

REVIEW ARTICLE

Polycythemia vera: Advances in molecular pathogenesis and emerging therapeutic strategies

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Abstract

Polycythemia vera (PV) is a classic Philadelphia chromosome-negative myeloproliferative neoplasm characterized by clonal erythrocytosis, expansion of myeloid lineages, and a high risk of thrombotic complications and progression to myelofibrosis or acute myeloid leukemia. The discovery of *JAK2* mutations, particularly *JAK2* V617F and exon 12 variants, has transformed the understanding of PV biology and established constitutive activation of Janus kinase (JAK)-signal transducer and activator of transcription signaling as a central pathogenic mechanism. However, PV pathogenesis extends beyond *JAK2* dependency and involves aberrant activation of mitogen-activated protein kinase and phosphoinositide 3 kinase-protein kinase B pathways, epigenetic dysregulation, chronic inflammation, niche remodeling, and metabolic reprogramming. Increasing evidence suggests that PV evolves through stepwise clonal expansion, influenced by co-mutations in *TET2*, *DNMT3A*, *ASXL1*, and other regulators of chromatin and DNA methylation. These molecular insights have facilitated the development of targeted therapies, including JAK inhibitors, interferon formulations, epigenetic modulators, and metabolism-targeting strategies. Yet, major clinical challenges persist, including treatment resistance, intolerance to cytoreductive therapy, inadequate disease modification, and the prevention of thrombotic and fibrotic progression. This review synthesizes current knowledge on the molecular mechanisms underlying PV pathogenesis and discusses therapeutic strategies that integrate genetic, inflammatory, and metabolic vulnerabilities, highlighting future opportunities for personalized therapy and disease interception.

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1. Introduction

Polycythemia vera (PV) is a chronic Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) defined by clonal expansion of hematopoietic stem and progenitor cells (HSPCs) with predominant erythroid proliferation.^{1,2} Clinically, PV presents with elevated hemoglobin/hematocrit, splenomegaly, constitutional and microvascular symptoms (for example, fatigue, pruritus, erythromelalgia), and an increased risk of arterial and venous thrombosis.¹⁻⁴ While PV most commonly affects middle-aged and older adults, younger patients are also affected, and the disease phenotype can vary substantially between individuals.⁵

The identification of activating mutations in *JAK2*, most notably *JAK2* V617F⁶⁻⁸ and less frequently exon 12 variants⁹⁻¹¹, fundamentally transformed the understanding of PV biology. These somatic alterations produce constitutive Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway activation, rendering HSPCs hypersensitive to cytokines such as erythropoietin and driving excessive erythropoiesis as well as expansion of myeloid lineages.¹⁰⁻¹⁴ Nevertheless, *JAK2* activation does not fully account for observed heterogeneity: allele burden¹⁵, mutation order, and co-occurring mutations in epigenetic regulators (eg, *TET2*, *DNMT3A*, *ASXL1*), spliceosome components, and metabolic genes modulate disease phenotype, progression risk, and therapeutic responses.^{12,16-26}

Beyond primary oncogenic lesions, PV pathogenesis is shaped by non-genetic processes, including epigenetic remodeling, sustained inflammatory signaling, metabolic reprogramming, and maladaptive interactions with the bone marrow microenvironment. Chronic inflammation, characterized by elevated cytokines such as interleukin (IL)-6, IL-1 β , and tumor necrosis factor (TNF)- α , contributes to symptom burden and selectively favors expansion of mutant clones.²⁷⁻³³ Metabolic adaptations in PV cells, including increased glutamine metabolism, oxidative phosphorylation, and reactive oxygen species (ROS) generation, further support proliferative capacity and may create exploitable therapeutic vulnerabilities.³⁴⁻³⁶ Microenvironmental remodeling, mediated by mutant megakaryocytes and altered stromal signaling, underlies progression to post-PV myelofibrosis (MF) in a subset of patients.^{37,38} Yet, the clinical utility of these molecular features remains limited by the lack of prospective validation and standardized intervention thresholds.

Therapeutically, management of PV balances thrombotic risk reduction and control of myeloproliferation.^{1,2} Phlebotomy and low-dose aspirin remain foundational for most patients, while cytoreductive therapy, predominantly hydroxyurea (HU), serves high-risk individuals.^{1,39-41} Interferon- α formulations offer disease-modifying potential with reductions in mutant allele burden^{42,43}, and JAK inhibitors such as ruxolitinib provide effective symptom control and spleen reduction, particularly in HU-resistant or -intolerant cases.^{44,45} Nonetheless, current therapies often fail to eliminate the malignant HSPC reservoir or reliably prevent progression to MF or acute leukemia.

This review synthesizes contemporary mechanistic insights into PV pathogenesis and examines how these advances inform current and emerging therapeutic strategies. Emphasis is placed on integrating genetic,

epigenetic, inflammatory, metabolic, and niche-related perspectives that collectively shape disease behavior and therapeutic opportunities.

2. Genetic landscape and clonal evolution in polycythemia vera

Polycythemia vera is fundamentally a clonal MPN driven by defined somatic mutations that alter signaling outputs in HSPCs. The pathogenic architecture of PV is characterized by a highly conserved hierarchy of driver mutations, a spectrum of cooperating genetic lesions, and an evolutionary trajectory that dictates clinical heterogeneity, disease progression, and therapeutic responsiveness. Understanding the genetic landscape is therefore central to elucidating PV biology and improving clinical management.

The canonical molecular hallmark of PV is the *JAK2* V617F mutation⁶⁻⁸, present in over 95% of cases.⁴⁶ This point mutation in exon 14 of the *JAK2* gene substitutes phenylalanine for valine at position 617, resulting in constitutive activation of the JAK-STAT signaling pathway independent of cytokine stimulation.⁴⁷⁻⁴⁹ Mutant *JAK2* promotes excessive proliferation and survival of erythroid, megakaryocytic, and myeloid progenitors, thereby establishing the phenotypic core of PV. In a minority of *JAK2* V617F-negative patients, *JAK2* exon 12 mutations, typically in-frame insertions, deletions, or duplications, generate similar hyperactive kinase signaling, predominantly driving erythrocytosis with fewer abnormalities in leukocyte and platelet lineages.^{9,50} *JAK2* exon 12-mutated PV often presents with isolated erythroid expansion and is more frequently diagnosed in younger individuals, highlighting a distinct clinical and molecular subtype.⁵¹

While *JAK2* mutations serve as the initiating events in nearly all PV cases, the full genomic landscape extends beyond these primary lesions.^{23,26} Cooperating mutations in epigenetic regulators are common and contribute to disease evolution. Genes encoding regulators of DNA methylation (*TET2*, *DNMT3A*), histone modification (*ASXL1*, *EZH2*), and chromatin remodeling (*IDH1/2*) frequently acquire somatic mutations during clonal expansion.^{12,16-26} These lesions modulate self-renewal capacity, transcriptional plasticity, and inflammatory signaling, enabling mutant clones to outcompete normal hematopoiesis. Notably, *TET2* and *DNMT3A* mutations often precede acquisition of *JAK2* V617F in a subset of patients, suggesting a stepwise, multilayered clonal evolution that mirrors age-related clonal hematopoiesis.^{17,21,25,52,53} In contrast, *ASXL1*, *EZH2*, and *IDH1/2* mutations are typically associated with later stages of disease and correlate with a higher risk of fibrotic transformation or leukemic progression.^{18,24,25,54,55}

Beyond epigenetic modifiers, mutations affecting RNA splicing machinery (*SRSF2*, *SF3B1*, *U2AF1*), transcription factors (*RUNX1*), and tumor suppressors (*TP53*) can emerge as subclonal events during the disease course.^{54,56} Although less frequent in classical PV, these lesions have substantial prognostic implications. The acquisition of high-risk mutations, particularly in *TP53*, *ASXL1*, and *SRSF2*, marks a molecular shift toward post-PV MF or blast-phase transformation. Such mutational patterns align with evolutionary pressure induced by inflammation, aging, and, in some instances, long-term cytoreductive therapy.⁵⁴

The dynamic process of clonal competition and selection drives the clinical phenotype of PV.¹⁵ Patients may harbor multiple genetically distinct clones at diagnosis, with the dominant clone determined by intrinsic proliferative advantage and extrinsic microenvironmental cues.⁵⁵ Longitudinal sequencing studies reveal that clonal complexity increases over time, even in clinically stable disease.^{57,58} Importantly, *JAK2* V617F allele burden itself correlates with disease features: higher allelic loads associate with increased erythrocytosis, splenomegaly, and thrombotic risk.^{15,58,59} Conversely, the emergence of additional driver mutations often shifts the disease toward fibrosis or leukemic transformation, underscoring the value of molecular surveillance.⁶⁰

Despite the rich genetic landscape described above, several important questions remain unanswered from a clinical standpoint. First, although higher *JAK2* V617F allele burden correlates with more pronounced erythrocytosis and thrombotic risk^{15,58,59}, prospective studies have not established a threshold above which cytoreductive therapy should be intensified or below which it can be safely de-escalated. Current guidelines continue to rely on age and thrombosis history rather than allele burden for risk stratification^{1,2}, representing a disconnect between molecular epidemiology and clinical decision-making. Second, the presence of co-mutations such as *ASXL1*, *SRSF2*, or *TP53* clearly associates with adverse outcomes^{61,62}, yet routine sequencing is not universally performed at diagnosis, and when performed, there is no consensus on how to act upon these findings. In addition, the observation that *TET2* or *DNMT3A* mutations often precede *JAK2* V617F^{17,21,25,52,53} has implications for understanding clonal evolution, but does this knowledge translate into a clinical action, such as monitoring individuals with clonal hematopoiesis of indeterminate potential who carry these mutations for progression to overt MPN? Currently, no such surveillance guidelines exist. While the genetic landscape of PV is increasingly well mapped, its integration into clinical practice remains aspirational rather than routine.

In summary, PV arises from a genetically driven clonal disorder of HSPCs dominated by *JAK2* mutations but shaped by a broad array of cooperating lesions that influence clonal fitness and clinical evolution (Table 1). Integration of genomic data into risk stratification frameworks is transforming contemporary PV management and informing precision-based therapeutic strategies. As sequencing technologies advance, delineating the timing, interplay, and functional consequences of PV-associated mutations will remain central to understanding disease biology and improving patient outcomes.

3. Molecular pathogenesis of polycythemia vera

Polycythemia vera arises from a series of molecular perturbations that disrupt the regulatory circuitry governing HSPCs. Although the disease is genetically initiated by activating *JAK2* mutations, its pathogenesis reflects a complex interplay among dysregulated cytokine signaling^{13,14}, aberrant epigenetic states^{12,16-26}, altered metabolic programs^{35,63,64}, and pathological interactions with the bone marrow microenvironment.^{37,38} These factors collectively drive erythrocytosis, myeloid hyperplasia, chronic inflammation, and the risk of progression to MF or acute leukemia.

As detailed in Section 2, *JAK2* mutations drive constitutive JAK-STAT activation. Mechanistically, this ligand-independent signaling generates persistent STAT3, STAT5, and STAT1 activation.^{10,65-68} These transcriptional programs induce expression of anti-apoptotic genes (e.g., *BCL-XL*, *MCL1*), cell cycle regulators (e.g., *CCND1*), and erythroid lineage determinants, thereby promoting cytokine-independent proliferation and survival.⁶⁹⁻⁷² Persistent STAT5 activation also enhances erythropoietin hypersensitivity, explaining the exaggerated erythroid response characteristic of PV.^{69,70}

Beyond canonical JAK-STAT signaling, mutant *JAK2* activates multiple downstream cascades, including the phosphoinositide 3 kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways.^{6,73-76} These signaling axes collectively enhance anabolic metabolism, protein synthesis, and cellular proliferation. Hyperactivation of PI3K-AKT-mTOR contributes to increased oxidative phosphorylation, elevated ROS, and metabolic reprogramming that favors expansion of mutant clones.^{73,76,77} Concurrent MAPK/ERK signaling supports cell cycle progression and megakaryocytic and granulocytic proliferation, thereby contributing to the pan-myeloproliferative phenotype observed in many patients.⁷⁴

Table 1. Key genetic alterations and their clinical and functional roles in PV

Mutation category	Representative genes	Primary functional impact	Clinical and biological relevance
Driver mutations	<i>JAK2</i> V617F ($\approx 95\%$), <i>JAK2</i> exon 12 variants	Constitutive JAK-STAT activation; cytokine-independent proliferation	Diagnostic hallmark; correlates with erythrocytosis, splenomegaly, pruritus; higher allele burden associated with increased thrombotic risk and progression to myelofibrosis
Epigenetic regulators	<i>TET2</i> , <i>ASXL1</i> , <i>DNMT3A</i> , <i>EZH2</i> , <i>IDH1/2</i>	Altered DNA methylation and histone modification; disrupted hematopoietic self-renewal	<i>TET2</i> and <i>DNMT3A</i> mutations may precede <i>JAK2</i> in clonal hierarchy; <i>ASXL1</i> and <i>EZH2</i> mutations predict poor prognosis and higher risk of leukemic transformation
Transcription factors	<i>TP53</i> , <i>RUNX1</i> , <i>ETV6</i>	Impaired genomic stability, transcriptional regulation, and lineage differentiation	Associated with aggressive disease phenotype; <i>TP53</i> mutations are enriched in post-PV AML; often late events in clonal evolution
Spliceosome components	<i>SRSF2</i> , <i>U2AF1</i> , <i>SF3B1</i>	Abnormal RNA splicing affecting multiple hematopoietic pathways	Occur in a minority of PV patients; confer poor prognosis and increased risk of myelofibrosis progression
Signaling pathway genes	<i>CBL</i> , <i>LNK/SH2B3</i> , <i>NRAS</i> , <i>KRAS</i>	Hyperactivation of cytokine and RAS-MAPK signaling	Frequently subclonal; associated with increased proliferative drive and progression to advanced MPN stages
Clonal hematopoiesis-associated genes	<i>TET2</i> , <i>DNMT3A</i> , <i>ASXL1</i> (CHIP-type mutations)	Age-related clonal expansion and altered hematopoietic fitness	Order of mutation acquisition influences phenotype: <i>TET2</i> -first tends to less thrombosis; <i>JAK2</i> -first confers higher thrombotic risk
Markers of clonal evolution and disease progression	<i>ASXL1</i> , <i>SRSF2</i> , <i>TP53</i> , <i>IDH1/2</i>	Accumulation of secondary mutations driving fibrosis or leukemic transformation	Predictive of poor outcome, ruxolitinib resistance, and inferior survival in post-PV myelofibrosis and AML

Abbreviations: AML: Acute myeloid leukemia; CHIP: Clonal hematopoiesis of indeterminate potential; JAK: Janus kinase; MAPK: Mitogen-activated protein kinase; MPN: Myeloproliferative neoplasm; PV: Polycythemia vera; RAS: Rat sarcoma proto-oncogene; STAT: Signal transducer and activator of transcription.

Epigenetic dysregulation further amplifies the pathogenic effects of mutant *JAK2*. Multiple studies have demonstrated that *JAK2* V617F localizes to the nucleus, where it phosphorylates histone H3 at tyrosine 41 (H3Y41), thereby excluding the chromatin-associated protein (heterochromatin protein 1 alpha) and altering transcriptional accessibility.⁷⁸⁻⁸³ This epigenetic rewiring enhances expression of critical hematopoietic regulators, including *MYC*. In addition, cooperating mutations in epigenetic modifiers, such as *TET2*^{16,25,84}, *DNMT3A*^{19-21,25}, *ASXL1*^{18,25,85,86}, and *EZH2*^{85,86}, perturb DNA methylation patterns and chromatin organization, establishing a permissive environment for sustained clonal expansion. These lesions impair differentiation pathways, reinforce self-renewal, and facilitate the transition from early PV to MF or leukemic transformation.

The pathogenesis of PV is also shaped by a distinctive pro-inflammatory milieu. While a comprehensive discussion of thromboinflammatory mechanisms is provided in Section 4, we briefly note here that mutant *JAK2* promotes excessive cytokine production, including IL-1 β , IL-6, TNF- α , and transforming growth factor

(TGF)- β , thereby establishing a chronic inflammatory state that accelerates clonal selection.^{29,46,87}

The bone marrow microenvironment itself is both a target and a driver of PV pathology. Mutant HSPCs demonstrate altered adhesion to stromal cells, mediated partly through dysregulation of CXCR4 and integrin pathways.^{88,89} This abnormal adhesion enhances niche retention of mutant cells while reducing their responsiveness to physiological regulatory mechanisms.⁹⁰ Concurrently, stromal cells exposed to pro-inflammatory cytokines become activated and secrete additional growth factors, creating a feed-forward loop that amplifies mutant cell fitness.⁹¹

Finally, metabolic reprogramming is increasingly recognized as an essential component of PV biology.^{34,92} *JAK2*-mutant HSPCs exhibit increased mitochondrial mass, enhanced oxidative phosphorylation, and elevated fatty acid oxidation.³⁵ These metabolic adaptations support the high proliferative activity of mutant clones and intersect with signaling pathways such as mTOR and STAT5 to sustain disease progression.^{34,66,73}

In summary, the molecular pathogenesis of PV is driven by constitutive JAK-STAT signaling, reinforced by cooperative epigenetic lesions, metabolic reprogramming, inflammatory activation, and pathological remodeling of the bone marrow niche. Although these processes are often presented as equally important, their relative contributions to PV pathogenesis differ substantially. JAK-STAT signaling is the primary driver, supported by the presence of *JAK2* mutations in >95% of patients and the clinical efficacy of JAK inhibitors.⁴⁶ However, *JAK2* mutations alone are not entirely sufficient for disease initiation, as evidenced by their detection in individuals with clonal hematopoiesis who never develop PV. Inflammation and metabolic reprogramming contribute importantly to disease progression and are closely intertwined with JAK-STAT signaling, yet no agent targeting these pathways alone has demonstrated clinical efficacy comparable to JAK inhibition in controlled trials, although this may reflect their interdependence rather than their irrelevance. Thus, while JAK-STAT remains the primary actionable node, inflammation and metabolism represent secondary vulnerabilities that warrant further investigation, particularly in combination with JAK inhibition. These interconnected processes underlie the hallmark features of PV and provide multiple opportunities for therapeutic intervention.

4. Disease progression and thromboinflammatory complications

Disease progression in PV follows a biologically complex and clinically heterogeneous trajectory, shaped by evolving genetic lesions, chronic inflammation, and cumulative alterations in the bone marrow microenvironment.⁹³ Although the majority of patients initially present with isolated erythrocytosis and a manageable symptom burden, PV is inherently a progressive clonal disorder. Over time, a subset of patients transitions to post-PV MF or leukemic transformation, conditions associated with markedly inferior prognosis.^{93,94} Parallel to this evolution, PV confers a persistent risk of thrombosis, a leading cause of morbidity and mortality, driven by the convergence of hematologic abnormalities, endothelial dysfunction, and inflammation-mediated vascular injury.^{95,96}

Clonal progression is underpinned by the acquisition of additional genetic and epigenetic alterations that enhance malignant fitness and disrupt normal hematopoietic regulation.⁹⁷ While *JAK2* V617F or *JAK2* exon 12 mutations initiate disease, secondary mutations in epigenetic regulators (*ASXL1*, *EZH2*, *DNMT3A*), splicing factors (*SRSF2*, *U2AF1*), and tumor suppressors (*TP53*) often emerge during advanced stages.¹⁰ These mutations

confer proliferative advantage, impair differentiation, and increase genomic instability.⁹⁸ Clinically, this molecular evolution manifests as progressive splenomegaly, anemia, constitutional symptoms, and increasing marrow fibrosis. The transition to post-PV MF is characterized by elevated levels of pro-fibrotic cytokines, such as TGF- β and platelet-derived growth factor, which stimulate stromal cell activation and extracellular matrix deposition, ultimately replacing normal hematopoietic tissue.⁹⁹⁻¹⁰¹

Chronic inflammation represents a critical driver of both disease progression and vascular risk in PV. *JAK2*-mutant hematopoietic cells secrete an array of inflammatory mediators, including IL-1 β , IL-6, TNF- α , C-X-C motif chemokine ligand 8 (CXCL8), and ROS, that propagate a pro-inflammatory and pro-fibrotic milieu.^{46,87,102} Persistent activation of neutrophils, monocytes, and platelets fuels systemic inflammation, contributing not only to the competitive advantage of mutant clones but also to thrombotic predisposition.¹⁰³⁻¹⁰⁷ Inflammatory cytokines further disrupt endothelial homeostasis, increase vascular permeability, and enhance the expression of adhesion molecules, thereby promoting aberrant interactions between blood cells and the endothelial surface.¹⁰⁸

The thrombotic complications of PV are among its most clinically significant features, accounting for a substantial proportion of disease-related deaths.⁹¹ Both arterial and venous thromboses are observed, with a predilection for cerebrovascular events, myocardial infarction, deep vein thrombosis, and splanchnic vein thrombosis.^{109,110} Several hematologic abnormalities characteristic of PV contribute to this risk. Elevated hematocrit increases blood viscosity, reducing laminar flow and promoting shear-induced platelet activation.^{111,112} Concurrent leukocytosis, particularly neutrophilia, plays an increasingly recognized pathogenic role.^{104,113} Activated neutrophils release neutrophil extracellular traps (NETs), web-like chromatin structures that activate platelets, facilitate coagulation, and damage the endothelium.¹¹⁴⁻¹¹⁶ Platelets themselves exhibit hyperactivity, driven by JAK-STAT-mediated signaling changes, increased thromboxane synthesis, and heightened interaction with leukocytes.^{117,118} Together, these disruptions create a highly thrombogenic cellular environment.

Endothelial dysfunction is another critical contributor to thromboinflammation.¹¹⁹ *JAK2* V617F is detectable not only in hematopoietic cells but also in endothelial cells in several patients, suggesting clonal involvement beyond the hematopoietic compartment.^{108,120,121} Mutant endothelial cells exhibit aberrant activation, increased expression of P-selectin and E-selectin, reduced nitric oxide production, and impaired antithrombotic signaling.^{118,119,122,123} These

abnormalities potentiate vascular inflammation and promote platelet adhesion, reinforcing the cycle of clot formation and vascular injury.

As the disease progresses, the interplay between clonal expansion, marrow fibrosis, and systemic inflammation becomes increasingly pathological. In advanced PV or post-PV MF, splenomegaly and extramedullary hematopoiesis exacerbate cytopenias, while elevated TGF- β levels foster a microenvironment conducive to further fibrosis and hematopoietic failure.¹²⁴⁻¹²⁶ Additionally, the emergence of high-risk mutations such as *TP53* or *IDH1/2* marks a shift toward leukemic transformation.¹²⁷ The resulting blast-phase PV or secondary acute myeloid leukemia is associated with poor response to therapy and a survival duration measured in months.¹²⁸

The mechanisms described above have direct implications for clinical practice. First, thrombosis risk in PV is not solely determined by hematocrit. Leukocytosis and systemic inflammation also directly promote thrombosis. From a clinical standpoint, patients with persistent leukocytosis or elevated inflammatory markers despite adequate hematocrit control warrant consideration of more intensive cytoreductive therapy, such as switching from HU to interferon or ruxolitinib, as these agents reduce inflammatory markers. Second, the detection of high-risk co-mutations during longitudinal follow-up, while not yet

justifying therapy change outside of clinical trials, should prompt two actions: (i) increased vigilance for clinical signs of progression (e.g., worsening splenomegaly, new cytopenias, constitutional symptoms); (ii) discussion with the patient about enrollment in prospective studies evaluating early intervention strategies in mutation-positive individuals. Third, the finding of endothelial *JAK2* V617F expression highlights a potential mechanistic link between the vasculature and thrombosis, but this remains investigational with no current clinical application.

In summary, disease progression and thromboinflammatory complications in PV arise from a multifaceted network of molecular, cellular, and microenvironmental abnormalities (Figure 1). Chronic inflammation, hematologic dysregulation, endothelial dysfunction, and clonal genetic evolution converge to drive both fibrotic transformation and heightened thrombotic risk. These mechanisms not only shape long-term clinical outcomes but also underscore the need for early risk assessment, targeted therapeutic intervention, and ongoing molecular monitoring throughout the disease course.

5. Current standard treatments

The current therapeutic landscape for PV is designed to reduce thrombotic risk, control myeloproliferation,

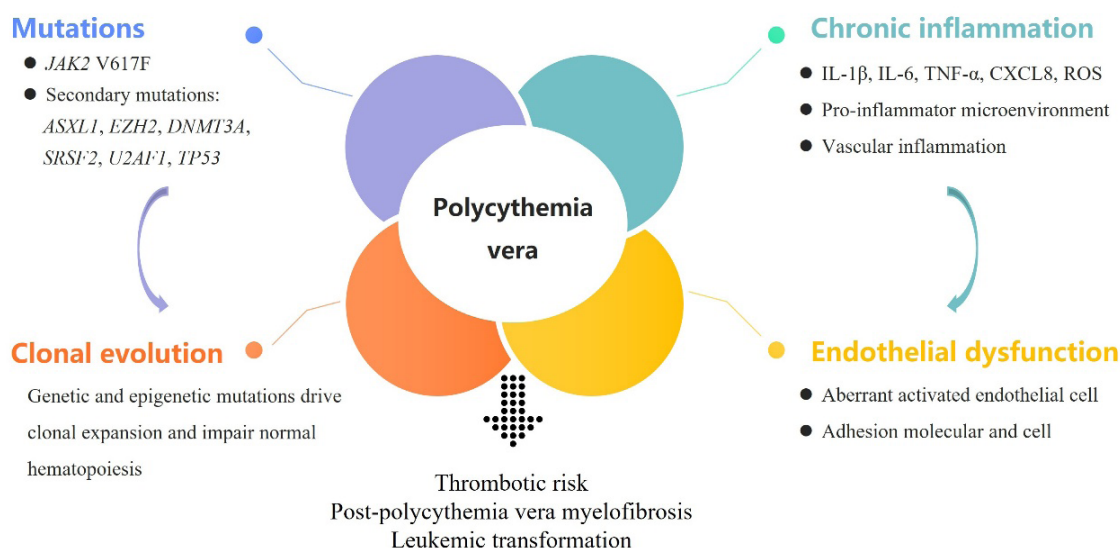


Figure 1. Integrated mechanisms in polycythemia vera and disease progression. The figure illustrates the interconnected drivers of polycythemia vera pathogenesis and their clinical consequences. Genetic drivers, including *JAK2* V617F mutations and cooperative lesions in second mutations, initiate clonal expansion (blue panel). Chronic inflammation (green panel) and endothelial dysfunction (brown panel) amplify disease severity and thrombotic risk. Clonal evolution toward myelofibrosis or leukemic transformation is driven by the accumulation of high-risk mutations (orange panel). Abbreviations: CXCL8: C-X-C motif chemokine ligand 8; IL: Interleukin; ROS: Reactive oxygen species; TNF: Tumor necrosis factor.

alleviate symptom burden, and delay disease progression (Table 2).^{1,2,129,130} Treatment decisions incorporate patient age, history of thrombosis, cardiovascular comorbidities, and molecular features such as *JAK2* allele burden. Standard risk stratification classifies patients into low-risk and high-risk categories, with emphasis on maintaining hematocrit control and mitigating thromboinflammation.^{1,2}

Phlebotomy and low-dose aspirin form the foundation of therapy for most patients.¹ Phlebotomy remains the most direct means of reducing hematocrit to below 45%, a threshold strongly associated with reduced risk of cardiovascular and thrombotic events.^{130,131} By decreasing blood viscosity and improving microvascular flow, phlebotomy provides rapid control of erythrocytosis.¹²⁹⁻¹³¹ In parallel, daily low-dose aspirin (75–100 mg) is recommended for nearly all PV patients without contraindications.^{41,130,132} Aspirin targets platelet hyperreactivity, reduces thromboxane-mediated aggregation, and attenuates microvascular symptoms such as erythromelalgia and headaches, thereby addressing key components of the thromboinflammatory milieu.^{41,133}

Patients designated as high-risk, typically those older than 60 years or with a prior thrombotic event, require cytoreductive therapy in addition to phlebotomy and aspirin.^{134,135} HU is the first-line cytoreductive agent due to its efficacy, tolerability, and long track record of use.¹³⁶ HU decreases erythroid, myeloid, and megakaryocytic proliferation, thereby reducing leukocytosis and

thrombocytosis, both of which contribute significantly to thrombotic risk.¹³⁶ For patients who are intolerant or resistant to HU, cytoreductive alternatives include interferon- α (particularly pegylated formulations) and ruxolitinib, a *JAK1/2* inhibitor.^{130,131}

Interferon- α has become increasingly favored in younger patients and women of childbearing potential due to its ability to induce molecular responses, reduce *JAK2* V617F allele burden, and restore more normal hematopoiesis.¹³⁷⁻¹³⁹ Pegylated interferon- α improves tolerability while preserving the immunomodulatory and anti-proliferative effects that may delay or prevent disease progression.^{139,140} Ruxolitinib, approved for PV that is refractory or intolerant to HU, exerts potent suppression of *JAK-STAT* signaling, improves hematocrit control, reduces splenomegaly, and alleviates symptom burden, including pruritus, fatigue, and microvascular disturbances.^{1,130,134,141,142} Importantly, ruxolitinib also mitigates inflammation and may reduce thromboinflammatory activity by lowering cytokine levels.⁶⁵

In addition to pharmacologic treatments, management includes rigorous control of cardiovascular risk factors such as hypertension, smoking, and hyperlipidemia, all of which modulate thrombosis risk in PV.^{143,144} Long-term monitoring of blood counts, spleen size, and molecular markers guides treatment adjustment and early detection of progression toward MF or leukemic transformation.

Table 2. Current standard treatments for PV

Therapeutic class	Agent/approach	Mechanism of action	Clinical benefits	Limitations/safety concerns
Phlebotomy	Phlebotomy	Reduces hematocrit and blood viscosity; restores HCT target < 45%	Rapid hematocrit normalization; first-line in low-risk PV	Does not control leukocytosis or thrombocytosis; iron deficiency; no effect on clonal evolution
Antiplatelet therapy	Low-dose aspirin	Irreversible COX-1 inhibition; decreases thromboxane A2 production	Reduces arterial thrombotic risk; improves microvascular symptoms	GI bleeding risk; limited benefit for venous thrombosis
Cytoreductive therapy (first-line)	HU	Inhibits ribonucleotide reductase; suppresses myeloid proliferation	Controls erythrocytosis, leukocytosis, thrombocytosis, and splenomegaly	HU resistance/intolerance (10–20%); cytopenias; mucocutaneous ulcers; possible leukemogenic concern
Interferon therapy	Pegylated IFN- α 2a/ropeginterferon- α -2b	Immune modulation; direct targeting of <i>JAK2</i> -mutant stem/progenitor cells; reduces allele burden	Disease-modifying potential; effective in young patients; molecular remissions	Flu-like symptoms; autoimmune complications; psychiatric toxicity; slower onset than HU
<i>JAK</i> inhibition (second-line)	Ruxolitinib	<i>JAK1/2</i> inhibition reduces inflammatory cytokine signaling	Effective in HU-resistant/intolerant PV; improves HCT, symptoms, and splenomegaly	Cytopenias; infections (herpes zoster); limited clonal eradication

Abbreviations: COX: Cyclooxygenase; GI: Gastrointestinal; HCT: Hematocrit; HU: Hydroxyurea; IFN: Interferon; *JAK*: Janus kinase; PV: Polycythemia vera.

The above summary presents an orderly picture of PV management, but real-world practice is considerably more complex. First, treatment sequencing is not standardized: when HU fails, guidelines recommend either pegylated interferon or ruxolitinib, but no head-to-head trials exist. Selection therefore depends on patient-specific factors. Interferon is generally preferred in younger patients or in those for whom disease modification is a priority, whereas ruxolitinib is often preferred in patients with significant splenomegaly or constitutional symptoms^{1,130,134,137-139,141,142}, though these recommendations rest on expert consensus rather than comparative efficacy data. Second, resistance to ruxolitinib is increasingly recognized yet poorly characterized in PV. No standardized definition exists, mechanisms of acquired resistance remain understudied, and management strategies (dose escalation, add-on HU, or switch to interferon) are supported only by case series. Third, real-world challenges include medication access and tolerability: ruxolitinib is expensive and not universally reimbursed; interferon causes flu-like symptoms and mood disturbances, leading to frequent discontinuation; and regular phlebotomy visits may place a substantial burden on working patients or those living in rural areas. These practical realities significantly affect outcomes and should inform guideline development.

6. Emerging and investigational therapies

The therapeutic landscape for PV is rapidly evolving as advances in molecular biology reveal new vulnerabilities in *JAK2*-mutant hematopoiesis. Although current standard therapies effectively control hematocrit and reduce thrombotic events, they do not fully address the underlying clonal architecture or prevent disease progression in all patients. Consequently, emerging therapies aim to modulate aberrant signaling pathways, target disease-driving stem cells, correct epigenetic dysregulation, and reduce inflammation to achieve deeper and more durable disease modification.^{1,2,130,145}

Novel interferon formulations represent a major area of therapeutic innovation. Ropeginterferon- α -2b, a long-acting mono-pegylated interferon, has demonstrated superior tolerability and sustained molecular responses compared with earlier interferons.^{146,147} Clinical studies show that ropeginterferon reduces *JAK2* V617F allele burden, restores polyclonal hematopoiesis, and may delay transition to MF.^{137,146,148} Its capacity to directly target the malignant clone and modulate immune responses positions it as a promising disease-modifying backbone for long-term therapy.

Second-generation JAK inhibitors are also under active evaluation. While ruxolitinib remains the only approved

JAK1/2 inhibitor for HU-resistant or -intolerant PV,^{1,130} investigational agents, such as fedratinib and momelotinib, may offer alternative mechanisms of JAK/STAT pathway suppression with improved symptom control or hematologic modulation.^{27,149-151} These agents may benefit patients with suboptimal responses to ruxolitinib and could broaden the therapeutic arsenal for advanced or refractory disease.

Given the central role of chronic inflammation and aberrant cytokine signaling in PV, targeting inflammatory pathways represents another promising strategy. Inhibitors of IL-1 β (e.g., canakinumab), IL-6, or TNF- α are being explored to reduce systemic inflammation, mitigate vascular injury, and potentially curtail clonal evolution.¹⁵²⁻¹⁵⁵ Modulation of NET formation and endothelial dysfunction is also under investigation to reduce thromboinflammatory risk.^{156,157}

Epigenetic regulators have emerged as critical contributors to clonal evolution, making them compelling therapeutic targets.¹⁵⁸ Agents targeting bromodomain and extra-terminal motif proteins¹⁵⁹, lysine-specific demethylase 1^{160,161}, or mutant *IDH1/2*¹⁶² may reverse transcriptional dysregulation and impair stem cell self-renewal. Early-phase studies suggest synergy between epigenetic inhibitors and interferon or JAK inhibitors¹⁶³, opening new avenues for combination therapy.

Finally, therapies directed at mutant hematopoietic stem cells are gaining momentum. Approaches involving cellular immunotherapy, including vaccines targeting mutant *JAK2* and *CALR* epitopes or engineered T-cell therapies, aim to selectively eliminate the malignant clone while sparing normal hematopoiesis.¹⁶⁴⁻¹⁶⁸ Although early in development, these strategies represent the frontier of precision and immune-based therapy in PV. The key emerging and investigational therapies discussed above are summarized in [Table 3](#).

Not all emerging approaches are equally likely to change clinical practice. We propose a three-tier framework based on current evidence: Tier 1 (ready for broader adoption) includes ropeginterferon- α -2b, with phase 3 data showing superior molecular responses and tolerability^{137,146,148}; Tier 2 (promising, needs confirmatory data) includes JAK inhibitor combinations with interferon or epigenetic agents, which have early phase promise but lack phase 3 data^{98,163,169}; Tier 3 (mechanistically attractive, unproven) includes anti-inflammatory, metabolic, and immunotherapeutic strategies, with no clinical data on PV-relevant endpoints. This framework aims to prioritize clinical and research efforts. Collectively, emerging and investigational therapies hold the promise of transforming the long-term management of PV by delivering deeper

Table 3. Emerging and investigational therapies for PV

Therapy type	Agent/strategy	Mechanism of action	Clinical benefits	Limitations/safety considerations
Epigenetic modulators	Givinostat (HDAC inhibitor)	Inhibits HDACs involved in JAK2-driven epigenetic changes; selectively suppresses JAK2-mutant cells	Hematologic response in HU-resistant PV; symptom improvement	GI toxicity; long-term safety evaluation ongoing
Iron metabolism regulators	Rusfertide (Hepcidin mimetic)	Restricts iron availability; suppresses erythropoiesis	Reduces or eliminates phlebotomy need; maintains HCT control	Injection-site reactions; long-term effects not fully known
p53 pathway activators	Idasanutlin (MDM2 inhibitor)	Activates p53-mediated apoptosis in JAK2-mutant progenitors	Potential clonal suppression; disease modification	GI toxicity; discontinuations in trials; program revised
Epigenetic repressors of stemness	Bomedemstat (LSD1 inhibitor)	Inhibits LSD1; interferes with self-renewal and megakaryocyte-driven fibrosis	Reduces allele burden, spleen size, and symptoms; slows fibrosis	Dysgeusia; cytopenias; requires longer-term validation
Long-acting interferon (investigational expansion)	Ropeginterferon- α -2b (new indications and combinations)	Durable IFN activity enabling sustained clonal targeting	Deeper molecular responses compared with HU; expanding first-line potential	IFN-related autoimmune and psychiatric toxicity
Next-generation JAK inhibitors	Fedratinib, momelotinib (under evaluation)	Alternative JAK inhibition with complementary selectivity	Potential options for HU-resistant or HU-intolerant patients: reduce inflammation	Fedratinib: GI toxicity/risk of Wernicke encephalopathy; momelotinib: anemia in other MPN
HSP90 inhibitors	HSP90 inhibitors	Destabilize JAK and multiple signaling proteins	Potential eradication of the malignant clone	Early-phase; high off-target toxicity
Combination therapies	IFN + JAK inhibitor + ruxolitinib	Dual pathway targeting (clonal + inflammatory suppression)	Enhanced hematologic and molecular responses; potential disease modification	Combination toxicity; optimal dosing not yet defined

Abbreviations: GI: Gastrointestinal; HCT: Hematocrit; HDAC: Histone deacetylase; HSP90: Heat shock protein 90; HU: Hydroxyurea; IFN: Interferon; JAK: Janus kinase; LSD1: Lysine-specific demethylase 1; MDM2: Mouse double minute 2 proto-oncogene; MPN: Myeloproliferative neoplasm; PV: Polycythemia vera.

molecular remissions, reducing thromboinflammation, and preventing disease progression.

7. Biomarkers for diagnosis, prognosis, and treatment response

Biomarkers play a central role in the modern diagnostic and therapeutic framework for PV, enabling accurate disease classification, risk stratification, and longitudinal monitoring (Figure 2).^{1-4,170,171} Advances in molecular genetics, immunophenotyping, and inflammatory profiling have expanded the range of clinically actionable biomarkers, allowing a more nuanced understanding of disease behavior and treatment responsiveness.

7.1. Diagnostic and prognostic biomarkers

JAK2 mutations remain the cornerstone of PV diagnosis.⁴⁶ Detection of the *JAK2* V617F mutation, present in approximately 95% of patients, or *JAK2* exon 12 mutations in the remaining patients, is incorporated into the World Health Organization diagnostic criteria.^{1,2,172} Higher allele burdens correlate with increased erythrocytosis, splenomegaly, pruritus, and thrombotic risk^{15,58,59,173}, suggesting closer thrombotic surveillance in these patients. Moreover, dynamic changes in allele burden can serve as molecular indicators of treatment efficacy, particularly in patients receiving interferon-based therapies, where progressive allele reduction is associated with restoration of polyclonal hematopoiesis.^{139,174-176} Beyond *JAK2*, co-mutation profiling has emerged as a powerful prognostic tool. Mutations in epigenetic regulators (*TET2*, *ASXL1*,

DNMT3A), splicing factors (*SRSF2*, *U2AF1*), and tumor suppressors (*TP53*) provide insight into clonal architecture and disease trajectory.⁹⁷ Certain mutations, such as *ASXL1*, *SRSF2*, or *TP53*, are associated with increased risk of leukemic transformation, reduced survival, and poor response to cytoreductive therapy.^{61,62} Comprehensive next-generation sequencing at diagnosis and during follow-up increasingly informs treatment decisions^{177,178}, although its routine application remains limited by cost and the lack of prospective data demonstrating that mutation-directed therapy improves outcomes.

7.2. Monitoring biomarkers

Hematologic and clinical biomarkers continue to guide routine disease management.² Hematocrit remains the primary biomarker for monitoring therapeutic adequacy, with sustained reductions below 45% associated with a significant reduction in major cardiovascular events.⁹⁴ Persistent leukocytosis and thrombocytosis are also important biomarkers¹⁷⁹, as elevated white blood cell counts have been associated with increased thrombosis risk and may indicate inadequate cytoreductive control.^{180,181} Failure to normalize leukocytosis with cytoreductive therapy should therefore prompt consideration of treatment modification.

Given the central role of inflammation in PV pathogenesis, inflammatory biomarkers such as C-reactive protein, IL-6, TNF- α , and CXCL8 are gaining recognition.^{87,182} Elevated levels of inflammatory cytokines correlate with symptom severity, splenomegaly, and the

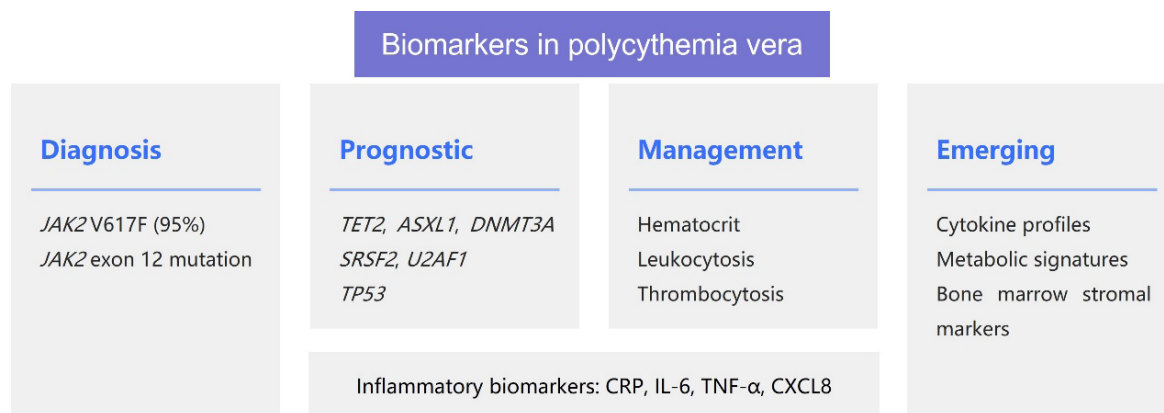


Figure 2. Key biomarker categories used in polycythemia vera. The figure organizes PV biomarkers into four functional categories based on their clinical utility. Diagnostic biomarkers (left): *JAK2* V617F and *JAK2* exon 12 mutations establish clonal diagnosis according to the World Health Organization's criteria. Prognostic biomarkers (center left): Co-mutations inform risk of thrombosis, myelofibrosis, and leukemic transformation. Management biomarkers (center right): Hematocrit (target < 45%), white blood cell count, and platelet count guide therapy intensity and monitoring frequency. Emerging biomarkers (right): Inflammatory cytokines, metabolic signatures, and bone marrow stromal markers are currently under investigation but may refine risk stratification in the future. This framework helps clinicians distinguish which biomarkers are ready for routine use from those that still require validation.

risk of progression to MF.¹⁸³ From a clinical standpoint, persistent elevation of inflammatory markers despite adequate hematocrit control supports consideration of switching from HU to interferon or ruxolitinib, as these agents have demonstrated anti-inflammatory effects. Importantly, reductions in inflammatory cytokines during ruxolitinib therapy reflect treatment response and may precede hematologic improvement.¹⁸⁴

7.3. Emerging biomarkers and future directions

Emerging biomarkers include circulating cytokine profiles, metabolic signatures, and bone marrow stromal markers, which provide deeper insights into disease biology.^{34,91,185-188} Unlike the established markers discussed above, these investigational markers are not yet ready for routine clinical use. However, ongoing research is exploring their potential to refine risk stratification, predict progression, and guide personalized therapeutic strategies.

Together, established and emerging biomarkers are reshaping PV management by enabling precise diagnosis, predicting clinical outcomes, and quantifying treatment response, thereby supporting a more individualized and biologically informed approach to patient care.

8. Clinical challenges and future directions

Despite significant advances in understanding the molecular and clinical features of PV, substantial challenges remain in optimizing long-term outcomes. Current therapies effectively reduce hematocrit and mitigate the risk of thrombosis, yet they do not uniformly prevent disease progression, eradicate the malignant clone, or fully resolve symptom burden. Addressing these persistent gaps requires both improved therapeutic strategies and more refined tools for disease monitoring.

One major clinical challenge is the heterogeneity of patient response to standard therapies. While phlebotomy, HU, and interferon provide reliable hematologic control for many patients, a subset develops intolerance, resistance, or suboptimal molecular responses.^{130,189} Identifying predictors of treatment failure remains an unmet need. Moreover, while ruxolitinib offers symptomatic and inflammatory relief in HU-resistant or -intolerant patients, it does not consistently reduce *JAK2* allele burden or prevent transformation to MF or acute leukemia.^{190,191} These limitations underscore the need for agents capable of targeting disease-driving hematopoietic stem cells and modifying the natural history of PV.

A second challenge is the risk of disease progression, driven by clonal evolution, chronic inflammation, and fibrosis. Although the molecular mechanisms underlying progression are increasingly understood, clinical tools for

predicting transition to MF or leukemic transformation remain imperfect.^{93,192} Longitudinal monitoring using next-generation sequencing, cytokine profiling, and advanced imaging may offer earlier detection of high-risk changes, but incorporation into routine practice requires validation and standardization.^{193,194}

Thromboinflammatory complications also remain a central concern. Even with optimized hematocrit control, patients remain at elevated risk of arterial and venous thrombosis due to persistent leukocytosis, platelet activation, endothelial dysfunction, and systemic inflammation.^{119,179-182,195-197} Future strategies must move beyond hematocrit reduction to address the underlying inflammatory and prothrombotic drivers of vascular disease in PV.

Looking forward, several promising directions are likely to redefine PV management. These include development of next-generation interferons with improved tolerability and disease-modifying potential, selective JAK inhibitors tailored to resistance mechanisms, and targeted agents directed at epigenetic regulators, splicing machinery, or metabolic vulnerabilities of *JAK2*-mutant stem cells.¹⁹⁸ Combination therapies, such as interferon plus JAK inhibition or JAK inhibition plus epigenetic therapy, are being explored to achieve deeper molecular remissions.^{98,169} Immune-based therapies, including peptide vaccines and engineered immune cells targeting mutant *JAK2*, offer the potential to eradicate the malignant clone.

Ultimately, future progress will depend on integrating molecular biomarkers, personalized treatment approaches, and therapies capable of altering disease trajectory. Advancing these goals promises to transform PV from a managed chronic malignancy into a condition with true potential for durable remission.

9. Conclusion

Polycythemia vera represents a paradigmatic MPN in which a single, recurrent driver mutation, most commonly *JAK2* V617F, initiates a cascade of molecular, cellular, and inflammatory abnormalities that shape disease onset, progression, and clinical outcome. Over the past decade, significant advances in genomics, stem cell biology, and cytokine signaling have refined our understanding of PV pathogenesis and revealed the multifaceted interplay between clonal hematopoiesis, chronic inflammation, and vascular dysfunction. This expanding knowledge base has translated into more precise diagnostic criteria, improved risk stratification, and the development of targeted therapies that address both the proliferative and symptomatic dimensions of the disease.

Despite these achievements, PV remains a chronic, progressive malignancy with persistent unmet needs. Standard therapies such as phlebotomy, low-dose aspirin, HU, and interferon provide effective control of hematocrit and reduce thrombotic risk, yet they do not uniformly prevent evolution to MF or acute leukemia.^{190,191} Furthermore, thromboinflammatory complications continue to drive morbidity and mortality even in patients with well-controlled blood counts, underscoring the importance of addressing the inflammatory and endothelial components of disease biology.^{119,179-182,195-197} The heterogeneity of treatment responses, both hematologic and molecular, underscores the complexity of PV and the need for personalized therapeutic approaches.

Emerging treatments offer meaningful opportunities to transform the disease course. Next-generation interferons, selective JAK inhibitors, epigenetic modulators, and immune-directed therapies hold promise for achieving deeper molecular remissions, reversing clonal expansion, and potentially altering long-term outcomes.^{1,130} Advances in biomarker discovery, including mutation profiling, allele burden dynamics, cytokine signatures, and stromal markers, are poised to refine prognostication and support more individualized treatment decisions. Moreover, emerging insights into the interplay among inflammation, thrombosis, and clonal fitness open new avenues for therapeutic intervention beyond traditional cytoreductive strategies.^{98,169}

Looking ahead, the integration of genomic monitoring, precision medicine, and combination therapeutic strategies is likely to redefine the standard of care in PV. Continued efforts to understand the mechanisms governing disease initiation, progression, and therapeutic resistance will be essential for developing curative approaches. Ultimately, the future of PV management lies in bridging molecular understanding with clinical innovation, enabling a shift from disease control to true disease modification and long-term remission.

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Conflict of interest

The authors declare no conflicts of interest.

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