deciphehr™
connecting the dots of rare disease

SUPPORTING SUSPECT PATIENT RECOGNITION FOR FURTHER CLINICAL EVALUATION

PNH Program Implementation Guide

PNH=paroxysmal nocturnal hemoglobinuria.

deciphEHR™ provides educational resources to help health systems, hospitals, and specialty practices leverage their electronic health record (EHR) systems. Data from the EHR system may help triage suspect patients for further clinician evaluation.

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AstraZeneca Rare Disease

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- Paroxysmal nocturnal hemoglobinuria (PNH) is a **rare, chronic, devastating,** and **potentially life-threatening disease** characterized by uncontrolled terminal complement activation due to an acquired mutation in the hematopoietic stem cells.[1]
- The uncontrolled activation of the terminal complement pathway can result in **thrombosis, organ damage,** or **early mortality**.[1]
- Thrombosis is the **#1 cause of death in PNH,** accounting for approximately **40% to 67% of known deaths in PNH patients** and **increasing the risk for mortality by up to 14-fold.**[2,3]
- Due to the rare nature of the disease combined with the heterogeneity and generalizability of PNH symptoms, **diagnoses are often delayed or missed.**[4]
- The objective of this guide is to help HCPs understand the clinical presentation of PNH and leverage EHR data to triage suspect PNH patients for testing. Specifically, the program will make use of relevant patient history data, disease codes, suspect patient lists, and best practice alerts (BPAs).

Key Sections

HCP=healthcare provider.

1

Clinical Criteria for PNH

Signs and symptoms of PNH can include a wide range of severe, unpredictable, and potentially life-threatening complications. Rapid recognition of the signs and symptoms of PNH and early diagnosis are important to patient management.[4]

Diagnostic Challenges

~80% OF PATIENTS diagnosed with PNH are misdiagnosed or undiagnosed after their initial visit with an HCP because of the diagnostic difficulties, and nearly 1 in 4 patients are delayed in diagnosis for more than 5 years.[5]

PNH is a heterogenous disease with features that vary widely in severity from subclinical PNH, which can present as asymptomatic, to catastrophic events.[1,6-8] This variability can make recognition of PNH difficult.

63% OF PATIENTS manifest PNH as a comorbidity with other bone marrow failure syndromes (BMFS) such as aplastic anemia (AA) and myelodysplastic syndromes (MDS).[9]

37% OF PATIENTS present with PNH, with no known BMFS.[9]

PNH patients can have extensive diagnostic delays due to the generalization of their symptoms and the lack of awareness of PNH; therefore, many at-risk patients are undertested and underdiagnosed.[4,5,10]

ICCS guidelines suggest:

- Routine, **annual PNH screening** (high-sensitivity flow cytometry on peripheral blood [HSFC-PB]) testing in patients with underlying BMFS: eg, AA, MDS.*[11,12]
- Patients with AA warrant PNH testing upon their AA diagnosis, every 6 months for 2 years, and then annually if a clone is not detected.*[11]

*Lactate dehydrogenase (LDH) should also be used to assess prognosis and treatment plans immediately upon clone detection.[1,2]

Signs, Symptoms, and Risk Factors Suggesting Testing for PNH

Laboratory findings in a patient with PNH often include:

- Coombs-negative*[12]
- Elevated LDH and high reticulocytes, or low haptoglobin, or high total bilirubin[1,13,14]
- Evidence of organ damage from hemolysis and/or thrombosis[1]
- Evidence of bone marrow failure syndromes (~63% of patients)†[9]

Additional signs and symptoms of PNH can be very generalizable and vary widely such as fatigue, dyspnea, dysphagia, chest pain, abdominal pain, erectile dysfunction, and esophageal spasms. Comorbidities vary significantly as well and consist of pulmonary hypertension, chronic kidney disease, and unexplained cytopenias.[7-9,12,15-17] The following should strongly indicate the initiation of PNH testing using flow cytometry[2,11,18-23]:

Major Risk	Threshold
LDH	≥1.5 x ULN
Reticulocyte count	>ULN
Haptoglobin	<LLN
Unconjugated bilirubin	>ULN
Coombs test	Negative
Hemoglobinuria	Present

Minor Risk	Threshold
Bilirubin	>ULN
Hemoglobin	<LLN
Platelets	Low normal/low
WBCs	<LLN

ULN=upper limit of normal
LLN=lower limit of normal
LDH=lactate dehydrogenase
AST=aspartate aminotransferase
ALT=alanine transaminase
WBC=white blood cell

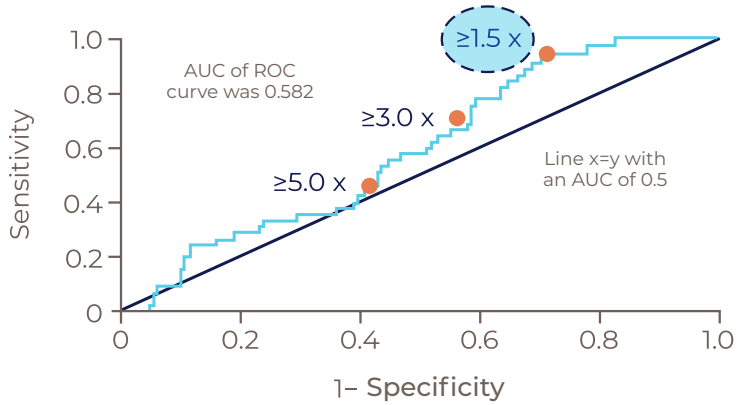
Diagnostic Criteria for PNH

The gold standard diagnostic test to confirm the diagnosis of PNH is high sensitivity flow cytometry on peripheral blood (HSFC-PB).[1,23,24]

Once positive for PNH, LDH levels should be monitored regularly to assess disease severity and prognosis.‡[2]

- Low RBC clone size compared to WBC clone size is indicative of intravascular hemolysis[12,24]
- LDH ≥1.5x the ULN has been shown to significantly increase the risk for thrombosis and be a predictor of premature mortality in patients with PNH[2,21]

ROC curve for LDH cutoff for detecting TE



The graph demonstrates that an LDH threshold of ≥1.5 x ULN is the most sensitive for detecting thrombosis. 96% of patients with thrombosis were detected using this threshold.[21]

AUC=area under the curve
ROC=receiver operating characteristic
TE=thrombotic event

*Coombs direct antiglobulin testing (DAT) is key for differential diagnosis of PNH. A positive Coombs test indicates autoantibody-mediated hemolysis and largely rules out PNH (except for very rare cases), while a negative Coombs test indicates PNH remains a potential differential diagnosis and is highly recommended to be tested for.[14,25]

†Bone marrow examination can help to differentiate classic PNH from PNH that develops in the setting of other bone marrow disorders if a BMFS has not yet been diagnosed.[11,14]

‡It is recommended to use annual HSFC-PB to continually screen patients with an underlying BMFS for the development of PNH.[11,12]

For Laboratory Scientists: High sensitivity flow cytometry on peripheral blood (HSFC-PB) for diagnosis of PNH should assess red blood cells (RBCs) and white blood cells (WBCs).*[1,12,18] While clone size for each cell lineage is important (eg, granulocytes/neutrophils, monocytes, and RBCs), granulocytes/neutrophils are thought to give the most accurate estimate of PNH clone size.[18] Of note, evaluation of RBCs alone may underreport clone size due to hemolysis and the dilution effect of transfusions; therefore, HSFC-PB is suggested to always be performed on WBCs in addition to RBCs.[12,24] Additionally, it is advised to use FLAER/CD24 or FLAER/CD157 combinations in addition to "routine" CD55- and/or CD59-based approaches for the most sensitive detection of PNH granulocytes/neutrophils.[18] Clear reporting is essential for appropriate clinical decisions and should include[1,12,24]:

- Clone size for each cell lineage (ie, granulocytes/neutrophils, monocytes, and RBCs)
- Proportion of Type II and III (percentage of GPI-deficient cells) as well as total RBCs
- Sensitivity level used (0.01% high-sensitivity analysis is ideal)
- All previous flow results in order to monitor clonal expansion
- Possible clinical significance of any change in clone size

*Evaluate RBCs and WBCs using >1 reagent (rather than RBCs alone)

FLAER=fluorescent aerolysin; GPI=glycosylphosphatidylinositol

2

A Guide to Generating Suspect PNH Patient Lists

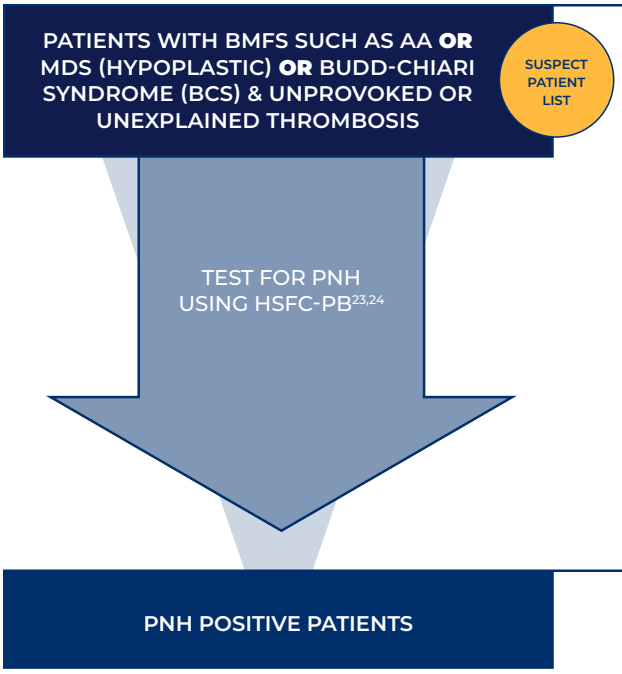
With PNH, patients may stay undiagnosed or misdiagnosed for extended periods of time.[4] This toolkit may help reduce the incidence of undiagnosed and misdiagnosed patients by utilizing the EHR and evidence-based diagnostic criteria to generate suspect patient lists, which may help increase awareness of suspect PNH patients for further evaluation by HCPs.[26]

Suggested Clinical Criteria for Suspect PNH Patient Lists

In an EHR system, a suspect patient list, also referred to as a patient list report, is a list of patients meeting certain clinical criteria. Generating a suspect patient list requires the same clinical criteria used to make a PNH diagnosis. In addition to creating a list of suspect PNH patients for further clinical evaluation, a suspect patient list can also be used to flag patient charts with a BPA to recommend PNH testing or clinical referral.

Please see the charts below for guidance.

Patients With High-Risk Comorbidities



The pertinent medical codes (ie, ICD-10, SNOMED) associated with these criteria can be found in the EHR.

In addition to immediately testing for PNH, it is recommended by ICCS guidelines to annually test for PNH using HSFC-PB to continually screen patients with underlying bone marrow failure syndrome (AA and MDS) for the development of PNH.*[11,12,23,24]

The recommended medical codes that may be used to triage suspect PNH patients can be found in Appendix B Table 1

Other codes for consideration that may be used to triage suspect PNH patients with comorbidities can be found in Appendix B Table 2

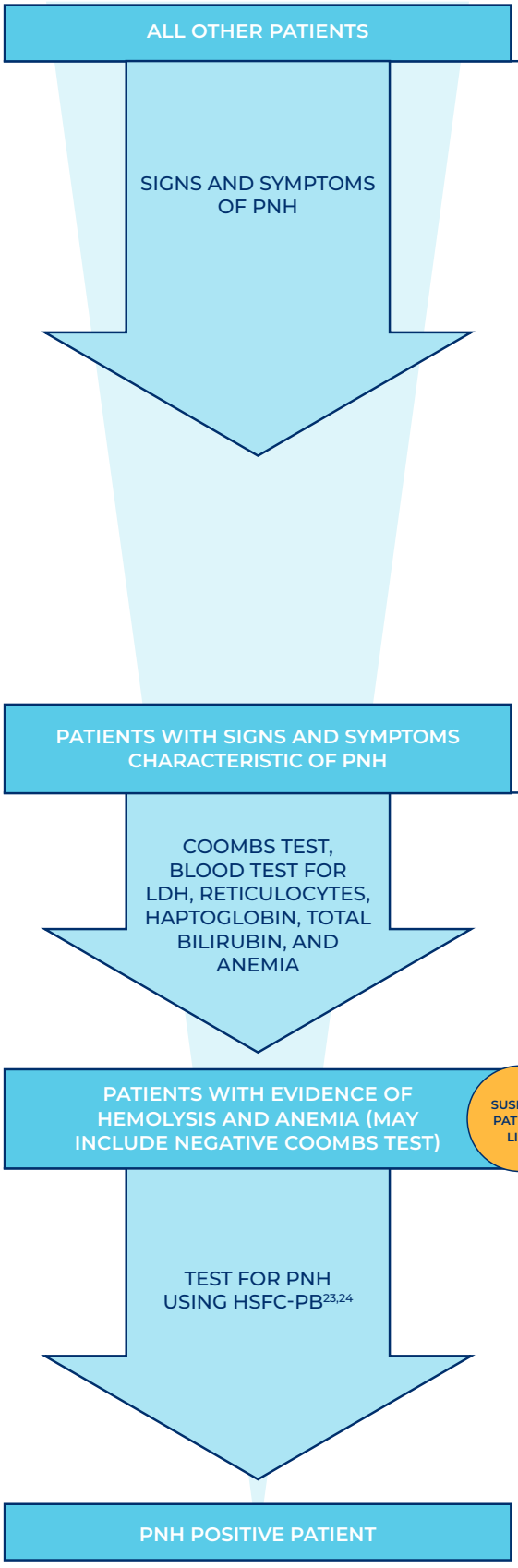
PNH diagnosis can be captured in the EHR as SNOMED and ICD-10 codes. Once positive for PNH, LDH levels should be monitored to assess disease severity and prognosis.[2]

- Low RBC clone size compared to WBC clone size is indicative of intravascular hemolysis.[12,24]
- LDH ≥1.5x the ULN has been shown to significantly increase the risk for thrombosis and be a predictor of premature mortality in patients with PNH.[2,21]

For codes indicating patient has been diagnosed with PNH, see Appendix B Table 5

*See *Clinical Criteria for PNH* and consult with your local lab for any further questions on how to understand a PNH HSFC-PB pathology report.

All Other Patients at Risk for PNH



Symptom-specific ICD-10 codes and test results as LOINC codes can exist in the EHR and be leveraged to identify patients who have signs, symptoms, and comorbidities characteristic of PNH. Signs, symptoms, and diagnoses include:[7-9,10,12,15-17]

Signs and symptoms:

- Fatigue
- Shortness of breath
- Dyspnea
- Hemoglobinuria
- Abdominal pain
- Erectile dysfunction
- Chest pain
- Esophageal spasm

Diagnoses:

- Chronic kidney disease
- Pulmonary hypertension
- Unexplained thrombosis
- Unexplained hemolysis
- Persistent unexplained cytopenias

Using strictly signs and symptoms of PNH as testing flags may result in a plethora of false positives. **For more sensitive PNH testing flags, patients may need to meet the additional criteria.**

For other codes that may be used to triage suspect PNH patients, see Appendix B Table 4

Test results can exist in the EHR as LOINC codes and be leveraged to identify suspect patients recommended to receive as a flag for PNH testing.*

- Coombs test should be negative[12]
- Evidence of hemolysis includes LDH ≥1.5x the upper limit of normal and high reticulocytes, or low haptoglobin, or high total bilirubin[2,14]
- Evidence of anemia should be examined to detect intravascular hemolysis[12,14]

For other codes that may be used to triage suspect PNH patients, see Appendix B Table 4

PNH diagnosis can be captured in the EHR as SNOMED and ICD-10 codes. Once positive for PNH, clone size and LDH levels should be monitored to assess disease severity and prognosis.[2]

- Low RBC clone size compared to WBC clone size is indicative of intravascular hemolysis.[12,24]
- LDH ≥1.5x the upper limit of normal (ULN) has been shown to significantly increase the risk for thrombosis and be a predictor of premature mortality in patients with PNH.[2,21]

For recommended medical codes that may be used to triage suspect PNH patients, see Appendix B Table 3

For codes indicating patient has been diagnosed with PNH, see Appendix B Table 5

*See *Clinical Criteria for PNH* and consult with your local lab for any further questions on how to understand a PNH HSFC-PB pathology report.

IMPORTANT NOTE: While EHR systems may assist providers in generating suspect patient lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation. It is important to indicate that the final suspect list of patients will be sent to the HCP(s) for review. Including criteria for a suspect patient list helps explain to the HCP why the patient is on the report.

For IT Department: High-Level Technical Considerations for Generating Suspect Patient Lists

To leverage EHR codes effectively to build a suspect patient list, you should engage with your healthcare organization's IT department to manage and configure suspect patient lists. See below for an example process and considerations for establishing a suspect patient list in Epic EHR.

In Epic EHR, a suspect patient list is referred to as a **patient list report** (a report that identifies all patients meeting certain clinical criteria).

When configuring a suspect patient list, consider addressing the following questions:

- What will the suspect patient list be named?
- Who will own the suspect patient list? (eg, HCP super user or practice)
- What criteria will be used to determine which patients appear on the suspect patient list based on comorbidities, laboratory results, and signs and symptoms?
- What information will be included on the patient list report? (see clinical criteria above, eg, Coombs test result, LDH level, AA diagnosis)

Additional considerations for creating an effective suspect patient list:

- The suspect patient list should exclude patients that are deceased or have been ruled out as PNH patients*
- Suspect patient lists will be impacted by the data stored in your EHR; for example, any testing that has been conducted and recorded by an outside facility may not be recorded in the EHR, which may lead to a patient being erroneously excluded from the suspect patient list
- Identify and engage with users that have the security privileges and/or technical expertise to configure and monitor suspect patient lists in your EHR
- Consider consulting with epidemiologists to optimize suspect patient list criteria, if available to your institution

*Patients with high-risk comorbid conditions such as other BMFS are recommended to complete annual flow cytometry to continually screen for the development of PNH; a single negative HSFC-PB test should not be considered as permanently ruling out PNH.[11]

Note: The above considerations may not be applicable to all EHR systems. Please consult with your IT department for specific processes and considerations. An example of creating patient lists in other EHR software can be found here:

- https://support.drchrono.com/hc/en-us/articles/202376054

Alternatively, your IT department can create patient lists by creating SQL queries allowing near real-time information extraction that can more rapidly account for any changes to suspect patient list criteria.[27,28] This method may be more efficient and can allow for machine learning and rapid patient list requirement updates, but will only be applicable if all EHR data is mapped to an existing data warehouse.

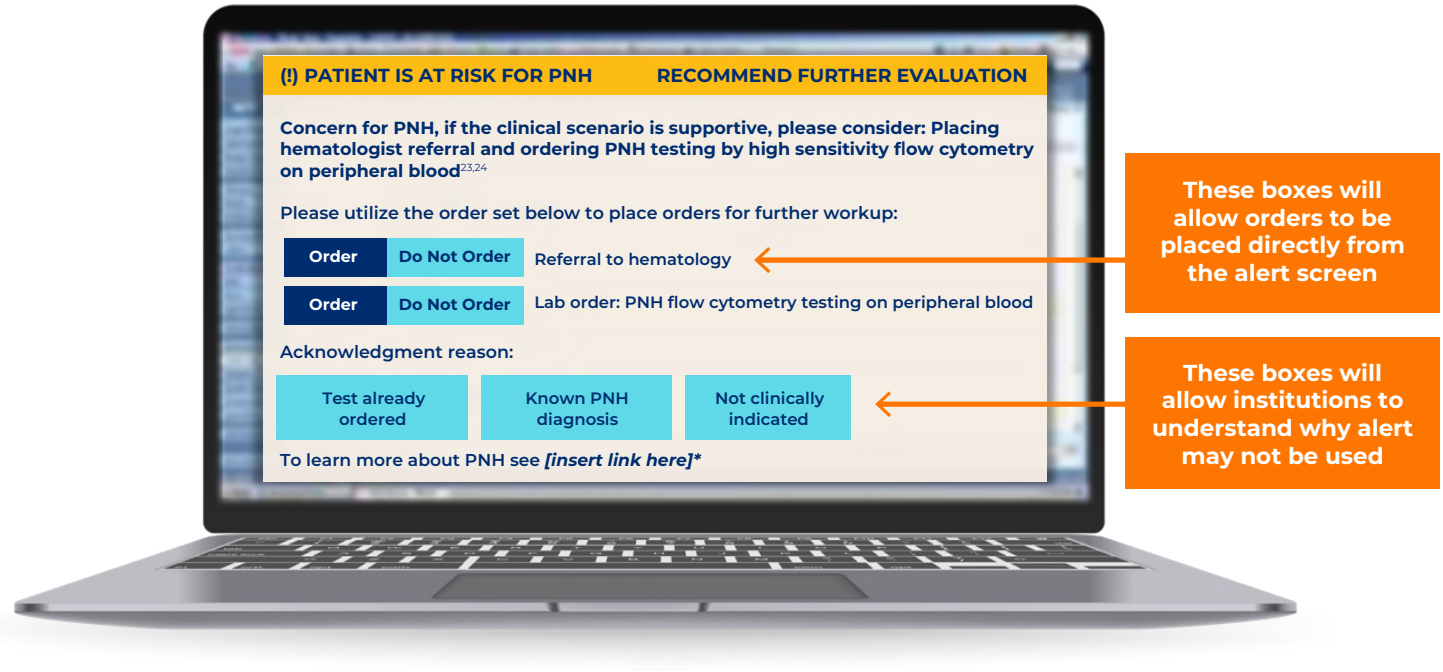
AA=aplastic anemia, BMFS=bone marrow failure syndromes, HSFC-PB=high sensitivity flow cytometry on peripheral blood, SQL=structured query language.

3

Best Practice Alerts to Help HCPs Triage a Suspect PNH Patient

Use Suspect Patient Criteria and Diagnostic Best Practices to Create Alerts

Using the data in the EHR to surface information in a patient's health record can be the first step in recognizing a suspect PNH patient. BPAs can be created using clinical criteria and the data in the EHR to help alert and guide an HCP in further assessing for PNH. An example BPA can be found below.



Illustrative example. BPA should meet institutional guidelines and be specific based on criteria that led to BPA. Consult with clinical and IT teams for effective implementation.

*Further disease state education may be linked to a PNH page in your institution's EHR system or to an outside resource such as:

- https://pnhsource.com/pnh-for-physicians
- https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/
- https://www.uptodate.com/contents/treatment-and-prognosis-of-paroxymal-nocturnal-hemoglobinuria

High-Level Technical Considerations for Generating BPAs

Automated BPAs can promote quality care by assisting HCPs in providing timely access to diagnostic best practices (eg, gold-standard techniques to test for PNH), reducing false negatives driven by less accurate testing. BPAs can also reduce inefficiency by decreasing the manual effort for HCPs in the diagnostic process.[29] Each EHR system is unique in how to establish automated BPAs, so you should engage with your healthcare organization's IT department. For example, in Epic EHR, a system is in place called "Best Practice Advisories" that allows organizations to deliver HCPs with messages through storyboard alerts, interruptive/active alerts, or passive alerts.*[29,30] These customized, practice-specific alerts can be programmed by the institution's IT team with assistance from clinical leadership to fire according to predetermined triggers, either individual or in combination, using inclusionary or exclusionary logic.[30] IT staff can be provided the suggested BPAs listed above triggered by patients meeting the suggested clinical criteria.

When making an IT request, clinical leaders should be involved in establishing the clinical criteria for BPAs. Consider including the following information to ensure that the suspect patient list is appropriately configured:

- The name for the alert
- The frequency of the alert based on established clinical guidelines
- Indicate where the alert should be placed
- Identify which providers should see the alert

Additional consideration for creating a BPA:

- Privileges on who can configure a BPA may be selective to specific users with security privileges or technical expertise (eg, data scientists in the IT department); therefore, these stakeholders should be identified and engaged with as early as possible

Optimizing BPAs

Improving the visual design of clinical BPAs may help providers recognize medical conditions faster.[30,31] Five presentation elements that have been suggested for EHR alerts include:

1. Physically organize different information by placing it into bordered blocks
2. Be consistent with visual cues (eg, typeface fonts and colors)
3. Use typeface font size and "weight" to help organize and emphasize information
4. Apply color to the boxes used to organize the information
5. Consider the use of three-dimensional effects (to accommodate users who are color blind)

*It has been found that there is a **7.7x greater likelihood a BPA will be followed** by an HCP if the alert is active rather than passive.[32]

Note: BPAs may require governance oversight, consult with your CMIO/CIO.

For a comprehensive list of suggestions, please see *Informatics and interaction: Applying human factors principles to optimize the design of clinical decision support for sepsis*.[31]

4

Additional Considerations

There are subtle differences between the various EHR systems. Each has similar functionality, but there may be differences such as the naming conventions of EHR system features. Additionally, organizations may have established protocols or patient portals for communicating sensitive health information identified by a BPA. The following section highlights some of these considerations.

The toolkit is provided for informational purposes only and does not substitute the internal review of your institution. Please coordinate with your institution's approval process before implementing an EHR build.

Naming Conventions

- Generating and maintaining suspect patient lists empowers organizations to surface patients who meet certain clinical and demographic criteria. These may also be named "worklists" depending on the system[30,33]
- BPAs allow organizations to notify providers when certain clinical activities should be prioritized for a particular patient. This functionality can account for a variety of clinical variables throughout the patient journey and may also be named "discern alerts"[30,34,35]
- Standardized order sets allow providers to easily understand and order the most relevant tests and management options for patients who meet certain disease criteria or are being seen in a particular department. These may also be known as "power plans" depending on the system[36,37]

Each organization may also have its own vocabulary/terms allowed in drop-down lists, formulary, and lab codes. Engage with IT stakeholders at your organization to align on institution-specific variations.

Patient Communication Considerations

HCPs should follow established communication protocols, especially those related to communicating sensitive information to patients. The BPA can include a link to resources for HCPs to leverage when communicating a PNH diagnosis/test results (https://pnhsource.com/pnh-for-physicians/pnh-resources/) and a link that can connect HCPs with PNH experts for guidance (https://pnhsource.com/pnh-for-physicians/talk-to-an-expert/).

HCPs may also be provided with resources they can give their patient as they begin to understand their diagnosis, such as: https://pnhsource.com and https://www.aamds.org/patients/learn-about-your-disease.

Note: EHR systems have patient portals that allow patients to stay in touch with their care teams, review their schedules, access personalized patient educational materials, and be more involved in managing their health. These portals may be one way to communicate the need for a follow-up appointment. Some examples of patient portals include:

- Epic MyChart
- Cerner® HealtheLife℠
- Meditech Health Portal
- Allscripts® FollowMyHealth®

The patient list and BPA functionality already exist in many EHR systems. Alexion did not sponsor, design, create, or otherwise modify this functionality in any manner. The instructions have not been designed to and are not tools and/or solutions for meeting Meaningful Use, Advancing Care information, and/or any other quality/accreditation requirement.

5

Implementing, Monitoring, and Maintaining a Program

The following section provides further guidance on how to implement the deciphEHR™ program in your healthcare organization as well as how to monitor and maintain the program. To assess the program, including surfaced suspect patients, you will need to monitor it on an ongoing basis. Remember, it will be essential to be clear about what you want to achieve and how you will measure it.

Step 1:

Establish a Clinical Program Lead

- It is important to establish a Clinical Program Lead for the project (a medical specialist with expertise in PNH, most likely a hematologist) who can answer questions and help direct and oversee successful program implementation
- The Clinical Program Lead can communicate the value of the program to stakeholders throughout the healthcare organization by sharing the deciphEHR™ PNH Disease Overview and the Rare Disease Overview
- The Clinical Program Lead can provide ongoing support, including monitoring the program and continuing to champion the use of EHR across multiple specialties for rapid triage of suspect PNH patients
- Clinical Program Leads provide support to establish a diagnostic plan based on the clinical criteria for PNH, suggestions for developing suspect patient lists, and BPAs to help HCPs triage suspected PNH patients

Step 2:

Identify, engage, and communicate with organizational stakeholders*

- Identify and collaborate with relevant stakeholders within your healthcare organizations who are important in implementing the deciphEHR™ program and encouraging sustainable success
- Stakeholders may vary depending on the organization but may include:

Clinical Leadership

» Pathology and Specialty Medical Staff*
» Laboratory
» Pharmacy

Administrative Leadership

» IT/EHR Resource(s)
» Data Scientist (if available)
» Quality Director

*You may consider inviting input from representative medical staff during the initiation, implementation, and maintenance of this program.

- For stakeholder involvement, see here

Step 3:

Establish an implementation and support team

- Consider including the following members on your implementation and support team*:

  - » Clinical Program Lead†
  - » Specialty/Physician Representative(s)‡
  - » Implementation/ Project Manager
  - » Super User
  - » EHR Analyst (EHR Builder, Suspect Patient List, BPA Builder)
  - » Workflow Redesign/ Process Engineer
  - » Report Writer/ Measurement and Tracking Lead

*Depending on the size and type of your organization, your organization may assign employees to more than one role.
†You may consider an additional stakeholder who has experience leading the implementation of BPAs.
‡For most applicable physicians, see here.

Step 4:

Develop and execute the implementation plan

- Engage relevant stakeholders and implementation team to establish the adoption, scope, implementation, and rollout of the program

- Leverage the clinical criteria for PNH (see Section 1) to create suspect patient list for future clinical evaluation by (see Section 2 for technical considerations):
  - » Including recommended medical codes in the Appendix B
  - » Engaging clinical leadership and Super User with IT departments for most effective implementation

- Establish BPAs for HCPs based on clinical criteria (see Section 3 for technical considerations)
  - » Provide PNH education within the clinical alert using web links such as: https://rarediseases.info.nih.gov/diseases/7337/paroxysmal-nocturnal-hemoglobinuria or https://rarediseases.org/rare-diseases/paroxysmal-nocturnal-hemoglobinuria/
  - » Provide PNH resources for HCPs with suspect or confirmed PNH patients such as: https://pnhsource.com/pnh-for-physicians/pnh-resources/
  - » Engage clinical leadership and Super User with IT departments for most effective implementation

Note: While EHR systems may assist providers in generating suspect patient lists, it is the sole responsibility of the HCP to make a diagnosis based on in-person patient evaluation.

Step 5:

Develop a monitoring and evaluation framework[38-40]

- The Measurement and Tracking Lead may be in charge of continuing to monitor and evaluate suspect PNH patient lists on a routine (eg, monthly, bimonthly) basis to assess the effectiveness of the program (the Super User may be engaged in this process)
- Effectiveness of the program should be measured based on defined metrics for success (for examples see Step 6)
- The Clinical Program Lead and Super User can monitor and evaluate the BPA program to assess its usefulness and effectiveness in assisting HCPs (eg, through HCP interview)

Step 6:

Measure success[38]

- Metrics for success should be determined at the start of implementation and should be continually measured to assess the success of the program. Metrics for success may include:
  - » Amount of time from suspect patient alert or on a report to the HCP for evaluation to rule in or rule out PNH
  - » Number of times an HCP acts on a BPA
  - » Number of patients for which an alert helps the HCP to confirm a PNH diagnosis

Step 7:

Ongoing improvement[38]

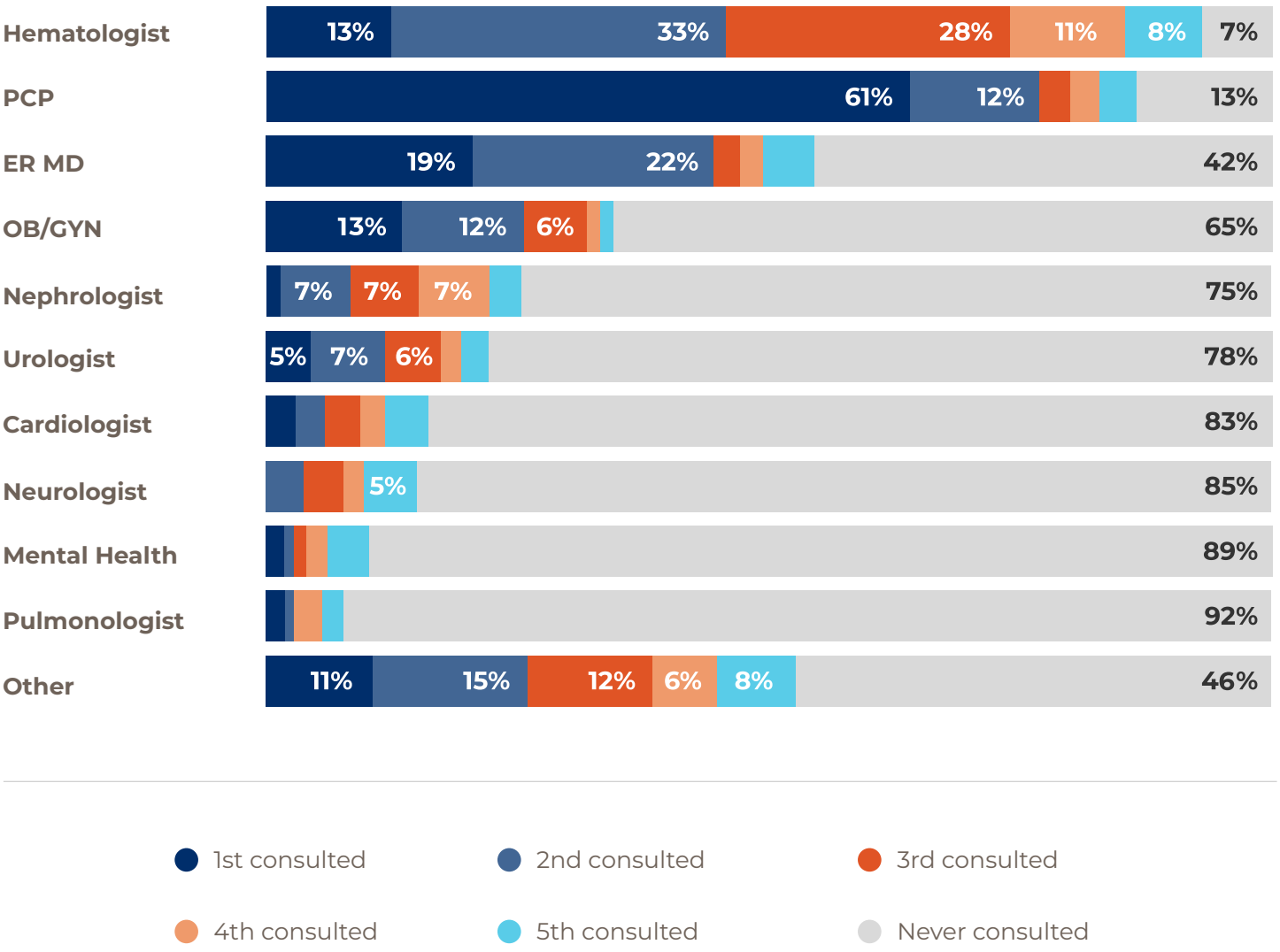
- Engage with Clinical Program Lead to assess PNH diagnostic criteria to ensure they are current
  - » Determine the appropriate timeframe for reassessment based on institutional standards (eg, annually)
  - » Check deciphEHRrare.com for updates
- Evaluate the effectiveness of PNH suspect patient lists and BPAs to triage suspect patients to confirm or rule out PNH
- In case of clinical concerns, reference your implementation and support team
- For EHR implementation troubleshooting and support, consider contacting your EHR provider

6

Appendix A: Medical Staff Considerations

Identify and collaborate with relevant stakeholders within your healthcare organizations (including specialists) who may see undiagnosed PNH patients. See the list of possible specialists below. Learn, understand, and comply with your institution's requirements for implementing.

Patients presenting PNH symptoms are most likely to visit the following HCPs on the path to diagnosis[4]:



PCP=primary care physician; OB/GYN=obstetrician/gynecologist; ER MD=emergency room physician

6

Appendix B: Medical Codes to Support Suspect Patient Lists and BPAs

The clinical criteria for PNH that are required for a patient to appear on the suspect patient list are consistent across all age groups. The medical codes that represent these criteria and suggestions for how to best use these codes are found here in the appendix.

EHR Code Types

The EHR system contains multiple code types, each containing unique information. These codes can be used in combination to triage suspect PNH patients. Below are examples of code types that can be found in the EHR:

- **ICD-10:** International Classification of Diseases, tenth revision, a globally used diagnostic code for epidemiology, health management, and clinical purposes
- **SNOMED:** Systematized Nomenclature of Medicine Clinical Terms, a common language for systems to adopt for indexing, storing, retrieving, and aggregating clinical data
- **LOINC:** Logical Observation Identifiers Names and Codes, a database and universal standard for identifying medical laboratory observations
- **CPT:** Current Procedural Terminology, a uniform language for coding medical services and procedures such as surgeries, diagnostic tests, evaluation, and management services
- **HCPCS:** Healthcare Common Procedure Coding System, a collection of standardized codes that represent basic medical procedures, supplies, products, and services

Suggestions for Leveraging EHR Codes

All codes are listed at the parent level. Determining level of specificity (eg, specific codes within parent trees) is at the discretion of the institution. The institution is responsible for selection of codes based on the specific situation and patient needs.

- Suggested codes for generating suspect patient lists have been divided by:
  1. Patients with BMFS such as AA and hypoplastic MDS or Budd-Chiari Syndrome (BCS) & unprovoked thrombosis
  2. All other patients
- No one code has been found to have high specificity and sensitivity for PNH; therefore, it is suggested that codes be used in combination to develop suspect patient lists
- Codes may change over time; please visit the respective code sites for up-to-date codes
  - » An Excel spreadsheet version is also available on the web page for your convenience
- The codes used to triage patients to the suspect patient list may also be used to develop BPAs

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Suggested Codes for the Suspect Patient Lists Indicated in Section 2

Table 1: Recommended codes for patients with high-risk comorbidities

For patients with high-risk comorbid conditions, it is suggested that all patients with any of the following codes be triaged for testing. For patients with MDS and unexplained thrombosis, to improve specificity, your institution may want to only flag those patients that also present with a code for hemolysis or cytopenia (eg, MDS AND [hemolysis OR cytopenia]).[10,12]

For a visual representation of this suspect patient list, see Section 2.

Code Type	Code	Code Description	Suggestions for Implementation
Aplastic Anemia Codes			
SNOMED	306058006	Aplastic anemia	High-priority code
SNOMED	191256002	Idiopathic aplastic anemia (disorder)	High-priority code
SNOMED	55907008	Acquired aplastic anemia (disorder)	High-priority code
Aplastic Anemia Codes (continued)			
ICD-10	D61.9	Aplastic anemia	High-priority code
ICD-10	D61.1	Aplastic anemia, drug-induced	High-priority code
ICD-10	D61.2	Aplastic anemia due to other external agents	High-priority code
ICD-10	D61.09	Other constitutional aplastic anemia	High-priority code
ICD-10	D61.3	Idiopathic aplastic anemia	High-priority code
ICD-10	D61.89	Other specified aplastic anemias and other bone marrow failure syndromes	High-priority code
Myelodysplastic Syndrome Codes			
SNOMED	109995007	Myelodysplastic syndrome (disorder)	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
ICD-10	D46.9	Myelodysplastic syndrome, unspecified	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
Budd-Chiari Syndrome Codes			
SNOMED	82385007	Budd-Chiari syndrome (disorder)	High-priority code
ICD-10	I82.0	Budd-Chiari syndrome (disorder)	High-priority code
Thrombosis Codes			
SNOMED	439127006	Thrombosis (disorder)	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
SNOMED	76612001	Hypercoagulability state (finding)	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
SNOMED	111293003	Venous thrombosis (disorder)	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
SNOMED	17920008	Portal vein thrombosis (disorder)	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
SNOMED	429098002	Acute embolism and thrombosis of unspecified vein	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
ICD-10	I81	Portal vein thrombosis	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Thrombosis Codes (continued)			
ICD-10	I82.90	Acute embolism and thrombosis of unspecified vein	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
ICD-10	I74.8	Embolism and thrombosis of other arteries	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
ICD-10	I82.890	Acute embolism and thrombosis of other specified veins	High-priority code, may be used in combination with codes for hemolysis or cytopenia to improve specificity
Cytopenia Codes			
SNOMED	50820005	Cytopenia	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	415285009	Refractory cytopenia with multilineage dysplasia	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	415286005	Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	302215000	Thrombocytopenic disorder (disorder)	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	165517008	Neutropenia (finding)	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	127034005	Pancytopenia (disorder)	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	D61.818	Other pancytopenia	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	D46.A	Refractory cytopenia with multilineage dysplasia	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	D46.B	Refractory cytopenia with multilineage dysplasia and ringed sideroblasts	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	D69.6	Thrombocytopenia, unspecified	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	D70.9	Neutropenia, unspecified	May be used in combination with codes for MDS and/or thrombosis to improve specificity
Hemolysis Codes			
SNOMED	15601008	Intravascular hemolysis (finding)	May be used in combination with codes for MDS and/or thrombosis to improve specificity
SNOMED	73320003	Hemolysis (finding)	May be used in combination with codes for MDS and/or thrombosis to improve specificity
ICD-10	R74.0	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase (LDH)	May be used in combination with codes for MDS and/or thrombosis to improve specificity

Table 2: Additional codes for patients with high-risk comorbidities

Additional codes that may be useful in identifying PNH patients with comorbid AA, MDS, BCS, or thrombosis are listed below. These codes may not have high specificity for PNH, but may still indicate a suspect PNH patient. The decision on how to implement these codes should be aligned with your institution's Clinical Leadership.

Code Type	Code	Code Description	Suggestions for Implementation
Other Codes			
SNOMED	234467004	Thrombophilia (disorder)	May indicate increased chance of thrombosis, may surface additional undiagnosed PNH patients
ICD-10	D68.69	Other thrombophilia	May indicate increased chance of thrombosis, may surface additional undiagnosed PNH patients

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Other Codes (continued)			
ICD-10	D68.59	Other primary thrombophilia	May indicate increased chance of thrombosis, may surface additional undiagnosed PNH patients
CPT	36430	Under Venipuncture and Transfusion Procedures	Treatment may indicate BMFS, may be used as a BMFS proxy to triage additional patients
HCPCS	J0894	Injection, decitabine, 1 mg	Treatment indicating MDS, may be used as an MDS proxy to triage additional patients
HCPCS	J9025	Injection, azacitidine, 1 mg	Treatment indicating MDS, may be used as an MDS proxy to triage additional patients
CPT/HCPCS	85044	Reticulocytes count - manual - Analyst evaluates a stained blood smear slide under a microscope to determine the reticulocyte count	Elevated reticulocyte count may indicate BMFS/PNH
CPT/HCPCS	85045	Reticulocytes count - automated - Analyst uses an automated hematology analyzer to determine the reticulocyte count	Elevated reticulocyte count may indicate BMFS/PNH
CPT/HCPCS	38221	Bone marrow biopsy - sternum or pelvic bone	Bone marrow testing procedure, may be used to triage additional patients with BMFS
CPT/HCPCS	38222	Bone marrow biopsy - aspiration technique	Bone marrow testing procedure, may be used to triage additional patients with BMFS
CPT/HCPCS	88305	Surgical Pathology Procedures - The physician, typically a pathologist, performs a level IV examination of a surgical pathology specimen	Bone marrow testing procedure, may be used to triage additional patients with BMFS
LOINC	26615-5	Erythrocytes.CD55:PrThr:Pt:Bld:Ord	Decreased erythrocytes may indicate a BMFS such as AA
LOINC	26616-3	Erythrocytes.CD59:PrThr:Pt:Bld:Ord	Decreased erythrocytes may indicate a BMFS such as AA
LOINC	33662-8	Erythrocytes.CD59 deficient/100 Cells.235a:NFr:Pt:Bld:Qn	Decreased erythrocytes may indicate a BMFS such as AA
LOINC	60474-4	Reticulocytes:NCnc:Pt:Bld:Qn:Automated count	Elevated reticulocyte count may indicate BMFS/PNH

Table 3: Recommended codes for all other patients

For all other patients, it is suggested that all patients with hemolysis AND anemia be triaged. The following codes can be used as high-priority codes to identify patients with hemolytic anemia. To increase specificity, your institution may consider only triaging suspect patients who have evidence of hemolytic anemia AND a Coombs-negative test.

For a visual representation of this suspect patient list, see Section 2.

Code Type	Code	Code Description	Suggestions for Implementation
Hemolytic Anemia Codes			
SNOMED	4854004	Acquired hemolytic anemia	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
SNOMED	62403005	Glucose-6-phosphate dehydrogenase deficiency anemia	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
SNOMED	111407006	Hemolytic uremic syndrome	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
SNOMED	191169008	Hereditary elliptocytosis	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
SNOMED	38911009	Hereditary hemolytic anemia	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Hemolytic Anemia Codes (continued)			
SNOMED	55995005	Hereditary spherocytosis	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
SNOMED	61261009	Hemolytic anemia (disorder)	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D59.9	Acquired hemolytic anemia, unspecified	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D55.0	Glucose-6-phosphate dehydrogenase deficiency anemia	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	P55.9	Hemolytic disease of newborn (unspecified)	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D59.30	Hemolytic uremic syndrome	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D58.1	Hereditary elliptocytosis	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D58.9	Hereditary hemolytic anemia	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D58.0	Hereditary spherocytosis	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D59.8	Other acquired hemolytic anemias	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
ICD-10	D59.4	Other nonautoimmune hemolytic anemias	High-priority code, may be used in combination with codes for negative Coombs test for increased specificity
Coombs Test Codes			
LOINC	1007-4	Direct antiglobulin test.polyspecific reagent:PrThr:Pt:RBC:Ord	May be used in combination with codes for hemolytic anemia to improve specificity
LOINC	51006-5	Coombs test	May be used in combination with codes for hemolytic anemia to improve specificity
LOINC	1007-4	DAT - PolySpecific reagent	May be used in combination with codes for hemolytic anemia to improve specificity
LOINC	51006-5	DAT - Unspecified reagent	May be used in combination with codes for hemolytic anemia to improve specificity

Table 4: Other codes for triaging all other patients with PNH

Additional codes that may be useful in identifying PNH patients are listed below. These codes may not have high specificity for PNH, but may still indicate a suspect PNH patient. The decision on how to implement these codes should be aligned with your institution's Clinical Leadership.

Code Type	Code	Code Description	Suggestions for Implementation
Other Codes			
ICD-10	R82.3	Hemoglobinuria	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	D59.6	Hemoglobinuria due to hemolysis from other external causes	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Code Type	Code	Code Description	Suggestions for Implementation
Other Codes (continued)			
SNOMED	68600005	Hemoglobinuria	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	84229001	Fatigue (finding)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	R53.83	Fatigue	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	267036007	Dyspnea (finding)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	R06.02	Shortness of breath	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	40739000	Dysphagia (disorder)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	20301004	Dysphasia (finding)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	R13.10	Dysphagia, unspecified	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	21522001	Abdominal pain (finding)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	R10.9	Unspecified abdominal pain	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	709044004	Chronic kidney disease (disorder)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	N18.9	Chronic kidney disease, unspecified	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	29857009	Chest pain (finding)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	R07.9	Chest pain, unspecified	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
SNOMED	70995007	Pulmonary hypertension (disorder)	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 3
ICD-10	I27.20	Pulmonary hypertension, unspecified	Sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 2
CPT/HCPCS	80069	Renal function panel	May indicate renal failure, a sign/symptom of PNH, may consider implementing this code in addition to other more specific codes from Table 2

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

Table 5: Codes indicating a PNH diagnosis

These codes may indicate PNH diagnosis and may be considered as exclusionary criteria for the suspect patient list to decrease continued flagging of patients who have already been triaged and assessed.

Code Type	Code	Code Description	Suggestions for Implementation
Diagnosis Codes for Exclusion			
SNOMED	1963002	Paroxysmal nocturnal hemoglobinuria (disorder)	Indicates PNH diagnosis, may consider removing from suspect patient list to decrease continued flagging
ICD-10	D59.5	Paroxysmal nocturnal hemoglobinuria	Indicates PNH diagnosis, may consider removing from suspect patient list to decrease continued flagging
Test Codes for Exclusion			
LOINC	35468-8	Cells.FLAER:PrThr:Pt:Bld:Ord	Results from HSFC using FLAER may indicate PNH, based on test result, may consider removing from suspect patient list to decrease continued flagging
LOINC	77948-8	Cells.FLAER/100 cells:NFr:Pt:XXX:Qn	Results from HSFC using FLAER may indicate PNH, based on test result, may consider removing from suspect patient list to decrease continued flagging

The above codes and suggested use cases for codes are illustrative. Any code implementation should be aligned with Clinical Leadership at your institution.

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