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How do general practitioners manage patients with cancer symptoms? A videovignette study

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BMJ Open How do general practitioners manage patients with cancer symptoms? A video-vignette study

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ABSTRACT

Objectives: Determine how general practitioners (GPs) manage patients with cancer symptoms.

Design: GPs reviewed 24 video-vignettes and case notes on patients with cancer symptoms and indicated whether they would refer the patient and/or prescribe medication, and/or undertake further investigation. According to available guidelines, all cases warranted a referral to a specialist or further investigations.

Setting: Australian primary care sector.

Participants: 102 practising GPs participated in this study, including trainees.

Interventions: The research was part of a larger randomised controlled trial testing a referral pro forma; however, this paper reports on management decisions made throughout the study.

Primary and secondary outcome measures: This paper reports on how the participants would manage the patients depicted in each vignette.

Results: In more than one-in-eight cases, the patient was not investigated or referred. Patient management varied significantly by cancer type (p<0.001). For two key reasons, colorectal cancer was the chosen referent category. First, it represents a prevalent type of cancer. Second, in this study, colorectal cancer symptoms were managed in a similar proportion of options—that is, prescription, referral or investigation. Compared with vignettes featuring colorectal cancer participants were less likely to manage breast, bladder, endometrial, and lung cancers with a 'prescription only' or 'referral only' option. They were less likely to manage prostate cancer with a 'prescription only', yet more likely to manage it with a 'referral with investigation'. With regard to pancreatic and cervical cancers, participants were more likely to manage these with a 'referral only' or a 'referral with investigation'.

Conclusions: Some patients may receive a delayed cancer diagnosis, even when they present with typical cancer symptoms to a GP who can access relevant diagnostic tests.

Trial registration number: ACTRN12611000760976.

INTRODUCTION

Australians who experience symptoms do not have direct access to specialists, but are required to consult a general practitioner

Strengths and limitations of this study

- Many Western nations position general practitioners (GPs) as the gatekeeper to specialist services, while enabling their access to diagnostic tests. This can be particularly helpful in cancer care.
- GPs were invited to review video-vignettes of patients with possible cancer symptoms and decide how they would manage these patients.
- There was limited evidence that appropriate tests would be ordered, and a significant proportion of high-risk cases were not immediately referred for further investigation or specialist opinion.
- The study design did not examine the reasons for the GP decisions.
- Some patients may receive a delayed cancer diagnosis, even when they present with typical cancer symptoms to a GP who can access relevant diagnostic tests.

(GP) or attend an emergency department.¹ Akin to other health systems,² the Australian health system positions GPs as the gatekeeper to specialist services.³

In Australia, GPs can refer for a range of tests including ultrasounds and CT scans and, with specific indications, some MRI. In some Australian jurisdictions, GPs can also directly refer for gastroscopy and colonoscopy. This represents a greater range of tests relative to other health systems, like in the UK.⁴

GP access to diagnostic tests is particularly helpful in cancer care.⁵ It can optimise the timely receipt of appropriate treatment and as such reduce, if not avert, the personal, social and economic costs of cancer.^{6–8} Given the complexity of health systems, it can be difficult (if not impossible) to isolate definitive causal relationships between GP diagnostic tests and cancer outcomes.⁹ ¹⁰ However, GP access to diagnostic tests is likely to help identify those patients who require urgent care.¹¹





As part of a larger pre-post, randomised control trial of an interactive online referral pro forma, ¹² the review of data reported here focused on how Australian GPs manage patients with cancer symptoms. The intervention tested in the original trial did not aim to guide GP referral, investigation or prescribing practices—as such, its focus is not germane to the focus of this review, which encompasses data from both phases. ¹²

METHODS

Following clearance from the relevant ethics committee, the research team recruited GPs in seven Australian states and territories to participate in this study via email, newsletters and personal contact. Recruitment was facilitated by primary care networks, university departments, research networks and personal contacts. GPs were eligible to participate if they were currently in practice, including registrars (or vocational trainees), and had internet access. As such, the exact number of GPs who were aware of the project cannot be ascertained.

Participants were invited to consider the symptoms of patients presented as video-vignettes and to determine how they would manage the patient. This was conducted in two phases—before the participants were provided with an interactive referral pro forma, and afterwards. The pro forma aimed to improve the quantity and quality of patient information communicated between primary and secondary care clinicians. The focus of this paper, however, is to determine how GPs respond to patients with different cancer symptoms, regardless of whether this was before or after using the pro forma.

Guided by the 2005 referral guidelines for suspected cancer of the National Institute for Health and Clinical Excellence (NICE),¹³ 24 video-vignettes were developed by six GPs, four videos for each of six cancer types (table 1). These guidelines were selected as they indicate the need for specialist referral based on specific highrisk presentations; furthermore, at the time of the study, no equivalent Australia-wide guidelines were available for all cancer types. The video-vignettes comprised a 4 min video monologue delivered by an actor–patient accompanied by case notes containing the patient's medical history, current medication, allergies and previous consultations. The video included an off-camera commentary by an actor–doctor describing clinical signs to be found at this visit.

After accessing a secured research website, participants: provided demographic information; received the

Cancer type	Case details
Bladder	76-year-old woman with asymptomatic frank haematuria
Breast	35-year-old with asymptomatic, firm breast lump and skin dimpling
Breast	69-year-old with skin changes consistent with Paget's disease of the breast
Cervical	34-year-old with CIN 2
Colorectal Endometrial	60-year-old with unexplained iron deficiency anaemia, abdominal pain and right iliac fossa abdominal mass 65-year-old with PMB
Lung	58-year-old lifelong smoker with haemoptysis, breathlessness and weight loss
Oesophageal	66-year-old with 10 kg weight loss and dysphagia for solids
Pancreatic	57-year-old with 5 kg weight loss, jaundice, generalised pruritus and pancreatic mass on abdominal ultrasound scan
Prostate	55-year-old with a PSA of 22, urinary frequency, haematuria, hesitancy and terminal dribbling
Lung	49-year-old smoker with cervical lymphadenopathy, haemoptysis and a 2 cm mass on chest X-ray
Colorectal	65-year-old with rectal bleeding, diarrhoea, fatigue and rectal mass
Bladder	65-year-old man with frank asymptomatic haematuria
Breast	38-year-old with a 3-month history of breast lump, dimpling of skin and axillary lymphadenopathy
Breast	71-year-old with a breast lump and peau d'orange
Cervical	36-year-old with CIN 2 and postcoital bleeding
Colorectal	62-year-old man with a 2-month history of constipation, abdominal pain, hepatomegaly and iron deficiency anaemia
Endometrial	62-year-old with several episodes of PMB
Lung	60-year-old woman with cough, dyspnoea, weight loss, hoarseness, pleural effusion and clubbing
Lung	61-year-old man with cough, suspicious lesion on chest X-ray and haemoptysis
Oesophageal	69-year-old man with dysphagia for solids, weight loss, dyspepsia and fatigue
Pancreatic	60-year-old man with abdominal pain, chronic pancreatitis, weight loss, jaundice and pancreatic mass on abdominal ultrasound scan
Prostate	70-year-old abnormal digital rectal examination findings, PSA of 25, chronic retention, prostatism and low back pain
Colorectal	63-year-old woman with altered bowel habits, iron deficiency anaemia, abdominal pain, weight loss and rectal bleeding

case notes of each patient; viewed the video-vignette of the consultation once and received examination findings. Participants then chose to: (1) prescribe medication; (2) order diagnostic tests and/or (3) refer the patient to a specialist. Participants documented the prescription, the test, and/or the referral as they would when consulting a *bona fide* patient. Each participant viewed and managed 24 video-vignettes.

Participants were recompensed for their participation and could claim continuing medical education points. Progress through the video-vignettes could be tracked online and reminders were issued to those who had not completed the study after 2 weeks of inactivity.

Statistical analysis

Descriptive statistics (number and percentage) were used to report participants' management of each scenario, preintervention and postintervention. A multinominal logistic model was used to assess the influence of demographic information and specialty on the ways the participants chose to manage the patient, with particular reference to: 'prescription only', 'investigation(s) only', 'referral only' and 'referral with investigation(s)'. 'Investigation only' was selected as the base outcome, and the relative risk ratio of 'prescription only', 'referral only' and 'referral and investigation' are reported. User-defined parsimonious models were constructed in a backward elimination fashion from the full model. The full model included: (1) participants' demographic data—notably age, gender, country of graduation, number of years since graduation, years of GP experience, Fellowship of the Royal Australian college of General Practitioners (FRACGP), clinic remoteness (4 categories: major cities, inner regional, outer regional and remote/very remote), role within their primary practice, patients consulted per week (3 categories: <100, 100-149, ≥150), direct patient care hours per week (4 categories: <11, 11-20, 21-40, ≥ 41), non-English consultation (no and yes), number of GPs within their primary practice, and number of patient sessions per week and (2) cancer type. Only variables with p<0.05 were retained in the final model. The categories of some variables were regrouped as noted, before they were entered into the model, due to their small number. In the regression, preintervention and postintervention data were pooled according to cancer types. Given the lack of independence between participant responses, regression models were adjusted by estimating the cluster effect using the 'vce' option within Stata. p Values of <0.05 were considered statistically significant. Stata MP 13.1 (StataCorp, Texas, USA) was used to perform the analysis.

RESULTS

Between August 2011 and August 2012 (inclusive), 102 GPs were recruited. Participants were mainly from Western Australia (46%) and Victoria (25%), with a

mean age of 43 years (table 2). On average, the participants had 13 years of GP experience; however, 24% were trainees. Most participants primarily practised in a capital city or another metropolitan area.

Patient management varied by cancer case. Before the intervention, relatively few participants managed the patient with a 'prescription only' (range=1.0–10.8%, mean=2.8%, table 3). After the intervention, more chose to manage the patient with a 'prescription' (9.8–32.6%, mean=21.5%) or an 'investigation only' (range=25.0–71.7%, mean=43.5%). Of all the demographic data pertaining to the doctors, the only factor that appeared to influence their decisions was the geographical location of their practice (p<0.001 of the overall Wald test after regression).

Patient management also varied significantly by cancer type (p<0.001 of the overall Wald test, table 4). Colorectal cancer symptoms were managed almost equally across the choice of options with a similar proportion managed with each of the three options. Compared to the management of colorectal cancer symptoms, participants were less likely to manage breast, bladder, endometrial and lung cancer symptoms with a 'prescription' or 'referral only'. They were less likely to manage prostate cancer with a 'prescription only', yet more likely to manage it with a 'referral with investigation'. With regard to pancreatic and cervical cancers, participants were more likely to manage these with a 'referral only' or a 'referral with investigation', relative to the management of colorectal cancer. Compared with those who practised in a major city, participants who practised in a remote or very remote practice were significantly less likely to opt for a 'prescription' or a 'referral only', yet more likely to manage the patient with an 'investigation only' (see table 4). The investigations and treatment options suggested are presented in table 5.

DISCUSSION Findings

According to the 2005 NICE guidelines, all cases in this study warranted a specialist review within 2 weeks. ¹³ The research results suggest that in more than one-in-eight cases, the patient was not investigated or referred, despite symptoms that were highly suggestive of cancer. In some cases, the indication for the drugs prescribed as per table 5 was unclear and in the case of endometrial cancer, the prescription of oestrogen replacement therapy may have actually advanced cancer progression. ¹⁸

Compared to cases presenting with colorectal symptoms, participants were more likely to refer a patient presenting with symptoms of pancreatic, prostate or cervical cancer, with or without further investigation. These cases included relatively more objective signs of pathology sourced from a laboratory and/or radiological report. This suggests that, despite the UK guidelines,



	Participants	National	
	Mean	SD	compariso
Age, years	43	11.8	50.5*
Years after graduation	19	11.3	
Years as GP	13	11.1	
GPs in primary practice	8	4.1	
GP sessions/week	6	3.0	
	N°	%	
Male	58	56.9	60.9%† ¹⁷
Graduated in Australia	73	71.6	65.9%†
GP registrar	24	23.5	3.8%‡
FRACGP	58	56.9	56.8¶
Accredited practice	101	99.0	88.6¶
Position			
Principal	21	20.6	
Non-principal	63	61.8	
Other	18	17.6	
State			
New South Wales	13	12.7	33.1%‡
Queensland	7	6.8	19.5%‡
Victoria	25	24.5	25.1%‡
South Australia	7	6.9	8.4%‡
Tasmania	1	1.0	2.6%‡
Western Australia	47	46.1	9.1%‡
Australian Capital Territory	2	2.0	1.5%‡
Region of primary practice			·
Capital city	49	48.0	66.3%¶
Other metropolitan area	38	37.3	7.6%¶
Large rural area	5	4.9	6.7%¶
Small rural area	6	5.9	7.1%¶
Other rural area	3	2.9	10.6%¶
Remote centre	1	1.0	0.6%¶
Remoteness of the region	•	1.0	0.070
Major city	73	71.6	71.5%‡
Inner regional area	15	14.7	18.9%‡
Outer regional area	10	9.8	7.8%‡
Remote area	3	2.9	1.2%‡
Very remote area	1	1.0	0.6%‡
Patients consulted, per week	•	1.0	0.0704
<100	49	48.0	
100–149	30	29.4	
150–149	20	19.6	
>199	3	3.0	
Direct patient care, h/week		0.0	
<11	11	10.8	1.2%¶
11–20	21	20.6	12.2%¶
21–40	47	46.1	53%¶
41–60	20	19.6	53% 32.1%¶
>60	20 3		
	3	2.9	1.4%¶
Non-English patient consultations, %	0.4	90.0	70 G0/¶
0	84	82.3	72.6%¶
<25	17	16.7	21.7%¶
25–50 >50	0 1	0 1.0	2.9%¶ 2.8%¶

^{*}Sourced from Britt *et al*. ¹⁴ and the Australian Institute of Health and Welfare. ¹⁵ †Sourced from Britt *et al*. ¹⁴

[‡]Sourced from General Practice Education and Training Limited. 16 §Sourced from the Primary Health Care Research & Information Service. 17 ¶Compared to GPs involved in Britt *et al.* 14 FRACGP, Fellowship of the Royal Australian college of General Practitioners; GP, general practitioners.

Table 3 GP management decisions* **Prescription** Investigation(s) Referred with investigation(s) only only Referral only N° % N° Cancer % Preintervention (n=102) Bladder 1.0 58 56.9 16 15.7 27 26.5 1 **Breast** 3 2.9 71 69.6 15 14.7 13 12.7 53 52.0 22 **Breast** 11 10.8 16 15.7 21.6 Cervical 4 3.9 3 2.9 72 70.6 23 22.5 Colorectal 2 2.0 19 18.6 66 64.7 15 14.7 3 Endometrial 2.9 39 38.2 33 32.4 27 26.5 58 12 31 Lung 1 1.0 56.9 11.8 30.4 1 23 22.5 49 29 Oesophageal 1.0 48.0 28.4 2 2.0 55 34 33.3 **Pancreatic** 11 10.8 53.9 **Prostate** 1.0 13 12.7 65 63.7 23 22.5 Total 29 2.8 348 34.1 399 244 23.9 39.1 Postintervention (n=92) 38 12.0 Lung 25 27.2 41.3 18 19.6 11 35 20 30 Colorectal 38.0 21.7 32.6 7.6 7 Bladder 15 54 9 14 16.3 58.7 9.8 15.2 **Breast** 13 14.1 56 60.9 8 8.7 15 16.3 **Breast** 14 15.2 57 62.0 9 9.8 12 13.0 20 19 20 Cervical 21.7 33 35.9 20.7 21.7 37.0 Colorectal 21 22.8 34 21 22.8 16 17.4 Endometrial 15 16.3 46 50.0 12 13.0 19 20.7 66 12 9 9.8 71.7 5 13.0 Lung 5.4 Lung 18 19.6 42 45.7 15 16.3 17 18.5 Oesophageal 26 28.3 29 31.5 18 19.6 19 20.7 Pancreatic 30 32.6 23 25.0 29 31.5 10 10.9 Prostate 14 15.2 36 39.1 16 17.4 26 28.3 Colorectal 22 23.9 26 28.3 22 23.9 22 23.9 Total 21.5 560 43.5 231 17.9 220 17.1 277

Table 4 Factors associated with GP cancer management (n=2308)						
	rrr (95% CI)		rrr (95% CI)		rrr (95% CI)	
Prescription only vs Video investigation(s) only		Referral only vs investigation(s) only		Referral with investigation(s) vs investigation(s) only		
Cancer (colorectal, rrr=1)						
Breast	0.21	(0.14 to 0.32)***	0.14	(0.09 to 0.22)***	0.42	(0.28 to 0.65)***
Bladder	0.17	(0.10 to 0.30)***	0.16	(0.09 to 0.27)***	0.60	(0.37 to 0.95)*
Endometrial	0.26	(0.15 to 0.46)***	0.37	(0.23 to 0.60)***	0.88	(0.57 to 1.36)
Prostate	0.38	(0.20 to 0.73)**	1.18	(0.82 to 1.71)	1.65	(1.05 to 2.60)*
Pancreatic	1.17	(0.68 to 2.02)	1.78	(1.10 to 2.86)*	2.15	(1.30 to 3.56)**
Cervical	0.83	(0.51 to 1.36)	1.82	(1.30 to 2.54)***	1.98	(1.30 to 3.02)***
Lung	0.32	(0.21 to 0.46)***	0.17	(0.11 to 0.26)***	0.57	(0.39 to 0.83)**
Oesophageal	0.64	(0.42 to 0.99)*	0.92	(0.63 to 1.34)	1.52	(1.01 to 2.29)*
Clinic remoteness (major city, rrr=1)						
Inner regional	0.84	(0.44 to 1.62)	0.46	(0.29 to 0.73)***	0.82	(0.38 to 1.75)
Outer regional	0.57	(0.17 to 1.95)	1.13	(0.50 to 2.51)	1.15	(0.50 to 2.64)
Remote/very remote	0.05	(0.01 to 0.25)***	0.42	(0.26 to 0.67)***	0.41	(0.09 to 1.83)

Results are rrr for the participant groups whose management was 'prescription only', 'referral only' or 'referral with investigation' compared to those who selected 'investigations only' (rrr=1). Results were derived from one multinomial logistic regression with the adjustment of clustering effect due to assessment of different cancers made by the same participant.

*p<0.05; **p<0.01; ***p<0.001.

rrr, relative risk ratio.

*Percentages may not total 100% due to rounding.



Cancer type	Investigations	Prescriptions ordered	
Breast	Mammogram, fine-needle biopsy, full blood count, renal function test, liver function test, ultrasound scan	Antifungals, antibiotic tablets or creams, steroid creams, antihistamines	
Lung	CT scan/chest X-ray, ultrasound scan, fine-needle aspiration, bronchoscopy, spirometry, lung biopsy, full blood count, renal function test, liver function test, coagulation studies, ferritin, sputum microscopy and culture/cytology, Mantoux test	Steroid tablets, antibiotics, diuretics, codeine, steroid inhalers, β -agonist inhalers	
Prostate	Urine microscopy and culture, urine cytology, PSA, CT, ultrasound scan, full blood count, renal function, liver function test, X-ray	Opiates, paracetamol, non-steroidal anti-inflammatory tablets, α -blockers, 5α -reductase enzyme inhibitors	
Bladder	Urine microscopy and culture, urine cytology, PSA, CT, ultrasound scan, full blood count, renal function, liver function test, intravenous pyelogram	Nil	
Colorectal	Colonoscopy/gastroscopy, CT/ultrasound scan, stool culture and sensitivity, cytology, faecal occult blood test, full blood count, renal function test, liver function test, erythrocyte sedimentation rate, iron studies, lipase, calcium, magnesium, phosphate	Paracetamol, iron supplements, iron injections, laxatives, antispasmodics, vitamin C, opiates	
Pancreatic	Full blood count, renal function test, liver function test, blood glucose, coagulation profile, amylase, lipase, bilirubin, CT, ultrasound scan/bone scan	Paracetamol, codeine, opiates, cholestyramine, vitamin B ₁₂ , proton-pump inhibitors	
Oesophageal	Barium swallow/chest X-ray, CT/ultrasound scan, gastroscopy, full blood count, renal function test, liver function test, iron studies, coagulation studies, urea breath test/ <i>Helicobacter pylori</i> serology	Antiemetics, food supplements, proton-pump inhibitors	
Cervical	Vaginal swab MCS/Pap smear, human papilloma virus cytology, urine culture and sensitivity, chlamydia, gonorrhoea PCR, human immune deficiency virology, hepatitis B, hepatitis C, syphilis serology, VDRL, full blood count, renal function test, liver function test, ferritin, ultrasound scan/CT, colposcopy/endoscopy	Nil	
Endometrial	US pelvic/vaginal, full blood count, renal function test, liver function test, iron studies, coagulation studies, Pap smear/swab, urine culture and sensitivity, X-ray, CT, hysteroscopy	Oestrogen replacement vaginal pessaries	

these participants may have been reticent to refer patients without further investigation—this was particularly the case for breast, bladder, endometrial and lung cancers where the patient presented with signs and symptoms, without confirmatory laboratory tests. Notably, in the case of lung cancer, a suspicious lesion on a chest X-ray did not appear to warrant immediate referral in most cases.

The participants appeared to have different views on how to manage patients with cancer symptoms—and the reason for these opinions could not be gleaned (eg, X-ray for endometrial cancer). This might suggest that the participants collectively recognised both the advantages and disadvantages associated with further investigation. The former may include the efficient use of limited diagnostic and subsequent specialist services. This may be particularly advantageous for patients who do not reside in close proximity to specialist services. This was suggested by the study results, as participants who practised in rural and remote locations were more likely to request further investigation prior to referral; yet research suggests that cancer outcomes in these locations are worse than in metropolitan areas. 19 The disadvantages associated with locally conducted investigation

may include the financial cost to the patient, as well as delayed specialist advice and care. 20

Strengths and weaknesses of the study

A key strength of this study is consistency in both the cases reviewed by the participants and the way they reviewed the cases. Furthermore, participants were unaware of the case content before commencing the study. As such, participants did not simply include GPs with a particular interest in cancer care.

However, the study is limited in four key ways. First, it did not enable interaction between the participant and the patient, or the participant and the specialist. Such communication is likely to promote effective patient care. Second, data were not collected on review plans to better understand the participants' perspectives on the case. This may be particularly relevant for the option, 'investigation only', where a subsequent review may help to confirm a diagnosis and lead to referral. Third, since the participants differed from GPs who practise in Australia, the generalisability of the findings is limited. Similarly, the number of participants from very remote areas was limited to four. Finally, data were not collected on participants' reasons

for their selected patient management strategy. Despite these limitations, the results from this study reveal an important need to examine how patient outcomes are affected by the ways GPs respond to patients' cancer symptoms.

Comparison with other literature

Although the findings from this study may cause concern, the study is limited by the use of videovignettes, which prevented participants from interacting with the patient or their families. Such interactions may increase the prospect of referral.²¹ Research also suggests that a cancer diagnosis can be missed where there are: atypical presentations, non-specific presentations, very low prevalence rates, comorbidities and/or perceptual features.²² All cases in this study were typical and devoid of distracting features. Furthermore, participants were more inclined to manage the patient with investigations or a referral when using the interactive referral pro forma. As the pro forma required detailed patient information, participants may have been prompted to request additional evidence-like that of a pathology reportbefore referring the patient to a specialist. The risk in this case is of false negative investigation findings. Furthermore, a recent report on delayed cancer diagnoses noted a 'lack of reporting culture in primary care compared with acute hospitals... [As such] any analysis will show only a small proportion of incidents in primary care, and from general practice in particular'. ²³ This may explain the limited literature on potential delays to cancer diagnosis within primary care. The data presented here suggest a risk of delay. The review also concluded that some of the factors that contribute to practitioner delay included: symptom misattribution and/or no examination or investigation of malignancy. The data presented in this paper support these conclusions.

Implications for clinicians and policymakers

Results from this study suggest that some patients may receive a delayed cancer diagnosis, even when they present with typical cancer symptoms to a GP who can access relevant diagnostic tests. There was limited evidence that appropriate tests would be ordered, and a significant proportion of cases were not immediately referred for further investigation or specialist opinion. Therefore, better cancer outcomes may not be solely explained by GP access to investigations, but rather to other factors that were beyond the scope of this study. These may include expedient access to specialists via the private healthcare sector or different systems of care.

Future directions

Research is required to understand how GPs filter and use clinical information to determine the management of patients who present with cancer symptoms. Research is also required to identify efficient and

effective referral pathways for these patients as they traverse the health system and progress along the care continuum.

CONCLUSION

Patients may receive a delayed cancer diagnosis, even when they present with typical cancer symptoms to a GP who can access relevant diagnostic tests. Although this may be partly improved through improved access to diagnostic tests, there are likely to be additional elements that influence the ways in which potential cancer symptoms are identified and managed within the context of primary care.

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Contributors MJ conceived the study. VP undertook data collection. XM took primary responsibility for data analyses. CO led the write-up. PM and AD provided academic guidance. All authors contributed to the writing and preparation of this manuscript.

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