased the diagnostic interval for colorectal cancer by 10 days, and four or more conditions by 32 days in the average patient.

Influencing participation in cancer screening. Competing demands may also influence participation in cancer screening, as suggested by the lower probability of appropriate screening in individuals with diabetes, HIV infection or depression. Multi-morbid patients with complex needs and their healthcare providers have to deal with competing demands and fragmentation of care involving multiple specialist services, possibly interfering with access to preventive services[59,60 61 62].

Overall, the competing demands mechanisms can explain, at least partly, the higher risk of advanced cancer stage among patients with more severe or complex chronic conditions, such as severe neurological, pulmonary or cardiac conditions and multi-morbidity.

Pathological/biological mechanisms

The impact of chronic diseases on timely cancer diagnosis and cancer stage might also be influenced by biological mechanisms at tumour level affecting cancer progression. A 'pathological hypothesis'[28] is supported by some studies[5,22,100]. For example, chronic conditions such as severe renal diseases may be associated with a compromised immune system and metastatic prostate cancer[28]. Moreover, research on diabetes suggests direct and indirect effects of insulin on cancer growth in patients with diabetes and/or obesity[103,104]. Poorly controlled type 2 diabetes is associated with increased risk of advanced colorectal cancer[24], possibly due to biological effects of chronic hyperinsulinemia and poor glycaemic control. Pathophysiological interactions between some chronic diseases (including diabetes and chronic renal disease), ageing and cancer progression have been suggested as possible explanations for the greater risk of advanced stage in different cancers[4,103,104 26].

Surveillance mechanism/opportunities for earlier diagnosis

Influencing help-seeking for cancer symptoms. In contrast to previously discussed mechanisms leading to more advanced cancer at diagnosis, some conditions can be associated with a 'surveillance

effect', which offers opportunities for earlier diagnosis. This is the case when a condition requiring regular monitoring can enable the reporting of cancer symptoms during healthcare encounters to monitor the chronic condition. For example, hypertension and chronic urinary diseases can lead to more prompt help-seeking for possible cancer symptoms, such as rectal bleeding or cough[74]. Sometimes patients feel that help-seeking for vague symptoms is only appropriate if the consultation is 'justified' by a co-existing morbidity[105], consistent with UK evidence that 'not wanting to waste the GP's time' can be a barrier to help-seeking[106].

Influencing the diagnostic interval. A chronic disease can also offer healthcare providers opportunities to evaluate the possibility of cancer. This can apply to situations when cancer signs/symptoms are not mentioned by patients, but are noticed by healthcare providers when patients are seen for managing a chronic disease[83]. In some cases, the cancer is detected incidentally when undergoing investigations for another condition[66].

Influencing participation in cancer screening. Chronic conditions can also offer opportunities for accessing screening, which might explain the increased likelihood of cancer screening in individuals with musculoskeletal conditions[63].

Overall, the surveillance mechanism, influencing both patients and healthcare providers, can contribute to the protective effect of some chronic conditions, such as hypertension, dyslipidemia or musculoskeletal problems, associated with a lower risk of advanced cancer stage.

Additional mechanisms

Some additional mechanisms of influence have emerged from the review (Box 2 and Supplementary Tables 2-3), which integrate previously hypothesised theories. The following mechanisms are associated with longer patient and diagnostic intervals:

Repeated consultations and patient worries of appearing hypochondriac. Patients might not seek help for possible cancer symptoms, due to worry of being seen as hypochondriac, particularly in the context of mental health conditions[51]. Frequent help-seeking of patients can also influence the doctor's interpretation of symptoms in light of anxiety disorders. According to a study on colorectal cancer[70], patients with higher consultation rates for a variety of complaints were referred less for

investigations, possibly because healthcare providers sometimes perceive frequent help-seekers as being over-vigilant about body changes.

Sometimes multiple visits can be due to complex diagnostic processes[83]: investigations can lead to the diagnosis of previously undetected morbidities, distracting healthcare providers from the underlying cancer, which is eventually diagnosed after subsequent consultations.

In some patients, mental health issues can also influence participation in colorectal cancer screening when anxiety disorders interfere with enema administration[107].

Over-reassurance following investigations performed for a chronic disease. Over-reassurance can influence both patients and doctors following diagnostic investigations performed in relation to a chronic disease management; moreover, reluctance to refer patients again after a negative test (which may however not be specific enough or appropriately targeted to possible cancer) can lead to longer time intervals before the cancer diagnosis[66 82]. GP interviews show also that pre-existing conditions can contribute to misinterpretation of tests or to symptoms being attributed to chronic diseases when a chest x-ray is negative[85].

Fatalism. Poor health status associated with multi-morbidity can lead to patient's reluctance to undergo invasive cancer investigations[73,76]. Similar mechanisms might also contribute to explaining the lower likelihood of patients participating in cancer screening in case of poor health status and disability associated with multi-morbidity[57]. Mental health conditions are also associated with a lower likelihood of cancer screening, which might be explained in part by patient's lack of motivation or feeling overwhelmed.

Communication problems. Some chronic diseases (dementia, mental health, hearing problems) can lead to communication difficulties between patients and healthcare providers leading to longer patient and/or diagnostic intervals[23].

In contrast, mechanisms associated with shorter patient and diagnostic intervals also emerged, including the following:

Self-efficacy and positive expectations. Familiarity with the healthcare provider due to chronic diseases may affect patient's self-efficacy and facilitate help-seeking and communication regarding other health concerns[76]. Moreover, patients with chronic diseases can acquire substantial experience, allowing them to identify subtle changes in their symptoms compared to their underlying disease, which can trigger help-seeking[66]. Patients with chronic diseases can also have previous positive healthcare experiences motivating them to seek help promptly when they anticipate that a prescription can alleviate symptoms[66].

Specialist services for patients with chronic diseases. Specialised care pathways for patients with chronic diseases or nurse-led 'disease management programs' for some chronic diseases (e.g. diabetes, COPD) may facilitate help-seeking for other health concerns[76]. Moreover, guidelines and criteria for accessing diagnostic services targeting patients with specific conditions might have a positive impact on cancer diagnosis, by facilitating prompt access to healthcare professionals and/or testing for higher risk sub-groups[72,76].

IMPROVING CANCER DIAGNOSIS IN COMORBID PATIENTS

A comprehensive framework

By integrating the available evidence, we developed a comprehensive framework of the likely mechanisms through which chronic diseases can interfere with or facilitate timely cancer diagnosis influencing participation in cancer screening, help-seeking for cancer symptoms, diagnostic strategies and use of investigations (Figure 2). Novel mechanisms of influence have emerged (Box 2), which integrate previously hypothesised theories, including the 'alternative explanations', 'competing demands', 'surveillance effect'[12,22,28,86] and 'pathological hypothesis[22,100]. Novel mechanisms associated with longer patient and diagnostic intervals include false reassurance/over-reassurance (among doctors and patients) following investigations performed for a chronic disease; patient worries of appearing hypochondriacal; fatalism, due to poor health status associated with multi-morbidity, leading to reluctance to undergo invasive cancer investigations. In contrast, self-efficacy and positive expectations (related to their chronic conditions), as well as health services and guidelines targeting patients with specific conditions might have a positive impact on cancer diagnosis, by facilitating prompt access to healthcare for these higher risk sub-groups.

It is noteworthy that the identified associations represent 'average' effects in population groups. At individual level, additional factors (related to the patient or tumour) can come into play; moreover, for each patient multiple mechanisms may co-occur simultaneously.

Some chronic conditions, including dementia, neurological, pulmonary, cardiac and psychiatric disorders, are associated with a particularly high risk of late cancer diagnosis across cancer types. In contrast, hypertension and hypercholestolaemia and some benign musculoskeletal and gastrointestinal diseases can be associated with earlier diagnosis.

Psychiatric illness and dementia are associated with late diagnosis of breast, prostate and gastro-intestinal cancers. Psychiatric illnesses might provide alternative explanations for cancer symptoms which can be misinterpreted (by both patients and doctors) as reflecting the underlying psychiatric conditions or medications[23]. Communication difficulties and worries of appearing hypochondriac may also interfere with reporting of cancer symptoms in patients with mental health problems[51,73]. As psychiatric conditions are common in the general population[23,108,109], interventions to support the diagnostic process in these patients are needed. Patients with mental health conditions tend to consult frequently but may have difficulties when appraising their symptoms or communicating their healthcare needs. Thus, interventions for their treating physicians may be particularly justified.

Limitations of the current evidence

Definitions of chronic diseases and data collection methods vary substantially across studies and this might have contributed to the variability of findings. Effects of chronic diseases might be influenced by their severity, but such information is rarely reported. Some studies suggested that competing demands mechanisms might affect particularly older patients, but evidence on effect modification by socio-demographic characteristics is scant. As the majority of studies are based on retrospective reports by cancer patients, recall bias might have influenced the findings[110]. More than half of included studies did not specifically aim to investigate the effects of chronic diseases, and relevant information often emerged only after in-depth examination of full-text publications. Publication bias might have limited the number of studies showing no impact.

Implications for policy and practice

The reviewed evidence and the proposed theoretical frameworks can inform the development of targeted strategies aimed at improving early cancer diagnosis for people with pre-existing conditions. The global burden of chronic diseases and multimorbidity has increased over the last decades[111], possibly due to lifestyle factors and improved life expectancy[112-116], with more than half of the population aged 60 years or older in high income countries having a chronic condition and a quarter having multimorbidity[113,117,118]. Further, one in four deaths before the age of 60 are due to chronic conditions[16 111]. This underscores the importance of improving cancer diagnosis and management in the context of chronic diseases[16,119-121].

According to the Social Cognitive Theory[122] a person's decision to seek help can be influenced by various factors, including their perceived ability to discuss a symptom and receive help ('self-efficacy'), socio-cultural and structural barriers, opportunities and 'outcome expectations'. Self-efficacy is affected by previous experiences and it can influence both patient help-seeking and doctor decision-making. In that context, chronic diseases present both 'opportunities' to discuss cancer symptoms[105], but also 'barriers' if the patient and/or doctor perceive the pre-existing condition as more important[12 123]. Developing guidelines that take multi-morbidity into account and improving access to appropriate diagnostic services can have positive effects on timely cancer diagnosis. Conceptual models of diagnostic safety[7,11,124,125] can help identifying specific areas for improvement; they highlight how system and cognitive factors can contribute to prolonging the time before cancer diagnosis, with missed opportunities potentially occurring during the different phases of the diagnostic process (initial assessment; diagnostic test performance and interpretation; follow-up and coordination)[7]. This is in line with the findings of the current review, highlighting how various steps along the diagnostic pathway can be influenced by the presence of chronic diseases, calling for multi-faceted interventions.

When patients present with multiple conditions, it is often necessary to prioritise how much time is dedicated to the optimal management of serious pre-existing diseases against investigating new and possibly vague symptoms, particularly in the context of limited consultation time. Allowing sufficient time during primary care encounters remains paramount. Information technology[126] and electronic health records could be used by primary care providers to identify complex patients, allowing to plan allocation of time and optimizing the provision of care, for example by involving specialist nurses before and/or after a visit dedicated to multi-morbid patients. Similar approaches have been suggested in a recent project for the management of multi-morbidity[127]. Patients that are at

increased risk could benefit from information technology-enabled monitoring systems. There is also scope for enhancing the surveillance effect, by explicitly building in a cancer symptom enquiry to routine surveillance of chronic diseases.

Multi-disciplinary diagnostic centres (recently introduced in England and Denmark[128-131]) for patients with serious but non-specific symptoms could also be useful in the case of diagnostic complexities due to multi-morbidity. Greater integration between primary and secondary care, as well as wider use of 'disease management programs' coordinated by specialist nurses (for example, for patients with diabetes or mental health problems), could allow patients to have easier access to healthcare providers.

More effort should be dedicated to raising both patient and healthcare provider awareness on the benefits of cancer screening in patients with multi-morbidity. Information material specifically targeted at higher risk groups, addressing possible difficulties or concerns might be useful. Integration of the management of chronic conditions and cancer screening protocols would seem justified. Primary care-based preventive programmes, based on patients' age and risk profiles might be more acceptable for patients and more cost-effective[132,133].

Care coordination, including follow-up after investigations and safety-netting are crucial for multi-morbid patients, considering the risk of false reassurance after investigations for a chronic disease possibly leading to later cancer diagnosis. By sharing the diagnostic plan with patients and clearly communicating when there is uncertainty, patients might feel more empowered to raise concerns. Moreover, giving patients easy and timely access to their medical records and inviting them to pro-actively follow-up test results might contribute to preventing diagnostic delays[83,134].

Research priorities

Further research is warranted on the impact of chronic diseases on clinicians' decision-making regarding diagnostic strategies and use of investigations. The limited available information is only indirectly provided by a few interview studies and significant event audits. Studies examining cognitive processes, including vignette studies, may be particularly useful[135-138].

There is limited evidence on specific symptom-morbidity pairs[46,51,66,83]: for example, breathlessness in patients with chronic lung or cardiac morbidities leading to longer diagnostic intervals in lung cancer. Large studies based on linked electronic health records and trials evaluating different diagnostic

strategies for patients with specific morbidity-symptom pairs could help identify optimal diagnostic approaches for diagnosing cancer earlier for patient sub-groups with common chronic diseases.

Qualitative studies, including both patients and healthcare providers, could offer a deeper understanding of psychological factors influencing help-seeking and diagnostic decision-making in complex clinical situations. Multidisciplinary research, involving cognitive psychologists, could provide insights into the role of cognitive mechanisms or situational awareness, in influencing decision-making in such circumstances.

Patients' and doctors' tolerance of uncertainty can also influence diagnostic decision-making[138]; this is especially relevant for patients with multi-morbidity and poor overall health status and when chronic diseases (for example, cardiac conditions) increase the risk associated with invasive investigations. Patient's preferences when considering trade-offs between risks and benefits that may result from investigations become particularly important in such situations and a better understanding of the role of shared decision-making for patients with multi-morbidity is needed[137,139].

Finally, tailored risk-assessment tools need to be developed that take chronic morbidities into account, in order to support clinicians in the decision-making process when evaluating the possibility of cancer in patients with multi-morbidities. Currently available tools are based on generic algorithms[1], but more sophisticated approaches might take advantage of artificial intelligence.

Conclusions

Chronic diseases have multiple and sometimes contrasting effects on timely cancer diagnosis, acting through various mechanisms and affecting different aspects of the diagnostic process. By evaluating disease-specific effects on participation in cancer screening, help-seeking for potential cancer symptoms and use of investigations, interventions can be identified to minimise the risk of diagnosis of cancer at an advanced stage or through emergency presentation in the growing number of individuals with chronic diseases. Interventions could include the development of tailored diagnostic approaches encompassing risk-assessment tools and clinical guidelines targeting specific symptom-morbidity pairs, appropriate time and resource allocation in primary care for patients with complex needs, greater integration of diagnostic services between primary and secondary care and involvement of specialist nurses in the diagnostic process to optimise the management of multi-morbid patients and expedite cancer diagnosis.

References

1   Hamilton, W., Walter, F. M., Rubin, G. & Neal, R. D. Improving early diagnosis of symptomatic cancer. *Nature Reviews Clinical Oncology* **13**, 740, doi:10.1038/nrclinonc.2016.109 (2016).

2   Swann, R. *et al.* Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. *The British journal of general practice : the journal of the Royal College of General Practitioners* **68**, e63-e72, doi:10.3399/bjgp17X694169 (2018).

3   Ritchie, C. S. *et al.* Association between patients' perception of the comorbidity burden and symptoms in outpatients with common solid tumors. *Cancer* **123**, 3835-3842, doi:10.1002/cncr.30801 (2017).

4   Extermann, M. Interaction between comorbidity and cancer. *Cancer control : journal of the Moffitt Cancer Center* **14**, 13-22, doi:10.1177/107327480701400103 (2007).

5   Klil-Drori, A. J., Azoulay, L. & Pollak, M. N. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nature reviews. Clinical oncology* **14**, 85-99, doi:10.1038/nrclinonc.2016.120 (2017).

6   Scott, S. E., Walter, F. M., Webster, A., Sutton, S. & Emery, J. The model of pathways to treatment: conceptualization and integration with existing theory. *Br J Health Psychol* **18**, 45-65, doi:10.1111/j.2044-8287.2012.02077.x (2013).

7   Lyratzopoulos, G., Vedsted, P. & Singh, H. Understanding missed opportunities for more timely diagnosis of cancer in symptomatic patients after presentation. *Br J Cancer* **112 Suppl**, S84-91, doi:10.1038/bjc.2015.47 (2015).

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. *Journal of health services research & policy* **17**, 110-118, doi:10.1258/jhsrp.2011.010113 (2012).

9   Macdonald, S., Macleod, U., Campbell, N. C., Weller, D. & Mitchell, E. Systematic review of factors influencing patient and practitioner delay in diagnosis of upper gastrointestinal cancer. *Br J Cancer* **94**, 1272-1280, doi:10.1038/sj.bjc.6603089 (2006).

10   Mitchell, E., Macdonald, S., Campbell, N. C., Weller, D. & Macleod, U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. *Br J Cancer* **98**, 60-70, doi:10.1038/sj.bjc.6604096 (2008).

11   Zhou, Y. *et al.* Diagnosis of cancer as an emergency: a critical review of current evidence. *Nat Rev Clin Oncol* **14**, 45-56, doi:10.1038/nrclinonc.2016.155 (2017).

12   Corkum, M. *et al.* Impact of comorbidity and healthcare utilization on colorectal cancer stage at diagnosis: literature review. *Cancer causes & control : CCC* **23**, 213-220, doi:10.1007/s10552-011-9875-8 (2012).

13   Lawal, A. K. *et al.* What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review. *BMC Med* **14**, 35, doi:10.1186/s12916-016-0580-z (2016).

14   Elliss-Brookes, L. *et al.* Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. *Br J Cancer* **107**, 1220-1226, doi:10.1038/bjc.2012.408 (2012).

15   NICE. *NICE Pathways. Available at www.nice.org.uk/about/what-we-do/our-programmes/about-nice-pathways (Last accessed October 2018).*

16   The Academy of Medical Sciences. *Multimorbidity: a priority for global health research. April 2018. Available at https://acmedsci.ac.uk/policy/policy-projects/multimorbidity (Last accessed October 2018).*

17   Geraci, J. M., Escalante, C. P., Freeman, J. L. & Goodwin, J. S. Comorbid disease and cancer: the need for more relevant conceptual models in health services research. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **23**, 7399-7404, doi:10.1200/jco.2004.00.9753 (2005).

18   Weller, D. *et al.* The Aarhus statement: improving design and reporting of studies on early cancer diagnosis. *Br J Cancer* **106**, 1262-1267, doi:10.1038/bjc.2012.68 (2012).

19   Gurney, J., Sarfati, D. & Stanley, J. The impact of patient comorbidity on cancer stage at diagnosis. *Br J Cancer* **113**, 1375-1380, doi:10.1038/bjc.2015.355 (2015).

20   Gonzalez, E. C., Ferrante, J. M., Van Durme, D. J., Pal, N. & Roetzheim, R. G. Comorbid illness and the early detection of cancer. *Southern medical journal* **94**, 913-920 (2001).

21 El-Charnoubi, W. A., Svendsen, J. B., Tange, U. B. & Kroman, N. Women with inoperable or locally advanced breast cancer -- what characterizes them? A retrospective review of 157 cases. *Acta oncologica (Stockholm, Sweden)* **51**, 1081-1085, doi:10.3109/0284186x.2012.707788 (2012).

22 Fleming, S. T., Pursley, H. G., Newman, B., Pavlov, D. & Chen, K. Comorbidity as a predictor of stage of illness for patients with breast cancer. *Medical care* **43**, 132-140 (2005).

23 O'Rourke, R. W. *et al.* Psychiatric illness delays diagnosis of esophageal cancer. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus* **21**, 416-421, doi:10.1111/j.1442-2050.2007.00790.x (2008).

24 Siddiqui, A. A. *et al.* Elevated HbA1c is an independent predictor of aggressive clinical behavior in patients with colorectal cancer: a case-control study. *Digestive diseases and sciences* **53**, 2486-2494, doi:10.1007/s10620-008-0264-4 (2008).

25 Xiao, H. *et al.* Impact of Comorbidities on Prostate Cancer Stage at Diagnosis in Florida. *American journal of men's health* **10**, 285-295, doi:10.1177/1557988314564593 (2016).

26 Yasmeen, S. *et al.* Risk of advanced-stage breast cancer among older women with comorbidities. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **21**, 1510-1519, doi:10.1158/1055-9965.epi-12-0320 (2012).

27 Desai, M. M., Bruce, M. L. & Kasl, S. V. The effects of major depression and phobia on stage at diagnosis of breast cancer. *International journal of psychiatry in medicine* **29**, 29-45, doi:10.2190/0c63-u15v-5nur-tvxe (1999).

28 Fleming, S. T., McDavid, K., Pearce, K. & Pavlov, D. Comorbidities and the risk of late-stage prostate cancer. *TheScientificWorldJournal* **6**, 2460-2470, doi:10.1100/tsw.2006.383 (2006).

29 Gornick, M. E., Eggers, P. W. & Riley, G. F. Associations of race, education, and patterns of preventive service use with stage of cancer at time of diagnosis. *Health services research* **39**, 1403-1427, doi:10.1111/j.1475-6773.2004.00296.x (2004).

30 Reid, B. C., Warren, J. L. & Rozier, G. Comorbidity and early diagnosis of head and neck cancer in a Medicare population. *American journal of preventive medicine* **27**, 373-378, doi:10.1016/j.amepre.2004.07.018 (2004).

31 Sikka, V. & Ornato, J. P. Cancer diagnosis and outcomes in Michigan EDs vs other settings. *The American journal of emergency medicine* **30**, 283-292, doi:10.1016/j.ajem.2010.11.029 (2012).

32 Fazio, L., Cotterchio, M., Manno, M., McLaughlin, J. & Gallinger, S. Association between colonic screening, subject characteristics, and stage of colorectal cancer. *The American journal of gastroenterology* **100**, 2531-2539, doi:10.1111/j.1572-0241.2005.00319.x (2005).

33 Gross, C. P. *et al.* Relation between Medicare screening reimbursement and stage at diagnosis for older patients with colon cancer. *Jama* **296**, 2815-2822, doi:10.1001/jama.296.23.2815 (2006).

34 Henry, K. A., Sherman, R. & Roche, L. M. Colorectal cancer stage at diagnosis and area socioeconomic characteristics in New Jersey. *Health & place* **15**, 505-513, doi:10.1016/j.healthplace.2008.09.003 (2009).

35 Zafar, S. Y. *et al.* Comorbidity, age, race and stage at diagnosis in colorectal cancer: a retrospective, parallel analysis of two health systems. *BMC cancer* **8**, 345, doi:10.1186/1471-2407-8-345 (2008).

36 Raval, A. D., Madhavan, S., Mattes, M. D. & Sambamoorthi, U. Association between Types of Chronic Conditions and Cancer Stage at Diagnosis among Elderly Medicare Beneficiaries with Prostate Cancer. *Population health management* **19**, 445-453, doi:10.1089/pop.2015.0141 (2016).

37 McPhail, S. *et al.* Emergency presentation of cancer and short-term mortality. *Br J Cancer* **109**, 2027-2034, doi:10.1038/bjc.2013.569 (2013).

38 Salika, T. *et al.* Associations between diagnostic pathways and care experience in colorectal cancer: evidence from patient-reported data. *Frontline Gastroenterol* **9**, 241-248, doi:10.1136/flgastro-2017-100926 (2018).

39 Pruitt, S. L., Davidson, N. O., Gupta, S., Yan, Y. & Schootman, M. Missed opportunities: racial and neighborhood socioeconomic disparities in emergency colorectal cancer diagnosis and surgery. *BMC cancer* **14**, 927 (2014).

40   Sikka, V. Cancer Diagnosis and Outcomes In Michigan Emergency Departments Versus Other Settings. *Annals of Emergency Medicine* **56**, S92-S92 (2010).

41   Rabeneck, L., Paszat, L. F. & Li, C. Risk factors for obstruction, perforation, or emergency admission at presentation in patients with colorectal cancer: a population-based study. *The American journal of gastroenterology* **101**, 1098-1103 (2006).

42   Askari, A. *et al.* Defining characteristics of patients with colorectal cancer requiring emergency surgery. *International journal of colorectal disease* **30**, 1329-1336, doi:10.1007/s00384-015-2313-8 (2015).

43   Wallace, D. *et al.* Identifying patients at risk of emergency admission for colorectal cancer. *Br J Cancer* **111**, 577-580, doi:10.1038/bjc.2014.300 (2014).

44   Beckett, P., Tata, L. & Hubbard, R. Risk factors and survival outcome for non-elective referral in non-small cell lung cancer patients–Analysis based on the National Lung Cancer Audit. *Lung Cancer* **83**, 396-400 (2014).

45   Markar, S. R. *et al.* Emergency Presentation of Esophagogastric Cancer: Predictors and Long-term Prognosis. *Annals of surgery* **267**, 711-715, doi:10.1097/sla.0000000000002224 (2018).

46   Mitchell, E., Rubin, G., Merriman, L. & Macleod, U. The role of primary care in cancer diagnosis via emergency presentation: qualitative synthesis of significant event reports. *Br J Cancer* **112 Suppl**, S50-56, doi:10.1038/bjc.2015.42 (2015).

47   Shawihdi, M. *et al.* Variation in gastroscopy rate in English general practice and outcome for oesophagogastric cancer: retrospective analysis of Hospital Episode Statistics. *Gut* **63**, 250-261 (2014).

48   Solsky, I. *et al.* Gastric cancer diagnosis after presentation to the ED: The independent association of presenting location and outcomes. *Am J Surg*, doi:10.1016/j.amjsurg.2017.10.030 (2017).

49   Tsang, C., Bottle, A., Majeed, A. & Aylin, P. Cancer diagnosed by emergency admission in England: an observational study using the general practice research database. *BMC health services research* **13**, 308, doi:10.1186/1472-6963-13-308 (2013).

50   Vajdic, C. M. *et al.* Health service utilisation and investigations before diagnosis of cancer of unknown primary (CUP): A population-based nested case-control study in Australian Government Department of Veterans' Affairs clients. *Cancer epidemiology* **39**, 585-592, doi:10.1016/j.canep.2015.02.006 (2015).

51   Black, G. *et al.* Patients' Experiences of Cancer Diagnosis as a Result of an Emergency Presentation: A Qualitative Study. *PloS one* **10**, e0135027 (2015).

52   Gunnarsson, H., Holm, T., Ekholm, A. & Olsson, L. I. Emergency presentation of colon cancer is most frequent during summer. *Colorectal Dis* **13**, 663-668, doi:10.1111/j.1463-1318.2010.02270.x (2011).

53   Mitchell, A. D., Inglis, K. M., Murdoch, J. M. & Porter, G. A. Emergency room presentation of colorectal cancer: a consecutive cohort study. *Annals of surgical oncology* **14**, 1099-1104, doi:10.1245/s10434-006-9245-z (2007).

54   Gunnarsson, H. *et al.* Heterogeneity of Colon Cancer Patients Reported as Emergencies. *World Journal of Surgery* **38**, 1819-1826 (2014).

55   Guilcher, S. J. *et al.* Level of disability, multi-morbidity and breast cancer screening: does severity matter? *Preventive medicine* **67**, 193-198, doi:10.1016/j.ypmed.2014.07.025 (2014).

56   Lofters, A. *et al.* Screening for cervical cancer in women with disability and multimorbidity: a retrospective cohort study in Ontario, Canada. *CMAJ open* **2**, E240-247, doi:10.9778/cmajo.20140003 (2014).

57   Kiefe, C. I., Funkhouser, E., Fouad, M. N. & May, D. S. Chronic disease as a barrier to breast and cervical cancer screening. *Journal of general internal medicine* **13**, 357-365 (1998).

58   Klabunde, C. N. *et al.* Influence of Age and Comorbidity on Colorectal Cancer Screening in the Elderly. *American journal of preventive medicine* **51**, e67-75, doi:10.1016/j.amepre.2016.04.018 (2016).

59   Chan, W. *et al.* Impact of socio-economic status on breast cancer screening in women with diabetes: a population-based study. *Diabetic medicine : a journal of the British Diabetic Association* **31**, 806-812, doi:10.1111/dme.12422 (2014).

60   Lipscombe, L. L., Hux, J. E. & Booth, G. L. Reduced screening mammography among women with diabetes. *Archives of internal medicine* **165**, 2090-2095, doi:10.1001/archinte.165.18.2090 (2005).

61   Kendall, C. E. *et al.* A cross-sectional population-based study of breast cancer screening among women with HIV in Ontario, Canada. *CMAJ open* **5**, E673-e681, doi:10.9778/cmajo.20170038 (2017).

62   Vigod, S. N., Kurdyak, P. A., Stewart, D. E., Gnam, W. H. & Goering, P. N. Depressive symptoms as a determinant of breast and cervical cancer screening in women: a population-based study in Ontario, Canada. *Archives of women's mental health* **14**, 159-168, doi:10.1007/s00737-011-0210-x (2011).

63   Martin-Lopez, R. *et al.* Inequalities in uptake of breast cancer screening in Spain: analysis of a cross-sectional national survey. *Public health* **127**, 822-827, doi:10.1016/j.puhe.2013.03.006 (2013).

64   Wee, C. C., McCarthy, E. P., Davis, R. B. & Phillips, R. S. Obesity and breast cancer screening. *Journal of general internal medicine* **19**, 324-331, doi:10.1111/j.1525-1497.2004.30354.x (2004).

65   Ferrante, J. M., Chen, P. H. & Jacobs, A. Breast and cervical cancer screening in obese minority women. *Journal of women's health (2002)* **15**, 531-541, doi:10.1089/jwh.2006.15.531 (2006).

66   Birt, L. *et al.* Responding to symptoms suggestive of lung cancer: a qualitative interview study. *BMJ open respiratory research* **1**, e000067 (2014).

67   Corner, J., Hopkinson, J. & Roffe, L. Experience of health changes and reasons for delay in seeking care: a UK study of the months prior to the diagnosis of lung cancer. *Social science & medicine (1982)* **62**, 1381-1391, doi:10.1016/j.socscimed.2005.08.012 (2006).

68   Teppo, H. & Alho, O. P. Comorbidity and diagnostic delay in cancer of the larynx, tongue and pharynx. *Oral oncology* **45**, 692-695, doi:10.1016/j.oraloncology.2008.10.012 (2009).

69   Van Hout, A. M., de Wit, N. J., Rutten, F. H. & Peeters, P. H. Determinants of patient's and doctor's delay in diagnosis and treatment of colorectal cancer. *European journal of gastroenterology & hepatology* **23**, 1056-1063, doi:10.1097/MEG.0b013e32834c4839 (2011).

70   Brandenbarg, D. *et al.* Possible missed opportunities for diagnosing colorectal cancer in Dutch primary care: a multimethods approach. *The British journal of general practice : the journal of the Royal College of General Practitioners* **68**, e54-e62, doi:10.3399/bjgp17X693905 (2018).

71   Mor, V., Masterson-Allen, S., Goldberg, R., Guadagnoli, E. & Wool, M. S. Pre-diagnostic symptom recognition and help seeking among cancer patients. *Journal of community health* **15**, 253-266 (1990).

72   McLachlan, S. *et al.* Symptom perceptions and help-seeking behaviour prior to lung and colorectal cancer diagnoses: a qualitative study. *Fam Pract* **32**, 568-577, doi:10.1093/fampra/cmv048 (2015).

73   Renzi, C., Whitaker, K. L., Winstanley, K., Cromme, S. & Wardle, J. Unintended consequences of an 'all-clear' diagnosis for potential cancer symptoms: a nested qualitative interview study with primary care patients. *The British journal of general practice : the journal of the Royal College of General Practitioners* **66**, e158-170, doi:10.3399/bjgp16X683845 (2016).

74   Salika, T., Lyratzopoulos, G., Whitaker, K. L., Waller, J. & Renzi, C. Do comorbidities influence help-seeking for cancer alarm symptoms? A population-based survey in England. *Journal of public health*, 1-10, doi:10.1093/pubmed/fdx072 (2017).

75   Smith, S. M. *et al.* Factors contributing to the time taken to consult with symptoms of lung cancer: a cross-sectional study. *Thorax* **64**, 523-531, doi:10.1136/thx.2008.096560 (2009).

76   Cunningham, Y. *et al.* Symptom appraisal of potential lung cancer symptoms among people with chronic obstructive pulmonary disease – the challenge of multimorbidity (Under review).

77   Burgess, C. C., Ramirez, A. J., Smith, P. & Richards, M. A. Do adverse life events and mood disorders influence delayed presentation of breast cancer? *J Psychosom Res* **48**, 171-175 (2000).

78   Robinson, K., Christensen, K., Ottesen, B. & Krasnik, A. Socio-demographic factors, comorbidity and diagnostic delay among women diagnosed with cervical, endometrial or ovarian cancer. *European Journal of Cancer Care* **20**, 653-661 (2011).

79   Walter, F. M. *et al.* Symptoms and patient factors associated with longer time to diagnosis for colorectal cancer: results from a prospective cohort study. *Br J Cancer* **115**, 533-541, doi:10.1038/bjc.2016.221 (2016).

80   Cheung, D., Evison, F., Patel, P. & Trudgill, N. Factors associated with colorectal cancer occurrence after colonoscopy that did not diagnose colorectal cancer. *Gastrointestinal endoscopy* **84**, 287-295.e281, doi:10.1016/j.gie.2016.01.047 (2016).

81   Nikonova, A., Guirguis, H. R., Buckstein, R. & Cheung, M. C. Predictors of delay in diagnosis and treatment in diffuse large B-cell lymphoma and impact on survival. *British journal of haematology* **168**, 492-500, doi:10.1111/bjh.13150 (2015).

82   Wagland, R. *et al.* Facilitating early diagnosis of lung cancer amongst primary care patients: The views of GPs. *Eur J Cancer Care (Engl)* **26**, doi:10.1111/ecc.12704 (2017).

83   Mitchell, E. D., Rubin, G. & Macleod, U. Understanding diagnosis of lung cancer in primary care: qualitative synthesis of significant event audit reports. *British Journal of General Practice* **63**, e37-e46, doi:10.3399/bjgp13X660760 (2013).

84   Singh, H. *et al.* Missed opportunities to initiate endoscopic evaluation for colorectal cancer diagnosis. *The American journal of gastroenterology* **104**, 2543-2554, doi:10.1038/ajg.2009.324 (2009).

85   Bjerager, M., Palshof, T., Dahl, R., Vedsted, P. & Olesen, F. Delay in diagnosis of lung cancer in general practice. *The British journal of general practice : the journal of the Royal College of General Practitioners* **56**, 863-868 (2006).

86   Mounce, L. T. A., Price, S., Valderas, J. M. & Hamilton, W. Comorbid conditions delay diagnosis of colorectal cancer: a cohort study using electronic primary care records. *Br J Cancer* **116**, 1536-1543, doi:10.1038/bjc.2017.127 (2017).

87   Walter, F. M. *et al.* Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. *Br J Cancer* **112 Suppl**, S6-S13, doi:10.1038/bjc.2015.30 (2015).

88   Allison, P., Franco, E. & Feine, J. Predictors of professional diagnostic delays for upper aerodigestive tract carcinoma. *Oral oncology* **34**, 127-132 (1998).

89   Fisher, D. A. *et al.* Risk factors for advanced disease in colorectal cancer. *The American journal of gastroenterology* **99**, 2019-2024, doi:10.1111/j.1572-0241.2004.40010.x (2004).

90   Fisher, D. A. *et al.* Determinants of medical system delay in the diagnosis of colorectal cancer within the Veteran Affairs Health System. *Digestive diseases and sciences* **55**, 1434-1441, doi:10.1007/s10620-010-1174-9 (2010).

91   Friese, C. R. *et al.* Diagnostic delay and complications for older adults with multiple myeloma. *Leukemia & lymphoma* **50**, 392-400, doi:10.1080/10428190902741471 (2009).

92   Friese, C. R. *et al.* Timeliness and quality of diagnostic care for medicare recipients with chronic lymphocytic leukemia. *Cancer* **117**, 1470-1477, doi:10.1002/cncr.25655 (2011).

93   Huo, Q. *et al.* Delay in diagnosis and treatment of symptomatic breast cancer in China. *Annals of surgical oncology* **22**, 883-888, doi:10.1245/s10434-014-4076-9 (2015).

94   Braithwaite, D. *et al.* Screening outcomes in older US women undergoing multiple mammograms in community practice: does interval, age, or comorbidity score affect tumor characteristics or false positive rates? *J Natl Cancer Inst* **105**, 334-341, doi:10.1093/jnci/djs645 (2013).

95   Robertson, D. J. *et al.* Colorectal cancers soon after colonoscopy: a pooled multicohort analysis. *Gut* **63**, 949-956, doi:10.1136/gutjnl-2012-303796 (2014).

96   Chopra, D. & Hookey, L. C. Comorbid Illness, Bowel Preparation, and Logistical Constraints Are Key Reasons for Outpatient Colonoscopy Nonattendance. *Canadian journal of gastroenterology & hepatology* **2016**, 2179354, doi:10.1155/2016/2179354 (2016).

97   Koido, S. *et al.* Factors associated with incomplete colonoscopy at a Japanese academic hospital. *World journal of gastroenterology* **20**, 6961-6967, doi:10.3748/wjg.v20.i22.6961 (2014).

98   Shah, H. A., Paszat, L. F., Saskin, R., Stukel, T. A. & Rabeneck, L. Factors associated with incomplete colonoscopy: a population-based study. *Gastroenterology* **132**, 2297-2303, doi:10.1053/j.gastro.2007.03.032 (2007).

99   Jaen, C. R., Stange, K. C. & Nutting, P. A. Competing demands of primary care: a model for the delivery of clinical preventive services. *The Journal of family practice* **38**, 166-171 (1994).

100   Newschaffer, C. J. *et al.* Does comorbid disease interact with cancer? An epidemiologic analysis of mortality in a cohort of elderly breast cancer patients. *The journals of gerontology. Series A, Biological sciences and medical sciences* **53**, M372-378 (1998).

101   Feinstein, A. R. THE PRE-THERAPEUTIC CLASSIFICATION OF CO-MORBIDITY IN CHRONIC DISEASE. *Journal of chronic diseases* **23**, 455-468 (1970).

102   Mills, K. *et al.* Understanding symptom appraisal and help-seeking in people with symptoms suggestive of pancreatic cancer: a qualitative study. *BMJ open* **7**, e015682, doi:10.1136/bmjopen-2016-015682 (2017).

103   Giovannucci, E. *et al.* Diabetes and cancer: a consensus report. *Diabetes care* **33**, 1674-1685, doi:10.2337/dc10-0666 (2010).

104   Simon, T. G. *et al.* Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: Results from two prospective cohort studies. *Hepatology (Baltimore, Md.)* **67**, 1797-1806, doi:10.1002/hep.29660 (2018).

105   Whitaker, K. L., Macleod, U., Winstanley, K., Scott, S. E. & Wardle, J. Help seeking for cancer 'alarm' symptoms: a qualitative interview study of primary care patients in the UK. *The British journal of general practice : the journal of the Royal College of General Practitioners* **65**, e96-e105, doi:10.3399/bjgp15X683533 (2015).

106   Forbes, L. J. *et al.* Differences in cancer awareness and beliefs between Australia, Canada, Denmark, Norway, Sweden and the UK (the International Cancer Benchmarking Partnership): do they contribute to differences in cancer survival? *Br J Cancer* **108**, 292-300, doi:10.1038/bjc.2012.542 (2013).

107   Hall, N. *et al.* Concerns, perceived need and competing priorities: a qualitative exploration of decision-making and non-participation in a population-based flexible sigmoidoscopy screening programme to prevent colorectal cancer. *BMJ open* **6**, e012304, doi:10.1136/bmjopen-2016-012304 (2016).

108   NHS Digital. Adult Psychiatric Morbidity in England - 2007, Results of a household survey. Available at https://digital.nhs.uk/data-and-information/publications/statistical/adult-psychiatric-morbidity-survey/adult-psychiatric-morbidity-in-england-2007-results-of-a-household-survey (Last accessed May 2018).

109   WHO. Prevalence of mental disorders. Available at www.euro.who.int/en/health-topics/noncommunicable-diseases/mental-health/data-and-resources (Last accessed May 2018).

110   Solbjor, M., Skolbekken, J. A., Saetnan, A. R., Hagen, A. I. & Forsmo, S. Could screening participation bias symptom interpretation? An interview study on women's interpretations of and responses to cancer symptoms between mammography screening rounds. *BMJ open* **2**, doi:10.1136/bmjopen-2012-001508 (2012).

111   WHO. *Global status report on noncommunicable diseases 2010. World Health Organization 2011. Available at http://www.who.int/nmh/publications/ncd_report_full_en.pdf (Last accessed October 2018)*.

112   van Leersum, N. J. *et al.* Increasing prevalence of comorbidity in patients with colorectal cancer in the South of the Netherlands 1995-2010. *International journal of cancer. Journal international du cancer* **132**, 2157-2163, doi:10.1002/ijc.27871 (2013).

113   Barnett, K. *et al.* Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet* **380**, 37-43, doi:10.1016/s0140-6736(12)60240-2 (2012).

114   Gijsen, R. *et al.* Causes and consequences of comorbidity: a review. *Journal of clinical epidemiology* **54**, 661-674 (2001).

115   Taylor, A. W. *et al.* Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC public health* **10**, 718, doi:10.1186/1471-2458-10-718 (2010).

116   Zulman, D. M. *et al.* Multimorbidity and healthcare utilisation among high-cost patients in the US Veterans Affairs Health Care System. *BMJ open* **5**, e007771, doi:10.1136/bmjopen-2015-007771 (2015).

117   Mujica-Mota, R. E. *et al.* Common patterns of morbidity and multi-morbidity and their impact on health-related quality of life: evidence from a national survey. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation* **24**, 909-918, doi:10.1007/s11136-014-0820-7 (2015).

118   Department of Health (2012). Report. Long-term conditions compendium of Information: 3rd edition.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216528/dh_134486.pdf (Last accessed 10 March 2018).

119 Boyd, C. M. *et al.* Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. *Jama* **294**, 716-724, doi:10.1001/jama.294.6.716 (2005).

120 Mutasingwa, D. R., Ge, H. & Upshur, R. E. How applicable are clinical practice guidelines to elderly patients with comorbidities? *Canadian family physician Medecin de famille canadien* **57**, e253-262 (2011).

121 Cassell, A. *et al.* The epidemiology of multimorbidity in primary care: a retrospective cohort study. *The British journal of general practice : the journal of the Royal College of General Practitioners* **68**, e245-e251, doi:10.3399/bjgp18X695465 (2018).

122 Bandura, A. Health promotion from the perspective of social cognitive theory. *Psychology & Health* **13**, 623-649, doi:10.1080/08870449808407422 (1998).

123 Smith, S. M. *et al.* Factors contributing to the time taken to consult with symptoms of lung cancer: a cross-sectional study. *Thorax* **64**, 523-531, doi:10.1136/thx.2008.096560 (2009).

124 Singh, H. & Graber, M. L. Improving Diagnosis in Health Care — The Next Imperative for Patient Safety. *New England Journal of Medicine* **373**, 2493-2495, doi:10.1056/NEJMp1512241 (2015).

125 Singh, H. & Sittig, D. F. Advancing the science of measurement of diagnostic errors in healthcare: the Safer Dx framework. *BMJ Qual Saf* **24**, 103-110, doi:10.1136/bmjqs-2014-003675 (2015).

126 Murphy, D. R. *et al.* Electronic health record-based triggers to detect potential delays in cancer diagnosis. *BMJ Qual Saf* **23**, 8-16, doi:10.1136/bmjqs-2013-001874 (2014).

127 Salisbury, C. *et al.* Management of multimorbidity using a patient-centred care model: a pragmatic cluster-randomised trial of the 3D approach. *Lancet (London, England)* **392**, 41-50, doi:10.1016/s0140-6736(18)31308-4 (2018).

128 Fuller, E., Fitzgerald, K. & Hiom, S. Accelerate, Coordinate, Evaluate Programme: a new approach to cancer diagnosis. *The British journal of general practice : the journal of the Royal College of General Practitioners* **66**, 176-177, doi:10.3399/bjgp16X684457 (2016).

129 Moseholm, E. & Lindhardt, B. O. Patient characteristics and cancer prevalence in the Danish cancer patient pathway for patients with serious non-specific symptoms and signs of cancer-A nationwide, population-based cohort study. *Cancer epidemiology* **50**, 166-172, doi:10.1016/j.canep.2017.08.003 (2017).

130 Naeser, E., Fredberg, U., Moller, H. & Vedsted, P. Clinical characteristics and risk of serious disease in patients referred to a diagnostic centre: A cohort study. *Cancer epidemiology* **50**, 158-165, doi:10.1016/j.canep.2017.07.014 (2017).

131 Foster, A., Renzi, C. & Lyratzopoulos, G. Diagnosing cancer in patients with 'non-alarm' symptoms: Learning from diagnostic care innovations in Denmark. . *Cancer epidemiology* **54** 101-103 (2018).

132 Grunfeld, E. *et al.* Improving chronic disease prevention and screening in primary care: results of the BETTER pragmatic cluster randomized controlled trial. *BMC family practice* **14**, 175, doi:10.1186/1471-2296-14-175 (2013).

133 Mazza, D. & Mitchell, G. Cancer, ageing, multimorbidity and primary care. *Eur J Cancer Care (Engl)* **26**, doi:10.1111/ecc.12717 (2017).

134 Almond, S., Mant, D. & Thompson, M. Diagnostic safety-netting. *The British journal of general practice : the journal of the Royal College of General Practitioners* **59**, 872-874; discussion 874, doi:10.3399/bjgp09X472971 (2009).

135 Sheringham, J. *et al.* Variations in GPs' decisions to investigate suspected lung cancer: a factorial experiment using multimedia vignettes. *BMJ Qual Saf* **26**, 449-459, doi:10.1136/bmjqs-2016-005679 (2017).

136 Meyer, A. D., Payne, V. L., Meeks, D. W., Rao, R. & Singh, H. Physicians' diagnostic accuracy, confidence, and resource requests: A vignette study. *JAMA Internal Medicine* **173**, 1952-1958, doi:10.1001/jamainternmed.2013.10081 (2013).

137 Bhise, V. *et al.* Patient perspectives on how physicians communicate diagnostic uncertainty: An experimental vignette study. *International journal for quality in health care : journal of the International Society for Quality in Health Care* **30**, 2-8, doi:10.1093/intqhc/mzx170 (2018).

138   Bhise, V. *et al.* Defining and Measuring Diagnostic Uncertainty in Medicine: A Systematic Review. *Journal of general internal medicine* **33**, 103-115, doi:10.1007/s11606-017-4164-1 (2018).

139   Berger, Z. D. *et al.* Patient centred diagnosis: sharing diagnostic decisions with patients in clinical practice. *BMJ (Clinical research ed.)* **359**, j4218, doi:10.1136/bmj.j4218 (2017).

Figure 1: Overview of studies providing evidence on the role of chronic diseases in influencing the diagnosis of cancer (studies providing quantitative evidence are shown here)

Key (legend):
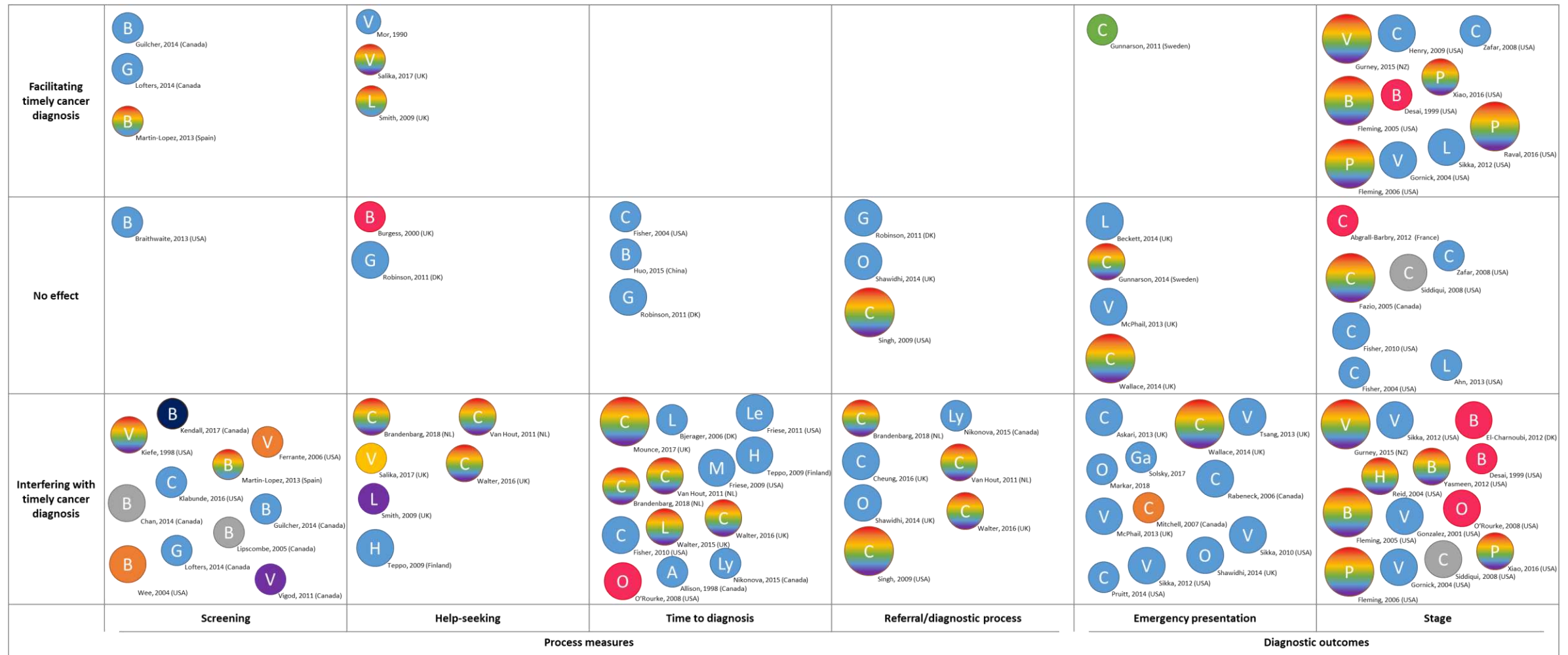
A=Aero-digestive
B=Breast
C= Colorectal
Ga=Gastric
G=Gynaecological
H=Head and neck
M=Myeloma
Le=Leukaemia

L= Lung
Ly=Lymphoma
O=Oesophageal
P=Prostate
V=Various

Various specific chronic conditions

Not chronic condition specific

Mental health condition

Cardiovascular disease

Diabetes

Obesity

Respiratory disease

Hypertension

HIV

Notes: Circle size reflects the quality of evidence based on MMAT scores. The same study may appear in multiple cells if there was more than one outcome.

Figure 2: Mechanisms through which chronic diseases (comorbidity) can facilitate or interfere with the timely diagnosis of cancer