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A 61 year old man with a one month history of back pain visits his general practitioner (GP). He has hypertension, has never smoked, and reports fatigue for several months. The pain is keeping him awake at night. He has not lost weight. Clinical examination is normal. The differential diagnosis for this patient is wide, including potential malignant causes such as pancreatic, myeloma, and prostate cancer or metastatic disease.

Cancer can be difficult to identify from many of the common symptoms are non-specific and low risk, and even the most well known “alarm” symptoms have relatively low positive predictive values (PPVs) for underlying malignancy\(^1\); for example, weight loss has a PPV for underlying malignancy of only 0-3.3\(^2\); while rectal bleeding has a PPV of 2.2-15.8\(^2\). Cancer markers used in hospital settings, when applied to low risk primary care patients, have low positive predictive values and high false positive rates\(^4\). Identifying patients whose non-specific symptoms may be caused by cancer, rather than benign disease, is therefore a challenge for primary care physicians.

While formal diagnosis usually happens in secondary care, the first suspicion of cancer generally occurs in primary care. Patients whose symptoms represent an approximate risk of cancer of ≥3\% are recommended by the National Institute for Health and Care Excellence (NICE) for urgent investigation, often by referral.\(^3\) Those with estimated risk <3\% may receive an initial panel of primary care investigations, or triage testing, to stratify risk. Triage tests can provide clues to help identify patients for referral, and crucially can point towards the site of an underlying malignancy. This is particularly useful when the patient’s vague symptoms could be caused by several different cancer types, and can guide decision making on any need for further investigation.

This article discusses blood tests to detect or stratify risk for possible cancer in primary care and presents evidence for their use in symptomatic patients. First we consider tests that are not specific for any one type of cancer but which may help primary care providers stratify risk of malignancy. Then we discuss specific markers for certain types of cancer. Blood tests that might be used for screening asymptomatic patients, tests for less common malignancies (eg, gastrin, prolactin) or for monitoring patients with known malignancies, are beyond the scope of this article.

### What you need to know

| What | How |
|------|-----|
| **Triage** blood tests in primary care, such as haemoglobin, platelets, serum calcium level, liver function tests, and inflammatory markers such as C reactive protein and erythrocyte sedimentation rate may provide “clues” to cancer in patients with non-specific symptoms | Triage tests do not have the performance characteristics of rule-out tests |
| Evidence supports the use of only a small number of specific cancer markers, such as CA125 and PSA, in primary care | |

### Search strategy

In August 2019 we replicated the search strategy used by NICE in its most recent guidance, NG12, restricted to papers published after 2014 (2011 for ovary) as the NICE searches had been performed before that date. LM, SB, and WH worked in pairs to assess candidate abstracts for blood tests used in primary care, and extracted full texts for relevant hits, supplemented by a large personal library of existing references.

### What is the next investigation?

#### Non-specific blood tests or clues for cancer

Several non-specific tests, commonly used in primary care, can provide “clues” towards possible cancer. Tests with a PPV for cancer of >1\%, including haemoglobin, platelet count, serum calcium, liver function tests, and inflammatory markers such as C reactive protein (CRP) and erythrocyte sedimentation rate...
Results were significant for a slightly raised platelet count raised the possibility of underlying malignancy. The patient was aged 64, 89 years old, at presentation. He gave a history of night sweats, weight loss, and a feeling of tiredness, and his full blood count showed a haematological disorder. The overall blood count and differential were performed, and the results were normal, indicating that no primary malignancy was present. However, the presence of night sweats and weight loss suggested that the patient may have an underlying cancer-related illness. The patient was referred to a secondary care provider for further investigations.

Specific cancer markers

Despite the proliferation of cancer biomarker research in secondary care, there is a shortage of relevant primary care studies, with no new markers entering primary care usage since Sturgeon et al's review in 2009. The small number of cancer specific tests validated for diagnosis of cancer in primary care settings are summarised in the infographic (fig 1). These tests should be used in symptomatic patients, rather than as a non-specific cancer screen. Even well known cancer markers that are part of routine clinical practice, such as prostate specific antigen (PSA) and cancer antigen 125 (CA125), have a limited evidence base. In the case of PSA, because so many men who develop prostate cancer will be asymptomatic, the positive predictive value of a positive test does not necessarily mean that the test makes cancer less likely, though neither result is definitive; that is, if these test results are normal, cancer may still be present. None of these tests has sufficient sensitivity to act as a “rule out” test, with the possible exception of the combination of a normal plasma viscosity or ESR plus normal full blood count, which may be used as a simple rule out for myeloma.

In the context of low risk symptoms, negative tests provide some reassurance. However, if symptoms continue or change, further investigation may still be warranted. Ideally, the rationale for and implications of a negative or positive test result should be discussed before ordering these tests so as to allow for shared decision making with patients.

Outcome

The general practitioner was concerned by the presence of night sweats and weight loss, and the patient was referred to secondary care for further investigations. The patient was a man aged 64, 89 years old, at presentation. He gave a history of night sweats, weight loss, and a feeling of tiredness, and his full blood count showed a haematological disorder. The overall blood count and differential were performed, and the results were normal, indicating that no primary malignancy was present. However, the presence of night sweats and weight loss suggested that the patient may have an underlying cancer-related illness. The patient was referred to a secondary care provider for further investigations.

Future research

Many cancer biomarkers are being investigated, particularly for cancers considered “hard to diagnose,” such as pancreas and ovary, or for early detection of cancer recurrences. However, of the candidate cancer biomarkers, few are expected to be tested for in clinical practice. Future research to evaluate markers for a potential diagnostic role should aim to quantify the false-positive rates, clinician and patient acceptability, and health economic aspects in order to determine how these tests should best be used.

Contributors

LM performed the searches, LM, SB, and WH reviewed abstracts and extracted full texts. JW, WH, and SB wrote the first draft of the article with input from LM and SC. All authors contributed to the intellectual content, edited the manuscript and approved the final version for submission.

Competing interests

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Figure

Predictive values of diagnostic blood tests as non-specific cancer markers, based on primary care studies or reviews

**Fig 1** Primary care studies or review investigating the diagnostic role of blood tests as non-specific cancer markers: with positive predictive values (PPVs) ≥1% and <1%