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REVIEW

Erythrocytosis: Diagnosis and investigation

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Abstract

An absolute erythrocytosis is present when the red cell mass is greater than 125% of the predicted. This is suspected when the hemoglobin or hematocrit is above the normal range. An erythrocytosis can be classified as primary or secondary and congenital or acquired. The commonest primary acquired disorder is polycythemia vera. The diagnostic criteria for PV have evolved over time and this is the main diagnosis managed in hematology clinics. There are a variety of rare congenital causes both primary and secondary. In particular in young patients and/or those with a family history a congenital cause is suspected. There remains a larger cohort with acquired erythrocytosis mainly with non-hematological pathology. In order to explore for a cause of erythrocytosis, measurement of the erythropoietin level is a first step. A low erythropoietin level indicates a primary cause and a normal or elevated level indicates a secondary etiology. Further investigation is then dictated by initial findings and includes mutational testing with PCR and NGS for those in whom a congenital cause is suspected. Following this possibly bone marrow biopsy, scans, and further investigation as indicated by history and initial findings. Investigation is directed toward the identification of those with a hematological disorder which would be best managed following guidelines in hematology clinics and referral elsewhere in those for whom there are non-hematological reasons for the elevated hemoglobin.

KEYWORDS

congenital, diagnostic pathway, erythrocytosis, hemoglobin, investigation

1 | INTRODUCTION

Erythrocytosis refers to an elevation in hemoglobin (Hb) concentration and/or hematocrit (Hct) level above the established normal range for a specific population. It can be classified into two types: absolute erythrocytosis and relative erythrocytosis. Absolute erythrocytosis was traditionally confirmed by a red cell mass (RCM) exceeding 125% above the average predicted value based on gender and body mass.¹ Relative erythrocytosis on the other hand refers to situations where there is a reduction in plasma volume, but the RCM remains within the normal range.² Much of the literature and practice in this field concerns the criteria for diagnosis of polycythemia vera (PV). These have significantly

evolved over time. We will discuss these below and then move to discuss the classification of different causes of erythrocytosis, diagnostic tools, and processes before finally discussing who should be referred and how referrals could be managed in terms of pre-screening and ongoing management.

2 | EVOLUTION OF DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA

Traditional thresholds for considering erythrocytosis were Hemoglobin (Hb) levels exceeding 18.5 g/dL in males and 16.5 g/dL in females

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as proposed by the WHO diagnostic criteria in 2001 and maintained in 2008.³ These are thresholds for the diagnosis of PV and have been found to be inadequate as surrogate markers for absolute erythrocytosis.⁴ Their specificity for predicting increased RCM was high but sensitivity was low.⁵ Furthermore studies indicate that hematocrit (Hct) consistently outperforms Hb concentration in accurately identifying individuals with an increased red cell mass.^{5,6} Higher Hct levels indicate a greater likelihood of true erythrocytosis, with values surpassing 0.60 for males and 0.56 for females, indicative of absolute erythrocytosis, which obviates the need for further confirmation studies.^{2,7,8} This created difficulties in distinguishing individuals with JAK2 mutations who have other Myeloproliferative Neoplasms (MPNs) from those with “masked” or prodromal PV leading to potentially inappropriate prognostication and management. Patients with masked PV (mPV) have JAK2 mutations and display bone marrow morphology typical of PV but fail to meet the WHO Hb criteria.^{6,9–11} In relevant publications when compared to overt PV, patients with mPV have poorer outcomes concerning myelofibrotic or leukemic transformation and survival, with no variation observed in the rate of thrombosis.^{12,13} This is potentially due to an overlooked or delayed diagnosis, leading to inappropriate management strategies.^{11,14}

The criterion used Hb level as a surrogate marker for increased RCM with less focus on the Hct level, which has resulted in differing opinions on the reliability of Hb versus Hct in characterizing RCM and assessing therapy response as demonstrated by CYTO-PV clinical trial where Hct level was used as a reference to monitor and manage cardiovascular risks associated with PV.⁹

On the other hand, patients with mPV are often missed cases according to the criteria. In one study, thrombocytosis was the most

frequent CBC finding in 64% of 118 patients with mPV, with a history of previous thrombosis. Misdiagnosis can result in the erroneous exclusion of phlebotomies, which are necessary for PV patients to reach a therapeutic Hct target.¹⁵

At the same time specifically concerning a diagnosis of PV the British Society for Haematology (BSH) reviewed the evidence and proposed that a Hct exceeding 52% in males and 48% in females, or a RCM exceeding 125% of the predicted value, suggests an elevated RCM and a diagnosis of PV in the presence of a typical JAK2 mutation.^{2,8} Between the WHO 2001 and the BSH and WHO 2008 criteria JAK2 mutations were described which have significantly enhanced our ability to diagnose PV. The BSH criteria were revised in 2019⁶ but these thresholds remained unchanged (Table 1).

The 2016 WHO criteria for diagnosing PV introduced significant changes from the 2008 classification. This was due to the recognition of mPV through retrospective studies.^{14,16} The revised criteria included lowering the required Hb levels and introducing Hct cutoff levels¹⁶ of 16.5 g/dL and 49% for men and 16 g/dL and 48% for women. Erythropoietin (EPO) levels were maintained. The bone marrow pathology was changed from a minor to a major criteria and the previous endogenous in vitro endogenous erythroid colony (EEC) formation test was eliminated.^{14,16,17} The importance of bone marrow histology in distinguishing between different types of MPNs has also been discussed at length. Studies have shown that bone marrow histopathology can help differentiate PV from secondary polycythemia and other MPNs.^{18–20} The BSH however do not mandate a bone marrow histological examination in the presence of an increased Hct and evidence of clonal disease in every patient. These characteristics are sufficient evidence to make a diagnosis of PV. However, it is

TABLE 1 Diagnostic criteria of polycythemia vera (PV) as per BSH,⁶ WHO,²² and ICC²³ classifications.

| BSH 2019 | WHO 2022 | ICC 2022 |
|---|--|--|
| 1-JAK2-positive polycythemia vera: (requires both criteria) A1 High hematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted) A2 Mutation in JAK 2 | Major criteria: 1. Hemoglobin >16.5 g/dL (men) Hemoglobin >16.0 g/dL (women) or Hematocrit >49% (men) Hematocrit >48% (women) 2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of JAK2 or JAK2 exon 12 mutation | Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass 2. Presence of JAK2V617F or JAK2 exon 12 mutation 3. Bone marrow biopsy showing age- adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia |
| 2-JAK2-negative polycythemia vera: (requires A1–A4 plus another A or two B criteria) A1 Raised red cell mass (>25% above predicted) OR hematocrit ≥0.60 in men, ≥0.56 in women A2 Absence of mutation in JAK 2 A3 No cause of secondary erythrocytosis A4 Bone marrow histology consistent with polycythemia vera A5 Palpable splenomegaly A6 Presence of an acquired genetic abnormality (excluding BCR::ABL1) in the hematopoietic cells B1 Thrombocytosis (platelet count >450 × 10 ⁹ /l) B2 Neutrophil leucocytosis (neutrophil count >10 × 10 ⁹ /l in non-smokers, ≥12.5 × 10 ⁹ /l in smokers) B3 Radiological evidence of splenomegaly B4 Low serum erythropoietin | Minor criterion: Subnormal serum erythropoietin level *The diagnosis of PV requires either all three major criteria or the first two major criteria plus the minor criterion | Minor criterion: Subnormal serum erythropoietin level *The diagnosis of PV requires either all three major criteria or the first two major criteria plus the minor criterion |

Abbreviations: BSH, British Society for Haematology; ICC, International Consensus Classification; WHO, World Health Classification.

advised if there are any atypical features and at baseline to access any degree of fibrosis particularly in younger patients who are likely to have a long disease history.⁶

The removal of the EEC test, which correlates strongly with the presence of the *JAK2* mutation was welcomed as very few institutions were able to perform this and the test lacks accurate standardization. It is also time-consuming and very costly. Therefore, it has limited practical use.^{9,14} However, a concern arose that using new lower Hb and Hct cutoffs to determine whom to screen for potential PV could lead to an excess of diagnostic examinations,¹⁶ particularly if a large segment of the healthy population is included. It has been shown that the application of the low Hb threshold outlined by WHO to the Canadian population revealed that ~4.1% of unselected male subjects and 0.35% of female subjects had Hb values equal to or above the specified threshold. This suggests a potential increase in the number of individuals classified as “potential PV patients” by up to 12-fold in males and 3-fold in females compared to current standards.^{15,21} Therefore, it is crucial to carefully evaluate for possible causes of secondary polycythemia and perform a diagnostic workup for PV in the presence of clinical and/or laboratory features associated with MPN.^{16,21}

In 2022 new diagnostic criteria for PV were published from the 2022 WHO classification²² and International Consensus Classification (ICC).²³ These are mostly the same as those in the 2016 WHO criteria with minor changes, and are summarized in Table 1. The RCM assessment has been removed as a diagnostic criterion for PV in the 2022 WHO criteria as it is a test that is rarely available has become in routine clinical practice.²² Additionally the ICC criteria emphasized the need for *JAK2V617F* diagnostic assays with <1% sensitivity and stated that BM trephine biopsy is not mandatory for diagnostic purposes in patients with *JAK2* mutation and a sustained erythrocytosis (Hb concentrations of >18.5 g/dL in men or >16.5 g/dL in women and Hct values of >55.5% in men or >49.5% in women).²³

2.1 | Classification of an erythrocytosis

Erythrocytosis is categorized as primary or secondary based on the underlying cause. (Table 2). Primary erythrocytosis is caused by an intrinsic defect in the erythroid progenitor cell while secondary is caused by external factors which boost red cell production, mainly due to increased EPO production, for various reasons. Both primary and secondary causes can be further classified as either congenital or acquired. In a significant number of cases, an explanation for erythrocytosis cannot currently be discovered despite extensive testing and these cases are labeled “idiopathic erythrocytosis,” a diagnosis of exclusion see Figure 1.^{6,24,25}

Congenital causes are germ-line and thus it is an inherited erythrocytosis. Primary congenital/hereditary causes are very rare. These include mutations in the *erythropoietin receptor* gene (*EpoR*) and *SH2B3* (*LNK*) mutations. Secondary congenital/hereditary erythrocytosis can be caused by various defects, including mutations in genes involved in the oxygen-sensing pathway such as *VHL*, *EGLN1* (*PHD2*),

EGLN2 (*PHD1*), and *EPAS1* (*HIF2A*), as well as high oxygen-affinity Hbs. Other causes of secondary hereditary erythrocytosis include gain-of-function mutation in the *EPO* gene, methemoglobinemia, bisphosphoglycerate mutase deficiency, *SLC30A10* mutations with hypermagnesemia, and hereditary increase in adenosine triphosphate.²⁵ Pathogenic mutations in the *PIEZO1* gene have been found recently in individuals with idiopathic erythrocytosis, in association with manifestations of hereditary xerocytosis (iron overload, splenomegaly, hemolysis, decreased venous p50).^{26,27}

Among these secondary causes mutations in Hb genes have been described a long time ago and are the most frequent abnormalities causing secondary erythrocytosis. Despite the fact that high oxygen-affinity Hbs and methemoglobinemia are red cell abnormalities they are best classified as secondary erythrocytosis because the nature of the abnormal Hb leads to a relative hypoxia and thus Epo production to drive increased red cell production.

Overall, the prevalence of these rare hereditary disorders is entirely unknown as we are only aware of described individual individuals. They are very rare but there may be areas where specific inherited genetic lesions are described where there are clusters of cases. Likewise, there is no specific clinical picture. These cases are frequently completely asymptomatic and discovered on a CBC. The typical patient in whom one would suspect a congenital erythrocytosis is a young adult and in those with a family history.

The classical cause of primary acquired erythrocytosis is PV, typically caused by an acquired *JAK2* mutation driving blood cell production. A common cause of secondary erythrocytosis is hypoxia which leads to increased EPO production as compensatory mechanism and a drive to red cell production. Central hypoxia is seen in conditions such as chronic lung disease, right-to-left cardiopulmonary shunts, living at high altitudes, obstructive sleep apnea, and smoking. Local renal hypoxia is seen in cases of renal artery stenosis, end-stage renal disease, hydronephrosis and renal cysts (polycystic kidney disease). Various tumors have been described associated with pathological production of EPO, including cerebellar hemangioblastoma, renal cell carcinoma, hepatocellular carcinoma, uterine leiomyoma, pheochromocytoma, and meningioma. Drugs causing secondary erythrocytosis include erythropoiesis-stimulating agents, androgen preparations, testosterone, diuretics,^{8,24,25} and more recently studies showed that antidiabetic agents (sodium-glucose cotransporter 2 inhibitors; e.g., canagliflozin, empagliflozin) can also lead to a secondary acquired erythrocytosis.^{26,28} Other factors can lead to acquired secondary erythrocytosis, such as post-renal transplant and most commonly lifestyle factors such as smoking and excess alcohol.⁶

3 | INVESTIGATIONS OF BENEFIT IN EXPLORATION OF AN ERYTHROCYTOSIS

3.1 | Erythropoietin

Erythropoietin is a glycoprotein hormone, naturally produced by the peritubular cells of the kidney, which controls red blood cell

TABLE 2 Classification of erythrocytosis.

| Classification of erythrocytosis | | |
|---|--|--|
| 1-Primary erythrocytosis | | |
| Congenital | | Acquired |
| <i>EpoR</i> mutation | | Polycythemia vera |
| <i>SH2B3</i> (<i>LNK</i>) mutation | | |
| 2-Secondary erythrocytosis | | |
| Congenital | | Acquired |
| -Oxygen-sensing pathway gene mutations such as in <i>VHL</i> , <i>EGLN1</i> (<i>PHD2</i>), <i>EGLN2</i> (<i>PHD1</i>) <i>EPAS1</i> (<i>HIF2A</i>) | | Central hypoxia |
| -High oxygen-affinity Hbs. | | Chronic lung disease |
| -Gain-of-function mutation in the <i>EPO</i> gene | | Right-to-left cardiopulmonary shunts |
| -Methemoglobinemia | | Living at high altitude |
| -Bisphosphoglycerate mutase deficiency | | Obstructive sleep apnea |
| -SLC30A10 mutations with hypermagnesemia | | Smoking |
| -Hereditary increase in adenosine triphosphate. | | Renal hypoxia |
| -PIEZO1 gene mutation. | | Renal artery stenosis |
| | | End-stage renal disease |
| | | Hydronephrosis |
| | | Renal cysts (polycystic kidney disease) |
| | | EPO producing tumors |
| | | Cerebellar hemangioblastoma |
| | | Renal cell carcinoma |
| | | Hepatocellular carcinoma |
| | | Uterine leiomyoma |
| | | Pheochromocytoma |
| | | Meningioma |
| | | Drugs |
| | | Erythropoiesis-stimulating agents |
| | | Androgen preparations |
| | | Testosterone |
| | | Diuretics |
| | | Anti-diabetic agents (sodium-glucose cotransporter 2 inhibitors) |
| | | Others |
| | | Alcohol excess |
| | | Post renal transplant |
| | | TEMPI syndrome |
| 3-Idiopathic erythrocytosis | | |

production. A low EPO level suggests primary erythrocytosis, while normal or elevated levels suggest secondary erythrocytosis. The physiological response to a rise in Hb is suppression of the EPO level, therefore with a raised Hb a normal EPO level suggests an increased EPO drive and therefore a secondary erythrocytosis. After careful history and examination of cases of erythrocytosis, measurement of serum EPO can aid in the diagnosis of erythrocytosis and guide the direction of further investigation.^{6,29}

Low EPO was considered a diagnostic marker for PV even before the discovery of *JAK2V617F* mutations and was used as a minor diagnostic criterion. A study showed that quantification of low EPO had excellent diagnostic accuracy. When combined a high Hct and the presence of *JAK2V617F* mutation, it had high sensitivity and specificity. However, adding EPO or *JAK2V617F* mutation did not improve

diagnostic accuracy, but combining both improved sensitivity without compromising specificity. A diagnosis of PV can be reliably made through a combination of Hct and qualitative *JAK2V617F* mutation analysis, but we would still strongly encourage use of EPO testing.³⁰ Studies have shown that multiple comorbidities can impact the levels of Hb and Hct in the body such as chronic obstructive pulmonary disease, obstructive sleep apnea, congestive heart failure, and liver cirrhosis. This can increase the level of erythropoietin (EPO). Therefore, the minor EPO criterion may not be entirely reliable for patients with these conditions in addition to PV.³¹

Concerning secondary erythrocytosis EPO levels can be normal or high. The finding of a high EPO level certainly indicates a secondary erythrocytosis either congenital or acquired. This finding will prompt further evaluation for congenital gene mutations if seems appropriate

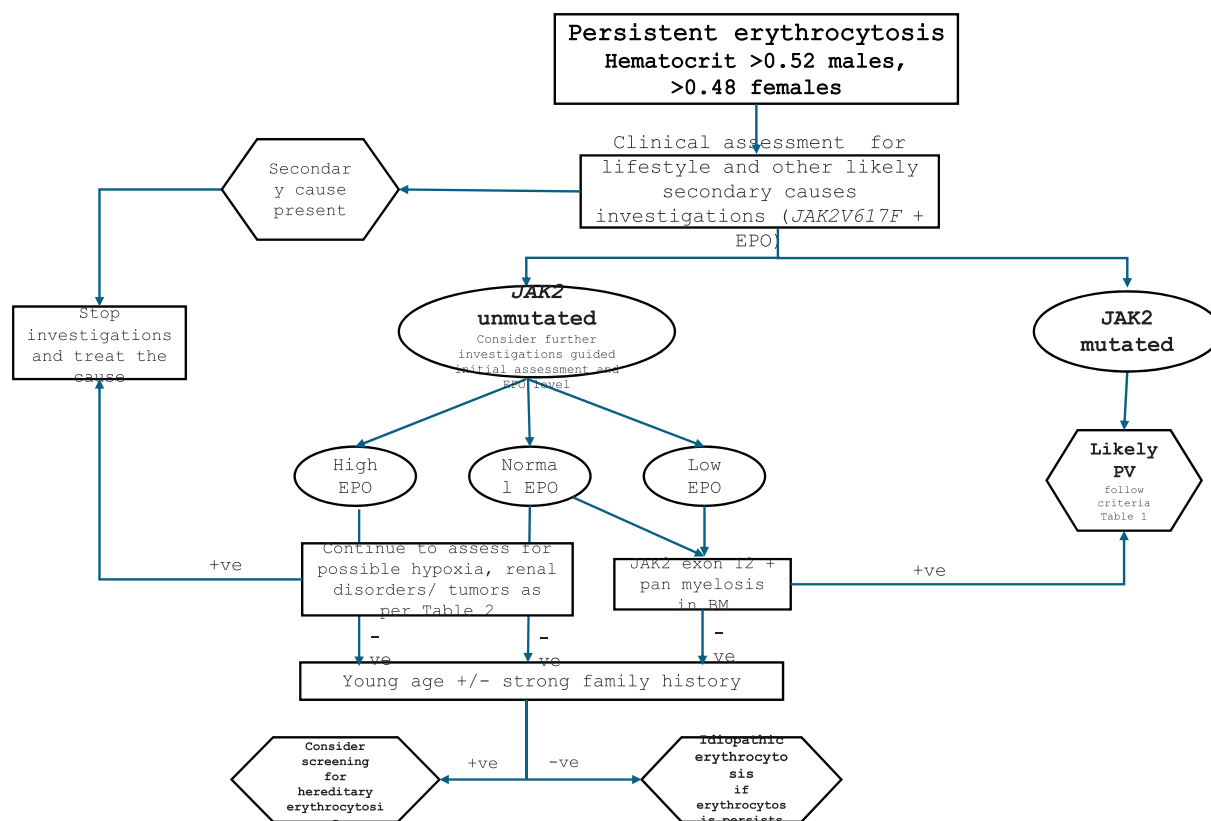


FIGURE 1 Investigations of erythrocytosis (Source: adapted from BSH guidelines of PV 2019)⁶

and evaluation for acquired secondary cause such as EPO-producing tumors (Table 2).

3.2 | Bone marrow biopsy

Bone marrow biopsy is an important diagnostic tool for distinguishing specific subtypes of myeloproliferative disorders and the histopathology of bone marrow is highly predictive in distinguishing PV from secondary polycythemia.²⁰ The bone marrow biopsy of PV patients displays hypercellularity for their age with trilineage growth (panmyelosis) with erythroid, granulocytic, and megakaryocytic proliferation. The megakaryocytes are pleomorphic and mature with differences in size.¹⁵ However, according to the WHO classification and ICC, a bone marrow biopsy is not necessary for diagnosing cases with a JAK2 mutation and sustained erythrocytosis (Hb levels). 18.5 g/dL in men (Hct, 55.5%) or 16.5 g/dL in women (Hct, 49.5%).^{22,23}

Up to 20% of patients show BM fibrosis ≥ 1 ,^{15,32} which increases the risk of progression to post-PV myelofibrosis, but has no impact on overall or leukemia-free survival.^{33,34} Although such events do not alter the diagnostic label if other WHO-defined formal criteria are fulfilled, they may have a significant impact on prognosis³² and future treatment decision-making. The bone marrow examination at diagnosis facilitates the detection of abnormal karyotype.³² The most frequent sole abnormalities were +9 (5%), Loss of Y (4%), +8 (3%), and

del(20q) (3%) which have shown to have an adverse impact on overall survival and leukemia-free survival.³⁵

3.3 | Mutational testing/next-generation sequencing (NGS)-PV

The JAK2V617F mutation was the first disease-driver mutation detected in MPN. Almost all (c.98%) patients with PV are positive for JAKV617F (exon 14) mutation, and the remaining patients mainly present alterations in JAK exon 12. Its presence is considered a major diagnostic criterion of PV (see above). As a consequence, this test is often the first one performed and is often recommended for patients with atypical venous thrombosis especially cerebral and splanchnic.⁶ In the absence of a JAK2 mutation, the diagnosis of PV becomes less likely, and workup for secondary erythrocytosis is advised.^{6,32}

It has been demonstrated that both peripheral blood and bone marrow samples provide equally informative results in the detection and quantification of JAKV617F mutation, with a sensitivity and specificity of 100%.^{32,36} The JAK2V617F test is reliable in identifying PV from other causes of increased Hb/Hct with a sensitivity rate of 97% and a specificity rate of almost 100%.³²

A variety of different techniques can be used to detect JAK2 mutations including allele-specific PCR, sanger sequencing, and NGS. There are pros and cons of each methodology which are discussed in Cross et al.³⁷ The level of sensitivity of the test is important and is recommended to be >1%.

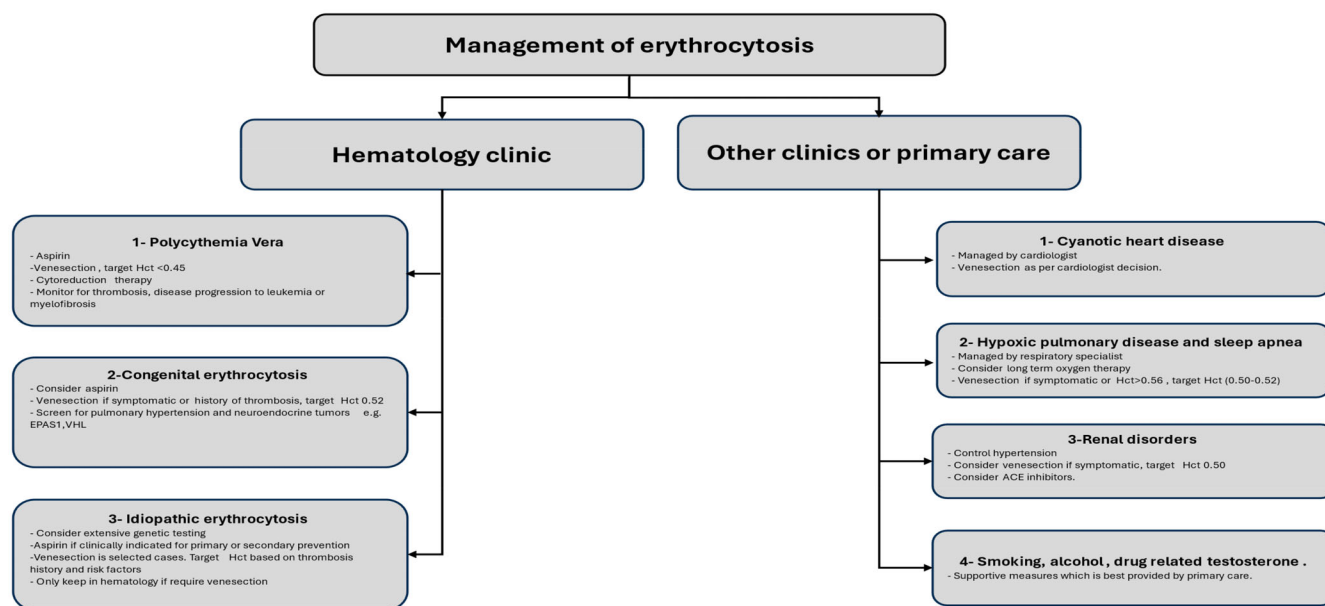


FIGURE 2 Management of erythrocytosis (Source: adapted from BSH guidelines 2019).⁶

The emergence of next-generation sequencing (NGS) has enabled the identification of non-driver mutations in 53% of patients with PV.³⁸ Like other MPNs, these include mutations involved in alternative splicing (e.g., *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*), epigenetic mutations (e.g., *TET2*, *DNMT3A*, *IDH1*, *IDH2*, *ASXL1*, *EZH2*), miRNA deregulation and intracellular signaling (e.g., *SH2B3*, *NF1*, *NRAS*, *KRAS*, *CBL*, *FLT3*, *PPM1D*, *ERBB*) and several transcription factors (e.g., *NF-E2*, *TP53*, *RUNX1*, *CUX1*, *ETV6*).³⁹ The most common mutations were in *TET2*, *ASXL1*,^{38,39} and *DNMT3A*.³⁹ The combined prevalence of mutations in *ASXL1*, *SRSF2*, and *IDH2* were 15% cases. These are adverse mutations, as they were associated with inferior survival rates and significant risks for leukemia-free and myelofibrosis-free survival.³⁸ Recently, genetic mutations of the *NF-E2* and *LNK* (*SH2B3*) genes have been found to be a potential source of PV development.³⁹ Currently, NGS is used to screen for other mutations in PV, maybe risk stratification now and in the future.^{40,41} This type of risk stratification may help in long-term therapeutic strategy.

3.4 | Mutational testing/next-generation sequencing-congenital erythrocytosis

Congenital erythrocytosis is extremely rare but over time new genetic lesions have been discovered. They should be suspected in young patients with long-standing erythrocytosis or those with a family history.^{6,25,42} These include mutations in the *EPO* receptor and genes in the oxygen sensing pathway (*VHL*, *EGLN1*, *EGLN2*, *EPAS1*), high oxygen affinity haemoglobinopathies caused by mutations in the globin genes *HBA1*, *HBA2*, *HBB*, and 2,3-bisphosphoglycerate deficiency as a result of *BPGM* mutations (Table 2). Guidance for further investigations and mutational analysis of patients with suspected hereditary erythrocytosis were based in the past upon *EPO* levels and *P50*

analysis.⁶ Serum *EPO* is low in patients with *EPOR* mutations, while it is normal or high in other types of congenital erythrocytosis. However, NGS panels for testing genes associated with hereditary erythrocytosis are becoming available. These panels include all the known genes associated with congenital erythrocytosis and the globin genes. It is likely by looking directly at the genetic sequence that such panels will gradually replace the labor-intensive and time-consuming like *P50* measurements a test which is now rarely available.^{6,25}

The challenges of NGS testing are well recognized. A major challenge is the assessment of a Variant of Unknown Significance (VUS), especially in the rare disease setting. Attempts to address this conundrum have accumulated in large collaborations facilitating in silico studies and further exploration of family studies.⁴³ Again, through collaborations, issues such as non-coding regions will be addressed. Currently many barriers exist for the inclusion of non-coding regions in the rare disease setting. This is due to the lack of knowledge of the associated variant. However, progress has been made in this area when disease-causing non-coding regions have been discovered using phenotypically selected cohorts. This field will continue to develop and impact selection and updating panel design.

However, there are certain regions where a particular mutation in the genes in the oxygen sensing pathway is suspected as the likely candidate gene. For instance, in central Asia and Northern India the *VHL* mutation found in Chuvash polycythemia is more common. In such areas, it may make sense and be less expensive to exclude *VHL* mutations by end-point PCR as an initial investigation.

3.5 | Workload management in hematology

When a patient is referred with an increased Hb, the clinician may want a *JAK2* mutation screen carried out before referral. This will

allow the identification of those with acquired clonal disease who should be referred to hematology. Those who are negative and do not have acquired clonal disease but have other non-hematological causes for the raised Hb may avoid referral to hematology.

Once a patient has been assessed, we follow the BSH guidelines⁶ avoiding the indiscriminate introduction of venesection or phlebotomy preferring instead that patients have the primary cause of their abnormality assessed and addressed.

We would consider that those patients who should attend a hematology service would include those patients with PV and selected patients with inherited or idiopathic erythrocytosis. This may also include the rarer patients with secondary erythrocytosis who are treated with venesection. Those with non-hematological causes of secondary erythrocytosis should be followed by the appropriate specialty or primary care (see Figure 2). There are a group of patients now being identified with Clonal Hematopoiesis of Indeterminate Potential (CHIP). Services for patients with a diagnosis of CHIP still need to be specified and these patients may be followed in primary care or in hematology clinics.

4 | CONCLUSION

The investigation pathway for patients with a suspected erythrocytosis has evolved over the past two decades as a result of new findings improving our understanding of the pathogenesis of conditions such as PV—for example, the JAK2 mutations. In addition, there have been advances in technology. Examples of this would include improvements in EPO assays and the development of NGS approaches making other diagnostic tests such as p50 and EEC largely redundant. The pathway for investigating and indeed managing these patients is complex but can be navigated with a thorough and evidence-based approach with a high degree of accuracy. This is important as suspicion of erythrocytosis is a common cause for referral and finding on routine blood tests. Knowledge of the patient's history, lifestyle, medications and situation is vital to this process.

AUTHOR CONTRIBUTIONS

All authors contributed to the writing of the manuscript, revised and approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest for this paper.

DATA AVAILABILITY STATEMENT

No new data in this manuscript.

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