A **MONTHLY** PERSONALIZED MEDICAL MAGAZINE

MAY
2025 Edition

ATGC life

THE PIONEER IN GENETIC TESTING & REPORTING

AI-Integrated Genomics:
Advances in Precision Medicine

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Genetic Science powered by K&H

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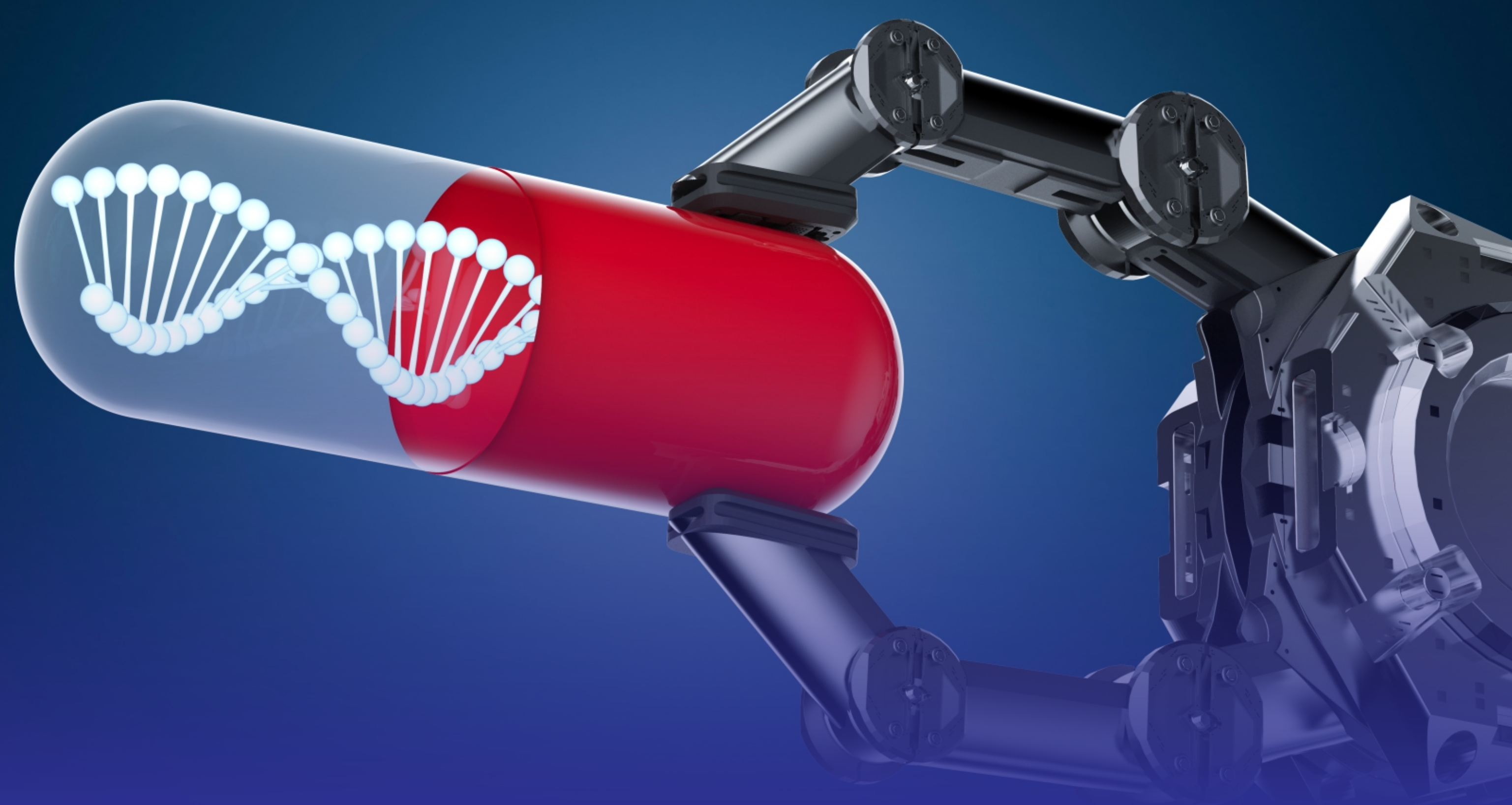

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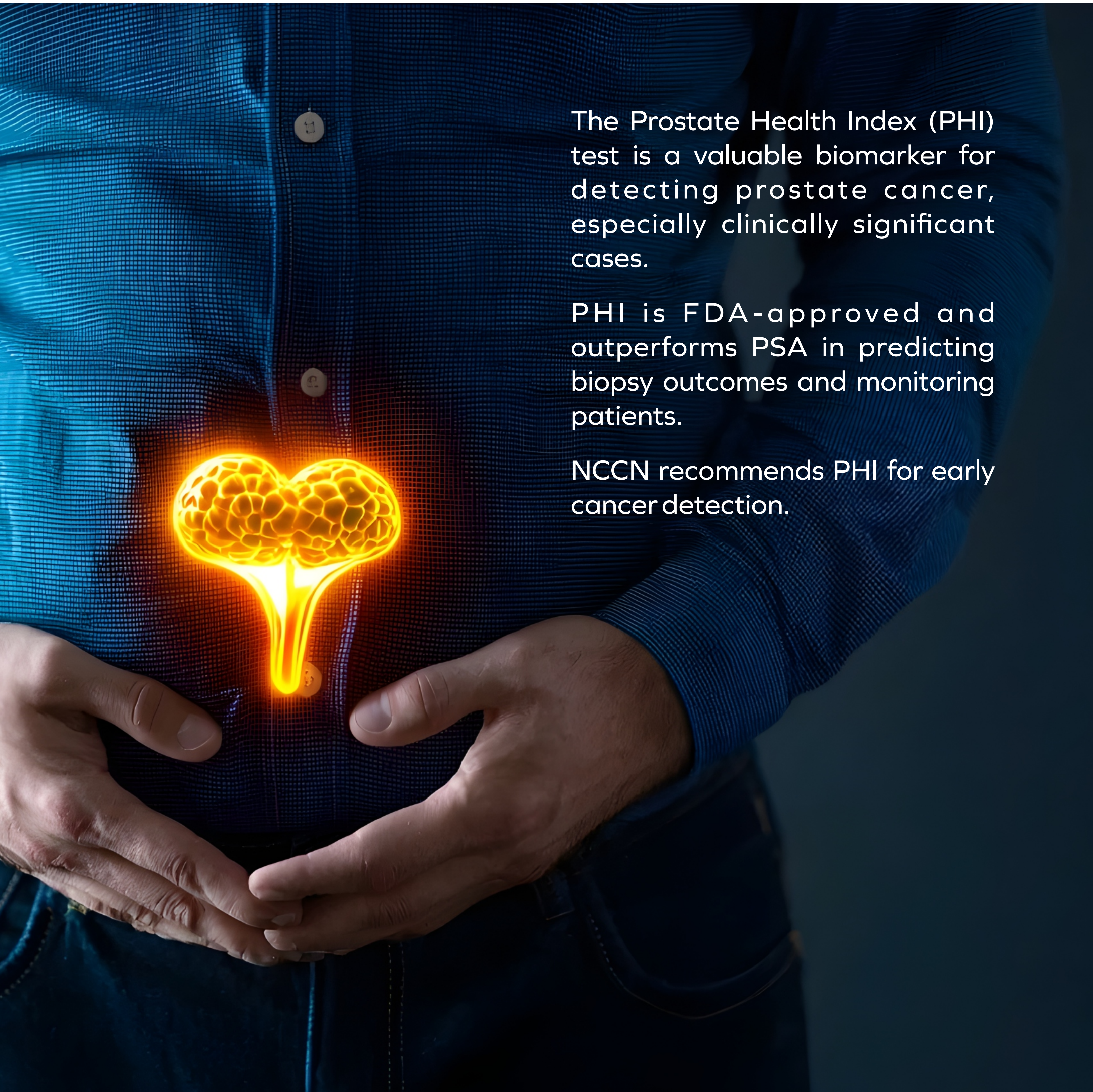
Prostate Health Index **phi**

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.

In this edition, we explore the transformative convergence of artificial intelligence, genomics, and personalized medicine.

From AI-enabled variant interpretation to whole-person genomics and pediatric screening, the field is evolving rapidly toward more precise, preventive healthcare. AI tools are revolutionizing how clinicians interpret complex genetic variants, especially in rare diseases, by integrating genomic and phenotypic data with unprecedented speed and accuracy.

Whole-person genomics expands our lens beyond DNA, incorporating environmental, microbiome, and lifestyle factors to better understand disease risk and progression. Pediatric genomics is shifting clinical care from reactive to proactive, enabling early detection and intervention in childhood disorders. Meanwhile, gene-based therapeutics—powered by CRISPR and other platforms—are offering curative potential for once-incurable diseases.

As we integrate these innovations, it's crucial to address challenges such as algorithmic bias, data privacy, and equitable access. This issue underscores how genomics, when combined with ethical AI and clinical rigor, is reshaping the future of precision medicine.
Stay tuned for more cutting-edge discoveries in our upcoming editions.

Warm regards,

Dr. Hima J. Challa
Director, GenepoweRx

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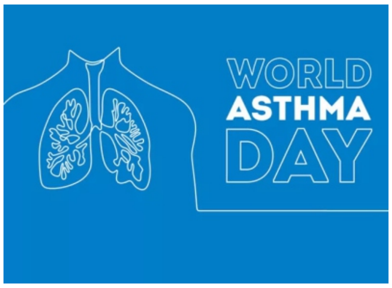

AI-Enabled Genomic Diagnostics: Accelerating Variant Interpretation and Disease Detection

As the volume of genomic data continues to grow exponentially, traditional methods of variant interpretation are proving insufficient in terms of speed, scalability, and precision. Artificial Intelligence (AI), particularly machine learning (ML), is emerging as a transformative tool in genomics, enabling faster and more accurate diagnosis of genetic disorders, including rare diseases. This convergence of AI with genomics has opened new frontiers in personalized medicine, enhancing clinicians' ability to offer timely, tailored interventions.

AI models, trained on curated variant databases and clinical annotations, are improving this process. Tools like PrimateAI and EVE (Evolutionary model of variant effect) analyze patterns in sequence data to predict the pathogenicity of variants. Unlike traditional rule-based methods such as ACMG guidelines, these tools offer scalable, probabilistic predictions.
A 2024 study published in Nature Genetics demonstrated that explainable AI models could classify digenic variants—mutations across two genes that contribute jointly to a disease phenotype with over 85% accuracy [1]. This marks a leap forward in detecting complex inheritance patterns that would otherwise go unnoticed.

AI is impactful in identifying rare diseases where genotype-phenotype associations are poorly understood. By integrating electronic health record (EHR) data, phenotypic features, and genomic data, AI can detect patterns suggestive of rare conditions. For instance, the Fabric GEM platform uses natural language processing (NLP) to extract clinical features from EHRs and correlate them with sequencing data, significantly improving diagnostic rates in neonatal intensive care units [2].

While AI offers speed and efficiency, it is not without limitations. Models trained on biased datasets may fail in underrepresented populations. There is also the challenge of interpretability—black-box predictions may be difficult for clinicians to trust without clear rationales. Ethical concerns include informed consent for algorithmic diagnosis, data privacy, and AI-driven automation potentially replacing human oversight.

The integration of AI into genomic diagnostics is still evolving. Federated learning, where models are trained across decentralized datasets without moving sensitive data is being explored to improve performance across diverse populations. Additionally, AI tools are being developed to predict drug response based on pharmacogenomic markers, pushing precision medicine further into mainstream care. Though several AI tools are evolving for prediction of the diseases, human sources are required for complicated cases and for Cross verifications.

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Whole-Person Genomics: Integrating Genetic, Environmental, and Lifestyle Factors

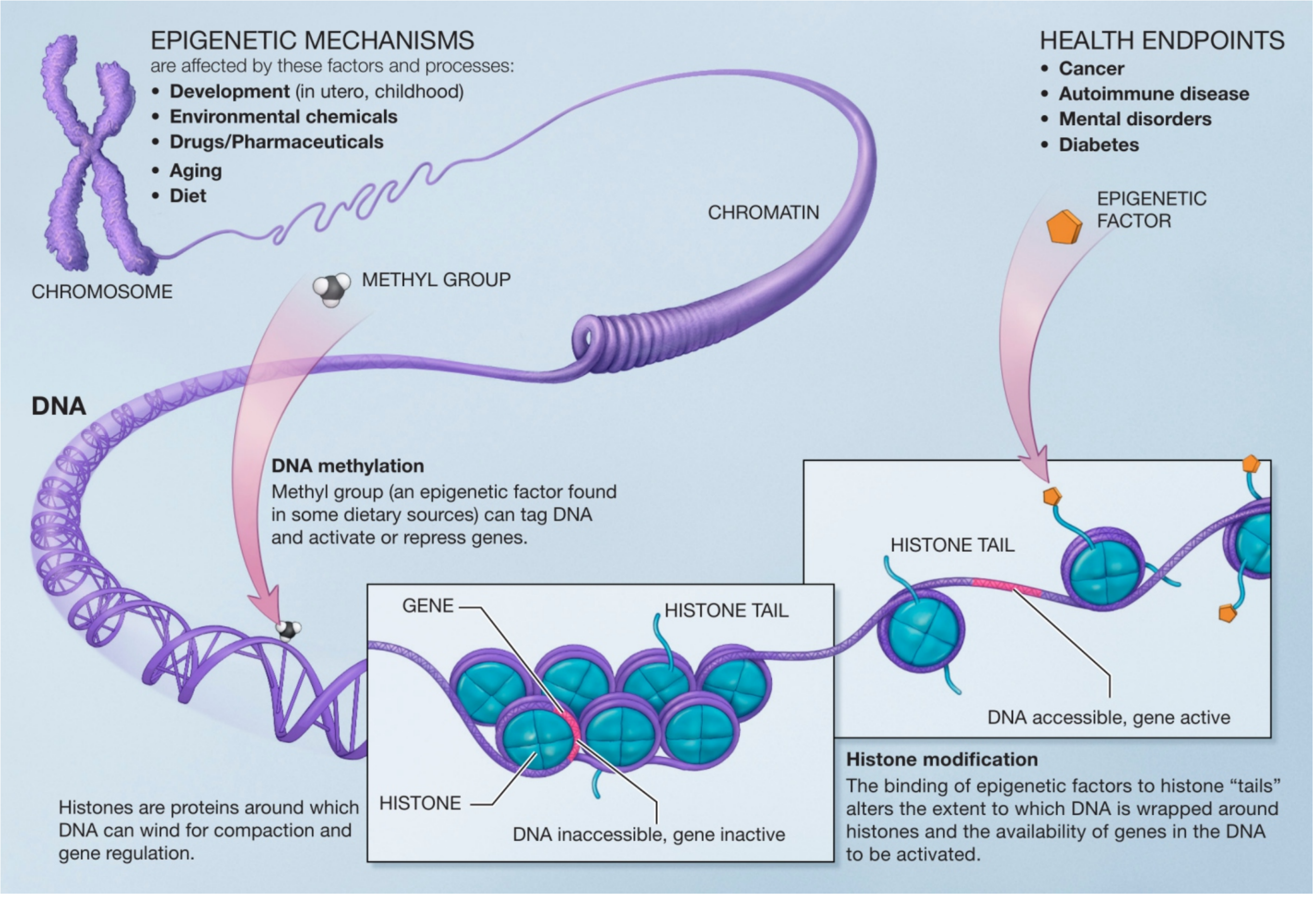
While classical genetics has illuminated the role of single-gene mutations in monogenic diseases, the complexity of most human disorders cannot be captured by DNA alone. The current paradigm shift in precision medicine recognizes that genomic risk is shaped not only by variants but also by interactions with environmental, epigenetic, and lifestyle factors. This integrated approach sometimes referred to as whole-person genomics embraces a systems biology perspective, enabling a more nuanced understanding of health and disease.

At the heart of this evolution is the move from variant-centric diagnostics to data-informed holistic care. Personalized genomics companies, including ours, are developing tools and frameworks that combine polygenic risk scores (PRS), epigenetic profiling, microbiome data, and lifestyle metrics to deliver individualized prevention and treatment strategies.

The Science of Gene-Environment Interactions

Genotype alone rarely determines phenotype. Environmental factors like diet, pollutants, stress, infections can significantly modulate gene expression. These interactions are mediated through epigenetic modifications, such as DNA methylation, histone modifications, and non-coding RNAs, which influence transcription without altering the DNA sequence.

One landmark study from the NIH Roadmap Epigenomics Project demonstrated that methylation profiles in monozygotic twins diverge significantly with age and lifestyle differences, correlating with phenotypic discordance in complex traits like metabolic syndrome and depression [1]. Such findings underscore the importance of considering environmental exposures in clinical genomics.



Polygenic Risk Scores: Quantifying Complex Trait Risk

Most common diseases like cardiovascular disease, type 2 diabetes, neurodegenerative disorders arise from the cumulative effect of hundreds or thousands of variants, each with small individual effect sizes. Polygenic risk scores (PRS) aggregate these effects to quantify a person's inherited risk for a specific condition.

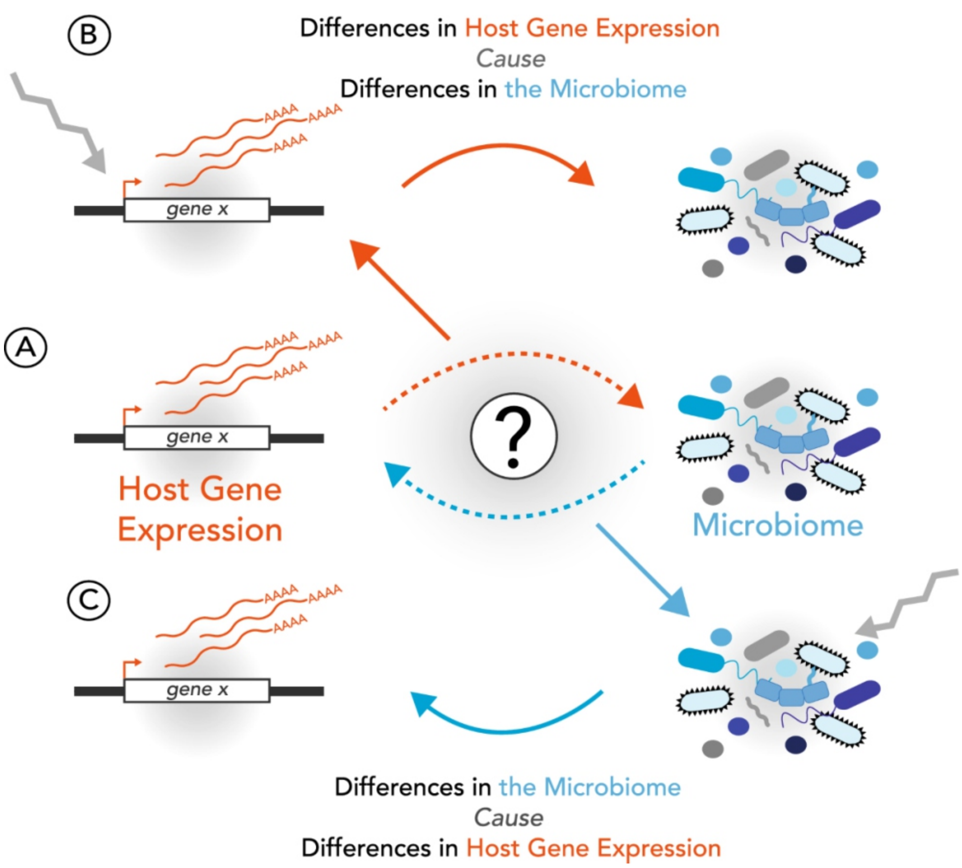
For example, a 2023 study published in Nature Medicine reported that individuals in the top 5% PRS for coronary artery disease had a threefold higher risk, independent of traditional risk factors such as cholesterol levels or smoking status [2]. PRS can thus stratify individuals for early intervention, even in the absence of family history.

Microbiome and Gene Expression Interplay

The gut microbiome, often called the "second genome," plays a critical role in modulating host metabolism, immune response, and even neurodevelopment. Recent studies have revealed that microbiota composition can influence epigenetic regulation through microbial metabolites like butyrate and folate, which affect DNA methylation and histone acetylation [3]. In one study, fecal microbiota transplantation in patients with metabolic syndrome induced not only microbiome shifts but also altered host gene expression in the liver and adipose tissue [4]. This evidence strengthens the rationale for integrating microbiome sequencing into personalized genomics platforms, particularly for metabolic and autoimmune disorders.

Challenges and Ethical Considerations

Despite the promise, challenges remain. Polygenic risk models often lack portability across populations due to underrepresentation in GWAS datasets. Integrating microbiome or wearable data requires robust data governance frameworks, as privacy concerns loom large. Furthermore, the clinical utility of some epigenetic biomarkers remains under investigation. To ensure ethical deployment, our clinic adheres to informed consent protocols, promotes transparency in risk communication, and continually validates algorithms across diverse cohorts.



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Genomic Medicine in Pediatrics: Early Screening, Preventive Strategies, and Clinical Implementation

Advancements in genomics are reshaping the landscape of pediatric medicine. Early-life genetic screening, once limited to a few inborn errors of metabolism, is now expanding to encompass a broad spectrum of monogenic and multifactorial conditions. By detecting pathogenic variants at birth or even prenatally, clinicians can intervene early, mitigate disease progression, and, in some cases, alter the course of lifelong health trajectories. With the convergence of whole-genome sequencing, and AI-powered variant interpretation, pediatric genomics is shifting from reactive treatment to proactive prevention.

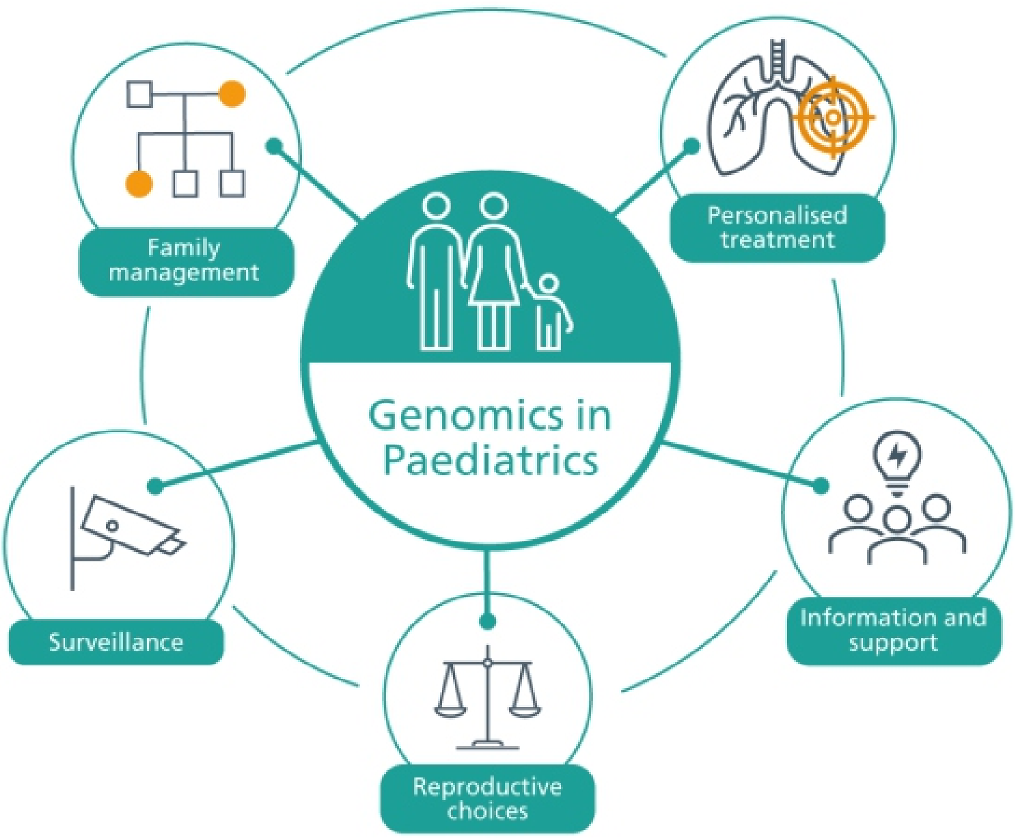
The integration of pediatric genomics into routine care demands robust genetic counseling frameworks. Parents receiving genomic results must understand not only the implications of diagnostic findings, but also incidental or adult-onset conditions discovered during sequencing.

Ethical issues include:

- **Consent and autonomy:** Infants cannot consent to sequencing; thus, decisions rest with parents, raising concerns about future autonomy.
- **Variants of uncertain significance (VUS):** Communicating uncertain results can cause anxiety without offering actionable guidance.
- **Disparities in access:** Families in underserved communities may lack access to genomics-based care, exacerbating health inequities.

To address these, our clinic follows the ACMG guidelines for reporting secondary findings and employs pediatric genetic counselors trained in family-centered communication.

Genomic technologies are transforming pediatric medicine from the earliest stages of life. By moving from reactive to preventive care, clinicians can offer children not just treatment but a healthier future. While challenges remain in implementation, ethics, and interpretation, early genomic screening is poised to become a cornerstone of precision pediatrics, empowering both clinicians and parents to make informed, life-changing decisions.



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Gene-Based Therapeutics and Genome Editing: Clinical Translation, Regulatory Landscape, and Future Directions.

Gene therapy has transitioned from an aspirational research concept to a clinical reality in multiple fields, particularly for monogenic disorders. Driven by advances in vector technology, regulatory approvals, and gene-editing platforms like CRISPR-Cas9, the field now offers FDA-approved therapies and hundreds of ongoing trials worldwide. However, discerning what's clinically validated versus what remains theoretical is essential for clinicians, researchers, and patients alike.

This subtopic explores the current status of gene therapies, the landscape of CRISPR-based interventions, and what patients and providers should realistically expect from this rapidly evolving domain.

Gene Therapy: From Bench to Bedside

Gene therapy refers to the modification or replacement of faulty genes to correct disease processes. Approaches include gene addition, gene silencing, and genome editing. Delivery systems primarily rely on adeno-associated viruses (AAVs), lentiviruses, or non-viral nanoparticle platforms.

Two landmark approvals illustrate gene therapy's clinical viability:

- **Spinal Muscular Atrophy (SMA):**

  Onasemnogene abeparvovec-xioi (Zolgensma) delivers a functional SMN1 gene via an AAV9 vector. Approved by the FDA in 2019, it offers one-time curative potential for SMA in infants.

- **Sickle Cell Disease (SCD) and β-Thalassemia:**

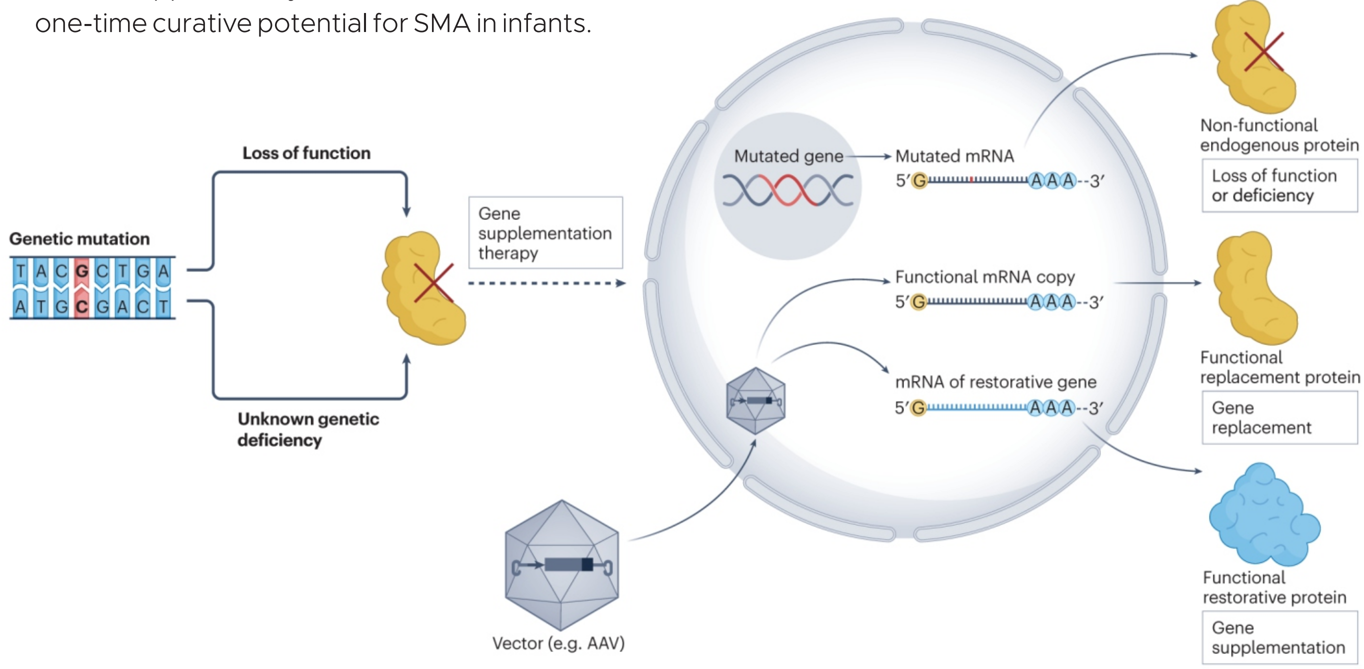
  In 2023, the FDA approved exagamglogene autotemcel (Casgevy), a CRISPR-Cas9-based therapy co-developed by Vertex Pharmaceuticals and CRISPR Therapeutics. This ex vivo therapy edits hematopoietic stem cells to reactivate fetal hemoglobin (HbF) expression, mitigating sickling in red blood cells.

- Other approvals include Luxturna (RPE65 mutation-associated retinal dystrophy) and Roctavian (hemophilia A), further highlighting the therapeutic diversity of gene-based interventions.

Ongoing Clinical Trials and Emerging Indications

The clinical trial pipeline includes hundreds of gene therapy programs targeting:

- **Neurological diseases** (e.g., Huntington's disease, Rett syndrome, ALS)
- **Oncological applications** (e.g., CAR-T cells in leukemia/lymphoma)
- **Metabolic disorders** (e.g., OTC deficiency, Fabry disease)
- **Immunodeficiencies** (e.g., ADA-SCID, Wiskott-Aldrich syndrome)



Ex vivo editing (editing cells outside the body and re-infusing them) remains safer for hematologic disorders, while in vivo approaches (direct gene delivery) are expanding in muscle, eye, and liver diseases due to tissue-specific tropism of AAV serotypes.

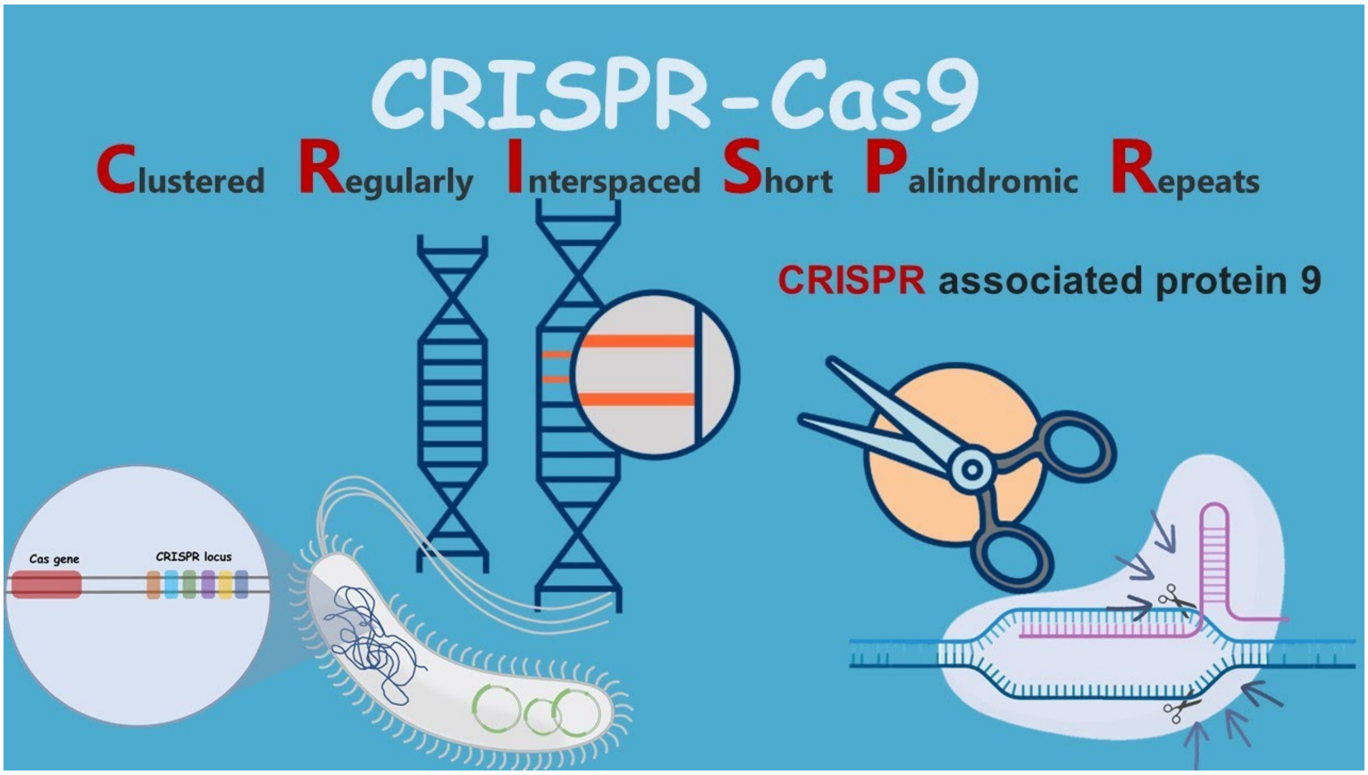
CRISPR-Cas9: Beyond the Buzz

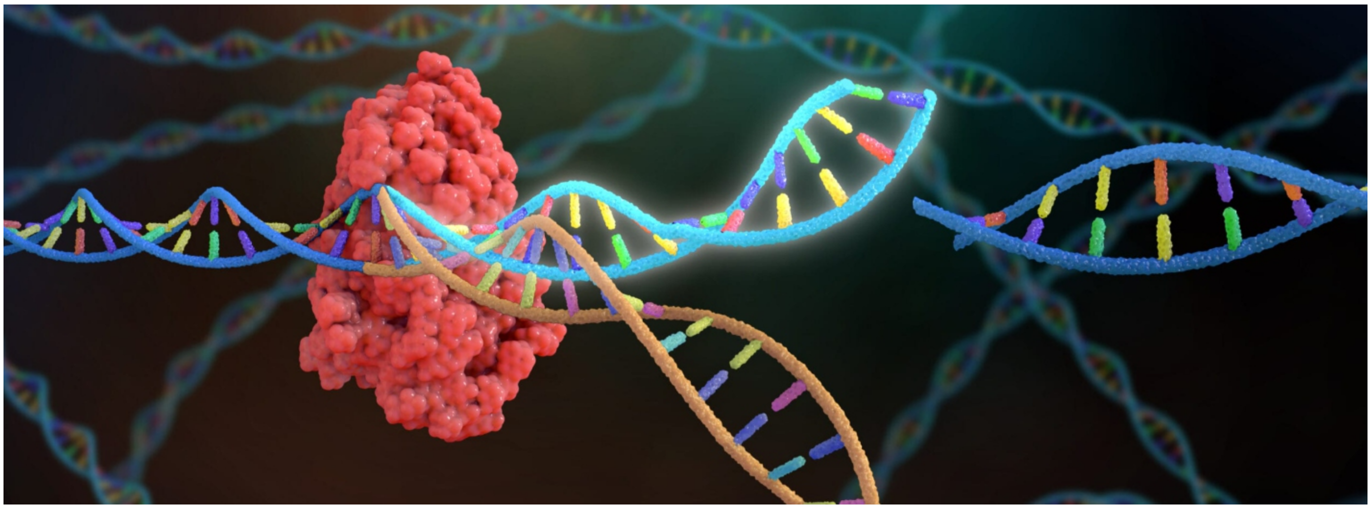
CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) and associated enzymes like Cas9 have revolutionized gene editing. Their precision, cost-effectiveness, and scalability have enabled their integration into therapeutic strategies.

Current CRISPR modalities include:

- **CRISPR-Cas9**
- **Base editing**
- **Prime editing**

While Casgevy represents the first FDA-approved CRISPR therapy, dozens more are in development, including editors targeting the liver, retina, and brain. Companies like Beam Therapeutics are developing base editors for point mutation correction with fewer off-target effects.





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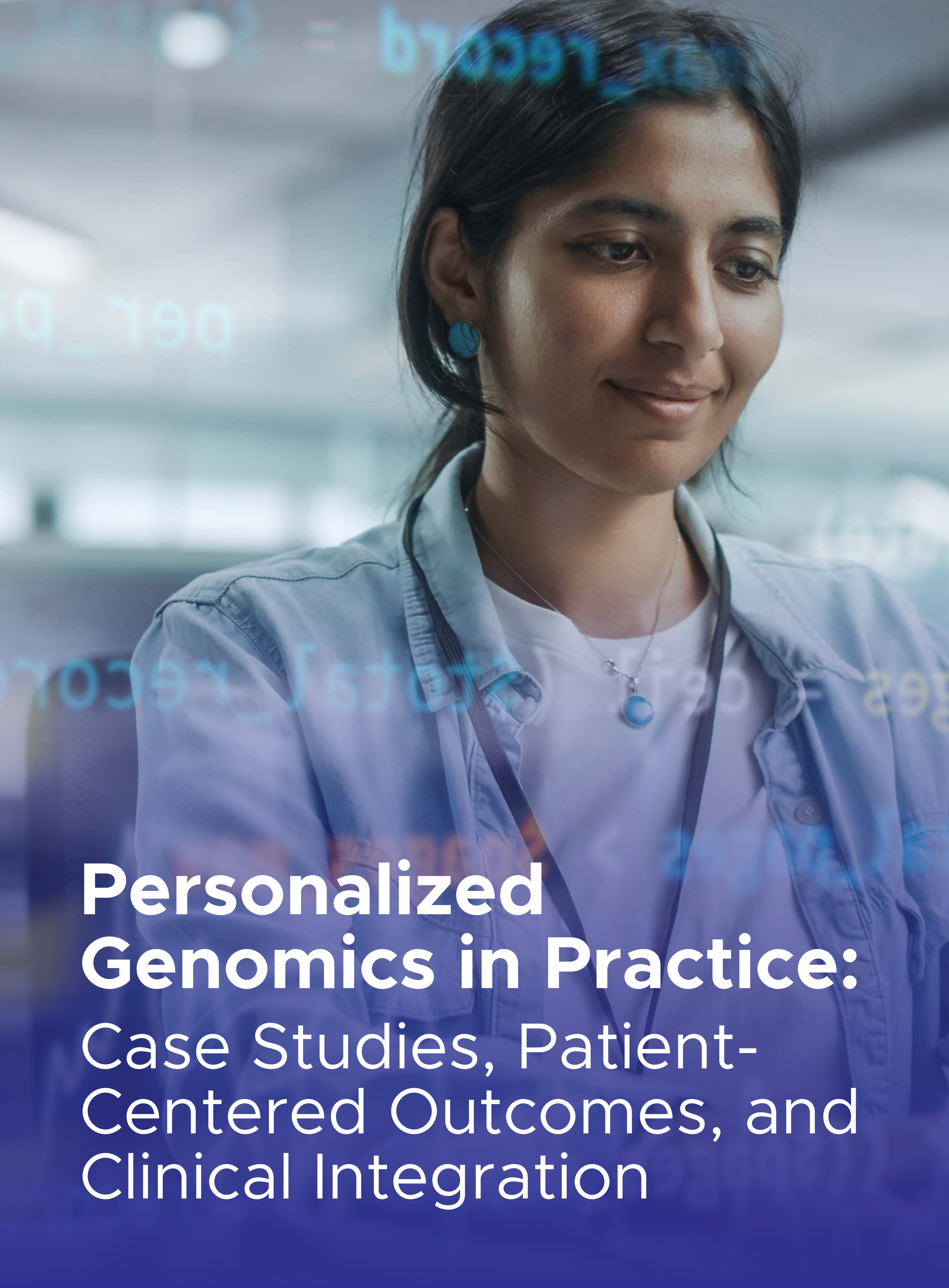

Personalized Genomics in Practice:

Case Studies, Patient-Centered Outcomes, and Clinical Integration

Personalized Genomics in Practice: Case Studies, Patient-Centered Outcomes, and Clinical Integration

The integration of genomics into routine clinical practice has revolutionized the concept of patient-centered care. By transitioning from reactive to predictive and preventive healthcare, personalized genomics offers a roadmap for individualized diagnosis, treatment, and monitoring. Beyond molecular pathways and variant reports, the true essence of genomic medicine lies in how patients experience and benefit from tailored interventions.

In this section, we explore real-world experiences of individuals who have navigated their medical conditions through genomic diagnostics, early interventions, and tailored therapeutics highlighting how genetic data, when coupled with clinical insight and compassionate care, transforms live.

Personalized Genomics in Action: Clinical Narratives

Case 1: Early Diagnosis of a Rare Disorder Through Whole Genome Sequencing

A 7-month-old male infant presented with global developmental delay, microcephaly, and unexplained seizures. Despite multiple clinical evaluations, standard metabolic and neuroimaging tests remained inconclusive. Whole exome sequencing revealed a de novo pathogenic variant in the TUBB2B gene, associated with cortical dysplasia and Autism spectrum disorders [1].

Upon diagnosis:

- Targeted antiepileptic therapy was initiated.
- Parents received genetic counseling regarding recurrence risk.
- A multidisciplinary neurodevelopmental program was implemented.

Outcome: The timely genetic diagnosis enabled early intervention, improved seizure control, and helped the family prepare emotionally and practically for future care.

“Having a name for our child’s condition gave us clarity and direction. We felt empowered to make the right choices,” - Parent testimony (with consent).

Case 2: Cancer Predisposition Screening Saves a Life

A 41-year-old asymptomatic woman with a family history of breast cancer underwent multigene panel testing, which identified a pathogenic variant in BRCA1. Subsequent histopathology of breast tissue revealed early-stage, non-invasive carcinoma, which was completely excised during surgery. A potentially life-threatening cancer was detected and treated before it became symptomatic, demonstrating the life-saving potential of predictive genetic testing.

The Role of Clinics: Beyond Data to Dialogue

Genomic testing alone is not transformative - it is the interpretation, context, and delivery of results that define the patient journey. At our clinic, we emphasize:

1. **Pre-test Counseling:** Managing expectations, assessing readiness, and ensuring informed consent.
2. **Post-test Interpretation:** Genetic data is explained in context with lifestyle, family history, and clinical parameters.
3. **Psychosocial Support:** Emotional and psychological well-being are addressed alongside medical management.
4. **Lifelong Engagement:** Patients receive longitudinal follow-up as new discoveries arise and interpretations evolve.

Art, Expression, and the Healing Process

Personalized medicine is not only a scientific breakthrough but also a deeply personal experience. We’ve encouraged patients to express their genomic journeys through:

- Journals documenting diagnostic odysseys.
- Visual art capturing emotional milestones.
- Voice recordings describing their hopes and concerns.

These expressions not only help patients process complex feelings but also humanize genomic medicine for healthcare providers and future patients.

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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.

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