A **MONTHLY** PERSONALIZED MEDICAL MAGAZINE

JUNE
2025 Edition

ATGC life

THE PIONEER IN GENETIC TESTING & REPORTING

Beyond Hemostasis: Genomic Frontiers in Bleeding Disorders

Innovative Genomic Disruptions and Precision Strategies in Hemorrhagic Conditions

GenepoweRx®
Genetic Science powered by K&H

Road No. 36, Jawahar Nagar,
Jubilee Hills, Hyderabad

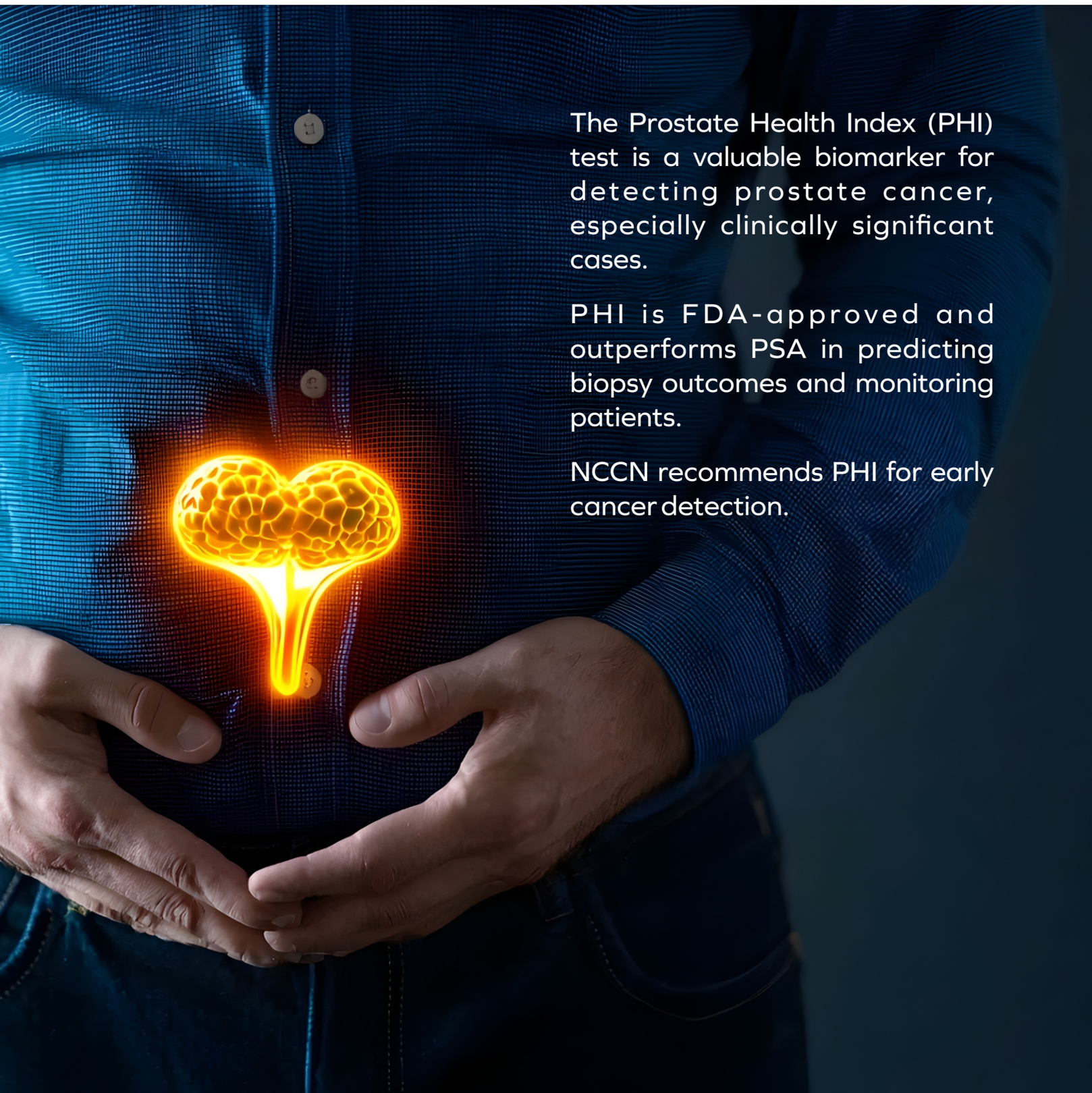
+91 950-222-2300
info@genepowerx.com
www.genepowerx.com

Table of Contents

GenepoweRx®
Genetic Science powered by K&H

Prostate Health Index phi

Ideal for men:
50 years or older
PSA range: 2-10 ng/mL



The Prostate Health Index (PHI) test is a valuable biomarker for detecting prostate cancer, especially clinically significant cases.

PHI is FDA-approved and outperforms PSA in predicting biopsy outcomes and monitoring patients.

NCCN recommends PHI for early cancer detection.

Editorial Note

Dear Readers,

Welcome to the june 2025 edition of ATGC Life, where we spotlight the genomic revolution in bleeding disorders. From rare coagulopathies discovered through deep sequencing to CRISPR-driven therapeutic strategies and polygenic risk modeling, this issue bridges cutting-edge science with clinical relevance.

As personalized genomics reshapes our understanding of hemostasis, we aim to provide insights that are not only innovative but actionable for clinicians and researchers alike.

We hope this edition informs and inspires your work toward precision care in hematology.

Warm Regards,

Dr. Hima J. Challa
Director, GenepoweRx

Dr. Hima J. Challa
Director, GenepoweRx

MD FACP, MD in Internal Medicine, USA, Professional Degree in Medical Genomics, Harvard Medical School , Masters in Nutrition Science, Texas Women University,

Founding member of Pharmacogenomics Research Network, Program Director, Internal Medicine residency program, Campbell University

Ultra-Rare Genetic Coagulopathies: New Entities from Deep Sequencing

The landscape of bleeding disorders has dramatically evolved with the advent of deep sequencing technologies. While common conditions like hemophilia A, hemophilia B, and von Willebrand disease are well-characterized, the genomic era has uncovered a new tier of ultra-rare coagulopathies. These disorders often unidentifiable by conventional diagnostic methods are being delineated through whole-genome sequencing (WGS), transcriptomics, and integrative multi-omics.

One of the most remarkable outcomes from this genomic revolution is the identification of novel pathogenic variants within non-coding regions and regulatory elements of coagulation genes. Enhancers, silencers, and untranslated regions (UTRs) have been shown to play pivotal roles in gene expression regulation. Variants in these regions affecting genes such as F11, GGCX, and PROS1 have been linked to cryptic bleeding tendencies in patients with previously unexplained phenotypes.

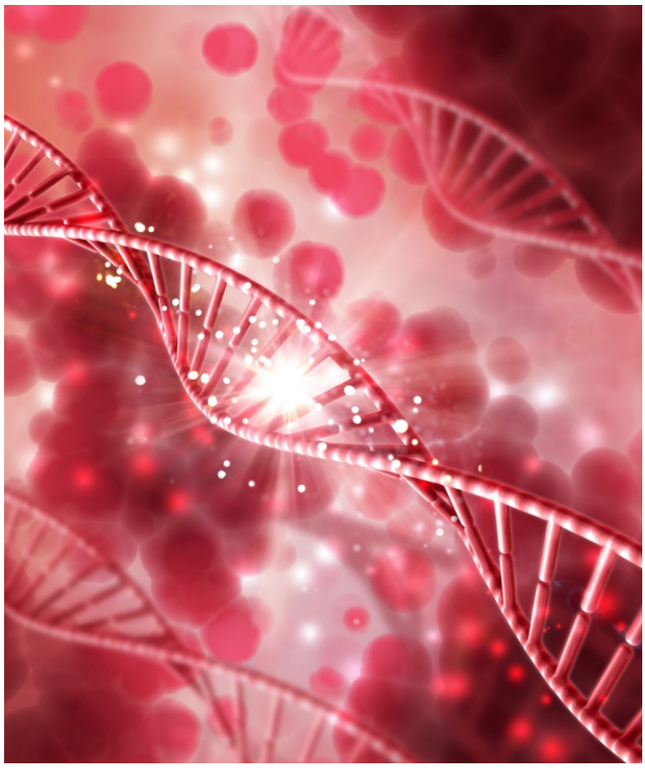
Moreover, compound heterozygosity and digenic inheritance have added layers of complexity. Cases with mutations in both F5 and TFPI, or in GPIBA and GPIX, challenge the traditional Mendelian classification of bleeding disorders. These combinations may result in overlapping clinical presentations, making phenotype-genotype correlations more demanding yet critical.

We are entering into reanalyzing exome-negative patients using advanced AI-assisted variant prioritization tools, identifying causative mutations previously overlooked due to their localization in poorly annotated genomic regions. These efforts are not only expanding the catalog of bleeding disorders but also contributing to the creation of variant databases specific to the Indian population, which is significantly underrepresented in global datasets.

Modifier genes are another frontier gaining traction. Genes like KLKB1, encoding prekallikrein, or SERPINA10, encoding protein Z-dependent protease inhibitor, have been implicated in modulating the severity and expression of primary bleeding disorders. A patient with mild hemophilia B exhibiting excessive bleeding was found to harbor a loss-of-function mutation in KLKB1, emphasizing the need for functional interaction mapping.

This emerging understanding of ultra-rare coagulopathies has direct clinical relevance. It informs decisions regarding prophylaxis, transfusion strategy, and eligibility for gene therapy. For genetic counselors, this data is crucial in evaluating familial risk and reproductive planning.

The expansion of sequencing and multi-omic profiling into clinical practice marks a shift from symptom-based diagnosis to molecular taxonomy. With each new discovery, the hemostatic genome reveals its intricacy, prompting the development of tailored diagnostic algorithms and precision-based interventions. As more of these ultra-rare conditions come to light, it is essential to integrate genomics into the early diagnostic workup of unexplained bleeding cases.



Reference:

- Millar, C.M., et al. (2021). "Uncovering rare bleeding disorders through genomic medicine." Blood, 138(2), 110-119.
- Bastida, J.M., et al. (2018). "Inherited bleeding disorders: Beyond hemophilia and von Willebrand disease." Journal of Thrombosis and Haemostasis, 16(9), 1701–1711.
- Downes, K., et al. (2019). "Rare variants in coagulopathy genes revealed by whole-genome sequencing." Nature Genetics, 51, 1310–1316.

The Next Wave: Polygenic Risk Scores (PRS) for Bleeding Tendency

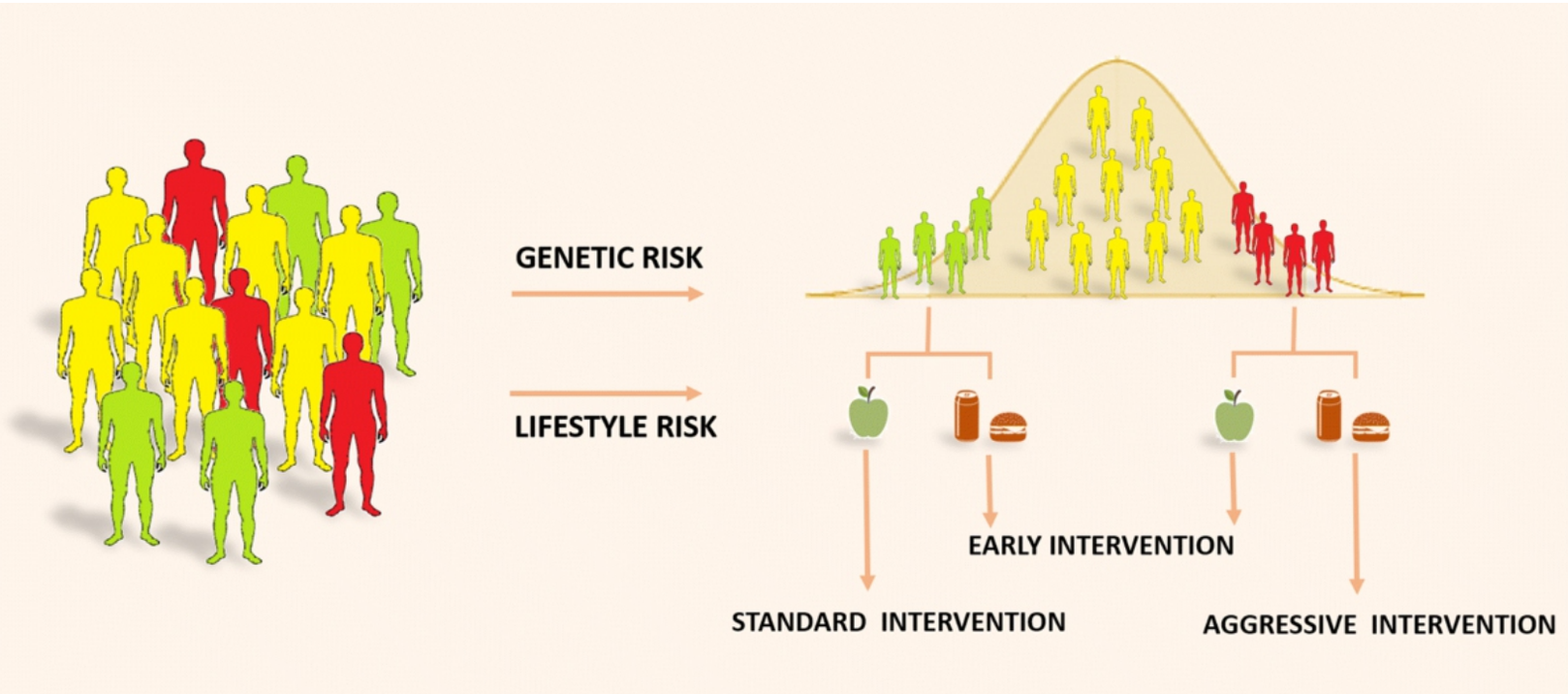
Traditionally, bleeding disorders have been viewed through the lens of monogenic inheritance, where a mutation in a single gene explains the clinical phenotype. However, recent insights from large-scale genomic studies have shifted this perspective, highlighting the importance of polygenic contributions to bleeding risk. Polygenic Risk Scores (PRS), which aggregate the effects of numerous common variants, are now emerging as powerful tools to stratify hemorrhagic risk, especially in patients with mild or acquired bleeding symptoms.

The concept of PRS hinges on the cumulative burden of single nucleotide polymorphisms (SNPs), each with a small effect size but collectively capable of modifying hemostatic balance. Studies involving biobank-scale datasets such as UK Biobank and FinnGen have identified PRS signatures for traits like platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels, factors that influence bleeding propensity.

Beyond diagnostic augmentation, PRS also holds promise in pharmacogenomics. Patients with elevated bleeding PRS may respond differently to anticoagulant therapy, requiring dose adjustments or alternative regimens. Integrating PRS into electronic health records and clinical decision-support systems can optimize therapeutic strategies, especially in personalized medicine settings.

However, challenges remain. Interpretation of PRS must consider ancestry, gene-gene interactions, and environmental modifiers such as diet, infection, and physical trauma. Ethical concerns surrounding incidental findings and genetic discrimination also warrant attention.

Future research is focused on creating multi-omic risk scores that combine PRS with transcriptomic, proteomic, and epigenetic data for a more holistic assessment. Machine learning algorithms are being employed to refine PRS models and predict individual bleeding trajectories over time



Reference:

- Sakaue, S., et al. (2021). "Polygenic risk scores across diverse cohorts reveal ancestry-specific patterns of genetic risk." Nature Genetics, 53(10), 1314–1321.
- Terao, C., et al. (2020). "Polygenic architecture of platelet count and its impact on bleeding risk." Nature Communications, 11, 5581.
- Inouye, M., et al. (2018). "Genomic risk prediction of bleeding complications during anticoagulant therapy." European Heart Journal, 39(2), 119–126.

Modeling Bleeding Disorders Using Induced Pluripotent Stem Cells (iPSCs): A Precision Medicine Frontier

The application of induced pluripotent stem cells (iPSCs) in the study of bleeding disorders is opening an innovative path for disease modeling, drug testing, and therapeutic discovery. iPSCs, which are somatic cells reprogrammed into a pluripotent state, retain the genetic makeup of the donor, including any pathogenic variants. This allows researchers to create personalized, patient-specific models of bleeding disorders, especially those with complex or unknown genetic backgrounds.

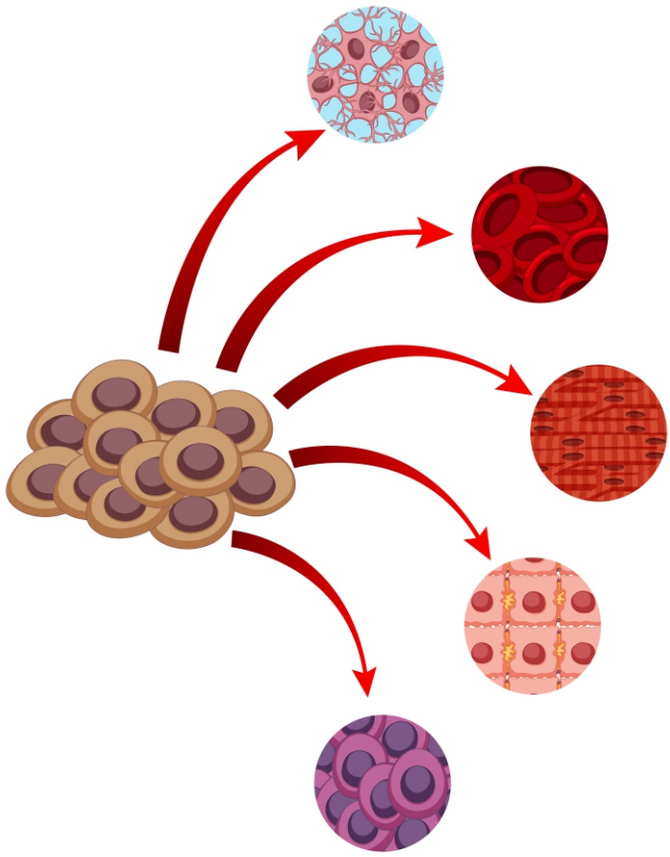
For disorders such as hemophilia A or B, iPSCs derived from patients' fibroblasts or blood cells can be differentiated into hepatocyte-like cells (HLCs), the key producers of clotting factors VIII and IX. These HLCs faithfully recapitulate the disease phenotype, including deficient protein production or secretion, making them valuable platforms for studying variant-specific effects. Similarly, iPSC-derived endothelial cells are being used to study von Willebrand disease and platelet function abnormalities.

Importantly, iPSC-based systems allow for high-throughput drug screening. For example, iPSC-derived megakaryocytes can be used to test compounds that enhance platelet production or function in inherited thrombocytopenias. This capability is crucial for identifying patient-specific treatments in the absence of approved targeted therapies.

In regenerative medicine, gene-corrected iPSCs are being explored for autologous transplantation. Proof-of-concept studies have shown that correcting the F8 gene in hemophilia A-derived iPSCs, followed by differentiation and engraftment into animal models, restores clotting activity. While clinical translation requires overcoming challenges such as immune compatibility and tumorigenicity, these advances signal a promising future for cellular therapies.

From a scientific standpoint, iPSCs offer a bridge between genotype and phenotype. They help elucidate disease mechanisms, reveal compensatory pathways, and validate candidate drug targets. Integration with transcriptomics, proteomics, and functional assays transforms iPSCs into versatile research tools, empowering both discovery and translational pipelines.

Despite their promise, iPSC models require standardization. Variability in reprogramming efficiency, differentiation protocols, and epigenetic memory can influence results. Collaboration across academic, clinical, and industry partners is essential to establish reproducibility and scalability.



Reference:

- Lancellotti, S., et al. (2020). "Patient-specific iPSCs to model inherited bleeding disorders: A new tool for precision medicine." Blood Transfusion, 18(3), 193–204.
- Huang, J., et al. (2018). "Disease modeling using iPSCs for hemophilia A." Cell Reports, 25(5), 1404–1416.
- Olmer, R., et al. (2021). "iPSC-based platforms for drug screening and disease modeling in hematological disorders." Stem Cell Reports, 16(7), 1593–1608.

CRISPR in Hemostasis: Correcting Inherited Bleeding Disorders at the Genetic Level

CRISPR-Cas9 gene editing technology has emerged as a transformative approach in the correction of monogenic disorders, and its application in inherited bleeding disorders such as hemophilia A and B, Glanzmann thrombasthenia, and Bernard-Soulier syndrome is gaining momentum. Unlike conventional therapies that require lifelong factor replacement or platelet transfusions, CRISPR offers the potential for a single, curative intervention by precisely correcting pathogenic mutations at the DNA level.

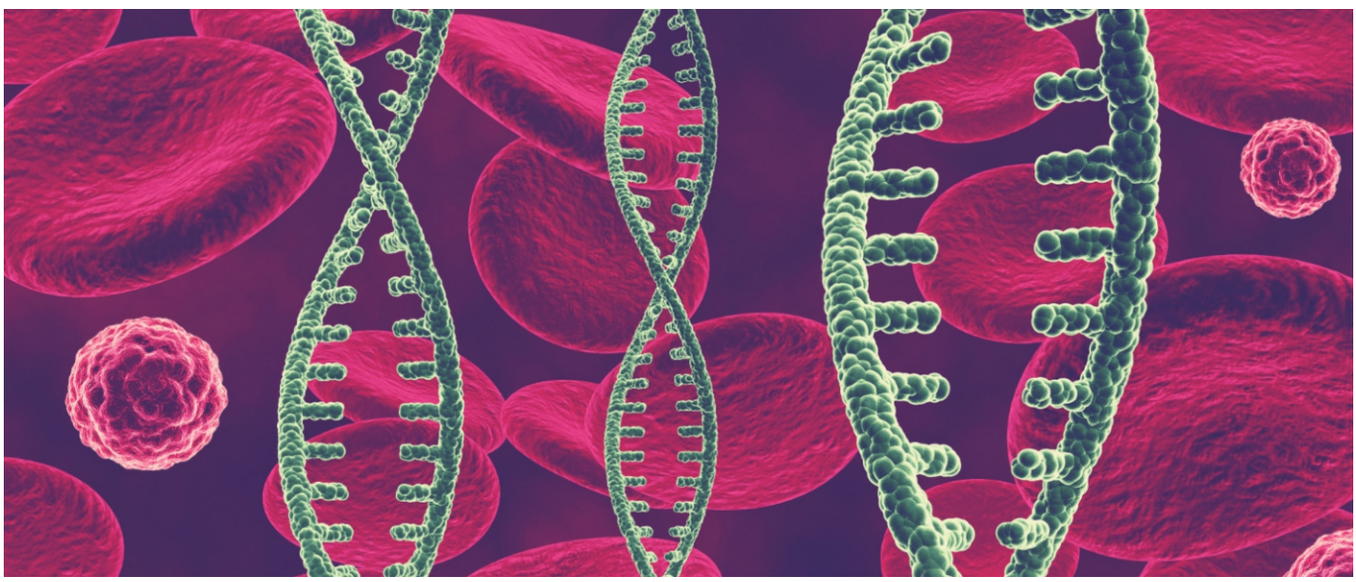
In preclinical studies, CRISPR-mediated editing of the F8 and F9 genes in hepatocytes has demonstrated restored expression of functional clotting factors VIII and IX, respectively. Notably, researchers have utilized adeno-associated virus (AAV) and lipid nanoparticle-based delivery systems to target the liver, the native site of clotting factor production. These methods have shown sustained hemostatic correction in mouse and non-human primate models of hemophilia.

Beyond hemophilia, platelet function disorders are also being explored. In Glanzmann thrombasthenia, CRISPR correction of ITGA2B or ITGB3 mutations in patient-derived megakaryocytes has shown restoration of integrin **α**IIb**β**3 expression, enabling platelet aggregation in vitro. These advances point toward the potential for autologous CRISPR-edited hematopoietic stem cell (HSC) therapies, minimizing immunogenic complications.

Recent clinical developments underscore the momentum. In 2023, a first-in-human trial using CRISPR-edited HSCs for hemophilia B (targeting the F9 R338L mutation) commenced in Europe, marking a significant step from bench to bedside. While still in early phases, this trial will be instrumental in determining the safety, efficacy, and durability of in vivo gene correction.

Challenges remain, particularly concerning off-target effects, immune responses to Cas9 proteins, and ensuring efficient delivery and editing in the relevant cell types. To address these, researchers are turning to novel base editing and prime editing platforms, which allow for even greater precision without inducing double-stranded breaks.

For personalized genomics companies, CRISPR represents an intersection of diagnostics and therapy. Accurate variant classification, patient-specific guide RNA design, and real-time editing efficacy monitoring are all domains where integrated genomic analysis is essential. As ethical and regulatory frameworks evolve, the role of genomics-guided CRISPR therapeutics in bleeding disorders is poised to shift from theoretical promise to clinical routine.



Reference:

- Pasi, K.J., et al. (2020). "Targeting gene therapy in hemophilia with CRISPR-Cas9." Nature Reviews Drug Discovery, 19, 775–776.
- Dever, D.P., et al. (2016). "CRISPR/Cas9 beta-globin gene targeting in human hematopoietic stem cells." Nature, 539(7629), 384–389.
- Schiroli, G., et al. (2019). "Precise gene editing in hematopoietic stem cells to treat inherited bleeding disorders." Cell Stem Cell, 24(4), 590–602.

Pharmacogenomics in Bleeding Disorders: Tailoring Anticoagulant and Hemostatic Therapy

Pharmacogenomics has emerged as a crucial enabler in the personalization of treatment for bleeding disorders, especially in the context of anticoagulant use and replacement therapies. Genetic variability among individuals can significantly impact drug metabolism, efficacy, and toxicity. This is particularly relevant for medications such as warfarin, heparin, direct oral anticoagulants (DOACs), and desmopressin.

One of the most extensively studied examples is warfarin, whose dosing is influenced by polymorphisms in CYP2C9 and VKORC1 genes. Individuals carrying variants such as CYP2C9*2 or *3 alleles show reduced metabolic clearance of warfarin, increasing their risk for bleeding complications. Similarly, VKORC1 promoter variants affect the sensitivity to warfarin by altering expression levels of vitamin K epoxide reductase. Genotype-guided dosing algorithms have demonstrated improved therapeutic range maintenance and reduced incidence of adverse events in multiple clinical trials.

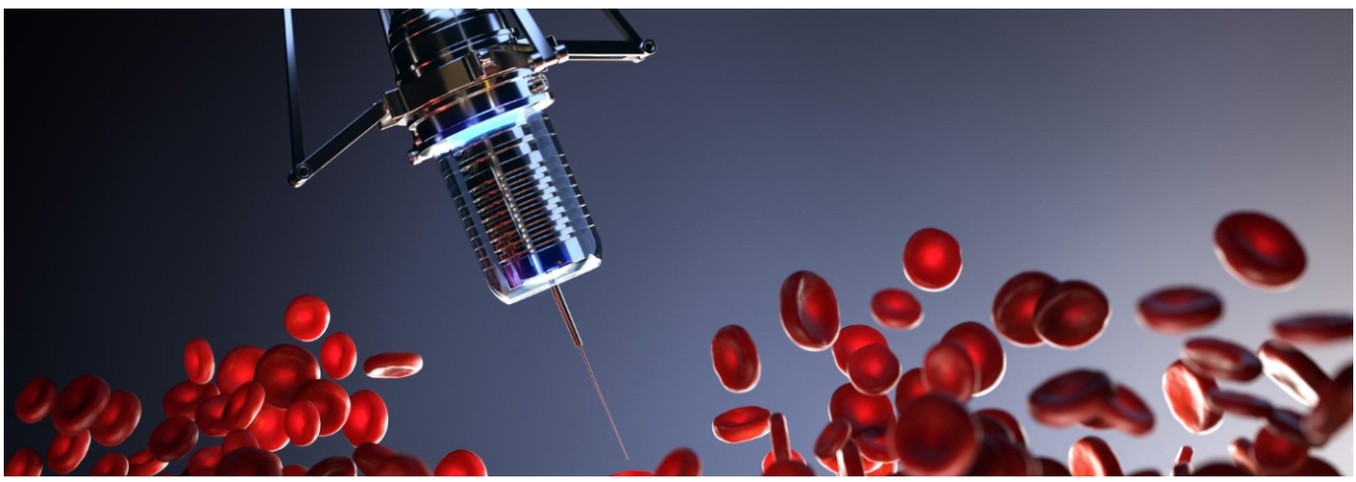
In patients receiving heparin, genetic variants in antithrombin (SERPINC1), heparin cofactor II (SERPIND1), and platelet factor 4 (PF4) have been linked to heparin resistance or increased risk of heparin-induced thrombocytopenia (HIT). Precision strategies now consider genotyping these variants before initiating heparin therapy in at-risk populations, including those with a family history of coagulopathy.

Desmopressin (DDAVP), used in mild hemophilia A and von Willebrand disease (VWD), also shows interindividual variation in responsiveness. Genetic modifiers such as AVPR2 and VWF gene haplotypes may explain partial or poor responses to DDAVP, necessitating pharmacogenomic screening to predict therapy success and avoid ineffective treatment.

For DOACs like apixaban and rivaroxaban, genes encoding drug transporters (ABCB1) and metabolizing enzymes (CYP3A4/5) can influence pharmacokinetics. Recent studies have indicated a link between ABCB1 polymorphisms and plasma drug concentrations, thereby affecting bleeding risk. Although routine pharmacogenomic testing for DOACs is not yet standard, growing evidence supports its utility, particularly in elderly patients or those with complex comorbidities.

From a precision medicine perspective, integrating pharmacogenomic data with electronic health records and clinical decision-support tools can enhance therapy safety and effectiveness. For personalized genomics companies, this presents an opportunity to build actionable genetic panels that not only diagnose inherited bleeding disorders but also guide therapeutic interventions.

As healthcare moves toward individualized therapy, pharmacogenomics will play an increasingly central role in optimizing anticoagulant and hemostatic treatments, improving outcomes, and reducing avoidable complications in patients with bleeding disorders.



Reference:

- Johnson, J.A., et al. (2017). "Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing." Clinical Pharmacology & Therapeutics, 102(3), 397–404.
- Pereira, N.L., et al. (2019). "Pharmacogenomics in cardiovascular therapeutics: Ready for prime time?" Circulation Research, 124(6), 999–1000.
- Mega, J.L., et al. (2020). "Genetic variants associated with oral anticoagulant pharmacokinetics and bleeding risk." Nature Reviews Cardiology, 17(1), 56–67.

Meet the Doctors

Dr Kalyan Uppaluri is the co-founder and the owner of GenepoweRx Personalized medicine clinic and research institute, He did his medical training at the prestigious Gandhi Medical College. He then moved to the United States, where he specialized in Internal Medicine at the McLaren Hospital, Michigan. He also got a degree in Medical Genomics from Ivy league Institute, Stanford University and pursued Cancer research at Wayne State University.

Dr Hima Challa graduated from Gandhi Medical college and was among top few in her batch. She specialized in Internal Medicine at St. Joseph Mercy Oakland, Michigan in United States. She graduated in Medical genomics from the Ivy league Institution of Harvard Medical School. She also holds a master's in nutrition science from the Texas Women University and in integrative medicine from Arizona University.

GenepoweRx®
Genetic Science powered by K&H

Suit#2B Plot No.240, Nirvana
Road No.36, Jubilee Hills
Hyderabad - 500033, India

+91 95022 22300
info@khdreamlife.com
www.genepowerx.com