

Accepted Manuscript

British Journal of General Practice

Describing the potential of non-specific symptoms-based pathways for diagnosing less common cancers

Chapman, Dave; Poirier, Veronique; Fitzgerald, Karen; Nicholson, Brian; Hamilton, William

DOI: <https://doi.org/10.3399/BJGP.2020.1108>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 15 December 2020

Revised 30 March 2021

Accepted 07 April 2021

© 2021 The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>). Published by British Journal of General Practice. For editorial process and policies, see: <https://bjgp.org/authors/bjgp-editorial-process-and-policies>

When citing this article please include the DOI provided above.

Author Accepted Manuscript

This is an 'author accepted manuscript': a manuscript that has been accepted for publication in British Journal of General Practice, but which has not yet undergone subediting, typesetting, or correction. Errors discovered and corrected during this process may materially alter the content of this manuscript, and the latest published version (the Version of Record) should be used in preference to any preceding versions

**Describing the potential of non-specific symptoms-based pathways for
diagnosing less common cancers**

Dave Chapman ^a., Veronique Poirier ^a., Karen Fitzgerald ^a., Brian. D Nicholson ^b.,
Willie Hamilton ^c., & on behalf of the ACE MDC projects ^d

^a Cancer Research UK

^b Nuffield Department of Primary Care Health Sciences, University of Oxford.

^c University of Exeter Medical School (Primary Care)

Authors' contact details:

<p>Mr Dave Chapman (corresponding author) Health Services Innovation Research Manager (ACE) Cancer Research UK 2 Redman Place, London, E20 1JQ e-mail: dave.chapman@cancer.org.uk</p>	<p>Dr Veronique Poirier Programme Data Manager (ACE) Cancer Research UK 2 Redman Place, London, E20 1JQ</p>
<p>Ms Karen Fitzgerald Head of Policy and Implementation Research (ACE) Cancer Research UK 2 Redman Place, London, E20 1JQ</p>	<p>Dr Brian D Nicholson NIHR Academic Clinical Lecturer Nuffield Department of Primary Care Health Sciences University of Oxford Oxford, OX2 6GG</p>

<p>Prof Willie Hamilton</p> <p>Professor of Primary Care Diagnostics</p> <p>College House</p> <p>St Luke's Campus, Magdalen Road</p> <p>Exeter, EX1 2LU</p>	
--	--

^d ACE MDC projects

Airedale MDC pilot:

- Dr Alan Hart Thomas, Respiratory Consultant
- Dawn Gulliford, Cancer Patient Services Manager
- Dr Helena Rolfe, Cancer Lead GP
- Airedale MDC clinical team

Greater Manchester MDC pilots:

- Dr Matthias Hohmann, Oldham CCG GP Cancer Lead
- Chris Repperday, Data Analyst, Greater Manchester Cancer Alliance
- Susan Sykes, Senior Programme Manager, Greater Manchester Cancer Alliance
- Dr Sarah Taylor, Greater Manchester Cancer Alliance GP Cancer Lead
- Greater Manchester MDC clinical teams

Leeds MDC pilot:

- Angie Craig, LTHT Assistant Director of Operations and Diagnostic Lead
- James Dawson, Assistant Information Manager
- Dr Sarah Forbes, GP Cancer Lead
- Helen Ryan, Macmillan Leeds Cancer Programme Project Lead (Early Diagnosis)
- Dr Rob Turner, Consultant Clinical Oncologist

- Leeds ACE MDC Clinical Team and Steering Group

London MDC pilots:

- Mush Ahmad, Data Manager
- Felicity Carson, Senior Project Manager
- Donna Chung, Head of Centre for Cancer Outcomes, North Central and East

London Cancer Alliance (formerly London Cancer, hosted by UCL Partners)

- Dr David Graham, Consultant Gastroenterologist
- Dr Andrew Millar, Consultant Gastroenterologist
- Sara Taiyari, Senior Project Manager
- London MDC clinical teams

Oxford MDC pilot:

- Dr Claire Friedemann Smith, SCAN Researcher
- Prof. Fergus Gleeson, Consultant Radiologist
- Dr Shelley Hayles, Planned Care and Cancer Clinical Lead
- Zoe Kaveney, Senior Project Manager
- Dr Brian Nicholson, Macmillan GP and Senior Clinical Researcher
- Oxford MDC clinical team

Accepted Manuscript – BJGP – BJGP:2020.1108

Background:

Although less common cancers account for over half of all cancer diagnoses in England, their relative scarcity and complex presentation, often with non-specific symptoms, means that patients often experience multiple primary care consultations, longer times to diagnosis and poorer clinical outcomes. An urgent referral pathway for non-specific symptoms, the Multidisciplinary Diagnostic Centre (MDC), may address this problem.

Aim:

To examine the less common cancers identified during the MDC pilots and consider if such an approach improves the diagnosis of these cancers.

Design and Setting:

A service evaluation of five MDC pilot projects in England to 31st March 2019.

Method:

Data items were collected by pilot sites in near-real time, based mainly on the English cancer outcomes and services dataset, with additional project specific items. Simple descriptive and comparative statistics were used, including chi-squared tests for proportions and t-tests for means where appropriate.

Results:

From 5,134 referrals, 378 cancers were diagnosed, of which 218 (58%) were less common. Over 30 different less common tumour types were diagnosed within this cohort. 23% of MDC patients with less common cancers had ≥ 3 more GP consultations before referral and, at programme level, a median time of 57 days was recorded from GP urgent referral to treatment for these tumour types.

Conclusion:

A non-specific symptomatic referral route diagnoses a broad range of less common cancers, and can support primary care case management for patients with symptoms of possible cancer that do not qualify for a site-specific urgent referral.

Key words:

Multi-disciplinary Diagnostic Centre; MDC; non-specific symptoms; less common cancers; primary health care; urgent cancer referral.

How this fits in:

We piloted five Multidisciplinary Diagnostic Centres (MDCs) across ten English sites as a rapid referral route for the investigation of primary care patients with non-specific cancer symptoms. Most cancers diagnosed by the MDCs were “less common” cancers comprising thirty different tumour types. These cancers typically have longer diagnostic intervals and have poor clinical outcomes. The broad range of less common cancers diagnosed rapidly by MDCs emphasises the value of diagnostic pathways that aim to establish the cause of symptoms instead of ruling out individual tumour types.

Introduction

Rare and less common cancers (hereafter 'less common cancers') account for almost half of all cancer diagnoses in England and over half of all cancer deaths^{1, 2, 3}. This broad term incorporates over 200 different tumour types, excluding the four most common malignancies: breast, colorectal, lung and prostate (hereafter 'common cancers')⁴.

With the exception of cervical cancer, there is currently no established screening programme for less common cancers⁵ and recognition of disease relies upon on the development and presentation of symptoms^{6,7,8}. In many cases, these cancers present with non-specific symptoms, which can also originate from multiple benign conditions^{6, 9, 10, 11}. For example, unexpected weight loss is associated with several cancers at all cancer stages but may also arise from serious and non-serious diagnoses associated with a wide range of body systems^{12, 13}. Additionally, the relative scarcity of less common cancers often makes the risk of cancer in symptomatic patients lower than the UK's recommended 3% threshold for urgent cancer investigation, even when symptoms are highly specific to the cancer^{5, 6, 9, 14}. The range of possible conditions and the low likelihood of cancer complicates the choice and timing of diagnostic investigation in primary care.

The diagnostic process for both patients diagnosed with less common cancers and those presenting with non-specific symptoms is often characterised by multiple primary care consultations, investigations, and referrals^{15, 16, 17, 18, 19}. Lengthy intervals from presentation to diagnosis are common^{6, 16, 17, 20}, as is diagnosis by emergency presentation^{16, 21, 22}, with both being associated with high rates of advanced stage diagnosis¹⁶, worse survival²³, and a poorer experience of care^{3, 24}.

A Multidisciplinary Diagnostic Centre (MDC) approach was piloted in England, establishing a dedicated pathway for patients presenting with non-specific symptoms indicative of possible cancer. An evaluation by the Accelerate Coordinate Evaluate (ACE) Programme, which aimed to improve cancer pathways and

associated outcomes through the provision of evidence-based information and support ²⁵, demonstrated that the MDC approach diagnosed a broad range of cancers, including a notable proportion of less common cancers ¹⁰. In this study, we examine in detail the less common cancers identified during the MDC pilots and consider if such an approach has benefit for the diagnosis of these cancers.

Method:

MDC projects

The ACE Programme evaluation comprised five projects in England, incorporating ten operational MDC pilot sites (Airedale, Greater Manchester (x2), Leeds, London (x5) and Oxford) ¹⁰.

Projects were established to assess a dedicated urgent referral route for patients presenting with a predetermined range of non-specific symptoms for which there was no clear diagnostic approach. The pathway predominantly offered a single referral route for primary care, although a number of projects also allowed a smaller volume of referrals from other agencies ^{10, 26}.

Individual hospital sites were launched at different times from December 2016 to January 2018. To reflect the evaluation's design, programme-funded activity with the MDC pilots concluded on 31st March 2019.

Referral criteria

MDC project referrals were limited to adult patients aged ≥ 18 years (in Oxford ≥ 40 years), presenting with non-specific but concerning symptoms, such as unexplained weight loss, non-specific pain, unexplained appetite loss, and persistent fatigue. Eligibility criteria varied at project level, and are detailed in Supplementary Table 1, but all projects focused exclusively on patients of clinical concern whose non-specific symptoms were potentially indicative of cancer or other serious disease ^{10, 26}. To be eligible for referral, the patient's symptoms also had to be ineligible for a tumour-specific urgent referral pathway.

Patients with previous cancers were considered eligible for referral, provided that they had non-specific symptoms only.

Data collection and analysis

A programme dataset was agreed by all MDC projects to ensure a uniform approach to data collection. Data items were based mainly on the English cancer outcomes and services dataset (COSD) ²⁷, with additional project specific items, focusing on secondary care presentation, diagnostic process of cancers and other diseases. Data management arrangements varied by MDC project, and used a combination of local healthcare IT systems and bespoke data systems, with data items collected as close to real-time as possible ¹⁰. Minor recoding was applied by programme evaluators to align the data for analysis.

Simple descriptive and comparative statistics are used, including chi-squared tests for proportions and t-tests for means where appropriate, which concentrate on diagnoses of less common cancers within this referral cohort. These have been aggregated to a programme level to provide greater scope for analysis. No formal power calculation was made relating to the expected cancer yield.

This study on less common cancers, which covers MDC pathway activity to 31st March 2019, is one of several pathway analyses and contributes to existing evidence on initial MDC results ¹⁰. Further analyses are planned on MDC diagnostic activity and will consider the overall use of CT as a diagnostic investigation and any impact on pathway time, in addition to the pathway's diagnosis of non-cancer disease.

Although common cancers have dedicated referral pathways in place ⁹, and often present with recognised high-risk site-specific symptoms, patients with these cancers may experience non-specific symptoms, and thus enter the MDC pathway. As the pathway aims to provide a route to diagnosis for symptomatic patients whose cancer is indistinguishable at point of presentation, data on the presentation of common cancers has been included to reflect the difficulty facing the referrer.

A list of symptoms was identified in the dataset and developed with clinical guidance to describe patients whose presentation is suggestive of cancer but does not indicate a specific diagnostic approach ¹⁰. This range of symptoms, which included some conditions and signs that are not strictly symptoms, is described in Supplementary Figure 1.

Results:

To 31st March 2019, 5,134 patients were referred to the pilot MDCs. 218 (58%) of a total of 378 cancers diagnosed were less common cancers (Table 1) The most common diagnoses related to upper GI (39%), haematological (25%), and urological (14%) cancers. For 5 cancers, a confirmed diagnosis was recorded but without additional information on tumour-site.

Table 1: Anatomical sites of less common cancers diagnosed in the MDC

In addition to cancers diagnosed, 2,061 patients were diagnosed with at least one non-cancer condition, with the majority (42%) of cases relating to conditions of the digestive system, including gastritis and duodenitis, and diverticular disease. A variety of other non-cancer disease was evident, including conditions relating to abnormal clinical and laboratory findings (12%) (mainly abnormal findings on diagnostic imaging of lung), and respiratory disease (7%), including diagnoses of bronchiectasis, emphysema, and other interstitial pulmonary disease. Diseases of the genitourinary system (7%) were also diagnosed, as were several types of benign neoplasm (6%).

Table 2 describes the age, sex and presenting features of patients diagnosed with cancer in the MDC. Symptoms accounting for <5% of symptoms overall have been grouped and classified as 'other'.

Table 2: Presenting features of MDC patients by cancer type (n; % cancer cases)

Patients diagnosed with less common cancers had a median age of 74 years (range 30-93 years old). The most common reasons for referral to the MDC for less common and for common cancers, respectively, were: weight loss (26%; 27%), GP 'clinical suspicion' (17%; 20%), nausea / appetite loss (14%; 14%), and pain (11%; 11%). However, there was no difference in the association between the reason for referral and a diagnosis of a common or less common cancer ($\chi^2=0.19$, with 7 degrees of freedom). The majority (68%) of patients diagnosed with less common cancers presented with ≥ 2 non-specific symptoms, with the most common pairings being 'weight loss and nausea' (n=57), and 'weight loss and GP 'clinical suspicion'' (n=57). Based on 210 completed patient records, 25% of patients overall had ≥ 3 consultations with their GP before referral (23% less common; 28% common).

Table 3 describes the presenting features of patients diagnosed with the three most frequently diagnosed less common cancers - kidney, non-Hodgkin's lymphoma and pancreas.

Table 3: Presenting features of MDC patients diagnosed with kidney, non-Hodgkin's lymphoma and pancreatic cancers

Variation was noted at a tumour-specific level, with kidney cancers more commonly diagnosed in patients aged ≤ 75 years, having also presented with higher proportions of weight loss (33%) and fatigue (13%), in addition to a lower proportion of GP 'clinical suspicion' (9%). The proportion of GP 'clinical suspicion' was highest (21%) for diagnoses of non-Hodgkin's lymphoma, and rates of nausea/appetite loss were higher

in pancreatic cancers (17%). Non-Hodgkin's lymphoma was associated with higher rates of presentation with ≥ 2 non-specific symptoms. Due to small sample sizes, this information is provided for descriptive purposes only.

Table 4 provides details of the duration from GP urgent referral to the start of any cancer treatment. Data on interval time from GP urgent referral to start of cancer treatment were only available for 135 of 218 (62%) less common cancer diagnoses. Interval times have been provided at tumour-site level in cases where there was a sufficient number of cases to support analysis. In some instances, the number of cases was too small to calculate the centiles reliably. Rates have been provided for median, IQR and 90% centile relating to the pathway's treatment interval. As these figures respectively include and compensate for outlier records, and provide a figure representative of 90% of the pathway's activity, they collectively provide a balanced and robust representation of pathway time to cancer treatment.

Table 4: Reported interval time in the MDC from GP urgent referral to start of any cancer treatment

Table 5 shows the stage distribution of cancers diagnosed in the MDC, and indicates that most diagnoses were of a late stage (III/IV). However, a notable proportion of early stage diagnoses were recorded for these cancers, including for kidney cancers (29%).

Table 5: Stage distributions of less common cancers diagnosed in the MDC

Discussion:

Summary

This study has demonstrated that a dedicated urgent referral pathway focusing on non-specific symptoms rapidly identifies a broad range of less common cancers, with over 30 different tumour types detected from a total of 218 less common cancers. The MDC pathway recorded an overall cancer conversion rate of 7%, with over half the diagnoses being of less common cancers (an identification rate ~4% for these cancers). An MDC referral therefore selects a population with an overall cancer positive predictive value exceeding the 3% recommended for urgent investigation ⁹. Crucially, it provides a pathway for the diagnosis of rarer cancers which individually fall beneath this 3% threshold, but are collectively above it.

Strengths and limitations

This study has several limitations. The MDC provides a referral route for a new cohort of patients, for whom a direct comparator is not available, and this study examines the diagnosis of less common cancers, for which national statistical information is less complete than for common cancers. Both of these factors have tempered judgements on the MDC's possible impact compared to existing pathways for individual less common cancers. Analyses in this study have also been restricted by the relatively small numbers of some less common cancers, although this is a challenge common to diagnostic studies of any uncommon disease ^{28, 29}. Although presentation with non-specific symptoms, both individually and in combination, has been considered, it has not been possible to ascribe any significance to these analyses due to the level of bias introduced into the study by the establishment of the pathway's referral criteria. Therefore, whilst the presence of these symptoms will be heightened within the study, it is not possible to extrapolate this to a wider population.

A direct comparison with national 62 day wait performance was hampered by a lack of published data at tumour-site level, and by the MDC's unique focus on non-specific symptoms as a patient cohort, meaning

that a viable comparator for the pathway's treatment interval could not be established. Due to the time-limited nature of the evaluation, judgements regarding the longer-term impact of the pathway on patient outcomes have not been possible, but further research into this area would be of great value. Finally, the study focuses on the results of a service evaluation and, although measures were established to support data collection and reporting, some variation was noted in data completeness and in the interpretation of some data items at project level. In cases where variation and/or incomplete recording was noted, for example, performance status and comorbidity, data items were excluded from the study.

Comparison with existing literature

Other studies have examined the presenting features and diagnostic pathways of several less common cancers ^{6, 20}. Many of these have indicated that less common cancers are subject to longer diagnostic intervals and have poor clinical outcomes regarding stage and mortality ^{8, 20, 22, 30}. Similarly, several recent studies have considered the merits of diagnostic pathways for non-specific symptoms ^{10, 16}, albeit with a wider focus on cancer overall. Our study adds to this body of evidence by considering the impact of non-site-specific symptomatic referral on the diagnosis of a broad range of less common cancers.

Implications for research and/or practice

The challenge facing primary care in diagnosing less common cancers presenting with non-specific symptoms is well documented. As an urgent referral pathway for non-specific symptoms, the MDC diagnosed a higher proportion of less common cancers. This was anticipated as presentation with non-specific symptoms is considered normal for several less common cancers, including some of those frequently diagnosed in the MDC; for example, upper GI (20%: non-specific; 7% characteristic) and haematology (12%: non-specific; 8% characteristic) ¹⁶, compared to breast and prostate (0.61%: non-specific; 16%: characteristic; and 10%: non-specific; 22%: characteristic, respectively, though these figures relate to urological cancers as a whole) ¹⁶.

In this study, 26% of patients in the MDC had ≥ 3 GP consultations before referral. This figure is below the equivalent rate of 32% for patients with non-specific symptoms reported in the National Cancer Diagnosis Audit ¹⁶, and is suggestive of a reduction in pre-referral consultation activity for this cohort. As the number of consultations before referral has been shown to have validity as a measure of the wider primary care interval ³⁰, it is arguable that such a reduction via the MDC pathway could support faster diagnosis for some less common cancers, and for patients with non-specific symptoms overall.

In addition to cancer diagnoses, over 2,000 patients were diagnosed with at least one non-cancer condition, with these diagnoses representative of a broad range of non-malignant disease. As non-specific symptoms can potentially stem from multiple benign and/or serious conditions, the MDC's focus on resolving symptoms rather than ruling out specific disease enables such a spectrum of diagnoses to occur. This approach can also support connectivity across the surrounding healthcare system through informed onward referral at point of diagnosis within the MDC, and may have benefit regarding ongoing patient surveillance for certain diagnosed conditions.

At a programme level, a median time of 57 days from GP urgent referral to treatment was recorded for less common cancers within the MDC, which is in-line with the national 62 day wait standard ³¹. Treatment intervals varied by tumour-site, with notably shorter median intervals reported for sarcoma, upper GI and 'other' cancers, but longer intervals identified for haematology and urology. A partial comparison against national 62 day wait compliance suggests the MDC is faster for oesophago-gastric cancers (75%: MDC; 71%: England) ³² but moderately slower for other 'selected' cancer sites (60% MDC; 68.8%: England) ³³. As the study relates to activity within pilot sites, it is plausible that these interval times may improve as the pathway matures and becomes fully embedded and resourced. Cumulatively, by reducing pre-referral activity and providing a swift overall time to treatment, the MDC may also lessen the chance of diagnosis via emergency presentation, which is common for both non-specific symptoms ¹⁶ and many less common cancers such as kidney ^{14, 21, 34, 35}, non-Hodgkin's lymphoma ^{21, 34}, and pancreas ^{21, 34, 36}.

Most cancers within the MDC were diagnosed at a late stage, which may reflect the systemic nature of some of the non-specific symptoms eligible for MDC referral. Even so, 21% of less common cancers were diagnosed at stage 1 and 2, with rates varying by tumour-site but limited by insufficient numbers in some instances. Where site-specific data was available, early stage diagnosis for pancreatic cancer was consistent with the national rate (MDC: 23%; England (2018): 23%)³⁷, suggesting that the pathway may offer benefit for some tumour-sites with very poor early stage diagnosis. The proportion of early stage diagnosis was lower for cases of non-Hodgkin's lymphoma (MDC: 24%; England (2018): 30%)³⁷ and kidney cancer (MDC: 29%; England (2018): 57%)³⁷. However, when interpreting this information, it is necessary to consider the strong association between non-specific symptoms and late stage diagnosis. As the MDC focuses exclusively on this patient cohort, it will be disadvantaged in any comparison to national figures, within which this patient cohort will not be visible.

To gain a more comprehensive understanding of the MDC's impact on pathway interval times and variation amongst differing diagnoses, further research, and the publication of cancer waiting time data for less common cancers will be required. It is important to gauge whether any benefits gained by faster times to diagnosis lead to earlier initiation of cancer treatment. Such work should also consider how current system capacity and access to specialist treatment may affect interval times, particularly given the specialist requirements for some rarer cancers. Further pathway evaluation is also merited on the balance of benefit and harm associated with diagnostic investigation, as only a minority of referrals with possible malignancy actually result in a cancer diagnosis. This additional information would contribute to the evidence-base regarding non-specific symptoms and rarer cancers, and would directly inform the development and implementation of the rapid diagnostic centre model in England³⁸, which has evolved from the MDC approach. As these new pathways are established throughout England, it will be important to retain a focus on non-specific symptoms as a distinct cohort of patients, in order to build upon the potential demonstrated within the MDC pilots. Such an approach may also offer an opportunity to develop

a dedicated, integrated diagnostic interface between primary and secondary care, in support of the swift recognition, referral and diagnosis of cancers presenting with non-specific symptoms.

Conclusion:

The MDC evaluation has shown that a non-specific symptomatic referral route diagnoses a broad range of less common cancers, and can support primary care case management for patients with symptoms of possible cancer that do not qualify for an urgent site-specific referral.

^d ACE MDC projects

Airedale MDC pilot:

- Dr Alan Hart Thomas, Respiratory Consultant
- Dawn Gulliford, Cancer Patient Services Manager
- Dr Helena Rolfe, Cancer Lead GP
- Airedale MDC clinical team

Greater Manchester MDC pilots:

- Dr Matthias Hohmann, Oldham CCG GP Cancer Lead
- Chris Repperday, Data Analyst, Greater Manchester Cancer Alliance
- Susan Sykes, Senior Programme Manager, Greater Manchester Cancer Alliance
- Dr Sarah Taylor, Greater Manchester Cancer Alliance GP Cancer Lead
- Greater Manchester MDC clinical teams

Leeds MDC pilot:

- Angie Craig, LTHT Assistant Director of Operations and Diagnostic Lead

- James Dawson, Assistant Information Manager
- Dr Sarah Forbes, GP Cancer Lead
- Helen Ryan, Macmillan Leeds Cancer Programme Project Lead (Early Diagnosis)
- Dr Rob Turner, Consultant Clinical Oncologist
- Leeds ACE MDC Clinical Team and Steering Group

London MDC pilots:

- Mush Ahmad, Data Manager
- Felicity Carson, Senior Project Manager
- Donna Chung, Head of Centre for Cancer Outcomes, North Central and East London Cancer Alliance (formerly London Cancer, hosted by UCL Partners)
- Dr David Graham, Consultant Gastroenterologist
- Dr Andrew Millar, Consultant Gastroenterologist
- Sara Taiyari, Senior Project Manager
- London MDC clinical teams

Oxford MDC pilot:

- Dr Claire Friedemann Smith, SCAN Researcher
- Prof. Fergus Gleeson, Consultant Radiologist
- Dr Shelley Hayles, Planned Care and Cancer Clinical Lead
- Zoe Kaveney, Senior Project Manager
- Dr Brian Nicholson, Macmillan GP and Senior Clinical Researcher
- Oxford MDC clinical team

Funding:

The ACE Programme (MDC) was a joint early diagnosis of cancer initiative between NHS England, Cancer Research UK, and Macmillan Cancer Support.

Funding for the Programme Management of the ACE Programme was provided by Cancer Research UK.

The five MDC projects received programme funding to support the development and trial of pilot pathways in accordance with their status as ACE Programme sites.

BDN was supported by National Institute for Health Research (NIHR) doctoral research fellowship (DRF-2015-08-18) and an NIHR Academic Clinical Lectureship. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the Department of Health. WH is Director of the multi-institutional CanTest Research Collaborative funded by a Cancer Research UK Population Research Catalyst award (C8640/A23385).

Ethical approval:

The ACE evaluation was classified as a service evaluation and was therefore not subject to ethics approval.

Competing interests:

The authors of the paper declare no conflict of interest.

Acknowledgments:

We would like to thank the following:

Sean Duffy (West Yorkshire and Harrogate Cancer Alliance), Sara Hiom (Cancer Research UK), Rosie Loftus (Macmillan Cancer Support), and Carol Ferguson (West Yorkshire and Harrogate Cancer Alliance) and the

NAEDI Steering Group (<https://www.cancerresearchuk.org/health-professional/diagnosis/early-diagnosis-initiative>) for forming and launching the MDC initiative.

MDC patients;

MDC project clinical teams from:

- Airedale General Hospital
- Manchester University NHS Foundation Trust (Wythenshawe Hospital) & The Northern Care Alliance (Royal Oldham Hospital)
- Leeds St James University Hospital (Specialist Cancer Centre)
- London: North Middlesex University Hospital, University College London Hospital (Specialist Cancer Centre), Southend University Hospital, Queens (BHRUT) & the Royal Free Hospital
- Oxford University Hospitals Trust (Specialist Cancer Centre)

ACE Programme partners; NHS England, Cancer Research UK, and Macmillan Cancer Support;

References:

1. Office for National Statistics (2016)
Available from:
www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2016
2. <https://www.ndrs.nhs.uk/wp-content/uploads/2019/05/FINAL-SHARE-SLIDE-DECK-Development-in-data-for-rare-and-less-common-cancers-220519.pdf>
3. Cancer52. (2018) Getting a better deal for people for rare and less common cancers: the next ten years
4. Cancer52 (2014). A report from Cancer52 on National Cancer Intelligence Network data on rare and less common cancers.
Available from: https://docs.wixstatic.com/ugd/e22361_632a99df161844ea92afc7ba6fd90a12.pdf
5. Hamilton, W. Five misconceptions in cancer diagnosis. *Br J Gen Pract* (2009), **59**, 441-447
6. Koo, M., Hamilton, W., Walter, F. M., et al. Symptom signatures and diagnostic timeliness in cancer patients: a review of current evidence. *Neoplasia* (2018), Feb **20**, 165-174
7. Swann, R., McPhail, S., Witt, J., et al. Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. *Br J Gen Pract* (2018), e63-72
8. Neal, R. D., Tharmanathan, P., France, B., et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *BJC* (2015), **112**, s92-s107
9. National Institute for Health and Care Excellence. (2015) Suspected cancer: recognition and referral. NICE guideline (NG12)

10. Chapman, D., Poirier, V., Vulkan, D., et al. First results from five multidisciplinary diagnostic centre (MDC) projects for non-specific but concerning symptoms, possibly indicative of cancer. *BJC* (2020), **123**, 722-729
11. Jørgensen, S. F., Ravn, P., Thorsen, S., et al. Characteristics and outcomes in patients with non-specific symptoms and signs of cancer referred to a fast track cancer patient pathway; a retrospective cohort study. *BMC Cancer* (2017), **17**, 809
12. Nicholson, B. D., Hamilton, W., Koshiaris, C., et al. The association between unexpected weight loss and cancer diagnosis in primary care: a matched cohort analysis of 65 000 presentations. *BJC* (2020), **122**, 1848-1856
13. Nicholson, B. D., Hamilton, W., O'Sullivan, J., et al. Weight loss as a predictor of cancer in primary care: a systematic review and meta-analysis. *Br J Gen Pract* (2018), **68**, e311-e322
14. Schmidt-Hansen, M., Berendse, S. & Hamilton, W. The association between symptoms and bladder or renal tract cancer in primary care: a systematic review. *Br J Gen Pract* (2015), e769
15. Lyratzopoulos, G., Neal, R. D., Barbieri, J. M., et al. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. *Lancet Oncol* (2012), **13**, 353-365
16. Pearson, C., Poirier, V., Fitzgerald, K., et al. Cross-sectional study primary care data and cancer registration data to investigate patients with cancer presenting with non-specific symptoms. *BMJ Open* (2020), **10**, e033008
17. Lyratzopoulos, G., Wardle, J. & Rubin, G. Rethinking diagnostic delay in cancer: how difficult is the diagnosis? *BMJ* (2014), **349**, g7400
18. NHS England Cancer Patient Experience Survey, Quality Health (2016)

19. Abel, G. A., Mendonca, S. C., McPhail, S., et al. Emergency diagnosis of cancer and previous general practice consultations: insights from linked patient survey data. *Br J Gen Pract* (2017), e377
20. Lyratzopoulos, G., Saunders, C. L., Abel, G. A., et al. The relative length of the patient and primary care interval in patients with 28 common and rarer cancers. *BJC* (2015), **112**, s35-s40
21. Abel, G. A., Shelton, J., Johnson, S., et al. Cancer-specific variation in emergency presentation by sex, age, and deprivation across 27 common and rarer cancers. *BJC* (2015), **112**, s129-s136
22. Zhou, Y., Mendonca, S. C., Abel, G. A., et al. Variation in 'fast-track' referrals for suspected cancer by patient characteristic and cancer diagnosis: evidence from 670 000 patients with cancers of 35 different sites. *BJC* (2018), **118**, 24-31
23. National Cancer Registration and Analysis Service. (2020) Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2018. (accessed Sept 2020)
<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/stageatdiagnosisandchildhoodpatientsfollowedupto2018>
24. NHS England. (2019) National Cancer Patient Experience Survey (accessed Sept 2020):
https://www.ncpes.co.uk/wp-content/uploads/2020/06/CPES-2019-National-Report_V1.pdf
25. Fuller, E., Fitzgerald, K. & Hiom, S. Accelerate, coordinate, evaluate programme: a new approach to cancer diagnosis. *Br J Gen Pract* (2016), **66**, 176-177
26. ACE Programme (Cancer Research UK). (2019) Identifying distinguishing features of the MDC model within the five ACE projects. ACE Programme
https://www.cancerresearchuk.org/sites/default/files/distinguishing_features_of_the_mdc_model_edit.pdf
27. National Cancer Registration and Analysis Service. (2019) Cancer outcomes and services dataset – version 8. http://www.ncin.org.uk/collecting_and_using_data/data_collection/cosd
28. Panageas, K. S. Clinical trial design for rare cancers: why a less conventional route may be required. *Expert review of clinical pharmacology* (2015), **8:6**, 661-663

29. Gagne, J. J., Thompson, L., O'Keefe, K., et al. Innovative research methods for studying treatments for rare diseases: methodological review. *BMJ* (2014), **349**, g6802
30. Lyratzopoulos, G., Abel, G. A., McPhail, S., et al. Measures of promptness of cancer diagnosis in primary care: secondary analysis of national audit data on patients with 18 common and rarer cancers. *BJC* (2013), **108**, 686-690
31. NHS Digital. (2020) Cancer waiting times data collection (CWT) (accessed Sept 2020)
<https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/cancerwaitingtimescwt>
32. NHS England. (2019) Implementing a timed oesophago-gastric cancer diagnostic pathway: a handbook for local health and care systems (accessed Sept 2020)
<https://www.england.nhs.uk/wp-content/uploads/2018/04/implementing-a-timed-oesophago-gastric-cancer-pathway.pdf>
33. NHS England. (2020) Cancer waiting times annual report 2019-20 (accessed Sept 2020)
<https://www.england.nhs.uk/statistics/statistical-work-areas/cancer-waiting-times/cwt-annual-reports/cancer-waiting-times-annual-report-2019-20/>
34. National Cancer Registration and Analysis Service. (2020) Routes to diagnosis 2006-16 (accessed Sept 2020) http://www.ncin.org.uk/publications/routes_to_diagnosis
35. Shepherd, E., Neal, R. D., Rose, P., et al. Clinical features of kidney cancer in primary care: a case-control study using primary care records. *Br J Gen Pract* (2013), e250
36. Basuroy, R., Bouvier, C., Ramage, J. K., et al. Delays and routes to diagnosis of neuroendocrine tumours. *BMC Cancer* (2018), **18**, 1122
37. Public Health England. (2020) National Disease Registration Service: Staging data in England. Stage group by Clinical Commissioning Group, Sustainability and Transformation Partnership or Cancer Alliance by cancer type for 21 cancer types. (Accessed Oct 2020):
https://www.cancerdata.nhs.uk/stage_at_diagnosis

38. NHS England. (2019) Rapid diagnostic centres: vision and 2019-20 implementation specification
<https://www.england.nhs.uk/wp-content/uploads/2019/07/rdc-vision-and-1920-implementation-specification.pdf>

Accepted Manuscript – BJGP – BJGP:2020.1108

Table 1: Anatomical sites of less common cancers diagnosed in the MDC

Tumour group; N (%)	Tumour description (ICD 10 code)	Number
Upper GI; 84 (39)	Malignant neoplasm of pancreas (C25)	43
	Malignant neoplasm of stomach (C16)	11
	Malignant neoplasm of liver and intrahepatic bile ducts (C22)	11
	Malignant neoplasm of oesophagus (C15)	9
	Malignant neoplasm of gallbladder (C23)	6
	Malignant neoplasm of other and unspecified parts of biliary tract (C24)	3
	Malignant neoplasm of other and ill-defined digestive organs (C26)	1
Haematological; 54 (25)	Non-Hodgkin's lymphoma (C82-86 & C96)	32
	Multiple myeloma and malignant plasma cell neoplasms (C88 & C90)	12
	Hodgkin's disease (C81)	5
	Acute myeloblastic leukaemia (C92-C95)	1
	Other leukaemia of specified cell type (C94)	3
	Lymphoid leukaemia (C91)	1
Urological; 31 (14)	Malignant neoplasm of kidney, except renal pelvis (C64)	25
	Malignant neoplasm of bladder (C67)	5
	Malignant neoplasm of renal pelvis (C65)	1
Other; 18 (8)	Malignant neoplasm without specification of site (C80)	15
	Malignant neoplasm of adrenal gland (C74)	1
	Malignant neoplasm of other and ill-defined sites (C76)	1
	Secondary malignant neoplasm of other sites (C79)	1
Gynaecological; 9 (4)	Malignant neoplasm of ovary (C56-C57)	8
	Malignant neoplasm of uterus, part unspecified (C55)	1
Sarcoma; 9 (4)	Malignant neoplasm of retroperitoneum and peritoneum (C48)	7
	Malignant neoplasm of pelvic bones, sacrum and coccyx (C41)	1
	Malignant neoplasm of other connective and soft tissue (C49)	1
Skin; 5 (2)	Malignant melanoma of the skin (C43)	5
Lung / Pleura; 4 (2)	Mesothelioma (C45)	3
	Malignant neoplasm of thymus (C37)	1
Head & Neck; 2 (1)	Malignant neoplasm of dorsal surface of tongue (C02)	1
	Malignant neoplasm of mouth (C06)	1
Lower GI; 1 (0)	Malignant neoplasm of small intestine (C17)	1
Brain/CNS; 1 (0)	Malignant neoplasm of cerebrum, brain, unspecified (C71)	1
Total cancers		218

Table 2: Presenting features of MDC patients by cancer type

	Less common cancers (all)		Common cancers	
	N	%	N	%
<i>Patient age range (persons) *</i>				
<50 years	7	3	5	3
50-75 years	114	52	78	50
>75 years	97	44	72	47
All cases	218	-	155	-
<i>Presenting feature</i>				
Weight loss	132	26	99	27
GP 'clinical suspicion'	90	17	74	20
Nausea/appetite loss	71	14	52	14
Pain	58	11	40	11
Fatigue	47	9	39	10
Abnormal test results (bloods; urine etc.)	30	6	26	7
Anaemia	29	6	14	4
'Other' symptoms (with <5% instances)*	59	11	29	8
Total symptoms recorded	516	100	373	100
N (%) presentation with ≥2 symptoms (including GP 'clinical suspicion')	148/218 (68)		109/155 (70)	
N (%) of patients with ≥3 GP consultations prior to referral based on available records	27/116 (23)		25/90 (28)	

* no significant differences were seen between the sexes

*other symptoms include: patient / family concern; general condition; respiratory problem; jaundice; bloating; change in bowel habit; lymphadenopathy; thrombocytosis; hypercalcaemia; DVT . Despite being considered a site-specific symptom, jaundice was included as a referral criterion in London MDC to reflect locally determined clinical priorities.

Table 3: Presenting features of MDC patients diagnosed with kidney, non-Hodgkin's lymphoma and pancreatic cancers

	Kidney (C64)		Non-Hodgkin's Lymphoma (C82-86 & C96)		Pancreas (C25)	
	N	%	N	%	N	%
<i>Patient age range (persons) *</i>						
<50 years	-	-	-	-	-	-
50-75 years	16	64	16	50	22	50
>75 years	9	36	16	50	21	50
All cases	25	100	32	100	43	100
<i>Presenting feature</i>						
Weight loss	18	33	20	25	29	26
GP 'clinical suspicion'	5	9	17	21	18	16
Nausea/appetite loss	7	13	11	14	19	17
Pain	5	9	8	10	16	14
Fatigue	7	13	5	6	9	8
Abnormal test results (bloods; urine etc.)	3	6	6	7	8	7
Anaemia	5	9	6	7	3	3
'Other' symptoms (with <5% instances overall)*	4	7	8	10	10	9
Total symptoms recorded	54	100	81	100	112	100
N (%) presentation with ≥2 symptoms (including GP 'clinical suspicion')	17/25 (68)		24/32 (75)		30/43 (70)	

* no significant differences were seen between the sexes

*other symptoms include: patient / family concern; general condition; respiratory problem; jaundice; bloating; change in bowel habit; lymphadenopathy; thrombocytosis; hypercalcaemia; DVT. Despite being considered a site-specific symptom, jaundice was included as a referral criterion in London MDC to reflect locally determined clinical priorities.

Table 4: Reported interval time in the MDC from GP urgent referral to start of any cancer treatment

	Median days	Number	IQR	90% centile	% ≤62 days
Less common cancers (all cases) *	57	135	34-78	110.6	54
Gynaecology	50	6	25.5-70.8	78.5	50
Haematology	65	34	26.2-87.5	110.7	44
Other	39	9	21-49	65.4	78
Sarcoma	41	5	36-44	55.4	80
Upper Gi tract	47	52	32.8-66.5	93.1	63
Urology	74	21	48-110	163	33
Haematology – NHL only	63	25	27-90	108	44
Upper Gi tract – Pancreas only	45	31	31.5-63	82	71
Upper Gi tract –Oesophago-gastric	46	12	31.2-62.2	67.8	75
Urology – Kidney only	74	17	48-110	144.4	35
'Selected' cancer sites **	49	109	29-71	97.4	60

* At tumour group level, cancers with diagnoses N<5 have been excluded

** Selected cancer sites are defined as having ICD 10 codes that are not breast, lower GI, lung, skin or urological. The cohort has been constructed to reflect available data published as part of national cancer statistics (where it is referred to as 'other')

Accepted Manuscript – EIGP-2020-1108

Table 5: Stage distributions of less common cancers diagnosed in the MDC

	Less common cancers (all)	Kidney (C64)	Non-Hodgkin's Lymphoma (C82-86 & C96)	Pancreas (C25)
Early stage (I/II)	31 (21%)	5 (29%)	4 (24%)	8 (23%)
Late stage (III/IV)	120 (79%)	12 (71%)	13 (76%)	27 (77%)
Unknown	65	8	15	8
Incomplete	2	-	-	-
Sub-total	151	17	17	35
Total	218	25	32	43

Accepted Manuscript – BJGP – BJGP.2020.1108