Diagnosis in Primary Care and referral pathway for patients with a raised haematocrit

Why implement this pathway?

A raised haemoglobin or haematocrit is a common finding and can be a reason for referral. This document aims to facilitate investigation of such patients in Primary Care and reduce hospital referrals.

Common causes of a raised haematocrit

a) True increase in the number of red blood cells. This can be a primary bone marrow problem e.g. Polycythaemia Vera (PV) (see below) or secondary to other medical conditions e.g. hypoxia.
b) Decrease in plasma volume. This is apparent polycythaemia.
c) Or a mixture of the two.

Polycythaemia Vera (PV). Here acquired mutations in blood cells leads to inappropriate red cell proliferation. ~95% of PV patients have an acquired mutation in a gene called JAK2 that regulates erythropoiesis[1]. The mutation is known as JAK2 V617F. As these patients have inappropriately high red cell numbers, they do not need as much erythropoietin (EPO) to drive red cell production. Thus, PV is characterised by the JAK2 mutation and low serum EPO levels.

Secondary polycythaemia. Usually results from increased serum EPO in response to chronic hypoxia, or, more rarely, due to malignant or benign tumours releasing erythropoietin-mimetic agents (e.g. renal or hepatic cancer or uterine fibroids). The JAK2 mutation will be negative and serum EPO is usually abnormal (either high or low). A full list of secondary causes is listed in **Appendix 3**.

Apparent polycythaemia. Reduction in the plasma volume is usually related to modifiable factors – e.g. high body mass index, heavy smoking, excess alcohol consumption, use of thiazide diuretics. Patients with apparent polycythaemia are probably the **majority** of those who are referred with a high haematocrit. These patients are negative for the JAK2 mutation. They usually have a normal serum EPO level. A haematocrit > 0.6 male, > 0.56 female is less likely to be due to an apparent erythrocytosis.

Combined causes. An example is smoking can cause a reduction in plasma volume and hypoxia (secondary polycythaemia).

Why is it important to make a correct diagnosis?

Patients with a high haemoglobin can be at risk of venous/arterial thrombo-embolic disease. There are two parts to management.

First, the haematocrit can be lowered. The target haematocrit is determined, in part, by diagnosis of polycythaemia. In PV the target haematocrit is 0.45.

For secondary and apparent polycythaemia, the target haematocrit is usually 0.54. This can vary occasionally. For example, for patients with a thromboembolic history it may be prudent to keep the haematocrit lower (e.g. 0.5). This can be discussed with a haematology consultant or the primary hospital consultant looking after that patient.

Second, it is important that **ALL** other additional risk factors for thrombosis, such as hypertension and smoking history, are addressed. This is critical to provide an integrated management strategy. This is often best done in Primary Care.

Finally, and as a separate point, PV patients need regular Haematology follow up to detect the 2-8% that will transform myelofibrosis or the 1-3% that will transform to Acute Myeloid Leukaemia.
Patients without a primary myeloproliferative disorder do not have a risk of disease transformation. **Which patients with a high haemoglobin require investigation?**

Patients with a high haematocrit (Hct) >0.52 in men, >0.48 in women[1] on two separate occasions (i.e. two months apart)[2] or a one off value of Hct >0.6 male, 0.56 female.

As patients with apparent polycythaemia are a significant proportion of those with a high haematocrit, the initial assessment should therefore focus on lifestyle factors (smoking and excess alcohol), a history of thrombosis, features causal of secondary polycythaemia (e.g. hypoxic lung disease).

Suggested Investigations in Primary Care

- History and examination including smoking history and history of thrombosis
- Full blood count and film
- JAK2 mutation testing
- Serum erythropoietin level (EPO)
- Serum ferritin
- Renal and liver function tests [1]
- Patients should be screened for hypertension, hyperlipidaemia, diabetes

The above blood tests can be requested by sending:
1) 2 EDTA tubes (purple top) for blood count, blood film and JAK2 mutation testing and two SST tubes (yellow top) for serum ferritin and EPO level. Send all these with a Haematology request form to Haematology.
2) One Lithium Heparin tube (green top) for renal, liver enzymes, lipid profile and (fluoride) blood sugar tests to Biochemistry.

Which patients require referral? (Appendix 1)
1) **Patient is positive for the JAK2 mutation**. Refer to Haematology Outpatients.

2**) Patients negative for the mutation but with other features suggestive of a myeloproliferative disease**. Hct >0.6 male or >0.56 female in the absence of a cause for secondary polycythaemia. Other factors that would suggest MPN include high platelets and/or white count, enlarged spleen, family history of myeloproliferative disease, previous history of thrombosis. This will be rare group and should be referred to Haematology Outpatients.

3) **Patients negative for the JAK2 mutation, but with an abnormally high serum EPO level**. Refer to haematology to exclude an EPO secreting malignancy.

4) **Apparent polycythaemia**. Lifestyle risk factors should be addressed first. Tackling cigarette smoking and excess alcohol intake changing from thiazide diuretics to alternative anti-hypertensive agents may reduce the haematocrit. These patients can be referred for venesection if the haematocrit is persistently greater than 0.54.

5) **Secondary Polycythaemia**. A small number of patients have an obvious secondary cause for the raised haematocrit such as hypoxic lung disease. These patients should be referred directly to the chest physicians in the first instance.

How to refer a new patient to Haematology (Appendix 2)?
Please send or fax the completed referral form (Appendix 2) to the Administration Offices, Level 2, Cancer and Haematology Centre, Churchill Hospital. Fax No: 01865 235260. The patient will be contacted directly and sent an appointment for the outpatient department where appropriate. If would like to discuss the case prior to referral first, then please bleep the on call haematology SpR on bleep 1836 via switchboard.

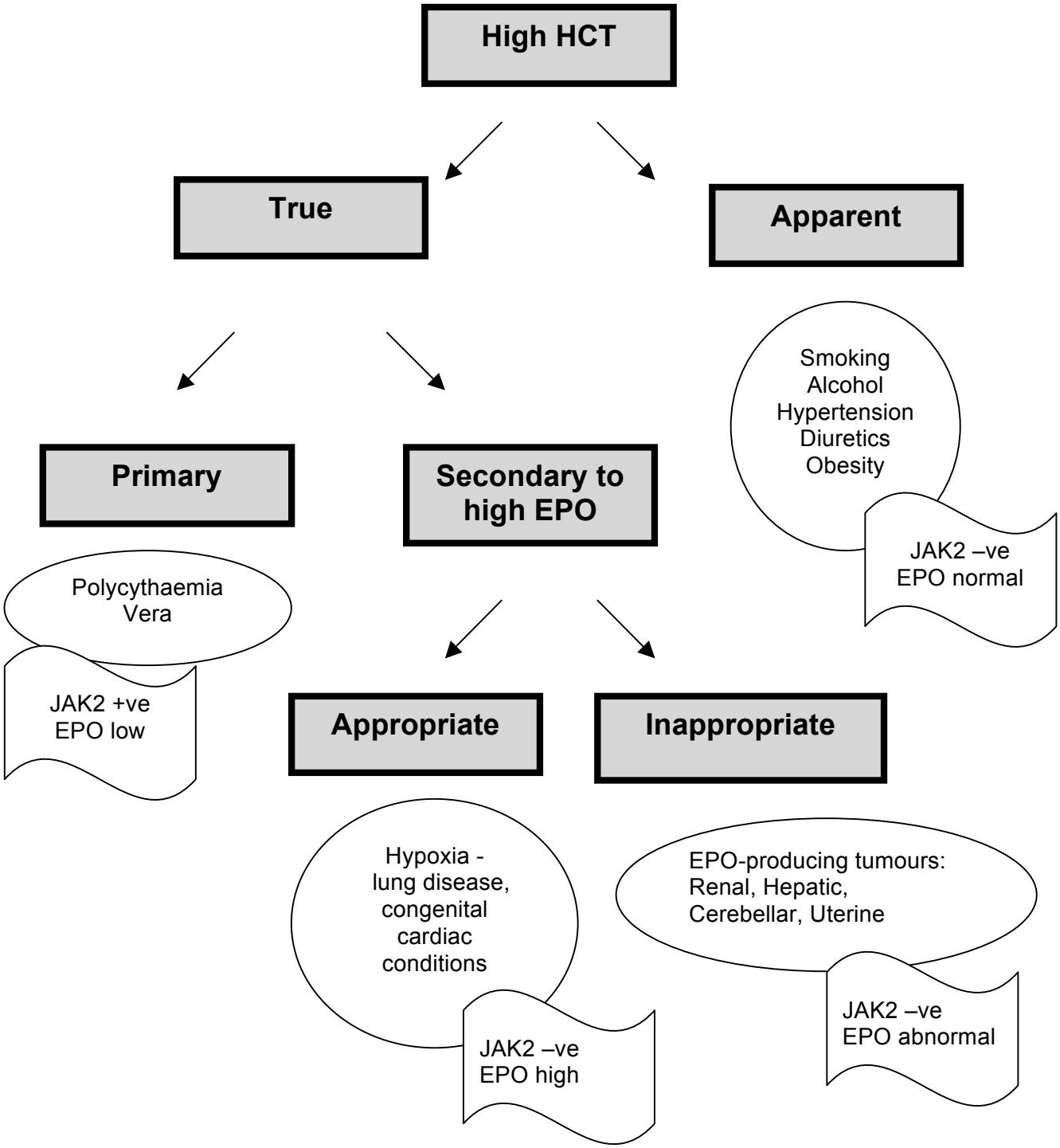
References:

[1]*Amendment to the diagnosis and investigation of polycythaemia/erythrocytosis*
British Journal of Haematology 2007; 138 (6): 821-2
[2]*Guidelines for the Diagnosis, Investigation and Management of Polycythaemia/Erythrocytosis.*
British Journal of Haematology 2005; 130(2): 174-95

Review

Name	Revision	Date	Version	Review date
Dr Adam Mead	Minor	Oct 2011	2.0	Oct 2013

Appendix 1


High HCT
True
Apparent
Primary
Secondary to high EPO
Smoking
Alcohol
Hypertension
Diuretics
Obesity
JAK2 –ve
EPO normal
Polycythaemia Vera
JAK2 +ve
EPO low
Appropriate
Inappropriate
Hypoxia - lung disease, congenital cardiac conditions
JAK2 –ve
EPO high
EPO-producing tumours: Renal, Hepatic, Cerebellar, Uterine
JAK2 –ve
EPO abnormal

Appendix 2

Primary Care Referral Form for Polycythaemia

Please Fax to 01865 235260

Administration Offices, Level 2, Cancer and Haematology Centre, Churchill Hospital, Old Road, Headington, Oxford, OX3 7LJ

Patient Name:	DOB:
Address:	Hospital /NHS No.:
GP:	

Brief Clinical History:
Current medication:

FBC (1^{st}):	FBC (2^{nd}):
$JAK2^{V617F}$ present:	Serum EPO:
Ferritin:	

Smoking history:	Current smoker: Y/N
Height (m):	Weight (kg):
ETOH history:	Family Hx:
Palpable spleen: Y/N	

Other risk factors for thrombosis:
History of previous thrombosis:

Date

Appendix 3

Classification of the absolute erythrocytoses [adapted from 2]

Primary Myeloproliferative Disease

Polycythaemia Vera (PV) ($JAK2^{V617F}$ mutation positive or negative) Exon 12 mutations

Apparent Polycythaemia

Heavy smoking High alcohol intake Hypertension particularly thiazide use

Secondary Polycythaemia

Congenital High oxygen-affinity haemoglobin 2, 3-Biphosphoglycerate mutase deficiency Erythropoietin receptor-mediated Chuvash erythrocytosis (VHL mutation) Hypoxia-driven Central hypoxic process Chronic lung disease Right-to-left cardiopulmonary vascular shunts Carbon monoxide poisoning Smoker's erythrocytosis Hypoventilation syndromes including sleep apnoea Local renal hypoxia Renal artery stenosis End-stage renal disease Hydronephrosis Renal cysts (polycystic kidney disease) Pathologic EPO production Tumours Hepatocellular carcinoma Renal cell cancer Cerebellar haemangioblastoma Parathyroid carcinoma/adenomas Uterine leiomyomas Pheochromocytoma Meningioma Exogenous EPO Drug associated Treatment with androgen preparations Post renal transplant erythrocytosis Idiopathic erythrocytosis