Practice Patterns in the Diagnosis and Treatment of Polycythemia Vera in the Post-*JAK2* V617F Discovery Era

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Abstract

Polycythemia vera (PV) is an acquired clonal hematopoietic stem cell disorder characterized by an overproduction of red blood cells, white blood cells, and platelets; thrombotic and hemorrhagic complications; and an increased risk of transformation to myelofibrosis and acute leukemia. In 1967, the Polycythemia Vera Study Group proposed the optimal approach to diagnosis and treatment of PV, and in 2002, investigators from Johns Hopkins University School of Medicine surveyed the practice patterns of hematologists as they pertained to PV. Since this survey, the *JAK2* V617F mutation was discovered, leading to a new era of discovery in the disease pathogenesis, diagnosis, and classification and treatment of PV. Our objective was to survey hematologists in the diagnosis and treatment of PV in the modern, post-*JAK2* V617F discovery era. An anonymous 17-question survey was emailed to members of the Myeloproliferative Neoplasm (MPN) Research Foundation database and Aplastic Anemia and MDS International Foundation. A total of 71 surveys were used in the analysis. Diagnostic testing varied according to the respondent's clinical experience and practice type. In addition, there were marked differences in target hematocrit and platelet count among those surveyed. There continue to be variations in diagnosis and treatment of PV despite WHO guidelines and the *JAK2* discovery. US-based guidelines for MPNs are needed to create consistency in the management of PV and other MPNs.

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Background

Polycythemia vera (PV) is an acquired clonal hematopoietic stem cell disorder characterized by an overproduction of red blood cells (and other mature blood elements), thrombotic and hemorrhagic complications, and transformation to a myelofibrotic and, rarely, an acute leukemic phase. PV carries an incidence rate of 1.0 case per 100,000 persons (prevalence rate of 44–57 per 100,000 persons) and, in general, is a disease of older age, with the median age at diagnosis of 61 years.^{1,2} The median survival of PV is 18.9 years (range, 10.9–27.8 years based on risk group) and is significantly lower

than age- and sex-matched controls.^{3,4} PV has a chronic course, with thrombosis a major cause of morbidity and mortality. Less common, but feared complications, include transformation to myelofibrosis and acute leukemia.^{3,5,6}

In 1967, the Polycythemia Vera Study Group (PVSG) was established to develop the optimal approach to diagnosis and treatment of PV, developing major and minor criteria for diagnosis and investigating management strategies. Of the 3 studied regimens (phlebotomy alone, chemotherapy [chlorambucil] with phlebotomy, and radiotherapy [³²P] with phlebotomy),

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improved survival was seen with phlebotomy. In addition, these studies found that the incidence of acute leukemia was increased in patients treated with chlorambucil and ^{32}P , and the incidence of myelofibrotic transformation was similar with all 3 treatment modalities.⁷⁻⁹

In 2002, investigators from Johns Hopkins University School of Medicine surveyed 1,000 members of the American Society of Hematology (ASH) regarding their practice patterns as they pertained to PV, with the objective to determine the impact of PVSG studies on diagnosis and treatment of erythrocytosis and thrombocytosis.¹⁰ They found that the most commonly used diagnostic tests included red cell mass studies, erythropoietin levels, and arterial blood gases. The initial therapy used was phlebotomy and most respondents used a target hematocrit of 44% or less, but a significant minority used targets of 50% or greater despite PVSG recommendations. Less uniformity was noted regarding the treatment of thrombocytosis; although most clinicians treated a platelet count of greater than $1,000 \times 10^9/\text{L}$, a significant number used a lower threshold for treatment, or treated only those with symptomatic thrombocytosis. Hydroxyurea was the most commonly used medication to treat thrombocytosis, especially among academic physicians; otherwise, anagrelide was used by private practice physicians (44.6% vs 36.3% in academic practice; $P=.02$) and physicians who had recently completed their training (1-5 years, 51% vs >10 years, 39%; $P=.01$). Among respondents, 55% avoided interferon in treatment of thrombocytosis and 15% avoided aspirin. The study authors concluded that there was considerable variation in the diagnosis and treatment of PV by ASH members depending on region, practice type, specialty, and years of clinical experience.

Since that survey was completed, there has been an immense era of discovery in the pathogenesis, diagnosis, and classification of PV and other myeloproliferative neoplasms (MPNs), mostly due to the discovery of the JAK2 V617F mutation and its role in MPNs.¹¹⁻¹⁵ As a result, diagnostic criteria for PV evolved to include this molecular marker and most of the PVSG criteria were abandoned, as was published in the more recently revised WHO diagnostic criteria for PV.¹⁶ Therapeutic strategies have also expanded, because there is renewed interest in pegylated interferon-alpha because of its promise in achiev-

ing molecular and hematologic remission in PV.¹⁷ Further, ruxolitinib, a JAK1/JAK2 inhibitor, has been approved for PV in patients with intolerance or resistance to hydroxyurea.¹⁸ The optimal hematocrit target in PV, which has been debated for 3 decades, has been confirmed to be 45% or less, according to a recently published randomized study.^{19,20} Finally, although high-dose aspirin was associated with an increased risk of bleeding, a randomized study from the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) investigators suggested that 100 mg of daily aspirin significantly lowered the combined risk of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, and major venous thrombosis (relative risk, 0.40; 95% CI, 0.18-0.91).²¹ However, this claim was later challenged in a Cochrane review of 630 patients with PV, which found that low-dose aspirin was associated with a statistically nonsignificant reduction in fatal thrombotic events and all-cause mortality.²²

The impact of these changes in diagnostic and therapeutic strategies on practice patterns in the modern/post-JAK2 V617F era of PV is unknown, especially because US-based guidelines do not yet exist, but are in development.²³ Our objective was to again survey hematologists regarding diagnosis and treatment of PV as it applied to the modern, post-JAK2 V617F discovery era to evaluate the impact of new diagnostic criteria and treatments for PV.

Methods

An anonymous Institutional Review Board-approved a 17-question survey pertaining to the diagnostic and therapeutic strategies for PV, which was disseminated to members of the MPN Research Foundation (MPNRF) database ($N=847$) and Aplastic Anemia and MDS International Foundation (AAMDSIF; $N=24,061$) through an email blast from each foundation inviting members to participate via a hyperlink (Figure 1). On the introductory page of the survey, participants were provided information regarding the study's purpose and its voluntary and anonymous nature. By participating in the survey, participants gave informed consent. One survey was excluded because the surveyor responded that he/she had zero patients with PV in the practice. All other returned surveys were

SECTION 1: Demographics**Q1 I consider myself primarily a/an**☐ MD/DO ☐ PhD ☐ MD/PhD ☐ Industry/Pharmacy**Q1B I consider myself primarily a/an**☐ Hematologist ☐ Oncologist**Q2 Where is your primary site of clinical practice?**☐ Private practice setting ☐ Academic practice setting**Q3 How many years of clinical experience have you had since completing training?**☐ <1 ☐ 1–5 ☐ 6–10 ☐ ≥11**Q4 How many PV patients are in your practice?**☐ 0 ☐ 1–5 ☐ 6–10 ☐ 11–15 ☐ >16**SECTION 2: Diagnosis****Q5 What tests or findings do you find useful in diagnosing polycythemia vera?****Choose all that apply**

☐ Complete blood count ☐ Bone marrow aspirate and biopsy ☐ JAK2 V617F testing
☐ JAK2 exon 12 testing ☐ Cytogenetics ☐ Erythropoietin level
☐ Presence of splenomegaly ☐ Endogenous erythroid colony formation
☐ Arterial oxygen saturation ☐ Red cell mass testing
☐ Normal hemoglobin with low iron stores
☐ Vitamin B12 binding protein

Q6 How do you characterize PV to patients?

☐ Blood disorder or syndrome ☐ Blood neoplasm ☐ Chronic leukemia
☐ Pre-leukemia/myelodysplastic syndrome ☐ Form of cancer ☐ Other (specify) _____

SECTION 3: Treatment**Q7 What is your target hematocrit for phlebotomy?**

☐ <42% for women and <45% for men ☐ <45%; I do not distinguish by gender
☐ <50% ☐ <55%

Q8 What is your platelet target or goal?

☐ <400 × 10⁹/L ☐ 400–600 × 10⁹/L ☐ 600–1,000 × 10⁹/L
☐ <1,000 × 10⁹/L ☐ Thrombocytosis is treated only in presence of symptoms

Q9 What prompts you to treat PV with cytoreduction?**Choose all that apply**

☐ Erythrocytosis ☐ Advanced age (>60 years)
☐ Microvascular complications (transient ischemic attacks, erythromelalgia, visual disturbance, migraine headaches)
☐ Venous or arterial thrombosis history ☐ Pruritus ☐ Weight loss ☐ Fatigue
☐ Thrombocytosis ☐ Leukocytosis ☐ Splenomegaly

Q10 What agents do you use for cytoreduction?**Indicate for all as follows: 1=preferred agent, 2=second-line agent**

☐ Anagrelide ☐ Hydroxyurea ☐ Pegylated interferon-alfa
☐ Recombinant interferon-alfa ☐ Busulfan ☐ ³²P

Q11 Do you recommend aspirin for all PV patients (unless contraindicated)?☐ Yes ☐ No**Q12 Are there any agents that you avoid due to the side effect profile?**

☐ Anagrelide ☐ Hydroxyurea ☐ Phlebotomy ☐ Pegylated Interferon-alfa
☐ Recombinant Interferon-alfa ☐ Aspirin ☐ Busulfan ☐ ³²P

Q13 Is there an age range in which you would avoid the use hydroxyurea?☐ Age ≤18 y ☐ Age ≤40 y ☐ Age ≤60 y ☐ No age criteria**Q14A Which of the following agents do you believe can modify the natural history of PV (prevent transformation to myelofibrosis or leukemia)?**

☐ Anagrelide ☐ Hydroxyurea ☐ Phlebotomy
☐ Pegylated interferon-alfa ☐ Recombinant interferon-alfa ☐ JAK inhibitors

Q14B Which of the following agents do you believe may accelerate/cause the development of myelofibrosis?

☐ Anagrelide ☐ Hydroxyurea ☐ Phlebotomy
☐ Pegylated Interferon-alfa ☐ Recombinant interferon-alfa ☐ JAK inhibitors ☐ None of the above

Q14C Which of the following agents do you believe may accelerate/cause the development of leukemia?

☐ Anagrelide ☐ Hydroxyurea ☐ Phlebotomy
☐ Pegylated interferon-alfa ☐ Recombinant interferon-alfa ☐ JAK inhibitors ☐ None of the above

Q15 What do you perceive the usefulness of JAK2 inhibitors will be in PV?

☐ Potential to cure ☐ Potential to prolong survival ☐ Improvement of systemic symptoms
☐ Decrease in phlebotomy needs ☐ Treatment of thrombocytosis
☐ Treatment of leukocytosis ☐ Treatment of splenomegaly

Figure 1. Survey instrument.

used in the data set. After surveys were collected, tables were constructed to compare practice patterns based on independent variables (respondent

characteristics). The Fisher exact test was used to compare responses, with a *P* value of less than 0.05 considered statistically significant.

Results

Respondent Characteristics

A total of 72 people completed the survey and 71 surveys were used for further analysis. Most responses (66 of 71) were from the MPNRF (response rate, 7.8%) and the remaining were from the AAMDSIF (response rate, ≈0%). Education varied in respondents, with most (67.6%) an MD/DO, 26.8% an MD/PhD, 2.8% a PhD, and 2.8% industry/pharmacy (Table 1). Most (84.1%) considered themselves hematologists, and 83.1% practiced in an academic setting (Table 1); 11.6% (8 of 69) classified themselves as oncologists; and 4.4% (3 of 69) classified themselves as hematologists/oncologists. The amount of clinical experience of respondents varied, with most (36 of 69; 52.2%) having more than 16 years of experience, followed by 12 of 69 (17.4%) having 6 to

10 years of experience; 18.8% of respondents reported having 5 years or less of clinical experience. Most respondents (32 of 69; 46.4%) reported having 16 or more patients with PV in their practice, whereas 26 of 69 respondents (37.6%) reported having 1 to 10 patients with PV.

Diagnosis of PV

The commonly used tests reported by respondents to diagnose PV were the CBC (91.6%), JAK2 V617F testing (90.1%), and erythropoietin level (83.1%) (Figure 2). Bone marrow aspirate/biopsy was more commonly used than red cell mass testing (57% vs 23%; $P<.0001$). Physicians in an academic setting considered JAK2 V617F testing more useful than those in a private practice (94.9% vs 66.7%; $P=.01$) and there was a trend toward greater use of erythropoietin level in the academic setting (86.4% vs 66.7%; $P=.11$) (Table 2). There was also a trend toward use of cytogenetics in diagnosing PV among oncologists compared with hematologists (37.5% vs 13.8%; $P=.17$) (Table 3). Respondents with more patients with PV in their practice were more likely to report JAK2 V617F testing as useful in diagnosing PV ($P=.01$), and those with fewer patients with PV in their practice were more likely to report cytogenetics as being useful ($P=.02$) (Table 4).

When counseling patients, 73.2% of respondents characterized PV as a blood neoplasm. The next most common characterization was a “blood disorder or syndrome” (22.5%); respondents from academic and private practices also characterized PV this way, but in different proportions (79.7% and 41.7% as a blood neoplasm, respectively; $P=.012$).

Treatment of PV

Target hematocrit varied in this cohort. A total of 48% of respondents used a sex-dependent hematocrit target (<42% for women and <45% for men) for phlebotomy, whereas 41.8% targeted a hematocrit of less than 45% universally (Figure 3). Target platelet count also varied, with a target of less than 400 $\times 10^9/L$ being most common (34.3% of respondents), followed by a target of 400 to 600 $\times 10^9/L$ (32.8% of respondents) (Figure 4). Platelet goals did not vary by practice type or specialty. Although 74.7% of respondents recommended aspirin for all patients unless contraindicated, respondents in academic practices were more likely to universally recommend

Table 1. Demographics

	Number of Respondents (N=71)	%
Education		
MD/DO	48	67.6
PhD	2	2.8
MD/PhD	19	26.8
Industry/Pharmacy	2	2.8
Practice type		
Academic	59	83.1
Private	12	16.9
Specialty^a		
Hematology	58	84.1
Oncology	8	11.6
Hematology/Oncology	3	4.4
Clinical experience (y)^a		
<1	4	5.8
1–5	9	13.0
6–10	12	17.4
11–15	8	11.6
>16	36	52.2
Patients seen with polycythemia vera (N)^a		
1–5	13	18.8
6–10	13	18.8
11–15	11	15.9
>16	32	46.4

^a2 respondents did not respond.

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Figure 2. Diagnostic testing reported most useful to diagnose polycythemia vera. Abbreviations: BM, bone marrow; CBC, complete blood count; EPO, erythropoietin; Hgb, hemoglobin; sat, saturation.

aspirin (79.7%) compared with those in private practice (50%) ($P=.01$). A trend was seen for those with fewer years of experience to universally recommend aspirin compared with those with more years of experience ($P=.2$).

The preferred cytoreductive agent was hydroxyurea (82%) (Figure 5), with anagrelide and pegylated interferon (peg-IFN) being the preferred second-line treatments (36.6% and 35.2%, respectively). Thrombosis history (71.8%), microvascular complications (70.4%), and age older than 60 years (56.3%) were the most common indications for cytoreduction. Almost half of respondents believed thrombocytosis was an indication for cytoreductive therapy (43.7%); 50.8% of respondents prescribed hydroxyurea regardless of age, whereas 32.8% avoided its use in patients younger than 40 years. Respondents with more than 16 years of experience were more likely to prescribe hydroxyurea regardless of patient age compared with those with less experience ($P=.02$). A total of 28% of respondents believed that hydroxyurea could accelerate the development of leukemia, and 26.8% believed that anagrelide could accelerate myelofibrosis. Respondents most commonly avoided ^{32}P (66.2%), busulfan (59.2%), and recombinant interferon- α (rIFN) (32.4%) due to side effects. Respondents believed that peg-IFN (45.1%), rIFN (33.8%), and JAK inhibitors (JAKi) (29.6%) had the potential to modify the natural history of PV. Respondents perceived that JAKi would be most useful in improving symptoms (78.9%), reducing splenomegaly (73.2%), and decreasing phlebotomy needs (56.3%); fewer believed in its potential to prolong survival (33.8%) or to cure PV (8.5%).

Table 2. Diagnostic Testing by Practice Type

Diagnostic Test	Private (%)	Academic (%)	P Value
CBC	83.3	93.2	.27
Bone marrow aspirate/biopsy	41.7	59.3	.34
JAK2 V617F testing	66.7	94.9	.01
JAK2 exon 12 testing	41.7	59.3	.34
Cytogenetics	8.3	16.9	.68
Erythropoietin level	66.7	86.4	.11
Splenomegaly	50.0	59.3	.75
Endogenous erythroid colony formation	0	13.6	.34
Arterial oxygen saturation	25	47.5	.21
Red cell mass testing	8.3	25.4	.27
Normal hemoglobin with low iron stores	25	27.1	.99
Vitamin B12 binding protein	8.3	6.8	.99

Discussion

This article presents results from a survey of practice patterns in the diagnosis and treatment of PV in the modern/post-JAK2 V617F era as a follow-up to the 2002 survey conducted by Johns Hopkins University.¹⁰ Our survey focused on the diagnosis of PV and its treatment strategies, including concerns regarding long-term adverse effects and the potential for future therapies. Most of the respondents were experienced academic hematologists with medical degrees.

Regarding diagnostic strategies, it appears that hematologists/oncologists have adopted WHO criteria, because the respondents considered CBC, JAK2 V617F testing, and erythropoietin levels to be the most useful diagnostic tools. However, practice type did influence the preferred diagnostic test. Academic physicians were more likely than those in private practice to use JAK2 V617F testing, and there was a trend toward greater use of erythropoietin levels. Clinical experience also influenced diagnostic testing: physicians with more patients with PV in their practice were more likely than those with fewer patients to use JAK2 testing, whereas clinicians with

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Table 3. Diagnostic Testing by Specialty

Diagnostic Test	Hematology (%)	Oncology (%)	Hematology/Oncology (%)	P Value
CBC	93.1	87.5	100	.59
Bone marrow aspirate/biopsy	58.6	50.0	66.7	.88
JAK2 V617F testing	91.4	87.5	100	.66
JAK2 exon 12 testing	60.3	50.0	33.3	.59
Cytogenetics	13.8	37.5	0	.17
Erythropoietin level	82.8	100	66.7	.25
Splenomegaly	58.6	50.0	66.7	.88
Endogenous erythroid colony formation	13.8	0	0	.71
Arterial oxygen saturation	44.8	50.0	33.3	.99
Red cell mass testing	27.6	0	0	.24
Normal hemoglobin with low iron stores	29.3	12.5	33.3	.63
Vitamin B12 binding protein	8.6	0	0	.99

fewer patients with PV were more likely to report cytogenetics as a useful diagnostic test. There was also a trend toward using cytogenetics among oncologists compared with hematologists.

There was considerable variation in PV treatment among respondents. Interestingly, there was an almost even divide in goal target hematocrit between a sex-dependent hematocrit goal (47.8% of respondents) and a hematocrit goal of less than 45% regardless of sex (41.8% of respondents), despite recent recommendations that phlebotomy should target the latter. In addition, similar to the 2002 survey study, there was a significant minority (10.5%) that

used a target hematocrit of 50% or greater. Target platelet goals varied significantly in this cohort, with almost one-third of respondents treating for target less than $400 \times 10^9/L$, 400 to $600 \times 10^9/L$, and only if symptomatic, respectively, which is not surprising given that there are no guidelines on this topic and platelet count has shown no correlation with thrombotic events.²⁴ Given these inconsistencies, practitioners would benefit from US-based guidelines for the management of PV and other MPNs.

Respondents did not universally recommend aspirin to all patients with PV. Physicians in private practice were significantly less likely to prescribe

Table 4. Diagnostic Testing by Number of Patients With Polycythemia Vera in Practice

Diagnostic Test	1–5 Patients (%)	6–10 Patients (%)	11–15 Patients (%)	≥16 Patients (%)	P Value
CBC	92.3	84.6	100.0	96.9	.33
Bone marrow aspirate/biopsy	53.8	38.5	72.7	62.5	.33
JAK2 V617F testing	84.6	76.9	100.0	100.0	.01
JAK2 exon 12 testing	46.2	53.8	54.5	65.6	.63
Cytogenetics	30.8	30.8	18.2	3.1	.02
Erythropoietin level	76.9	92.3	81.8	87.5	.67
Splenomegaly	53.8	53.8	72.7	59.4	.77
Endogenous erythroid colony formation	7.7	7.7	0	18.8	.49
Arterial oxygen saturation	61.5	53.8	36.4	37.5	.42
Red cell mass testing	23.1	23.1	36.4	18.8	.67
Normal hemoglobin with low iron stores	23.1	30.8	27.3	28.1	1.00
Vitamin B12 binding protein	7.7	0	0	12.5	.63

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Figure 3. Target hematocrit in polycythemia vera.

aspirin compared with physicians in academic practice. In addition, a trend was seen for physicians who recently completed training to universally recommend aspirin more often than the most experienced practitioners. This difference may reflect awareness of previous data from the PVSG that associated the 325-mg dose of aspirin with higher rates of hemorrhage.²⁵

Most respondents agreed on cytoreductive strategies and its indications, with hydroxyurea being the preferred agent in 82% of respondents, and thrombosis history, microvascular complications, and age older than 60 years being the most common indications. The evidence base for use of hydroxyurea in PV is actually scarce,²⁶ with efficacy typically extrapolated from results in randomized studies of patients with essential thrombocythemia.^{27–29} Almost one-third of respondents avoided hydroxyurea in patients younger than 40 years, likely due to fears that it could accelerate transformation to leukemia, as 28% of respondents believed. The association between hydroxyurea and secondary leukemia is controversial, and difficult to prove with certainty given the limitations of studies examining this question.³⁰ The more experienced respondents were more likely to prescribe hydroxyurea regardless of age compared with less experienced respondents, and 66% of respondents avoided ³²P due to potential side effects. Interestingly, peg-IFN was thought by many (45%) to modify the natural history of PV, but it was not the preferred first- or second-line cytoreductive agent, likely due to its many side effects. Lastly, most respondents believed that JAKi were useful for improving symptoms and reducing splenomegaly, and fewer believed it had the potential to cure PV. This

Figure 4. Target platelet count in polycythemia vera.

perception is in keeping with clinical data regarding improvement in symptom burden.

In the more than 10 years since the prior survey, differences and similarities can be seen in the respondents' diagnostic and therapeutic strategies for treating PV. Diagnostics now heavily rely on newly discovered molecular testing, and the use of red cell mass and arterial blood gas has decreased considerably. Cytogenetics have recently been reported to have a significant influence on prognosis, and the impact of additional somatic mutations identified by next-generation sequencing is under evaluation. Target platelet count has become more variable; in 2002, most respondents initiated treatment for patients with platelet counts greater than 1,000 x 10⁹/L, which is now the minority opinion. Commonly a trigger for treatment, the platelet count itself has not been shown to correlate with thrombosis.^{24,31} In regard to the hematocrit threshold for treatment, there is a persistent minority of respondents who continue to target a hematocrit of 50% or greater. Hydroxyurea continues to be the preferred cytoreductive agent both then and today, and respondents continue to avoid busulfan and ³²P.

Figure 5. Preferred cytoreductive therapy in polycythemia vera. Abbreviation: IFN, interferon.

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There are limitations of this study. Respondents were primarily academic hematologists, which may skew responses. However, this is the physician subgroup that has the most exposure to and experience with treating patients with PV. Furthermore, despite the large proportion of academic hematologists among respondents, there was still considerable heterogeneity with regard to some aspects of PV management. Our response rate was low, with less than 8% of MPNRF members responding and even fewer members of the AAMDSIF. Despite a lower-than-hoped-for response rate, this survey serves a role as a “pre-guideline” view of PV practice—thankfully, the first US-based guidelines for MPNs are in development.²³

Conclusions

This article presents results of a survey of practice patterns in the diagnosis and treatment of PV in the modern/post-JAK2 V617F era as a follow-up to the 2002 survey conducted by Johns Hopkins University.¹⁰ There continue to be considerable variations in the diagnosis and treatment of PV. Practitioners would benefit from US-based guidelines for MPNs, which are currently in development.

Editor's Note: The NCCN Guidelines for MPNs were recently released and are available at NCCN.org. They will also be published in the December 2016 issue of JNCCN.

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