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Amendment to the guideline for diagnosis and investigation of polycythaemia/erythrocytosis

We published an evidence-based guideline for the diagnosis, investigation and management of polycythaemia/erythrocytosis (McMullin *et al*, 2005). It has subsequently been reported that the mutation *JAK2*V617F is present in approximately 95% of patients with polycythaemia vera (PV) especially if a polymerase chain reaction-based detection method is used (Baxter *et al*, 2005; James *et al*, 2005; Kralovics *et al*, 2005; Levine *et al*, 2005). Moreover different *JAK2* mutations (affecting exon 12) are found in patients with PV who lack the V617F mutation (Scott *et al*, 2007). The presence of these abnormalities has implications for the diagnosis and therefore investigation of polycythaemia. *JAK2* mutations (both V617F and exon 12 mutations) can be detected in the peripheral blood using one of several sensitive molecular methods and are not associated with relative or secondary erythrocytosis. We therefore propose that the diagnostic criteria for PV should be adapted as shown in Table I, as suggested by Campbell and Green (2006).

This simplifies the diagnosis and the need for investigation in those who are *JAK2* mutation positive. In the *JAK2* negative group, the platelet count threshold is raised from 400×10^9/l to 450×10^9/l, which is in keeping with the upper limit of the normal range in most laboratories.

These diagnostic criteria will alter the number and sequence in which investigations need to be carried out. Start with a thorough history and examination, to identify most patients with a secondary cause and arrange confirmatory investigations. Then stage 1 initial screening tests will identify those with JAK2-positive clonal disease in whom there is no need to proceed further with further investigations:

Stage 1

1 History and examination
2 Full blood count/film
3 *JAK2* mutation
4 Serum ferritin
5 Renal and liver function tests

Stage 2 investigations

If the initial screening tests are negative for a *JAK2* mutation and there is no obvious secondary cause then further investigations are indicated. A red cell mass is required first

Table I. Modified diagnostic criteria for polycythaemia vera.

JAK2-positive polycythaemia vera	
A1	High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)*
A2	Mutation in *JAK2*
Diagnosis requires both criteria to be present	
JAK2-negative polycythaemia vera	
A1	Raised red cell mass (>25% above predicted) OR haematocrit $\geq$0.60 in men, $\geq$0.56 in women.
A2	Absence of mutation in *JAK2*
A3	No cause of secondary erythrocytosis
A4	Palpable splenomegaly
A5	Presence of an acquired genetic abnormality (excluding *BCR-ABL*) in the haematopoietic cells
B1	Thrombocytosis (platelet count $>450 \times 10^9$/l)
B2	Neutrophil leucocytosis (neutrophil count $> 10 \times 10^9$/l in non-smokers; $>12.5 \times 10^9$/l in smokers)
B3	Radiological evidence of splenomegaly
B4	Endogenous erythroid colonies or low serum erythropoietin
Diagnosis requires A1 + A2 + A3 + either another A or two B criteria	

*Dual pathology (co-existent secondary erythrocytosis or relative erythrocytosis) may rarely be present in patients with a *JAK2*-positive myeloproliferative disorder. In this situation, it would be prudent to reduce the haematocrit to the same target as for polycythaemia vera.

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and if an absolute erythrocytosis is confirmed then the following tests are appropriate.

1 Red cell mass
2 Arterial oxygen saturation
3 Abdominal ultrasound
4 Serum erythropoietin level
5 Bone marrow aspirate and trephine
6 Cytogenetic analysis
7 Erythroid burst-forming unit (BFU-E) culture

Stage 3

For those patients who do not fulfil either set of criteria and who have erythrocytosis there are a number of specialised tests that may need to be considered. Some of these are listed below.

1 Arterial oxygen dissociation
2 Sleep study
3 Lung function studies
4 Gene mutations *EPOR, VHL, EGLN1* (also known as *PHD2*)

Mary F. McMullin
John T. Reilly
Peter Campbell
David Bareford
Anthony R. Green
Claire N. Harrison
Eibhlin Conneally
on behalf of the National Cancer Research Institute, Myeloproliferative Disorder Subgroup
and Kate Ryan
on behalf of the British Committee for Standards in Haematology

Department of Haematology, Belfast City Hospital, Belfast, UK
E-mail: m.mcmullin@qub.ac.uk

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The disappearance of two alleles of *JAK2* V617F from peripheral blood of a polycythaemia vera patient correlates with transformation into myelofibrosis

Polymerase chain reaction (PCR) analysis for the V617F mutation of the Janus Kinase 2 gene (*JAK2*) has been recently introduced in order to define patients with polycythaemia vera (PV), as this mutation has been discerned in 99% of cases (Jamieson *et al*, 2006; Scott *et al*, 2007). We present a 59-year-old Jewish man diagnosed with PV 10 years ago. A DNA sample taken from peripheral blood leucocytes after 7 years of hydroxycarbamide (also known as hydroxyurea) treatment was recently evaluated for *JAK2* V617F. The sample was homozygous for *JAK2* V617F when analysed by two methods:

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