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SPOTLIGHT REVIEW

Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms

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The 2001 World Health Organization (WHO) treatise on the classification of hematopoietic tumors lists chronic myeloproliferative diseases (CMPDs) as a subdivision of myeloid neoplasms that includes the four classic myeloproliferative disorders (MPDs)—chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF)—as well as chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES) and 'CMPD, unclassifiable'. In the upcoming 4th edition of the WHO document, due out in 2008, the term 'CMPDs' is replaced by 'myeloproliferative neoplasms (MPNs)', and the MPN category now includes mast cell disease (MCD), in addition to the other subcategories mentioned above. At the same time, however, myeloid neoplasms with molecularly characterized clonal eosinophilia, previously classified under CEL/HES, are now removed from the MPN section and assembled into a new category of their own. The WHO diagnostic criteria for both the classic *BCR–ABL*-negative MPDs (that is PV, ET and PMF) and CEL/HES have also been revised, in the 2008 edition, by incorporating new information on their molecular pathogenesis. The current review highlights these changes and also provides diagnostic algorithms that are tailored to routine clinical practice.
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Introduction

When William Dameshek (1900–1969) described the concept of 'myeloproliferative disorders (MPDs)' in 1951,[1] he considered chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and erythroleukemia (Di Guglielmo's syndrome) as the original members of the group. Over the years, erythroleukemia has been re-defined as acute erythroid leukemia or its variants,[2] leaving the other four as the classic MPDs. In its 2001 monograph,[3] the World Health Organization (WHO) committee for the classification of myeloid neoplasms assigned the classic MPDs under the broader category of chronic myeloproliferative diseases (CMPDs), which also included chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES) and 'CMPD, unclassifiable'.[4] The CMPDs were in turn considered as one of four major categories of chronic myeloid neoplasms, the other three being myelodysplastic syndromes (MDSs), MDS/MPD and mast cell disease (MCD).[3]

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It is now well established that CMPDs share a common stem cell-derived clonal heritage[5] and their phenotypic diversity is attributed to different configurations of abnormal signal transduction, resulting from a spectrum of mutations affecting protein tyrosine kinases or related molecules.[6,7] In principle, therefore, histology-based classification and diagnostic criteria for these disorders can be refined by employing molecular disease markers; for example, the presence of *BCR–ABL* in the context of a chronic myeloid neoplasm is pathognomonic of CML. Accordingly, the 2008 revision of the WHO document on the classification and diagnosis of CMPDs (now referred to as myeloproliferative neoplasms) has incorporated new information on the molecular pathogenesis of both *BCR–ABL*-negative classic MPDs[8–15] and clonal eosinophilic disorders.[16–19] In the current review, we discuss these changes and provide practical diagnostic algorithms that are in line with the formal 2008 WHO criteria.

The 2001 WHO classification system for chronic myeloid neoplasms

As mentioned above, the 2001 WHO classification system recognizes four separate categories of chronic myeloid neoplasms: CMPD, MDS, MDS/MPD and MCD.[3] The CMPD category includes the four classic MPDs (that is CML, PV, ET and PMF) as well as CNL, CEL/HES and 'CMPD, unclassifiable'.[4] The central and shared feature in CMPDs is effective clonal myeloproliferation (that is peripheral blood granulocytosis, thrombocytosis or erythrocytosis) that is devoid of dyserythropoiesis, granulocytic dysplasia or monocytosis. The presence of any one of the latter three features mandated disease assignment to either the MDS or MDS/MPD category.[3]

Myelodysplastic syndromes is considered when myeloid cell dysplasia (one or more lineages) is associated with ineffective hematopoiesis (that is peripheral blood cytopenia).[20] In this regard, although dyserythropoiesis is a common and diagnostic feature in MDS, unilineage dysplasia affecting a non-erythroid cell line can occur in MDS-unclassified (that is neutropenia or thrombocytopenia associated with dysplasia that is restricted to either the granulocyte or megakaryocyte lineage). It should be noted, however, that abnormal megakaryocyte morphology is also seen in CMPD but, in this instance, it is associated with peripheral blood thrombocytosis, granulocytosis or erythrocytosis.

The MDS/MPD category is also characterized by erythroid and/or granulocytic dysplasia.[3] Unlike the case with MDS, however, there is peripheral blood evidence of effective myeloproliferation, often in the form of leukocytosis and/or monocytosis. In other words, patients with MDS/MPD display features that are characteristic of both MDS and CMPD. Included in the MDS/MPD category are chronic myelomonocytic

leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML) and 'MDS/MPD, unclassifiable'.[3] It should be noted that the 'M' in aCML stands for 'myeloid' as opposed to 'myelogenous', which is the case in CML.

As for the subcategories of MDS/MPD, diagnoses in both CMML and JMML require the presence of peripheral blood monocytosis ($\geqslant 1 \times 10^9$ l^{-1}). In aCML, *BCR–ABL*-negative left-shifted granulocytosis is accompanied by granulocytic dysplasia.[21] 'MDS/MPD, unclassifiable' is reserved for the clinical phenotype that displays histological characteristics of both MDS and MPD and yet does not fulfill the diagnostic criteria for CMML, JMML or aCML.[3] 'MDS/MPD, unclassifiable' includes the WHO provisional entity of 'refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T)'; however, the use of the term RARS-T should be restricted to patients who display both dyserythropoiesis (in addition to ringed sideroblasts) and megakaryocytes similar to those in ET, PV or PMF.[22,23]

The 2008 WHO classification of myeloproliferative neoplasms

In the revised 2008 WHO classification system for chronic myeloid neoplasms, the phrase 'disease', in both CMPD and MDS/MPD, is replaced by 'neoplasm'; that is 'CMPD' is now referred to as 'myeloproliferative neoplasm (MPN)' and 'MDS/MPD' as 'myelodysplastic/myeloproliferative neoplasm (MDS/MPN)'. In addition, the MPN category now includes MCD whereas the previous CMPD subcategory of CEL/HES is now reorganized into HES, 'CEL not otherwise categorized (CEL-NOC)' and 'myeloid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*' (Table 1).[16–19] The latter group is now assigned a new category of its own whereas both HES and CEL-NOC remain subcategories of MPNs (Table 1). These revisions underscore (i) the neoplastic nature of CMPDs, thus the change from 'disease' to 'neoplasm',[24–33] (ii) the fact that MCD represents another clonal stem cell disease that is akin to other members of MPNs[34–36] and (iii) the presence of molecularly distinct categories among patients with primary eosinophilia.[16–19]

Table 1 The 2008 World Health Organization classification scheme for myeloid neoplasms

1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
   - 3.1 Chronic myelogenous leukemia
   - 3.2 Polycythemia vera
   - 3.3 Essential thrombocythemia
   - 3.4 Primary myelofibrosis
   - 3.5 Chronic neutrophilic leukemia
   - 3.6 Chronic eosinophilic leukemia, not otherwise categorized
   - 3.7 Hypereosinophilic syndrome
   - 3.8 Mast cell disease
   - 3.9 MPNs, unclassifiable
4. MDS/MPN
   - 4.1 Chronic myelomonocytic leukemia
   - 4.2 Juvenile myelomonocytic leukemia
   - 4.3 Atypical chronic myeloid leukemia
   - 4.4 MDS/MPN, unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
   - 5.1 Myeloid neoplasms associated with PDGFRA rearrangement
   - 5.2 Myeloid neoplasms associated with PDGFRB rearrangement
   - 5.3 Myeloid neoplasms associated with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

The 2008 WHO diagnostic criteria for PV, ET and PMF

The first formal attempt in establishing diagnostic criteria for the classic, *BCR–ABL*-negative MPNs focused on PV and was undertaken by the Polycythemia Vera Study Group (PVSG), in 1967.[37] The PVSG subsequently published similar diagnostic criteria for ET.[38] However, the PVSG 'diagnostic' criteria for PV and ET were formulated, primarily, to exclude other causes of erythrocytosis and thrombocytosis, respectively, and establish uniformly applied criteria for entering patients into clinical trials. A major weakness of the PVSG criteria was its suboptimal use of bone marrow histology as a diagnostic tool, which was effectively addressed by the 2001 WHO diagnostic criteria.[4]

The revisions[39] in the 2008 WHO diagnostic criteria for PV, ET and PMF were instigated by the discovery of *JAK2* mutations (for example. *JAK2*V617F, *JAK2* exon 12 mutations) in virtually all patients with PV.[8–13,40–45] Because *JAK2*V617F is myeloid neoplasm-specific and not found in other causes of polycythemia,[46–48] it has lent itself to being a sensitive diagnostic marker for PV.[44] However, in the context of myeloid neoplasms, *JAK2*V617F is not specific for PV and is found in approximately 50% of patients with ET,[49–54] PMF[55,56] or RARS-T,[57–61] and at a lesser frequency in other myeloid neoplasms,[62–70] but not in lymphoid tumors.[46,71–73] Therefore, mutation screening for *JAK2*V617F cannot be used to distinguish one MPN from another, but it does complement histology in the diagnosis of both ET and PMF by excluding the possibility of reactive thrombocytosis or myelofibrosis (Table 2).

At present, laboratory detection of a *JAK2* mutation is not compulsory to make a PV diagnosis since an occasional patient might not display either an exon 12 or an exon 14 *JAK2* mutation in routine clinical samples.[13] Similarly, the absence of *JAK2*V617F has little diagnostic value in ET or PMF since approximately half of the patients are negative for the mutation.[50,55] Furthermore, current assay systems for screening *JAK2* mutations are not standardized and the possibility of both false-positive or false-negative test results should not be ignored, especially in the context of highly sensitive allele-specific assays and low mutant allele burden in the peripheral blood, respectively.[42,74] These issues were taken into account in preparing the revised 2008 WHO document, where MPD-consistent bone marrow histology is listed as a required criterion for the diagnosis of ET, PMF and *JAK2* mutation-negative PV and biologically relevant laboratory and clinical markers are added as minor criteria to solidify a specific diagnosis (Table 2).[39] Finally, the availability of a molecular marker (that is *JAK2*V617F) along with increased utility of bone marrow histology has made it possible to lower the platelet count threshold for ET diagnosis from 600 to 450×10^9 l^{-1} and to consider a PV diagnosis at a lower than the WHO-defined hemoglobin target, in the presence of a persistent increase in hemoglobin level in excess of 2 g dl^{-1} from baseline (Table 2).[75,76]

Point-of-care diagnostic algorithms in PV, ET, PMF and primary eosinophilia

An 'increased' hemoglobin or hematocrit does not always equate with a true increase in red cell mass (that is true polycythemia) whereas true PV can sometimes be masked by a normal-appearing hematocrit because of an associated increase

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Table 2 The 2008 World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis

2008 WHO diagnostic criteria

	Polycythemia vera[a]	*Essential thrombocythemia*[a]	*Primary myelofibrosis*[a]
Major criteria	1 Hgb $>18.5\,g\,dl^{-1}$ (men) $>16.5\,g\,dl^{-1}$ (women) or Hgb or Hct >99th percentile of reference range for age, sex or altitude of residence or Hgb $>17\,g\,dl^{-1}$ (men), or $>15\,g\,dl^{-1}$ (women) if associated with a sustained increase of $\geqslant 2\,g\,dl^{-1}$ from baseline that cannot be attributed to correction of iron deficiency or Elevated red cell mass >25% above mean normal predicted value	1 Platelet count $\geqslant 450\times10^{9}\,l^{-1}$	1 Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).
	2 Presence of *JAK2*V617F or similar mutation	2 Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid Proliferation.	2 Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
		3 Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3 Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive marrow fibrosis
		4 Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive thrombocytosis	
Minor criteria	1 BM trilineage myeloproliferation 2 Subnormal serum Epo level 3 EEC growth		1 Leukoerythroblastosis 2 Increased serum LDH 3 Anemia 4 Palpable splenomegaly

Abbreviations: CML, chronic myelogenous leukemia; EEC, endogenous erythroid colony; Epo, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; WHO, World Health Organization.
[a]Diagnosis of polycythemia vera (PV) requires meeting either both major criteria and one minor criterion or the first major criterion and 2 minor criteria. Diagnosis of essential thrombocythemia requires meeting all four major criteria. Diagnosis of primary myelofibrosis (PMF) requires meeting all three major criteria and two minor criteria.
[b]Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

in plasma volume, especially in the presence of marked splenomegaly (that is inapparent PV).[77,78] As such, the distinction among the three *BCR–ABL*-negative classic MPNs (that is PV, ET and PMF) is not always apparent from the hemoglobin or hematocrit reading. In the past, the PVSG advocated the use of red cell mass (RCM) measurement to address the aforementioned shortcomings in the diagnosis of PV.[79] However, such practice was based mostly on a conceptual argument rather than systematic evidence and the 2001 WHO criteria instead emphasized the value of histology in this regard.[80–82]

The association of a *JAK2* mutation with virtually all patients with PV has erased any residual interest in the use of RCM measurement for distinguishing PV from 'secondary' or 'apparent' polycythemia.[13,83,84] Therefore, peripheral blood *JAK2*V617F screening is currently the preferred initial test for evaluating a patient with suspected PV (Figure 1).[85–90] In this regard, we encourage the concomitant determination of serum erythropoietin (Epo) level in order to minimize the consequences of false-positive or false-negative molecular test results (*vide supra*), and also address the infrequent but possible occurrence of *JAK2*V617F-negative PV.[13,74,91–93] In other words, it is highly unlikely that true PV will be both *JAK2*V617F-negative and display normal or elevated serum Epo level.[48] On the other hand, mutation screening for an exon 12 *JAK2* mutation and bone marrow examination should be considered in a *JAK2*V617F-negative patient who displays subnormal serum Epo level (Figure 1).[12,13]

Because *JAK2*V617F also occurs in approximately 50% of patients with either ET or PMF,[51] it is reasonable to include mutation screening in the diagnostic work-up of both thrombocytosis (Figure 2) and bone marrow fibrosis (Figure 3); the presence of the mutation excludes the possibility of reactive myeloproliferation (with the caveat that very low-level positivity might be encountered with use of highly sensitive allele-specific assays)[74] whereas its absence does not exclude an underlying MPN. As such, bone marrow morphological examination is often required for making the diagnosis of both ET and PMF (Figures 2 and 3).[94]

At times, the distinction between PV and *JAK2*V617F-positive ET/PMF might not be clear cut but the therapeutic relevance of being precise in this regard is dubious.[95] We therefore recommend, in such instances, strict adherence to the 2008 WHO criteria for making a working diagnosis and close monitoring of the patient to capture any substantial changes that might warrant revision of diagnosis. Similarly, the possibility of CML mimicking either ET or PMF should always be entertained, especially in the absence of *JAK2*V617F.[96–98] The

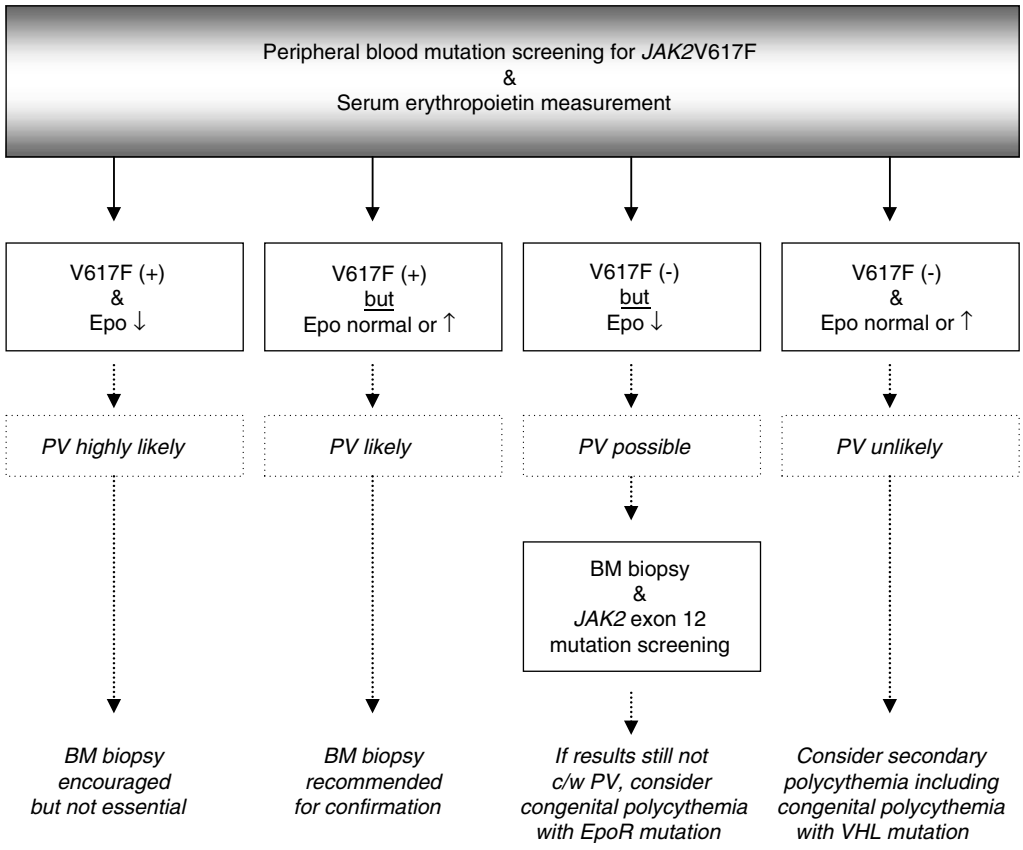

Figure 1 Diagnostic algorithm for suspected polycythemia vera. Key: PV, polycythemia vera; SP, secondary polycythemia; CP, congenital polycythemia; BM, bone marrow; V617F, JAK2V617F; Epo, erythropoietin; EpoR, erythropoietin receptor; VHL, von Hippel–Lindau; c/w, consistent with.

issue is addressed primarily by including cytogenetic studies during bone marrow examination for both PMF and ET and considering fluorescent *in situ* hybridization (FISH) for *BCR–ABL* in the absence of the Ph chromosome but the presence of dwarf bone marrow megakaryocytes (Figures 2 and 3).

Diagnosis in the non-classic MPNs (CNL, HES, CEL-NOC, MCD and 'MPN, unclassifiable'), in general, requires the absence of *BCR–ABL*, dyserythropoiesis, granulocyte dysplasia or monocytosis ($\geqslant 1 \times 10^9 l^{-1}$). CNL is considered in the presence of $\geqslant 25 \times 10^9 l^{-1}$ leukocytes in the peripheral blood accompanied by >80% segmented neutrophils or bands, <10% immature granulocytes and <1% myeloblasts (<5% blasts in the bone marrow).[99] When MCD is suspected, one should consider bone marrow examination with tryptase stain, bone marrow mast cell flow cytometry to look for phenotypically abnormal mast cells (that is CD25-positive), and if available, mutation screening for *KIT*D816V; a working diagnosis can be made in the presence of bone marrow aggregates of morphologically abnormal mast cells or, when histology is equivocal, the presence of either *KIT*D816V or phenotypically abnormal mast cells.[100] 'MPN, unclassifiable' is considered when an MPN clinical phenotype does not meet diagnostic criteria for either the classic or the other non-classic MPNs.[3]

Comprehensive and accurate evaluation of primary eosinophilia requires bone marrow examination with tryptase stain, T-cell clonal studies and immunophenotype, cytogenetic studies and molecular studies to detect *FIP1L1-PDGFRA*.[101] These studies should enable one to distinguish between 'molecularly-characterized myeloid neoplasms associated with eosinophilia', CEL-NOC, and HES (Figure 4). The former category includes *PDGFRA*, *PDGFRB* and *FGFR1* rearranged myeloid neoplasms associated with eosinophilia.[16–19] In the absence of these molecular markers, CEL-NOC or HES is considered; diagnosis in both requires the presence of $\geqslant 1.5 \times 10^9 l^{-1}$ PB eosinophil count, exclusion of secondary eosinophilia, exclusion of other acute or chronic myeloid neoplasm, and no evidence for phenotypically abnormal and/or clonal T lymphocytes.[102] In addition, diagnosis of HES requires absence of both cytogenetic abnormality, and >2% peripheral blasts or >5% bone marrow blasts (Figure 4).[102]

The future: towards genetic classification and diagnosis of myeloid neoplasms

The prospect of genetic classification and diagnosis in myeloid neoplasms started with the 1960 discovery of the Philadelphia (Ph) chromosome in CML.[103] Since then, the Ph chromosome has been molecularly characterized as *BCR–ABL*[104] and additional pathogenetically relevant mutations have been described in both other classic and non-classic MPNs: *JAK2*V617F in PV, ET and PMF;[8,9,11,105] *JAK2* exon 12 mutations in PV;[12,13,15] *MPL*W515L/K in ET or PMF;[41–43] *PDGFRA*, *PDGFRB* or *FGFR1* rearrangements in molecularly characterized myeloid neoplasms associated with eosinophilia;[16,18,19] *KIT*D816V and other *KIT* mutations in MCD;[106] and RAS pathway mutations, including *RAS*, *PTPN11* or *NF1*, in JMML.[107–109] Such discoveries in the molecular pathogenesis

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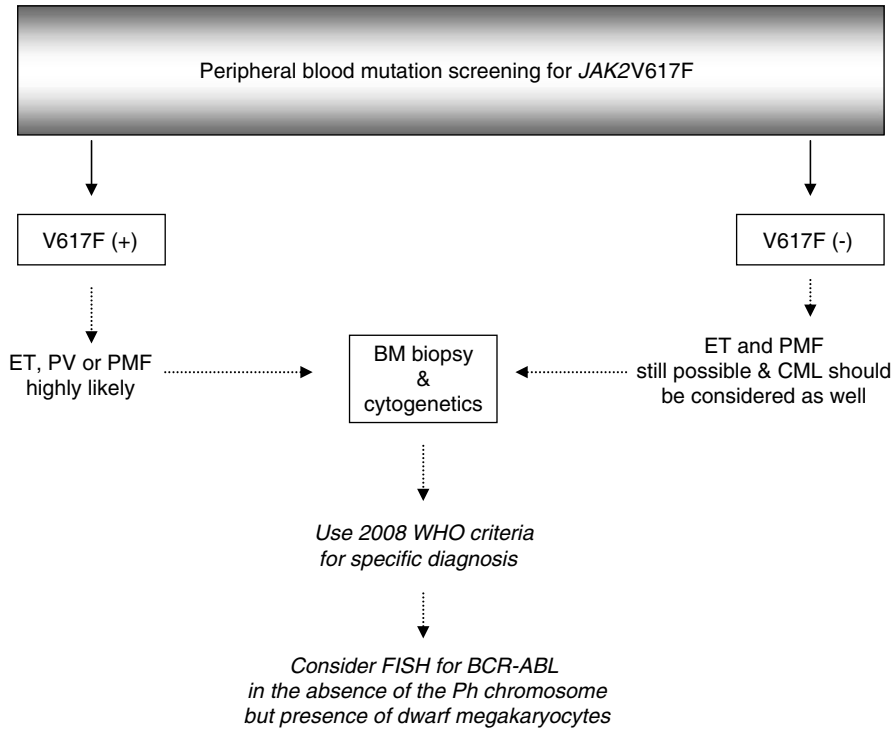

Figure 2 Diagnostic algorithm for suspected essential thrombocythemia. Key: PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WHO, World Health Organization; RT, reactive thrombocytosis; FISH, fluorescent *in situ* hybridization; Ph, Philadelphia; BM, bone marrow; V617F, JAK2V617F.

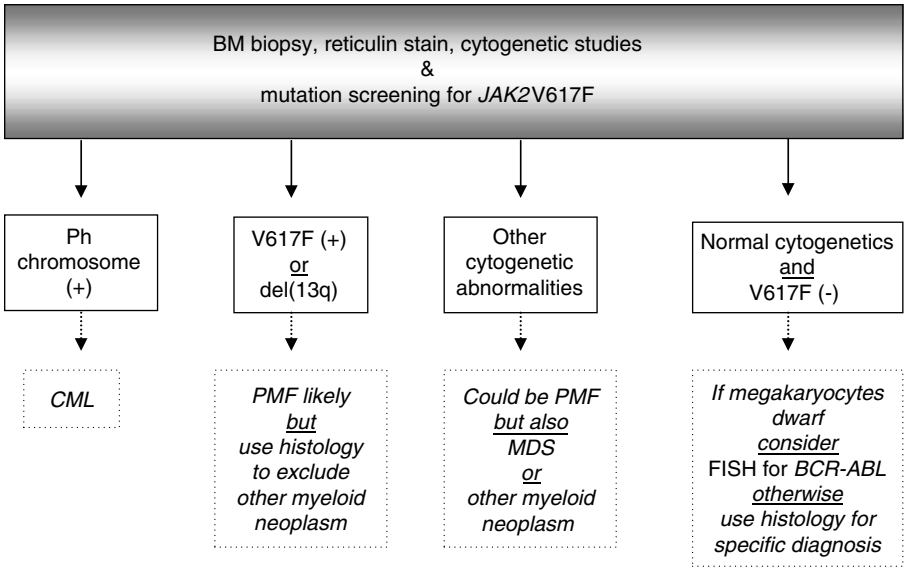

Figure 3 Diagnostic algorithm for suspected primary myelofibrosis. Key: PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; FISH, fluorescent *in situ* hybridization; Ph, Philadelphia; BM, bone marrow; V617F, JAK2V617F.

of myeloid neoplasms will ultimately lead to a predominantly genetic classification system with disease-specific molecular markers that are relevant to both diagnosis and treatment.[110] For example, mutation screening for *FIP1L1-PDGFRA* (detected by FISH or reverse transcriptase-polymerase chain reaction), *PDGFRB*-rearrangement (detected by karyotype or FISH) or *FGFR1* translocation (detected by karyotype) is now essential for accurate disease classification and choosing appropriate therapy in a patient with primary eosinophilia, thus validating the CML–*BCR–ABL* paradigm.[101] We expect more of such changes in future revisions of the WHO monograph as anatomic pathology continues to be enhanced by molecular information and the

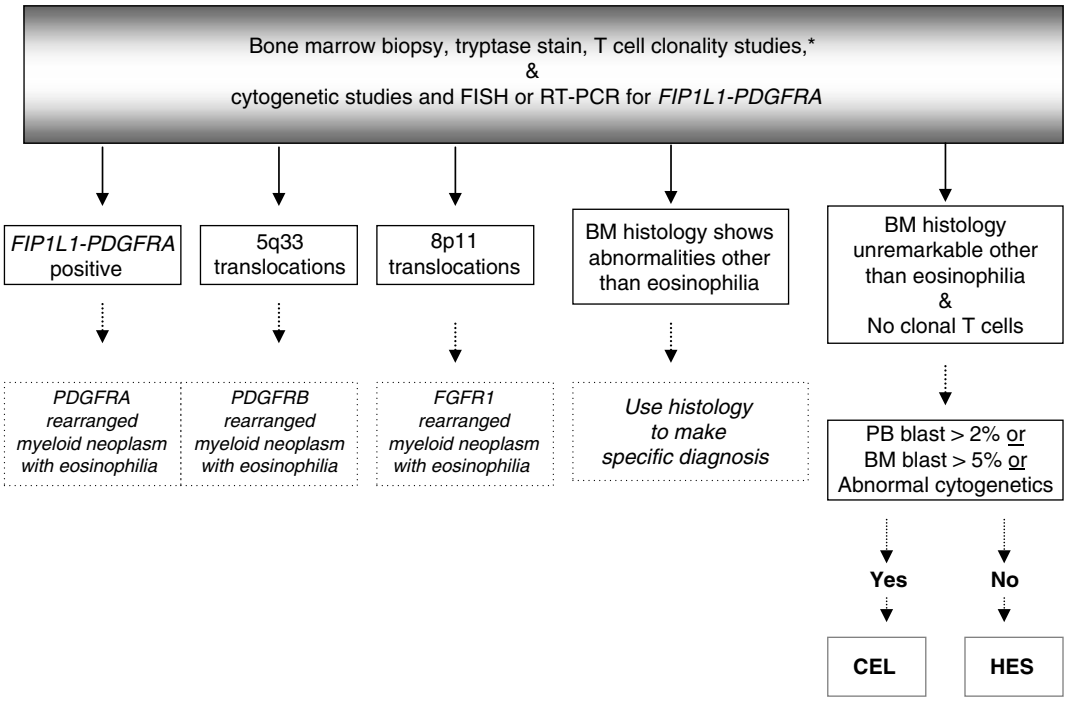

Figure 4 Diagnostic algorithm for primary eosinophilia ($\geqslant 1.5 \times 10^9\,l^{-1}$ blood eosinophil count). Key: CEL, chronic eosinophilic leukemia; HES, hypereosinophilic syndrome; FISH, fluorescent *in situ* hybridization; BM, bone marrow; PB, peripheral blood; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor. *T-cell receptor gene rearrangement studies and immunophenotyping.

natural history of molecular marker-positive but otherwise latent disease becomes better defined.[111–114]

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