GP Referral Guidelines

for

South Wales Cancer Network

Document Control Sheet

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1.0	Dr Jessica Anderson Dr Steve Knapper	South Wales Haematology Cancer Network Group
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Haematology Referral Guidelines

The following guidelines are designed to assist you in referral of patients from primary and secondary care to the Department of Clinical Haematology.

We have aimed to cover most situations where haematology referral might be considered but we are, of course, happy to discuss cases falling outside the scope of this guidance or where the GP or hospital Consultant considers a specialist opinion to be required.

The guidance aims to facilitate prioritisation of urgent cases whilst avoiding the unnecessary referral of patients who are unlikely to benefit from a specialist opinion.
For non-urgent conditions, a suggested series of investigations, appropriate for the primary care setting, is included for use prior to referral.

Following receipt of a referral, if it is felt by the reviewing Consultant that outpatient attendance is *not* required, written or telephone advice will be provided.

Cases requiring rapid, direct assessment by Haematology should be discussed by telephone with either the on-call Haematology SpR or Consultant.

Please note: these guidelines refer to adult patients and not to children who will normally be seen in Paediatrics.

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REFERRAL GUIDELINE FOR NEUTROPENIA

Definition of Neutropenia: Neutrophil count <1.7 x 10^9/l

Causes of Neutropenia: viral infection, sepsis, drugs, autoimmune disorders, bone marrow failure due to aplasia, malignant infiltration or B12 / folate deficiency

Refer if:

- *Persistent* (>2 tests 4-6 weeks apart) neutropenia <1.0 x 10^9/l
- Neutropenia associated with:
  other cytopenias, lymphadenopathy or splenomegaly

Urgent referral if:

- Neutrophils < 0.5 x 10^9/l (significant risk of serious infection)

Patients with active sepsis in association with unexplained neutropenia < 0.5 x 10^9/l should be discussed by telephone with a consultant haematologist to arrange urgent direct assessment

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination
- Autoimmune screen
- Haematinics: B12 and folate
- Immunoglobulins and serum electrophoresis
- Consider discontinuation of potentially precipitating medications
- Repeat FBC in 4-6 weeks – viral neutropenias are frequently transient

Referral for specialist opinion also should be considered for:

- Neutropenia associated with increased susceptibility to infection
- Other unexplained, *progressive* neutropenia

REFERRAL GUIDELINE FOR THROMBOCYTOPENIA

Definition of Thrombocytopenia: Platelet count < 150 $x10^9$/l
Bleeding symptoms are rare with platelets >50 x 10^9/l
Risk of spontaneous bleeding increases with platelets <20 x 10^9/l

Causes of Thrombocytopenia: Immune peripheral consumption (ITP), any cause of bone marrow failure (aplasia, malignant infiltration, myelodysplasia, B12 / folate deficiency), alcohol, drugs, sepsis, hypersplenism, disseminated intravascular coagulation (DIC) and TTP / HUS

Refer if:

- Persistent (>2 tests 4-6 weeks apart) *unexplained* thrombocytopenia <80 $x10^9$/l

Urgent referral if:

- Platelet count < 50 x 10^9/l
- Platelet count < 80 x 10^9/l associated with any of the following:
  - Other Cytopenia (Hb < 100g/l, Neutrophils < 1 x 10^9/l)
  - Splenomegaly
  - Lymphadenopathy
  - Pregnancy
  - Forthcoming surgery

Patients with platelets <20 x 10^9/l or active bleeding should be discussed by telephone with Consultant Haematologist to arrange urgent direct assessment

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination – may exclude platelet clumping artefact
- Autoimmune profile
- Haematinics: B12 and folate
- Liver biochemistry and γGT
- Immunoglobulins and serum electrophoresis
- Alcohol history
- Consider discontinuation of potentially precipitating medications
- Repeat FBC in 4-6 weeks

Referral for specialist opinion should also be considered for:

- Thrombocytopenia in patients with a history of thrombosis

REFERRAL GUIDELINE FOR THROMBOCYTOSIS

Definition of Thrombocytosis: Platelet count >450 x 10^9/l

Causes of Thrombocytosis: Myeloproliferative neoplasm (note patients can develop thrombosis or bleeding, due to abnormal platelet function).
Reactive Causes include: Infection, inflammation, chronic bleeding, trauma or neoplasia

Urgent referral if:

- Unexplained Platelet count >1000 x 10^9/l
- Platelet Count 450-1000 x 10^9/l associated with any of the following:
  - Recent arterial or venous thrombosis
    (including DVT/PE, CVA/TIA, PVD, MI/unstable angina)
  - Neurological symptoms
  - Abnormal bleeding

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination
- Ferritin – investigate and treat iron deficiency
- CRP
- Look for and treat reactive causes: infection, inflammation, neoplasia

Referral for specialist opinion should also be considered for:

- Persistent (>2 tests 6-8 weeks apart) *unexplained* thrombocytosis

REFERRAL GUIDELINE FOR POLYCYTHAEMIA

Definition of Polycythaemia: Haematocrit > 0.52 (males), > 0.48 (females)

Causes of Polycythaemia:

Primary (Polycythaemia vera)
Secondary (eg hypoxic lung disease, EPO-secreting tumours)
Relative due to plasma depletion eg diuretics

Refer if:

- Persistently (>2 tests 6-8 weeks apart) elevated Hct >0.52 (males) or >0.48 (females) **in association with any of the following:**
  - Previous venous or arterial thrombosis
  - Splenomegaly
  - Raised white cell or platelet count
  - Pruritus

Urgent referral if:

- Extreme raised Hct >0.60 (males) or >0.56 (females) in absence of cyanotic congenital heart disease
- Hct >0.52 (males) or > 0.48 (females) in association with any of the following:
  - Recent arterial or venous thrombosis
    - Neurological symptoms
    - Visual loss
    - Abnormal bleeding

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Confirm with repeat FBCs over time (uncuffed blood samples) eg 2-3 monthly
- Modify known associated lifestyle factors:
  - smoking, alcohol, consider changing thiazides to non-diuretic anti-hypertensive agents
- Consider respiratory or cardiology input in the case of hypoxic lung disease / cardiac failure respectively

Referral for specialist opinion should also be considered for:

- Persistent *unexplained* elevated haematocrit in the absence of above factors (Male >0.52 or Female >0.48)

REFERRAL GUIDELINE FOR PARAPROTEIN

Definition: A paraprotein is a monoclonal protein band detected in the serum by electrophoresis. Small faint bands require confirmation by immunofixation and the lab will do this automatically.

Disorders characterised by the production of a paraprotein include monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma and Waldenströms Macroglobulinaemia. Paraproteins may also be a feature of CLL, NHL or Amyloidosis.

Referrals to Haematology **should <u>not</u>** be made for patients with raised immunoglobulin levels in the absence of a monoclonal paraprotein band on serum electrophoresis. Polyclonal gammopathy implies a non-specific immune reaction and is not associated with underlying haematological disorders. Common causes of polyclonal increases in immunoglobulins include chronic infection, inflammation and neoplasia.

MGUS:
This is frequent in the elderly with monoclonal bands being present in 3-5% of over 70s and up to 10% of over 90s, with most cases being detected as an incidental finding. The overall risk of progression to Myeloma and other lymphoproliferative conditions is low (around 1% pa).

Elderly patients with low level paraproteins (IgG <15g/l or IgA <10g/l), in the absence of the signs or symptoms listed below, may not require referral and may be suitable for monitoring in the community on a 6-12 monthly basis. To help risk stratify patients suitable for monitoring in the community, the local Haematologist may request that a 'serum free light chain' assay (SST tube) is performed in the community. It should be noted that the serum free light chain ratio (SFLC ratio) is also raised in renal impairment.

Findings which suggest a possible diagnosis of Multiple Myeloma (or other haematological malignancy) in the presence of a new paraprotein and require urgent referral are:

- Hypercalcaemia
- Unexplained renal impairment
- Anaemia or other cytopenias
- Immune paresis
- Urinary Bence Jones proteins
- Bone pain or pathological fracture
- Radiological lesions reported as suggestive of myeloma
- Hyperviscosity symptoms (headache, visual loss, acute thrombosis)
- Lymphadenopathy or splenomegaly
- Lymphocytosis

Patients with suspected spinal cord compression should be discussed by telephone with Consultant Haematologist to arrange urgent direct assessment

Referral for specialist opinion should be considered for:

- Other newly-identified paraproteins not meeting the above criteria for urgent referral

Discharge policy for patients with MGUS:

- Patients with uncomplicated paraproteins may be discharged from clinic for community monitoring after completing a period of initial investigation.
- Information at the time of discharge will include a plan for monitoring in primary care as well as clearly defined individualised patient criteria for re-referral to the Haematology Department.

REFERRAL GUIDELINE FOR ANAEMIA

Definition of Anaemia: Hb <130g/l (males), < 115g/l (females)

Appropriate investigation and treatment of anaemia is determined by its cause and clinical context. Borderline asymptomatic anaemias, in the absence of other cytopenias or iron deficiency, may not require further investigation or treatment according to clinical judgement of the assessing physician.

Systematic clinical evaluation and appropriate supplementary investigation are key and will influence both the urgency and direction of initial clinical investigation.

Iron deficiency should be referred to gastroenterology / gynaecology as appropriate for further investigation.

Uncomplicated B12 / folate deficiency does not require referral to Haematology (see Macrocytosis guideline).

Urgent Referral advised if:

- Leucoerythroblastic anaemia (based on blood film report)
- Acute haemolytic anaemia (we will usually contact you directly from the lab about these patients)
- Unexplained progressive *symptomatic* anaemia
- Anaemia in association with any of the following:
  - Splenomegaly or lymphadenopathy
  - Other cytopenias

*Patients with **suspected aplastic anaemia** (neutrophils < 0.5 x10^9/l, platelets <50 x10^9/l) or **acute haemolytic anaemia** should be discussed with Consultant Haematologist by telephone to arrange urgent direct assessment.*

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Careful history focussing on duration, symptoms, bleeding, diet, drug and family history
- Blood film examination and reticulocyte count
- Ferritin, B12 and folate
- Immunoglobulins and protein electrophoresis, urine for Bence Jones proteins
- Renal and liver biochemistry
- Monitor FBC for evidence of progression over time

Referral for specialist opinion also should be considered for:

- Persistent unexplained symptomatic anaemia

REFERRAL GUIDELINE FOR MACROCYTOSIS

Definition of Macrocytosis: MCV > 100 fl

Causes of Macrocytosis: B12 and folate deficiency, excess alcohol consumption, hypothyroidism, reticulocytosis and myelodysplastic syndrome. Macrocytosis is a normal physiological finding in pregnancy and is seen routinely in patients taking hydroxycarbamide, methotrexate and certain anti-retroviral agents.

Appropriate investigation in primary care prior to referral:

- B12 and folate levels (plus Intrinsic Factor antibodies in B12 deficiency)
- Blood film examination and reticulocyte count
- Liver and thyroid biochemistry and γGT
- Immunoglobulins and protein electrophoresis with urine for Bence Jones proteins
- Alcohol history and appropriate lifestyle modification

Refer if:

- Suspected myelodysplastic syndrome (based on blood film report)
- MCV >100fl **with accompanying cytopenia** (excluding B12 / folate deficiency see below)
- Persistent *unexplained* MCV >105fl

Guidance on the diagnosis of Vitamin B12 deficiency

Uncomplicated B12 or folate deficiency does not require routine referral for haematology outpatient assessment.

The clinical features of B12 deficiency are highly variable. Mildly reduced B12 levels are common and less than 10% of such patients show clinical evidence of deficiency. Only a limited correlation is seen between FBC abnormalities and the presence of neurological manifestations, with entirely normal FBC findings in 20-30% of cases presenting with neurological symptoms.

- B12 levels above 400ng/l confirm adequate body stores and retesting within 2 years is unnecessary.
- Repeating the test once the patient is on replacement therapy is of no value.
- Vitamin B12 testing should not be performed in pregnancy as results are entirely unreliable. Any queries should be discussed with the Consultant Haematologist on-call.
- Intrinsic factor antibodies may be found in up to 35% of cases of pernicious anaemia and, when detected, are considered diagnostic. A negative result is unhelpful; intrinsic factor antibodies should thus not be used as a screening test for B12 deficiency.

Suggested interpretation of serum B12 assay results

B12 level	**Action**
<100ng/l	B12 deficiency very likely - treat as indicated
100-150ng/l	Deficiency possible. Treat if clinically appropriate; otherwise repeat after 3-6 months and review
150-300ng/l	Intermediate level. Consider treatment, particularly if other evidence of deficiency eg neuropathy or macrocytosis. Otherwise repeat after 6 months and review.
300-400ng/l	B12 deficiency unlikely but seek further advice if suggestive features present e.g. neuropathy. Otherwise repeat after 6 months and review.
> 400ng/l	B12 stores normal. Stores adequate for 2 years

REFERRAL GUIDELINE FOR LYMPHOCYTOSIS

Definition of Lymphocytosis: Lymphocyte count > 5 x 10^9/l.

Causes of Lymphocytosis: A transient, reactive lymphocytosis is frequently seen in acute viral infection, particularly infectious mononucleosis. Chronic lymphocytosis is characteristic of Chronic Lymphocytic Leukaemia (CLL), the incidence of which peaks between 60 and 80 years of age. In its early stages this condition is frequently asymptomatic with treatment only being required on significant progression.

Urgent referral advised if:

- Lymphocytosis is associated with any of the following:
  - Anaemia, thrombocytopenia or neutropenia
  - Splenomegaly
  - Progressive lymphadenopathy
  - 'B' Symptoms (weight loss >10%, drenching sweats, unexplained fever)
- Lymphocytosis in excess of 30 x 10^9/l

Appropriate investigation in primary care for patients with lymphocyte count > 5 x 10^9/l not meeting criteria for urgent referral:

- Glandular fever screen if appropriate
- Repeat FBC in 4-6 weeks – viral lymphocytoses are frequently transient
- Lifestyle modification – smoking is a well-recognised cause of reactive lymphocytosis

Referral for specialist opinion should also be considered for:

- Persistent lymphocytosis > 5 x 10^9/l not fulfilling criteria for urgent referral particularly if there is lymphadenopathy

Asymptomatic patients with mild incidental lymphocytosis may not benefit from referral and investigation. Patients are often elderly with extensive co-morbidity and a diagnosis of e.g. early CLL often causes significant psychological morbidity for patients who do not require treatment. It may be recommended on the blood film report that continued monitoring in primary care e.g. every 4-6 months is appropriate. We are, of course, happy to discuss individual cases as appropriate.

Please see also below related referral guideline for lymphadenopathy.

REFERRAL GUIDELINE FOR LYMPHADENOPATHY

Causes of Lymphadenopathy:

- Occurs in infective and neoplastic conditions
- May be isolated, involving a single node or nodes within an anatomical grouping, or generalised.
- Isolated lymphadenopathy frequently results from local infection or neoplasia.
- Suspicions of lymphoma should be heightened by the presence of generalised or progressive lymphadenopathy, hepatosplenomegaly or accompanying 'B' symptoms (>10% weight loss in 6 months, drenching sweats, unexplained fevers).

Refer urgently as 'urgent suspected cancer':

- Persistent lymphadenopathy >6 weeks with no obvious infective precipitant
- Lymphadenopathy for <6 weeks in association with any of the following:
  - B symptoms (see above)
  - Hepatosplenomegaly
  - Rapidly enlarging nodes
  - Disseminated / generalised nodal enlargement
  - Anaemia / leucopenia / thrombocytopenia
  - Hypercalcaemia

NB: Solitary neck nodes should generally be referred to ENT rapid access Head and Neck clinic for assessment in the first instance, while isolated axillary or groin nodes should be referred to general surgery. If lymphoma is confirmed histologically, the patient will be seen urgently by Haematology..

If in any doubt over who to refer to, or whether urgent referral is required, we would suggest discussion with a Consultant Haematologist who will be pleased to offer advice on both the optimal timing and best route for referral.

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Full blood count
- Glandular fever screen
- Consider HIV test
- Close monitoring of symptoms and progress of lymphadenopathy

REFERRAL GUIDELINE FOR LEUCOCYTOSIS

Definition of Leucocytosis: White Cell Count >11 x 10^9/l.

Causes of Leucocytosis: Differential diagnosis is wide, ranging from normal response to infection through to haematological malignancies including acute leukaemias. Detection of a leucocytosis should prompt scrutiny of the differential white cell count, other FBC parameters and blood film examination.

The following should be referred by telephone for *immediate* haematology assessment:

- New suspected Acute Leukaemia
- New suspected Chronic Myeloid Leukaemia with either of the following:
  - White cell count >100 x 10^9/l
  - Hyperviscosity symptoms (Headache, visual loss, acute thrombosis)

Both of these will normally be identified by us in the lab. A Consultant Haematologist or SpR will contact the general practice to arrange urgent patient assessment / admission.

The following should be referred urgently for outpatient assessment:

- Leucoerythroblastic blood picture (from blood film report)
- New Chronic Myeloid Leukaemia not meeting the above criteria
- *Unexplained* leucocytosis with white cell count >50 x 10^9/l

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Blood film examination with differential white cell count
- Careful history and assessment for 'reactive' causes: infection, inflammation or neoplasia
- Examination for lymphadenopathy, splenomegaly
- A minor non-specific leucocytosis or neutrophilia is often seen in smokers

Referral for specialist opinion should be considered for:

- *Unexplained persistent (>2 tests 6-8 weeks apart):*
  - White cell count >20 x 10^9/l
  - Neutrophilia >15 x 10^9/l
  - Eosinophilia > 5 x 10^9/l
  - Monocytosis >2 x 10^9/l
  - Basophilia >0.2 x 10^9/l

REFERRAL GUIDELINE FOR HAEMOCHROMATOSIS

Hereditary Haemochromatosis is an autosomal recessive condition predisposing to pathological iron overload which may affect the liver, pancreas, heart, pituitary gland and joints.

Over 90% of cases are caused by homozygous (C282Y) mutation of the HFE gene which can be detected by PCR.

A raised ferritin is **not** specific for Haemochromatosis and may also be elevated in other conditions, particularly other causes of liver disease, alcohol excess, infection, inflammation or neoplastic disease.

A normal fasting transferrin saturation and serum ferritin, confirmed on repeat testing, largely excludes a diagnosis of Haemochromatosis; in the case of family screening, however (where there has been a confirmed diagnosis of Hereditary Haemochromatosis in a family member), genetic testing for HFE gene mutations is also recommended.

Urgent outpatient referral advised if:

- Elevated ferritin ***with evidence of otherwise unexplained 'end organ damage'*** (congestive cardiac failure, liver dysfunction, diabetes or hypogonadism)

Appropriate investigation in primary care for patients not meeting criteria for urgent referral:

- Repeat ferritin in 4-6 weeks
- Check liver function tests, fasting glucose, fasting transferrin saturation
- Careful alcohol history
- Consider 'reactive' cause: infection, inflammation, neoplasia

Referral for specialist opinion also should be considered for:

- Persistent *unexplained* raised ferritin
- Genetic counselling / screening of first degree relatives of hereditary haemochromatosis cases

The following table is a guide to waiting times for referrals meeting the above criteria. These may be changed at the discretion of the appointing Consultant Haematologist:

Referral Condition	Status	Time (Weeks)
Neutropenia	Urgent	2
	General	22
Thrombocytopenia	Urgent	2
	General	22
Thrombocytosis	Urgent	2
	General	22
Polycythaemia	Urgent	2
	General	22
Paraproteins	Urgent	2
	General	22
Anaemia	Urgent	2
	General	22
Macrocytosis	General	22
Lymphocytosis	Urgent	2
	General	22
Lymphadenopathy	Urgent	2
Leucocytosis	Urgent	2
	General	22
Haemochromatosis	Urgent	10
	General	22