**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**

The authors declare no competing financial interests.

**Acknowledgements**

This research arises from the CanTest Collaborative, which is funded by Cancer Research UK (C8640/A23385).

CR acknowledges funding from the BMA TP Gunton research grant.

HS is partly supported by the VA Health Services Research and Development Service Center for Innovations in Quality, Effectiveness and Safety (CIN13-413).

GL acknowledges funding from Cancer Research UK (Advanced Clinician Scientist Fellowship Award, grant number A18180).

**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 pulmonary, cardiac, neurological and psychiatric conditions are associated with longer patient and diagnostic intervals and advanced stage at diagnosis. 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, such as false reassurance by investigations performed for chronic disease monitoring, or patient worry of appearing hypochondriac. By considering the specific effects of chronic diseases on the diagnostic process and its outcomes, 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 at diagnosis.
- There is evidence that pulmonary, cardiac, neurological 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[4,5]: i) Many conditions share common risk factors with cancer; for example, chronic obstructive pulmonary disease (COPD) and lung cancer are both associated with tobacco smoking; similarly, high alcohol intake and obesity increase the risk of both cancer and non-neoplastic chronic conditions. ii) Chronic conditions can influence the risk of developing cancer and cancer prognosis through specific biological mechanisms; for example, diabetes increases the risk of developing colorectal, breast, endometrial, pancreatic and other cancers through a complex biological pathways related to insulin-like growth factors, insulin resistance, compensatory increased insulin levels and prolonged hyperglycemia[6-8]; similarly, some chronic infections (such as hepatitis C) and conditions characterized by dysregulation of the immune systems can also increase the risk of developing cancer through specific biological mechanisms. iii) Certain treatments for chronic diseases can influence cancer incidence and aggressiveness; for example, nonsteroidal and anti-inflammatory drugs used for arthritis[9], aspirin for cardiovascular disease[10] or metformin for diabetes might reduce the risk of cancer in some patients[6 11]. iv) Lastly, chronic conditions can affect the timeliness of cancer diagnosis by influencing the diagnostic process[12-14]. In this review we focus on the latter aspect of the association between chronic diseases and cancer.

In particular, we herein examine 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[15-18], we also consider 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. This is important for improving cancer outcomes given the increasing number of individuals with pre-existing conditions[1 19].

**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.

The Charlson Comorbidity Index, which was originally developed to predict 1-year mortality in hospitalized patients, assigns weights to different chronic conditions providing a summary comorbidity score. The weights are based on the ratio of the mortality risk for patients with the condition of interest versus the risk for patients without that condition[20,21]. Disease severity and duration and some diseases, such as psychiatric conditions, that might be particularly relevant for timely cancer diagnosis, are not taken into account when calculating either the Carlson index or similar summary measures. Overall, there is no gold-standard for measuring comorbidity in the context of cancer[5] and little is known on the performance of summary comorbidity measures when evaluating diagnostic timeliness.

At the same time, many studies include information on specific chronic diseases (as opposed to composite 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).

The review includes original research based on quantitative, qualitative and mixed methods. Qualitative studies are included to acquire insights into the complex effects of chronic conditions and underlying mechanisms. The available evidence refers to cohort (n=31), cross-sectional (n=25) and case-control (n=6) studies, as well as case-series (n=13) and qualitative studies (n=11). A quality score was assigned to each reference according to the Mixed Methods Appraisal Tool (MMAT)[22] (further details on the review methods are provided in the Supplementary Box and Figure). The MMAT is a validated quality assessment tool, allowing to evaluate each study based on various criteria specific for the different study designs (highest possible score 100, if all criteria are met). Most studies received a MMAT score of 75 or 50 (35 and 31 studies, respectively); a score of 100 was given to 11 studies; only 1 study was scored 25. Details on MMAT score, study design and sample characteristics are provided in the Supplementary table.

**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[23] this definition considers the Model of Pathways to Treatment[12,14], the Routes to Diagnosis[24] and NICE pathways guidance[25].*

**Multimorbidity:** co-existence of several conditions (two or more) in an individual. Both non-communicable diseases (including history of cancer and non-neoplastic diseases) and chronic infectious diseases (HIV, hepatitis C) are encompassed. *Definition in line with recommendations from the UK Academy of Medical Sciences[19].*

**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[21] (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[26]. 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[14].*

**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[26]. 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[14].*

## 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[27-41], others showing no effect[42-44] and some reporting a reduced risk of advanced stage[27,30,33,36,39,40,44-46] for patients with chronic diseases (Figure 1).

An increased risk of advanced stage was found for most of the 42 examined chronic diseases examined in a large New Zealand study of 14,096 patients with different cancers[27]. 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[30,31] (e.g. advanced breast cancer: OR=1.27, $p<0.01$[30]; advanced oesophageal cancer occurring in 37% versus 18% ($p=0.009$) of patients with and without psychiatric illness[31]). Moreover, according to large US studies[41,47] individuals with psychiatric conditions and with dementia are also more likely to be diagnosed with colon cancer at an unknown stage (for example, dementia versus non-dementia individuals: 24% versus 7.4%, $p<0.001$; adjusted OR=2.12; 95%CI 1.77-2.55) and using non-invasive methods (imaging, laboratory tests without histological confirmation) rather than with tissue evaluation (dementia versus non-dementia individuals: adjusted OR=2.02; 95%CI 1.63-2.51)[47].

As reported by a US study including 11,312 patients, those with alcohol and tobacco-related chronic conditions have a higher risk of advanced stage head and neck cancers compared to non-comorbid patients (39% versus 6%; $p<0.05$), irrespective of consultation frequency[38]. The risk of advanced stage was also increased by severe renal disease, substance abuse and vascular conditions among prostate cancer patients[36], and by diabetes, haematological and psychiatric morbidities among breast cancer patients[30] (ORs between 1.15 and 2.06) in two large US studies. According to another US population-based cohort study[40], end stage renal disease (ESRD) patients on dialysis have a higher likelihood of non-localized prostate cancer at diagnosis compared to non-ESRD individuals (13.7% versus 6.5%; adjusted RR=2.23; 95%CI 1.35-4.13, controlling for socio-demographic factors and comorbidity index); in contrast, they have a lower likelihood of advanced colorectal cancer (39.0% versus 50.9%; adjusted RR=0.81; 95%CI 0.66-0.98).

A lower likelihood of advanced cancer stage was also reported for individuals with hypertension, dyslipidemia and coronary artery disease in a large US study on prostate cancer patients (ORs between 0.67 and 0.84)[36] and for individuals with benign breast, gastrointestinal, musculoskeletal

and cardiovascular conditions in another large US study on breast cancer patients (ORs between 0.62 and 0.87)[30].

One small study (including 72 women), reported different effects by type of psychiatric morbidity: major depression increased the risk of advanced breast cancer, while phobia decreased the risk[35]. Information on consultation frequency was not available. Heterogeneous effects have also been reported for diabetes, depending on its severity[32]: poorly controlled diabetes was associated with advanced colorectal cancer (OR=2.1; 95%CI 1 to 4.4; p=0.02), 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.

In summary, the evidence suggests that the presence of chronic diseases is associated with cancer stage at diagnosis, but effects vary by condition. Some diseases, such as dementia, neurological, pulmonary, cardiac and major psychiatric disorders are associated with an increased risk of advance stage at diagnosis across cancer types. In contrast, hypertension, dyslipidemia, benign gastrointestinal and musculoskeletal conditions, are associated with a lower risk of advanced stage, across cancers. Heterogeneous effects on advanced cancer stage were reported for end stage renal disease, increasing the risk for prostate cancer and decreasing it for colorectal cancer.

**Diagnosis of cancer as an emergency**

Across various countries, a substantial minority of cancer patients are diagnosed in an emergency context[17]. Efforts to prevent emergency presentations are justified because such diagnoses are associated with worse clinical outcomes and patient experience[24,48,49]. The majority of evidence suggests that patients affected by chronic conditions have a higher risk of diagnosis of cancer as an emergency[39,48,50-62] (Figure 1). An English study on emergency diagnosis of any cancer reported a 1.3 risk ratio (95%CI 1.1-1.7) for patients with any comorbidity compared with those without (i.e. Charlson comorbidity score of 1 versus 0)[60]. Similarly, compared with patients without any comorbidity, the risk of emergency colorectal cancer diagnosis was higher for patients with one comorbidity (OR=1.5; 95%CI 1.4-1.6) and even higher for 3+ comorbidities (OR=2.0; 95%CI 1.8–2.2)[48]. This concords with a US study showing higher risks of emergency presentations for colorectal and lung cancer (OR=1.89; 95%CI 1.7-2.2 and OR=3.79; 95%CI 3.1-4.6, respectively) among patients with one versus no chronic disease[39].

Only a few studies examined the effect of specific conditions on emergency cancer diagnoses[54,62-66],

and some conditions appear to be associated with particularly high risks, including dementia, cardiac and neurological diseases[54] (dementia OR=2.46; 95%CI 2.2-2.8; congestive heart failure OR=1.49; 95%CI 1.4-1.6). Among women younger than 60 years of age, benign gynaecological and new onset gastrointestinal conditions were associated with particularly higher risks of emergency colon cancer diagnosis (adjusted OR=3.41; 95%CI 1.17-9.93 and 2.84; 95%CI 1.04-7.70, respectively, after accounting for symptomatic presentation, other comorbidities and socio-demographic factors)[62]. Obesity has also been associated with emergency presentations[65].

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[64]. Likewise, hypertension monitoring in primary care was also associated with a lower likelihood of emergency colon cancer diagnosis in a longitudinal UK population-based study, taking symptoms, various comorbidities and socio-demographic factors into account (for example, among 70-79 year old women adjusted OR=0.62; 95%CI 0.43-0.92,)[62].

In summary, similar to the impact on cancer stage, some conditions, such as dementia, neurological and cardiac conditions are associated with an increased risk of emergency diagnosis. In contrast, hypertension can be associated with a lower risk of emergency cancer diagnosis. This is also in line with previously mentioned studies reporting a lower risk of advanced cancer stage at diagnosis for hypertensive patients. Hypertension is a risk factor associated with cardiovascular diseases, rather than a chronic disease per se. However, it is worth considering that its management, which can involve frequent healthcare contacts, can influence diagnostic timeliness.

## 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 one chronic condition compared to those with none (adjusted OR 1.31; 95%CI 1.17-1.46, controlling for age, education, country of birth and other socio-demographic factors) or two or more conditions (adjusted OR=1.2; 95%CI 1.05-1.32), according to a large Canadian population-based cohort study[67]. However, after accounting for disability, which is often associated with chronic conditions, women with severe disability are less

likely to participate in breast screening compared with those with moderate (adjusted OR=0.72; 95%CI 0.63–0.82) or no disability (adjusted OR=0.88; 95%CI 0.78–0.99)[67]. The highest screening proportion (75%) was observed among women with one chronic condition and moderate disability, with the lowest referring to women with two or more conditions and severe disability (61%)[67]. Similarly, a large Canadian study using linked data reported that women with a no chronic condition and no disability had the highest proportion of cervical cancer screening (64.5%), while the lowest proportion was observed among women with two or more morbidities and severe disability (39.8%)[68]. Studies in the US have also reported how 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[69]. Further, according to a large population-based cohort study in the US, participation in colorectal cancer screening decreases with increasing levels of comorbidity (88% of 65-69 year old individuals underwent screening if their Charlson score was 0 versus 82% if their score was $\geq$4, p<0.001)[70].

Considering specific chronic conditions, two large US population-based surveys have shown that women aged 40 years or older with diabetes are more likely than those without to be screened for colorectal cancer[71,72]; specifically, screening prevalence was 63% versus 60% (p<0.05) among diabetic versus non-diabetic women, adjusted OR=1.14; 95%CI 1.04-1.24, accounting for socio-demographic factors, health insurance, body mass index and smoking[71]. The opposite effect was reported by a different US population-based survey among older women (≥67 years) (adjusted OR=0.79; 95%CI 0.70-0.88)[73]. These American studies were limited to women only, but an English prospective survey of 55-year old men and women has shown a lower probability of flexible sigmoidoscopy screening for individuals with diabetes compared to those without (adjusted OR=0.48; 95%CI 0.25-0.94)[74].

Women with diabetes were also less likely to participate in breast cancer screening compared to non-diabetic women in two large Canadian studies[75,76] (60% versus 66%; OR=0.79, 95%CI 0.78-0.80, after adjustment for socio-economic status and overall comorbidity)[75]. Similarly, two other Canadian studies, found a lower participation in breast cancer screening in women with HIV infection (50% versus 63%)[77] or depression (46% versus 62%; adjusted OR=0.63; 95%CI 0.40-0.97)[78], while evidence from Spain indicates that this was also the case in obese women (64% versus 69%)[79]. Two US studies have also reported how obesity is associated with a lower participation in breast[80] and cervical[81] screening, after adjustment for socio-demographic factors, health care access, general health status, other comorbidities and health-seeking behaviour.

In contrast, musculoskeletal conditions are associated with a higher probability of breast screening in a Spanish study (75% versus 63% in women with and without musculoskeletal conditions; adjusted OR=1.46; 95%CI 1.22-1.77)[79].

In summary, individuals with multiple chronic disease are less likely to participate in breast, cervical and colorectal cancer screening, especially if there is associated disability. Regarding specific conditions, HIV infection, depression and obesity are associated with a lower probability of cancer screening. In contrast, musculoskeletal conditions are associated with a higher probability. Heterogeneous effects have been reported for individuals with diabetes.

**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[63,82-86], with some diseases being associated with shorter[87] and others with longer patient intervals[88-92], while some studies[93-95] found no such effects (Figure 1).

A study of patients with lung cancer[91] 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[90] highlighted how pre-existing cardiac conditions were associated with a lower likelihood of help-seeking for change in bowel habit (OR=0.4; 95%CI 0.2-1.0); in contrast, hypertension increased help-seeking for persistent cough (OR=2.0; 95%CI 1.1-3.5) or abdominal bloating (OR=2.3; 95%CI 1.1-4.8) and chronic urinary diseases increasing help-seeking for rectal bleeding (OR=5.8; 95%CI 1.4-23.8). A small Japanese study on 134 cancer patients reported how individuals with dementia had sought help less frequently for cancer symptoms compared to individuals without dementia (8% versus 63%, $p<0.001$)[96].

In summary, the evidence on the effects of chronic diseases on help-seeking is heterogeneous, depending on the chronic condition and cancer site. While some studies showed no association, others reported longer patient intervals, for example when chronic conditions and cancer have overlapping symptomatology (COPD and lung cancer) or when 'serious' diseases (cardiac conditions) are present; in contrast, hypertension is associated with help-seeking for potential cancer symptoms.

**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[58,94,97-99] 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[94] or on gastroscopy rates among oesophago-gastric cancer patients[58].
On the other hand evidence on the effects of specific chronic diseases is provided by several studies[2,40,57,82,85,86,88,89,95,99-102]. In particular, congestive heart failure or coronary artery disease can lead to missed opportunities to refer patients promptly for endoscopic examination[101], 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 (adjusted OR=4.0; 95%CI 1.1-13.9)[85]. End stage renal disease can have heterogeneous effects according to a US cohort study, increasing the likelihood of colonoscopy/flexible sigmoidoscopy (OR=3.65; 95%CI 1.21-11.03) and decreasing the likelihood of PSA testing (OR=0.59; 95%CI 1.21-11.03)[40].

***Diagnostic interval (from first presentation to diagnosis).*** Some studies examined disease-specific effects on the diagnostic interval[31,57,82,83,85,86,88,95,100,103,104]; others only examined the overall effect of any chronic disease[84,94,98,99,102,105-110] (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[108,109] and one on lymphoma[98]. For example, chronic lymphocytic leukemia patients with a pre-existing condition (versus none) had OR=2.83 (95%CI 2.5-3.3) for a prolonged diagnostic interval (defined as longer than the average time of 63 days between first symptomatic presentation and diagnosis)[109]. A longer diagnostic interval was also reported among upper aero-digestive tract cancer patients with a pre-existing disease versus none (OR=2.84; 95%CI 1.35-5.98)[105] and for oral cancers (42% of individuals with sever comorbidity level had a diagnostic interval $\geq$1 year, compared to 7% among individuals with modest or no comorbidity, p=0.002) [84]. Among laryngeal cancer patients[105], 42% experienced a diagnostic interval of more than one year if Charlson comorbidity score$\geq$3, compared to 7% if comorbidity score 0-2.

A UK cohort study on colorectal cancer based on electronic primary care records[103] showed that specific diseases are associated with longer intervals before the cancer diagnosis: inflammatory

bowel disease was the condition most strongly associated with an increase in the diagnostic interval (a median increase of 26 days [14 to 39]; and a geometric mean value 1.33-fold greater [95%CI 1.18-1.51] in patients with inflammatory bowel disease, controlling for age and gender); other conditions associated with significantly longer diagnostic intervals were coronary heart disease (15 days [7 to 24]), anxiety/depression (9 days [3 to 17]) and diverticular disease (14 days [3 to 27]). 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[95]. 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, $p<0.001$)[31].

***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[111] 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; 95%CI 1.1-1.3)[97]. Such occurrences are thought to primarily reflect missed lesions or incomplete polypectomy at the index colonoscopy[112]. Pre-existing diseases might lead to difficulties with bowel preparation[113] and/or increased technical difficulties for the endoscopist[114,115] or reduced patient tolerance during the examination, interfering with the endoscopic examination and possibly increasing the risk of missed lesions.

In summary, the evidence on the effects of chronic conditions on the diagnostic process indicates that they are associated with a lower likelihood of prompt specialist referral and lower use of specialist investigation (such as colonoscopy) and with prolonged diagnostic intervals. For some conditions, including cardiac and psychiatric conditions, such findings have been reported across cancer types; for other conditions (inflammatory bowel disease or diverticular disease) this applies to specific cancers presenting with similar symptomatology (colorectal cancer). Differently from other conditions, end stage renal disease can be associated with a higher likelihood of colonoscopy/flexible sigmoidoscopy.

**MECHANISMS OF INFLUENCE**

While quantitative research has allowed to document associations with diagnostic outcomes, thus far, there is a lack of quantitative studies specifically designed to evaluate the mechanisms by which chronic diseases might influence the cancer diagnosis (Box 2). Currently, details on possible mechanisms are mostly 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.[18,30,36,103] | COPD and lung cancer[82,91]; IBD/IBS/diverticular disease and colon or ovarian cancer[86,103]; Beta-blocker or statin-associated GI symptoms and CRC[88] |
| • **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.[116] | Cardiac conditions and CRC[90,103]; |
| • **Pathological hypothesis**: Some chronic conditions or their treatments interact with cancer pathogenesis, influencing cancer aggressiveness at the cellular or physiological level.[30,117] *(For related effects in the opposite direction see below)* | Diabetes and CRC[32,118] |
| **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[89] |
| • **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. [86] | Mental health conditions and colorectal cancer[63,85,86] |
| • **Fatalism** (due to morbidity-related poor health) leading to reluctance to undergo investigations or cancer screening. | Multi-morbidity and breast or colorectal cancers[69,89] |
| • **Communication problems** due to specific chronic conditions. | Dementia, mental health, hearing problems and GI cancers[31,47,96] |
| **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 or they might recommend cancer screening.[119] | Hypertension or musculoskeletal conditions and CRC[62,79,90,92] |
| **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. | COPD and lung cancer[82,92] |
| • **Positive expectations** due to previous experiences with chronic disease management. | Treatment of COPD-associated chest infections and lung cancer[82] |
| • **Priorities** with respect to diagnosing cancer early or facilitating access to health services for patients with specific conditions. | COPD 'management programs' and lung cancer[92] |
| • **Pathological hypothesis**: Interactions between chronic conditions/treatments and cancer (e.g. aspirin) can reduce the risk of metastasis (via effects on platelet functions and other effects). Biological interactions can also influence symptoms, for example, end stage renal disease can be associated with GI bleeding (due to uremic platelet dysfunction and anticoagulation given during dialysis), increasing the likelihood of early cancer diagnosis.[40] | Aspirin and CRC[10]; end stage renal disease and CRC[40] |

*Notes: COPD Chronic Obstructive Pulmonary Disease; IBS Irritable bowel syndrome; IBD Inflammatory bowel disease; CRC Colorectal cancer; GI Gastro-intestinal.*

## MECHANISMS INTERFERING WITH TIMELY DIAGNOSIS

### 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[88,120] 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[63,82,86,88,91]. 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[57 82] when symptoms are attributed by the doctor to a pre-existing disease or its treatments, despite repeated symptomatic presentations[63,86]. Alternative explanations can also be reinforced by doctor-patient interactions[83,88] (Supplementary Table 3). Interviews with GPs[102] 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[103] 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[86] and significant event audits[57] 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[90] 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[89]. For example patients with congestive heart failure or coronary artery disease, might not be referred promptly for endoscopic investigation of possible colorectal cancer symptoms[101]. Another study[103] 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[75,76 77 78].

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'[36] is supported by some studies[6,30,117]. For example, chronic conditions such as severe renal diseases may be associated with a compromised immune system and metastatic prostate cancer[36]. Moreover, research on diabetes suggests direct and indirect effects of insulin on cancer growth in patients with diabetes and/or obesity[118,121]. Poorly controlled type 2 diabetes is associated with increased risk of advanced colorectal cancer[32], 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[4,118,121 34].

Pathological and biological interactions can also have the opposite effect, reducing the risk of advanced cancer stage. For example, patients on dialysis for end stage renal disease will likely have uremia-related platelet dysfunction and be on regular anticoagulant treatment, increasing the

probability of gastrointestinal bleeding. This might explain the higher likelihood of colonoscopy and early detection of colorectal cancer in these patients[40].

**Novel 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:

***Patient worries of appearing hypochondriac and repeated consultations.*** 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[63]. 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[86], 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[100]: 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[122].

***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[82 99]. 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[102].

***Fatalism.*** Poor health status associated with multi-morbidity can lead to patient's reluctance to undergo invasive cancer investigations[89,92]. 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[69]. 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[31]. In addition, patients with dementia and mental health conditions can also have difficulties with problem-solving behaviour and decision-making possibly interfering with timely cancer diagnosis[47,96].

**MECHANISMS FACILITATING TIMELY DIAGNOSIS**

**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[90]. Sometimes patients feel that help-seeking for vague symptoms is only appropriate if the consultation is 'justified' by a co-existing morbidity[123], consistent with UK evidence that 'not wanting to waste the GP's time' can be a barrier to help-seeking[124].

***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[100]. In some cases, the cancer is detected incidentally when undergoing investigations for another condition[82].

***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[79].

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

### Novel mechanisms

The following additional mechanisms of influence associated with shorter patient and diagnostic intervals have emerged from the review (Box 2 and Supplementary Tables 2-3):

***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[92]. 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[82]. 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[82].

***Priorities and 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[92]. 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[88,92].

## 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 and Box 3).

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**Box 3: Framework interpretation (see also Figure 2)**

Chronic diseases can make the diagnosis of cancer less or more timely (red or green arrows in figure 2, respectively). These effects may be mediated through various mechanisms (red and green boxes) influencing distinct steps along the diagnostic pathway. Chronic diseases and their treatments may also influence cancer progression (top, yellow arrow) through pathological interactions (increasing or reducing the risk of rapid progression). Other factors (bottom, yellow boxes) including patient, healthcare and tumour factors, can also influence diagnostic timeliness.

Movements along the pathway are not always linear; some steps may be repeated before diagnosis (blue and orange circles and dotted orange arrow), especially if patients initially receive a non-cancer diagnosis (orange box). When symptoms persist or evolve, the patient will likely re-appraise symptoms and seek help. Chronic non-cancer diagnoses can possibly delay help-seeking through various mechanisms (alternative explanations, competing demands, worry to be seen as hypochondriac, fatalism due to poor health status). In contrast, tests or medical consultations performed for a chronic disease, might allow earlier diagnosis of cancer (surveillance effect).

Cancer can sometimes be diagnosed as an emergency (dark red box), for example when repeated consultations did not lead to a timely cancer diagnosis (e.g. colorectal cancer progresses to bowel obstruction in patients with diverticular disease) due to chronic conditions with overlapping symptoms providing an alternative explanation.

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Novel mechanisms of influence have emerged (Box 2), which integrate previously hypothesised theories, including the 'alternative explanations', 'competing demands', 'surveillance effect'[18,30,36,103] and 'pathological hypothesis[30,117]. 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. Patients' overall health status and prognosis, in relation to their chronic diseases, can also influence healthcare providers' decision-making and recommendations to their patients regarding screening as well as diagnostic 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. In particular, age, socio-economic factors (associated with multi-morbidity)[125] and social support might modify the effect of chronic diseases on diagnostic processes and outcomes. 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[31]. Communication difficulties and worries of appearing hypochondriac may also interfere with reporting of cancer symptoms in patients with mental health problems[63,89]. In addition, dementia and other mental disorders can be associated with cognitive impairment and difficulties in problem-solving and decision-making, which might interfere with cancer screening, adherence to medical recommendations and diagnostic investigations[41,47,96]. For example, cognitive impairment and emotional issues might complicate the informed consent process, discouraging healthcare providers from recommending invasive investigations[41]; patients might also not undergo investigations due to difficulties in adhering to specific recommendations (e.g. bowel preparation for

colonoscopy)[122]. The relationship between dementia and cancer is particularly complicated, as some studies suggested also a direct biological effect, with patients with Alzheimer's disease possibly being less likely to develop cancer, as well as less likely to be diagnosed with cancer through screening[126].

As mental health conditions are common in the general population[31,127,128], 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, communicating their healthcare needs and navigating the healthcare system. Thus, interventions for their treating physicians and supporting access to healthcare services may be particularly justified.

***Aggregate comorbidity measures***

While commonly used summary measures, such as the Charlson Comorbidity Index, originally developed for predicting mortality, can provide useful information on the overall burden of comorbidity experienced by individuals, their use for evaluating the impact of chronic diseases on diagnostic timeliness should be carefully considered. All the chronic diseases included in the Charlson index are associated with an increased mortality risk (albeit with different weights). In contrast, not all chronic conditions increase the risk of advanced disease. Thus, the same weighted sum used on the basis of associations with mortality could lead to uninformative results in the context of diagnostic timeliness studies, given that some conditions may increase and others decrease the risk of advanced cancer at diagnosis.

While summary measures may offer some advantages in terms of statistical analysis, rather than weighting each condition based on their impact on mortality, different weights would be necessary in order to adopt the index for evaluating diagnostic timeliness. Weights might also depend on the cancer type.

Moreover, severity and duration of the chronic condition and related treatments are not considered in commonly used comorbidity indices, while they can influence diagnostic processes and outcomes. In addition, some diseases, such as psychiatric conditions, that can be particularly relevant in the context of timely cancer diagnosis, are not included. Overall, existing summary indices, while being a useful measure of overall burden of comorbidity, have important limitations and need to be adapted and validated before using them for evaluating the effect of chronic diseases on timely cancer diagnosis. Considering each chronic condition individually may have important merits, providing useful insights and allowing the development of targeted healthcare interventions.

## 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 and duration, 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[129]. 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. Most studies report prevalence odds ratios, which might provide a biased estimate of the prevalence rate ratio if the rare disease assumption is not met (when the outcome of interest is fairly common). Absolute estimates and their difference are particularly useful from a clinical point of view, but studies do not consistently report them.

## Implications for policy and practice

The reviewed evidence and the proposed theoretical framework can inform the development of targeted strategies aimed at improving early cancer diagnosis for people with pre-existing conditions (Exemplified in Box 4).

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**Box 4: How the framework can help develop strategies for improving timely cancer diagnosis**

The proposed framework can be used by healthcare providers, policy-makers and researchers for identifying targets and possible actions for improving timely cancer diagnosis for patients with chronic conditions and to identify relevant processes leading to more advanced cancer. Disentangling the mechanisms will allow the development of possible interventions. For example, individuals with mental health conditions are less likely to participate in cancer screening and can delay help-seeking for possible cancer symptoms. They are also less likely to be promptly referred if they develop cancer symptoms. This suggests that interventions are needed in both the pre-symptomatic and symptomatic stages.

Moreover, identifying specific mechanisms involved can suggest possible targets for interventions. For example, individuals with mental health conditions might be more likely to worry about being perceived as hypochondriac and be more prone to fatalism because of poor health status (due to multi-morbidity), with an increased risk of delays in help-seeking for symptoms. They might also worry about investigations and how to navigate the healthcare system, interfering with screening and diagnostic testing. Such information can inform the development of appropriate support for these vulnerable patients.

The primary care interval can also be influenced by similar mechanisms. Doctors might dismiss possible cancer symptoms, interpreting them in light of anxiety disorders in patients with mental health conditions who consult frequently ('hypochondriac effect'); patients' poor health status might also affect doctors' propensity to refer them for invasive investigations. Clinical decision-support tools and healthcare models promoting greater care integration might be needed here.

The framework can also highlight areas and mechanisms where chronic diseases could offer opportunities for earlier diagnosis. For example, through the surveillance effect, whereby frequent encounters with healthcare providers can offer opportunities for diagnosing cancer earlier, could be used in the case of patients with mental health conditions. Novel technologies allowing less invasive and simpler cancer tests, for example quantitative FIT, could be particularly useful for patients whose clinical condition may make it difficult to tolerate a colonoscopy.

Finally, the framework can be used by researchers to identify areas where evidence is lacking and further studies are needed.

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The global burden of chronic diseases and multimorbidity has increased over the last decades[130], due to lifestyle factors and improved life expectancy[131-135], 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[132,136,137]. Further, one in four deaths before the age of 60 are due to chronic conditions[19 130]. This underscores the importance of improving cancer diagnosis and management in the context of chronic diseases[19,125,138,139].

According to the Social Cognitive Theory[140] 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[123], but also 'barriers' if the patient and/or doctor perceive the pre-existing condition as more important[18 141]. 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[13,17,142,143] 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)[13]. 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[144] 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[145]. 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 Denmark and England[146-149]) for patients with serious but non-specific symptoms could also be useful in the case of diagnostic complexities due to pre-existing chronic diseases. Although such centres have not been specifically developed for patients with pre-existing conditions, ongoing evaluations of their effectiveness in achieving timely cancer diagnosis in complex patients could generate relevant evidence in the near future[149,150].

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. It also remains important to ensure that screening recommendations take the severity of chronic conditions and the presence of life-limiting conditions into account, evaluating benefits and risks[151]. 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[152,153].

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[100,154].

**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[155-158].

There is limited evidence on specific symptom-morbidity pairs[57,63,82,100]: 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. Studies analyzing data from electronic health records could also be used for evaluating the effects of treatments for chronic conditions on timely cancer diagnosis at population level, expanding the currently limited evidence [10,86].

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[158]; 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. Considerations on the overall prognosis and life expectancy[159,160], in relation to pre-existing chronic conditions (which might include history of cancer) can play an important role in influencing diagnostic decisions. 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[157,161].

Finally, tailored risk-assessment tools need to be developed that take chronic morbidities and their treatments 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 the timeliness of 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 lower 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 (including the availability of specialist nurses) and greater integration of diagnostic services between primary and secondary care to optimise the management of multi-morbid patients and expedite cancer diagnosis.

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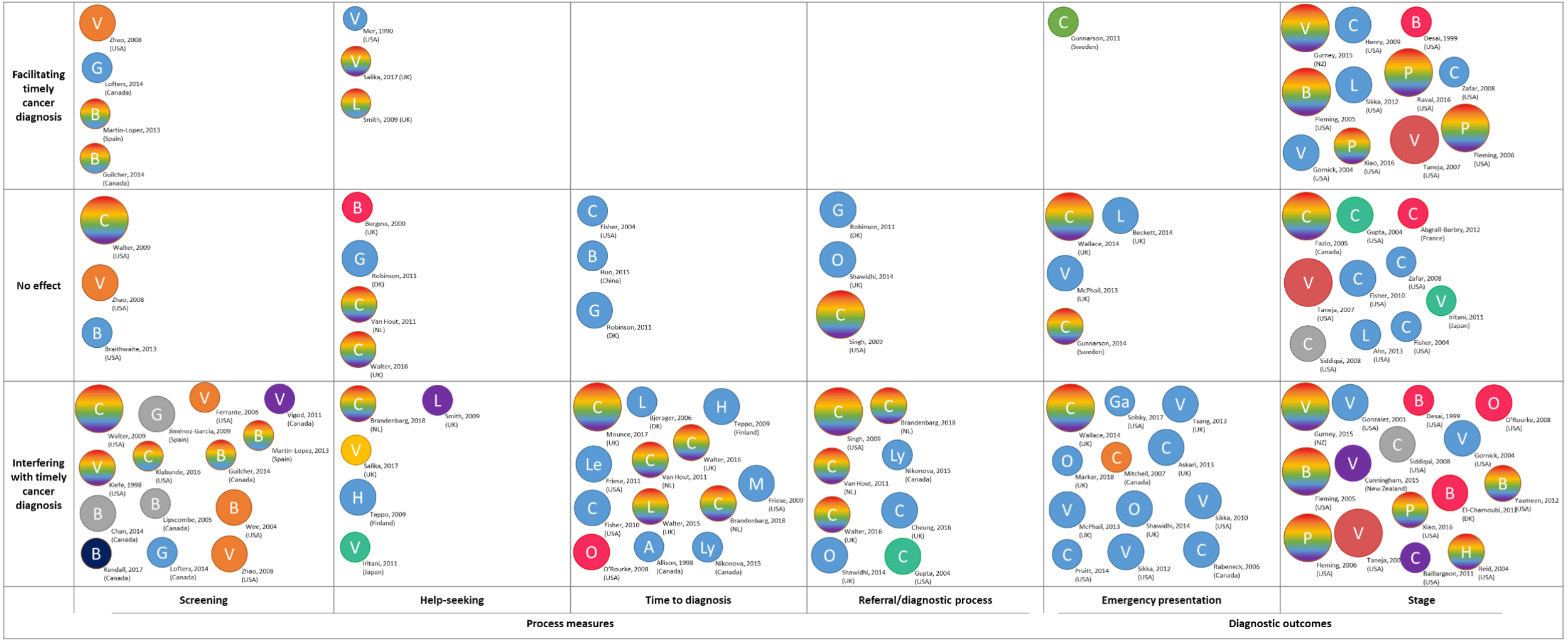
**Figure 1: Overview of studies providing evidence on the role of chronic diseases in influencing the diagnosis of cancer (studies providing quantitative evidence are shown here)**




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
Kidney disease
Dementia

*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 can influence the timely diagnosis of cancer along the diagnostic pathway**