Interventions to reduce diagnostic errors in cancer care within primary care settings: a protocol for an evidenced gap map [EGM]

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Background

Diagnostic errors in healthcare contribute significantly to preventable harm including considerable morbidity and mortality (Graber et al., 2005; Hogan et al., 2015; Newman-Toker et al., 2020). At its broadest, diagnostic errors have been defined as the failure to "(a) establish an accurate and timely explanation of the patient's health problem(s) or (b) communicate that explanation to the patient" (Balogh et al., 2015 p.85), emphasising outcome rather than specific diagnostic processes (Graber et al., 2005; Newman-Toker, 2014).

Whilst diagnostic errors can occur anywhere in the healthcare system, diagnostic errors in primary care have been recognised as a priority safety area globally (Cresswell et al., 2013; Singh et al., 2017a). A general practitioner typically provides primary care and is usually the first point of contact for patients and acts as a gatekeeper for referrals to specialist care (Singh et al., 2017a; World Health Organization, 2018). A diagnostic error rate of 4.3% is reported among adults in English primary care (95% CI 3.6% to 5.2%) with approximately 40% leading to severe harm (Cheraghi-Sohi et al., 2021). It has been estimated that this could equate to approximately 15 million missed diagnostic opportunities annually in the UK; with up to 6 million cases of potentially avoidable moderate to severe harm (Cheraghi-Sohi et al., 2021). Similar rates have been reported in the US (Singh et al., 2014).

Whilst the disparities in health care access and outcomes are widely reported there are limited data on the relationship between protected groups and diagnostic errors, that seem likely to include disparities by age, race and ethnicity, sex, gender, geographic location, socioeconomic status and disability (Ibrahim & Pronovost, 2021). Theoretical explanations include unconscious biases in clinical decision-making (Iudici et al., 2024), and cultural differences such as language barriers (Bell et al., 2023; Car et al., 2016). Another important disparity is diagnostic overshadowing, particularly for people with learning disabilities where clinicians may misattribute medical symptoms to the cognitive impairments associated with learning disabilities (England & Improvement, 2019; NHS England, 2022).

Diagnostic process breakdowns: where diagnostic errors may occur

Medical misdiagnosis in the literature is usually framed as commencing after the patient has sought healthcare (Cresswell et al., 2013) and can occur in any phase of an often-complex diagnostic process. Singh et al (2017) outline five key diagnostic processes where missed diagnosis may occur illustrated in Figure 1, including 1) the patient-provider clinical encounter (e.g., inadequate history taking; failure to order tests or make referrals); 2) performance and/or interpretation of diagnostic tests; 3) follow-up and tracking of diagnostic information (e.g., delays in follow up of abnormal test results); 4) subspecialty and referral related communication and coordination (e.g., access and

quality of contact with appropriate specialists); and 5) and patient behaviour (e.g., failure to provide accurate medical history).

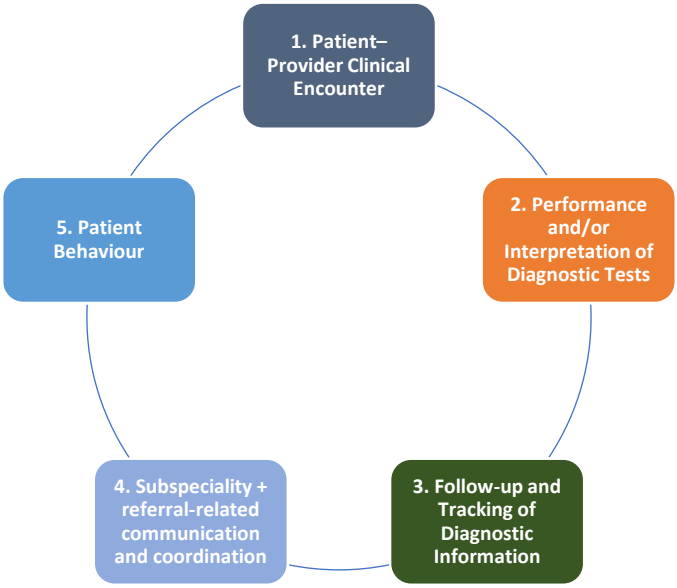

Figure 1. Five key breakdown points proposed by Singh et al 2013.

The most recent prevalence studies in the UK (Cheraghi-Sohi et al., 2021) and US (Singh et al., 2013) indicate that process breakdowns in the patient-provider encounter are the most common, occurring in 58% of cases in the UK sample (N=89) and 78.9% in the US sample (N=272). The relative impact of the remaining processes varies but when combined indicates a substantial impact of system failures in addition to breakdowns in the patient-clinician encounter. These findings from retrospective studies are corroborated with evidence from surveys of general practitioners (Car et al., 2016; Ely et al., 2012) and malpractice claims (Aaronson et al., 2019; Gandhi et al., 2006) which supports and strengthens the evidence.

Conditions Prone to Diagnostic Errors

Vascular events, infections, and cancers, sometimes referred to as the "Big Three", have been shown to account for approximately 75% of serious harms from diagnostic errors including serious morbidity and mortality (Newman-Toker et al., 2019). Furthermore, fifteen conditions within these categories[1] account for nearly half of all serious harms. Consistent with evidence in the process breakdown section, approximately 85% of causes were attributed to clinical judgment factors (Newman-Toker et al., 2019).

Based on US malpractice claims, misdiagnosis of the "Big Three" are not distributed equally across practice settings with missed vascular events and infections most prominent in hospital emergency departments and missed cancer diagnoses likely leading claims in outpatient settings including primary care (Newman-Toker, 2018; Newman-Toker et al., 2024). Consistent with this, data from a

[1] The vascular category includes stroke, myocardial infarction, venous thromboembolism, aortic aneurysm and dissection, and arterial thromboembolism; the infection category includes sepsis, meningitis and encephalitis, spinal abscess, pneumonia, and endocarditis, and the cancer category includes lung cancer, breast cancer, colorectal cancer, prostate cancer, and melanoma.

clinical negligence scheme in the UK show that cancer is the most common cause of claims (9.3% of 401 claims) in general practice (NHS resolution, 2022) with bowel and breast cancer being the most common. Similarly, audit data on patients diagnosed with cancer showed that of all avoidable delays (n= 3273) approximately half occurred within primary care (Swann et al., 2020). This is consistent with data from a small clinical study showing that approx. 25% of diagnostic errors in English primary care (n=74) were related to cancer (Avery et al 2021). The audit also revealed disparities in delayed cancer diagnosis, with increased delay for older patients, non-white patients and the most deprived patients (Swann et al., 2020). Challenges in diagnosing cancer in children and younger people is also regularly cited as a major concern (Walker, 2021).

Collectively, whilst these studies do not report on the overall rate at which these diagnostic errors occur in all patients (i.e., incidence), they indicate that diagnostic errors for cancer are particularly prevalent and problematic for English primary care. Delayed cancer diagnoses are unequivocally harmful, linked with lower survival rates, more aggressive treatments, worsened quality of life and increased healthcare cost (Forster et al., 2022; Hanna et al., 2020). Furthermore, certain cancers are rising in people under 50 years old who are often more challenging to diagnose (Gunn, 2024). Whilst there have been some reported improvements (Swann et al., 2023) system pressures such as COVID-19, financial strain, and workforce shortages seem likely to have exasperated the problem in recent years.

Interventions

A range of interventions have been developed and evaluated to attempt to reduce diagnostic errors in primary care, targeting both individual (Graber et al., 2012) and system-level causes (Dave et al., 2022; McDonald et al., 2013). However, broad reviews of diagnostic errors have not disaggregated effects by health condition and setting so it is not possible to isolate the effects for cancer within primary care settings, for example (Dave et al., 2022; Graber et al., 2012; McDonald et al., 2013).

Several reviews have looked at diagnostic errors in cancer within primary care specifically. Common types of interventions for reducing diagnostic errors in cancer conditions include decision support tools (such as electronic clinical decision support); diagnostic techniques (e.g., use/access to novel diagnostic tools; guidelines); educational interventions (e.g., audit and feedback, diagnostic reasoning skills, simulation-based training) and workflow optimisation (tracking systems, reminder tools, interactive proformas for referrals (Chima et al., 2019; Goulart et al., 2011; Mansell et al., 2011; Schichtel et al., 2013). These interventions are informed by a variety of theories, but broadly can be categorised into psychological theories to address individual cognitive biases (Kahneman, 2003; Klein, 2008), systems approaches to optimise organisational workflows (Singh et al., 2017b), and behaviour change theories to promote the uptake of new practices(Michie et al., 2011). These interventions target the breakdown points in Singh et al.'s 2013 model suggesting their relevance to the UK English primary care context.

The inadequacy of the current evidence base to inform decision making in this area has been recognised by the Department of Health and Social Care (DHSC), England who commissioned this review. Across existing systematic reviews focusing on cancer, the findings show some beneficial effects for educational interventions on specific content areas, audit and feedback, interactive education, and computerised reminder systems; the findings for decision support tools are mixed. However, these systematic reviews are either limited methodologically e.g., in terms of search strategy and/or are outdated (Chima et al., 2019; Goulart et al., 2011; Mansell et al., 2011; Schichtel et al., 2013).

The evidence suggests that focusing on errors in diagnosing cancer in primary care settings would be useful given its prominence in harmful diagnostic errors. This conclusion aligns with previous research advocating for a focus on diagnostic errors in specific conditions (Newman-Toker et al., 2024) and is supported by representatives from English primary care and cancer care programs.

Aims and Objectives

The aim of this research is to develop understanding of the potential public health impact of interventions for reducing diagnostic errors in cancer conditions within primary care. In this protocol we describe Stage 1 of a larger, two-staged programme of work.

The first stage involves the production of an Evidence and Gap Map (EGM) that will provide a high-level overview of the evidence on interventions for reducing diagnostic errors in cancer care within primary care settings (Stage 1). The EGM will help to inform the scope of an Effectiveness Review (Stage 2) on this topic which will be registered as a separate protocol.

EGMs are underpinned by systematic searches that capture the evidence on a defined topic and characterise the key features visually in a user-friendly and interactive way (Campbell et al, 2022; Shemilt et al, 2022). An EGM aims to describe the key characteristics of the evidence base but does not synthesise findings to evaluate the effectiveness or process of interventions (Schmucker et al., 2013, Gough et al., 2017). Transparently mapping the literature in this way should help identify subtopics with sufficient evidence suitable for an informative in-depth synthesis and highlight areas with limited or no research which can support efficient resource allocation for under-explored topics (Sutcliffe et al., 2017, Saran & White, 2018).

This approach should reduce the risk of conducting redundant reviews on topics already adequately addressed and unhelpful reviews with limited or no evidence. Furthermore, the review process in the subsequent effectiveness review will be streamlined as most relevant studies for synthesis will have already been identified in the EGM.

This EGM aims to address the following questions:

Research question 1: What is the extent of current evidence evaluating the impact of interventions for reducing diagnostic errors in cancer care within primary care settings?

Research question 2: What subtopic(s) would be an appropriate focus for an informative in-depth review of outcome evaluations of interventions in this area?

Methods

We will identify and describe the extant body of research evidence on interventions that aim to reduce diagnostic errors in cancer care within primary care settings.

Eligibility criteria

Studies will be screened for inclusion based on the following criteria:

Topic: To be eligible studies must be explicit that the intervention aims to reduce diagnostic errors in cancer care. This may include studies on reducing delay in cancer diagnosis, improvement of referral processes and cancer investigation methods.

Population and Setting:

Interventions conducted within Primary care will be eligible. Any type of primary care model will be eligible for inclusion.

High-income countries classified by the World Bank[2] will be eligible. Lower-middle-income countries will be excluded due to differences in healthcare infrastructure and diagnostic practices which are not likely to be generalisable to more developed countries (Singh et al., 2017b).

Interventions can target any type of cancer, however, if the number of studies retrieved is too large we may restrict the search to interventions that target the cancers most strongly linked with diagnostic errors (e.g., Swann et al., 2020).

Interventions targeting health care practitioners and support staff involved in the diagnoses of cancer conditions within primary care settings including general practitioners, nurses, and other support staff will be eligible. Interventions aimed at increasing patient involvement in diagnosis, including both adults and children, will also be eligible.

Intervention: All types of interventions will be included unless it is judged by the review team to not be implementable in a UK primary care setting, in which case, it will be excluded with a clear rationale provided.

Broad public health interventions on screening and help-seeking and interventions that involve general practice screening reminders will be excluded as these involve asymptomatic populations. The UK's two-week wait programmes for cancer care and other similar programmes that focus on efficiency *following* a referral from primary care will be excluded.

Interventions delivered to individual health care practitioners or groups or applied at the practice/service level are eligible.

Study design: Any intervention outcome evaluation, or systematic review of intervention outcomes (including overviews of reviews). Randomised and non-randomised evaluations will be eligible.

Comparison: any comparator that does not include the intervention will be eligible

Outcome: Any quantitative measure of diagnostic performance (e.g., accuracy, detection); efficiency (time to diagnosis; stage of disease at diagnosis, delays in access to a specialist); management behaviours (e.g., appropriateness of care, tests ordered); provider knowledge and beliefs (content knowledge, confidence, attitudes); patient behaviour and engagement (attendance at appointments, provision of accurate medical details); and patient clinical outcomes (e.g., survival or mortality rates) regardless of measure and type of reporting will be eligible.

Date limit: a date limit will be applied across the searches to capture data from 2005 onwards. This is to ensure that the evidence is relevant to current practice. Studies from 2004 or earlier will therefore be excluded. If the searches identify a high volume of evidence, we will refine the scope by focusing on the more recent evidence only.

Publication type: intervention outcome evaluation studies and systematic reviews will be eligible. Evaluations reported in journal articles (including conference papers) and PhD theses will be included. Conference abstracts without a full journal paper, letters and editorials will be excluded as these typically have insufficient data, as will books, which typically rely on empirical evaluations

[2] World Bank country classifications by income level for 2024-2025 accessed November 2024

published elsewhere, such as in journals. Preprints will also be excluded, as they are not finalised works.

Language: there will be no language restrictions

Search strategies

Comprehensive systematic searches for primary and secondary research of intervention outcome evaluation studies will be conducted. An information specialist will work in collaboration with the review team to develop the search strategies for the map. Exploratory searches and examination of key papers will be utilised to develop the structure of the search and decide on the best combination of concepts to include within the strategy. The search strategy will include a range of topic key words, synonyms and subject headings for each concept, combined using Boolean operators. A date limit will be applied to the search results to capture studies from 2005 onwards. Language or geographical limits will not be used.

We will search databases of published articles, PhD theses and conference papers. A wide range of databases will be searched spanning the medical, health, primary care, health promotion, public health, and social sciences literature. See Table 1 for a preliminary list of databases. The list will be finalised after further discussion and development of the search strategy.

Table 1. Preliminary list of databases:

Database	**Interface**
MEDLINE Embase PsycINFO Health Management and Information Consortium KSR Evidence	Ovid
CINAHL	Ebsco
Science Citation Index Social Science Citation Index Emerging Sources Citation Index Conference Proceedings Citation Index - Science Conference Proceedings Citation Index - Social Science and Humanities	Web of Science
Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR)	Wiley
Database of Abstracts of Reviews of Effects (DARE) Health Technology Assessment Database	CRD website
International Health Technology Assessment Database (INAHTA)	INAHTA website
Proquest Theses and Dissertations	ProQuest
DoPHER TRoPHI	Eppi centre website

The reference lists of eligible reviews will be scanned for relevant primary studies. Since the key purpose of the map is to inform the design of the subsequent Effectiveness Review (Stage 2) rather than to provide an exhaustive set of studies, supplemental searches such as citation searching of primary studies, contacting authors, obtaining articles that are either not publicly available or unavailable through institutional access at University College of London or University of York and

searching relevant websites will be reserved for Stage 2, once the focus of the in-depth review has been determined.

All search results will be imported into EndNote 20 reference management software and duplicate records removed.

Selection of studies

Bibliographic records will be imported into EPPI Reviewer software v6 which will be used to manage the review process (Thomas et al., 2023) .

Title-abstract screening

Title-abstract screening will be conducted using the 'priority screening mode' within EPPI Reviewer. This mode utilises 'active learning' of the ongoing eligibility decisions made manually by the researchers during the screening process. As decisions are made, unscreened records are continuously reprioritised with those ranked most likely to be eligible placed at the top of the manual screening list. This allows the records most likely to be eligible to be identified first and for reviewers to halt the screening process when the likelihood of obtaining eligible studies is low and does not warrant additional screening effort, improving efficiency. Any unscreened records will be set aside and categorised as 'yet unscreened by humans' and replenished in any review update.

An incremental number of title-abstract records will be pilot screened independently by two reviewers (MR, PD). Their decisions will be compared until a high degree of agreement (90% or more) on inclusion/exclusion is achieved. The remaining title-abstract records will be screened by one reviewer only, except for records flagged by a reviewer as having uncertain eligibility which will be discussed between the reviewers.

The full-text articles for those title-abstract records assessed as potentially eligible will subsequently be manually screened for inclusion.

Full-text screening

Potentially relevant records will be screened independently by two reviewers unless the volume of eligible studies makes double screening inefficient, in which case records will be screened by one reviewer after achieving 100% agreement on a subset of training records (except for those flagged by a reviewer as having uncertain eligibility which will be discussed between the reviewers).

Screening disagreements and uncertainties will be resolved by consensus or by consulting a third reviewer as arbiter if necessary.

Non-English language papers will be translated into English using Google Translate before screening.

Data extraction

Depending on the number of studies identified as eligible we will prioritise extraction of information from the most up to date evidence (last 10 to 15 years only progressing to earlier work if insufficient current work is located)

As in our EGM on active travel (Hollands et al. 2024) we will first prioritise the extraction of information from up to date systematic reviews. This will help us to refine the scope of the map by not describing subtopics that are already adequately synthesised within a recent, existing high quality systematic review. Following this, data will be extracted from the primary research reports in subtopics not already comprehensively covered in the reviews. A prototype classification system to characterise the studies and structure of the map is described below. This will be tested and refined

iteratively using subsets of articles coded independently by two reviewers (MR, PD) . Refinements will be agreed by consensus among the reviewers, involving a third reviewer as arbiter if necessary. Further increments of articles will be extracted by two reviewers until a high degree of agreement is achieved (90% or more), and no substantive changes to the classification system is required. At that point we will either continue with double coding or move to single coding if a more efficient approach is required to keep to the project timetable.

It is planned to extract the following data to identify appropriate sub-topics for the Effectiveness Review in Stage 2. However, these characteristics may be augmented and refined during the data extraction process based on emergent evidence. We will not contact authors to identify missing data, as the primary purpose of the map is to inform the topic of Effectiveness Review in Stage 2. Any missing data will be characterised as 'not reported'.

Prototype classification system to characterise and structure the Map:

Publication characteristics: Reference details; year of publication; type of publication (systematic review; primary evaluation; thesis and other grey literature); and availability of full text.

Setting characteristics: Region (North America, UK; other Europe; Asia-Pacific; Oceania; Other regions). This level of categorisation is deemed suitable for the map as only interventions judged to be relevant to UK context will be included.

Population target(s): Cancer condition(s) targeted (e.g., cancer generally or specific types such as breast, lung, colorectal); Patients targeted: adults, children, family (adults and children).

Intervention characteristics: A broad categorisation of intervention types including but not limited to diagnostic decision support; diagnostic techniques; education interventions; workflow optimisation and patient engagement/safety-netting.

Process breakdown point(s) targeted: Using Singh et al.'s 2013 model each intervention will be mapped onto the process breakdown point(s) that it targets: patient-clinician encounter; performance and/or interpretation of diagnostic tests; follow-up and tracking of diagnostic information; subspecialty and referral related communication and coordination and patient behaviour.

Outcome characteristics: Effectiveness of interventions for reducing diagnostic errors will be broadly categorised as measure(s) of diagnostic errors (e.g., accuracy, detection); diagnostic efficiency (time to diagnosis; stage of disease at diagnosis, delays in access to specialist); management behaviours (e.g., appropriateness of care, tests ordered); provider knowledge and beliefs (increased knowledge and skill); patient clinical outcomes (e.g., survival or mortality rates); and other patient outcomes (e.g., engagement).

Study design: Randomised or non-Randomised evaluation design.

Equity dimensions: We are not anticipating that equity data will be commonly reported. However, we will used a prototype checklist developed at the EPPI centre (available at https://eppi.ioe.ac.uk/cms/Default.aspx?tabid=3939) to explore the range of potentially relevant equity dimensions. Provisionally, we will assess whether the intervention targets and/or reports disaggregated data for the following equity groups**:** race/ethnicity; age (e.g. children; young people; elderly); socioeconomic status (e.g. income, employment, geography); and disability (e.g., learning disability, severe mental health conditions). Whilst the checklist includes a wider set of population

subgroups, we will limit coding to those identified as relevant in Swann et al.'s English audit (2020) study, and those of interest to our stakeholders at DHSC and NHS England.

Study quality: recent existing systematic reviews may be appraised for quality using AMSTAR-2 (Shea et al., 2017), to refine the scope of the map and/or Effectiveness Review. However, we will not appraise the quality of primary studies as the map does not involve synthesis of their findings. Quality appraisal will be conducted on included studies in the Effectiveness Review (Stage 2) which this EGM is designed to inform.

Presentation of the results

An EGM of the evidence will be produced. This will consist of the key dimensions extracted during the data extraction process detailed above. This data will be presented in a digital, online, interactive format using EPPI Reviewer's visualisation software (EPPI-Vis)(Thomas et al, 2022). The format, selection and presentation of the Map's dimensions will be chosen in collaboration with stakeholders of this review at DHSC and NHS England to optimise its appearance and useability.

The EGM will be accompanied by a descriptive narrative summary describing the characteristics of the extant body of research on interventions for reducing diagnostic errors in cancer care within primary care settings. The EGM will either be written up as a separate report or it will form the first Part of a larger report that will also include the Effectiveness Review in Stage 2. This will be decided in collaboration with DHSC and NHS England after the map has been produced.

Use of the Evidence Map to inform the Effectiveness Review (Stage 2)

In collaboration with NHS England and DHSC the map will be used to identify subtopics suitable for the Effectiveness Review in Stage 2. It will also inform our protocol for the Effectiveness Review, which will be registered on PROSPERO and the Open Science Framework. At this stage, we may also carry out additional non-systematic scoping work to locate contemporary and complementary qualitative data on experiences within the subtopic(s) identified as potentially relevant for the Effectiveness Review to ensure their relevance for current practice.

The map will be of wider interest too. For example, it might highlight sub-topics beneficial for future synthesis that cannot be covered in our Effectiveness Review. It may also highlight important gaps in the primary studies and therefore provide useful information for NIHR and other funding bodies.

Stakeholder engagement

There is ongoing policy stakeholder involvement with colleagues at DHSC and NHS England in developing and finalising the methods and products of this work. No public involvement is planned.

Draft Timeline*

Tasks by month (1 to 10)	1	2	3	4	5	6	7	8	9	10	11
Searches											
Screening of records (title-abstract & full text)											
Data extraction											
Evidence Gap Map production											
Draft report and circulate to DHSC and NHS England. Finalise report incorporating feedback											
Develop protocol for Effectiveness Review (Stage 2) in collaboration with DHSC and NHS England											

*Timings are based on the EGM being digitised and written up as a separate report; however, they will likely be shorter if a static version of the map is produced and included as part of a broader report that combines the map and the effectiveness review.

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