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Expert guidance on when to screen, monitor, and initiate complement inhibition therapy in patients without classical PNH

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Key Points

- Treatment decisions should be guided by PNH clone size, hemolysis, hemoglobin level and thrombotic history, PNH-related symptoms, and BMF.
- Monitor patients with a PNH clone not yet on complement inhibitors, or those with a thrombotic event or worsening hemolysis symptoms.

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired hematologic disease characterized by complement-mediated hemolysis with or without overt hemoglobinuria and is associated with bone marrow failure (BMF). PNH can be classified into 3 subcategories: classical (hemolytic) PNH, PNH with underlying BMF, and subclinical PNH. The optimal approach for patients with underlying BMF or subclinical PNH is not clearly defined. In addition, recommendations for screening and monitoring nonclassical patients are dated. A modified Delphi panel consisting of 10 hematologists and hematologist-oncologists evaluated 414 patient scenarios on 2 separate occasions and participated in a moderated in-person meeting. Consensus statements were developed based on the second round of ratings. After the meeting, the panel agreed on 90% of the ratings and made recommendations on when to screen patients for a PNH clone, when to initiate complement inhibitor treatment, and when to reevaluate patients with a PNH clone who are not yet on treatment. For example, it is appropriate to initiate complement inhibition in patients with a PNH clone size ≥10% who had a recent thrombotic event with laboratory evidence of hemolysis. Further evidence is required to improve recommendations for patients with small (<10%) PNH clone sizes.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disorder resulting from an acquired hematopoietic stem cell mutation in the *PIGA* gene, rendering cells susceptible to complement-mediated hemolysis. It is characterized by various degrees of bone marrow (BM) failure (BMF) and may present with or without hemoglobinuria. Patients often present with symptoms of anemia, may suffer from fatigue, and are prone to thrombotic events (TEs).[1] Thrombosis represents the leading cause of mortality in patients with untreated PNH, and its prevention is 1 of the main goals of treatment.[2] PNH is typically classified into 3 subcategories: classical PNH (hemolytic), PNH with underlying BMF, and subclinical PNH.[1,3-5] Although treatment guidelines published between 2016 and 2019 exist for patients with classical PNH,[6-8] the optimal approach for patients with PNH with underlying BMF is less

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The full-text version of this article contains a data supplement.

clear. In addition, several new complement inhibitors have been approved (pegcetacoplan in May 2021,[9] iptacopan in December 2023,[10] danicopan [in combination with a complement component 5 (C5) inhibitor] in April 2024,[11] and crovalimab in June 2024)[12] since the publication of previous guidance.

Current recommendations for PNH with underlying BMF emphasize treating the underlying BM disorder, screening for glycosylphosphatidylinositol-deficient cells with flow cytometry, and monitoring for the expansion of the PNH clone or disease progression.[6-8] However, registry studies have reported TEs in some of these patients, which suggests that complement inhibition may be beneficial in some patients with PNH clones and underlying BMF.[13]

Furthermore, patients with subclinical PNH, defined by the absence of clinical or laboratory evidence of hemolysis,[6,14] have generally not been included in treatment recommendations for complement inhibitors. The existing literature suggests that outcomes are worse among patients with classical PNH (eg, significant intravascular hemolysis [lactate dehydrogenase (LDH) >1.5 × upper limit of normal], a PNH clone size >50%,[15-22] and either evidence of end-organ damage or significant symptoms attributed to PNH [eg, debilitating fatigue, abdominal pain]) and to initiate complement inhibitor treatment.[6-8] However, for patients who do not meet these criteria, there remains uncertainty about the optimal approach to screening, monitoring, and initiation of complement inhibitor therapy.[7,8] Supplementing current recommendations, particularly regarding the initiation of complement inhibitor treatment for patients with nonclassical PNH, represents an important step toward optimizing patient care and potentially preventing or reducing the incidence of TEs.[23,24] This study aims to establish expert consensus on when to screen for a PNH clone, how to monitor patients without classical PNH, and when to initiate complement inhibitor treatment.

Methods

We used the RAND/University of California, Los Angeles–modified Delphi panel method to develop expert consensus on the screening, monitoring, and initiation of complement inhibitor therapy in patients with PNH. The process comprised several sequential steps: selection of expert clinicians with help from study sponsor and panel chairs, completion of a focused literature review, preparation of detailed rating materials, administration of an initial survey (round 1), convening of an in-person meeting to review and discuss areas of disagreement, distribution of a follow-up survey (round 2), and quantitative analyses of panel agreement and disagreement across scenarios.

Panelist composition

We systematically and quantitatively assessed the perspectives of 10 physicians, including 8 hematologists and 2 hematologist-oncologists, using the modified Delphi panel method. Panelists were selected based on experience, availability, and interest in participation. Ten panelists were included and had an average of 27 years (range, 12-48) of clinical experience managing patients with PNH, seeing an average of 45 patients with PNH per year (on average, 23 patients with classical PNH, 9 patients with PNH with underlying BMF, and 13 patients with subclinical PNH; range, 12-103). Nine panelists were from the United States (3 from the Midwest, 3 from the Northeast, 1 from the West, and 2 from the South), and 1 panelist was from Germany. The panelists received honoraria from the study sponsor, Novartis Pharmaceutical Corporation. Novartis provided input on the composition of the panel but did not provide input on the methodology or results or conclusions of the panel. Modified Delphi panels do not involve human subjects, as defined in 45 Code of Federal Regulations part 46; thus, institutional review board approval was not required.

Literature review

After panel recruitment, we conducted a targeted literature review on the management of patients with nonclassical presentations of PNH. We reviewed literature on the diagnosis and management of PNH[6] and 2 recent consensus treatment recommendations, 1 from a Belgian expert panel[8] and the other from the Canadian PNH network.[7] To identify additional relevant publications, we performed 2 structured searches in PubMed. Titles and abstracts were screened for relevance, and 47 articles were included in the final review. The complete list of included studies is provided in the supplemental Data (Appendix A).

Rating form development

The rating form (structured survey) was then developed over the course of several months in collaboration with all panelists through a series of individual video calls. These discussions allowed panelists to share their clinical insights and real-world experiences as the rating form evolved. All panelists approved the final rating form before its distribution to the panel for completion. The rating form ultimately included 6 core clinical characteristics, including underlying BMF (ie, a concomitant diagnosis of aplastic anemia [AA], myelodysplastic syndrome [MDS], or myelofibrosis), white blood cell PNH clone size, PNH-attributable symptoms, recent TE attributable to PNH, laboratory evidence of hemolysis, and hemoglobin levels (Table 1).

Table 1. Definitions of PNH-associated characteristics included in the rating form

Characteristic	Categories and definitions
Underlying BMF diagnosis	A concomitant diagnosis of AA, MDS, or myelofibrosis[25]
PNH clone size	Measured by flow cytometry in leukocytes (granulocytes or monocytes): • >50% (for patients with classical PNH) • >25%-50% (for patients with classical PNH) • 10%-25% • detectable to <10%
PNH-attributable symptoms	Presence of ≥1 of the following: chest pain, abdominal pain, SOB, dyspnea, dysphagia, fatigue, weakness, jaundice, erectile dysfunction, hemoglobinuria
Recent PNH- attributable TE	Occurring within the last 2 years, regardless of being provoked
Laboratory evidence of hemolysis	Based on LDH, reticulocyte count, bilirubin, haptoglobin
Hemoglobin	≥12 g/dL 10-12 g/dL <10 g/dL

SOB, shortness of breath.

Table 2. Rating form questions and associated scales

Table(s) in rating form*		1	← 3 →	5	← 7 →	9
Tables 1-6	Rate the appropriateness of making a recommendation to initiate a complement inhibitor	Highly inappropriate; risks outweigh the benefits		Not sure or risks and benefits balanced		Highly appropriate; benefits outweigh the risks
Tables 7-8	Rate when to reevaluate the appropriateness of initiating a complement inhibitor to treat PNH	Not again until symptoms change	In 1 y	In 6 mo	In 3 mo	As soon as possible (because I want to start treatment)
Table 9	Rate the appropriateness of screening for a PNH clone	Highly inappropriate; risks outweigh the benefits		Not sure or risks and benefits balanced		Highly appropriate; benefits outweigh the risks

*Refer to supplemental Data (Appendix B).

Rating form components

In the first section of the form, panelists rated the appropriateness of initiating a US Food and Drug Administration (FDA)–approved complement inhibitor (a C5 inhibitor [eg, eculizumab, ravulizumab], a complement component 3 inhibitor [pegcetacoplan], and a factor B inhibitor [iptacopan]) for each patient scenario. Danicopan was excluded because it is only approved as an add-on therapy to C5 inhibitors and is not typically started as first-line treatment. Crovalimab was not discussed in the rating form given the short time between its approval and the panel deliberations. In the second section, panelists considered when they would reevaluate the appropriateness of initiating a complement inhibitor in a subset of patients who were not yet started on one. In the final section, panelists rated the appropriateness of screening patients for a PNH clone using flow cytometry. Patients with underlying BMF with large PNH clones (25%-100%) were considered along with classical PNH.

Each panelist independently completed the final rating form, which consisted of 414 unique patient scenarios, each rated on a 9-point scale from 1 to 9 (Table 2). For example, when evaluating different treatments, a score of 1 indicated that a complement inhibitor was considered inappropriate, with risks clearly outweighing benefits; a score of 5 denoted uncertainty or that the risks and benefits seemed balanced; and a score of 9 signified that a complement inhibitor was appropriate, with benefits clearly outweighing risks. The central tendency and spread of responses were summarized using median and range.

Panel meeting

During a professionally moderated in-person meeting in July 2025, panelists were provided a summary document displaying their individual ratings, the group median, and the range of ratings. Disagreement for a given scenario was defined as the presence of ≥2 ratings in the 1-to-3 range and ≥2 ratings in the 7-to-9 range. Only aggregated, anonymized ratings were shared during the in-person meeting to keep individual responses anonymized. Given this definition of disagreement, it was possible to have agreement on statements in which as many as 2 of the panelists disagreed with the rest of the panel (for example, consensus that a complement inhibitor is recommended could mean the majority [≥8 of 10 panelists] agreed that a complement inhibitor is recommended but up to 2 panelists felt it is inappropriate).

Where agreement was reached, ratings were grouped into 1 of 3 categories: appropriate, uncertain, or inappropriate. During the meeting, panelists shared their rationale for their ratings and discussed the definitions and categories used in the scenarios. After the discussion, panelists completed a second round of ratings, which were analyzed using the same criteria as the first round. Based on these second-round ratings, statements summarizing areas of consensus were drafted, circulated among the panel, and revised for clarity.

Results

The panel agreed on 90% of the second-round ratings, compared with 74% of the first-round ratings. Agreement that a scenario was appropriate or likely was defined as ≥8 of the 10 panelists providing a rating between 7 and 9, with ≤2 panelists disagreeing; agreement that a scenario was inappropriate or unlikely was defined as ≥8 of the 10 panelists providing a rating between 1 and 3. The guidance presented in Table 3 summarizes the panel's recommendations on when to screen for a PNH clone. Figures 1A-B include recommendations on when to initiate complement inhibitor therapy. Table 4 presents the consensus on when to reevaluate the appropriateness of initiating complement inhibitor therapy. The final rating form is provided in the supplemental Data (Appendix B).

Every clinical scenario is different, with its own set of complex characteristics. In practice, many other clinical and nonclinical factors, beyond those addressed later, can influence when to screen patients for a PNH clone, when to initiate complement

Table 3. Expert consensus on when to screen for a PNH clone

Patient characteristic	Conditions for screening
Underlying BMF	Current or previous diagnosis of AA Current or previous diagnosis of low-risk MDS (in particular, the hypocellular variants, or if accompanied by unexplained iron deficiency and/or evidence of hemolysis)
Thrombotic complications	Arterial or venous thrombosis(1) involving unusual sites (specifically in the cerebral venous sinus, splanchnic, or abdominal vasculature), (2) that is unexplained, or (3) at any site that progresses despite being on adequate anticoagulation therapy.
Unexplained Coombs-negative hemolysis	May be accompanied by: • Unexplained cytopenias • Iron deficiency • Hemoglobinuria Episodic and otherwise unexplained dysphagia or abdominal pain

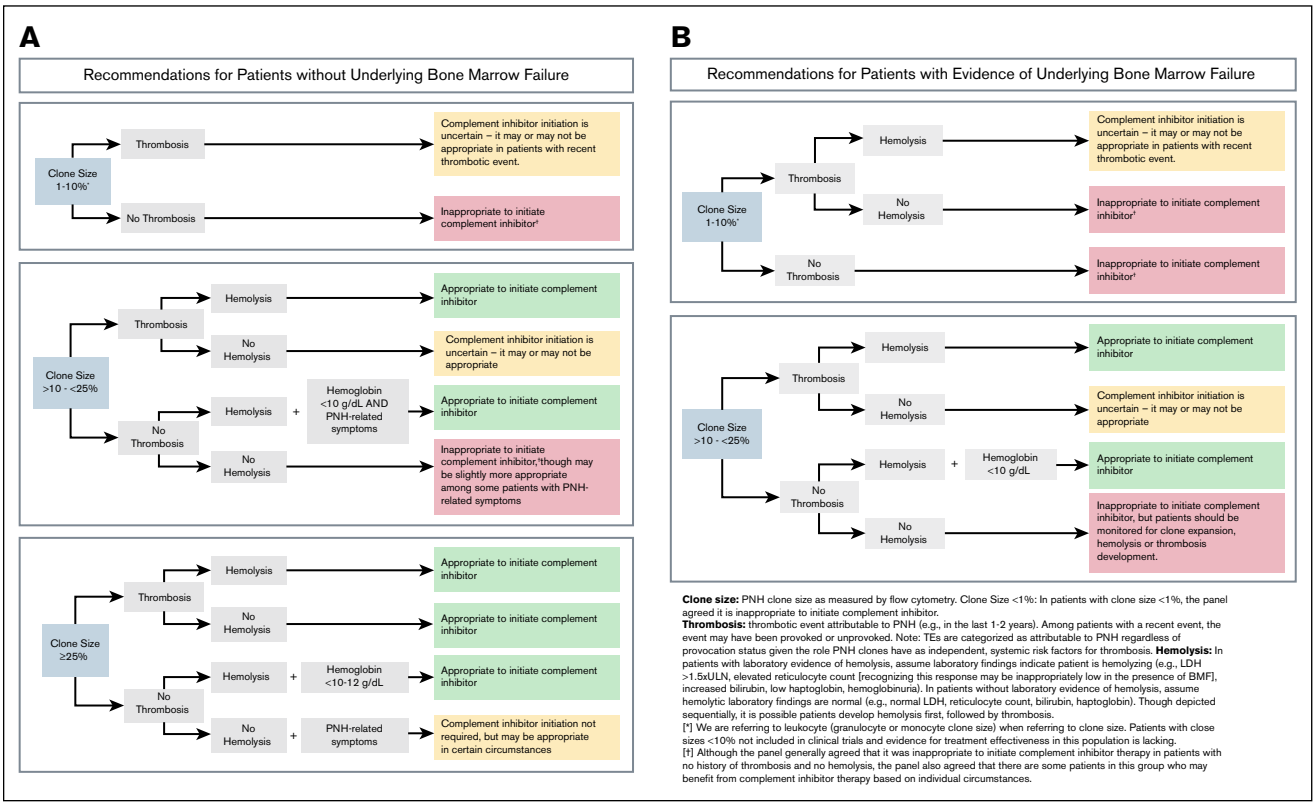

Figure 1. Recommendations for complement inhibitor treatment for patients with and without underlying BMF. (A) Recommendations for patients without underlying BMF. Clone size: PNH clone size as measured by flow cytometry. Clone size <1%: in patients with clone size <1%, the panel agreed that it is inappropriate to initiate complement inhibitor treatment. Thrombosis: TE attributable to PNH (eg, in the last 1-2 years). Among patients with a recent event, the event may have been provoked or unprovoked. Note: TEs are categorized as attributable to PNH regardless of provocation status given the role PNH clones have as independent, systemic risk factors for thrombosis. Hemolysis: for patients with laboratory evidence of hemolysis, assume laboratory findings indicate that the patient is hemolyzing (eg, LDH >1.5 × upper limit of normal [ULN], elevated reticulocyte count [recognizing this response may be inappropriately low in the presence of BMF], increased bilirubin, low haptoglobin, hemoglobinuria). For patients without laboratory evidence of hemolysis, assume hemolytic laboratory findings are normal (eg, normal LDH, reticulocyte count, bilirubin, haptoglobin). Though depicted sequentially, it is possible that patients develop hemolysis first, followed by thrombosis. (B) Recommendations for patients with evidence of underlying BMF. Clone size: PNH clone size as measured by flow cytometry. Clone size <1%: for patients with clone size <1%, the panel agreed that it is inappropriate to initiate complement inhibitor. Thrombosis: TE attributable to PNH (eg, in the last 1-2 years). Among patients with a recent event, the event may have been provoked or unprovoked. Note: TEs are categorized as attributable to PNH regardless of provocation status given the role PNH clones have as independent, systemic risk factors for thrombosis. Hemolysis: for patients with laboratory evidence of hemolysis, assume laboratory findings indicate that the patient is hemolyzing (eg, LDH >1.5 × ULN, elevated reticulocyte count [recognizing this response may be inappropriately low in the presence of BMF], increased bilirubin, low haptoglobin, hemoglobinuria). For patients without laboratory evidence of hemolysis, assume hemolytic laboratory findings are normal (eg, normal LDH, reticulocyte count, bilirubin, haptoglobin). Though depicted sequentially, it is possible that patients develop hemolysis first, followed by thrombosis.

inhibitor treatment, and when to reevaluate patients with a PNH clone who are not yet on treatment. For instance, we assume that patients are reasonably adherent to their care plan and are not subject to health insurance restrictions or financial limitations. The ratings provided are for patients with PNH who are not pregnant; at the time of the panel, systematic data on safety and efficacy during pregnancy were available only for eculizumab.[26] It was also presumed that patients had completed, or would complete, the updated vaccination recommendations or were receiving prophylactic antibiotics by the time of treatment initiation.[27]

When to screen for a PNH clone

Experts agreed that clinical or laboratory features suggestive of PNH (Table 3) should prompt testing for a PNH clone by high-sensitivity flow cytometry using fluorescent aerolysin on peripheral blood. Patients for whom this evaluation is appropriate include those with BMF syndromes (eg, AA or hypocellular, low-risk MDS, when accompanied by an unexplained iron deficiency or evidence of hemolysis); patients with unexplained thrombosis, especially at atypical sites (eg, cerebral or splanchnic venous system); and individuals with nonimmune hemolysis of unclear etiology,

Table 4. Expert consensus on when to follow up with patients not yet on complement inhibitors

Recent TE	Recommendation
Yes	It is appropriate to reassess the need for treatment as soon as possible if the patient has experienced a recent TE or if symptoms potentially related to PNH are present (eg, chest pain, abdominal pain, SOB, dysphagia, fatigue/weakness, jaundice, erectile dysfunction, dark urine).
No	Among patients without a recent TE, it is generally appropriate to reevaluate the need for treatment within 3-6 mo.

Recent TEs should be considered as primary, independent trigger for an urgent evaluation regardless of the presence or absence of other symptoms potentially related to PNH. The inclusion of symptoms potentially related to PNH in this category helps ensure that symptomatic burden is prioritized, but the absence of symptoms does not undermine the urgency of evaluation after a recent TE.

particularly when associated with cytopenias, iron deficiency, hemoglobinuria, or episodic abdominal pain or dysphagia. These findings align with previous expert consensus regarding the clinical and laboratory triggers that should prompt screening for a PNH clone.[28]

Complement inhibitor treatment initiation

Experts emphasized that a goal of PNH management is to initiate complement inhibitor therapy before the occurrence of thrombosis because TEs remain the leading cause of morbidity and mortality in this population.[29,30] Thrombosis should therefore not be viewed as a prerequisite for treatment initiation. The panelists agreed that treatment decisions should primarily be guided by PNH clone size, evidence of hemolysis, hemoglobin level, and thrombotic history, while also considering symptoms potentially related to PNH and the presence or absence of underlying BMF.

Among patients with no evidence of underlying BMF (eg, does not have a concomitant diagnosis of AA, MDS, or myelofibrosis) (Figure 1A), it is considered appropriate to initiate complement inhibitor therapy when the leukocyte (granulocyte or monocyte) PNH clone (hereafter referred to as "PNH clone") is $\geq$25% in size and accompanied by laboratory evidence of hemolysis (eg, elevated LDH, reticulocyte count, and bilirubin and decreased haptoglobin)[31] to reduce the risk of thrombosis. Treatment is also considered appropriate for patients with clones 10% to 25% who have had a recent TE attributable to PNH (eg, within the last 1-2 years, provoked or unprovoked, may or may not include elevated D-dimer) and who have evidence of hemolysis. Conversely, for patients with the same clone size (10%-25%), treatment is considered inappropriate when there is neither laboratory evidence of hemolysis nor a recent TE. Treatment is also considered inappropriate for patients with a PNH clone $\leq$10% without a recent TE. The panel felt that symptoms associated with PNH (eg, fatigue/weakness, erectile dysfunction, abdominal pain) are unlikely to be etiologically related to PNH in patients with subclinical clones 1% to 10% and certainly those with very small clone sizes (<1%). However, for patients with clones 1% to 10%, the use of complement inhibitor treatment is uncertain and will depend on individual circumstances, particularly if patients have had a recent TE (Figure 1A). For patients with a PNH clone <1%, it is inappropriate to initiate treatment.

Among patients with evidence of other underlying BMF (eg, a concomitant diagnosis of ongoing AA or MDS) (Figure 1B), complement inhibitor therapy is considered appropriate to initiate among patients with a PNH clone 10% to 25% in size who have had a recent TE and laboratory evidence of hemolysis or who have not had a recent TE but have laboratory evidence of hemolysis and low hemoglobin (<10 g/dL). Treatment is considered inappropriate for patients without a recent TE and without laboratory evidence of hemolysis, although such patients should be closely monitored because the PNH clone may expand or hemolysis may develop as patients recover, in which case PNH therapy may become necessary. Treatment is also considered inappropriate with smaller clone sizes (1%-10%), unless patients have had a recent TE and laboratory evidence of hemolysis, in which case its use is uncertain and will depend on individual circumstances.

The panelists agreed that any of the FDA-approved complement inhibitors (C5 inhibitors [eg, ravulizumab or eculizumab], a complement component 3 inhibitor [pegcetacoplan], or a factor B inhibitor [iptacopan]) are appropriate for treatment initiation in eligible patients. Because there are no head-to-head comparisons of the proximal vs terminal complement inhibitors in treatment-naive patients with PNH, the choice of therapy should be based on discussions between clinicians, their patients, and insurers. Any associated BMF syndrome with significant neutropenia and/or thrombocytopenia should be treated on its own merits because complement inhibition is not expected to improve cytopenias except for the component of the anemia caused by hemolysis.

Follow-up of patients not yet on complement inhibitors

The panelists agreed that ongoing monitoring is necessary for patients with a detectable PNH clone who have not yet initiated complement inhibitor therapy. The need for treatment should be reassessed as soon as possible in the event of a TE or the emergence of symptoms suggestive of increased hemolytic disease activity, such as fatigue (if possible, as measured by the Functional Assessment of Chronic Illness Therapy–Fatigue assessment)[32,33] or weakness, abdominal or chest pain, dysphagia, jaundice, dark urine, or erectile dysfunction. Even among patients without a recent TE, it is generally appropriate to reevaluate the need for treatment within 3 to 6 months of the first discovery of the PNH clone. Given the dynamic nature of PNH clones, patients with very small clones (<1%) and/or stable clones are recommended to undergo reassessment annually. More frequent monitoring is recommended for patients with AA or hypoplastic MDS with a known small PNH clone who are receiving immunosuppressive therapy because clonal expansion may occur and therapy directed at the PNH clone may become necessary or small PNH clones may disappear. The recommendations for when to follow up with patients who are not yet on complement inhibitor therapy are summarized in Table 4. Although Table 4 groups recent TE with symptoms potentially related to PNH for high priority monitoring, it is appropriate to consider a recent TE as an independent event, the presence of which alone warrants immediate assessment, regardless of the presence or absence of other symptoms.

Discussion

This study evaluated expert consensus on when to screen for a PNH clone, when to initiate complement inhibitor treatment, and when to reassess patients not yet receiving complement inhibitors. An expert panel of 10 hematologists and hematologist-oncologists completed 414 ratings, each a unique patient scenario. The panel recommended screening for PNH in patients with underlying BMF, a TE, or unexplained Coombs-negative hemolysis. The panel also recommended that the initiation of complement inhibitor treatment be guided by laboratory evidence of hemolysis, severity of anemia, and history of TE for clone sizes ≥10% and favored initiating therapy for patients with hemolysis regardless of TE for clones >25%. Treatment was generally considered inappropriate for PNH clones ≤10%. Although treatment initiation criteria among patients with and without underlying BMF overlap, there are subtle distinctions. For example, for patients with underlying BMF and a small clone size (ie, 1%-10%), the requirement for concurrent laboratory evidence of hemolysis before treatment initiation serves to link a TE to the patient's PNH clone and distinguish it from possible reasons for clotting related to the underlying BMF. Similarly, among patients with underlying BMF and moderate clone size (ie, 10%-25%), the requirement for anemia alone (without the need for PNH-related symptoms), provided there is laboratory evidence of active hemolysis (eg, LDH >1.5 × upper limit of normal, elevated reticulocyte count, increased bilirubin, low haptoglobin, hemoglobinuria), acknowledges the reduced hematopoietic reserve in these patients. For patients not yet receiving complement inhibitor treatment, the panel recommended reassessment as soon as possible after a TE and within 3 to 6 months of the first discovery of the PNH clone for patients without a recent TE. Panelists rated the initiation of complement inhibition as appropriate for certain patients with smaller clone sizes (<10% and 10%-25%), particularly those experiencing TEs. However, high-level prospective evidence supporting this management approach is currently lacking in trial and registry data. The panel's recommendations reflect a real-world, risk-averse clinical consensus prioritizing the prevention of complications. Further data are required to evaluate the true preventative efficacy of complement inhibitor treatment in small-clone cohorts.

Our panel's categorization of PNH clone sizes into 4 tiers (1% to <10%, 10%-25%, >25%-50%, >50%) is substantiated by established literature and registry data, specifically the >50% threshold, which aligns with the definition of classical PNH, whereas the <10% threshold identifies subclinical populations often seen in BMF.[5,34] This stratification is further supported by the International PNH Registry, which uses 10% and 50% benchmarks to link clone size to symptomatic burden.[35] Our use of granular intermediate categories between 10% and 50% is consistent with International Clinical Cytometry Society/European Society for Clinical Cell Analyses guidelines, which recommend precise clone quantification to guide clinical management.[36,37] Providing granularity within the 10%-to-50% range allowed the panel to address the inflection point of high disease activity that often escalates once a clone exceeds 30%.[38] These thresholds facilitated nuanced discussion, particularly for treatment initiation.

Through the modified Delphi panel process, we expanded upon previous recommendations by convening an expert panel that incorporated emerging data on thrombotic risk and the availability of new therapies. Our consensus guidance provides a key distinction from existing guidance by developing recommendations based on clone size and evidence of underlying BMF. This delineation is important because patients with underlying BMF may become anemic, have more dynamic clones as they recover from BMF, and have hemolysis masked by a low reticulocyte count but may later recover to hemolyze. Previous guidance suggested using a >50% PNH granulocyte threshold[6,8] and specific disease-related morbidities, with no differentiation in treatment recommendations for underlying BMF.[6-8] This panel provided additional guidance for patients with a clone size ≥25%, for whom complement inhibitor therapy was recommended in the presence of either a recent TE or evidence of hemolysis. The panel further provided guidance for patients with underlying BMF and a PNH clone of 10% to 25%, recommending complement inhibitor treatment if there is evidence of hemolysis and hemoglobin <10 g/dL. Differentiating treatment based on clone size and evidence of underlying BMF is important, and refining existing clinical understanding may help inform timely, evidence-aligned treatment decisions for patients with PNH.

The panel reached a consensus that it is appropriate to screen for a PNH clone using flow cytometry of peripheral blood for patients with clinical features suggestive of hemolysis, thrombosis, or BMF. These recommendations align with previous guidance, such as those from the 2018 Belgian expert panel[8] and the 2019 Canadian PNH Network expert panel,[7] which similarly identified high-risk groups warranting evaluation, particularly patients with hemoglobinuria, Coombs-negative intravascular hemolysis (particularly with iron deficiency), venous thrombosis in atypical locations (eg, Budd-Chiari syndrome, mesenteric or portal vein thrombosis, or cerebral vein thrombosis), AA (screened at diagnosis and annually thereafter), and refractory anemia–MDS and those with episodic dysphagia or abdominal pain with biochemical evidence of intravascular hemolysis. This panel reaffirmed and refined these established criteria, which underscores the importance of targeted screening for patients most likely to have a PNH clone. There is limited guidance on when to reassess patients with PNH who are not yet receiving complement inhibitor treatment. Because PNH is rare, longitudinal data on its natural history remain sparse, despite efforts to capture this information through PNH registries and country-specific cohorts.[7,15,17,18,22,35,39-47] Standard practice supports annual monitoring of clone size by flow cytometry.[2,3,8,48] This panel's guidance emphasizes that reassessment should occur as soon as possible after a TE or the onset of PNH-related symptoms. For all other patients, reassessment within 3 to 6 months is considered appropriate. These distinctions are meaningful because they facilitate more timely recognition of disease progression.

Several other C5 inhibitors have, in recent years, received FDA approval and are available for clinical use. Because no head-to-head trials have compared proximal and terminal complement inhibitors in treatment-naive patients, the panel recommended that treatment selection be guided by shared decision-making between clinicians and their patients and that medication access/availability should be considered. After treatment initiation, therapeutic response should be carefully assessed by degree of improvement in anemia and improvement in hemolysis markers. For patients with a significant component of BMF or in settings with no access to or

an inability to receive complement inhibitor therapy, hematopoietic stem cell transplantation may be considered.

Consensus was not reached for patients with underlying BMF and a PNH clone size of 1% to 10%, a recent TE, evidence of hemolysis, and hemoglobin levels ≥10 g/dL. This uncertainty likely reflects limited evidence on the clinical significance of small PNH clones in the context of BMF, particularly their effect on the rate of thrombosis or symptomatic disease, and regarding the extent to which low hemoglobin is attributable to hemolysis.[49] Current literature on the management of PNH does not differentiate between patients with or without underlying BMF and generally recommends against starting complement inhibitor therapy unless the clone size is >10%.[6] Our panel differed by acknowledging that some patients who develop TE with clones <10% with concurrent hemolysis may benefit from complement inhibition. Considering that subclinical TEs do occur,[50] additional evidence is needed to clarify the risk of morbidity and mortality among patients with clone sizes <10% and to better understand the trade-offs between initiating and withholding complement inhibitor therapy in this population or initiating prophylactic anticoagulation.

This process has several limitations inherent to the modified Delphi panel method. First, although the panel comprised 10 predominantly US-based panelists with considerable expertise managing PNH, their perspectives may not reflect those of all providers or providers outside of the United States. Second, because some complement inhibitor therapies are relatively new, data on their use in patients with PNH remain limited, and most evidence reviewed by panelists on complement inhibitor therapy came from the initial eculizumab studies.[51,52] Third, every clinical scenario is different, and this guidance may not capture all possible clinical circumstances. Although our rating form focused on individual clinical scenarios, we recognize that screening, monitoring, and treatment decisions are optimally managed and shared among a multidisciplinary team to best coordinate care. Finally, the evidence base for this study was largely drawn from previous consensus panels and secondary analyses, not randomized controlled trials. The RAND/University of California, Los Angeles–modified Delphi panel method is most reproducible when consensus is drawn from a strong evidence base.[53]

We hope this guidance can be a useful resource for health care professionals and serve as the foundation for additional research, particularly on the care of patients with clone sizes <10%. Our recommendations are intended to provide general guidance for experienced clinicians who treat patients with PNH and are not designed to supersede individual physician and patient decision-making. Physicians should continue to use their clinical expertise and refer to established guidelines to screen, monitor, and initiate complement inhibitor therapy in patients with PNH. As new research and evidence emerge, the guidance presented here should be reevaluated.

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Authorship

Contribution: V.P., H.T.D.M., A.S., J.W., and D.J.K. conceptualized and designed the study; H.T.D.M., E.S., A.S., and J.W. curated the data; H.T.D.M., A.S., and J.W. administered the project; V.P., H.T.D.M., A.S., E.S., J.W., and D.J.K. wrote the original draft; and all authors performed the formal data analysis, interpreted the data, created the visualizations, reviewed and edited the manuscript and met the International Committee of Medical Journal Editors authorship criteria and approved the final version of the manuscript.

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