Created by: Strategic Evidence, Cancer Research UK
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Scottish Referral Guidelines for Suspected Cancer Update – Evidence Review (Haematological)

The purpose of this document is to synthesise and critique evidence and insight related to referral guidelines for suspected haematological cancer. Key themes have been determined from the literature. For each key theme e.g. individual symptoms, the papers are summarised separately with some high-level synthesis to provide steer on how this may impact referral guidelines. At the end of the document, a table comparing NG12 and SRG guidelines can be found for reference.

This document includes evidence on the following topics:

- Individual symptoms
- Symptom combinations
- Investigation findings
- Safety netting
- Risk stratification
- Emerging topics

Background

Haematological cancers represent three main groups of cancers: leukaemia, lymphoma and multiple myeloma, and these are further divided into subtypes.

Stage at diagnosis, survival or route to diagnosis data for haematological cancers is not publicly available in Scotland. In England, for all haematological cancers combined, the highest proportion (33.5%) are diagnosed following a GP referral, with urgent referrals accounting for 20.6% of all referrals. Relatively high proportions (26.6%) are diagnosed via emergency presentation, with the majority of these being stage 4 diagnoses (where unknown stage is excluded). Survival for those diagnosed with haematological cancer via an emergency route is significantly worse compared to other routes[6,7], highlighting the importance of timely diagnosis via a managed route.

Staging of haematological cancers does not follow the typical tumour node metastasis (TNM) system that is used for most cancers. Leukaemia is staged according to the Binet and Rai systems; lymphoma is staged using the Lugano system; and multiple myeloma is staged according to the International Staging System.

A 2019 report by Bloodwise, based on England data, highlighted the impact of stage at diagnosis on survival for multiple myeloma and lymphoma[3]. The report found that for those diagnosed with multiple myeloma, 84% of those diagnosed at an early stage will survive their disease for 5-years or more, compared with 26% if diagnosed at a later stage. For Hodgkin's lymphoma, 94% will survive their disease for 5-years or more if diagnosed at an early stage, compared to 73% if diagnosed at a later stage. For the most common type of non-Hodgkin's lymphoma, 80% will survive their disease for 5-years or more if diagnosed at an early stage, compared to 40% at a later stage[1].

Earlier and timelier diagnosis is a key issue that is particularly pertinent for haematological cancers. Patients often experience delays along the pathway, which could be attributed to the fact that these cancers are associated with many different symptoms (within and between cancer types) that do not have a strong positive predictive value for cancer individually[1]. The broad symptom signature of these cancers can make it challenging for GPs to differentiate between those with a benign concern, or those who should be investigated for suspected haematological cancer. The National Cancer Patient Experience Survey (2022) found that people diagnosed with haematological cancers experienced the greatest percentage of multiple GP consultations (3+) prior to referral (38.4% of those with haematological cancer compared with 22.3% for all cancers combined)[2]. Those being investigated for multiple myeloma can experience long primary care and diagnostic intervals[4,] which have been associated with more advanced disease[5].

Search Strategy

Search terms: PubMed search for combinations of the following terms: blood, cancer, haematological, leukaemia, lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, symptomatic, presentation, primary care, PPV, risk, comorbidity, recognition and referral, lymphadenopathy, full blood count, FBC, diagnostic, pain, safety netting, family history, genetic predisposition, age, serum-free light chain, SFLC, Bence-Jones, electrophoresis.

Date: 2015 – present. In the table summaries, the only papers included from pre-2015 are those that are relevant for explaining differences in Scottish Referral Guidelines (SRG) and NICE NG12 guidelines. These have been gathered from NICE NG12 Evidence Review document.

Peer-reviewed literature

Note: grey rows in the table represent studies that have already been summarised earlier in the document.

[1] Note: this report did not provide definitions of 'early' or 'late' diagnosis

Topic: Individual Symptoms

Summary: Symptoms for these cancer sites tend to be non-specific, with low positive predictive values (PPVs) for single symptoms. The limited evidence available below still broadly support inclusion of these in the guidelines.

Lymphoma

- Papers 1 and 2 show that **lymphadenopathy** has the highest PPV as a single symptom for **lymphoma** (13% and 5.6% for non-Hodgkins lymphoma (NHL) and Hodgkin's lymphoma, respectively), which is included as a symptom in SRG guidelines. These papers also show that a **head and neck mass**, as well as **other masses**, had a higher PPV as a single symptom compared with other symptoms (2.3% for head and neck mass). This is **not currently in SRG guidelines** for **lymphoma**.
- SRG do not include **alcohol-induced lymph node pain** as a symptom for Hodgkin's lymphoma, however NG12 guidelines do. There is a lack of evidence post-2015 to suggest that alcohol-induced lymph node pain should be included as a symptom for Hodgkin's lymphoma, with no high-quality studies in the available literature reporting this as a symptom. The latest NICE evidence review did not include any studies that included this as a symptom.

Myeloma

- There is more available evidence for myeloma, compared to other haematological cancers.
- The non-specific nature of symptoms is particularly present in **multiple myeloma.** Across studies, **rib pain** and **back pain** were found to be frequent symptoms of multiple myeloma. These are not explicitly specified in SRG guidelines but may be encompassed by bone pain.
- Back pain is included in NG12 guidelines as an example of bone pain. The 2015 NICE NG12 evidence review did consider back pain as a symptom of multiple myeloma. This is based on a low number of studies that are not considered to be of high quality, based on the number of patients included.

Leukaemia

- For leukaemia, the available evidence suggests that SRG capture the most common symptoms, with **fatigue, bruising** and **lymphadenopathy** being frequently reported across studies. However, as single symptoms, paper 5 found low PPVs for these symptoms (<0.5%).

Paper number	Study	Cancer	Summary	Notes
1	Shephard, E. A., Neal, R. D., Rose, P. W., Walter, F. M., & Hamilton, W. T. (2015). Quantifying the risk of non-Hodgkin lymphoma in symptomatic primary care patients aged ≥40 years: a large case–control study using electronic records. *British Journal of General Practice*, *65*(634), e281–e288. https://doi.org/10.3399/BJGP15X684793	Non-Hodgkin's lymphoma (NHL)	This study aimed to identify the clinical features of **NHL** in primary care and quantify the risk associated with these features in symptomatic patients. PPVs were calculated for those aged ≥60. This age group was selected as it is near to the average age of NHL diagnosis. • **Lymphadenopathy** as a single symptom had a PPV of 13% • **Head and neck mass** as a single symptom had a PPV of 2.3% • **Two mass codes** (masses recorded anywhere in the body, excluding head and neck and lymphadenopathy, but there was some overlap between categories) at least 42 days apart had a PPV of 6.4% • Every other individual symptom had a PPV of less than 0.8%	Matched case–control study. Clinical Practice Research Datalink (CPRD) data from over 600 UK practices between 2000-2009. Patients: n= 23830 Cases: n= 4362 Controls: n=19468 **Limitation**: relies on accurate data recording. GPs can also record information in free text which wouldn't be captured.
2	Shephard, E. A., Neal, R. D., Rose, P. W., Walter, F. M., & Hamilton, W. T. (2015a). Quantifying the risk of Hodgkin lymphoma in symptomatic primary care patients aged ≥40 years: a case-control study using electronic records. *The British Journal of General Practice*:	Hodgkin's lymphoma	This study aimed to establish the symptom profile of **Hodgkin's lymphoma** and quantify the risk associated with symptoms in primary care in patients aged ≥40 years. PPVs were calculated for those ≥60 as this is near to the average age of diagnosis. PPV for those aged ≥60 were: • **Lymphadenopathy** PPV 5.6%	Matched case–control study. CRPD data from over 600 UK practices between 2000-2009. Patients: n= 1520 Cases: n= 283 Controls: n=1237

	The Journal of the Royal College of General Practitioners, *65*(634), e289–e294. https://doi.org/10.3399/BJGP15X684805		• **Head and neck mass** PPV 2.3% • **Other mass** PPV 0.03%	**Limitation**: relies on accurate data recording. GPs can also record information in free text which wouldn't be captured.
3	Shephard, E. A., Neal, R. D., Rose, P., Walter, F. M., Litt, E. J., & Hamilton, W. T. (2015). Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case-control study using electronic records. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *65*(631), e106–e113. https://doi.org/10.3399/BJGP15X683545	Multiple myeloma	This study aimed to identify and quantify the risk of **multiple myeloma** from specific clinical features reported by primary care patients. PPVs were calculated for those ≥60 as this is near to the average age of diagnosis. • Individual symptoms had low PPVs • **Rib pain** and **weight loss** as single symptoms had the highest PPVs at 0.2% • The rest were all ≤0.1% for single symptoms • Some symptoms (**back pain, rib pain, chest infections, chest pain** and **nosebleed**) became more common in patients with multiple myeloma compared with controls at approximately 2 years before diagnosis • Symptoms suggesting advanced disease (**fractures**, **weight loss**, **nausea**) are more common up to 1 year before diagnosis (especially within last 3 months)	Matched case–control study. CRPD data from over 600 UK practices between 2000-2009. Patients: n=14860 Cases: n=2703 Controls: n=12157 **Limitation**: relies on accurate data recording. GPs can also record information in free text which wouldn't be captured.
4	Seesaghur, A., Petruski-Ivleva, N., Banks, V. L., Wang, J. R., Abbasi, A., Neasham, D., &	Multiple myeloma	The aim of this study was to characterise the frequency and timing of clinical features in the primary care setting prior to multiple myeloma	Population based cohort study of 2646 newly diagnosed multiple

	Ramasamy, K. (2021). Clinical features and diagnosis of multiple myeloma: a population-based cohort study in primary care. *BMJ Open*, *11*(10). https://doi.org/10.1136/BMJOPEN-2021-052759		diagnosis. The study looked at a minimum 2-year baseline period prior to the multiple myeloma diagnosis date. • 49.1% of patients presented symptomatically with either bone pain and/or skeletal-related events during baseline (this occurred approximately 7 months prior to multiple myeloma diagnosis) • 47.5% had a baseline **bone pain** record, mainly affecting the **back** (33.7%) or **other joints** (17.3%) • Of symptomatic patients, 71% presented with **back pain** • Diagnostic intervals ranged from 6 months to over 12 months, with abnormal lab results for **CRAB** (hyperCalcaemia, Renal impairment, Anaemia, Bone lesions) criteria observed closer to diagnosis time (median 1-2 months). • Only 4.8% had a record of skeletal-related events	myeloma patients using the UK CRPD gold database between 2006 and 2016. **Limitation**: only looked at bone pain 2 years prior to diagnosis – patients may have had bone pain prior to start of baseline assessment period. The study also did not focus on other relevant tests such as protein electrophoresis or a Bence-Jones test, which may also be completed to assess for multiple myeloma.
5	Shephard, E. A., Hamilton, W., Neal, R. D., Rose, P. W., & Walter, F. M. (2016). Symptoms of adult chronic and acute leukaemia before diagnosis: large primary care case-control studies using electronic records. *The*	Leukaemia	This study aimed to identify the symptom profiles of chronic and acute leukaemia in adults in primary care. PPVs were calculated for those ≥60 as this is near to the average age of diagnosis.	Matched case–control study Clinical Practice Research Datalink (CPRD) data from over 600 UK practices between 2000-2009 Patients: n=20839

	British Journal of General Practice, *66*(644), e182. https://doi.org/10.3399/BJGP16X683989		• For chronic leukaemia, highest PPV was 0.35 for **lymphadenopathy** • **Weight loss, bruising** and **fatigue** all had PPVs of <0.01% • For acute leukaemia, all single symptoms had PPVs of <0.01	Cases: n=2877 CL, n=937 AL Controls: n=17025 **Limitation**: relies on accurate data recording. GPs can also record information in free text which wouldn't be captured.
6	Howell, D. A., Warburton, F., Ramirez, A. J., Roman, E., Smith, A. G., & Forbes, L. J. L. (2015). Risk factors and time to symptomatic presentation in leukaemia, lymphoma and myeloma. *British Journal of Cancer*, *113*(7), 1114. https://doi.org/10.1038/BJC.2015.311	All haematological	This study aimed to look at risk factors and time to symptomatic presentation in people diagnosed with leukaemia, lymphoma and multiple myeloma. • Of 785 patients, 654 reported at least one symptom • People diagnosed with NHL were most likely to report symptoms (95%) • Across all diagnoses, systemic symptoms were most common (particularly **extreme fatigue, tiredness, sweating at night, unexpected weight loss** and **pallor**) followed by **pain, chest problems, lymphadenopathy** and **bleeding** • **Extreme tiredness/fatigue** was commonly reported among patients with acute leukaemia (70.9%) and chronic myeloid leukaemia (61.2%)	Patients included are a subset of those participating in the 2010 National Cancer Patient Experience Survey (n=785 patients with haematological cancers). Results are for England only. **Limitations**: Symptom categories were haematology specific, limiting the reporting of other less typical symptoms, , particularly for the different types of lymphomas, where symptoms vary

			• **Night sweats** was most common in patients with chronic myeloid leukaemia (39.6%) and chronic lymphocytic leukaemia (35.2%) • **Pallor** and **bruising/bleeding** was most commonly reported by people diagnosed with an acute leukaemia • **Abnormal lumps** were the most common symptom reported in chronic lymphocytic leukaemia and NHL, along with **abdominal discomfort** • **Bone pain/discomfort** was the most frequently reported symptom of multiple myeloma	according to disease sites.
7	Zakkak, N., Barclay, M. E., Swann, R., McPhail, S., Rubin, G., Abel, G. A., & Lyratzopoulos, G. (2023). The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. *British Journal of Cancer 2023 130:2*, *130*(2), 297–307. https://doi.org/10.1038/s41416-023-02507-4	All haematological	This paper aimed to examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and to examine the relative frequency of cancer sites by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. • For **all haematological cancers**, of those that had recorded symptoms, the highest proportion of symptom group was **non-specific symptoms** (occurring in 29% of patients) • For **acute leukaemia**, of those that had a specified symptom, the symptom experienced by the highest proportion of patients was **fatigue** (25.9%)	Data from the National Cancer Diagnosis Audit 2018 were analysed. Among 55,122 patients included in the analysis, 54%) were men and 39% were 60–74 years old. For 11,066 (20%) patients, no presenting symptom was recorded. Data are from England only. **Limitations**: This was a case-only analysis (only patients with diagnosis of cancer

			• For **chronic lymphocytic leukaemia** this was also **fatigue** (7.75%) • For **Hodgkin's lymphoma** this was neck lump/mass (28.4%) • For **non-Hodgkin's lymphoma,** the most frequent symptom was **weight loss** (8.71%) • The most frequent symptom for patients with **multiple myeloma** was **back pain** (22.8%)	were included) – for example, no inferences can be made about the predictive value of certain symptoms for specific cancers.

Topic: Symptom Combinations
Summary: Symptom combinations in haematological cancers have a higher PPV compared to individual symptoms, and PPVs are even higher when combined with abnormal blood test results. **Non-Hodgkin Lymphoma** • When combined with abnormal blood/urine results, the PPV of some symptoms increased substantially. For example, for NHL, head and neck mass had a PPV of 2.3% as a single symptom, which increased to >5% when combined with abnormal blood tests such as raised liver function tests, low full blood count or raised inflammatory markers. **Myeloma** • Multiple myeloma has a wide symptom signature. Paper 7 reports that back pain is the most common presenting symptom of multiple myeloma, which was only present in 25% of patients. • No symptom combinations are currently included in SRG for multiple myeloma. Evidence has demonstrated that despite symptom combinations increasing PPVs, no symptom combination exceeded a PPV of >1.5%. However, when symptoms were combined with abnormal blood tests (especially hypercalcemia), PPVs were higher. For example, back pain (second episode) combined with hypercalcemia had a PPV of >10%. • **Back pain** and **rib pain** in combination were found to have a higher PPV than most other symptom combinations for **multiple myeloma**. Explicit reference to 'back' and 'rib' pain could be considered in the guidelines, as opposed to the umbrella term of bone pain.

Leukaemia

- Patients with **leukaemia** were also found to have a **higher mean number of presenting symptoms**.
- For leukaemia, all symptom combinations had a very low PPV for cancer.

Paper number	Study	Cancer	Summary	Notes
-	Shephard, E. A., Neal, R. D., Rose, P. W., Walter, F. M., & Hamilton, W. T. (2015). Quantifying the risk of non-Hodgkin lymphoma in symptomatic primary care patients aged ≥40 years: a large case–control study using electronic records. *British Journal of General Practice*, *65*(634), e281–e288. https://doi.org/10.3399/BJGP15X684793 This paper is also summarised above, see paper 1.	NHL	This study aimed to identify the clinical features of **NHL** in primary care and quantify the risk associated with these features in symptomatic patients. PPVs were calculated for those aged ≥60 (near to the average age of NHL diagnosis): • All three **mass** variables had a PPV of between 0.6% and >10% when combined with other symptoms • **Lymphadenopathy** had a PPV of 15% when combined with **leucocytosis** or **raised inflammatory markers**, and high PPVs in combination with other **abnormal blood results** • **Head and neck mass** also had high a PPV of >5% when combined with **abnormal blood results** • **Weight loss** only had a moderately high PPV when additional features were present such as **recurrent back pain** (PPV	See above.

			2.3%) or with **abnormalities in blood tests** (PPV up to 3.5%)	
-	Shephard, E. A., Neal, R. D., Rose, P. W., Walter, F. M., & Hamilton, W. T. (2015a). Quantifying the risk of Hodgkin lymphoma in symptomatic primary care patients aged ≥40 years: a case-control study using electronic records. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *65*(634), e289–e294. https://doi.org/10.3399/BJGP15X684805 This paper is also summarised above, see paper 2.	Hodgkin's lymphoma	This study aimed to establish the symptom profile of **Hodgkin's lymphoma** and quantify the risk associated with symptoms in primary care in patients aged ≥40 years. PPV combinations for those aged ≥60 were: • **Lymphadenopathy** combined with a **low full blood count** or **raised inflammatory markers** had a PPV of 2.5% and 2.2%, respectively	See above
-	Shephard, E. A., Neal, R. D., Rose, P., Walter, F. M., Litt, E. J., & Hamilton, W. T. (2015). Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case-control study using electronic records. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *65*(631), e106–e113. https://doi.org/10.3399/BJGP15X683545	Multiple myeloma	This study aimed to identify and quantify the risk of **multiple myeloma** from specific clinical features reported by primary care patients. PPVs for single symptoms in patients ≥60 years were reported: • Few combined symptoms had a PPV >1% • **Nosebleeds** and **backpain** had the highest combined PPV at 1.5% • **Backpain** and **rib pain** had a PPV of 1.1%	See above

	This paper is also summarised above, see paper 3.		• If **hypercalcaemia*** was present risks were considerably higher. For example, in combination with **back pain second episode, fracture, joint pain** and **rib pain** the PPV of hypercalcaemia was >10% • The presence of leucopenia also increased the PPV of some symptoms. For example, nosebleeds in combination with leucopenia had a PPV of >10% *Hypercalcaemia is usually detected by a serum calcium level test, which would likely be completed if a person presents with potential signs and symptoms of multiple myeloma in primary care. See *'Investigations'* section for more details.	
-	Shephard, E. A., Hamilton, W., Neal, R. D., Rose, P. W., & Walter, F. M. (2016). Symptoms of adult chronic and acute leukaemia before diagnosis: large primary care case-control studies using electronic records. *The British Journal of General Practice*, *66*(644), e182. https://doi.org/10.3399/BJGP16X683989	Leukaemia	This study aimed to identify the symptom profiles of **chronic and acute leukaemia** in adults in primary care. PPVs were calculated for those aged>60 years (average age of diagnosis). • For chronic leukaemia, **lymphadenopathy** with **cough** had the highest combined PPV of 0.27%	See above

	This paper is also summarised above, see paper 5.		• Many combinations were too rare to allow a PPV calculation • **Fever** with **infection** had the highest PPV at 0.13% for **acute leukaemia**	
-	Zakkak, N., Barclay, M. E., Swann, R., McPhail, S., Rubin, G., Abel, G. A., & Lyratzopoulos, G. (2023). The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. *British Journal of Cancer 2023 130:2*, *130*(2), 297–307. https://doi.org/10.1038/s41416-023-02507-4 This paper is also summarised above, see paper 7.	All haematological	This paper aimed to examine the relative frequency of presenting symptoms by cancer site (the 'symptom signature' of each cancer site), and to examine the relative frequency of cancer sites by presenting symptom (the 'cancer site case-mix' of each symptom), among incident cancer cases. Considering the 16 cancer site groups, a higher concentration of similar symptoms was observed among cancers relating to organs of the same body system or region. However, haematological cancers were found to be an exception to this and tended to present with more **diverse symptoms**. The most common presenting symptom of multiple myeloma was found to be back pain, and this was recorded in <25% patients. Chronic lymphoid leukaemia had high proportions of patients without any presenting symptoms (52%).	See above.

			Patients with leukaemia had, on average, a higher mean number of presenting symptoms (2 compared to the mean of 1.4). Observing a higher count of symptoms occurring in only >1% of cases indicates that a cancer site has a broader symptom signature. A total of 30 different symptoms was recorded in >1% of all patients with NHL (compared to 7 symptoms recorded in >1% of women with breast cancer).	

Topic: Investigation findings
Summary: For a GP to trigger diagnostic testing for haematological cancers, patients will have first presented with unexplained symptoms of haematological cancers that warrant further investigation, for example lymphadenopathy, fatigue, bruising or pallor. For multiple myeloma in particular, age is a factor likely to be taken into account when deciding which patients to send for further investigation, owing to the higher incidence in those >60 years old. Available evidence suggests that blood and urinary markers can be useful in the detection of potential haematological cancers in primary care. However, evidence investigating commonly used tests to aid recognition and referral of potential haematological cancers in a primary care setting has not been widely investigated. • National Cancer Diagnosis Audit (England, 2014) data found that 58% of those diagnosed with leukaemia underwent blood tests prior to diagnosis; 45% of those diagnosed with lymphoma and 61% of those diagnosed with multiple myeloma. In terms of imaging tests completed in primary care or ordered by primary care, 34% of those with an eventual diagnosis of lymphoma underwent imaging tests, compared to 27% of those with multiple myeloma and 8% of those with leukaemia.

- Both NG12 and SRG recommend the use of **full blood count** for symptoms suggestive of **leukaemia** and **multiple myeloma**.
- For **multiple myeloma**, **calcium** and **plasma viscosity** or **erythrocyte sedimentation rate** (ESR) are recommended in addition to full blood count in **NG12**. In those with hypercalcemia, leukopenia, abnormal plasma viscosity or ESR, more specific tests are recommended: NG12 recommend a **Bence-Jones protein urine test** and a **protein electrophoresis test**. This differs from SRG, which recommends **urine tests** and **serum electrophoresis** be performed if myeloma is suspected.
- Paper 8 demonstrates that **plasma viscosity** and **ESR** are useful in aiding investigation of potential **multiple myeloma** symptoms, which currently aren't included in SRG.

- Some evidence suggests urine **Bence-Jones protein tests** have been replaced by **serum free light chain** (SFLC) testing in clinical practice for investigating those with suspected multiple myeloma, due to the fact that SFLC assays are more sensitive and easier to conduct as they do not require 24-hour collection of urine[8].
- Paper 9 shows SFLC tests to be effective in diagnosing and monitoring oligosecretory myeloma.
- SRG recommend **serum electrophoresis** if **multiple myeloma** is suspected but do not emphasise the use of **SFLC** testing. This is recommended in NG35 (diagnosis and management guidelines) but not in NG12 (recognition and referral guidelines).

- Consideration is required to optimise the amount of tests requested and completed in primary care prior to referral, to reduce any unnecessary delays.
- Myeloma UK have produced a guideline for GPs[9], which notes GPs should request SFLC assay (or urine Bence-Jones test if SFLC is not available).

Paper number	Study	Cancer	Summary	Notes
8	Koshiaris, C., Van Den Bruel, A., Oke, J. L., Nicholson, B. D., Shephard, E., Braddick, M., & Hamilton, W. (2018). Early detection of multiple myeloma in primary care using blood tests: a case-control study in primary care. *The British*	Multiple myeloma	This study aimed to identify which blood tests may be useful in the detection of multiple myeloma in primary care. • Raised **plasma viscosity** had a likelihood ratio (LR)+ of 2 • **ESR** had LR+ of 1.9 • **C-reactive protein** (CRP) had a LR+ of 1.2	Matched case-control study in UK primary care using CRPD data. Symptom prevalence and blood tests were analysed up to 5 years before diagnosis in 2703

	Journal of General Practice : The Journal of the Royal College of General Practitioners, *68*(674), e586–e593. https://doi.org/10.3399/BJGP18X698357		• Normal **haemoglobin** had a LR- 0.42, **calcium** LR- 0.81 and **creatinine** LR- 0.8 • Test combination with the lowest LR- was all normal haemoglobin with calcium and plasma viscosity (LR- 0.06) (a negative likelihood ratio below 0.1 is considered to provide evidence to rule out diagnoses). • The authors suggest that based on this evidence, **plasma viscosity** and **ESR** are better for both **ruling in** and **ruling out** disease compared with CRP • Combination of **normal ESR** or **plasma viscosity** and **normal haemoglobin** is a simple **rule out** approach for patients being tested in primary care • Mean **calcium** and **creatinine** values rose rapidly in the last 3-6 months before diagnosis, whereas **ESR** and **plasma viscosity** values started to increase approximately **2 years** before diagnosis. • **Haemoglobin** values started to decrease approximately 3 years prior to diagnosis in multiple myeloma patients but not in controls. • **CRP** showed no difference between cases and controls.	cases and 12157 matched controls. **Limitation**: a potential limitation is missing data, as not all patients have been tested. This could lead to under or overestimation of sensitivity, specificity and LRs.
-	Seesaghur, A., Petruski-Ivleva, N., Banks, V. L., Wang, J. R.,	Multiple myeloma	The aim of this study was to characterise the frequency and timing of clinical features in the	See above.

	Abbasi, A., Neasham, D., & Ramasamy, K. (2021). Clinical features and diagnosis of multiple myeloma: a population-based cohort study in primary care. *BMJ Open*, *11*(10). https://doi.org/10.1136/BMJOPEN-2021-052759 This paper is also summarised above, see paper 4.		primary care setting prior to multiple myeloma diagnosis. The study looked at a minimum 2-year baseline period prior to the multiple myeloma diagnosis date. The International Myeloma Working Group recommends a series of investigations to evaluate patients with suspected multiple myeloma, to assess the CRAB (hypercalcemia, Renal impairment, Anaemia, Bone lesions) criteria. In the primary care setting, access to laboratory testing is readily available, and testing of these criteria can identify underlying causes of clinical features. During the 12 months prior to diagnosis, the proportion patients receiving CRAB-related diagnostic tests were: • 75.7% for renal impairment and anaemia • 50.4% for hypercalcaemia and renal impairment • 50.2% for hypercalcaemia and anaemia, • 48.9% for hypercalcaemia, renal impairment and anaemia • Only 18.9% underwent investigations for all CRAB criteria (26.7% symptomatic and 11.5% asymptomatic) Abnormal lab results for the CRAB criteria were observed closer to diagnosis time (median 1-2 months). Diagnostic tests to identify CRAB criteria were underused.	**Limitation**: Just focused on CRAB diagnostic criteria and did not investigate other relevant tests e.g. protein electrophoresis, Bence-Jones protein urine test, serum free light chain test or ESR

9	Heaney, J. L. J. *et al.* Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests. *Br J Haematol* **178**, 220–230 (2017).	Multiple myeloma	This study aimed to guide the integration of SFLC tests into clinical practice. The study demonstrated that SFLC tests were effective in diagnosing and monitoring oligosecretory myeloma. SFLC assessment might be of particular value when urine free-light chain levels are low and when urine samples are not received.	This study analysed blood and urine from 5573 newly diagnosed multiple myeloma patients.
10	Swann, R., McPhail, S., Shand, B., Rashbass, J., Witt, J., Abel, G. A., Hiom, S., Lyratzopoulos, G., & Rubin, G. (2018). Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *68*(666), e63–e72. https://doi.org/10.3399/BJGP17X694169	All haematological	This paper aimed to describe key aspects of the diagnostic process for cancer in primary care. For those with an eventual cancer diagnosis, the % of people that had blood tests in primary care prior to diagnosis was as follows: • 58.5% leukaemia • 45% lymphoma • 61.4% multiple myeloma The % of those that had imaging tests in/ordered by primary care prior to diagnosis was as follows: • 7.9% leukaemia • 34.3% lymphoma • 27.3% multiple myeloma	This paper comprised a clinical audit of cancer diagnosis in general practices in England. Data were collected on 17042 patients with a new diagnosis during 2014 from 439 practices. **Limitation:** Participating centres may differ from non-participating practices in terms of the diagnostic process so the

				findings may not be nationally representative.

Topic: Safety Netting				
Summary: There is some evidence that demonstrates an increased risk of cancer diagnosis within 3 months after presentation to primary care with fatigue, which could inform safety netting processes. Out of the cancers studied, leukaemia had the greatest relative increase in risk following presentation of fatigue. Abnormal test results could provide earlier opportunities to recognise and refer suspected haematological cancers. Previous research has suggested that declining haemoglobin levels could be detected 3 years prior to diagnosis of **haematological cancers**[10], and paper 12 suggests that **changes in inflammatory markers** can be detected in the year preceding a **Hodgkin's lymphoma** diagnosis. These findings also have implications for safety netting.				
Paper number	**Study**	**Cancer**	**Summary**	**Notes**
11	White, B., Rafiq, M., Gonzalez-Izquierdo, A., Hamilton, W., Price, S., & Lyratzopoulos, G. (2022). Risk of cancer following primary care presentation with fatigue: a population-based cohort study of a quarter of a million patients. *British Journal of Cancer*, *126*(11), 1627. https://doi.org/10.1038/S41416-022-01733-6	Leukaemia (and other cancers)	This paper aimed to examine cancer risk in patients presenting to primary care with new-onset fatigue, compared to general population estimates. • 47% of cancers were diagnosed within 3 months of the first presentation of fatigue • Site-specific cancer risk was higher in people presenting with fatigue than for the general population for most cancers studied, with	This paper used electronic health records from the CRPD GOLD to look at 250,606 patients in England during 2006-2015. **Limitation:** Some instances of fatigue may not be recorded by the GP due to variation in coding practices and this

			leukaemia having the greatest relative increase –3 to 4-fold greater than expected for men and 2-4-fold greater for women. Follow-up began with the patient's first eligible record of fatigue during the study period and ended either at 1 year following the record or at first cancer diagnosis, whichever was earlier • Excess cancer risk wanes rapidly after 3 months following fatigue presentation, which could inform duration of safety netting periods	paper only focuses on patients with fatigue who have sought medical help.
12	Rafiq, M., Abel, G., Renzi, C., & Lyratzopoulos, G. (2022a). Inflammatory marker testing in primary care in the year before Hodgkin lymphoma diagnosis: a UK population-based case-control study in patients aged ≤50 years. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *72*(721), E546–E555. https://doi.org/10.3399/BJGP.2021.0617	Hodgkin's lymphoma	This study aimed to examine pre-diagnostic inflammatory marker test use to identify changes that may define a potential window for earlier diagnosis. • Six common markers were selected: ESR, CRP, plasma viscosity, platelet count, ferritin concentration and albumin • 70.8% patients had an inflammatory marker test in	Matched case-control study in UK primary care using CPRD data between 2002-2016. inflammatory marker test use and findings were analysed in 839 Hodgkin's lymphoma patients and 5035 controls in the year pre-diagnoses.

			the year pre-diagnosis compared to 16.2% of controls Two-thirds of these patients had an abnormal test result and among these, 42.6% had no other red flag presenting symptom	**Limitations**: blood tests may have been requested by GP but not completed, or may not have been coded. Similarly, 'red flag' symptoms may not have been coded.

Topic: Risk Stratification

Summary: Risk factors for haematological cancers include age, family history, genetics and certain infections, but these factors have not been extensively studied. Cancer Research UK publishes information on the risk of multiple myeloma, acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, non-Hodgkin's lymphoma and Hodgkin's lymphoma.

There are slight differences in how symptoms are stratified between SRG and NG12 guidelines. For example, for multiple myeloma, guidelines suggest offering tests in those aged **>60** years with certain symptoms, whereas SRG do not specify an age range. This may be due to the age at which the majority of people are diagnosed with multiple myeloma, however there is no specific reference in NG12 evidence documentation to support this.

Monoclonal gammopathy of uncertain significance (MGUS) is a precursor condition for **multiple myeloma** and the risk increases with age. Approximately 3% of those aged >50 have MGUS. This risk increases to 5% in those >70 years old and 10% in those >85 years old[11]. Patients with MGUS have a 1% risk of developing multiple myeloma in the first year post-diagnosis, which increases by ~1% in each year following. The risk is higher in certain groups. MGUS is usually diagnosed via routine blood tests or found incidentally. Serum markers are currently used to stratify MGUS patients into clinical risk groups: these markers stratify according to **paraprotein size, paraprotein type** and **serum free light chain ratio**. There is currently no standardised national guidelines for how to follow up MGUS patients and it varies locally among secondary care services. There is evidence to suggest that risk of MGUS progressing to multiple myeloma can change over time, and paper 15 suggests this should inform annual blood tests to assess risk.

Paper number	Study	Cancer	Summary	Notes

14	Landgren, O. *et al.* Association of Immune Marker Changes With Progression of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma. *JAMA Oncol* **5**, 1293–1301 (2019).	Multiple myeloma	This is the first prospective study to longitudinally investigate the dynamics of serum immune markers in individuals with MGUS. This study suggests a person's risk of progressing from MGUS to multiple myeloma can change over time. Low-risk or intermediate-risk MGUS can convert to high-risk MGUS and progress to multiple myeloma within 5 years, with the same conversion patterns for light-chain MGUS. Risk factors associated with progressive MGUS were IgA isotype, 15g/L or more monoclonal spike, skewed serum free light chains radio, and severe immunoparesis. Risk factors associated with progressive light-chain MGUS were skewed serum free light chains radio and severe immunoparesis. The authors suggest that these findings support annual blood testing and risk assessment for patients with MGUS or light-chain MGUS, as well as yearly assessment of a patient's clinical risk status, rather than assessing risk at one time point at initial diagnosis, as is done currently.	Prospective cross-sectional cohort study, including 77469 adult aged 55-74 in the screening arm of the National Cancer Institute Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial who had a diagnosis of progressing MGUS (n=187) or stable MGUS (n=498). **Limitation**: this study is based in US, so may not be representative of UK health setting.

Emerging Topics

Risk prediction tools: There is limited evidence on the use of risk prediction tools in primary care for haematological cancers. One recent study[12] aimed to generate a clinical prediction rule to identify primary care patients who are at highest risk of multiple myeloma. Independent predictors of multiple myeloma included: older age; male; back, chest and rib pain; nosebleeds; low haemoglobin, platelets and white cell count; and raised mean corpuscular volume, calcium and ESR. A model including symptoms and FBC demonstrated an AUC of 0.84 and sensitivity of 62%. A second model included calcium and inflammatory markers as well, which demonstrated an AUC of 0.87 and a sensitivity of 72%. Both models discriminated well between people with and without multiple myeloma, but the FBC model was better calibrated than the all-test model. Implementation of these prediction rules could provide opportunities for earlier detection of multiple myeloma.

Prescription patterns: Research analysing prescription patterns prior to cancer diagnosis with the aim of identifying potential windows for earlier detection has increased. Evidence is limited for haematological cancers but one UK-based study[13] analysed steroid prescribing in 1232 Hodgkin's lymphoma patients and 7329 matched controls using primary care electronic health records (CRPD) between 1987 and 2016. This study aimed to examine steroid prescribing patterns pre-diagnosis to understand timing of associations and when healthcare use increases before cancer diagnosis. 46% of Hodgkin lymphoma patients had a steroid prescription in the 24 months preceding diagnosis, compared to 26% of controls. Among Hodgkin's lymphoma patients, steroid prescribing rates increased progressively from 7 months pre-diagnosis. This suggests steroid-treated symptoms may be an early presenting feature.

Obesity: According to a new US study published in *Blood Advances*, obesity could be associated with an increased risk of developing MGUS. The research found that being obese was associated with a 73% increase in the likelihood of developing MGUS compared with individuals from healthy BMI weight ranges[14].

Genetic predisposition: There is a growing body of evidence to suggest that variants in certain genes (for example DDX41, ETV6, CEBPA, RUNX1, ANKRD26 and GATA2) are associated with a significantly increased risk of haematological malignancy[15].

Other Insights

Working groups: The International Myeloma Working Group recommends a laboratory and imaging investigations to evaluate patients with suspected multiple myeloma, namely diagnostic imaging and blood tests to assess the CRAB, diagnostic criteria, which aligns with

SRG for multiple myeloma.
The working group have also produced recommendations developed by a panel of experts on multiple myeloma (based on evidence of published data through August 2017) and recommended initial work-up should include:

- Complete blood count
- Kidney function tests
- Serum protein electrophoresis with immunofixation
- Serum albumin
- B2 microglobulin
- Lactate dehydrogenase
- C-reactive protein
- Calcium
- Serum-free light chains
- 24 h protein collection
- Bone marrow studies

The guidelines do not specify whether these should be carried out in primary or secondary care.

Created by: Strategic Evidence, Cancer Research UK
Date created: April 2024

Comparison of Scottish Referral Guidelines and NG12 Guidelines for suspected haematological cancers

Cancer site	SRG	NG12

All cancers combined	**SRG guidelines do not differentiate between the different haematological cancers as NICE guidelines do. This box contains the general referral guidelines for all haematological cancers, and below are site-specific guidelines.**
	
	All people presenting with symptoms or signs suggesting haematological cancer should be referred to a team specialising in the management of haematological cancer, depending on local arrangement.
	
	Urgent suspicion of cancer referral
	
	• Blood count / film reported as suggestive of acute leukaemia or chronic myeloid leukaemia*
	• Lymphadenopathy (>2cm) persisting for six weeks or increasing in size or generalised (HIV status should always be checked if generalised)
	• Hepatosplenomegaly in the absence of known liver disease
	• Bone pain associated with a paraprotein and/or anaemia
	• Bone X-rays reported as being suggestive of myeloma
	• The following clinical features may also merit urgent referral:
	  ○ fatigue
	  ○ night sweats
	  ○ weight loss	

	○ itching ○ bruising ○ recurrent infections ○ bone pain ○ polyuria and polydipsia (hypercalcaemia) *will normally be identified in the laboratory and communicated to the clinician for management to be agreed.	
Leukaemia	Symptoms: Fatigue, pallor, bruising, bleeding and infections Some leukaemia's may present with lymphadenopathy and/or hepatosplenomegaly	Very urgent FBC (within 48 hours) to assess leukaemia in adults with any of the following: • pallor • persistent fatigue • unexplained fever • unexplained persistent or recurrent infection • generalised lymphadenopathy • unexplained bruising • unexplained bleeding • unexplained petechiae
Myeloma	Symptoms: bone pain, symptoms of anaemia, renal impairment and symptoms of hypercalcaemia such as polyuria and polydipsia If myeloma is suspected, urine as well as serum electrophoresis should be performed.	Offer FBC and blood tests for calcium and plasma viscosity or ESR to assess for myeloma in people ≥60 with persistent bone pain (particularly back) or unexplained fracture. Offer very urgent protein electrophoresis and Bence-Jones protein urine test (within 48 hours) to assess for myeloma in people ≥60 with

		hypercalcaemia or leukopenia and presentation consistent with myeloma. Offer very urgent protein electrophoresis and a Bence-Jones protein urine test (within 48 hours) to assess for myeloma if plasma viscosity or ESR and presentation are consistent with possible myeloma. Refer using suspected cancer pathway referral if results suggest myeloma.
Non-Hodgkin's lymphoma	Symptoms: fatigue, weight loss, night sweats, lymphadenopathy and hepatosplenomegaly	Consider suspected cancer pathway referral in adults presenting with unexplained lymphadenopathy or splenomegaly. Take into account any associated symptoms, particularly fever, night sweats, shortness of breath, pruritus or weight loss
Hodgkin's lymphoma	Symptoms: Clinical features at presentation are similar to those for non-Hodgkin's lymphoma, but 95% of people present with lymph gland involvement	Consider a suspected cancer pathway referral in adults presenting with unexplained lymphadenopathy take into account associated symptoms, particularly fever, night sweats, shortness of breath, pruritus, weight loss or alcohol-induced lymph node pain

1. Koo, M. M., Hamilton, W., Walter, F. M., Rubin, G. P. & Lyratzopoulos, G. Symptom Signatures and Diagnostic Timeliness in Cancer Patients: A Review of Current Evidence. *Neoplasia* **20**, 165 (2018).
2. National Cancer Patient Experience Survey 2018 Seeing a GP. (2020).
3. Bloodwise. The Current State of Blood Cancer Diagnosis in England. https://bcuk.cdn.ngo/documents/bloodwise-delayed-diagnosis-report_RIQgdp7.pdf (2019).

4. Howell, D. A. *et al.* Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematol* **13**, 9 (2013).

5. Friese, C. R. *et al.* Diagnostic delay and complications for older adults with multiple myeloma. *Leuk Lymphoma* **50**, 392–400 (2009).

6. Kane, E. *et al.* Emergency admission and survival from aggressive non-Hodgkin lymphoma: A report from the UK's population-based Haematological Malignancy Research Network. *Eur J Cancer* **78**, 53 (2017).

7. Howell, D. *et al.* Multiple myeloma: routes to diagnosis, clinical characteristics and survival – findings from a UK population-based study. *Br J Haematol* **177**, 67–71 (2017).

8. Dejoie, T. *et al.* Responses in multiple myeloma should be assigned according to serum, not urine, free light chain measurements. *Leukemia* **33**, 313 (2019).

9. Myeloma, MGUS and related conditions - A Guide for GPs.

10. Edgren, G. *et al.* Pattern of declining hemoglobin concentration before cancer diagnosis. *Int J Cancer* **127**, 1429–1436 (2010).

11. Kyle, R. A. *et al.* Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. *N Engl J Med* **378**, 241–249 (2018).

12. Koshiaris, C. *et al.* Clinical prediction tools to identify patients at highest risk of myeloma in primary care: a retrospective open cohort study. *The British Journal of General Practice* **71**, e347 (2021).

13. Rafiq, M., Abel, G., Renzi, C. & Lyratzopoulos, G. Steroid prescribing in primary care increases prior to Hodgkin lymphoma diagnosis: A UK nationwide case-control study. *Cancer Epidemiol* **81**, (2022).

14. Lee, D. J. *et al.* Mass spectrometry-detected MGUS is associated with obesity and other novel modifiable risk factors in a high-risk population. *Blood Adv* (2024) doi:10.1182/BLOODADVANCES.2023010843.

15. Clark, A. *et al.* Management of patients with germline predisposition to haematological malignancies considered for allogeneic blood and marrow transplantation: Best practice consensus guidelines from the UK Cancer Genetics Group (UKCGG),

CanGene-CanVar, NHS England Genomic Laboratory Hub (GLH) Haematological Malignancies Working Group and the British Society of Blood and Marrow Transplantation and cellular therapy (BSBMTCT). *Br J Haematol* **201**, 35–44 (2023).