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Commissioning Support Unit

Understanding diagnostic delays in Crohn's and Colitis: an evidence review for Crohn's and Colitis UK

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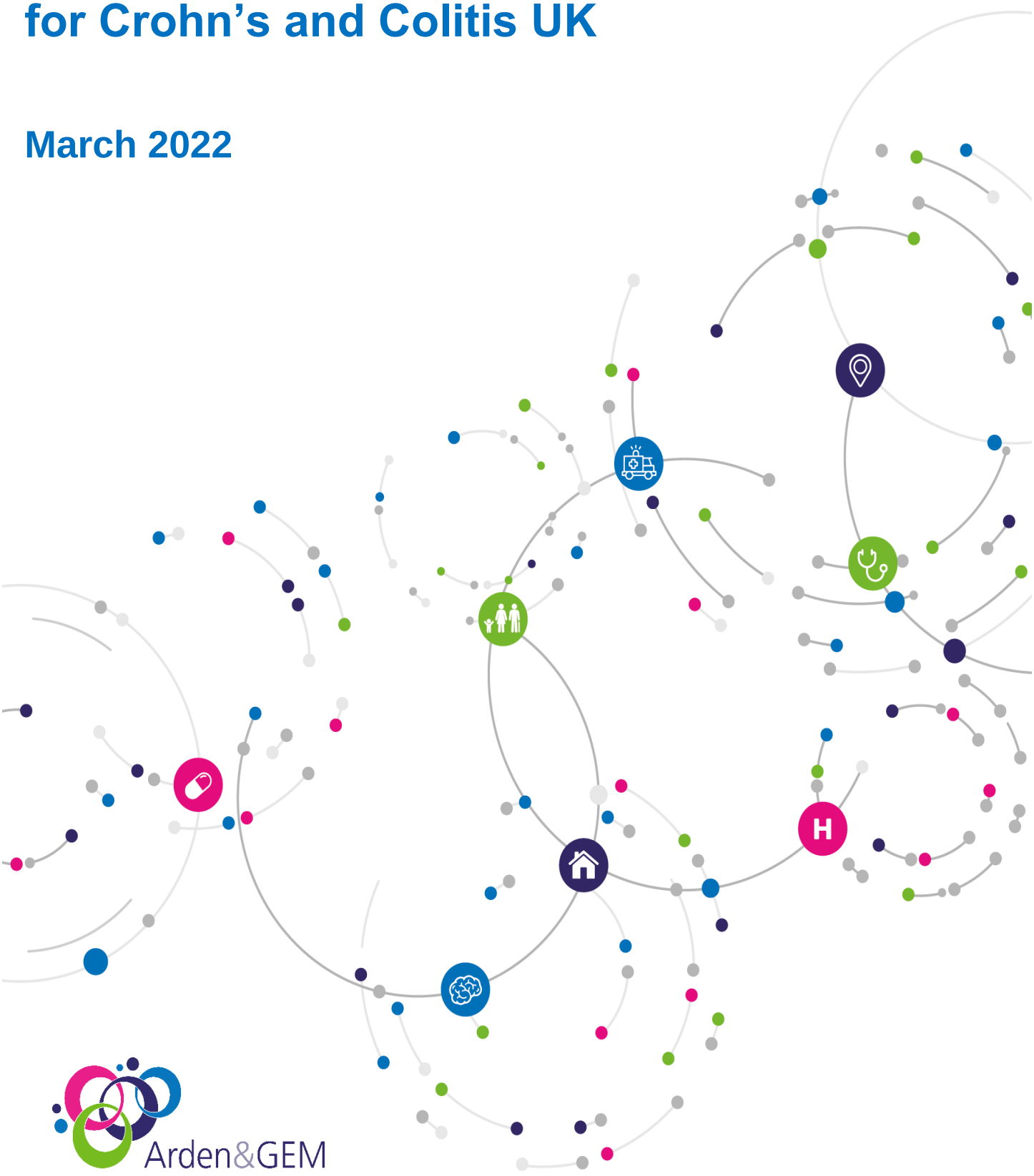

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Health and social care systems support

Contents

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1 Executive summary

1.1 Introduction

Crohn's Disease and Ulcerative Colitis are the most common inflammatory bowel disease (IBD) conditions (NICE 2013). The purpose of this evidence review is to help develop an understanding of where and why diagnostic delays occur in Crohn's and Colitis and to gain insights from how delays in diagnosis have been tackled in other comparative diseases which might help to address diagnostic delay issues in IBD. NHS Solutions for Public Health was commissioned by Crohn's & Colitis UK to produce this evidence review.

The key questions explored in this evidence review are:

1. What is the extent and nature of delayed diagnosis in people with Crohn's or Colitis in the UK and is there evidence for inequalities in the diagnosis pathway?
    a. Frequency of delayed diagnosis and time to diagnosis by geographical area and population subgroups if available
    b. Causes of delayed diagnosis/obstacles to early diagnosis at each stage in the diagnostic pathway, such as patient factors (demographics, awareness of symptoms and seeking medical help), primary care factors (GP awareness and referral process), system factors (such as access to laboratory investigations)
2. What has been shown to work in tackling delayed diagnosis of Crohn's or Colitis and other long-term conditions such as immune-mediated inflammatory conditions and conditions with primary symptoms expressed in the gut?

1.2 Methodology

This rapid evidence review was designed to identify, summarise and appraise the available evidence published since 1st January 2011. Searches for peer-reviewed studies were conducted on 20th December 2021 and 10th January 2022 on the electronic databases CINAHL, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials, Embase, Health Management Information Consortium (HMIC) and Medline. Searches for grey literature reports included database searches on NHS Evidence conducted in December 2021 and a review of key websites conducted in January 2022. Further targeted Google searches to follow up particular details or initiatives were conducted in January and February 2022. Key stakeholders were also consulted for any relevant reports or studies.

1.3 Key findings

1.3.1 The key findings for question 1: The extent and nature of delayed diagnosis

Twenty-three studies assessing the extent and/or nature of delayed diagnosis in people with Crohn's or Colitis in the UK were found. The study designs included surveys, case series, cohort studies, case control studies, audits, analyses of primary and/or secondary care databases and qualitative studies. Most studies covered England or the UK and included both people with Crohn's Disease or Colitis with few reporting a breakdown of results by population subgroup or geographical area.

The studies highlight a wide variability of experience amongst people with Crohn's or Colitis with a substantial percentage of people waiting several months or even years for a diagnosis. However, due to the large heterogeneity between the study designs and results, they do not

provide a clear picture of how often diagnosis is delayed, by how much, and whether differences exist between Crohn's and Colitis, different population subgroups and geographical areas.

A wide range of different potential causes of delay were proposed within the studies relating to different aspects of the diagnostic pathway. These included:

- Lack of awareness or understanding of IBD, Crohn's Disease and Colitis for both the public and GPs which could affect both patient behaviour in seeking medical advice and GP behaviour in the management or referral of patients
- Patients' characteristics, including higher household income, previous diagnosis of irritable bowel syndrome and previous diagnosis of depression, all of which could also introduce potential delay by affecting patient and/or GP behaviour
- Factors relating to the provision of services including access to and confidence in using faecal calprotectin testing in primary and/or secondary care, access to endoscopy and staffing levels
- Factors relating to the organisation of services including variability in whether services had agreed referral pathways between primary and secondary care in place for people with suspected IBD, the speciality that patients are referred to and the frequency of multi-disciplinary team meetings.

Limited evidence was found on the causes of delayed diagnosis in population subgroups.

1.3.2 The key findings for question 2: Interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases

Three studies were found assessing the impact of interventions on time to diagnosis/treatment and duration of symptoms prior to diagnosis in patients with Crohn's or Colitis, all of which assessed faecal calprotectin testing in primary care. A further four studies were found on comparative diseases, all of which focussed on cancer diagnosis. The studies tended to be small with most having sample sizes of between 42 and 274 and were of low to moderate quality. The main quality issues were a lack of an appropriate counterfactual or comparator with no attempt to adjust for differences between the population characteristics of the groups and many of the studies being limited to one centre, often with poor reporting of baseline characteristics of study populations meaning that the representativeness of the study population could not be assessed.

The evidence around faecal calprotectin testing in primary care was inconclusive with none of the studies being able to reliably demonstrate a reduction in time to diagnosis. In terms of learning from comparative diseases, very few evaluated interventions were found. These were limited to a rapid diagnostic centre for patients with vague and/or non-specific symptoms suspicious of cancer, risk assessment tools for suspected bowel and lung cancer in general practice, a health awareness campaign for breast, bowel and lung cancer and two-week wait referrals for suspected upper and lower gastrointestinal cancers. Based on the volume and strength of the evidence found for each it was not possible to reliably determine the impact of the interventions on delayed diagnosis in these diseases and hence whether similar interventions may work for IBD.

Notably no relevant evidence was found for some interventions for which studies might have been expected. Such potentially relevant interventions include screening for IBD in high-risk

groups, training, educational materials and Regional Clinical Champions to improve understanding of Crohn's Disease and Colitis amongst healthcare professionals, or on improving the efficiency and productivity of service pathways and processes such as triaging, telephone straight-to-test pathways, increasing diagnostic testing and workforce capacity, different use of existing workforce such as community pharmacy and digitisation of services.

1.4 Conclusions and recommendations

The studies highlight a wide variability of experience amongst people with Crohn's or Colitis with a substantial percentage of people waiting several months or even years for a diagnosis. Few studies were found reporting findings for Wales, Scotland and Northern Ireland with most studies covering England only or the UK with no breakdown of results by country. Limited evidence was found to reliably determine whether inequalities exist across the diagnosis pathway.

It is recommended that a statistical analysis of the IBD UK survey data could be used to make comparisons by country, region and population subgroup (if recorded in the data) to more reliably determine whether any differences in delays in diagnosis exist by area and population subgroup within the UK (IBD UK 2021).

The evidence base surrounding interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases is limited. Only three studies were found assessing the impact of interventions on time to diagnosis and other related outcomes in patients with Crohn's or Colitis, all of which assessed faecal calprotectin testing in primary care and none of the studies were able to reliably demonstrate a reduction in time to diagnosis. A further four studies were found on comparative diseases, all of which focussed on cancer diagnosis. However, based on the volume and strength of the evidence found for each it was not possible to reliably determine the impact of the interventions on delayed diagnosis in these diseases and hence whether similar interventions may work for IBD. No studies were found on other similar immune-mediated inflammatory conditions.

There is a need for high quality studies with appropriate comparators and adequately powered sample sizes to reliably determine whether promising interventions improve time to diagnosis in IBD and ultimately improve health outcomes for patients. Given the paucity of evidence in the area, it is recommended that key stakeholders are consulted on their experiences of most promising interventions and pathway redesign to focus future research.

2 Introduction

Inflammatory bowel disease (IBD) is a group of conditions that involve inflammation of the gastrointestinal tract, of which Crohn's Disease and Ulcerative Colitis are the most common (NICE 2013). The purpose of this evidence review is to help develop an understanding of where and why diagnostic delays occur in Crohn's and Colitis and to gain insights from how delays in diagnosis have been tackled in other comparative diseases which might help to address diagnostic delay issues in inflammatory bowel disease. NHS Solutions for Public Health was commissioned by Crohn's & Colitis UK to produce this evidence review.

The key questions explored in this evidence review are:

2. What is the extent and nature of delayed diagnosis in people with Crohn's or Colitis in the UK and is there evidence for inequalities in the diagnosis pathway?
    a. Frequency of delayed diagnosis and time to diagnosis by geographical area and population subgroups if available
    b. Causes of delayed diagnosis/obstacles to early diagnosis at each stage in the diagnostic pathway, such as patient factors (demographics, awareness of symptoms and seeking medical help), primary care factors (GP awareness and referral process), system factors (such as access to laboratory investigations)
3. What has been shown to work in tackling delayed diagnosis of Crohn's and Colitis and other long-term conditions such as immune-mediated inflammatory conditions and conditions with primary symptoms expressed in the gut?

The review also identifies and discusses gaps and weaknesses in the evidence base.

To meet the aims of this evidence review a broad search strategy was applied, looking for peer-reviewed and grey literature[1]. This report summarises the approach used for the identification and selection of relevant papers and discusses the key findings and limitations.

A recent report on the incidence and prevalence of IBD in the UK by the University of Nottingham reported that between 2000 and 2020, 103,609 people received a new diagnosis of IBD. This equates to incidence rates of 36.4, 37.3, 30.9 and 35.6 new cases per 100,000 person-years for England, Scotland, Wales and Northern Ireland respectively. The authors stated that the overall UK incidence was highest in 2000 to 2004 and then decreased but remained stable between 2005 and 2020 (Nartey et al 2021a). By disease group, the UK incidence rates per 100,000 person-years were 19.00 for Ulcerative Colitis, 13.33 for Crohn's Disease and 3.81 for IBD unclassified (Nartey et al 2021a). For Microscopic Colitis, the UK incidence rate per 100,000 person-years was 3.57 (Nartey et al 2021b).

There are different elements to the diagnostic process which could be considered to start with a person first experiencing symptoms and finish with a medical diagnosis of an IBD. This time period can be broken down into the time from the person's symptom onset to first presenting to primary care, the time from the first presentation to primary care to the GP making a referral to secondary care and the time from the GP's referral to the diagnosis of IBD by a secondary care specialist. Some indication of what sort of time period might be considered appropriate for these different elements can be gleaned from national guidance

[1] The term grey literature is used here to describe any report not published in a peer-reviewed journal

and standards produced by the National Institute of Health and Care Excellence (NICE) and the 2019 standards produced by IBD UK. For example, both the 2019 IBD standards and the NICE quality standard on IBD include a statement that people referred with suspected IBD are seen/ have a specialist assessment within four weeks of referral (NICE 2015, IBD UK 2019). In addition, the 2019 IBD standards include a statement that endoscopic assessment should be accessible within four weeks (IBD UK 2019).

These guidelines provide useful context. However, studies using any definition of a delayed diagnosis, or implying that a diagnosis could have been achieved earlier, were included in this review. An example of what might constitute a delayed diagnosis is a diagnosis that was unintentionally delayed while sufficient information was available earlier.

3 Methodology

3.1 Search strategy

This rapid evidence review was designed to identify, summarise and appraise the available evidence in a focused area. Whilst rapid evidence reviews are conducted more rapidly than systematic reviews with narrower questions and less extensive review methods[2], they employ the same systematic rigour in the identification and selection of evidence and transparency in the reporting of the methodology and decisions made.

The research questions, search frameworks and databases and websites to search for evidence were initially agreed with Crohn's & Colitis UK and were sent to stakeholders by Crohn's & Colitis UK for comments before finalisation. Stakeholders were asked to provide any relevant reports, publications or studies that they were already aware of and any examples of best practice in tackling late diagnosis. The research questions and search frameworks are presented in Appendix 1.

Searches for peer-reviewed studies were conducted on 20th December 2021 and 10th January 2022 on the electronic databases CINAHL, Cochrane Database of Systematic Reviews and Central Register of Controlled Trials, Embase, Health Management Information Consortium (HMIC) and Medline. Several approaches were used to search for relevant grey literature reports. Database searches on NHS Evidence were conducted in December 2021. A review of key websites was conducted in January 2022. Further targeted Google searches to follow up particular details or initiatives were conducted in January and February 2022 (see Appendix 2 for further details).

For both peer-reviewed and grey literature, we searched for UK studies published since 1st January 2011. We also reviewed the reference lists of selected eligible studies to check for additional potential studies. The detailed search strategies are provided in Appendix 2. Briefly, we searched for studies exploring the extent and nature of delayed diagnosis in people with Crohn's or Colitis in the UK and studies exploring what works in tackling delayed diagnosis in Crohn's and Colitis and other comparative long-term conditions.

[2] For example, by using one reviewer to screen search results rather than this being done independently by two reviewers

3.2 Study selection

Titles and abstracts were reviewed by one reviewer and those clearly ineligible were excluded. Full papers for studies that met the inclusion criteria, or where there was any uncertainty, were reviewed by one reviewer. A second senior reviewer independently reviewed 10% of the title/abstracts retrieved and full studies selected. Any disagreements or uncertainty about exclusion were discussed and a consensus reached.

Reasons for exclusion at the title and abstract stage included:

- Published prior to 2011 or non-UK study
- Conference abstracts, case reports, letters/comment, trial registrations, narrative reviews, animal studies
- Studies focusing on imaging techniques, treatment, burden of disease or predictors of disease outcomes
- Studies focusing on non-gastrointestinal cancers or other non-related conditions
- Clinical guidance on the diagnosis and management of conditions
- Studies about diagnostic issues or tests but not assessing the extent or cause of delayed diagnosis or the effectiveness of an intervention to tackle delayed diagnosis or improve time to diagnosis[3].

Additional reasons for exclusion after review of the full text for studies/reports included:

- No data or outcomes relating to time to diagnosis or tackling delayed diagnosis
- Non-comparative studies about an intervention for which a comparative study had been identified
- Studies relating to disease monitoring rather than diagnosis.

3.3 Data extraction and quality assessment

Data extraction and critical appraisal of the selected studies was conducted by one reviewer. The quality assurance lead independently checked 10% of the extracted study results and critical appraisal.

The papers identified for question 1 comprised a range of study designs. In some cases, only some of the outcomes reported by a study were of interest for this evidence review. The critical appraisal process for papers relating to question 1 was therefore tailored to the individual studies with commentary focusing on any areas of potential concern. Key areas considered in the assessment of quality included the identification/selection/size of the population; the level of detail provided about the study design/population/data sources; the year of data collection; the reporting of the outcome assessment and results and the appropriateness of the statistical analysis (where applicable).

Quality assessment of intervention studies (question 2) was conducted using an amended version of the Early Intervention Foundation (EIF) quality checklist which can be applied across different intervention study designs. We also developed a scoring system to provide

[3] Examples of studies on diagnostic issues or tests that did not meet the inclusion criteria include studies on the diagnostic accuracy of a test in distinguishing between people who do or do not have disease and studies describing or validating new tests

an overview of the level of confidence in the study's results. For further details of the quality checklist see Appendix 3.

4 The search results

The searches returned 7,839 studies or reports (4,852 identified through the peer-reviewed literature searches and 2,987 through the NHS Evidence grey literature searches). In addition, the review of the websites of 18 organisations[4] identified 32 potentially relevant reports for further review. The 12 studies or reports suggested by stakeholders were also reviewed for relevance against the inclusion criteria. Four of these studies were also identified by the searches for peer-reviewed publications. An additional two studies for potential inclusion were identified from follow-up of targeted Google searches or from the review of reference lists from selected studies.

138 studies were judged to be of potential relevance from the review of the title and abstract and were reviewed at full text. In total, 30 studies were selected for inclusion in the evidence review. Figure 1 below summarises the peer-reviewed and grey literature publications included and excluded at each stage of the evidence review.

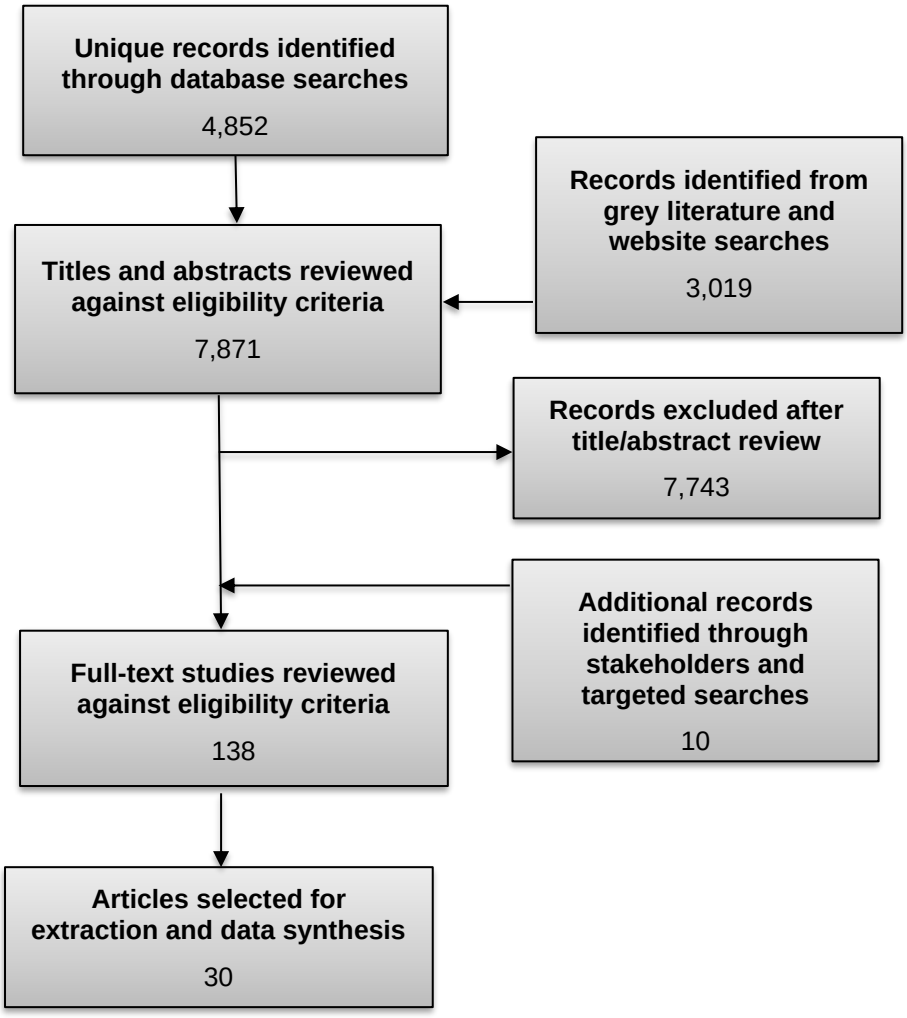

Figure 1. Summary of publications included and excluded at each stage of the evidence review

[4] The websites to search were agreed with Crohn's & Colitis UK

5 The key findings for question 1: The extent and nature of delayed diagnosis

A wide range of different types of studies were identified relating to question 1. These included large UK database studies using data from primary and secondary care, reviews of the records of patients treated at individual hospitals or NHS Trusts, surveys of patients or services and interviews with patients. The type of outcomes relating to the diagnostic period and the study populations and subgroups included also varied. In this section, the key findings from the included studies are structured by the nature of the outcomes reported:

- Section 5.1 focuses on the frequency of delayed diagnosis and/or time to diagnosis for the overall diagnostic period from symptom onset to diagnosis
- Section 5.2 focuses on time to diagnosis for different stages of the diagnostic pathway. For example, from the onset of symptoms to presentation to primary care, from presentation to referral to secondary care or from referral to secondary care appointment or diagnosis
- Section 5.3 focuses on evidence relating to the consequences of delays in diagnosis
- Section 5.4 focuses on potential causes of delays to diagnosis.

Further information and more detailed results from the individual studies for studies relating to question 1 are presented in Appendix 3.

Comparison of the results between the included studies is complicated by the differences in study design and also by how long ago patients were going through the diagnostic process. In survey and interview studies, the data was generally captured by asking people to reflect back on their experiences; in other studies precise dates for appointments in primary or secondary care were taken from databases or individual patient records. Both types of studies may be impacted by potential differences in what might be considered the start and end of the diagnostic process. The generalisability of the results from individual studies is also uncertain. For example, some of the more detailed results are from small samples of patients treated at one hospital or NHS Trust and the applicability to the experiences of patients diagnosed elsewhere is not clear. However, some of the larger database studies and surveys report data covering many years and it is not clear whether the experiences of patients who started the diagnostic process many years ago is similar to those who started more recently. The impact of the COVID-19 pandemic on services was explored in two studies (Ashton et al 2020, Kennedy et al 2020). The pandemic will have impacted patient's experiences of diagnosis and it is not clear how long the impact to services will continue. However, as the authors of one of the studies noted, the insights gained from the rapid adaptations of services during the pandemic may also present opportunities for positive changes to IBD services (Kennedy et al 2020).

Table 1 below provides an overview of the outcomes reported by the studies included for question 1, organised by the outcome categories listed in the search framework (Appendix 1). This table captures the different type of evidence identified relating to question 1, indicating where the source of the evidence was a 'database' study, an 'audit', a 'review' of patients from one or more hospitals, a 'survey' or 'interviews'. Table 1 also provides an indication of areas in which less evidence was identified. The populations and subgroups that the included studies cover are indicated, highlighting the subgroups for which data were identified and where subgroups results were reported or compared within individual studies.

Table 1: Overview of the included studies related to question 1

		Frequency of delayed diagnosis	Time to diagnosis	Prevalence and nature of initial misdiagnosis	Disease severity at diagnosis	Prevalence and duration of symptoms prior to diagnosis	Healthcare usage prior to diagnosis	Potential causes of delay	Clinical outcomes affected by delayed diagnosis
Age groups	**Study with comparison of or breakdown of results by age groups**	• IBD UK 2021 (patient and service survey)	• Fernandes et al 2021 (review) • Walker et al 2020a (review)	• Card et al 2014 (database) • Fernandes et al 2021 (review)		• Fernandes et al 2021 (review) • Nartey et al 2021a (database)		• IBD UK 2021 (patient/ service survey)	
	Adults	• Alexakis et al 2015 (interviews) • Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Canavan et al 2014 (database) • Goodhand et al 2012 (review) • IBD UK 2020a (patient survey) • Misra et al 2019 (review) • Taylor et al 2021 (review) • Ward et al 2013 (review)	• Alexakis et al 2015 (interviews)	• Misra et al 2019 (review)	• Barratt et al 2011 (patient survey) • Canavan et al 2014 (database) • Walker et al 2020a (review)	• Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Mukherjee et al 2015 (interviews) • Walker et al 2020a (review)	
	Children and young people		• Fernandes et al 2021 (review) • IBD UK 2020b (patient survey) • RCPCH & BSPGHN 2021 (audit)	• Fernandes et al 2021 (review) • Jones et al 2018 (review) • Paul et al 2017 (review)		• Fernandes et al 2021 (review)		• Ashton et al 2020 (survey of services) • RCPCH & BSPGHN 2021 (audit)	Ashton et al 2020 (survey of services)
	Adults and children (results not separately reported)	• RCGP and Crohn's & Colitis UK 2020 (patient and GP survey)	• Blackwell et al 2020 (database)	• Card et al 2014 (database)		• Blackwell et al 2020 (database) • Card et al 2014 (database)	• IBD UK 2021 (patient/ service survey)	• Blackwell et al 2020 (database) • Kennedy et al 2020 (survey for services) • Nartey et al 2021a (database) • RCGP and C&C UK 2020 (patient and GP survey)	

		Frequency of delayed diagnosis	Time to diagnosis	Prevalence and nature of initial misdiagnosis	Disease severity at diagnosis	Prevalence and duration of symptoms prior to diagnosis	Healthcare usage prior to diagnosis	Potential causes of delay	Clinical outcomes affected by delayed diagnosis
Country	**Study with comparison of or breakdown of results by UK countries**		• IBD UK 2020a (patient survey) • IBD UK 2020b (patient survey)					• IBD UK 2021 (patient/ service survey) • Nartey et al 2021a (database)	
	England (or location in England)	• Alexakis et al 2015 (interviews) • Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Fernandes et al 2021 (review) • Goodhand et al 2012 (review) • Misra et al 2019 (review) • Taylor et al 2021 (review) • Walker et al 2020a (review) • Ward et al 2013 (review)	• Alexakis et al 2015 (interviews) • Fernandes et al 2021 (review) • Jones et al 2018 (review) • Paul et al 2017 (review)	• Misra et al 2019 (review)	• Barratt et al 2011 (patient survey) • Fernandes et al 2021 (review) • Walker et al 2020a (review)	• Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Mukherjee et al 2015 (interviews) • Walker et al 2020a (review)	
	Scotland								
	Wales							• CRUK 2018 (database)	
	Northern Ireland								
	UK or multiple countries (results not separately reported)	• IBD UK 2021 (patient and service survey) • RCGP and Crohn's & Colitis UK 2020 (patient and GP survey)	• Blackwell et al 2020 (database) • Canavan et al 2014 (database) • RCPCH & BSPGHN 2021 (audit)	• Card et al 2014 (database)		• Blackwell et al 2020 (database) • Canavan et al 2014 (database) • Card et al 2014 (database) • Nartey et al 2021a (database)	• IBD UK 2021 (patient/ service survey)	• Ashton et al 2020 (survey of services) • Blackwell et al 2020 (database) • Kennedy et al 2020 (survey for services) • RCPCH & BSPGHN 2021 (audit) • RCGP and C&C UK 2020 (patient and GP survey)	Ashton et al 2020 (survey of services)

		Frequency of delayed diagnosis	Time to diagnosis	Prevalence and nature of initial misdiagnosis	Disease severity at diagnosis	Prevalence and duration of symptoms prior to diagnosis	Healthcare usage prior to diagnosis	Potential causes of delay	Clinical outcomes affected by delayed diagnosis
Ethnicity[5]	**Study with comparison of or breakdown of results by ethnic groups**		• Goodhand et al 2012 (review) • Misra et al 2019 (review)		• Misra et al 2019 (review)				
	Study on a specified ethnic group(s)	• Alexakis et al 2015 (interviews)	• Alexakis et al 2015 (interviews)	• Alexakis et al 2015 (interviews)				• Alexakis et al 2015 (interviews) • Mukherjee et al 2015 (interviews)	
	Study specifies proportion in different ethnic groups (but results not separately reported)	• Walker et al 2020a (review)	• Fernandes et al 2021 (review) • Walker et al 2020a (review)	• Fernandes et al 2021 (review)		• Fernandes et al 2021 (review) • Walker et al 2020a (review)		• Walker et al 2020a (review)	
Disease group[6]	**Study with comparison of or breakdown of results by IBD disease groups**		• Misra et al 2019 (review) • Walker et al 2020a (review)	• Card et al 2014 (database) • Fernandes et al 2021 (review) • Paul et al 2017 (review)	• Misra et al 2019 (review)	• Barratt et al 2011 (patient survey) • Blackwell et al 2020 (database)			
	Study on a specified IBD disease group		• Ward et al 2013 (review)	• Jones et al 2018 (review)					
	Study specifies proportion in different IBD disease groups (but results not separately reported)	• Alexakis et al 2015 (interviews) • IBD UK 2021 (patient and service survey) • Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Blackwell et al 2020 (database) • Fernandes et al 2021 (review) • Goodhand et al 2012 (review)	• Alexakis et al 2015 (interviews)		• Card et al 2014 (database) • Fernandes et al 2021 (review) • Walker et al 2020a (review)	• IBD UK 2021 (patient/ service survey) • Walker et al 2020a (review)	• Alexakis et al 2015 (interviews) • Blackwell et al 2020 (database) • Mukherjee et al 2015 (interviews) • Walker et al 2020a (review)	

[5] If a study did not provide any detail about the ethnicity of the participants, it is not listed in this table
[6] If a study did not provide any detail about the disease group of the participants (other than IBD), it is not listed in this table

5.1 The extent of delayed diagnosis in people with Crohn's or Colitis in the UK

This section summarises key findings relating to the frequency of delayed diagnosis and/or time to diagnosis for the overall diagnostic period from symptom onset to diagnosis, with a summary of the results for the nine studies with outcomes relevant to this section in Table 2. Table 2 indicates where results are for a general population (for example people in the UK with IBD) and where results are for a specific population subgroup.

Data from population surveys and a review of patient records at one NHS Trust reported figures for the proportion of patients who waited specified time periods for a diagnosis. The results from a survey conducted by IBD UK were reported in different publications with slightly different presentation of the results but are from the same data source. Bearing in mind the complications of comparing results between studies, it is noted that the results for the proportion of people who waited more than six months for a diagnosis was between 36% and 40% in both the results for people in the UK reported for the IBD UK survey (IBD UK 2021, IBD UK 2020a, IBD UK 2020b) and the review of 304 adults from one NHS Trust in England (Walker et al 2020a). The proportion of people in the UK who waited more than 12 months was also broadly similar at between 21% and 26% from these different data sources. The studies also indicate the variability of patient experience and that a proportion of patients wait several years for a diagnosis, although it is less certain what that proportion might be. Additionally, a study reporting the results of interviews with 20 young people with IBD from a Black or South Asian background, found that 60% experienced delays of difficulties in the time prior to their diagnosis. The time period for these delays is not clear although two participants were said to have reported ill-health for 'several years' before diagnosis (Alexakis et al 2015).

An average time to diagnosis was reported in four studies and varied, ranging from 2.3 to 13 months. But it was not always clear whether the figure reported was a median or mean or what the start and end of the diagnostic period was considered to be. The ranges around the averages, where reported, tended to be very wide supporting the sense of variability in patient experience.

Seven studies provided comparisons or breakdowns of data relating to time to diagnosis for subgroups of their populations and such comparisons within studies provide more useful data than comparisons of populations between studies. There was some evidence for a longer time to diagnosis for people with Crohn's Disease compared to Ulcerative Colitis or IBD unclassified (see Walker et al 2020a). However, in most cases, neither the data about the proportion of patients who waited specified time periods for a diagnosis nor the data about median time to diagnosis provided evidence for a statistically significant difference between subgroups:

- The data from the IBD UK survey found that figures were broadly similar for adults and children and young people (IBD UK 2021, IBD UK 2020a, IBD UK 2020b) and Walker et al (2020a) reported similar median overall times to diagnosis for their adult population and a subgroup of children. However, these studies did not report the results of statistical tests comparing adults and children. A review of 136 children with an IBD diagnosis referred to one tertiary level paediatric gastroenterology unit in England between 2004 and 2017 (Fernandes et al 2021) did statistically compare

children aged two to five years and children aged six to nine years and reported no statistically significant differences between the groups

- In two studies there were no significant differences in median time to diagnosis between the ethnic groups included in these studies. The first study was a review of 339 adults with IBD from hospitals in urban catchment areas with high South Asian populations in 2016 to 2017, which included patients characterised as 'White European', 'Indian', 'Pakistani' or 'other' (Misra et al 2019). The second study was a review from one NHS Trust in England in 2010 which compared 119 people of Bangladeshi descent with IBD to 119 White Caucasians who were matched for age at diagnosis and disease duration (Goodhand et al 2012)
- Data from the IBD UK survey was reported separately for the four countries of the UK. The proportions of people waiting for a diagnosis for different time periods does appear to vary between the countries. For example, the proportion of adults who waited more than six months for a diagnosis ranged from 38% in England to 48% in Wales. For children this ranged from 26% in Scotland and Northern Ireland to 44% in Wales. However, the number of patients with data available from the four UK countries varied considerably, with more than 70% of the data collected coming from England and the countries were not statistically compared
- One study (Walker et al 2020a) did report that the median overall time from symptom onset to diagnosis was statistically significantly longer for Crohn's Disease (by about four months) than Ulcerative Colitis or IBD unclassified. Another study (Misra et al 2019) also reported time to diagnosis separately for people with Crohn's Disease and Ulcerative Colitis. Medians were reported for different ethnic groups and the ranges were longer for Crohn's Disease (2.9 to 3.2 months) than Ulcerative Colitis (2.3 to 2.7 months). However, the analysis in this study was between ethnic groups rather than between disease groups.

The results of these comparisons should be treated with caution as the sample sizes were often small, and in some studies there was a considerable difference in the number of patients within the different groups being compared. Several studies did not report the results of any statistical comparison between groups and it is not clear if the studies that did do statistical analysis were sufficiently powered to detect significant differences between groups.

Table 2: Key findings on frequency of delayed diagnosis and/or time to diagnosis relating to the for the overall diagnostic period

Study details	General population	Results relating to a population subgroup category			
		Age	Country	Ethnicity	Disease group
RCGP and C&C UK 2020 UK survey from 2016 of people with IBD (n not reported)	• One in 3 (approximately 33%) waited more than 2 years for a diagnosis • One in 6 (approximately 17%) waited more than 5 years				
IBD UK 2021 UK survey from 2019-2020 of 2,121 adults, children and young people	• 39% waited more than six months for a diagnosis • 26% waited more than one year	The authors stated that figures were broadly similar for adults and children and young people but did not provide separate figures (however, see IBD 2020a and 2020b for results for adults and children)			
IBD 2020a UK survey from 2019 of 1,851 adults with IBD[7] England: 1,520 Scotland: 144 Wales: 110 N. Ireland: 77		The period between first speaking to a healthcare professional about symptoms to confirmation of diagnosis. Reported as proportion of people diagnosed in specified time periods: • <4 months: 41% • 4-6 months: 19%	Proportion waiting <4 months: • England: 42% • Scotland: 42% • Wales: 34% • N. Ireland: 39% Proportion waiting >6 months: • England: 38% • Scotland: 39%		

[7] Results by country are grouped for specific time periods to support interpretation of the results. See Appendix 3 for a more detailed breakdown of results

		• 7-12 months: 14% • 1-2 years: 11% • 2-5 years: 7% • >5 years: 8%[8]	• Wales: 48% • N. Ireland: 44% Proportion waiting >12 months: • England: 25% • Scotland: 27% • Wales: 25% • N. Ireland: 28% Proportion waiting >2 years: • England: 15% • Scotland: 13% • Wales: 10% • N. Ireland: 18%		
IBD 2020b UK survey from 2019 of 238 children with IBD England: 171 Scotland: 30 Wales: 9 N. Ireland: 28		Period between first speaking to a healthcare professional about symptoms to confirmation of diagnosis. Reported as proportion of people diagnosed in specified time periods: • <4 months: 43% • 4-6 months: 21% • 7-12 months: 14% • 1-2 years: 11% • 2-5 years: 7% • >5 years: 4%[9]	Proportion waiting <4 months: • England: 38% • Scotland: 57% • Wales: 55% • N. Ireland: 57% Proportion waiting >6 months: • England: 39% • Scotland: 26% • Wales: 44% • N. Ireland: 26%		

[8] These results equate to 59% of adults waiting more than 4 months for a diagnosis, 40% waiting more than 6 months, 26% waiting more than 12 months and 15% waiting more than 2 years

[9] These results equate to 57% of children waiting more than 4 months for a diagnosis, 36% waiting more than 6 months, 22% waiting more than 12 months and 11% waiting more than 2 years

			The proportion waiting >12 months: • England: 24% • Scotland: 16% • Wales: 22% • N. Ireland: 15% The proportion waiting >2 years: • England: 11% • Scotland: 13% • Wales: 11% • N. Ireland: 11%		
Walker et al 2020a Review of 304 adults and a subgroup of 35 children with a new IBD diagnosis between 2014 and 2017 at one NHS Trust in England CD: 31% UC: 64% IBD-unclassified: 5%		Adults: • The proportion of people diagnosed within 4 months, 6 months, 12 months and 2 years of symptom onset was 50%, 60%, 79% and 92% respectively[10] • Median overall time from symptom onset to diagnosis was 4.3 months (IQR 2.2 to 10.7) Children: • Median overall time from symptom onset to diagnosis was 4.1 months (IQR 2.3 to 7.1)			The median overall time from symptom onset to diagnosis was statistically significantly longer for CD (7.6 months, range 0 to 112) than UC (3.3 months, range 0 to 65) or IBD unclassified (3.9 months, range 0 to 16) ($p<0.001$)

[10] These results equate to 50% of people waiting more than 4 months for a diagnosis, 40% of people waiting more than 6 months, 21% waiting more than 12 months and 8% waiting more than 2 years

Fernandes et al 2021 Review of 136 children with an IBD diagnosis referred to one tertiary level paediatric gastroenterology unit in England between 2004 and 2017 Aged 2-5 years: 24% Aged 6-9 years: 76%		No statistically significant difference in time from symptom onset to diagnosis between age groups (p=0.37): • Aged 2 to 5 years: 13 months • Aged 6 to 9 years: 8 months No ranges reported No statistically significant differences in the proportion of children presenting with symptoms such as bloody diarrhoea, extra gastrointestinal manifestations and anaemia between age groups (p>0.05). The proportion experiencing such symptoms ranged from 57% to 83%			
Misra et al 2019 Review of 339 adults with IBD from hospitals in English urban catchment areas with high South Asian populations in 2016 to 2017 White European: 60% Indian: 20%				No statistically significant differences in median times from symptom onset to diagnosis for different ethnic groups with CD or UC (p value not reported) (see disease group column for medians)	For CD Median (IQR): • White European: 2.9 (0.9 to 8.5) • Indian: 3.0 (2.0 to 6.0) • Pakistani: 3.2 (2.0 to 5.3) • Other: 3 (2.0 to 3.2)

Pakistani: 7% Other: 11% Missing: 1% CD: 34% UC: 64% IBD unclassified: 2%					For UC Median (IQR): • White European: 2.3 (1.0 to 6.0) • Indian: 2.5 (0.98 to 4.0) • Pakistani: 2.7 (2.0 to 6.2) • Other: 2.5 (1.7 to 3.4)
Goodhand et al 2012 Review of 238 people with IBD from one NHS Trust in England in 2010				No statistically significant difference in median time to diagnosis[11] for 119 people of Bangladeshi descent (5 months (range 0 to 172)) and 119 White Caucasians matched for age at diagnosis and disease duration (5 months (range 0 to 134)) (p=0.59)	
Alexakis et al 2015; Nash et al 2011[12] Interviews with 20 young people				• 60% experienced delays or difficulties in the time prior	

[11] Time to diagnosis was not defined. It is not clear what the start and end points of the diagnostic period reported are
[12] Results from this study were identified in two publications

with IBD from a Black or South Asian background, 2010 London and Bristol				to their diagnosis • 40% reported no adverse experiences during the process of being diagnosed • Time to diagnosis ranged from 1 month to 3 years • 2 people reported ill-health for 'several years' before diagnosis	

CD – Crohn's Disease; IBD – Inflammatory Bowel Disease; IQR – interquartile range; N. Ireland – Northern Ireland; UC – Ulcerative Colitis

5.2 Elements of the diagnostic pathway

A review of 304 adults with a new IBD diagnosis between 2014 and 2017 at one NHS Trust in England compared delays at different stages of the diagnostic pathway (Walker et al 2020a)[13]. Although the results of this study should be treated with caution as they come from a small study from one NHS Trust, the study authors concluded that time to patient presentation is the largest component of the time to IBD diagnosis followed by the secondary care period (Figure 2 below). Figure 2 also shows that the time periods were longer for Crohn's Disease than Ulcerative Colitis or IBD unclassified.

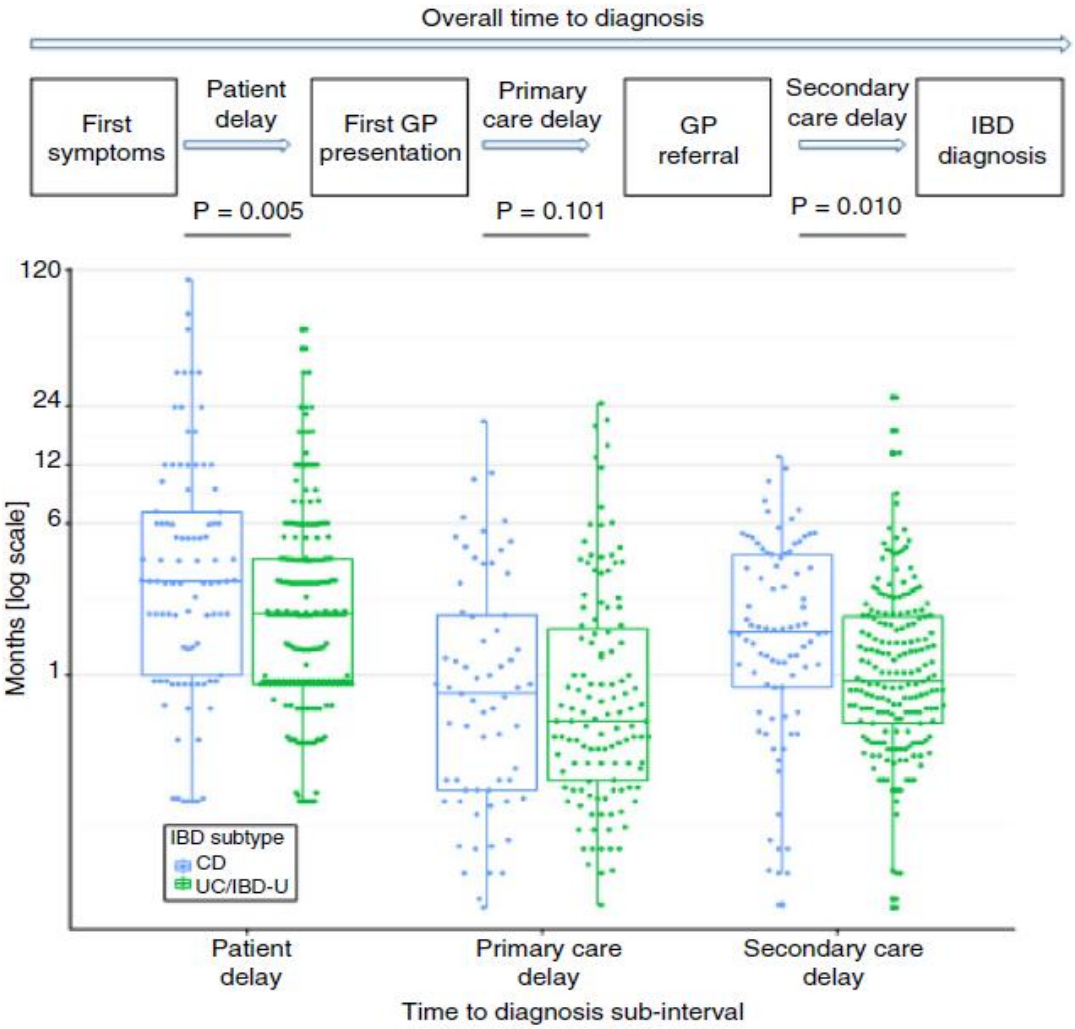

Figure 2: Overall time to diagnosis from Walker et al 2020a

A further 15 studies reported data on time to diagnosis or related outcomes for one or more stages of the diagnostic pathway. Results for these studies and more detail of the results for Walker et al (2020a) are presented by stage of the diagnostic pathway in the sections below.

[13] The study authors defined delay as a time to diagnosis greater than the upper quartile. This was calculated for three subintervals: the time from symptom onset to first GP presentation (patient delay); the time from first GP presentation to GP referral (primary care delay) and the time from GP referral to IBD diagnosis (secondary care delay)

Patient delay

One study focussed on the duration of the period from onset of symptoms to presentation to primary care.

In the review of 304 adults with IBD by Walker et al (2020a) (described above), the median time from symptom onset to first GP presentation was 2.1 months (IQR 0.9 to 5.1). The median duration of symptoms prior to patient presentation to a GP for abdominal pain (3 months, IQR 03 to 6.1), unintentional weight loss (4 months, IQR 0.9 to 6.1), anaemia (1.8 months, IQR 1.3 to 3.8), rectal bleeding (2.1 months, IQR 0.9 to 4.0) and altered bowl habit diarrhoea (2.1 months, IQR 0.9 to 6.0).

Walker et al (2020a) also reported median time from symptom onset to first GP presentation for subgroups of their population:

- For 35 children aged <18 years this was 3.0 months (IQR 0.9 to 5.0)
- For disease groups, this was statistically significantly longer for Crohn's Disease (3.0 months, range 0 to 107) than Ulcerative Colitis (2.1 months, range 0 to 59) or IBD unclassified (2.1 months, range 0 to 12) (p=0.017).

Primary care delay

Two studies focused on the duration of the period within the primary care system. Other studies included in this section relate to the prevalence and duration of symptoms prior to diagnosis (2 studies) and prevalence and nature of initial misdiagnosis (5 studies).

Duration of primary care delay

In the review of 304 adults with IBD by Walker et al (2020a) (described above), the median time from first GP presentation to GP referral was 0.1 months. Walker et al (2020a) also reported median time from first GP presentation to GP referral for subgroups of their population:

- For 35 children aged <18 years this was 0.1 months (IQR 0.0 to 0.7)
- For disease groups, there was no statistically significant difference for Crohn's Disease (0.3 months, range 0 to 20), Ulcerative Colitis (0.2 months, range 0 to 25) or IBD unclassified (0.3 months, range 0 to 4) (p=0.26).

A large UK database study from 1998 to 2016 with 19,555 adults and children with IBD reported results relating to the time period between presentation to primary care with chronic gastrointestinal symptoms and a secondary care appointment with a specialist[14] (Blackwell et al 2020). The proportion of patients receiving a secondary care appointment within four weeks was 6%, within six months was 32% and within 18 months was 50%. However, the authors found that these proportions were higher if they considered secondary care appointments with general medical or surgical appointments as well as appointments with a specialist (for example, the 23% were seen within four weeks, 61% within six months and 74% within 18 months) (Blackwell et al 2020). This study was an analysis of UK primary and

[14] Chronic GI symptoms was defined as 2 consultations within a 6-month period at least 6 weeks apart. The date of presentation with chronic GI symptoms was defined as the date of the second primary care physician consultation for GI symptoms. First specialist review was defined as the date of the first outpatient appointment recorded in HES with a gastroenterologist, paediatric gastroenterologist or colorectal surgeon

secondary care data from existing databases[15]. A potential limitation of this study is the number of years over which the patients were diagnosed. The potential impact of this is demonstrated by additional analysis conducted by the study authors which found that the proportion of people seen within four weeks was higher in more recent years compared to previous years. For example, the proportion seen by a specialist within four weeks was 2% from 2003 to 2006 and 15% from 2014 to 2016. Similarly the proportion seen in six months increased from 18% to 76% and the proportion seen in 18 months from 33% to 100% (Blackwell et al 2020).

Prevalence and duration of symptoms prior to diagnosis

The presence and duration of symptoms prior to diagnosis could reflect a period of opportunity where a diagnosis could perhaps have been made earlier. For example, the large UK database study by Blackwell et al (2020) (described above) found that people with IBD were around four times more likely to have visited their primary care physician with gastrointestinal symptoms than healthy controls matched for age and sex in the six to 18 months before diagnosis. The authors also concluded that about 10% of IBD patients had gastrointestinal symptoms five years before IBD diagnosis compared to about 6% in the background healthy population. Blackwell et al (2020) also reported the likelihood that people had visited their primary care physician with gastrointestinal symptoms by disease groups. The groups were not statistically compared:

- In the six to 18 months before diagnosis, for people with Crohn's Disease the likelihood was 29.1% vs 6.5% for healthy controls. For people with Ulcerative Colitis this was 23.9% vs 6.7%
- In the five years before IBD diagnosis, the likelihood was 10.4% for people with Crohn's Disease and 9.6% for people with Ulcerative Colitis. In both cases the likelihood was about 6% for healthy controls.

In a smaller UK database study of 1,184 adults who were diagnosed with IBD following an IBS diagnosis before July 2012, there were 13 extra cases of IBD per 10,000 person years in people with a prior IBS diagnosis compared to healthy controls matched for age and sex. Rates were particularly higher in the first six months after an IBS diagnosis (between 40 and 66 extra cases of IBD per 10,000 person years) (Canavan et al 2014). Limited information was available about the population included in this study and most of the patients are likely to have been diagnosed more than 10 years ago.

Prevalence and nature of initial misdiagnosis

Five studies reported results relating to people's experiences of receiving an alternative diagnosis prior to their diagnosis of IBD. In most cases these studies particularly focused on the extent and duration of initial diagnoses of irritable bowel syndrome (IBS) which is likely to have been made within primary care. A limitation of all the studies reported in this section is that much of the data dates from before the introduction of faecal calprotectin testing. For context, the NICE guidance recommending the use of faecal calprotectin testing to support clinicians with the differential diagnosis of IBD and IBS was published in October 2013 (NICE

[15] Primary care data were taken from the Clinical Practice Research Datalink. Secondary care outpatient data were taken from Hospital Episode Statistics

2013). Studies reporting data relating to access to and use of faecal calprotectin testing are reported in section 5.4.

In a large UK database study of 103,609 adults and children diagnosed with IBD between 2000 and 2020, the prevalence of a prior diagnosis of IBS[16] in people with IBD was 28.6% (Nartey et al 2021a). Nartey et al (2021a) also reported this outcome by age groups. The groups were not statistically compared:

- The prevalence of IBS ranged from 3.4% for children aged 0-9 years to over 30% for adults aged between 20 and 49 years old.

Three studies reported the time interval between a prior IBS diagnosis and IBD diagnosis which could be several years. In the large UK database study by Nartey et al (2021a) (described above), the median time interval was 3.5 years (IQR 0.6 to 9.5) for all ages. This was also reported by age group:

- The median time interval between a prior IBS diagnosis and IBD diagnosis was 0.2 years (IQR 0.1 to 1.7) for children aged 0-9 years and increased for each age group up to 8.0 years (IQR 2.7 to 14.7) for people aged more than 80 years old.

In the UK database study by Canavan et al (2014) (described above), the median time between IBS and IBD diagnosis was 1.7 years (IQR 0.49 to 4.6) and in another large UK database study of 20,193 adults and children from 1987 to 2010, 3% of the study population had IBS symptoms for more than 10 years before a diagnosis of IBD (Card et al 2014).

Two studies explored the potential impact of a prior diagnosis of IBS. One explored the potential rates of IBS misdiagnosis in people with IBD and the other the possibility that a diagnosis of IBS could prolong the time period before a patient is diagnosed with IBD:

The large UK database study by Card et al (2014) (described above), compared 20,193 adults and children with IBD to 20,193 controls without IBD to estimate the rate of potential IBS misdiagnosis[17] in people with IBD. The authors concluded that 10% of people were potentially initially misdiagnosed with IBS, with 4% occurring in the year before the diagnosis of IBD. When the study authors used a broader definition of prior IBS, to include both a diagnosis code for IBS or a prescription code for an antispasmodic drug, the percentage of people who may have been initially misdiagnosed with IBS rose to 20.5%. Card et al (2014) also examined the difference in potential misdiagnosis of IBS, using the broader definition, between subgroups of people. The groups were not statistically compared:

- A potential misdiagnosis of IBS was present for 26% of people with Crohn's Disease and 16% of people with Ulcerative Colitis
- A potential misdiagnosis of IBS was present in 23.5% of people aged less than 50 years old and 17% of people who were 50 years or older
- A potential misdiagnosis of IBS was present in 23% in females and 17.5% in males.

[16] A prior diagnosis of IBS was based on a diagnosis of IBS (diagnostic code) or a prescription for antispasmodic drugs

[17] Misdiagnosis was estimated by comparing the proportion of people with IBD that had a prior IBS diagnosis code to the rate of IBS that you would find in healthy people without IBD (i.e. by calculating the excess amount of IBS above what you would expect to see)

A survey of 458 adults with IBD who attended one hospital in England between 2006 and 2009 explored the impact of a prior diagnosis of IBS on the prodromal period i.e. the period of time with symptoms attributable to IBD before a medical diagnosis (Barratt et al 2011). Overall, 71% of adults with IBD had a prodromal period and the mean duration was statistically significantly longer for the 33% of adults whose symptoms were attributed to irritable bowel syndrome (IBS) than the 67% of adults who were not considered to have IBS (3 years, range 0.5 to 40 vs 1.5 years, range 0.25 to 37), (p=0. 01). Barratt et al (2011) also reported this outcome by disease group:

- A prodromal period was more common in the adults diagnosed with Crohn's Disease (94%) than those diagnosed with Ulcerative Colitis (48%)[18]
- The difference in the mean prodromal period between adults whose symptoms were, or were not, attributed to IBS was statistically significantly longer for those with Crohn's Disease (4 years, range 0.5 to 33 vs 2 years, range 0.8 to 37), (p=0.018). However, there was no statistically significant difference for those with Ulcerative Colitis (1 year, range 0.8 to 40 vs 1 year, range 0.25 to 12), (p≥0.05).
- The difference in the mean prodromal period between adults whose symptoms were, or were not, attributed to IBS was statistically significantly longer for those with Crohn's Disease (4 years, range 0.5 to 33 vs 2 years, range 0.8 to 37), (p=0.018). However, there was no statistically significant difference for those with Ulcerative Colitis (1 year, range 0.8 to 40 vs 1 year, range 0.25 to 12, (p≥0.05).

No subgroup analysis for this outcome was identified for different ethnic groups or UK countries. However, other potential misdiagnoses mentioned in interviews conducted in 2010 in London and Bristol with 20 young people with IBD from a Black or South Asian background included tuberculosis (2 participants), a tropical disease (1 participant) and a psychosomatic disorder (1 participant). Other initial diagnoses included IBS, stomach bug and stress-related disorders (figures not stated) (Alexakis et al 2015; Nash et al 2011).

Secondary care delay

Five studies focused on the duration of the period within the secondary care system. Other studies included in this section had results specifically relating to the standard that people should be seen in secondary care within four weeks of referral (3 studies) and changes to diagnosis within secondary care (3 studies).

Duration of secondary care delay

In the review of 304 adults with IBD by Walker et al (2020a) (described above), the median time from GP referral to IBD diagnosis was 1.1 months (IQR 0.5 to 2.1). Walker et al (2020a) also reported median time from GP referral to IBD diagnosis for subgroups of their population:

- For 35 children aged <18 years this was 1.3 months (IQR 0.5 to 2.1)
- For disease groups, this was statistically significantly longer for Crohn's Disease (1.6 months, range 0 to 13) than Ulcerative Colitis (0.9 months, range 0 to 27) or IBD unclassified (0.7 months, range 0 to 4) (p=0.027).

[18] The study authors suggested that patients with Ulcerative Colitis may have symptoms that are more alarming and less consistent with IBS which may prompt referral to secondary care

A UK survey of 1,851 adults with IBD conducted in 2019 (IBD 2020a) reported the time between referral by a GP to first appointment with a hospital specialist. For 29% of people this was less than four weeks, for 57% it was one to six months, for 6% it was seven to 12 months and for 2% it was more than one year. The remaining 6% were recorded as being privately diagnosed. This report also provided a breakdown by country. However, the number of patients with data available from the four UK countries varied considerably, with 82% of the data coming from England so the percentages should be interpreted with caution:

- The proportion of people seen in less than four weeks was 30% for England, 28% for Scotland, 26% for Wales and 15% for Northern Ireland. The proportion of people waiting more than six months was 7% for England, 11% for Scotland, 17% for Wales and 15% for Northern Ireland.

A UK survey of 238 children with IBD conducted in 2019 (IBD 2020b) also reported the time between referral by a GP to first appointment with a hospital specialist. For 29% of people this was less than four weeks, for 60% it was one to six months, for 2% it was seven to 12 months and for 3% it was more than one year. The remaining 6% were recorded as being privately diagnosed. This report also provided a breakdown by country, however, as with the IBD UK report for adults described above, the percentages should be interpreted with caution as 72% of the data came from England:

- The proportion of people seen in less than four weeks was 29% for England, 45% for Scotland, 11% for Wales and 22% for Northern Ireland. The proportion of people waiting more than six months was 6% for England, 0% for Scotland, 0% for Wales and 0% for Northern Ireland.

A review of 115 adults with Ulcerative Colitis from one hospital in England in 2007 to 2012 reported the mean (standard deviation) time between referral to first outpatient visit as 19.5 days (17.1) if patients were referred to a gastroenterology specialist and 23.2 days (22.1) if patients were referred to a colorectal specialist. There was no statistically significant difference between the groups (p=0.856) (Ward et al 2013). Ward et al (2013) also reported that the mean (standard deviation) time between referral to first colorectal clinic visit as 10.5 days (6.5) if patients were given a two-week wait referral and 34.5 days (24.5) if patients were given a routine referral. This study included a small number of patients with Ulcerative Colitis from one hospital and the applicability to the experiences of patients diagnosed elsewhere, or with other IBDs, is not clear.

Two studies focused on the time period between referral and endoscopy. A small review of 92 adults with IBD from the South Yorkshire area in 2014 to 2015 reported an average time between referral between primary care and diagnostic endoscopy of 34.5 days (range 18 to 70) (Taylor et al 2021). The review of 115 adults with Ulcerative Colitis by Ward et al (2013) (described above) reported the mean (standard deviation) time between referral to first endoscopy as 57.6 days (80.1) if patients were referred to a gastroenterology specialist and 42.8 days (26.4) if patients were referred to a colorectal specialist. There was no statistically significant difference between the groups referred to different specialities (p=0.364).

The four-week referral standard

Three studies reported results specifically relating to the standard that people should be seen in secondary care within four weeks of referral (NICE 2015, IBD UK 2019). One of these

studies was a survey conducted in 2019-2020 of 2,121 adults, children and young people with IBD and 166 IBD (IBD UK 2021). The results should be treated with caution as they are self-reported data and although the survey was conducted in 2019-2020, most patients were diagnosed more than two years ago. The proportion of patients who reported being seen in four weeks was 29%. The results from services were reported separating for adults and paediatrics:

- 21% of adult services and 38% of paediatric services reported being able to see at least 90% of patients with suspected IBD within four weeks of referral.

The remaining two studies were based on patient records and therefore may provide more accurate data. In an audit of 107 UK centres providing paediatric gastroenterology, hepatology and nutrition services in 2020, the proportion of children with suspected IBD seen by a specialist consultant within four weeks of referral was 80% if they were referred to a specialist centre and 43% if they were referred to a non-specialist centre (RCPCH and BSPGHAN 2021). In the review of 304 adults with a new IBD diagnosis by Walker et al (2020a) (described above) this was 63%.

Change to diagnosis

Three studies also explored potential misdiagnoses within a secondary care context, focusing on children who received an initial diagnosis of one form of IBD which was later amended.

- In a review of 136 children diagnosed with IBD at one paediatric gastroenterology unit in England from 2004 to 2017, 16 children (12%) received a change in diagnosis during the study period. Five were aged two to five years and 11 were aged six to nine years. Nine children were initially IBD unclassified with six changed to Crohn's Disease and three to Ulcerative Colitis. Three children change to IBD unclassified, one from Crohn's Disease and two from Ulcerative Colitis. The other four children changed from Ulcerative Colitis to Crohn's Disease (Fernandes et al 2021)
- In a review of 29 children who had received a colectomy for a diagnosis of Ulcerative Colitis at one paediatric centre in England from 2003 to 2014, seven (24%) later received a subsequent diagnosis of Crohn's Disease. The median time from the colectomy to the diagnosis of Crohn's Disease was 2.3 years (range 0.5 to 9) (Jones et al 2018)
- In a review of 26 children initially diagnosed with IBD-unclassified at one paediatric centre in England from 2004 to 2011, 65% received endoscopic re-evaluation and 40% had a changed diagnosis (seven to Crohn's Disease and three to Ulcerative Colitis). The median time to the diagnosis revision was 51 months (range 4 to 87) (Paul et al 2017).

5.3 The consequences of delay

This section summarises evidence relating to the consequences of delays. This includes results about healthcare usage before diagnosis (2 studies) and disease severity at diagnosis (1 study). This section also reports the results of a study on the impact of the COVID-19 pandemic on services in April 2020.

Two studies focused on visits to A&E and emergency presentation. The UK survey of 2,121 adults and children with IBD by IBD UK (described above), found that 41% of patients

reported having at least one visit to A&E before diagnosis and 12% reported at least three visits to A&E (IBD UK 2021). The review of adults with IBD by Walker et al (2020a) (described above) found that 19% of new diagnoses were made following an emergency presentation, of which 86% were referred to hospital by their GP and 14% self-presented to A&E. Walker et al (2020a) found that factors associated with initial presentation of IBD as an emergency in a multivariable analysis were duration of symptoms for less than six weeks (odds ratio (OR) 8.26, 95% CI 1.77 to 50.75) and anaemia (OR 19.01, 95% CI 3.76 to 60.48). In the analysis by Walker et al (2020a), there was no association between delayed overall time to diagnosis and a complicated disease course[19] (p=0.35) when people diagnosed following an emergency presentation were included in the analysis. However, people who presented as an emergency were statistically significantly more likely to have a complicated disease course (p<0.001). When people diagnosed following emergency presentation were excluded from the analysis there was an association between delayed diagnosis (more than two years from symptom onset) (p=0.038) and higher IBD-related hospital admission and corticosteroid use (p=0.043). However, there was no association between delayed diagnosis and IBD-related surgery (p=0.356), use of immunomodulators (p=0.117) and use of biologics (p=0.302) in the first year after diagnosis.

The study focusing on disease activity at presentation explored potential differences between several ethnic groups. This review of 339 adults with IBD from hospitals in urban catchment areas with high South Asian populations in 2016 to 2017 reported no statistically significant differences in disease activity indexes between ethnic groups at disease presentation (p not reported). For example, the mean Harvey Bradshaw Index scores at diagnosis (± 95% CI) were 6.2 (±4.1) for 'White European', 6.5 (±3.1) for 'Indian', 6.8 (±3.9) for 'Pakistani' and 6.4 (±3.4) for 'other'. A score of five to seven suggests mild disease activity (Misra et al 2019). The results of these comparisons should be treated with caution as the sample sizes were small with a considerable difference in the number of patients within the different groups being compared (60% of the population were 'White European'). It is not clear if the study was sufficiently powered to detect significant differences between groups.

A survey of 20 tertiary paediatric gastroenterology centres in England and Scotland reflecting on the impact of the COVID-19 pandemic on services in April 2020, found that 53% of 122 patients diagnosed with IBD were given a presumed diagnosis with no endoscopy or histological confirmation. Of these, 63% presented with moderate to severe disease (Ashton et al 2020).

5.4 The causes of delay

Tables 3 to 5 summarise potential causes of delay to diagnosis. These are organised according to whether the delay is likely to have been caused by a patient factor, a service or system factor occurring in the primary care stage of the pathway, or a service or system factor occurring in secondary care stage of the pathway. For further details of the results and limitations of the individual studies see Appendix 3.

[19] People were judged to have a complicated disease course if they had an IBD-related hospital admission, IBD-related surgery and/or biologic therapy in the first year after diagnosis

Table 3: Patient factors

Potential cause of delay	Key result	Population	Source
Limited or no understanding of Crohn's Disease and Colitis in the public	80% of survey respondents felt that understanding of Crohn's Disease and Colitis amongst the public was limited	10,222 UK adults, children and young people with IBD	Survey conducted in 2019 to 2020 (IBD UK 2021)
	Symptoms associated with increased patient delay in a multivariable analysis included presence of abdominal pain and presence of unintentional weight loss Conversely, the presence of rectal bleeding was associated with a decrease in patient delay in the multivariable analysis	304 adults with IBD from one hospital trust in England	Data from one Trust, 2014 to 2017 (Walker et al 2020a)
Household income	A higher household income was associated with increased patient delay in a multivariable analysis	304 adults with IBD from one hospital trust in England	Data from one Trust, 2014 to 2017 (Walker et al 2020a)

CI – confidence intervals; IBD – inflammatory bowel disease

Table 4: Primary care factors

Potential cause of delay	Key result	Population	Source
Lack of awareness of IBD in GPs	Over 70% of GP respondents had had no formal training in IBD	624 UK GPs	Survey, 2017 (RCGP and C&C UK, 2020)
	Interviewees who experienced delays in diagnosis reported a "widespread lack of awareness of IBD" affecting people from a Black or South Asian background amongst GPs	20 young people from a Black or South Asian background	Interviews, 2010 (Alexakis et al 2015; Nash et al 2011)
	Interviewees reported a perceived scepticism about their ailments	20 young people from a Black or South Asian background	
	Two-thirds of participants reported significant delays in having their IBD diagnosed due to a lack of referral by their GP (no further detail reported). None attributed the delay to their ethnic background	33 adults with IBD from the South Asian population	Interviews, year not stated (Mukherjee et al 2015)

Having a previous diagnosis of IBS	Patients with an IBS diagnosis were statistically significantly less likely to receive specialist review within 18 months of presentation with chronic GI symptoms to primary care (hazard ratio 0.77 (95% CI 0.59 to 0.99))	19,555 UK adults and children diagnosed with IBD	UK database study 1998 to 2016 (Blackwell et al 2020)
Having a previous diagnosis of depression	Patients with a diagnosis of depression were statistically significantly less likely to receive specialist review within 18 months of presentation with chronic GI symptoms to primary care (hazard ratio 0.78 (95% CI 0.61 to 0.99))	19,555 UK adults and children diagnosed with IBD	UK database study 1998 to 2016 (Blackwell et al 2020)
Access to and use of faecal calprotectin testing in primary care	33% of GP respondents were 'less than confident' or 'not confident' requesting faecal calprotectin tests or interpreting their results	624 UK GPs	Survey, 2017 (RCGP and C&C UK, 2020)
	The prevalence of faecal calprotectin testing in the UK rose from <0.1% in 2009 to 4.2% in 2019. In 2019 the prevalence of testing was 4.0% in England, 9.6% in Scotland, 0.8% in Wales and 1.0% in Northern Ireland	53,719 UK adults and children diagnosed with IBD	UK database study, 2009 to 2019 (Nartey et al 2021a)
Agreed referral pathway for suspected IBD between primary and secondary care	The percentage of services that did have an agreed pathway was 64% for services in England, 71% for Scotland, 54% for Wales and 57% for Northern Ireland	166 UK adult and paediatric IBD services	Survey conducted in 2019-2020 (IBD UK 2021)

CI – confidence intervals; IBD – Inflammatory Bowel Disease

As well as identifying potential causes of delay, a UK primary care database study by Blackwell et al (2020) also reported factors that were not associated with a delay to timely review by a specialist. These included age at presentation, sex, social deprivation or smoking status.

In addition, factors statistically significantly associated with a decrease in primary care delay in the multivariable analysis by Walker et al (2020a) were older age at IBD diagnosis (OR 0.96 95% CI 0.94 to 0.98) and symptoms for less than six weeks prior to GP presentation (OR 0.18 95% CI 0.08 to 0.36).

Table 5: Secondary care factors

Potential cause of delay	Key result	Population	Source
Access to faecal calprotectin testing in secondary care	30% of centres reported no, or reduced, access to faecal calprotectin testing during April 2020 due to the COVID-19 pandemic	20 paediatric gastroenterology centres in England and Scotland	Survey, April 2020 (Ashton et al 2020)

	27% of centres reported no access and 32% reported reduced access to faecal calprotectin testing in April 2020 due to the COVID-19 pandemic	125 UK adult and paediatric IBD services	Survey, April 2020 (Kennedy et al 2020)
Access to endoscopy	Services reported that 36% of people in Wales waited more than 8 weeks for an endoscopy	Diagnostic services in Wales	Database study, June 2017 (CRUK 2018)
	Approximately 35% of 20 centres[20] reported no access to urgent endoscopy for diagnosis of new IBD patients during April 2020	20 paediatric gastroenterology centres in England and Scotland	Survey, April 2020 (Ashton et al 2020)
	35% of services reported that all IBD-related endoscopy activities (including diagnostics) were cancelled in April 2020 due to the COVID-19 pandemic	125 UK adult and paediatric IBD services	Survey, April 2020 (Kennedy et al 2020)
	20% of 74 of non-specialised centres and 47% of 30 specialist centres reported that non-emergency endoscopy services had not been restored due to the COVID-19 pandemic	107 UK centres providing paediatric gastroenterology, hepatology and nutrition services	National audit, 2020 to February 2021 (RCPCH & BSPGHAN 2021)
	46% of specialist or non-specialist centres did not have local criteria for access to diagnostic endoscopy or for children presenting in an emergency nor timely access to endoscopy through clear and agreed pathways	107 UK centres providing paediatric gastroenterology, hepatology and nutrition services	National audit, 2020 to February 2021 (RCPCH & BSPGHAN 2021)
Staffing levels	Adult services who reported that they met IBD standards staffing recommendations was 31% for gastroenterologists, 37% for radiologists and 8% for histopathologists	166 UK adult and paediatric IBD services	Survey conducted in 2019-2020 (IBD UK 2021)
	37% of 27 specialist centres had less than three whole time equivalent paediatric gastroenterologists 18% of 77 non-specialist centres had no consultant paediatrician with a special interest in gastroenterology	107 UK centres providing paediatric gastroenterology, hepatology and nutrition services	National audit, 2020 (RCPCH & BSPGHAN 2021)
	The median number of whole-time equivalent gastroenterologists providing elective outpatient care was four (IQR 4 to 7.5) before the COVID-19 pandemic and two (IQR 1 to 4.8) in the six-week period following the onset of the pandemic	125 UK adult and paediatric IBD services	Survey, April 2020 (Kennedy et al 2020)

[20] Based on a graph showing that approximately 65% of centres allowed urgent endoscopy for diagnosis of new IBD patients

	The proportion of services with more than three whole-time equivalent gastroenterologists providing IBD care was 81% before the pandemic and 34% in the six-week period following the onset of the pandemic. 8% of services had no dedicated IBD clinician following the onset of the pandemic		
Referral pathway	Longer mean time to diagnosis were reported for those referred to surgical specialties (2.0 months in 2013 and 3.8 months in 2016) compared to those referred to gastroenterology (2 months in 2013 and 1.16 months in 2016) and via the colorectal 2-week wait pathway (0.64 months in 2013 and 0.6 months in 2016). Statistical significance of comparisons of referral routes not reported	248 patients with a new referral to IBD service in England	Before and after faecal calprotectin testing study, 2013 vs 2016 (Hicks et al 2020) (See section 6)
Frequency of multi-disciplinary team (MDT) meetings	The percentage of services that did report frequent MDT meetings was 68% for services in England, 39% for Wales and 57% for Scotland and Northern Ireland. For adult services this was 69% and for paediatric 47%	166 UK adult and paediatric IBD services	Survey conducted in 2019-2020 (IBD UK 2021)
	28% of services reported that all IBD multi-disciplinary team meetings were cancelled in April 2020 due to the COVID-19 pandemic	125 UK adult and paediatric IBD services	Survey, April 2020 (Kennedy et al 2020)

IBD – Inflammatory Bowel Disease; IQR – interquartile range; MDT – multi-disciplinary team

Conversely, factors statistically significantly associated with a decrease in secondary care delay in the multivariable analysis by Walker et al (2020a) were symptoms for less than six weeks prior to GP presentation (OR 0.14 95% CI 0.03 to 0.51), urgent GP referral (OR 0.12, 95%CI 0.04 to 0.35) and being triaged straight-to-test (OR 0.08, 95% CI 0.02 to 0.25).

Stakeholders were also invited to give their opinion of barriers to early diagnosis and reported the following causes of delay:

- Variation in IBD clinical nurse specialist support locally and nationally
- Variation in number of gastroenterologists across different areas of the country, highlighted in the British Society of Gastroenterology Workforce Report (Rutter 2022)
- Access to small bowel radiology, capsule endoscopy and a large backlog of endoscopy work
- Difficulties in implementing formal IBD referral pathways (clinic pathway and endoscopy pathways)
- De-prioritisation of non-cancer patients resulting in IBD patents having to wait longer for clinic appointments and then diagnostic colonoscopy. This has been exacerbated by the COVID-19 pandemic.

6 The key findings for question 2: Interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases

This section describes findings from seven studies assessing the effectiveness of interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other similar long-term conditions in the UK (Fallon et al 2019, Hamilton et al 2013, Hicks et al 2020, Sewell et al 2020, Turvill et al 2020, Walker et al 2020b, Williams et al 2020).

Three of the studies focussed on diagnosis of IBD (Hicks et al 2020, Turvill et al 2020, Walker et al 2020b) and the remaining four studies focussed on diagnosis of cancer (Fallon et al 2019, Hamilton et al 2013, Sewell et al 2020, Williams et al 2020). No studies were found on other similar immune-mediated inflammatory conditions. The majority of the studies were conducted in adults with only one study found in children (Walker et al 2020b). The study designs included one prospective cohort study, two retrospective cohort studies, three before and after studies and one audit. Where reported, the sample sizes ranged from 42 to 1,160 individuals. However, the studies tended to be small with most having sample sizes between 42 and 274. Further details on the design and results on the included studies are given in Appendix 3. All three studies on diagnosis of IBD assessed the impact of faecal calprotectin testing in primary care and the four studies on diagnosis of cancer assessed the impact of a pilot rapid diagnostic centre for patients with vague and/or non-specific symptoms suspicious of cancer, risk assessment tools for suspected bowel and lung cancer in general practice, health awareness campaigns for breast, bowel and lung cancer and two-week wait referrals for suspected upper and lower gastrointestinal cancers.

We assessed the quality of the included studies and assigned each a quality score summarising our level of confidence in their results. Most studies had quality summary scores indicating a moderate level of confidence in their results, with one study rated as low quality. The quality summary scores for each included study are given in Appendix 3. The main quality issues were a lack of an appropriate counterfactual or comparator, small sample size and no reference to sample size calculations meaning that it was not possible to determine whether the study was adequately powered, poor reporting of baseline characteristics of the study population meaning that the representativeness of the study population could not be assessed and no attempt to adjust for differences between baseline population characteristics of the groups.

6.1 Faecal calprotectin testing in primary care

Three studies were found assessing the effectiveness of faecal calprotectin testing in primary care in the UK (Hicks et al 2020, Walker et al 2020b, Turvill et al 2020). Two further studies were found but these were not included as they did not include comparative data on time to diagnosis (Freeman et al 2021, Turvill 2016).

A before and after study (Hicks et al 2020; n=248; moderate quality) of 104 patients referred to the IBD service at Leeds Teaching Hospitals NHS Trust with a diagnosis of IBD in 2013 (pre-faecal calprotectin testing introduction) and 144 patients referred in 2016 (post-faecal calprotectin testing introduction) found no statistically significant difference in time from referral to diagnosis (2013 vs 2016: 0.77 months vs 1.10 months (p=0.2)). In 2016, faecal calprotectin was checked in 48 (33%) patients prior to referral. Post-faecal calprotectin

testing introduction, an increase in the proportion of referrals leading to an IBD diagnosis from GPs to gastroenterology (3% vs 17%), a decrease from GPs to surgical specialities (18% vs 10%), a decrease via the two-week wait suspected cancer pathway (38% vs 28%), no difference in emergency admissions to hospital (10% vs 10%) and an increase in independent centres contracted to provide NHS care (16% vs 24%) was observed. However, no statistical comparison tests were reported for these results, so it is not clear whether any differences observed were statistically significant. Time to diagnosis was similar across all referral routes except for those referred to surgical specialties (2.0 vs 3.8 months), (p=0.220). A statistically significant decrease in time from diagnosis to treatment was found post-faecal calprotectin testing introduction (2013 vs 2016: 1.37 months vs 0.72 months, (p=0.01)). The authors commented that this may be due to the increased proportion of referrals directly to gastroenterology resulting in earlier access to treatment and the avoidance of unnecessary investigations and visits to different teams prior to commencing treatment. The results of this study should be treated with caution as the before and after design of the study means that it is uncertain whether changes observed are due to the intervention or differences in population characteristics between the groups or other external factors. Furthermore only 33% of the after group had faecal calprotectin measured and out of the 48 patients with faecal calprotectin measured, 12 did not have results available at the time of referral.

A prospective cohort study (Walker et al 2020b; n=42; moderate quality) compared children (aged between four and 18 years) diagnosed with IBD on the faecal calprotectin pathway (n=13) (intervention) to those diagnosed outside of the pathway (n=29) (control) between 2014 and 2017 in 48 GP practices and gastroenterology secondary care services at the Royal Devon and Exeter NHS Foundation Trust. The authors reported that faecal calprotectin testing had no effect on the total time to diagnosis (intervention vs control: median 53.0 days, IQR 32.0 to 56.0 vs 79.5 days, IQR 49.2 to 189.0, (p=0.11)). No difference was also reported for duration of symptoms before diagnosis (intervention vs control: median 4.0 months, IQR 2.0 to 8.0 vs 3.5 months, IQR 1.9 to 5.2, (p=0.30)) for those diagnosed on and off the faecal calprotectin pathway. The authors reported that a negative faecal calprotectin likely saved 64 referrals while a positive faecal calprotectin likely added nine referrals with a net saving of 55 referrals. The results of this study should be treated with caution due to its small sample size and it is unlikely that adjustments were made to take into account any differences between population characteristics of the groups.

An audit (Turvill et al 2020; n not reported; low quality) of records of all first colonoscopies (and flexible sigmoidoscopies) performed by York Teaching Hospital NHS Foundation Trust in patients aged 18 to 60 years during 2016 to 2018 compared patients referred via the York faecal calprotectin care pathway (YFCCP) from five primary care practices to those referred via other referral pathways. The audit reported a median time from the first faecal calprotectin test result >100 µg/g faeces to clinical diagnosis of 29 days (IQR 15 to 47) for those referred via the YFCCP. Referral times were not recorded in the non-YFCCP group. Instead, the authors compared results to a random selected sample (no further details provided), for which the median time from initial referral to clinical diagnosis was longer at 41 days (IQR 19 to 72). No statistical comparison tests were reported so it is not clear whether this represents a statistically significant difference. Furthermore, the time of the initial consult with the GP was not recorded for the YFCCP group so the later time of the first faecal calprotectin test was used to calculate referral times instead which will have biased the result in favour of the YFCCP group. The results of this study should be treated with caution for this

reason, and for the limited reporting of methods and results, and it is unlikely that adjustments were made to take account of any differences between population characteristics of the groups.

Summary: Three studies of low to moderate quality provide limited evidence of the impact of faecal calprotectin testing in primary care on time to diagnosis. Based on the results of these studies it was not possible to reliably determine whether faecal calprotectin testing in primary care reduced time to diagnosis of IBD. However, one of the studies observed an increase in referrals directly to gastroenterology associated with faecal calprotectin testing (statistical significance not reported) which the authors suggested may allow for earlier access to treatment and avoid unnecessary investigations in some cases. This study also observed a reduction in the number diagnosed via the two-week wait pathway (statistical significance not reported), which may result in a reduction in time to diagnosis as the authors reported that once malignancy has been excluded, these patients are at risk of getting "lost" within the system and experiencing delays in treatment.

Recommendations:
There is a need for high quality large studies with appropriate comparators to reliably determine the impact of faecal calprotectin testing in primary care on time to diagnosis in IBD.

One study observed that referrals to surgical specialties cause the greatest amount of delay in time to diagnosis and time to treatment. The authors recommended that this referral route should be discouraged by measuring faecal calprotectin levels where appropriate, and that further work, for instance through further training and education of primary care practitioners, is required to ensure patients with suspected IBD get referred to the most appropriate service in a timely manner.

6.2 Rapid diagnostic centres

One study (Sewell et al 2020) was found assessing the effectiveness of a pilot multidisciplinary rapid diagnosis centre (RDC) centre in Wales which allows GPs within targeted clusters to refer adults with vague and/or non-specific symptoms suspicious of cancer, who do not meet criteria for referral under an urgent suspected cancer pathway, to a RDC where they are seen within one week.

A cost effectiveness study which included data from a retrospective cohort study (Sewell et al 2020; n=274; moderate quality) compared 189 adults with vague and/or non-specific symptoms suspicious of cancer referred by their GP to a RDC at Neath Port Talbot Hospital (NPTH) for further investigation between June 2017 and May 2018 to 85 outcome-matched control patients within the Swansea Bay University Health Board referred to the urgent suspected cancer pathway by their GP but then downgraded to the non-urgent pathway. Amongst the RDC group, most patients presented with unexplained weight loss, pain, fatigue, and shortness of breath. The pilot RDC was found to reduce mean time to diagnosis from 84.2 days (SD 65.3) in the control group to 5.9 days (SD 3.4) in patients who were diagnosed directly at the RDC clinic and to 40.8 days (SD 30.0) if further investigations following RDC were warranted. 12% (n=23) of the RDC group were given a cancer diagnosis with referral to specialist, 16% (n=30) a non-cancer diagnosis, 36% (n=68) no serious pathology found with discharge to GP and 36% (n=68) no diagnosis. The proportion of

patients diagnosed with IBD in the non-cancer diagnosis group was not reported. The cost effectiveness analysis found that the RDC is cost effective if run at ≥80% capacity. The results of this study should be treated with caution as no population characteristics were reported for the control group and they may not be comparable to the RDC group as these were patients referred to the urgent suspected cancer pathway first and then downgraded. Furthermore, it is not clear how time to diagnosis was calculated for the control group as being referred to the urgent suspected cancer pathway first and then downgraded will add time to diagnosis and not all patients with vague and/or non-specific symptoms suspicious of cancer will follow this pathway.

Summary: One study of moderate quality provided limited evidence that a pilot RDC reduced time to diagnosis in adults with vague and/or non-specific symptoms suspicious of cancer, who do not meet criteria for referral under an urgent suspected cancer pathway compared to patients referred to the urgent suspected cancer pathway first and then downgraded.

Recommendations: There is a need for high quality studies with appropriate comparators to reliably determine the impact of RDCs for people with vague and/or non-specific symptoms suspicious of cancer on time to diagnosis of cancer and IBD.

6.3 Risk assessment tools

One study (Hamilton et al 2013) was found assessing the effectiveness of risk assessment tools (RATs) for suspected bowel and lung cancer in general practice in England.

A before and after study (Hamilton et al 2013; n=1,160 colorectal assessment; moderate quality) compared six-month periods before and after the distribution of RATs to assist GPs select patients for cancer investigations in 2010 to 2011. During the six-month intervention period, 1,160 colorectal assessments and 1,433 lung assessments were completed by 614 GPs from 165 practices in seven English cancer networks. The study reported that for suspected colorectal cancer, the distribution of RATs was associated with a 26% increase in two-week referrals (1,173 vs 1,477), a 15% increase in colonoscopies (1762 vs 2,032) and a 7% increase in cancers identified (134 vs 144). No results were reported on time to diagnosis. The study included qualitative interviews with 23 GPs and found that overall the RATs were perceived to be a valuable aid to diagnosis and encouraged GPs to think about referral thresholds and prompted them to investigate. GPs felt that the tool gave more credence to a decision to refer that had already been made, urged referrals that may not have been made and to confirm decisions not to refer. The results of this study should be treated with caution as the before and after design of the study means that it is uncertain whether changes observed are due to the intervention or differences in population characteristics between the groups or other external factors.

Summary: One study of moderate quality suggested that RATs for suspected bowel cancer in general practice increased cancer investigations and urgent referrals and more cancers were diagnosed. GPs reported that RATs encouraged them to think about referral thresholds and prompted them to investigate which the authors concluded may lead to earlier diagnosis. However, no results were reported on time to diagnosis.

Recommendations: There is a need for high quality studies with appropriate comparators to reliably determine the impact of RATs on time to diagnosis of bowel cancer and IBD.

6.4 Health awareness campaigns

One study (Williams et al 2020) was found assessing the effectiveness of a health awareness campaigns for breast, bowel and lung cancer.

A before and after study (Williams et al 2020, n=119, moderate quality) evaluated a community cancer awareness programme delivered to at least 5,500 people with a focus on people over 50 years of age and hard to reach groups, primarily Black, Asian and minority ethnic groups, in the most deprived areas of Manchester and Tameside and Glossop between September 2012 and March 2015. Personalised information on signs and symptoms, screening programmes, susceptibility, and prevalence of breast, bowel and lung cancer, barriers to early diagnosis, and signposting to mainstream services was delivered in a variety of settings including community groups, events, businesses and community centres delivered by peer-led volunteers mostly from areas of high deprivation. In total, 119 adults who had received information from peer-led champions between September 2012 and March 2015 and completed a Cancer Awareness Measures questionnaires before and after the intervention were included in the study. The authors reported a statistically significant increase in knowledge after the intervention for cancer screening programmes ($p<0.05$), recognition of warning signs for cancer ($p<0.05$), and recognition of risk factors for cancer in ($p<0.001$) and a decrease in perception of barriers to seeking help ($p<0.05$). In addition, 90.7% of participants before and 95.5% after the programme reported that they would not delay visiting a doctor if they experienced symptoms. The results of this study should be treated with caution due to its small sample size and the before and after design of the study means that it is uncertain whether changes observed are due to the intervention or differences in population characteristics between the groups or other external factor. Furthermore, convenience sampling was used therefore the study population may not be representative of the target population.

Summary: One study of moderate quality provided limited evidence that a peer-led community cancer awareness programme targeted at people over 50 years of age and hard to reach groups improved knowledge and perception of barriers.

Recommendations: There is a need for high quality studies with representative samples to reliably determine the impact of a variety of health awareness programmes on time to diagnosis of IBD and similar diseases. The study authors recommended that to improve the likelihood of knowledge retention, the intervention should be repeated on the same sample of people periodically.

6.5 Two-week wait referral pathway

One study (Fallon et al 2019) was found assessing the impact of the two-week wait (2WW) referral pathway in upper and lower gastrointestinal cancers.

A retrospective cohort study (Fallon et al 2019; n=509; moderate quality) compared the diagnosis, treatment and survival outcomes of two-week wait (2WW) referrals to non-2WW referrals (emergency referrals and routine referrals) in patients with upper gastrointestinal (UGI) and lower gastrointestinal (LGI) malignancies treated between 1 April 2015 and 31 March 2017 at Luton and Dunstable University Hospital. The study found no statistically significant difference between 2WW and non-2WW routes in stage of malignancy at time of presentation of referral for UGI patients ($p=0.058$; no further results reported) and for LGI

patients (p=0.829; no further results reported), rates of curative treatment considered for UGI patients (12/46 (26%) vs 35/102 (34%), OR 1.48, 95% CI 0.68 to 3.21, (p=0.321)) and for LGI patients (97/127 (76%) vs 68% (158/234), OR 1.59, 95% CI 0.97 to 2.62, (p=0.067)) and in median survival trend in UGI patients (multivariate hazard ratio (HR) 0.99, 95% CI 0.56 to 1.75, (p=0.963)) and LGI patients (multivariate HR 1.10, 95% CI 0.60 to 1.99, p=0.764)). The results of this study should be treated with caution as the non-2WW referral control group included emergency referrals so was not a comparison of 2-WW referrals vs routine referrals. Furthermore, the study is likely to be underpowered to detect small effect sizes and the populations of those referred under the 2WW pathway are likely to be different to those referred routinely and through emergency routes and it is not clear if these differences were adequately adjusted for.

Summary: One study of moderate quality provided limited evidence of the impact of two-week referrals on time to diagnosis. Based on the results of this study it is not possible to reliably determine whether two-week referrals impact on time to diagnosis of upper and lower gastrointestinal cancers and therefore no conclusions can be made on possible impact on IBD.

Recommendations: There is a need for high quality studies to reliably determine the impact of two-week referrals on time to diagnosis on IBD and cancer. The study authors recommended that the result of their study should be validated by a multicentre study with a longer follow-up of over five to ten years to test the hypothesis that 2WW achieves better curative resection rates and improved survival in UGI and LGI malignancies. They also recommended that 2WW pathway strategies that target delay in initial presentation following onset of symptoms, or delay from presentation to referral, may have a greater impact in gastrointestinal cancers than the current initiative of reducing time from referral to specialist review.

7 Gaps and weaknesses in the evidence base

7.1 Extent and nature of delayed diagnosis and causes in people with Crohn's or Colitis in the UK

Although a relatively large number of studies were found relating to delayed diagnosis in people with Crohn's or Colitis, the studies mostly reported limited results, and many were small and from a single service or geographical area with uncertainty about their applicability to other areas. Furthermore, the studies varied in their design, particularly the measurement of delayed diagnosis, and in the age of the data (i.e. when the patients were going through the diagnostic process) making it difficult to provide a clear answer about the extent and nature of delayed diagnosis across the UK.

Few studies were found reporting any findings for Wales, Scotland and Northern Ireland with most studies covering England only or the UK with no breakdown of results by country.

Most studies included both people with Crohn's and Colitis, but often results were not reported separately for each disease and no results were reported for Microscopic Colitis. It was therefore not possible to reliably assess any differences in time to diagnosis between the separate conditions.

Few studies were found that provided a breakdown of results by population subgroup and they were likely not to be adequately powered to detect small differences in diagnostic delay between the groups. It was therefore not possible to reliably assess the extent of any inequalities in diagnostic delay across the pathway.

It is possible that a statistical analysis of the IBD UK survey data could be used to make comparisons by country, region and population subgroup (if recorded in the data) to more reliably determine whether any differences in delays in diagnosis exist by area and population subgroup within the UK (IBD UK 2021).

7.2 Interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases

Few studies were found assessing interventions tackling delayed diagnosis in Crohn's or Colitis and other comparative diseases.

Only three studies were found on interventions tackling delayed diagnosis of IBD and these all evaluated faecal calprotectin testing in primary care. These studies were of low to moderate quality and based on the results of these studies it was not possible to reliably determine whether faecal calprotectin testing in primary care reduced time to diagnosis of IBD. There is a need for high quality evidence with appropriate comparators and adequately powered sample sizes to reliably determine whether faecal calprotectin testing in primary care reduces time to diagnosis of IBD.

A further four studies were found on interventions tackling delayed diagnosis of cancer and these assessed the impact of a pilot rapid diagnostic centre for patients with vague and/or non-specific symptoms suspicious of cancer, risk assessment tools for suspected bowel and lung cancer in general practice, health awareness campaigns for breast, bowel and lung cancer and two-week wait referrals for suspected upper and lower gastrointestinal cancers. All studies were of moderate quality and, except for 2WW referrals, provided some evidence of reduced time of diagnosis or related outcomes. However, based on the volume and strength of the evidence found it was not possible to reliably determine the impact of the interventions on delayed diagnosis in cancer and hence whether similar interventions may work for IBD. It is possible that some of these interventions might be useful in tackling the potential causes of delayed diagnosis to IBD identified in the included studies, particularly health awareness campaigns and initiatives around referral and diagnostic pathways. However, there is a need for high quality evidence with appropriate comparators and adequately powered sample sizes to reliably determine the effectiveness of these interventions and whether they could reduce time to diagnosis in IBD.

No studies were found assessing the impact of interventions tackling delayed diagnosis in immune-mediated inflammatory conditions.

A number of references to interventions that could potentially be useful in reducing time to diagnosis in IBD were identified in the course of searching for evidence for this review. However, these could not be formally included in the review as no eligible evidence was identified assessing the effectiveness of these interventions. Such interventions could include:

- Targeted screening for IBD in high-risk groups such as capsule endoscopy-based screening for first degree relatives of Crohn's Disease patients, and screening in patients with IBS and patients with spondyloarthritis
- Training and educational materials to help healthcare professionals recognise potential IBD. In 2017, RCGP and Crohn's & Colitis UK launched the Inflammatory Bowel Disease Toolkit, a user-friendly guide to IBD for GPs and other primary care professionals, as part of its Spotlight project to improve understanding of Crohn's Disease and Colitis. The Spotlight project also employed Regional Clinical Champions (colleagues with a professional interest in IBD) to deliver face to face local training. However, whilst the initiative received positive feedback (RCGP and Crohn's & Colitis UK 2020), no studies were found evaluating the impact of the Spotlight Project on time to diagnosis of IBD
- Improving the efficiency and productivity of service pathways and processes such as triaging, increasing diagnostic testing and workforce capacity, different use of existing workforce and digitisation of services. A study was found evaluating the impact of a telephone straight-to-test (tSTT) pathway[21] at Barts Health NHS Trust in reducing time to diagnosis for patients referred by primary care GPs with lower GI symptoms from 2013 to 2018. However, this study was not included as it has only been published as a conference poster. The conference poster reported that the average time from GP referral to diagnosis via the tSTT pathway was shorter than that reported in the ISBEN study. No further details were reported but it appears that the ISBEN study is a cohort study conducted in Norway so this comparison should be treated with caution

Furthermore, stakeholders highlighted a number of initiatives which may benefit from evaluation:

- Problem based referral for primary care teams (and others) to refer into with appropriate bloods, stool cultures and faecal calprotectin in order to triage into correct pathways
- Streamlined processes so patients are not being referred through different pathways
- IBD specific endoscopy and clinic queues in secondary care
- Safety netting, such as a patient letter saying you are being investigated for IBD please contact IBD nurse helpline if your symptoms worsen or if you have not heard from us after a certain number of weeks
- IBD MDT coordinators (like cancer coordinators) to help ensure appropriate endoscopy, clinic, bloods etc. have been appointed in a timely manner (aligned to IBD UK standards)
- Prospective IBD patient registry embedded into the electronic health record.

[21] The tSTT pathway is the delivery of an appropriate diagnostic service without the requirement for the patient to first attend an out-patient clinic hospital appointment. A specialist colorectal nurses scrutinise routine (18-week wait) and urgent (2-week wait) referrals. The priorities of the investigations are based on the information on referral letters and patient history during telephone assessment. The endoscopic assessment can be expedited in patients with features suggestive of IBD such as family history, raised faecal calprotectin and weight loss.

8 Conclusions and recommendations

8.1 Extent and nature of delayed diagnosis in people with Crohn's or Colitis in the UK

Twenty-three studies were found relating to the extent and/or nature of delayed diagnosis in people with Crohn's or Colitis in the UK. The studies covered a wide range of designs including surveys of patients or services, case series, cohort studies or case control studies, audits, analyses of primary and/or secondary care databases and qualitative studies. The studies ranged in size from 20 to 103,609 patients where reported. Collectively they covered patients and services over a 33-year time period (from 1987 to 2020) with seven studies including recent results from the last five years. The impact of the COVID-19 pandemic on services was explored in two of the included studies.

Just under half of the studies covered the whole of the UK or multiple countries within the UK (11 studies). However, only four studies provided a breakdown by country. The remaining studies covered one or multiple areas/centres in England with no breakdown of results by area/centre. No studies were conducted in Wales (except for 1 study that only reported on causes of delays), Scotland and Northern Ireland only. Most studies included both people with Crohn's and Colitis, where this was stated, but often results were not reported separately for each disease and no results were reported separately for Microscopic Colitis.

A wide range of outcomes relating to delayed diagnosis were reported in the studies focusing on a range of different aspects of the diagnostic pathway. Outcomes included frequency of delayed diagnosis (4 studies), time to diagnosis (12 studies), prevalence and nature of initial misdiagnosis (5 studies), disease severity at diagnosis (1 study), prevalence and duration of symptoms prior to diagnosis (7 studies), healthcare usage prior to diagnosis (2 studies), potential causes of delay (11 studies) and clinical outcomes affected by delayed outcomes (1 study). The differences between the studies and outcomes reported, along with different study time periods, made it difficult to compare results across the studies and to compare results for different population subgroups and geographical areas. Furthermore, each study design had different quality issues such as recall bias for patient surveys, for example, asking patients to recall length of time from symptom onset to diagnosis or the representativeness of reviews of patients from single centres or areas.

Bearing in the mind the complications of comparing results between studies, the proportion of people who waited more than six and 12 months for a diagnosis was reported by two studies and ranged between 36% and 40% for those waiting more than six months and between 21% and 26% for those waiting more than 12 months in the UK. The average time to diagnosis was reported in four studies and ranged from 2.3 to 13 months. A systematic review with meta-analyses evaluating the length of time to IBD diagnosis was returned in the stakeholder consultation (Jayasooriya 2022). The results could not be included as the systematic review is currently only published as a conference abstract and includes non-UK studies. However, it is worth noting that for high income countries, the pooled weighted median was reported to be 6.4 months (IQR 1.7 to 46.7) in Crohn's Disease and 2.5 months (IQR 0.3 to 23.0) in Ulcerative Colitis.

In terms of differences between adults and children, two studies reporting separate results for adults and children observed similar results for both groups, but the statistical significance

of these comparisons was not reported. One study reporting separate results for Crohn's and Ulcerative Colitis reported a statistically significant longer time to diagnosis for Crohn's Disease (by about four months) than Ulcerative Colitis or IBD unclassified.

No evidence was found to suggest differences in diagnostic delays between Black, Asian and minority ethnic groups or compared to White ethnic groups. Three studies reported results on the extent of delayed diagnosis for Black, Asian and minority ethnic groups. Two of which compared results across ethnic groups and found no differences in time to diagnosis. However, it is likely that these studies are not adequately powered to detect small differences between groups and one study included patients diagnosed over ten years ago.

In terms of differences between geographical areas, no large-scale studies were found formally comparing different areas, and given the differences in populations and study designs it would not be appropriate to compare results of studies conducted in different areas. Several large UK database studies and patient and service surveys collected data from across the UK but did not statistically compare data for the individual countries.

The data reported by the studies highlight a wide variability of experience amongst people with Crohn's or Colitis with a substantial percentage of people waiting several months or even years for a diagnosis. However, they do not provide a clear answer to how often diagnosis is delayed, by how much, and whether it is more delayed for certain subgroups and between Crohn's and Colitis. Limited evidence was found to assesses the extent of inequalities in the diagnosis pathway. While some studies did report results on population subgroups, they were often not adequately powered to detect small differences or did not conduct statistical comparison tests.

It is recommended that a statistical analysis of the IBD UK survey data could be used to make comparisons by country, region and population subgroup (if recorded in the data) to more reliably determine whether any differences in delays in diagnosis exist by area and population subgroup within the UK.

8.2 Causes of delayed diagnosis/obstacles to early diagnosis at each stage in the diagnostic pathway

Eleven studies were found assessing causes of delayed diagnosis or obstacles to early diagnosis in people with Crohn's or Colitis, seven covering the UK, three in England and one in Wales. No national studies conducted in Scotland and Northern Ireland were found. Limited evidence was found on the causes of delayed diagnosis in population subgroups.

A wide range of different potential causes of delay were proposed within the studies relating to different aspects of the diagnostic pathway.

Lack of awareness or understanding of IBD, Crohn's Disease or Colitis was raised as a potential issue for both the public and GPs which could affect both patient behaviour in seeking medical advice and GP behaviour in the management or referral of patients. This aspect was also highlighted in two studies focusing on people from ethnic subgroups. For example, one interview study with people with IBD from a Black or South Asian background reported a general impression of a widespread lack of awareness of IBD in people from a Black or South Asian background within primary care and highlighted a need for an improved

responsiveness to young people with IBD and culturally competent information about IBD. Another interview study of people with IBD from the South Asian population reported that two-thirds of participants experienced significant delays in having their IBD diagnosed due to a lack of referral by their GP (Mukherjee et al 2015). However, no participants attributed the delay to their ethnic background.

Factors relating to patients' characteristics that were associated with diagnostic delay included higher household income, previous diagnosis of IBS and previous diagnosis of depression, all of which could also affect patient and/or GP behaviour.

Factors relating more to the provision of services included access to and confidence in using faecal calprotectin testing in primary and/or secondary care, with some indication that this could vary across the UK. Access to endoscopy and staffing levels were also identified as factors that could cause delays. In some studies factors relating to the provision of services were particularly focused on issues caused by the COVID-19 pandemic. However, these issues have also been identified in a wider context. For example, the British Society of Gastroenterology Workforce Report published in February 2022 estimated a shortfall of consultant gastroenterologists in the UK, requiring the equivalent of an additional 147 whole time equivalent consultants (10.2% expansion) to provide the substantive consultant workforce needed to meet current demand. The authors noted considerable geographical variation in substantive consultant gastroenterologists and hepatologists throughout the UK, specifying populations in London South, Yorkshire and the Humber, Thames Valley, Wessex, the North and West of Scotland and North Wales as being poorly served (Rutter 2022). Furthermore, a survey of 166 UK adult services in 2019 to 2020 found that the IBD standards staffing recommendations were being met by only 31% for gastroenterologists, 37% for radiologists and 8% histopathologists. The Getting it Right First Time (GIRFT) Programme National Speciality report noted that capacity issues were leading to significant variation in waiting times for new patient appointments in gastroenterology outpatient clinics, ranging from one week to 27 weeks across Trusts. The authors did not specify which Trusts had the higher or lower waiting times (Oates 2021).

Factors relating to the organisation of services included variability in whether services had agreed referral pathways between primary and secondary care in place for people with suspected IBD. The speciality that patients are referred to was also identified as a potential factor as was the frequency of MDT meetings, with some indication that this could vary between adult and paediatric services and across the UK.

8.3 Interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases

The evidence base surrounding interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and other comparative diseases is limited. Only three studies were found assessing the impact of interventions on time to diagnosis and other related outcomes in patients with Crohn's or Colitis, all of which assessed faecal calprotectin testing in primary care. A further four studies were found on comparative diseases, all of which focussed on cancer diagnosis. No studies were found on other similar immune-mediated inflammatory conditions.

The studies tended to be small with most having sample sizes between 42 and 274 and were of low to moderate quality. The main quality issues were a lack of an appropriate

counterfactual or comparator with no attempt to adjust for differences between population characteristics of the groups and many of the studies being limited to one centre, often with poor reporting of baseline characteristics of study population meaning that the representativeness of the study population could not be assessed.

The evidence around faecal calprotectin testing in primary care was inconclusive with none of the studies being able to reliably demonstrate a reduction in time to diagnosis. However, there was some evidence to suggest that faecal calprotectin testing increased referrals directly to gastroenterology which may allow for earlier access to treatment and avoid unnecessary investigations in some cases. The same before and after study also observed a reduction in the number of patients diagnosed via the two-week wait pathway which may result in a reduction in time to diagnosis as once malignancy has been excluded, these patients are at risk of getting “lost” within the system and experiencing delays in treatment.

In terms of learning from comparative diseases, very few evaluated interventions were found. These were limited to a rapid diagnostic centre for patients with vague and/or non-specific symptoms suspicious of cancer, risk assessment tools for suspected bowel and lung cancer in general practice, a health awareness campaign for breast, bowel and lung cancer and two-week wait referrals for suspected upper and lower gastrointestinal cancers. Each intervention was evaluated by one study of moderate quality, and except for 2WW referrals, each reported reduced time of diagnosis or related outcomes. However, based on the volume and strength of the evidence found for each it was not possible to reliably determine the impact of the interventions on delayed diagnosis in these diseases and hence whether similar interventions may work for IBD.

Notably no relevant evidence was found for some interventions for which studies might have been expected. For example, no relevant evaluations were identified on targeted screening for IBD in high-risk groups, such as capsule endoscopy-based screening for first degree relatives of Crohn’s Disease patients, and screening in patients with IBS and patients with spondyloarthritis. Similarly, no evidence evaluating effectiveness in terms of impact on time to diagnosis was found on training, educational materials and Regional Clinical Champions to improve understanding of Crohn’s Disease and Colitis amongst healthcare professionals, including the RCGP and Crohn’s & Colitis UK Spotlight Project. Furthermore, no evidence was found on improving the efficiency and productivity of service pathways and processes such as triaging, telephone straight-to-test pathways, increasing diagnostic testing and workforce capacity, different use of existing workforce such as community pharmacy and digitisation of services.

There is a need for high quality studies with appropriate comparators and adequately powered sample sizes to reliably determine whether interventions such as health awareness campaigns, screening of high risk groups, improving understanding of healthcare professionals, faecal calprotectin testing, risk assessment tools and toolkits to identify red flags, rapid diagnostic centres and improving the efficiency and productivity of service pathways reduce time to diagnosis in IBD and ultimately improved health outcomes for patients. Given the paucity of evidence in the area, it is recommended that key stakeholders are consulted on their experiences of most promising interventions and pathway redesign to focus future research.

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Appendix 1: Research question and search frameworks

The evidence review addressed two questions:

1. What is the extent and nature of delayed diagnosis in people with Crohn's or Colitis in the UK and is there evidence for inequalities in the diagnosis pathway?
    a. Frequency of delayed diagnosis and time to diagnosis by geographical area and population subgroups if available
    b. Causes of delayed diagnosis/obstacles to early diagnosis at each stage in the diagnostic pathway, such as patient factors (demographics, awareness of symptoms and seeking medical help), primary care factors (GP awareness and referral process), system factors (such as access to laboratory investigations)
2. What has been shown to work in tackling delayed diagnosis of Crohn's and Colitis and other long-term conditions such as immune-mediated inflammatory conditions and conditions with primary symptoms expressed in the gut?

The frameworks used to guide the searches for each of the questions are set out below:

Search framework for question 1

	Inclusion/exclusion criteria
Population	People (adults and children) with Crohn's or Colitis living in the UK [Includes Crohn's Disease, Ulcerative Colitis, Microscopic Colitis and unspecified Colitis by a secondary care specialist]
Exposure	Delayed diagnosis or diagnosis in general
Outcomes	Frequency of delayed diagnosis (as defined by study/report e.g. a diagnosis that was unintentionally delayed while sufficient information was available earlier) Time to diagnosis Prevalence and nature of initial misdiagnosis Disease severity at diagnosis (measured by for e.g. Crohn's Disease activity index (CDAI, paediatric CDAI and Harvey Bradshaw Index) Prevalence and duration of GI symptoms and other symptoms prior to diagnosis Health care usage to manage symptoms prior to diagnosis Causes of delay in diagnosis including demographic, service and system factors associated with delayed diagnosis Clinical outcomes affected by delayed diagnosis such as health related quality of life measured by e.g. IBDQ or IMPACT questionnaire, growth and onset of puberty in children, surgery, biologic treatment, hospitalisation and mortality [Where available, results for population subgroups (e.g. ethnicity, UK region) will be extracted]

Study designs	Cohort studies Case control studies Surveys Case series Systematic reviews/grey literature narrative reviews and reports [Exclusions: case reports, letters, conference abstracts, publications only available as an abstract or summary and posters]
Date and language	Studies and reports published in English since 2011 [We will prioritise the most recent relevant evidence identified]

Search framework for question 2

	Inclusion/exclusion criteria
Population	People (adults and children), at high risk of, or diagnosed, with Crohn's or Colitis or comparative long-term conditions, living in the UK [Includes Crohn's Disease, Ulcerative Colitis, Microscopic Colitis and unspecified Colitis by a secondary care specialist and comparative long-term condition such as immune-mediated inflammatory conditions (e.g. rheumatoid arthritis) and conditions with primary symptoms expressed in the gut such as bowel cancer, irritable bowel syndrome and coeliac disease]
Intervention	Interventions aimed at tackling delayed diagnosis of Crohn's or Colitis and comparative diseases [Examples of interventions could include increasing awareness of the signs and symptoms amongst the medical profession and general population, toolkits to identify red flags, clinical risk prediction models and referral processes and pathways]
Comparator	Any comparator [Studies with no comparison group or counterfactual will be excluded unless a limited volume of controlled studies are found]
Outcomes	Frequency of delayed diagnosis (as defined by study/report e.g. a diagnosis that was unintentionally delayed while sufficient information was available earlier) Time to diagnosis Disease severity at diagnosis (measured by for e.g. Crohn's Disease activity index (CDAI), paediatric CDAI and Harvey Bradshaw Index) Clinical outcomes such as health related quality of life measured by e.g. IBDQ or IMPACT questionnaire, growth and onset of puberty in children, surgery, biologic treatment and hospitalisation Misdiagnosis Mortality

	[Where available results for population subgroups will be extracted]
Study designs	Systematic reviews and meta-analyses Controlled trials (randomised, cluster randomised, quasi-randomised or non-randomised) Comparative observational studies (cohort studies and comparative surveys) Before and after studies Evaluations including a counterfactual [We will use existing reviews summarising the evidence base for a particular intervention type and/or condition, where available, rather than individual primary studies] [Exclusions: narrative reviews, uncontrolled observational studies, case series, case reports, commentaries, letters, conference abstracts, publications only available as an abstract or summary and posters]
Date and language	Studies and reports published in English since 2011 [We will prioritise the most recent relevant evidence identified]

Appendix 2: Search strategies

Searches for peer-reviewed evidence

Database: CINAHL
Focus of search: Question 1 and Question 2 for Crohn's, Colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

#	Query
S17	S9 AND S15 Limiters - Published Date: 20110101-20221231; English Language
S16	S9 AND S15
S15	S13 NOT S14
S14	((MH "Africa+") OR (MH "America+") OR (MH "Asia+") OR (MH "Australia+") OR (MH "Andorra") OR (MH "Armenia") OR (MH "Austria") OR (MH "Azerbaijan") OR (MH "Belgium") OR (MH "Europe, Eastern+") OR (MH "France") OR (MH "Georgia (Republic)") OR (MH "Germany+") OR (MH "Gibraltar") OR (MH "Greece") OR (MH "Iceland") OR (MH "Ireland") OR (MH "Italy") OR (MH "Liechtenstein") OR (MH "Luxembourg") OR (MH "Mediterranean Region+") OR (MH "Monaco") OR (MH "Netherlands") OR (MH "Portugal") OR (MH "San Marino") OR (MH "Scandinavia+") OR (MH "Spain") OR (MH "Switzerland")) NOT ((MH "United Kingdom+") OR (MH "Europe"))
S13	S10 OR S11 OR S12
S12	TI ((bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's")) OR TI ((aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's")) OR TI ((armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's")) OR TI ((bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*)))))) OR AB ((bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's")) OR AB ((aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's")) OR AB ((armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's")) OR AB ((bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not

	(massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))))
S11	TI ((national health service* or nhs*)) OR TI ((english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) N5 english))) OR TI ((gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*)) OR AB ((national health service* or nhs*)) OR AB ((english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) N5 english))) OR AB ((gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*))
S10	(MH "United Kingdom+")
S9	S7 OR S8
S8	(MM "Colitis+/DI") OR (MM "Inflammatory Bowel Diseases+/DI")
S7	S3 AND S6
S6	S4 OR S5
S5	TI (diagnos* or detect* or screen*) OR AB (((early or earlier or late or later or delay* or missed or error*) N5 (diagnos* or detect*))) OR TI (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*) OR AB (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*) OR TI ((time* N5 (diagnos* or referral* or treatment)) OR AB ((time* N5 (diagnos* or referral* or treatment)) OR TI ((((frequen* or duration or time*) N3 symptom*) and (diagnos* or detect*))) OR AB ((((frequen* or duration or time*) N3 symptom*) and (diagnos* or detect*))) OR TI ((diagnos* N3 (pathway* or route*))) OR AB ((diagnos* N3 (pathway* or route*)))
S4	(MM "Diagnosis") OR (MH "Diagnosis, Delayed") OR (MM "Diagnosis, Digestive System") OR (MH "Diagnostic Errors+") OR (MH "Early Diagnosis")
S3	S1 OR S2
S2	TI ((inflammatory bowel disease? or crohn* or colitis)) OR AB ((inflammatory bowel disease? or crohn* or colitis))
S1	(MH "Colitis+") OR (MH "Inflammatory Bowel Diseases+")

Database: CINAHL
Focus of search: Question 2 for other comparative diseases
Search date: 10 January 2022
Search strategy:

#	**Query**
S15	S7 AND S13 Limiters - Published Date: 20110101-20221231; English Language

S14	S7 AND S13
S13	S11 NOT S12
S12	((MH "Africa+") OR (MH "America+") OR (MH "Asia+") OR (MH "Australia+") OR (MH "Andorra") OR (MH "Armenia") OR (MH "Austria") OR (MH "Azerbaijan") OR (MH "Belgium") OR (MH "Europe, Eastern+") OR (MH "France") OR (MH "Georgia (Republic)") OR (MH "Germany+") OR (MH "Gibraltar") OR (MH "Greece") OR (MH "Iceland") OR (MH "Ireland") OR (MH "Italy") OR (MH "Liechtenstein") OR (MH "Luxembourg") OR (MH "Mediterranean Region+") OR (MH "Monaco") OR (MH "Netherlands") OR (MH "Portugal") OR (MH "San Marino") OR (MH "Scandinavia+") OR (MH "Spain") OR (MH "Switzerland")) NOT ((MH "United Kingdom+") OR (MH "Europe"))
S11	S8 OR S9 OR S10
S10	TI ((bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's")) OR TI ((aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's")) OR TI ((armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's")) OR TI ((bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*)))))) OR AB ((bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's")) OR AB ((aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's")) OR AB ((armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's")) OR AB ((bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton

	or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))))
S9	TI ((national health service* or nhs*)) OR TI ((english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) N5 english))) OR TI ((gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*)) OR AB ((national health service* or nhs*)) OR AB ((english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) N5 english))) OR AB ((gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*))
S8	(MH "United Kingdom+")
S7	S3 AND S6
S6	S4 OR S5
S5	TI (((early or earlier or late or later or delay* or missed or error*) N5 (diagnos* or detect*))) OR AB (((early or earlier or late or later or delay* or missed or error*) N5 (diagnos* or detect*))) OR TI (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*) OR AB (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*) OR TI ((time* N5 (diagnos* or referral* or treatment)) OR AB ((time* N5 (diagnos* or referral* or treatment)) OR TI ((((frequen* or duration or time*) N3 symptom*) and (diagnos* or detect*))) OR AB ((((frequen* or duration or time*) N3 symptom*) and (diagnos* or detect*))) OR TI ((diagnos* N3 (pathway* or route*))) OR AB ((diagnos* N3 (pathway* or route*)))
S4	(MH "Diagnosis, Delayed") OR (MH "Diagnostic Errors+") OR (MH "Early Diagnosis")
S3	S1 OR S2
S2	TI ((rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary N2 cirrhosis))) OR AB ((rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary N2 cirrhosis)))
S1	(MH "Arthritis, Rheumatoid+") OR (MH "Psoriasis+") OR (MH "Lupus Erythematosus, Systemic+") OR (MH "Autoimmune Diseases") OR (MH "Hepatitis, Autoimmune")

Database: Cochrane
Focus of search: Question 1 and Question 2 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

ID	**Search**
#1	MeSH descriptor: [Colitis] explode all trees
#2	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#3	(inflammatory bowel disease or crohn* or colitis):ti,ab,kw
#4	#1 OR #2 OR #3
#5	MeSH descriptor: [Early Diagnosis] this term only
#6	MeSH descriptor: [Delayed Diagnosis] explode all trees
#7	MeSH descriptor: [Diagnostic Errors] explode all trees
#8	MeSH descriptor: [Diagnosis] this term only
#9	MeSH descriptor: [Diagnosis, Differential] explode all trees

#10	((((early or earlier or late or later or delay* or missed or error*) NEAR/5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*))):ti,ab,kw OR ((time* NEAR/5 (diagnos* or referral* or treatment))):ti,ab,kw OR ((((frequen* or duration or time*) NEAR/3 symptom*) and (diagnos* or detect*))):ti,ab,kw OR ((diagnos* NEAR/3 (pathway* or route*))):ti,ab,kw
#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	#4 AND #11
#13	MeSH descriptor: [Colitis] explode all trees and with qualifier(s): [diagnosis - DI]
#14	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees and with qualifier(s): [diagnosis - DI]
#15	#12 OR #13 OR #14

Database: Cochrane
Focus of search: Question 2 for other comparative diseases
Search date: 10 January 2022
Search strategy:

ID	**Search**
#1	MeSH descriptor: [Autoimmune Diseases] this term only
#2	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#3	MeSH descriptor: [Psoriasis] explode all trees
#4	MeSH descriptor: [Hepatitis, Autoimmune] explode all trees
#5	MeSH descriptor: [Liver Cirrhosis, Biliary] explode all trees
#6	((rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary NEAR/2 cirrhosis))):ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	MeSH descriptor: [Early Diagnosis] explode all trees
#9	MeSH descriptor: [Delayed Diagnosis] explode all trees
#10	MeSH descriptor: [Diagnostic Errors] explode all trees
#11	MeSH descriptor: [Diagnosis] this term only
#12	MeSH descriptor: [Diagnosis, Differential] explode all trees
#13	((((early or earlier or late or later or delay* or missed or error*) NEAR/5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*))):ti,ab,kw OR ((time* NEAR/5 (diagnos* or referral* or treatment))):ti,ab,kw OR ((((frequen* or duration or time*) NEAR/3 symptom*) and (diagnos* or detect*))):ti,ab,kw OR ((diagnos* NEAR/3 (pathway* or route*))):ti,ab,kw
#14	#8 OR #9 OR #10 OR #11 OR #12 OR #13
#15	#7 AND #14

Database: EMBASE
Focus of search: Question 1 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

ID	**Search**
1	exp *colitis/ or exp *inflammatory bowel disease/
2	(inflammatory bowel disease? or crohn* or colitis).ti,ab,kw.
3	1 or 2

4	early diagnosis/
5	Delayed Diagnosis/
6	exp Diagnostic Errors/
7	*diagnosis/ or diagnosis, differential/
8	(diagnos* or detect* or screen*).ti.
9	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
10	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
11	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
12	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	3 and 13
15	exp *colitis/di or exp *inflammatory bowel diseases/di
16	14 or 15
17	exp United Kingdom/
18	(national health service* or nhs*).ti,ab,in.
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
21	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
22	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
23	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
24	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	(exp africa/ or exp asia/ or exp Pacific Islands/ or "Australia and New Zealand"/ or "arctic and antarctic"/ or exp north america/ or exp "south and central america"/) not (exp United Kingdom/ or Europe/)

27	25 not 26
28	16 and 27
29	limit 28 to (english language and yr="2011 -Current")
30	limit 16 to ("systematic review" or "reviews (maximizes specificity)")
31	limit 30 to (english language and yr="2011 -Current")
32	29 or 31
33	conference*.pt.
34	32 not 33

Database: EMBASE
Focus of search: Question 2 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

ID	Search
1	red flag?.ti.
2	*symptom/ or *gastrointestinal symptom/ or *symptom assessment/
3	abdominal pain/ and (diarrhea/ or bloody diarrhea/ or chronic diarrhea/ or Fatigue/ or Body Weight Loss/)
4	(diarrhea/ or bloody diarrhea/ or chronic diarrhea/) and (Fatigue/ or Body Weight Loss/)
5	Fatigue/ and Body Weight Loss/
6	red flag?.ti,ab,kw.
7	(sign? or symptom? or presentation? or manifestation?).ti.
8	(((unexplained or common) adj3 (sign? or symptom? or presentation? or manifestation?)) or "signs and symptoms").ti,ab,kw.
9	((((abdom* or stomach) adj2 (ache? or pain? or discomfort or symptom?)) or stomachache?) and (diarrh?ea or runny stool? or ((blood or bleed) adj2 (stool? or f?ecal or rectal)) or tired* or fatigue or weight loss)).ti,ab,kw.
10	((diarrh?ea or runny stool? or ((blood or bleed) adj2 (stool? or f?ecal or rectal))) and (tired* or fatigue or weight loss)).ti,ab,kw.
11	((tired* or fatigue) and weight loss).ti,ab,kw.
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	clinical pathway/ or checklist/
14	(pathway? or protocol?).ti. or ((clinical or critical or care or diagnos* or refer*) adj (pathway? or protocol?)).ti,ab,kw.
15	In service Training/
16	health education/ or health literacy/ or exp health promotion/ or patient education/
17	((patient or public or community or social) adj5 (campaign? or publicity or educat* or promot* or aware* or marketing)).ti,ab,kw.
18	((general practitioner? or physician? or doctor? or nurse? or (health* adj2 (staff or personnel or worker? or professional?))) adj5 (campaign? or educat* or promot* or aware* or training)).ti,ab,kw.
19	Risk Assessment/ and (model? or tool? or toolkit).ti,ab,kw.
20	((risk? or prediction? or diagnos*) adj3 (model? or tool? or toolkit? or rule?)).ti,ab,kw.
21	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	early diagnosis/
23	Delayed Diagnosis/
24	exp Diagnostic Errors/

25	*diagnosis/ or diagnosis, differential/
26	(diagnos* or detect* or screen*).ti.
27	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
28	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
29	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
30	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
31	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	exp United Kingdom/
33	(national health service* or nhs*).ti,ab,in.
34	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
35	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
36	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
37	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
38	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
39	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
40	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	(exp africa/ or exp asia/ or exp Pacific Islands/ or "Australia and New Zealand"/ or "arctic and antarctic"/ or exp north america/ or exp "south and central america"/) not (exp United Kingdom/ or Europe/)
42	40 not 41
43	12 and 21 and 31 and 42
44	1 and 31 and 42
45	43 or 44
46	limit 45 to (english language and yr="2011 -Current")
47	conference?.pt.

48	46 not 47

Database: EMBASE
Focus of search: Question 2 for other comparative diseases
Search date: 10 January 2022
Search strategy:

ID	Search
1	*autoimmune disease/
2	exp *rheumatoid arthritis/
3	exp *psoriasis/
4	exp *systemic lupus erythematosus/
5	*autoimmune hepatitis/
6	*biliary cirrhosis/
7	((immune mediated inflammatory adj2 (condition? or disorder? or disease?)) or imid).ti,ab,kw.
8	(rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary adj2 cirrhosis)).ti,ab,kw.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	clinical pathway/ or checklist/
11	(pathway? or protocol?).ti. or ((clinical or critical or care or diagnos* or refer*) adj (pathway? or protocol?)).ti,ab,kw.
12	In service Training/
13	health education/ or health literacy/ or exp health promotion/ or patient education/
14	((patient or public or community or social) adj5 (campaign? or publicity or educat* or promot* or aware* or marketing)).ti,ab,kw.
15	((general practitioner? or physician? or doctor? or nurse? or (health* adj2 (staff or personnel or worker? or professional?))) adj5 (campaign? or educat* or promot* or aware* or training)).ti,ab,kw.
16	Risk Assessment/ and (model? or tool? or toolkit).ti,ab,kw.
17	((risk? or prediction? or diagnos*) adj3 (model? or tool? or toolkit? or rule?)).ti,ab,kw.
18	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	early diagnosis/
20	Delayed Diagnosis/
21	exp Diagnostic Errors/
22	*diagnosis/ or diagnosis, differential/
23	(diagnos* or detect* or screen*).ti.
24	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
25	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
26	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
27	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
28	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29	*early diagnosis/
30	*Delayed Diagnosis/
31	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti.

32	29 or 30 or 31
33	exp United Kingdom/
34	(national health service* or nhs*).ti,ab,in.
35	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
36	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
37	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
38	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
39	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
40	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	(exp africa/ or exp asia/ or exp Pacific Islands/ or "Australia and New Zealand"/ or "arctic and antarctic"/ or exp north america/ or exp "south and central america"/) not (exp United Kingdom/ or Europe/)
43	41 not 42
44	9 and 18 and 28 and 43
45	9 and 32 and 43
46	44 or 45
47	conference*.pt.
48	46 not 47
49	limit 48 to (english language and yr="2011 -Current")

Database: HMIC
Focus of search: Question 1 and Question 2 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021

Search strategy:

ID	Search
1	colitis/
2	(inflammatory bowel disease? or crohn* or colitis).mp.
3	1 or 2

Database: HMIC
Focus of search: Question 2 for other comparative diseases
Search date: 10 January 2022
Search strategy:

ID	Search
1	autoimmune diseases/
2	rheumatoid arthritis/
3	systema lupus erythematosus/
4	psoriasis/
5	((immune mediated inflammatory adj2 (condition? or disorder? or disease?)) or imid).mp.
6	(rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary adj2 cirrhosis)).mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	diagnosis/ or clinical diagnosis/ or differential diagnosis/ or early diagnosis/
9	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).mp.
10	(time* adj5 (diagnos* or referral* or treatment)).mp.
11	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).mp.
12	(diagnos* adj3 (pathway? or route?)).mp.
13	(diagnos* or detect* or screen*).ti.
14	8 or 9 or 10 or 11 or 12 or 13
15	7 and 14

Database: MEDLINE
Focus of search: Question 1 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

ID	Search
1	exp colitis/ or exp inflammatory bowel diseases/
2	(inflammatory bowel disease? or crohn* or colitis).ti,ab,kw.
3	1 or 2
4	early diagnosis/
5	Delayed Diagnosis/
6	exp Diagnostic Errors/
7	diagnosis/ or diagnosis, differential/
8	(diagnos* or detect* or screen*).ti.

9	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
10	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
11	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
12	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
13	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	3 and 13
15	exp *colitis/di or exp *inflammatory bowel diseases/di
16	14 or 15
17	exp United Kingdom/
18	(national health service* or nhs*).ti,ab,in.
19	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
20	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
21	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
22	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
23	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
24	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
25	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)
27	25 not 26
28	16 and 27
29	limit 28 to (english language and yr="2011 -Current")
30	limit 16 to ("systematic review" or "reviews (maximizes specificity)")
31	limit 30 to (english language and yr="2011 -Current")
32	29 or 31

Database: MEDLINE
Focus of search: Question 2 for Crohn's, colitis and other inflammatory bowel diseases
Search date: 20 December 2021
Search strategy:

ID	Search
1	red flag?.ti.
2	signs and symptoms/
3	abdominal pain/ and (Diarrhea/ or Fatigue/ or Weight Loss/)
4	Diarrhea/ and (Fatigue/ or Weight Loss/)
5	Fatigue/ and Weight Loss/
6	red flag?.ti,ab,kw.
7	(sign? or symptom? or presentation? or manifestation?).ti.
8	(((unexplained or common) adj3 (sign? or symptom? or presentation? or manifestation?)) or "signs and symptoms").ti,ab,kw.
9	((((abdom* or stomach) adj2 (ache? or pain? or discomfort or symptom?)) or stomachache?) and (diarrh?ea or runny stool? or ((blood or bleed) adj2 (stool? or f?ecal or rectal)) or tired* or fatigue or weight loss)).ti,ab,kw.
10	((diarrh?ea or runny stool? or ((blood or bleed) adj2 (stool? or f?ecal or rectal))) and (tired* or fatigue or weight loss)).ti,ab,kw.
11	((tired* or fatigue) and weight loss).ti,ab,kw.
12	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	Critical Pathways/
14	(pathway? or protocol?).ti. or ((clinical or critical or care or diagnos* or refer*) adj (pathway? or protocol?)).ti,ab,kw.
15	exp Inservice Training/
16	health education/ or consumer health information/ or health promotion/
17	exp Health Personnel/ed [Education]
18	((patient or public or community or social) adj5 (campaign? or publicity or educat* or promot* or aware* or marketing)).ti,ab,kw.
19	((general practitioner? or physician? or doctor? or nurse? or (health* adj2 (staff or personnel or worker? or professional?))) adj5 (campaign? or educat* or promot* or aware* or training)).ti,ab,kw.
20	Risk Assessment/ and (model? or tool? or toolkit).ti,ab,kw.
21	((risk? or prediction? or diagnos*) adj3 (model? or tool? or toolkit? or rule?)).ti,ab,kw.
22	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23	early diagnosis/
24	Delayed Diagnosis/
25	exp Diagnostic Errors/
26	diagnosis/ or diagnosis, differential/
27	(diagnos* or detect* or screen*).ti.
28	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
29	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
30	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
31	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
32	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

33	exp United Kingdom/
34	(national health service* or nhs*).ti,ab,in.
35	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
36	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
37	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
38	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.
39	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
40	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
41	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)
43	41 not 42
44	12 and 22 and 32 and 43
45	1 and 32 and 43
46	44 or 45
47	limit 46 to (english language and yr="2011 -Current")

Database: MEDLINE
Focus of search: Question 2 for other comparative diseases
Search date: 10 January 2022
Search strategy:

ID	Search
1	Autoimmune Diseases/
2	exp Arthritis, Rheumatoid/
3	exp Psoriasis/
4	exp Lupus Erythematosus, Systemic/

5	Hepatitis, Autoimmune/
6	Liver Cirrhosis, Biliary/
7	((immune mediated inflammatory adj2 (condition? or disorder? or disease?)) or imid).ti,ab,kw.
8	(rheumatoid arthritis or psoriatic arthritis or psoriasis or sjogren* syndrome or systemic lupus erythematosus or sle or autoimmune hepatitis or auto-immune hepatitis or (biliary adj2 cirrhosis)).ti,ab,kw.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	Critical Pathways/
11	(pathway? or protocol?).ti. or ((clinical or critical or care or diagnos* or refer*) adj (pathway? or protocol?)).ti,ab,kw.
12	exp Inservice Training/
13	health education/ or consumer health information/ or health promotion/
14	exp Health Personnel/ed [Education]
15	((patient or public or community or social) adj5 (campaign? or publicity or educat* or promot* or aware* or marketing)).ti,ab,kw.
16	((general practitioner? or physician? or doctor? or nurse? or (health* adj2 (staff or personnel or worker? or professional?))) adj5 (campaign? or educat* or promot* or aware* or training)).ti,ab,kw.
17	Risk Assessment/ and (model? or tool? or toolkit).ti,ab,kw.
18	((risk? or prediction? or diagnos*) adj3 (model? or tool? or toolkit? or rule?)).ti,ab,kw.
19	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	early diagnosis/
21	Delayed Diagnosis/
22	exp Diagnostic Errors/
23	diagnosis/ or diagnosis, differential/
24	(diagnos* or detect* or screen*).ti.
25	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti,ab,kw.
26	(time* adj5 (diagnos* or referral* or treatment)).ti,ab,kw.
27	(((frequen* or duration or time*) adj3 symptom?) and (diagnos* or detect*)).ti,ab,kw.
28	(diagnos* adj3 (pathway? or route?)).ti,ab,kw.
29	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	*early diagnosis/
31	*Delayed Diagnosis/
32	(((early or earlier or late or later or delay* or missed or error?) adj5 (diagnos* or detect*)) or (misdiagnos* or mis-diagnos* or undiagnos* or un-diagnos*)).ti.
33	30 or 31 or 32
34	exp United Kingdom/
35	(national health service* or nhs*).ti,ab,in.
36	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.
37	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.
38	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's " or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.
39	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.

40	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.
41	(bath or "bath's" or ((Birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's" or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachuse tts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.
42	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp oceania/) not (exp great britain/ or europe/)
44	42 not 43
45	9 and 19 and 29 and 44
46	9 and 33 and 44
47	45 or 46
48	limit 47 to (english language and yr="2011 -Current")

Searches for grey literature

We conducted seven searches on NHS Evidence using combinations of terms relating to inflammatory bowel diseases and diagnosis. For example, Crohn's, Colitis, inflammatory bowel disease or autoimmune disease combined with diagnosis, diagnostic pathway or delayed diagnosis. We used the filters for date of publication (January 2011 to December 2021), guidance and policy, evidence summaries, horizon scanning, evidence uncertainties, ongoing trials, practice-based information, implementation support and information for the public.

We searched the websites of agreed organisations for relevant reports in January 2022. The websites searched were NICE, NHS England, NHS Scotland, NHS Wales, NHS Northern Ireland, Department of Health and Social Care, Office for Health Improvement and Disparities, Royal College of General Practitioners, Royal College of Nursing, Royal College of Paediatrics and Child Health, Royal College of Physicians, Crohn's and Colitis UK, Crohn's in Childhood Research Association, European Crohn's and Colitis Organisation, Association of Coloproctology of Great Britain and Ireland, British Society of Gastroenterology, British Society of Paediatric Gastroenterology Hepatology and Nutrition and IBD UK. Where websites had a publications sections, these were reviewed for reports

meeting the inclusion criteria. Where this was not feasible, for example for more complex or wide-ranging websites, the search function was used for combinations of terms relating to inflammatory bowel disease, inflammatory conditions and diagnosis.

For the targeted Google searches we used filters for date of publication (January 2011 to January/February 2022) and for studies published on UK websites (.org.uk). We applied a pre-specified cut-off to screen the results of each of the Google searches, namely the first 100 results returned with the results ordered by relevance.

Appendix 3: Evidence summary tables

Included studies relating to question 1

Study	Population	Data source and year	Key results	Author's conclusions and recommendations	Quality appraisal
Alexakis et al 2015 Nash et al 2011 Qualitative study (interviews)	Young people with IBD from a Black or South Asian background N=20 Male: 65% Mean age (range) years: 20.1 (16 to 24) Asian/Asian British: 85% Mixed Asian/White: 5% Black/Black British: 10% CD: 65% UC: 30% Crohn's and Colitis: 5%	Participants recruited from 2 hospitals in London and 1 hospital in Bristol, 2010	***Frequency of delayed diagnosis*** Participants reporting that they experienced delays or difficulties in the time prior to diagnosis: 60% (12/20) The authors stated that the remaining participants (40%) reported no adverse experiences during the process of being diagnosed ***Time to diagnosis*** Time from symptom onset to diagnosis ranged from 1 month to 3 years. The authors stated that 2 participants reported ill-health for several years before diagnosis ***Prevalence and nature of initial misdiagnosis*** Participants reported being initially diagnosed with tuberculosis (2 participants) and a rare tropical disease (1 participant). Other initial diagnoses included IBS, stomach bug and stress-related diarrhoea (figures not stated)	The authors highlighted a need for an improved responsiveness to young people with IBD and culturally competent information about IBD	This qualitative study was reported in 2 separate publications. A grey literature project report (Nash et al 2011) and a peer reviewed publication (Alexakis et al 2015). Details were extracted from both reports The study included a small number of participants from 3 hospitals in England Limited specific detail was reported relating to experiences during diagnosis The most recently diagnosed patients included in this study would have been diagnosed more than 10 years ago

			One participant reported being referred for psychiatric evaluation for a psychosomatic disorder ***Potential causes of delayed diagnosis*** The authors stated that there were a number of reports of perceived scepticism of participant's ailments prior to diagnosis, particularly from primary care practitioners (no figures reported) The authors reported a general impression by participants who experienced delayed diagnosis of a widespread lack of awareness of IBD in people from a Black or South Asian background within primary care		
Ashton et al 2020 Survey	20 tertiary paediatric gastroenterology centres in England and Scotland	Survey of IBD services, conducted in May 2020 and reflecting on services in April 2020 compared to before the pandemic 100% of the centres invited responded, reflecting approximately 88% of the UK paediatric population	***Potential causes of delayed diagnosis*** Access to faecal calprotectin testing: • No access: 15% (3/20) • Reduced access: 15% (3/20) • No difference: 70% (14/20) Access to endoscopy: • No access: 15% (3/20) • Access to urgent endoscopy: 85% (17/20) • Access to routine endoscopy: 10% (2/20) Centres allowing urgent endoscopy for diagnosis of new IBD patients: Approximately 65% (only displayed graphically)	The authors stated that over 50% of children and young people presenting with a suspected diagnosis of IBD were diagnosed without histological diagnosis due to restrictions in access to endoscopy	This survey captured the impact of about 88% of UK paediatric IBD services at a particular point in time (April 2020). It is not clear how representative these data are of other time periods during the pandemic or the current status

			Clinical outcomes affected by delayed diagnoses Of 122 patients diagnosed with IBD, 65 (53%) were presumed diagnoses with no endoscopy or histological confirmation. Of these,63% were categorised as presenting with moderate to severe disease The authors stated that no patients with a presumed rather than confirmed diagnosis were started on anti-TNF therapy		
Barratt et al 2011 Survey	Adults (>18 years old) with a diagnosis of IBD (n=458) CD (n=230): • Male: 28% • Mean (range) disease duration: 15.5 years (1 to 52) UC (n=228): • Male: 43% • Mean (range) disease duration: 16.5 years (1 to 60)	Data from surveys sent to 980 patients who had attended an outpatient clinic at a Sheffield hospital between 2006 and 2009 The response rate was 47% Medical records were checked to determine whether patients had been	***Prevalence and duration of symptoms prior to diagnosis*** Proportion of patients reporting a prodromal period[24]: • IBD: 71% (326/458) • CD: 94% (216/230) • UC: 48% (110/228) Proportion of patients with a prodromal period who had prodromal IBS and mean (range) duration in years: • IBD: 33% (106/326); 3 (0.5 to 40) • CD: 30% (64/216); 4 (0.5 to 33) • UC: 38% (42/110); 1 (0.8 to 40) Proportion of patients with a prodromal period who did not have prodromal IBS and mean (range) duration in years: • IBD: 67% (220/326); 1.5 (0.25 to 37) • CD: 70% (152/216); 2 (0.8 to 37) • UC: 62% (68/110); 1 (0.25 to 12)	The authors concluded that the increased prodromal duration in patients with prodromal IBS may represent a failure to understand the overlap between IBS and IBD. The authors suggested that patients with UC may have symptoms that are more alarming and less consistent with IBS which may prompt referral to secondary care	This survey reported the experiences of patients from one hospital in England. Just under half the IBD patients sent the survey responded. It is not clear if the experiences of the patents who did respond were similar to those that did not. The generalisability of the results to patients diagnosed elsewhere is not clear The most recently diagnosed patients included in this study would have been diagnosed more than 10 years ago

[24] A period of time between the onset of symptoms attributable to the disorder and correct medical diagnosis of the disorder

		diagnosed with IBS	The mean prodromal period was statistically significantly longer for people with prodromal IBS compared to no prodromal IBS for both IBD (p=0.01) and CD (p=0.018). For people with UC, the prodromal period was 1 year for both patients with and without prodromal IBS (p≥0.05)		This survey also included data relating to 225 patients with celiac disease which were not extracted Data relating to symptoms at the time of survey completion were not extracted, including data from healthy controls without IBD
Blackwell et al 2020 Case control study	Adults and children diagnosed with IBD N=19,555 Crohn's Disease (CD): n=5,874 • Male: 46% Age at diagnosis: • <17 years: 8% • 17-39 years: 41% • >39 years: 51% Social deprivation: • IMD 1-3: 37% • IMD 4-5: 21% • Unknown: 42%	UK primary care data from the Clinical Practice Research Datalink, 1998 to 2016 Data were linked to Hospital Episode Statistics (HES) outpatient data where available	***Time to diagnosis*** Number (%) of patients seen in a fixed time period between presentation to primary care physician with chronic GI symptoms[25] and specialist review appointment (n=1,034): • Within 4 weeks: 58 (6%) • Within 6 months: 329 (32%) • Within 18 months: 513 (50%) Number (%) of patients seen in a fixed time period between presentation to primary care physician with chronic GI symptoms and a specialist or general	The authors concluded that there are excess GI symptoms 5 years before IBD diagnosis compared to the background population, which is probably attributable to undiagnosed disease. The authors also identified previous diagnoses of IBS and depression as being associated with delays in specialist review	This was a well conducted analysis of UK primary and secondary care data with a large sample of people with IBD and matched controls There were a number of inconsistencies in the reporting of data in different sections of the paper The patients included in the analysis were

[25] Chronic GI symptoms were defined as 2 consultations within a 6-month period at least 6 weeks apart. The date of presentation with chronic GI symptoms was defined as the date of the second primary care physician consultation for GI symptoms. First specialist review was defined as the date of the first outpatient appointment recorded in HES with a gastroenterologist, paediatric gastroenterologist or colorectal surgeon

	Ulcerative Colitis (UC): n=13,681 • Male: 53% Age at diagnosis: • <17 years: 3% • 17-39 years: 31% • >39 years: 67% Social deprivation: • IMD 1-3: 42% • IMD 4-5: 18% • Unknown: 41% Controls without IBD matched for age and sex N=78,114		internal medicine or general surgery appointment (n=1,307): • Within 4 weeks: 300 (23%) • Within 6 months: 796 (61%) • Within 18 months: 964 (74%) People presenting with chronic GI symptoms between 2014 and 2016 were more likely to receive specialist review within each timeframe than people presenting between 2003 and 2006: • Within 4 weeks: 15% vs 2% • Within 6 months: 76% vs 18% • Within 18 months: 100% vs 33% ***Prevalence and duration of symptoms prior to diagnosis*** People with IBD were 4 times more likely to visit their primary care physician for GI symptoms[26] than healthy controls between 18 and 6 months before diagnosis: • For CD vs controls: 29.1% vs 6.5%, risk difference 22.6% (95% CI 21.3 to 23.9) • For UC vs controls: 23.9% vs 6.7%, risk difference 17.2% (95% CI 16.4 to 18.0) Assuming the excess GI symptoms were attributable to undiagnosed IBD, the authors estimated that 22.6% of CD and 17% of UC individuals	The authors recommended that enhanced pathways are needed to accelerate specialist referral and timely diagnosis of IBD	diagnosed over an 18-year period up to 2016

[26] Symptoms of IBD included abdominal or perianal pain, diarrhoea and rectal bleeding. People were considered to have prevalent GI symptoms in a given year if their primary care physician recorded at least one code for GI symptoms in their medical records for that year

			were already symptomatic from undiagnosed IBD in the period 18 to 6 months before diagnosis GI symptoms at 5 years before IBD diagnosis[27]: • For CD: 10.4%. An excess of 4.2% (95% CI 3.2 to 5.2) relative to healthy controls • For UC: 9.6%. An excess of 4.0% (95% CI 3.4 to 4.6) relative to healthy controls ***Potential causes of delayed diagnosis*** People with a previous diagnosis of IBS were statistically significantly less likely to receive timely specialist review[28]: HR 0.77 (95% CI 0.59 to 0.99)[29] People with a previous diagnosis of depression were statistically significantly less likely to receive timely specialist review: HR 0.78 (95% CI 0.61 to 0.99)[29] People with chronic GI symptoms who did not attend their appointment (n=142) were 32% less likely to receive specialist review within 18 months (HR 0.68, 95% CI 0.52 to 0.89). The risk of missed appointments was similar regardless of sex, age at presentation, smoking status,		

[27] The figures attributed to CD and UC differ in the abstract and main text of the publication. The figures cited in the main text are extracted here
[28] Timely specialist review was defined as specialist review in the 18 months following presentation with chronic GI symptoms to a primary care physician
[29] The figures cited differ in the main text and Table 2 of the publication. The figures cited in Table 2 are extracted here

			socioeconomic status or a previous diagnosis of depression or IBS There was no statistically significant difference in the probability of timely specialist review by age at presentation, sex, social deprivation or smoking status		
Canavan et al 2014 Retrospective cohort study	Adults aged 18 to 75 years, diagnosed with IBD following an IBS diagnosis (n=1,184) Mean age at IBD diagnosis: 45 years No other baseline characteristics for these patients Controls without an IBS diagnosis at baseline matched for age and sex (n=569)	Cases to July 2012 with data from the UK primary care from the Clinical Practice Research Datalink and HES outpatient data	***Time between IBS and IBD diagnosis*** Median (IQR) time between diagnosis with IBS and diagnosis with IBD: 1.7 years (0.49 to 4.6) ***Prevalence and duration of symptoms prior to diagnosis*** Over the total follow-up period there was an absolute rate difference of 13 extra cases of IBD per 10,000 person-years in IBS patients compared to controls The overall incident risk ratio of IBD was 5.63 (95% CI 5.11 to 6.24). However, this was 3.98 (95% CI 3.54 to 4.45) if the IBD cases diagnosed in the first year after IBS diagnosis were excluded In the first 6 months after an IBS diagnosis, the incidence of IBD was between 16.8 and 24.5 times that seen in controls. This was an absolute rate difference of between 40 and 66 extra cases of IBD per 10,000 person years. The authors stated that the absolute difference was higher in younger age groups but that the risk ratios were not statistically significantly different according to age	The authors suggested that the IBS diagnosis did not reflect a final diagnosis, instead being part of the clinical pathway to a final diagnosis	This analysis of UK primary and secondary care data included a small number of patients diagnosed up to 2012. The majority of the patients included in this study are likely to have been diagnosed more than 10 years ago Limited detail was reported about the patients included in this analysis Overall incidence data were not extracted Data relating to celiac disease and colorectal cancer were not extracted

			In the 5 years after an IBS diagnosis, the incidence of IBD was between 2.6 and 5.0 times that seen in controls. This was an absolute rate difference of between 3 and 13 extra cases of IBD per 10,000 person years		
CRUK 2018 Database analysis	Diagnostic services in Wales No further details on services reported	Data from StatsWales for June 2017	***Potential causes of delayed diagnosis*** People referred for an endoscopy who are waiting more than 8 weeks: 36%	The authors noted that achieving earlier diagnosis will involve more diagnostic testing with drivers for more testing including a growing and aging population, symptom awareness campaigns, a lower threshold of risk to refer people with symptoms and improvements to screening programmes. The report refers to current initiatives to improve diagnostic services including pilots of multi-disciplinary diagnostic centres for patients who present with vague symptoms and the new National Imaging Academy for Wales (for training) The recommendations related to addressing immediate shortages in specific workforce groups, a more strategic approach to	The information relating to delayed diagnosis was extracted from a wider report on workforce. Limited detail was provided on the services included The data relates to a particular point in time (June 2017). It is not clear how representative these data are of other time periods or the current status

				workforce planning and more accurate information about workforce needs Areas of focus for the future included the use of artificial intelligence for diagnostic tests	
Card et al 2014 Case control study	Adults and children diagnosed with IBD (n=20,193) CD: 36.8% UC: 52.9% Indeterminate IBD: 10.3% Male: 48% Age at diagnosis (years): • 0-9: 0.8% • 10-19: 7.0% • 20-29: 14.3% • 30-39: 17.2% • 40-49: 16.1% • 50-59: 15.3% • 60-69: 14.0% • 70-79: 10.5% • 80-89: 4.5% • 90+: 0.4% Median follow-up: 5.23 years (IQR 2.13 to 9.28)	UK primary care data from the General Practice Research Database, 1987 to October 2010	***Prevalence and duration of IBS symptoms prior to IBD diagnosis*** Proportion of people with prior IBS[30] reported by the period of time before an IBD diagnoses (n=20,193): • 0-3 months (n=1,051): 5.20% (95% CI 4.90 to 5.51) • 3-6 months (n=596): 2.95% (95% CI 2.72 to 3.18) • 6-9 months (n=394): 1.95% (95% CI 1.76 to 2.14) • 9-12 months (n=324): 1.60% (95% CI 1.43 to 1.78) • 1-2 years (n=727): 3.60% (95% CI 3.34 to 3.86) • 2-3 years (n=510): 2.53% (95% CI 2.31 to 2.74) • 3-4 years (n=370): 1.83% (95% CI 1.65 to 2.02) • 4-5 years (n=329): 1.63% (95% CI 1.45 to 1.80) • 5-6 years (n=261): 1.29% (95% CI 1.14 to 1.45) • 6-7 years (n=244): 1.21% (95% CI 1.06 to 1.36)	The authors concluded that about 10% of IBD patients are initially misdiagnosed with IBS and that this misdiagnosis may persist for years. This figure rises to 20% if an IBS code or a prescription for antispasmodic drugs is used to represent misdiagnosis. The authors recommended screening IBS patients for IBD using faecal calprotectin testing	This was a well conducted analysis of UK primary care data with a large sample of people with IBD and matched controls The most recently diagnosed patients included in this study would have been diagnosed more than 10 years ago Results were extracted for the prevalence and duration of symptoms using the broader diagnosis of IBS (IBS code + antispasmodic drug) as this corresponds to the definition used for similar results in other studies. Data are also

[30] People with a prior IBS diagnosis code or a prescription code for an antispasmodic drug

	Controls without IBD matched for age, sex, diagnosis date and GP practice (n=201,93)		• 7-8 years (n=209): 1.04% (95% CI 0.90 to 1.17) • 8-9 years (n=171): 0.85% (95% CI 0.72 to 0.97) • 9-10 years (n=145): 0.72% (95% CI 0.60 to 0.83) • 10+ years (n=643): 3.18% (95% CI 2.94 to 3.43) ***Prevalence and nature of initial misdiagnosis*** • People with IBD misdiagnosed as IBS[31] at any time before diagnosis: 10.2% (cases 15.19% (95% CI 14.69 to 15.68) vs control 5.03% (95% CI 4.93 to 5.12)) The authors stated that many of the excess diagnoses occurred in the year before the diagnosis of IBD (cases 4.4% vs controls 0.4%, p<0.01) • People with IBD potentially misdiagnosed with IBS[32] at any time before diagnosis: 20.5% (cases 29.58% (95% CI 28.95 to 30.21) vs control 9.07% (95% CI 8.95 to 9.20); OR 3.0, 95% CI 2.8 to 3.2)		available for IBS code only in the paper Extracted difference between cases and control for any time period. Break down by time period also available in the paper

[31] Misdiagnosis was calculated by comparing the percent of IBD cases that had a prior IBS diagnosis code compared to the rate of IBS that you would expect in controls without IBD

[32] In this broader definition, misdiagnosis was calculated by comparing the percent of IBD cases that had a prior IBS diagnosis code or a prescription code for an antispasmodic drug compared to the rate of IBS that you would expect in controls without IBD

			In the results below the broader definition[32] of a potential misdiagnosis is used By disease group: • People with CD potentially misdiagnosed with IBS at any time before diagnosis: 26.2% (cases 34.9% vs control 8.7% (95% CI not reported); OR 3.6, 95% CI 3.3 to 4.0) • People with UC potentially misdiagnosed with IBS at any time before diagnosis: 16.0% (cases 25.2% vs control 9.2%, (95% CI not reported); OR 2.5, 95% CI 2.3 to 2.8) By gender: • Females with IBD potentially misdiagnosed with IBS at any time before diagnosis: 23.3% (cases 35.9% vs control 12.6%, (95% CI not reported)) • Males with IBD potentially misdiagnosed with IBS at any time before diagnosis: 17.5% (cases 22.8% vs control 5.3%, (95% CI not reported)) By age group: • People <50 years old with IBD potentially misdiagnosed with IBS at any time before diagnosis: 23.5% (cases 31.3% vs control 7.8%, (95% CI not reported)) • People ≥50 years old with IBD potentially misdiagnosed with IBS at any time before diagnosis: 16.7%		

			(cases 27.4% vs control 10.7%, (95% CI not reported)) By year of diagnosis: • People with IBD potentially misdiagnosed with IBS prior to 2004: 19.3% (cases 26.7% vs control 7.4%, (95% CI not reported)) • People with IBD potentially misdiagnosed with IBS after 2004: 21.8% (cases 32.5% vs control 10.7%, (95% CI not reported))		
Fernandes et al 2021 Retrospective cohort study	Children <10 years old diagnosed with IBD N=136 Aged 2-5 years: 24% Aged 6-9 years: 76% CD: 47% UC: 33% IBD unclassified: 20% White European ethnicity: 88% Follow-up: up to 10 years (range 1 to <10) (median follow-up not reported)	Patients referred to the tertiary level paediatric gastroenterology unit for the Southwest of England, 2004 to 2017	***Time to diagnosis*** Time from symptom onset to diagnosis[33]: • Children aged 2-5 years: 13 months • Children aged 6-9 years: 8 months No ranges were reported. There was no statistically significant difference between groups (p=0.37) ***Prevalence and nature of initial misdiagnosis*** Change in diagnosis during the study period: 12% (16/136) Changes in diagnosis by age group: • Children aged 2-5 years: 31% (5/16) • Children aged 6-9 years: 69% (11/16) Changes in diagnosis by type: • Changed from IBD unclassified to CD: 38% (6/16)	The authors did not state any conclusions relating to the diagnostic process	This was a retrospective review of the records of patients referred to one tertiary paediatric centre in England with a small sample size. The generalisability of the results to patients diagnosed elsewhere is not clear Patients were referred between 2004 and 2017. Many of the patients included in this study are likely to have been diagnosed more than 10 years ago The duration of follow-up varied from 1 to more than 10 years. It is possible that further

[33] It is not clear if the figures reported are a median or mean

			• Changed from IBD unclassified to UC: 19% (3/16) • Changed from UC to CD: 25% (4/16) • Changed from UC to IBD unclassified: 13% (2/16) • Changed from CD to IBD unclassified: 6% (1/16) ***Prevalence of symptoms prior to diagnosis*** Bloody diarrhoea at presentation: • Children aged 2-5 years: 70% • Children aged 6-9 years: 58% There was no statistically significant difference between groups (p=0.20) Extra gastrointestinal manifestations at presentation: • Children aged 2-5 years: 72% • Children aged 6-9 years: 57% There was no statistically significant difference between groups (p=0.13) Anaemia at presentation: • Children aged 2-5 years: 83% • Children aged 6-9 years: 57% There was no statistically significant difference between groups (p=0.17)		changes of diagnosis occurred after the study period Data relating to incidence were not extracted
Goodhand et al 2012 Case control study	People of Bangladeshi descent with IBD N=119 Male: 61%	Data from patient records at one NHS Trust in East London, 2010	***Time to diagnosis*** Median (range) time to diagnosis[34] (months): • Bangladeshi: 5 (0 to 172) • White Caucasian: 5 (0 to 134)	The authors did not draw any conclusions relating to time to diagnosis	This was a retrospective review of patient records at one NHS Trust with a small sample size. The generalisability of the

[34] Not further defined

	Mean (SE) age years: 29.6 (1.1) CD: 66% UC: 34% IBD unclassified: 0% Controls were White Caucasian people (of English, Scottish or Welsh descent) with IBD matched for age at diagnosis and disease duration N=119 CD: 52% UC: 41% IBD unclassified: 7% Statistically significant differences between the groups included people of Bangladeshi descent living in more socio-economically deprived areas than people of White Caucasian descent (p<0.0001) and more people of Bangladeshi descent were diagnosed with CD		There was no significant difference in time to diagnosis between groups (p=0.59)		results to patients diagnosed elsewhere is not clear Time to diagnosis was reported but was not a main focus of the study and was not defined. It is not clear what the start and end points of the diagnostic period reported are The two groups of patients were matched for age at diagnosis and disease duration but there were significant differences between the groups The patients included in this study would all have been diagnosed more than 10 years ago
IBD UK 2021 Patient and service survey	Adults, children and young people with IBD (n=10,222)	UK-wide IBD patient survey and service self-assessment,	***Frequency of delayed diagnosis*** • Respondents who had waited more than 1 year for a diagnosis: 26%	Recommendations relating to diagnosis included: • A public health campaign to raise	This survey reported the experiences of patients and services across the UK. The number of people who responded

	Adult and paediatric IBD services (n=166) across the UK CD: 52% UC: 44% IBD unspecified: 3% Microscopic Colitis: 1% Males (adults): 33% No difference in gender for paediatric responses (figure not reported) Diagnosis more than 2 years ago: 79% England: 82% Scotland: 8% Wales: 5% Northern Ireland: 52%	July 2019 to January 2020 Response to questions on diagnosis (n=2,121): Adults: 1,826 Children and young people: 295	• Respondents who had waited more than 6 months for a diagnosis: 39% The report states that the figures were broadly similar for adults and children and young people (figures not reported) • Respondents seen by a specialist within 4 weeks of referral: 29% • Adult services able to see ≥90% of patients with suspected IBD within 4 weeks of referral: 21% • Paediatric services able to see ≥90% of patients with suspected IBD within 4 weeks of referral: 38% ***Health care usage before diagnosis*** • Respondents who had ≥1 A&E visit before diagnosis: 41% • Respondents who had ≥3 A&E visits before diagnosis: 12% The authors stated that people who reported waiting longer for their diagnosis were more likely to visit A&E more often ***Potential causes of delayed diagnosis*** • 80% of respondents felt that the public have limited or no understanding of Crohn's and Colitis • 64% of services reported having an agreed referral pathway for suspected IBD between primary and secondary care in place. This was also reported by UK country: • England: 64%	awareness of the symptoms of Crohn's and Colitis • Upskilling of community healthcare professionals to recognise potential IBD • Consistent and appropriate use of faecal calprotectin testing in primary care as part of agreed referral pathways in every service between primary and secondary care and emergency and specialist teams • Resourcing to enable people with suspected IBD to be seen, investigated, diagnosed and treated in line with the time frames	to questions on diagnosis was about 20% of the total respondents. It is not clear why this was the case Data were collected between 2019 and 2020, however the majority of patients were diagnosed more than 2 years ago. The time period over which patients were diagnosed is not clear For the staffing figures, only data for gastroenterologist, radiologist and histopathologist were extracted as the other specialities included seemed unlikely to be involved in the diagnostic process This report refers to results from other studies e.g. in causes of delayed diagnosis. Only data relating to the survey results has been extracted. However, the report recommendations about diagnosis have been included

			• Scotland: 71% • Wales: 54% • Northern Ireland: 57% • 65% of services reported frequent MDT meetings (weekly or fortnightly). This was also reported by UK country and age group: • England: 68% • Scotland: 57% • Wales: 39% • Northern Ireland: 57% • Adult services: 69% • Paediatric services: 47% • Adult services meeting the IBD standards staffing recommendations for: • Gastroenterologists: 31% • Radiologists: 37% • Histopathologists: 8%		Results from the patient survey have also been reported in other publications (see IBD UK 2020a and IBD UK 2020b)
IBD UK 2020a Patient survey	Adults with IBD N=1,851 England: 1,520 Scotland: 144 Wales: 110 Northern Ireland: 77 No further detail on the population	UK-wide IBD patient survey, July to November 2019	***Time to diagnosis*** Time between first speaking to a healthcare professional about symptoms to confirmation of diagnosis. Reported as proportion of people diagnosed in specified time periods UK • Less than 4 weeks: 15% (283/1,851) • 1–3 months: 26% (486/1,851) • 4-6 months: 19% (346/1,851) • 7-12 months: 14% (253/1,851) • 1-2 years: 11% (200/1,851) • 2-5 years: 7% (135/1,851) • More than 5 years: 8% (148/1,851) England	The authors did not include any conclusions or recommendations	These data were extracted from IBD Benchmarking Tool reports. The reports for individual hospitals were used as a source of national averages for the UK, England, Scotland, Wales and Northern Ireland. Only data relating to questions on diagnostics were extracted The data are taken from a UK patient survey. The majority of respondents were from

			• Less than 4 weeks: 15% (232/1,520) • 1–3 months: 27% (409/1,520) • 4-6 months: 19% (287/1,520) • 7-12 months: 13% (198/1,520) • 1-2 years: 10% (156/1,520) • 2-5 years: 7% (110/1,520) • More than 5 years: 8% (128/1,520) Scotland • Less than 4 weeks: 15% (21/144) • 1–3 months: 27% (39/144) • 4-6 months: 19% (27/144) • 7-12 months: 12% (18/144) • 1-2 years: 14% (20/144) • 2-5 years: 8% (12/144) • More than 5 years: 5% (7/144) Wales • Less than 4 weeks: 16% (18/110) • 1–3 months: 18% (20/110) • 4-6 months: 17% (19/110) • 7-12 months: 23% (25/110) • 1-2 years: 15% (16/110) • 2-5 years: 5% (6/110) • More than 5 years: 5% (6/110) Northern Ireland • Less than 4 weeks: 16% (12/77) • 1–3 months: 23% (18/77) • 4-6 months: 17% (13/77) • 7-12 months: 16% (12/77) • 1-2 years: 10% (8/77) • 2-5 years: 9% (7/77) • More than 5 years: 9% (7/77) Time between referral by a GP to first appointment with a hospital specialist.		England. There is limited detail on the study population The time period over which patients were diagnosed is not clear Results from the patient survey have also been reported in other publications (see IBD UK 2020b and IBD UK 2021)

			Reported as proportion of people diagnosed in specified time periods UK • Less than 4 weeks: 29% (446/1,549) • 1–6 months: 57% (883/1,549) • 7-12 months: 6% (91/1,549) • More than one year: 2% (32/1,549) • Privately diagnosed: 6% (97/1,549) England • Less than 4 weeks: 30% (381/1,285) • 1–6 months: 57% (735/1,285) • 7-12 months: 5% (65/1,285) • More than one year: 2% (21/1,285) • Privately diagnosed: 6% (83/1,285) Scotland • Less than 4 weeks: 28% (33/116) • 1–6 months: 58% (67/116) • 7-12 months: 8% (9/116) • More than one year: 3% (4/116) • Privately diagnosed: 3% (3/116) Wales • Less than 4 weeks: 26% (23/88) • 1–6 months: 50% (44/88) • 7-12 months: 14% (12/88) • More than one year: 3% (3/88) • Privately diagnosed: 7% (6/88) Northern Ireland • Less than 4 weeks: 15% (9/60) • 1–6 months: 62% (37/60) • 7-12 months: 8% (5/60) • More than one year: 7% (4/60) • Privately diagnosed: 8% (5/60)		

IBD UK 2020b Patient survey	Children with IBD N=238 England: 171 Scotland: 30 Wales: 9 Northern Ireland: 28 No further detail on the population	UK-wide IBD patient survey, July to November 2019	***Time to diagnosis*** Time between first speaking to a healthcare professional about symptoms to confirmation of diagnosis. Reported as proportion of people diagnosed in specified time periods UK • Less than 4 weeks: 14% (34/238) • 1–3 months: 29% (69/238) • 4-6 months: 21% (50/238) • 7-12 months: 14% (33/238) • 1-2 years: 11% (26/238) • 2-5 years: 7% (17/238) • More than 5 years: 4% (9/238) England • Less than 4 weeks: 13% (22/171) • 1–3 months: 25% (43/171) • 4-6 months: 23% (40/171) • 7-12 months: 15% (25/171) • 1-2 years: 13% (23/171) • 2-5 years: 7% (12/171) • More than 5 years: 4% (6/171) Scotland • Less than 4 weeks: 17% (5/30) • 1–3 months: 40% (12/30) • 4-6 months: 17% (5/30) • 7-12 months: 10% (3/30) • 1-2 years: 3% (1/30) • 2-5 years: 10% (3/30) • More than 5 years: 3% (1/30) Wales • Less than 4 weeks: 11% (1/9)	The authors did not include any conclusions or recommendations	These data were extracted from IBD Benchmarking Tool reports. The reports for individual hospitals were used as a source of national averages for the UK, England, Scotland, Wales and Northern Ireland. Only data relating to questions on diagnostics were extracted The data are taken from a UK patient survey. The majority of respondents were from England. There is limited detail on the study population The time period over which patients were diagnosed is not clear Results from the patient survey have also been reported in other publications (see IBD UK 2020a and IBD UK 2021)

			• 1–3 months: 44% (4/9) • 4-6 months: 0% (0/9) • 7-12 months: 22% (2/9) • 1-2 years: 11% (1/9) • 2-5 years: 0% (0/9) • More than 5 years: 11% (1/9) Northern Ireland • Less than 4 weeks: 21% (6/28) • 1–3 months: 36% (10/28) • 4-6 months: 18% (5/28) • 7-12 months: 11% (3/28) • 1-2 years: 4% (1/28) • 2-5 years: 7% (2/28) • More than 5 years: 4% (1/28) Time between referral by a GP to first appointment with a hospital specialist. Reported as proportion of people diagnosed in specified time periods UK • Less than 4 weeks: 29% (56/191) • 1–6 months: 60% (114/191) • 7-12 months: 2% (3/191) • More than one year: 3% (6/191) • Privately diagnosed: 6% (12/191) England • Less than 4 weeks: 29% (40/137) • 1–6 months: 57% (78/137) • 7-12 months: 2% (3/137) • More than one year: 4% (6/137) • Privately diagnosed: 7% (10/137) Scotland • Less than 4 weeks: 45% (10/22)		

			• 1–6 months: 50% (11/22) • 7-12 months: 0% (0/22) • More than one year: 0% (0/22) • Privately diagnosed: 5% (1/22) Wales • Less than 4 weeks: 11% (1/9) • 1–6 months: 89% (8/9) • 7-12 months: 0% (0/9) • More than one year: 0% (0/9) • Privately diagnosed: 0% (0/9) Northern Ireland • Less than 4 weeks: 22% (5/23) • 1–6 months: 74% (17/23) • 7-12 months: 0% (0/23) • More than one year: 0% (0/23) • Privately diagnosed: 4% (1/23)		
Jones et al 2018 Retrospective case series	Children who received a colectomy for a diagnosis of Ulcerative Colitis (n=29) Median age at time of surgery: 12.7 years (range 3.3 to 18.2) Median follow-up: 6.7 years (range 0.8 to 11.7)	Data collected from one paediatric tertiary referral centre in Bristol, 2003 to 2014	***Prevalence and nature of initial misdiagnosis*** • Re-classification following histological examination of the colectomy sample: 0% • Subsequent diagnosis of CD during follow-up: 24% (7/29) • Time from colectomy to CD diagnosis (years): median 2.3; mean 3.8; range (0.5 to 9)	The authors suggest that a diagnosis of UC in children should be considered provisional with a potential later diagnosis of CD taken into account when considering treatment	This was a retrospective review of patient records at one centre with a small sample size. The generalisability of the results to patients diagnosed elsewhere is not clear Follow-up periods for individual patients varied, suggesting that some re-classification cases could have been missed There were some inconsistencies in the reporting of data

					between the text and tables included in the paper. The figures extracted were taken from the tables. The accuracy of the data relating to follow-up periods and time from colectomy to CD is not clear Participants were identified over an 11-year period up to 2014. Many of the patients included in this study are likely to have been diagnosed more than 10 years ago
Kennedy et al 2020 Survey	125 adult and paediatric IBD services across the UK England: 106 Scotland: 9 Wales: 8 Northern Ireland: 2 Adult gastroenterologists: 65 Adult IBD nurses: 53 Paediatric gastroenterologists: 21 Paediatric IBD nurses: 6 IBD surgeon: 1	Survey of IBD services, describing services in April 2020 compared to before the pandemic Responses represented approximately 70% of IBD services in the UK	***Potential causes of delayed diagnosis*** Median (IQR) number of WTE gastroenterologists providing elective outpatient care: • Before the pandemic: 4 (4 to 7.5) • In the 6-week period following onset of the pandemic: 2 (1 to 4.8) Proportion of services with >3 WTE gastroenterologists providing IBD care: • Before the pandemic: 81% (100/124) • In the 6-week period following onset of the pandemic: 34% (41/122) 8% (10/122) of services had no dedicated IBD clinician following onset of the pandemic	The authors noted that the changes in service delivery models and staffing will need to be considered in planning post-pandemic IBD care. The authors also noted that insights gained from the rapid adaptations of services during the pandemic may present opportunities for positive changes to IBD services	This survey captured the impact of about 70% of UK IBD services at a particular point in time (April 2020). It is not clear how representative these data are of other time periods during the pandemic or the current status. The outcomes are generally not specific to diagnostic services, instead representing issues that might have had an impact on diagnosis

	Dedicated IBD service: 71 General gastroenterology services providing IBD care: 53		Access to faecal calprotectin testing: • No access: 27% (33/122) • Reduced access: 32% (39/122) Access to endoscopy: 35% (44/125) service reported that all IBD-related endoscopy activities (including diagnostics) were cancelled 28% of services (34/122) reported cancelling all IBD MDTs The authors stated that exploration of the variation in provision of services around the UK, including faecal calprotectin and endoscopy did not reveal any particular clustering of loss of service in one region of the country (figures not reported)		Data relating to nursing not extracted as seemed less relevant to the duration of the diagnostic process
Misra et al 2019 Prospective cohort study	Adults >16 years with newly diagnosed IBD N=339 Male: 57% White European: 60% Indian: 20% Pakistani: 7% Other: 11% Missing: 1% Median age in years ranged from 19 to 40 CD: 34% UC: 64% IBD unclassified: 2%	Data collected using standardised case report forms at the first patient visit within 3 months of diagnosis. Data collected from hospitals from urban catchment areas with high South Asian populations (Northwest England, East Midlands, West	***Time to diagnosis*** Median time from symptom onset to diagnosis in months (IQR): Crohn's disease: • White European: 2.9 (0.9 to 8.5) • Indian: 3.0 (2.0 to 6.0) • Pakistani: 3.2 (2.0 to 5.3) • Other: 3 (2.0 to 3.2) Ulcerative Colitis: • White European: 2.3 (1.0 to 6.0) • Indian: 2.5 (0.98 to 4.0) • Pakistani: 2.7 (2.0 to 6.2) • Other: 2.5 (1.7 to 3.4) The authors stated that there were no statistically significant differences between ethnic groups in time to diagnosis (p value not reported)	The authors concluded that there were no significant differences between the ethnic groups for time to diagnosis or disease activity indexes at presentation	This was a prospective review of patients from several different centres, however the sample size was small. It is not clear if the sample size was sufficiently large to detect significant differences between the ethnic groups All patients included in this study would have been diagnosed within the last 10 years Data on incidence were not extracted

		Midlands, North West London) from a 1 year period from 1st February 2016 to 2017 and entered into the Epicom database	***Disease severity at diagnosis*** Mean (± 95% CI) Harvey Bradshaw Index scores[35] at diagnosis: • White European: 6.2 (4.1) • Indian: 6.5 (3.1) • Pakistani: 6.8 (3.9) • Other: 6.4 (3.4) Mean Simple Clinical Colitis Activity Index scores[36] at diagnosis • White European: 5.1 (3.1) • Indian: 6.3 (3.5) • Pakistani: 3.4 (2.9) • Other: 5.5 (3.7) The authors reported that there were no significant differences in disease activity indexes at presentation between ethnic groups (p value not reported)		
Mukherjee et al 2015 Qualitative study (interviews)	Adults with IBD, from the South Asian population N=33 Male: 39% Age range (years): 18 to 65 CD: 55%	Participants recruited from 5 gastroenterology clinics in England It is not clear when the interviews	***Potential causes of delayed diagnosis*** Two-thirds of participants reported significant delays in having their IBD diagnosed due to a lack of referral by their GP (no further detail reported) No participants attributed the delay to their ethnic background	The report recommendations did not specifically relate to diagnosis. However, they included a recommendation for increased awareness and understanding of IBD within South Asian communities	This qualitative study included a small number of participants. The time since diagnosis varied considerably. The year of the data collection was not clear but many of the study participants are likely to have been

[35] A Harvey Bradshaw Index score of <5 is classed as remission; a score of 5 to 7 is mild activity; a score of 8 to 16 is moderate activity and a score of >16 is severe activity (Info HBI | Harvey-bradshaw index (igibdscores.it))

[36] No score interpretation guideline was identified for the Simple Clinical Colitis Activity Index scores with different sources suggesting different cut-off points for remission. However the European Crohn's and Colitis Organisation suggested a cut-off of about <3 to suggest remission Simple Clinical Colitis Activity Index (SCCAI) | ECCO E-Guide (ecco-ibd.eu)

	UC: 42% Indeterminate Colitis: 3% Indian/British Indian: 61% Pakistani/British Pakistani: 27% Bangladeshi/British Bangladeshi: 12% Median (range) time since diagnosis: 6 years (3 months to 21 years)	were conducted			diagnosed more than 10 years ago Limited information was reported relating to experiences during diagnosis
Nartey et al 2021a Audit	Adults and children with a new diagnosis of IBD N=103,609 England: 86.6% Scotland: 7.3% Wales: 4.1% Northern Ireland: 2.0% Male: 49.2% Age (years): • <15: 3.4% • 15-19: 4.9% • 20-24: 7.5% • 25-29: 8.2% • 30-34: 8.5%	UK primary care from the Clinical Practice Research Datalink, 2000 to 2020 Data were linked to HES outpatient data where available	***Prevalence and duration of symptoms prior to diagnosis*** Prevalence of prior IBS (%) and time interval (median, IQR years) between prior IBS[37] and IBD diagnosis by age at IBD diagnosis (n=103,471): • All ages: 28.6%; 3.5 (0.6 to 9.5) • 0-9 years: 3.4%; 0.2 (0.1 to 1.7) • 10-19 years: 18.2%; 0.5 (0.2 to 1.5) • 20-29 years: 32.0%; 1.1 (0.3 to 3.8) • 30-39 years: 32.5%; 2.8 (0.6 to 7.5) • 40-49 years: 30.6%; 4.3 (0.9 to 10.4) • 50-59 years: 29.4%; 5.8 (1.1 to 12.6) • 60-69 years: 27.0%; 6.6 (1.6 to 13.9)	The report did not include any conclusions or recommendations	This was a well conducted analysis of UK primary and secondary care data with a large sample of people with newly diagnosed IBD The patients in this study were diagnosed with IBD over a 20-year period. Many of the cases are likely to have been diagnosed more than 10 years ago

[37] A prior diagnosis of IBS was based on a diagnosis of IBS or a prescription for antispasmodic drugs. A functional abdominal pain diagnosis was also considered but rarely occurred

	• 35-39: 8.7% • 40-44: 8.4% • 45-49: 8.0% • 50-54: 7.8% • 55-59: 7.5% • 60-64: 7.1% • 65-69: 6.3% • 70-74: 5.3% • 75-79: 4.0% • 80+: 4.4% Social deprivation: • IMD 1: 16.9% • IMD 2: 17.7% • IMD 3: 19.1% • IMD 4: 23.0% • IMD 5: 23.3%		• 70-79 years: 25.7%; 6.9 (1.9 to 13.6) • 80+ years: 24.4%; 8.0 (2.7 to 14.7) ***Potential causes of delayed diagnosis*** Prevalence of faecal calprotectin testing[38] within 1 year prior to IBD diagnosis 2009 to 2019 (n=53,719): • UK: 2.7% • England: 2.7% • Scotland: 3.4% • Wales: 1.4% • Northern Ireland: 0.6% In the UK, the prevalence of testing increased from <0.1% in 2009 to 4.2% in 2019. For the UK countries this was: • England: <0.1% in 2009 to 4.0% in 2019 • Scotland: <0.1% in 2009 to 9.6% in 2019 • Wales: 0% in 2009 to 0.8% in 2019 • Northern Ireland: 0% in 2009 to 1.0% in 2019		
Paul et al 2017 Retrospective case series	Children diagnosed with IBD-unclassified N=26 Male: 64%	Data collected from one paediatric tertiary referral centre in Bristol. Patients were diagnosed between 2004	***Prevalence and nature of initial misdiagnosis*** 65% (17/26) of children had received endoscopic re-evaluation 40% (10/25) changed diagnosis (7 to CD and 3 to UC)	The authors concluded that early repeat assessment of cases should be considered in patients with persistent symptoms or where surgery may be possible	This was a retrospective review of patient records at one centre with a small sample size. The generalisability of the results to patients diagnosed elsewhere is not clear

[38] Prevalence of faecal calprotectin testing was based on recording of a test in the general practice record within 1 year of initial diagnosis of IBD or first use of aminosalicylates in cases diagnosed at 15 years or older. The proportions were calculated from 2009 due to lack of testing prior to 2009

	Mean age at diagnosis: 10.1 years (range 1.4 to 16.1) Follow-up 4.5 to 11.5 years	to 2011, with follow-up review of records in 2016	Median (range) time to revision of diagnosis: 51 months (4 to 87)		Follow-up periods for individual patients varied, and one appears to have been lost to follow-up, suggesting that some re-classification cases could have been missed The most recently diagnosed patients included in this study would have been diagnosed more than 10 years ago
RCPCH and BSPGHN, 2021 Audit	107 centres providing paediatric gastroenterology, hepatology and nutrition services Non-specialist centres: 77 Specialised Gastroenterology: 27 Hepatology: 3	National UK audit conducted in 2020 with a data entry deadline of 28th February 2021 The authors reported a 78% response rate	***Time to diagnosis*** Proportion of children with suspected IBD seen by a specialist consultant within 4 weeks: • If referred to a specialist centre: 80% • If referred to a non-specialist centre: 43% ***Potential causes of delayed diagnosis*** 18% (14/77) of non-specialist centres had no consultant paediatrician with a special interest in gastroenterology provision 37% (10/27) specialist centres employed less than 3 WTE paediatric gastroenterologists 20% (15/74) of non-specialised centres and 47% (14/30) specialist centres reported that non-emergency endoscopy	The recommendations within this report were not specific to diagnostics. However, the recommendations included that non-specialised network centres should have a minimum of 1 full-time consultant paediatrician with a special interest in gastroenterology and hepatology and that specialist centres should employ at least 4 WTE paediatric gastroenterologists	This was a large UK-wide audit of services. The data were collected in 2020 and early 2021. The results reported may have been impacted by the effects of the Covid-19 pandemic during this period. It is not clear how representative these data are of other time periods during the pandemic or the current status

			services had not been restored due to the pandemic 46% (48/105) centres had neither local criteria for access to diagnostic endoscopy and for children presenting in an emergency nor timely access to endoscopy through clear and agreed pathways		
RCGP and C&C 2020 Surveys referenced in an impact report	People with IBD N not reported GPs across the UK N=624	A patient survey undertaken by Crohn's & Colitis UK in 2016 A GP survey undertaken by Crohn's & Colitis UK and the Royal College of GPs as part of the 2017 Spotlight Project	***Frequency of delayed diagnosis*** One in 3 people (approximately 33%) said that it has taken more than 2 years to get a diagnosis of IBD One in six people (approximately 17%) said that it has taken more than 5 years to get a diagnosis of IBD ***Potential causes of delayed diagnosis*** Over 70% of GPs had had no formal training in IBD 33% of GPs were 'less than confident' or 'not confident' requesting faecal calprotectin tests or interpreting their results	The report describes a project which aimed to improve awareness and understanding of IBD in primary care, improve time to diagnosis and develop template pathways and help GPs manage IBD flare-ups and provide ongoing support for patients. The report also describes the training resources and toolkits developed and the awareness raising activities conducted with some information on feedback from GPs	Results from these surveys were cited in this report. However, minimal detail was provided about the conduct of the surveys or the survey populations It is not clear when the participants would have been diagnosed with IBD
Taylor et al 2021 Retrospective cohort study	Adults with histologically proven IBD N=92	Secondary care hospital data from the South Yorkshire area, April 2014 to	***Time to diagnosis*** Average (range) time[39] between referral from primary care and diagnostic endoscopy: 34.5 days (18 to 70)	No conclusions or recommendations were made relating to IBD	Although this study was designed as a cohort study, only the results from the small group of patients with IBD have been extracted. The other group, and main

[39] The authors did not state whether the figures reported was a mean or median

	No baseline characteristics reported	September 2015			focus of the paper was people with coeliac disease All patients included in this study would have been diagnosed within the last 10 years Limited information was provided about the people with IBD. The description of the outcome reported was unclear
Walker et al 2020a Retrospective cohort study	Adults with a new IBD diagnosis N=304 CD: 31% UC: 64% IBD-unclassified: 5% Male: 52% White ethnicity: 95% Age at IBD diagnosis: 36.3 years (26.8 to 52.5) A subgroup-analysis of children aged <18 years was also conducted (n=35)	Data from 49 GP practices and gastroenterology secondary care services from one Trust in South West England, 2014 to 2017 Outcome data captured up to one year after diagnosis	***Frequency of delayed diagnosis*** Proportion of people diagnosed within a specified time period of symptom onset • 4 months: 50% • 6 months: 60% • 12 months: 79% • 2 years: 92% Proportion of people reviewed by a hospital specialist within 4 weeks of GP referral: 63% (191/304) ***Time to diagnosis*** **For all adults (median (IQR) months):** • Overall time from symptom onset to diagnosis: 4.3 (2.2 to 10.7) • Time from symptom onset to first GP presentation (patient delay): 2.1 (0.9 to 5.1)	The authors concluded that time to patient presentation is the largest component of time to IBD diagnosis. They also concluded that emergency presentation, but not delayed time to diagnosis, is associated with a complicated disease course	This was a retrospective review of patient records at one NHS Trust with a small sample size. The ranges reported for results suggest considerable variation in the figures for different patients. The generalisability of the results to patients diagnosed elsewhere is not clear All patients included in this study would have been diagnosed within the last 10 years The factors considered for the analysis of reasons for delay included sex, ethnicity,

			• Time from first GP presentation to GP referral (primary care delay): 0.3 (0.0 to 0.9) • Time from GP referral to IBD diagnosis (secondary care delay): 1.1 (0.5 to 2.1) The patient delay was statistically significantly longer than the primary and secondary care delay (p<0.001) **For individual disease groups (median (IQR; range) months):** Overall time from symptom onset to diagnosis: • CD: 7.6 (3.1 to 15.0; 0 to 112) • UC: 3.3 (1.9 to 7.3; 0 to 65) • IBD unclassified: 3.9 (2.0 to 7.2; 0 to 16) The overall time to diagnosis was statistically significantly longer for CD (p<0.001) Patient delay: • CD: 3.0 (0.9 to 6.7; 0 to 107) • UC: 2.1 (0.9 to 3.9; 0 to 59) • IBD unclassified: 2.1 (1.0 to 4.5; 0 to 12) The patient delay was statistically significantly longer for CD (p=0.017) Primary care delay: • CD: 0.3 (0.0 to 1.2; 0 to 20) • UC: 0.2 (0.0 to 0.8; 0 to 25) • IBD unclassified: 0.3 (0.0 to 0.7; 0 to 4) p=0.26 (no statistically significant difference)		age at IBD diagnosis, family history, income, smoking status, duration and type of symptoms, tests completed and nature of referral All results relate to the adult population unless otherwise specified

			Secondary care delay: • CD: 1.6 (0.6 to 3.7; 0 to 13) • UC: 0.9 (0.5 to 2.0; 0 to 27) • IBD unclassified: 0.7 (0.5 to 1.3; 0 to 4) The secondary care delay was statistically significantly longer for CD (p=0.0.027) **Subgroup analysis of children aged <18 years. Median (IQR) months:** • Overall time to diagnosis: 4.1 (2.3 to 7.1) • Patient delay: 3.0 (0.9 to 5.0) • Primary care delay: 0.1 (0.0 to 0.7) • Secondary care delay: 1.3 (0.5 to 2.1) ***Duration of symptoms prior to diagnosis*** Median (IQR) duration of symptoms (months) prior to patient presentation to GP: • Abdominal pain: 3.0 (0.3 to 6.1) • Unintentional weight loss: 4.0 (0.9 to 6.1) • Anaemia: 1.8 (1.3 to 3.8) • Rectal bleeding: 2.1 (0.9 to 4.0) • Altered bowel habit diarrhoea: 2.1 (0.9 to 6.0) ***Healthcare usage before diagnosis*** New diagnoses made following an emergency presentation: 19% (58/304)		

			Of these, 86% (50/58) were referred to hospital by their GP and 14% (8/58) self-presented to A&E ***Potential causes of delayed diagnosis*** In multivariable analysis: Factors associated with increased patient delay: • Presence of abdominal pain: OR 2.11 (95% CI 1.01 to 4.64) • Presence of unintentional weight loss: OR 2.57 (95% CI 1.21 to 5.50) • Estimated higher household income (for every increase in estimated income decile): OR 1.27 (95% CI 1.07 to 1.53) Factors associated with decreased patient delay: • Presence of rectal bleeding: OR 0.45 (95% CI 0.22 to 0.91) Factors associated with initial presentation of IBD as an emergency: • Duration of symptoms <6 weeks: OR 8.26 (95% CI 1.77 to 50.75) • Anaemia: OR 19.01 (95% CI 3.76 to 60.48) Factors associated with decreased primary care delay: • Older age at IBD diagnosis: OR 0.96 (95% CI 0.94 to 0.98)		

			• Shorter than 6-week symptom duration prior to GP presentation: OR 0.18 (95% CI 0.08 to 0.36) Factors associated with decreased secondary care delay[40]: • Symptoms <6 weeks prior to first GP presentation: OR 0.14 (95% CI 0.03 to 0.51) • Urgent GP referral: 0.12 (95% CI 0.04 to 0.35) • Being triaged straight-to-test: 0.08 (95% CI 0.02 to 0.25) ***Clinical outcomes affected by delayed diagnosis*** People who presented as an emergency were more likely to have a complicated disease course[41] (p<0.001) There was no association between delayed overall time to diagnosis and a complicated disease course (p=0.35) When patients with an emergency presentation were included in the analysis, there was no association between delayed diagnosis and receipt of corticosteroids, immunomodulators, aminosalicylates, biologics, exclusive enteral nutrition, more IBD-related hospitalisation or more surgeries		

[40] Analysis adjusted for workforce capacity
[41] People were judged to have a complicated disease course if they had an IBD-related hospital admission, IBD-related surgery and/or biologic therapy in the first year after diagnosis

			compared to patients with a timely diagnosis When patients diagnosed following emergency presentation were removed: There was an association with delayed diagnosis (more than 2 years from symptom onset) and: • Higher IBD-related hospital admission (p=0.038) • Corticosteroid use: p=0.043 There was no association with delayed diagnosis and the following factors within the first year after diagnosis: • IBD-related surgeries (p=0.356) • Use of immunomodulators (p=0.117) • Use of biologics (p=0.302)		
Ward et al 2013 Retrospective cohort study	Adults with newly diagnosed UC N=115 Male: 56% Speciality referred to: • Colorectal surgeons: 64% • Gastroenterology: 36% Age (median, range) in years: • Colorectal: 59.5 (19 to 94)	Data from one UK hospital in Birmingham, 2007 to 2012	***Time to diagnosis*** Mean (SD) time interval from referral to first outpatient visit (days): • Gastroenterology: 19.5 (17.1) • Colorectal: 23.2 (22.1) No significant difference (p=0.856) Referrals to colorectal clinics were also presented by nature of referral: • 2WW referral to colorectal: 10.5 (6.5) • Routine referral to colorectal: 34.5 (24.5) Mean (SD) time interval from referral to first endoscopy (days): • Gastroenterology: 57.6 (80.1)	The authors concluded that newly diagnosed patients with UC were more commonly first seen in colorectal surgery outpatient clinics than gastroenterology clinics. There was no difference in time between referral and first outpatient visit by speciality referred to	This was a retrospective review of patient records at one hospital with a small sample size. The generalisability of the results to patients diagnosed elsewhere is not clear It is not clear if the sample size was sufficient to demonstrate significant differences between groups

	• Gastroenterology: 36.0 (19 to 76) People referred to gastroenterology were statistically significantly younger (36.0 vs 59.6 years, p<0.01). There were no significant differences in gender, presenting symptoms or disease extent		• Colorectal: 42.8 (26.4) No significant difference (p=0.364)		The most recently diagnosed patients included in this study would have been diagnosed more than 10 years ago Data for time from outpatient visit to first treatment not extracted

Abbreviations: A&E – Accident and Emergency; Anti-TNF – anti-tumour necrosis factor; CD – Crohn's Disease; CI – confidence interval; GP – general practitioner; HES – Hospital Episode Statistics; HR – hazard ratio; IBD – Inflammatory Bowel Disease; IBS – irritable bowel syndrome; IMD – indices of deprivation; IQR – interquartile range; MDT – multi-disciplinary team; OR – odds ratio; SD – standard deviation; SE – standard error; UC – Ulcerative Colitis; UK – United Kingdom; WTE – whole time equivalent; 2WW – 2-week wait

Included studies relating to question 2

Reference	Population	Intervention & comparator	Key results	Authors' conclusions and recommendations	Quality appraisal
Fallon et al 2019 Retrospective cohort study Follow-up period: 1.5 to 3.5 years	N=509 Patients with upper gastrointestinal (UGI; n=148) and patients with lower gastrointestinal (LGI; n=361) malignancies treated between 1 April 2015 and 31 March 2017 at Luton and Dunstable University Hospital Baseline characteristics (n=509):	2-week wait (2WW) referral pathway (n=173) Comparator: Non-2WW routes of referral including emergency referrals and routine referral (n=336)	**Disease severity at diagnosis** Stage of malignancy at time of presentation between 2WW vs non-2WW routes of referral: UGI cohort: No difference (p=0.458) LGI cohort: No difference (p=0.829) **Clinical outcomes** Curative treatment considered between 2WW vs non-2WW routes of referral:	The authors concluded that 2WW referral does not achieve early diagnosis nor does it lead to an improvement in the rate of curative treatment in UGI and LGI malignancies. In addition, no improvement in short-term survival is seen in UGI malignancies nor in LGI malignancies on multivariate analysis Recommendations: The study authors recommended that the result of their study should be	Score = 6 (moderate level of confidence in results) Quality issues: Inappropriate control group which included emergency referrals so not a comparison of urgent vs routine referrals; small sample size; 1 hospital limiting generalisability

	Ratio of males to females: 105:43 in UGI cohort and 181:180 in LGI cohort Median age: 73 years (range 20 to 97) in UGI cohort and 73 years (range 25 to 101) in LGI cohort		UGI cohort: 12/46 (26%) vs 35/102 (34%) OR 1.48 (95% CI 0.68 to 3.21, p=0.321) LGI cohort: 97/127 (76%) vs 68% (158/234) OR 1.59 (95% CI 0.97 to 2.62, p=0.067) Median survival trend between 2WW vs non-2WW routes of referral: UGI cohort: 211 vs 174 days Multivariate HR 0.99 (95% CI 0.56 to 1.75, p=0.963) LGI cohort: 581 vs 536 days Multivariate HR 1.10 (95% CI 0.60 to 1.99, p=0.764) Paper does not report which factors were included in the multivariate analysis	validated by a multicentre study with a longer follow-up of over five to ten years to test the hypothesis that 2WW achieves better curative resection rates and improved survival in UGI and LGI malignancies. They also recommended that strategies that target delay in initial presentation following onset of symptoms, or delay from presentation to referral, may have a greater impact in GI cancers than the current initiative of reducing time from referral to specialist review	Data were not extracted for emergency vs non-emergency referrals as these results are not in scope

Hamilton et al 2013 Before and after study plus qualitative interviews	N=1,160 (subgroup of interest) 1,160 colorectal assessments (& 1,433 lung assessments) completed by 614 GPs from 165 practices in seven English cancer networks in 2010 to 2011 Baseline characteristics for total study population: Females: 1,413 (54.5%) Males: 1,162 (44.8%) Patients aged ≥70 years: 1,007 (38.8%) 23 GPs were interviewed	Risk assessment tools (RATs) to assist GPs select patients for cancer investigations 6-month periods before and after the distribution of RATs were compared	**Time to diagnosis** For suspected colorectal cancer, there were 304 more 2-week referrals (1,173 vs 1,477, 26% increase), 270 more colonoscopies (1,762 vs 2,032, 15% increase), and 10 more cancers identified (134 vs 144, 7% increase) **Qualitative outcomes** The RATs were perceived overall to be a valuable aid to diagnosis. In several instances the tool was perceived to give more credence to a decision to refer that had already been made. For some responders, the tool urged referrals that may not have been made. At other times, the tool was used to confirm decisions not to refer. The tool encouraged a deeper level of thinking about symptom presentations and raised awareness of symptom patterns and combinations, thereby promoting actions such as ensuring patients returned earlier for review	The authors concluded that the use of RATs was accompanied by an increase in cancer investigations and urgent referrals and more cancers were diagnosed. They also found that RATs encourage GPs to think about referral thresholds, prompt them to investigate and may lead to earlier diagnosis Recommendations: These results suggest that RATs have a role in ensuring the efficient use of both resources and specialist referral, thus supporting the quality, innovation, productivity and prevention agenda of the NHS	Score = 6 (moderate level of confidence in results) Quality issues: Before and after study therefore cannot be certain that changes observed are due to the intervention; limited baseline characteristics reported so not possible to determine if sample was representative
Hicks et al 2020 Before and after study Pre- and post-FC introduction	N=248 Patients with a new referral to IBD service at Leeds Teaching Hospitals NHS Trust and a diagnosis of IBD during 2013 and 2016 (pre- and post-	Faecal calprotectin (FC) testing in primary care Pre-FC testing in 2013 (n=104) Post-FC testing in 2016 (n=144)	**Time to diagnosis** Time from referral to diagnosis (2013 vs 2016): 0.77 months vs 1.10 months (p=0.2) Time from diagnosis to treatment (2013 vs 2016): 1.37 months vs 0.72 months (p=0.01)	The authors concluded that they could not demonstrate improved outcomes for diagnosis and treatment of IBD when FC is tested. They reported that FC is likely to have contributed to the increased proportion of referrals directly to gastroenterology as intended by the introduction of the	Score = 5 (moderate level of confidence in results) Quality issues: Before and after study therefore cannot be certain that changes observed are

	FC introduction, respectively) Baseline characteristics: Mean age: 43 years Male-to-female ratio: 50:50 Current smokers: 17%		In 2016, FC was checked in 48 (33%) patients prior to referral Out of the 48 patients with faecal calprotectin measured, 12 did not have results available at the time of referral Time from diagnosis to treatment (FC vs no FC in 2016 cohort only): 0.78 months vs 1.04 months (p=0.383) Time from referral to diagnosis (FC vs no FC in 2016 cohort only): 1.47 months vs 0.86 months (p=0.06) In 2016, time to diagnosis was significantly (p=0.001) shorter in patients aged ≥66 years (mean 0.4 months) than those aged ≤40 years (mean 1.5 months) Time to treatment however was significantly longer in patients aged ≥66 years (mean 1.4 months) than those aged ≤40 years (mean 0.6 month (p=0.034) Sources of referral leading to IBD diagnosis (2013 vs 2016): GP to gastroenterology: 3% vs 17% GP to surgical specialties: 18% vs 10% Emergency admissions to hospital: 10% vs 10% 2-week wait suspected cancer pathway: 38% vs 28%	calprotectin referral pathway, and that this could be a positive outcome for patients as in some cases it may allow for earlier access to treatment and avoid unnecessary investigations. They noted that direct referrals to gastroenterology also arguably improve patient experience as patients are not required to visit a number of different teams prior to commencing treatment, demonstrated by short time to treatment The authors noted that it is reassuring to observe the time to treatment amongst patients diagnosed via the 2-week wait pathway decreased in 2016, as there is a real concern raised that once malignancy has been excluded, these patients are at risk of getting "lost" within the system and experiencing delays in treatment. Similarly, those diagnosed incidentally via the bowel screening programme had a statistically significant improvement in the time to treatment rate, confirming that the service has improved the pathway for these patients' post-diagnosis Recommendations:	due to the intervention; small sample size; 1 IBD service limiting generalisability

			Independent centres contracted to provide NHS care: 16% vs 24% Mean time to diagnosis for those referred to: • surgical specialties: 2.0 months in 2013 & 3.8 months in 2016 • gastroenterology: 2 months in 2013 and 1.16 months in 2016 • via the colorectal 2-week wait pathway: 0.64 months in 2013 and 0.6 months in 2016 Statistical significance of comparisons of referral routes not reported **Clinical outcomes** Steroids at diagnosis (2013 vs 2016): 33.7% vs 39.6% (p=0.340) Surgery in the first year: 6.7% vs 5.6% (p=0.702) Biologics in the first year: 8.3% vs 16.1% (p=0.128)	Further work, for instance through further training and education of primary care practitioners, is required to ensure patients with suspected IBD get referred to the most appropriate service in a timely manner It is important to recognise that 30% of patients present via the 2-week wait pathway and 10% present as emergency admissions. These figures should be factored into service provision and planning It is particularly noticeable that referrals to surgical specialties cause the greatest amount of delay in time to diagnosis and time to treatment. This referral route should be discouraged by measuring FC levels where appropriate Further work is required to ensure appropriate use of this test, and it is hoped that initiatives such as the New Faecal Calprotectin Care Pathway will encourage this	
Sewell et al 2020 Retrospective cohort study and	N=274 Adults aged ≥18 who were referred by their GP to a pilot rapid	RDC for patients with vague symptoms based on the Danish cancer	Most patients presented with unexplained weight loss, pain, fatigue and shortness of breath	The authors concluded that RDC for patients presenting with vague or non-specific symptoms suspicious of cancer in primary care	Score = 5 (moderate level of confidence in results)

cost-effectiveness study	diagnosis centre (RDC) at Neath Port Talbot Hospital (NPTH) for further investigation of non-specific and/or vague symptoms that could be due to cancer between June 2017 and May 2018 Baseline characteristics (Intervention group; n=189): Male: 46% Mean age: 70 years (SD 12)	patient pathway for patients presenting with non-specific symptoms and signs of cancer. Patients seen within 1 week (n=189) Control: Outcome-matched patients within the Swansea Bay University Health Board, who were referred to the urgent suspected cancer (USC) pathway by their GP but then downgraded to the non-urgent pathway because of the absence of red-flag symptoms (n=85)	**Time to diagnosis** Mean time to diagnosis was 84.2 days (SD 65.3) in the control group This was reduced to 5.9 days (SD 3.4) in patients who were diagnosed directly at the RDC clinic and to 40.8 days (SD 30.0) if further investigations following RDC were warranted **Clinical outcomes** Final outcomes were: Cancer diagnosis with referral to specialist (n=23, 12%), non-cancer diagnosis (n=30, 16%), no serious pathology found with discharge to GP (n=68, 36%) and no diagnosis; continue investigations (n=68, 36%)	reduces time to diagnosis and provides excellent value for money if run at ≥80% capacity Recommendations: Patients presenting in general practice with vague or non-specific symptoms suspicious of cancer are currently underserved and RDC addresses an important unmet need	Quality issues: Control group were patients referred to USC first and then downgraded so this group of patients may not be representative of patients with non-specific/vague symptoms and downgrade to USC will add time to diagnosis; small sample size; 1 hospital limiting generalisability Note - time to diagnosis was assumed to be the time to first outpatient appointment, which may underestimate time to diagnosis
Turvill et al 2020 Audit	N=not reported Records of all first colonoscopies (and flexible sigmoidoscopies)	York faecal calprotectin (FC) care pathway (YFCCP) Comparator: Other non-	**Time to diagnosis** Referral times YFCCP group: Median time from the first FC test result >100 µg/g faeces to clinical	The authors concluded that this audit of FC activity and colonoscopy outcomes provides substantial supportive evidence for the effectiveness of the YFCCP and supports its wider	Score = 2 (low level of confidence in results) Quality issues:

	performed by York Teaching Hospital NHS Foundation Trust in patients 18 to 60 years during 2016 to 2018 Includes 5 primary care practices using new care pathway in York for 6 months Baseline characteristics not reported	YFCCP referral pathways	diagnosis was 29 days (IQR 15 to 47) Referral times were not recorded in the non-YFCCP group, however, in a random selected sample, the median time from initial referral to clinical diagnosis was 41 days (IQR 19 to 72)	implementation. They concluded that it is popular in primary care and is being used appropriately and has led to a reduction in absolute numbers of referrals Recommendations: In young patients, the YFCCP should be used more often	No sample size, baseline characteristics or statistical methods reported; unlikely that adjustments were made to take into account any differences between the groups; for YFCCP group time of the initial consult with the GP was not recorded therefore time of the first FC test was used to calculate referral times whereas for the comparator sample initial referral was used to calculate referral times resulting in bias in favour of YFCCP group; 1 Trust limiting generalisability
Walker et al 2020b Prospective cohort study	N=42 (for comparison of interest) Children aged between 4 and 18 years diagnosed with	Faecal calprotectin testing in primary care. Results	**Time to diagnosis** Median (IQR) time from first GP presentation to GP referral (intervention vs control): 32.0 days	The authors concluded that calprotectin testing of children with suspected IBD in primary care reduces secondary care referrals and associated diagnostic healthcare	Score = 6 (moderate level of confidence in results Quality issues:

Follow-up: 12 months	IBD on or off the calprotectin pathway between January 2014 and August 2017 in 48 GP practices and gastroenterology secondary care services at the Royal Devon and Exeter NHS Foundation Trust Baseline characteristics for total sample for comparison of interest; n=42: Females: 38% (16/42) Family history of IBD: 29% (10/34) CD: 48% (20/42) IBDU: 24% (10/42) UC: 29% (12/42) Red-flag symptoms: 83% (34/41) For intervention group for comparison of interest; n=13: Females: 46% (6/13) Family history of IBD: 33% (4/12) CD: 62% (8/13) IBDU: 23% (3/13) UC: 15% (2/13) Red-flag symptoms: 62% (8/13)	≥100 µg/g were deemed positive (n=13) Comparator: No faecal calprotectin testing in primary care (n=29)	(14.0 to 32.8) vs 18.5 (9.2 to 76.5) (p=0.91) Median (IQR) time from GP referral to diagnosis (intervention vs control): 21.0 days (15.5 to 47.5) vs 45.5 days (38.0 to 76.8) (p=0.15) Median (IQR) total time to diagnosis (intervention vs control): 53.0 days (32.0 to 56.0) vs 79.5 days (49.2 to 189.0) (p=0.11) Median (IQR) duration of symptoms before IBD diagnosis (intervention vs control): 4.0 months (2.0 to 8.0) vs 3.5 months (1.9 to 5.2) (p=0.30) Authors reported that a negative calprotectin likely saved 64 referrals while a positive calprotectin likely added 9 referrals with a net saving of 55 referrals (taken from main diagnostic accuracy study (n=195)	utilisation. However, they reported that calprotectin testing did not influence the time to diagnosis of IBD, but a negative test may have contributed to a reduction in outpatient referrals and secondary care investigations. They concluded that the optimal calprotectin cut-off threshold for distinguishing IBD from non-IBD was 110 µg/g Recommendations: The authors would not recommend stratifying paediatric referrals using red-flag symptoms alone	The intervention and control group for the comparison of interest are unlikely to be comparable groups as indicated by the differences observed in presence of red flag symptoms at baseline and these differences were not taken into account of in the analyses; small sample size; 1 Trust limiting generalisability Results on diagnostic accuracy not extracted Baseline characteristics extracted from supplement

	For control group for comparison of interest; n=29: Females: 34% (10/29) Family history of IBD: 27% (6/22) CD: 41% (12/29) IBDU: 24% (7/29) UC: 34% (10/29) Red-flag symptoms: 93% (26/28) Secondary care calprotectin prior to diagnosis: 73% (19/26) Red flag criteria include one or more of: unintentional weight loss, rectal bleeding; family history of IBD				
Williams et al 2020 Before and after study	N=119 119 adults who had received information from peer-led champions between September 2012 and March 2015 and completed a Cancer Awareness Measures questionnaires before and after the intervention	Community cancer awareness programme delivered to at least 5,500 people in Manchester and Tameside & Glossop between September 2012 and March 2015	**Qualitative outcomes** The authors reported a statistically significant increase in knowledge after the intervention for cancer screening programmes ($p<0.05$), recognition of warning signs for cancer ($p<0.05$), and recognition of risk factors for cancer in seven of the eleven options ($p<0.001$), and a decrease in perception of barriers to seeking help ($p<0.05$) 90.7% of participants before and 95.5% after the programme reported	The authors concluded that community awareness campaigns can help lower perception of barriers to seeking help and messages perceived as personally relevant may improve information processing Recommendations: To improve the likelihood of knowledge retention, it would be recommended for the intervention to be repeated on the same sample of people	Score = 5 (moderate level of confidence in results) Quality issues: Before and after study therefore cannot be certain that changes observed are due to the intervention; convenience sampling used

	Baseline characteristics: Female: 79% 50 years or above: 41.5% White British: 76.3% English first language: 90.7% Achieved O Level/GCSE grades A-C or above as their highest educational attainment: 79.8%	Personalised information on signs and symptoms, screening programmes, susceptibility, and prevalence of breast, bowel and lung cancer, barriers to early diagnosis, and signposting to mainstream services Focus was on people over 50 years of age and hard to reach groups, primarily Black, Asian and minority ethnic groups, in the most deprived areas of Manchester and Tameside & Glossop Delivered in a variety of settings including community groups, events, businesses and community	that they would not delay visiting a doctor if they experienced symptoms	periodically. If the intervention was delivered more than once, with brief reminders being issued from time to time, this could be more beneficial for when the participants have to make decisions on whether to attend screening	therefore sample may not be representative of total population; small sample size

		centres delivered by peer-led volunteers mostly from areas of high deprivation			

Abbreviations: CI – confidence interval; CD – Crohn's disease; FC – faecal calprotectin; g – grams; GP – general practitioner; HR – hazard ratio; IBD – Inflammatory Bowel Disease; IBDU – Inflammatory Bowel Disease unclassified; IQR – interquartile range; LGI – lower gastrointestinal; OR – odds ratio; RAT – risk assessment tool; RDC – rapid diagnostic centres; SD – standard deviation; µg – micrograms; UC – Ulcerative Colitis; UGI – upper gastrointestinal; UK – United Kingdom; USC – urgent suspected cancer; YFCCP – York faecal calprotectin care pathway; 2WW – 2-week wait

Appendix 4: Critical appraisal framework

The checklist used for the appraisal of studies assessing interventions was the quality checklist for quantitative evidence of intervention effectiveness, from the What Works Centre guide to evidence review methods (2019). This checklist is based on the Early Intervention Foundation Quality Checklist.

For this project we added a scoring system to provide an indication of overall level of confidence in the design, conduct and reporting of the study. The 10 elements of the checklist was scored either 1 (yes) or 0 (no, can't tell or N/A). The total score was used to assign each study an overall level of confidence of low (0-2), moderate (3-6) or high (7-10).

Question	Element	Response options
Was the evidence well-designed?	**Fidelity:** • The extent to which the intervention was delivered with fidelity is clear – i.e. if there is a specific intervention which is being evaluated, this has been well reproduced	Yes (1) No (0) Can't tell (0) N/A (0)
	Measurement: • The measures are appropriate for the intervention's anticipated outcomes and population. • Participants completed the same set of measures once shortly before participating in the intervention and once again immediately afterwards • An 'intent-to-treat' design was used, meaning that all participants recruited to the intervention participated in the pre/post measurement, regardless of whether or how much of the intervention they received, even if they dropped out of the intervention (this does not include dropping out of the study - which may then be regarded as missing data)	Yes (1) No (0) Can't tell (0) N/A (0)

	Counterfactual:
	• Assignment to the treatment and comparison group was at the appropriate level (e.g. individual, family, school, community)
	• The comparison condition provides an appropriate counterfactual to the treatment group. Consider:
	  • Participants were randomly assigned to the treatment and control group through the use of methods appropriate for the circumstances and target population OR sufficiently rigorous quasi-experimental methods (regression discontinuity, propensity score matching) were used to generate an appropriately comparable sample through non-random methods
	  • The treatment and comparison conditions are thoroughly described
		Yes (1)
		No (0)
		Can't tell (0)
		N/A (0)

Was the study carried out appropriately? Including appropriate sample	**Representative:** • The sample is representative of the intervention's target population in terms of age, demographics and level of need. The sample characteristics are clearly stated. • There is baseline equivalence between the treatment and comparison group participants on key demographic variables of interest to the study and baseline measures of outcomes (when feasible)	Yes (1) No (0) Can't tell (0) N/A (0)
	Sample size: • The sample size is sufficiently large to test for the desired impact. This depends most importantly on the effect size, however a suggestion could be e.g. a minimum of 20 participants have	Yes (1) No (0) Can't tell (0) N/A (0)

	completed the measures at both time points within each study group	
	Attrition: • A minimum of 35% of the participants completed pre/ post measures. Overall study attrition is not higher than 65% • The study had clear processes for determining and reporting drop-out and dose. Differences between study drop-outs and completers were reported if attrition was greater than 10% • The study assessed and reported on overall and differential attrition	Yes (1) No (0) Can't tell (0) N/A (0)
	Equivalence: • Risks for contamination of the comparison group and other confounding factors have been taken into account controlled for in the analysis if possible • Participants were blind to their assignment to the treatment and comparison group • There was consistent and equivalent measurement of the treatment and control groups at all points when measurement took place	Yes (1) No (0) Can't tell (0) N/A (0)
	Measures: • The measures used were valid and reliable. This means that the measure was standardised and validated independently of the study and the methods for standardisation were published. Administrative data and observational measures may also have been used to measure programme impact, but sufficient information was given to determine their validity for doing this • Measurement was independent of any measures used as part of the treatment • In addition to any self-reported data (collected through the use of validated instruments), the study also included assessment information independent of the study participants (e.g. an independent observer, administrative data etc)	Yes (1) No (0) Can't tell (0) N/A (0)
Was analysis appropriate?	• The methods used to analyse results are appropriate given the data being analysed (categorical, ordinal, ratio/ parametric or non-parametric, etc) and the purpose of the analysis • Appropriate methods have been used and reported for the treatment of missing data	Yes (1) No (0) Can't tell (0) N/A (0)
Is the evidence consistent?	• Are the findings made explicit? • Is there adequate discussion of the evidence both for and against the researcher's arguments? • Has the researcher discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)? • Are the findings discussed in relation to the original research question?	Yes (1) No (0) Can't tell (0) N/A (0)