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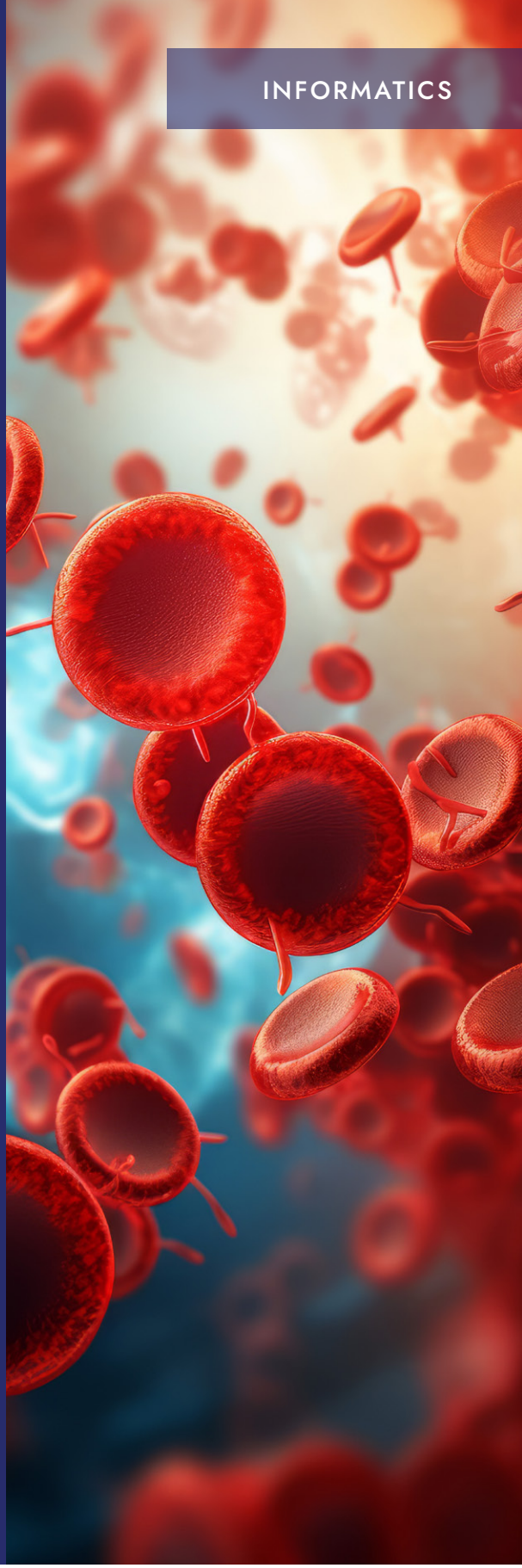


LITE PAPER

Paroxysmal Nocturnal Hemoglobinuria: The Current Testing Landscape and Emerging Therapies

Derek Lyle, M.D.
Chief Medical Officer,
NeoGenomics

Madhuri Paul, PhD
Client Engagement Manager,
NeoGenomics Informatics

Improving patients lives in rare disease by understanding the challenges and identifying opportunities through real-world data.

Paroxysmal Nocturnal Hemoglobinuria (PNH): The Current Testing Landscape and Emerging Therapies

Rare diseases, such as Paroxysmal nocturnal hemoglobinuria (PNH), present a clinical challenge given the difficulty diagnosing and effectively treating patients. Approximately 7,000 disorders have been classified as 'rare' to date, with many patients left undiagnosed due to the complexity of symptoms and presentation of these disorders.[1] With PNH, like other rare diseases, early diagnosis is essential for better management of the disease and improved outcomes.

PNH is a progressive disorder associated with increased morbidity and mortality, high rates of hospitalization, and poor quality of life. If left untreated, 20%-40% of PNH patients die within 5-6 years of diagnosis, and nearly 50% die 10 years after diagnosis.[2] Timely detection of PNH is a challenge due to poor disease awareness, nonspecific clinical features, and the heterogeneity of clinical presentation. Although diagnostic guidelines are available, an important factor in delayed diagnosis of PNH a lack of familiarity among non-specialist health care providers due to the rarity of PNH.[3,4] Diagnosis generally takes 2 to 5 years and often requires consultation with multiple providers with varying specialties. According to an online survey of 163 PNH patients, fewer than 40% of patients received their diagnosis within 12 months of symptom onset and 24% of all PNH diagnosis can take 5 years or longer.[5]

PNH Testing and Diagnosis

The path to PNH diagnosis is challenging predominantly because the clinical presentation is usually more subtle, with nonspecific symptoms due to intravascular hemolysis, thrombosis, and bone marrow failure that can be easily misdiagnosed.[4] Early diagnosis with high sensitivity flow cytometry testing performed on peripheral blood is the gold standard for PNH diagnosis due to its accuracy and sensitivity down to 0.01%.[2] The test requires evaluation of GPI anchored proteins in at least two lineages to ensure that the identified GPI-negative cell populations represent PNH clones and are not cells with aberrant expression of GPI-anchored protein.

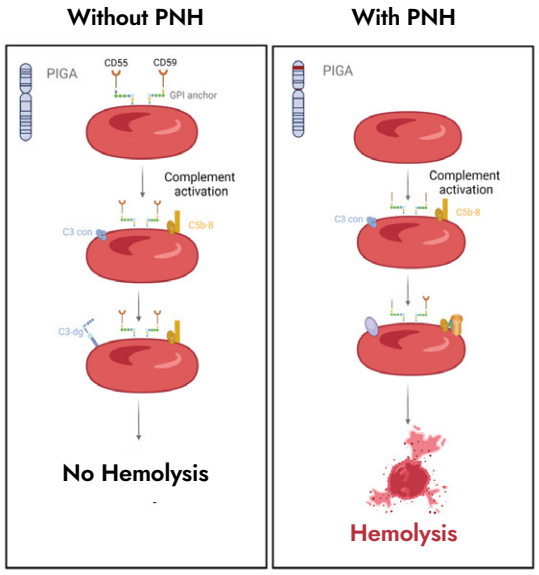
Screening every patient with anemia or thrombosis for PNH is not practical. However, patients with select clinical implications that may have an increased likelihood of harboring PNH clones should be considered for initial, and potentially, routine testing. Generally, one-third of patients have "classical PNH" associated with large PNH clones (~70%), hemolysis, multiple PNH symptoms, and an increased risk of thrombosis. The rest of the patients either have PNH with another bone marrow disorder (i.e. aplastic anemia, myelodysplastic syndrome) associated with hemolysis and relatively smaller clones, or asymptomatic subclinical PNH associated with small clones. Although only a minority of patients with PNH present with hemoglobinuria, any patient with unexplained hemoglobinuria should be tested for PNH. Testing is also recommended in patients when thrombosis coexists with intravascular hemolysis or cytopenia since thrombosis is a common complication of PNH with an occurrence in 40% of patients.[3,6,7,8]

DIAGNOSIS OF PNH CAN TAKE
2-5 YEARS

Understanding PNH

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal hematopoietic stem cell disorder caused by somatic mutations in the phosphatidylinositol glycan anchor biosynthesis class A (PIG-A) gene. The gene product of PIG-A is required for the biosynthesis of glycophosphatidylinositol (GPI) anchor. The clinical features of this disease arise as a result of uncontrolled complement-mediated hemolysis in unprotected red blood cells (RBC) with reduced or absent expression of GPI-anchored proteins (i.e. CD55, CD59) (*Fig. 1*). This rare blood disease is mainly characterized by the destruction of these defective RBCs (hemolysis) within the blood vessels (intravascular) or outside the blood vessels in liver and/or spleen (extravascular) leading to episodes of hemoglobin in the urine (hemoglobinuria)(*Fig. 1*).[3,4,7]

FIG.1



Normal RBCs express GPI-anchored proteins (i.e. CD55, CD59) protecting them from complement-mediated RBC destruction (hemolysis). PNH patients express an acquired somatic mutation in PIG-A gene, leading to reduced or absent expression of GPI-anchored proteins, making them susceptible to hemolysis.

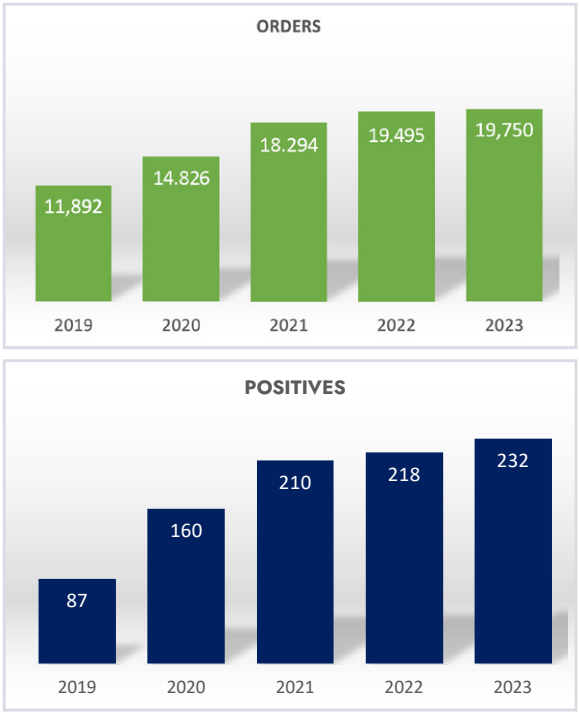
Utilizing real-world data to understand testing patterns

PNH has a global incidence of approximately 1.3 cases/million, with an estimated 400 to 500 PNH patients diagnosed per year in the United States.[9,10] In the last 12 months, testing at NeoGenomics has led to the diagnosis of 40-50% of PNH patients in the United States where the mean age of diagnosis was 53 years, 55% were male and 45% were female. A five-year retrospective analysis of the NeoNucleus™ database demonstrated a +66% increase in ordering patterns of ICCS-recommended high sensitivity PNH testing. High sensitivity PNH testing was found to be predominately ordered concurrently with the NeoGenomics Standard Leukemia/Lymphoma panel, which includes 24 key markers (CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD13, CD14, CD16, CD19, CD20, CD23, CD33, CD34, CD38, CD45, CD56, CD64, CD117, HLA-DR, kappa, and lambda). Despite the continued increase in testing, an improved understanding of PNH diagnosis is critical, especially in health care providers in regions with low testing rates *(Fig. 2)*.

FIG.2

BREAKDOWN OF PNH TESTING AND POSITIVITY OVER FIVE YEARS

Number of high sensitivity PNH test orders and positive results at NeoGenomics over 5 years.



ANALYSIS OF THE NEONUCLEUS™ DATABASE HIGHLIGHTS A

+66%

INCREASE IN PNH TESTING OVER THE LAST 5 YEARS

The PNH treatment landscape is evolving

In the last decade, a deeper understanding of the pathogenesis of PNH paved the way for a therapeutic shift from purely supportive approaches to complement-targeted therapies. This led to significant improvements in disease management, survival, and quality of life. Even though several compounds are under investigation for PNH treatment, few drugs are currently available out of clinical trials *(Fig. 3)*. The groundbreaking discovery of eculizumab, a C5 inhibitor, revolutionized the standard of care for PNH in 2007. Inhibition of complement activation by eculizumab is highly effective in reducing hemolysis and the risk of thrombosis in PNH patients. Ravulizumab, another C5 inhibitor developed from the same antibody clone as eculizumab, features an extended half-life. Several eculizumab biosimilars (i.e. BEKEMV, SB12) and novel C5 inhibitors (i.e. Cemdisiran, Crovalimab, Pozelimab and Tesidolumab) are available and in development as eculizumab approaches the expiration of its patent. Targeting complement activation at the level of C3 (Pegcetacoplan) also has a potential advantage of addressing intravascular and/or extravascular hemolysis by reducing the activation of the full complement cascade. Additionally, proximal inhibition of factor B (i.e. Iptacopan) or factor D (i.e. Vemircopan, Danicopan), serine proteases upstream of C3, are also effective.[2,11,12]

FIG.3

PNH PIPELINE

Overview of PNH therapeutic landscape.

FDA APPROVED	PHASE 3	PHASE 2
Eculizumab	Danicopan	BEKEMV
Pegcetacoplan	Tesidolumab	Crovalimab
Ravulizumab	Vemircopan	Pozelimab
		SB12

Leveraging real-world data to optimize PNH treatment

Studies of rare diseases are limited mainly due to small cohort size. Real-world data analysis can provide a more comprehensive understanding of the patient journey, prevalence rates, trends in biomarker results, and ordering patterns among community physicians. Through linkage with treatment and outcomes data, further analysis can be done to identify response rates and biomarker changes post-treatment. Monitoring of patients, especially their proportion of PNH cells by flow cytometry, at regular intervals, is crucial to detect spontaneous remission, as illustrated in *Fig. 4* with three PNH patients over the past 4-7 years.[13] Furthermore, as shown in the NeoNucleus™ database, 232 patients were diagnosed with PNH in the last 12 months at NeoGenomics, highlighting the value of high sensitivity PNH testing to allow for accurate patient diagnosing and monitoring to optimize treatment planning.

As one of the largest oncology testing laboratories in the US, NeoGenomics is a leading source of real-world data insights. Our team would welcome the opportunity to discuss your current programs and explore ways that we can partner to elevate the testing message in the community to make sure patients get the right test and the right treatment at the right time.

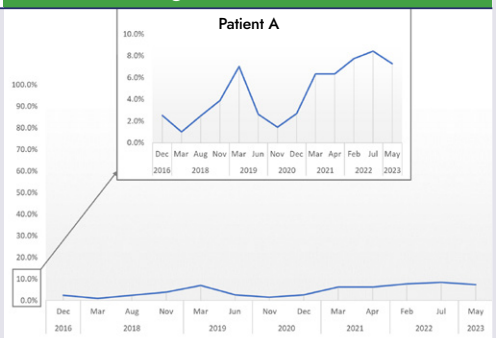
FIG.4

PATIENT JOURNEY THROUGH TESTING

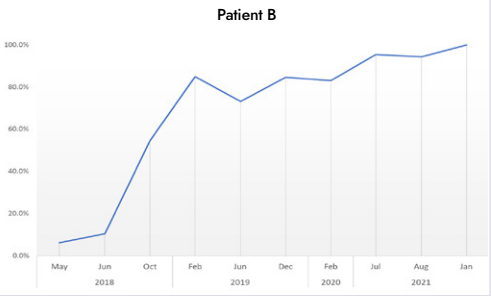
Analysis of three PNH patients' testing journey from the NeoNucleus™ database over 4-7 years.

Percentage of GPI Deficient Cells

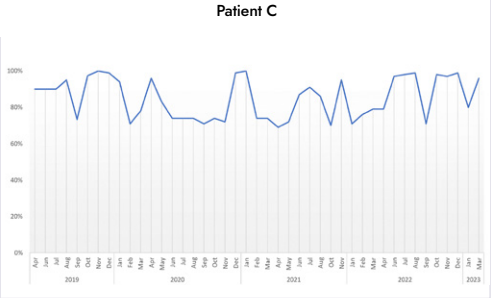
Patient A
Age: 61
Gender: Female
Diagnosis (2016): PNH with chronic pancytopenia and portal vein thrombosis.
Concurrent Tests: CD4/CD8 Ratio for BAL; Oncology Chromosome Analysis; Extended Leukemia/Lymphoma Panel; Full Blood & Bone Marrow Consult
Total high sensitivity (HS) PNH tests over 7 years: 13
Relevant Treatment: ravulizumab-cwvz IV every 8 weeks indefinitely



Patient B
Age: 76
Gender: Female
Diagnosis (2018): PNH
Concurrent Tests: TRBC1/LGL Add-On Panel; Standard Leukemia/Lymphoma Panel; T&B Tissue Panel
Total HSPNH tests over 4 years: 9
Relevant Treatment: unknown



Patient C
Age: 69
Gender: Female
Diagnosis (2018): PNH; Hematuria, unspecified
Concurrent Tests: TRBC1/LGL Add-On Panel; Standard Leukemia/Lymphoma Panel; T&B Tissue Panel
Total HSPNH tests over 5 years: 85
Relevant Treatment: unknown



FOOTNOTES / REFERENCES

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NEO GENOMICS
9490 NeoGenomics Way
Fort Myers, FL 33912
Phone: 866.776.5907 | Fax: 239.690.4237
www.neogenomics.com