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MYELOPROLIFERATIVE NEOPLASMS (B STEIN, SECTION EDITOR)

Next-Generation Sequencing in Myeloproliferative Neoplasms: Is This Indicated in All Patients?

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Abstract

Purpose of review To discuss the impact that next-generation sequencing has had on myeloproliferative neoplasm prognosis and treatment response.

Recent findings Extended genetic testing has led to a more comprehensive understanding of the mutational landscape in the myeloproliferative neoplasms. More refined prognostic models that predict disease course have therefore been developed. In myelofibrosis, this has led to a more nuanced prognostic assessment which is a necessary tool for the identification of potential transplant patients. The extended molecular profile may also help set expectations for ruxolitinib response duration. In essential thrombocythemia and polycythemia vera, elucidation of the molecular landscape beyond driving mutations may identify patients at risk for more rapid progression. However, results from testing are less likely to lead to action, at least in the current era.

Summary Use of next-generation sequencing has become routine in myelofibrosis, as a means of identifying patients at highest risk for progression, who may be eligible for transplantation. Extended genetic sequencing is still investigational in essential thrombocytosis and polycythemia vera, and not recommended by guidelines.

Keywords Myeloproliferative neoplasms · Next-generation sequencing · Polycythemia vera · Essential thrombocythemia · Myelofibrosis

Introduction

Myeloproliferative neoplasms (MPN) are a group of heterogeneous hematologic malignancies affecting one or more of the myeloid cell lineages (e.g., granulocytic, megakaryocytic, erythroid, or mast cell) [1]. Philadelphia chromosome–negative MPNs including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) [2] are characterized by three (typically) mutually exclusive driver mutations, involving *JAK2*, *MPL*, or *CALR*. The *JAK2* V617F mutation was initially discovered in 2005[3] and not only set a precedence for novel targeted therapies in these diseases, but also triggered increasing efforts into attaining a deeper genetic and molecular understanding. [4]. At their core, MPNs reflect dysregulated clonal proliferation of myeloid lineage stem cells thought to be triggered by an initial insult to one of the aforementioned driver genes. In the wild-type state, ligands bind to cell surface growth factor receptors and activate intracellular kinases of the *JAK* (Janus kinase) family. These latter in turn phosphorylate proteins of the signal transducer and activator of transcription (STAT) family that dimerize and translocate into the nucleus where they regulate expression of genes involved in cellular differentiation, proliferation and apoptosis[5]. Regardless of the type of driver mutation, unchecked JAK-STAT activation is a hallmark of MPN. Recently, the mechanism of *CALR*-induced JAK-STAT activation has been described—mutant *CALR* directly interacts with the thrombopoietin receptor, and is secreted (In an autocrine and paracrine fashion), acting as a "rogue" cytokine to activate cells with the thrombopoietin receptor [6].

JAK2 V617F is the most common of these mutations, observed in up to 98% of PV, 55% of ET, and 60% patients with PMF [7]. *MPL* mutations can be identified in approximately

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5% of ET and PMF. *CALR* mutations are detected in 25–30% of ET and PMF patients [2, 8], and has been only anecdotally identified in PV patients [9]. A very small percentage of MPN cases do not harbor any of these three driver mutations and are termed triple-negative (TN) MPNs. These are associated with poorer outcomes, in myelofibrosis, but a lower thrombosis rate in ET [1, 10]. Typically, the driver mutations are mutually exclusive, but a single-center recently reported on patients with mutations of both *JAK2* V617F and *CALR* in a cohort of 123 TN MPNs and found these 2 mutations to coexist in 4.2% of ET patients [11].

Up until the characterization of driver molecular profile of these MPNs, prognostication was based on clinical, laboratory, and demographic factors. Without question, the molecular era of MPNs has helped resolve some degree of heterogeneity in prognosis. For example, in PMF, type 1 *CALR* mutations (52 bp deletion, as opposed to type 2 *CALR* (5 bp insertion) have been associated with improved survival and a more indolent course [12]. *CALR*-ET has also been associated with a lower rate of thrombosis in ET patients [13]. Mutational analysis is now incorporated into prognostic assessments for MPN patients.

The molecular era of these MPNs has also observed an increasing interest in identifying additional mutations that would not only help risk stratify MPNs but also fuel a surge in targeted therapeutic agents. Accordingly, next-generation sequencing (NGS) has been increasingly utilized. Herein, we review the prognostic implications and potential applications for routine management of patients with MF, ET, and PV.

NGS in Myelofibrosis

Correlation between the extended genetic profile and clinical outcomes in MF was initially brought to light in 2013 by Vannucchi and colleagues, through analysis of 879 patients. Use of prognostic scoring systems to identify transplant-eligible or clinical trial patients were previously guided by scoring prognostic systems that relied on age and laboratory variables. Here, the presence of additional high-risk mutations was shown to impact overall and leukemia-free survival [14]. In the European cohort ($n = 483$), *ASXL1*, *EZH2*, and *SRSF2* mutations tended to cluster in the high-risk IPSS group. Similarly, in the Mayo group ($n = 396$), *ASXL1* and *SRSF2* were observed most frequently in the high-risk DIPSS-plus group. *ASXL1*, *SRSF2*, and *EZH2* associated with leukocytosis and circulating blasts in both cohorts [14]. Importantly, overall survival (OS) and transformation to leukemia were also correlated with the genetic profile. *ASXL1*, *SRSF2*, and *EZH2* mutations correlated with decreased survival as well as significantly increased risk of leukemic transformation in the European group. Risk of leukemia was also found to be significantly elevated with *IDH1/IDH2* mutations. The overall survival observations were all validated in the Mayo group while leukemic transformation was only associated with *SRSF2* and *IDH*1 mutations in the Mayo cohort [15]. Following this publication, *ASXL1*, *SRSF2*, *EZH2*, and *IDH1/2* mutations have been considered as high-risk mutations (HMR).

The number of HMR mutations present has also been shown to be of prognostic significance. In a study that involved 800 patients (a European cohort ($n = 537$) and a validation Mayo cohort ($n = 260$)), Guglielmelli et al. showed that not only did the 5 HMR mutations (*ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*) produce an IPSS/DIPSS—independent high risk subgroup with regard to OS and risk of AML transformation—the number of involved mutations also had prognostic implications. It was shown that patients harboring two or more HMR mutations had a significantly decreased OS and leukemia-free survival (LFS) when compared to patients with a single HMR mutation, or those without an HMR mutation [16]. These findings allowed the identification of a high-risk subgroup of patients, overlooked by standard prognostic scores that might benefit from closer monitoring or a more aggressive initial intervention such as stem cell transplantation.

As part of the efforts to further associate genetic makeup with clinical behavior/outcome, Tefferi et al. looked into the mutational profile of 570 patients to explore the synergistic interaction between *ASLX1* and *CALR* mutations and their prognostic implications. Here, a statistically significant survival advantage was observed in patients with a *CALR*-mutant/*ASXL1*-negative profile. Survival outcomes were worse in the absence of *CALR* and presence of *ASLX1*, and somewhat intermediate in the presence of both *CALR* and *ASLX1* in a similar fashion to the prognostic interplay that exists in AML patients between *FLT3* and *NPM1* mutations [17].

In keeping with adverse impact associated with *SRSF2*, the relevance of additional splicing mutations has also been explored. In a study of the genetic profile of 250 patients, the *U2AF1* mutation was identified in 16% of cases and was found to be statistically linked with the *ASXL1* mutation ($p = 0.03$), the *JAK2*V617F mutation ($p = 0.002$), older age ($p = 0.02$), hemoglobin < 10 g/dl ($p < 0.0001$), platelets < 100×10^9 ($p = 0.0001$), and an increased need for transfusion ($p < 0.0001$) [18]. *U2AF1* and the *SRSF2* mutations in a subsequent study were also shown to be statistically linked and associated with the *JAK2* and *MPL* mutations as opposed to the *CALR* mutation. That same study also showed that the genetic and molecular profile of patients post-stem cell transplant is dynamic and accounts for different clonal populations and so could be different from that observed prior to transplant and necessitates the post-transplant molecular monitoring of disease of not only driver mutations (*JAK2*, *MPL*, and *CALR*) but also of spliceosome gene mutations (*SRSF2*, *U2AF1*, and *SF3B1*) [19]. The *U2AF1* mutation was also shown to be

associated with older age in a subsequent study along with other recurrent genetic aberrations such as *SF3B1*, *RUNX1*, *CEBPA*, *TET2*, *PTPN11*, and *SETBP1* [20]. That study analyzed 182 Mayo Clinic patients with PMF and underscored other noteworthy clinical correlations such as *U2AF1* and *SRSF2* with anemia, *U2AF1* with thrombocytopenia, and higher risk DIPSS-plus score with *ASXL1* and *SRSF2* [20].

An examination of the genomic profile via high-resolution single nucleotide polymorphism (SNP) in MPN patients had established a link between alterations involving the *ETV6*, *RUNX1*, and *TP53* genes in *JAK2*V617F-negative MPNs and progression to acute myeloid leukemia [21]. More recently, these same mutations were again demonstrated in the MPN-blast phase though quite rare in the chronic phase [22]. Other common genetic aberrations identified in the blast phase of MPNs include *CBL*, *WT1*, and *IKZF1*, and these, in addition to *SRSF2* and *IDH1/2*, were found to be associated with an increased risk for disease progression [23].

Since the association between driver and additional somatic mutations and prognosis has become clearer since 2013, prognostic scoring systems have evolved to include molecular profiling. In a multi-center study of patients aged < 70 with PMF, clinical and molecular data were integrated and a multivariable model, the MIPSS70, was devised. Nine different variables that independently predict survival make up the MIPSS70 model: Hemoglobin (< 10 g/dl), leukocyte count (> 25 × 10^9), platelet count (< 100 × 10^9), circulating blasts (≥ 2%), fibrosis grade (≥ 2), constitutional symptoms, absence of *CALR 1*-like mutation, HMR category (presence of a mutation in any of the following, *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*) and the presence of 2 or more mutations in the HMR category of genes (see Table 1). Accordingly, patients were categorized into a low-risk group (0–1), intermediate-risk group (2–4), and a high-risk group (≥ 5). This model was further corroborated by the 5-year follow-up of the validation cohort showing an OS of 96%, 67%, and 34% in low-, intermediate-, and high-risk MIPSS70 groups respectively (Tables 1 and 2) [24]. As a complement, and when karyotypic information was available, the MIPSS70-plus model was also developed. The MIPSS70-plus model came about that incorporated 7 variables one of which was unfavorable karyotype while the other variables consisted of hemoglobin (< 10 g/dl), peripheral blasts (≥ 2%), presence of constitutional symptoms, ≤ 1 HMR mutation, *CALR*-negative status, and ≥ 2 HMR mutations (see Table 1). Patients were categorized into low- (≤ 2), intermediate- (3), high- (4–6), and very high- risk and model was again further corroborated via a 5-year follow-up showing overall survivals of 100%, 90% 76%, and 46.5% in low-, intermediate-, high-, and very high-risk MIPSS70-plus groups respectively (Tables 1 and 2) [24].

These models however did not address survival in secondary myelofibrosis (SMF). One particular scoring system, the MYSEC-PM (myelofibrosis secondary to PV and ET), looked into integrating both clinical and molecular data in one of the largest assembled cohorts of 685 patients with SMF, whereby particular mutations were associated with specific clinical presentations (such as *JAK2* positivity with leukocytosis and splenomegaly, increased incidence of blast phase in triple-negative patients). These associations would predict prognosis and survival in SMF patients [25]. MYSEC variables include age, hemoglobin, platelet count, and constitutional symptoms. These new prognostic scoring systems have great promise as not only do they incorporate consistently recognized independent risk factors for survival that previously constituted the IPSS and DIPSS scoring systems, but add to it the HMR mutations and cytogenetics thus providing clinicians with tools to make a more informed decision when initially selecting transplant or trials candidates [24, 26].

Aside from enhancing prognostic scoring systems, extended genetic testing may predict treatment response to the only approved drug for MF, ruxolitinib. Previously, one study demonstrated using COMFORT 2 data that ruxolitinib improved outcomes and overall survival in patients harboring one or more of the HMR gene mutations [27]. In another report, using a panel including 29 recurrent myeloid neoplasm aberrations in a cohort of PMF treated with ruxolitinib as part of a phase 1/2 trial [28], it was reported that patients who harbored one or more mutations of *ASXL1*, *EZH2*, or *IDH* had an inferior OS and a shorter time to treatment discontinuation (TTD) and a less significant reduction in spleen size [29]. Similarly, Spiegel et al. performed a broader mutational analysis on a cohort of 100 PMF patients (77 treated with ruxolitinib and 23 treated with momelotinib) that revealed a significant correlation between *ASXL1* and *EZH2* mutations and reduced time to treatment failure and OS independent of their DIPSS score [30]. At a later study looking into clonal evolution of PMF patients receiving either ruxolitinib or hydroxyurea, a positive *ASLX1* mutation status predicted a loss of spleen volume response to ruxolitinib at the 3-year mark [31]. One additional example of such role was the demonstration by Newberry et al. that patients who had acquired new mutations during treatment with ruxolitinib and thus had clonal evolution had poorer outcomes and shorter OS after discontinuation of treatment [32]. These observations further shed light on the potential role for NGS, not only in prognostication of PMF patients, but also in setting expectations regarding treatment response.

NGS in Polycythemia Vera/Essential Thrombocythemia

Following the prognostic impact on MF, extended genetic analysis has also been performed in PV and ET patients. In one series, the targeted sequencing of 18 genes including *JAK2*, *MPL*, *SH2B3*, *TET2*, *ASXL1*, *IDH1/2*, *DNMT3A*, *EZH2*, *SF3B1*, and *TP53* was performed in 50 *JAK2*V617F-

Table 1 MIPSS70 and MIPSS70-plus variables and associated points

Variables/associated points	MIPSS70 associated points	MIPSS70-plus associated points
Hemoglobin < 100 g/L	1	1
Leukocyte count (> 25×10^9/L)	2	
Platelet count (< $100 \times 10_9$/L)	2	
Circulating blasts ≥ 2%	1	1
Fibrosis grade ≥ 2	1	
Constitutional symptoms	1	1
≤ 1 HMR mutations	1	1
≥ 2 HMR mutations	2	2
CALR-negative status	1	2
Unfavorable karyotype		3

positive PV ($n = 28$) and ET ($n = 22$) patients, and prevalence and clinical implications (at the 3-year mark) were reported [33]. The most commonly mutated genes in the study population were *TET2*, *IDH1/2*, *ASLX1*, and *DNMT3A*, which are largely implicated in epigenetic regulatory mechanisms. On average, 1.6 mutations/patients were identified in both PV and ET subsets with *TET2* and *IDH* mutations being the most prevalent of these mutations at 20 and 10% respectively as compared to previous analyses where their prevalence had been established at around 12% and 2% respectively [34–36]. The association between *TET2* aberrations and disease progression (DP) at the 3-year follow-up failed to reach statistical significance despite a trend for DP in patients harboring the mutation. Disease progression was defined as leukocytosis (greater than 12×10^9), treatment-independent anemia, treatment-independent thrombocytopenia, splenomegaly, or thrombocytosis at the 3-year mark. Other noteworthy findings were that all the patients ($n = 5$) with *IDH* mutations had DP at the 3-year mark and patients with additional somatic mutations were more likely to have progression in accordance with previous observations by Lundberg et al. [36]. Previous studies had established an association between allelic burden of *JAK2*V617F in MPN, and PMF transformation, offering a useful disease-monitoring strategy [37, 38]. Results in this study [36] were consistent with these trends and showed that the burden of somatic mutations, in addition to the presence of *JAK2*, *CALR*, or *MPL*, predicted a reduced OS: As for the *TP53* mutations, these had long been associated with leukemic transformations in MPN [39], but none were detected in the 50 patients studied, likely owing to their established lower prevalence in the general MPN population [33, 36].

In another study, Ortmann et al. used NGS to screen 246 MPN patients with *JAK2* V617F mutations for the presence of *TET2* mutations and determined that the order in which these mutations were acquired had particular implications on clinical presentation and response to treatment. In fact, patients who had acquired *JAK2* mutations first had a tendency for a younger age, an elevated risk of thrombosis, and a higher likelihood of developing polycythemia vera. On the other hand, patients who had acquired *TET2* mutations first had a tendency for older age and a lower risk for thrombosis. Response of in vitro colonies to ruxolitinib differed by mutational order; "*JAK2* first" samples displayed more sensitivity to ruxolitinib than clones with "*TET2* first" mutations [40].

Tefferi et al. studied the mutational profile (targeting 27 gene mutations) of 316 Mayo Clinic patients with PV ($n = 133$) and ET ($n = 183$) [41]. Thirty percent of PV patients had one specific mutation, 20% had 2, and 3% had more than 3 mutations while 41% of ET patients had 1 mutation, 8% had 2, and 4% had more than 3. The most frequent associations among mutations in ET were the *ASXL1/EZH2*, *ASXL1/RUNX1*, and *ASLX1/IDH2* associations, while in PV, it was the *IDH2/KIT* and the *TET2/SH2B3* associations. As for phenotypic correlations, in ET, *TET2* mutations were associated with increased risk of thromboses (independent of any of the driver mutations status, but not validated in the Italian cohort) while that association was absent in the PV population. In ET, *TET2* and *SF3B1* mutations were both associated with increased age, *SF3B1* with increased platelet count, and *ASXL1* with palpable splenomegaly, while in PV, the only phenotypic association was palpable splenomegaly. As for clinical correlations, in PV patients, the *ASXL1*, *SRSF2*, and *IDH2* mutations were associated with decreased OS, and *SRSF2*, *IDH2*, and *RUNX1* mutations were associated with leukemia-free survival, while *SRSF2* and *RUNX1* were associated with myelofibrosis-free survival. In ET, *IDH2*, *EZH2*, and *SH2B3* predicted inferior survival. *TP53*, *EZH2*, and *SRSF2* were associated with adverse leukemia-free survival while *SF3B1* and *U2AF1* predicted adverse myelofibrosis-free survival. This study helped define particular mutations, deemed "adverse," that were associated with poorer overall survival. These mutations included *ASXL1*, *IDH2*, and *SRSF2*

Table 2 Risk stratification and OS (of validation cohort)

Risk	MIPSS70 score	Median OS (years)	MIPSS70-plus score	Median OS (years)
Low	0 to1	Not reached	0 to 2	Not reached
Intermediate	2 to 4	6.3	3	24.2
High	≥ 5	3.1	4 to 6	10.4
Very high	▪	▪	≥ 7	3.9

in PV and *SF3B1*, *SH2B3*, *U2AF1*, *IDH2*, *TP53*, and *EZH2* in ET [41].

In a further attempt at establishing associations between non-driver mutations and clinical outcomes in PV and ET, Senin et al. analyzed 51 recurrent mutations in 100 patients with either *JAK2*-positive PV or *JAK2*-positive ET. This study showed that PV/ET patients whose disease had progressed into AML had an increased rate of acquisition of new genetic mutations which suggested genetic instability, while in patients whose disease remained stable at the 10-year mark, there was a low incidence of new mutations, thus demonstrating a role for NGS in predicting genetic instability and disease progression. Aberrations that were most relevant with regard to transformation of disease to AML were variants of *ASXL1*, *TP53*, *IDH1/2*, *SRSF2*, and *RUNX1* [42]. Most of these mutations (*SRSF2*, *IDH1/2*, *RUNX1*, *TP53*) in addition to *DNMT3A* were also found to be associated with a higher risk of developing cytopenias during hydroxyurea therapy. Other noteworthy findings were the association between increased genetic instability and the *SRSF2* and *RUNX1* mutations. *SF3B1* and *IDH1/2* mutations were associated with increased myelofibrosis transformation while an overall decreased OS was seen in patients with *DNMT3A*, *SRSF2*, *SF3B1*, *IDH1/2*, and *RUNX1* mutations [42].

In ET and PV, a few studies have highlighted correlations between treatment response and the extended genetic profile. Previously, Quintas-Cardama et al. had demonstrated through analysis of the mutational profile of 83 PV/ET patients, an association between the prevalence of *TET2*, *ASXL1*, *DNMT3A*, *IDH*, and *EZH2* mutations and response to pegylated-interferon α-2a: the higher the frequency of these mutations, the less likely were the patients to achieve complete molecular response [43]. Similarly, a cohort of 31 patients with *CALR*-positive ET patients were treated with Interferon-α and the presence of *TET2*, *IDH2*, *ASXL1*, and *TP53* mutations was associated with poorer responses and lower *r* rates of achieving complete molecular response [44].

Paradigm Shift in Disease Classification?

In 2018, Grinfeld et al. published a comprehensive mutational analysis including more than 2000 patients and defined eight subgroups with shared biological features that correlated with distinct clinical outcomes [45]. Patients were initially classified into six subgroups depending on the presence or absence of particular chromosomal mutations such as *TP53* disruption or aneuploidy, MPN with chromatin or spliceosome mutations, presence of *CALR* mutations, presence of MPL mutations, homozygosity for *JAK2* or *NFE2* mutations, and heterozygosity for *JAK2* mutations. The remaining two subgroups were patients with either no driver mutations or no markers that were known or defining for one of the other 6 subgroups. The first subgroup of patients carrying *TP53* mutations was more prevalent in MF than ET/PV and demonstrated a much poorer prognosis and a higher probability of transformation to AML and death. The second subgroup with at least 1 of 16 myeloid cancer gene mutations, chromosome 7 and 7q mutations, and LOH at chromosome 4q demonstrated increased probability of transformation into MF and a shorter event-free survival. Patients with *MPL*- or *CALR*-mutated MF had a higher rate of AML transformation. The subgroup that was homozygous for the *JAK2* or *NFE2* mutation had a higher propensity for MF transformation while the *JAK2* heterozygous subgroup, which was most prevalent in ET, had a more favorable clinical course. Another notable clinical finding was the association of the subgroup with no identifiable driver mutation, with the female gender, younger age, and a more favorable clinical course with only 0.5% transforming into myelofibrosis and 1% into AML. Other MPN driver mutations defined a subgroup with the *TET2* and *DNMT3A* aberrations (Table 3). One interesting finding was that 38 patients of the studied cohort had mutations in *PPM1D* making it the eighth most commonly mutated sequence in MPN and was found to be detectable either at initial diagnosis or following exposure to hydroxyurea therapy.

Table 3 Eight genomic subgroups and their distinct clinical outcomes per Grinfeld et al.

Subgroup	Disease distribution/demographic	Impact
TP53 disruption or aneuploidy	Rare in ET/PV vs MF	*↑ AML and death
Chromatin/spliceosome mutation	≥ 1 mutation in 16 myeloid genes, LOH 4q, abn 7 or 7q	Enriched in MF, MDS/MPN *↑ MF transformation/↓EFS
CALR-MPN	ET or MF	↑ MF transformation
MPL-MPN	ET or MF	**MPL*-MF had ↑ AML
Homozygous *JAK2* or *NFE2*	Enriched for PV	*↑ MF transformation
Heterozygous *JAK2*	ET, some PV and MF	Favorable outcomes
MPN w/ other driver	e.g., *TET2/DNMT3A*	
MPN w/ no driver	?reactive or unidentified driver—young women	0.5% MF transformation, 1% AML over 8 years

*Compared to *JAK2* heterozygous subgroup

Adapted from Grinfeld et al. [45]

Here, there is a foreshadowing of a future classification of MPNs based on these shared biological features, as opposed to distinctions made by blood count values and morphology [45]. The comprehensive genomic information was also integrated with clinical, demographic, and laboratory features to create a personalized assessment (https://cancer.sanger.ac.uk/mpn-multistage).

Conclusions

In the molecular era of MPNs, the role of mutations has been increasingly established. First, the driver mutations helped underscore an essential aspect of disease pathogenesis, involving universal JAK-STAT activation. In addition to facilitating the diagnostic evaluation, recognition of universal JAK-STAT activation led to the development of targeted JAK inhibition for MF and PV. Further, driver mutations influence prognosis in MF, and thrombosis risk in ET. Extended genetic analyses have established a role for testing in MF, based on the impact on prognosis. Certain HMR mutations (and the number identified) are included in the most contemporary prognostic assessments. Given the risk/reward associated with stem cell transplant, it is paramount that hematologists have the most comprehensive and precise tools for prognostication. Apart from one (of many) factors used to select transplant candidates, the extended genetic profile may also help set expectations regarding response to standard therapies, such as ruxolitinib. Though NGS remains to a large extent a research tool, the NCCN recommends its use in selected cases such as to define clonality in triple-negative MPN disease, as well as a means of identifying MF patients at higher risk for progression [46]. European Leukemia Net recommendations are similar, suggesting the extended testing can be used to establish clonality in triple-negative MPN, and to aid in selection of transplant-eligible MF patients [47].

In ET/PV, a similar theme is emerging, regarding the impact of the extended genetic profile, and clinical outcomes. Unfortunately, no strong association has yet been established between additional mutations, and thrombosis, one of the more common clinical concerns. However, there are signals to suggest impact on progression. Currently, this information is less likely to be actionable of ET/PV patients, compared to MF—while HMR mutations may suggest transplant evaluation in MF; it is not likely that transplant would be performed in an ET/PV phase of the illness. Hence, guidelines do not yet endorse sending these panels routine in ET/PV.

Yet, studies like that of Grinfeld speculate upon a paradigm shift for MPNs—moving from classification resting on clinical and laboratory features, to that based on shared biology. The abundance of genomic information, coupled with comprehensive clinical data allows for a more personalized prognostic assessment. Information in this study highlighted subsets of ET, PV, and MF patients at particular risk for progression. Use of such information may dictate closer monitoring, referral for transplant, and/or conduct of more efficient clinical trials. We predict an increasing use of NGS, as is seen in other myeloid malignancies, but hope that such information not only refines prognosis but also leads to an actionable therapeutic plan, and impact on natural history for our MPN patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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