Genomic-Based Precision Medicine for Neurological and Kidney Disorders

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***Abstract*—BioGenomic Precision Medicine (BP Med), encompassing genomic developments from technology to clinical integration, offers a distinctive perspective on precision medicine in neuro and kidney disorders. In addition to an overview of BP Med, areas of neuro and kidney diseases for which genomic studies have provided insights into therapeutic strategies are considered, as well as cross-disciplinary clinical management of conditions with both neurodevelopmental and kidney features.**

Traditionally, precision medicine has focused on targeted therapies for small patient subsets sharing a disorder-associated mutation, epigenetic alteration, or biomarker. BP Med expands this logic from narrow disease targets to include broader and potentially more impactful insights by addressing foundational concepts and resources for the implementation of precision medicine, thereby indirectly enabling stratification of the entire affected population or improving response profiles for all patients, whether by counselling, treatment modulation in multi-organ dysfunctions, or secondary preventive strategies. BP Med invites integration of established but previously compartmentalized genomic knowledge into a more comprehensive and clinically useful frame. Without such inclusion, especially in the neurodevelopmental field, replication may remain elusive, independent comparisons across specialties may lack value, and resolution of plot holes may remain unfulfilled.

Keywords—BioGenomic Precision Medicine, Genomic Clinical Integration, Neurodevelopmental Disorders, Kidney Disease Genomics, Precision Therapeutics, Cross-Disciplinary Clinical Management, Multi-Organ Dysfunction, Patient Stratification, Genotype–Phenotype Correlation, Translational Genomics, Biomarker Discovery, Therapeutic Target Identification, Population-Level Precision Medicine, Genomic Counseling, Treatment Modulation Strategies, Secondary Prevention, Integrated Genomic Frameworks, Clinical Decision Support, Systems Precision Medicine.

I. INTRODUCTION

Large-scale DNA sequencing and related technologies are revolutionizing biology and medicine by enabling the use of genomic information to understand the mechanisms underlying complex diseases, particularly informative for stratifying patient populations or identifying drugs that would respond to treatment. Together, these discoveries, products of open data sharing and collaboration at scalable levels, support new approaches to precision medicine referred to as BioGenomic Precision Medicine (BMPM). BMPM leverages whole genome sequencing and other -omics technologies to identify the genetic contribution of disease through a literal (hierarchical) and biological reproducibility research framework, aiming for clinical application of predictive biomarkers.

BMPM expands the concept of precision medicine by including a wider spectrum of subcategories of biomarkers such as polygenic risk scores in common disorders, in contrast to traditional precision medicine for rare diseases. Understanding genetic driving mechanisms, stratifying patients, and defining precision clinical trial endpoints in neurodegenerative, neurodevelopmental, and psychiatric disorders are prime examples of applying genomic information. In kidney diseases, monogenic forms and their treatment represent the best-defined clinical applications, while the contribution of common risk factors remains under investigation.

A. Overview of BioGenomic Precision Medicine

BioGenomic Precision Medicine integrates systems biology with genomics to identify the genetic cause of human disease and the molecularly defined disease subtype. BioGenomic Precision Medicine is based on BioGenomic Precision Medicine integrates systems biology with genomics to identify the genetic cause of human disease and the molecularly defined disease subtype. Central hypothesis diverse disorders produce pathological sequences exhibiting common signatures across multiple studies. BioGenomic Precision Medicine differs from conventional P4 medicine in focusing on patient populations for whom therapeutics have been developed. To complement risk-based treatment using biomarkers of future disease, BioGenomic Precision Medicine adds biomarkers for patient stratification and for monitoring therapeutic response.

Knowledge accumulation in BioGenomic Precision Medicine has radically expanded over the past decade. Multitude of genomic test providers and clinical laboratories for both somatic and germline diseases. Graft-host disease, organ transplant rejection, sepsis and respiratory tract infections are now commonly diagnosed and treated through multi-omics biomarkers. Monogenic kidney disease is the first clinical area for which gene-based therapeutics are now approved. Pathogenic mechanisms and targeted therapeutics are characterised for many more kidney disorders. Neurodegeneration, neurodevelopment, and neuropsychiatric disease are increasingly understood at a genetic level, and subsequent BioGenomic Precision Medicine provides avenues for interventional trials stratified by genotype.

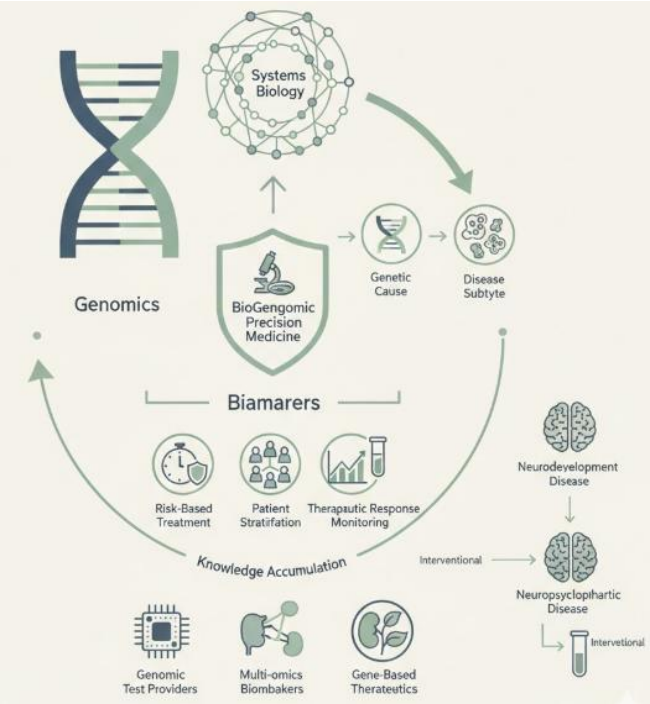


Fig 1: BioGenomic Precision Medicine: A Systems Biology Framework for Genotype-Stratified Therapeutics and Multi-Omic Disease Monitoring

II. FOUNDATIONS OF BIOGENOMIC PRECISION MEDICINE

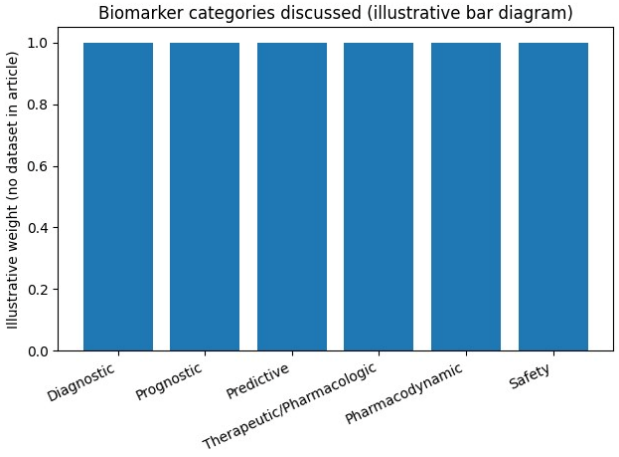
BioGenomic Precision Medicine rests on four pillars: (1) the bioethics of a systems biology approach, (2) an acceptance of scientific evidence of established reproductive potential, (3) the currently unparalleled capabilities of genomic technologies, and (4) the integration of available knowledge and technologies. The core statement is that clinical decisions based on BioGenomic Precision Medicine are more plausible, reproducible, and ethically acceptable when regulatory oversight is able to safeguard patients, healthcare workers, and society.

Bioethics demands a systems biology perspective, meaning that human health and disease must be considered not just in isolation but also in relation to the health and diseases of other organisms in the human ecosystem, be they pathogens or symbionts. The principlism that undergirds contemporary bioethics suggests that respect for the autonomy of persons, enhancement of their welfare, and consideration of justice, are appropriate for individual situations. The other three ethical approaches—utilitarianism, virtue ethics, and care ethics—demand also that broader concerns be considered as diseases affecting many persons have greater social costs. Such an ethical foundation does not oppose scientific research using induced pluripotent cells or organoids from humans. It does demand that the potential of such studies to yield substantial therapeutic benefits for many persons afflicted by disease is corroborated and that the possible risks to human or animal welfare or to the integrity of society are minimized.

A. Genomic Technologies and Data Integration

An array of sequencing platforms is available for Stanley et al.'s application in individualized BioGenomic Precision Medicine. Whole-genome, whole-exome, and transcriptome sequencing enable the identification of single nucleotide and structural variants, copy number variations, chromothripsis, and somatic mutations, as well as the detection of aberrant RNA splicing and fusion transcripts. Whole-methylome and mitochondrial genome sequencing, as well as large-scale methylome genotyping and quantitative measure of DNA methylation for candidate loci, help assess regulatory control. Beyond authentication of species, metabarcoding enables identification of multispecies microbial communities. Low-coverage shotgun sewage metagenomics further facilitates community profiling, followed by taxonomic annotation of lever-clustered assembled genomes to the species level. Bulk-tissue and single-cell RNA sequencing, or genome-wide assays of chromatin accessibility and histone modifications, assess transcriptome and epigenome landscapes. Mass spectrometry serves to quantify levels of proteins, peptidomes, and metabolites. Data from multimodal tissue imaging reveal spatial organization and in situ cell-properties.

Multi-omic data integration is paramount for generating more robust and functional conclusions than would be possible from individual datasets alone. Multi-omic profiling poses distinct integration challenges, and multiple approaches—ranging from canonical correlation analysis to artificial neural networks—are available to provide both fusion and alignment across modalities. Furthermore, standardized data formats and compatible bioinformatics pipelines enhance analysis of sequencing data originating from diverse laboratories, and a cloud-based infrastructure facilitates resource-sharing between research centres and hospitals while ensuring patient privacy and data-sharing consent.



Equation A) Polygenic Risk Score (PRS) equation (patient stratification)

Step 1 — Start from a risk model (logistic regression for case/control).
Let $Y \in \{0,1\}$ be disease status, and let G_i be the genotype for variant i coded as 0/1/2 risk alleles.

A standard model is:

$$\Pr(Y = 1 \mid G) = p, \qquad \text{logit}(p) = \ln\frac{p}{1-p}$$
$$= \alpha + \sum_{i=1}^{m} \beta_i G_i$$

Step 2 — Isolate the "genetic linear predictor."
Define:

$$\eta_G = \sum_{i=1}^{m} \beta_i G_i$$

Then:

$$\text{logit}(p) = \alpha + \eta_G$$

Step 3 — Define PRS as the genetic predictor.
That genetic component η_G is exactly the **polygenic risk score**:

$$\boxed{\text{PRS} = \sum_{i=1}^{m} \beta_i G_i}$$

Step 4 — Convert PRS into absolute risk (if needed).
From $\text{logit}(p) = \alpha + \text{PRS}$,

$$p = \frac{1}{1 + \exp\big(-(\alpha + \text{PRS})\big)}$$

Step 5 — Standardize PRS for interpretation across cohorts.
If PRS in the population has mean μ and SD σ, then:

$$\text{PRS}_z = \frac{\text{PRS} - \mu}{\sigma}$$

B. Biomarkers and Molecular Phenotyping

A broad range of biomarker categories is being implemented for BioGenomic Precision Medicine, including: diagnostic, prognostic, predictive, therapeutic (or pharmacological), pharmacodynamic, and safety biomarkers. These terms were defined in a 2001 consensus statement from the US National Institutes of Health and have been widely adopted. The standard reference for biomarker assay validation is the qualification framework of the critical path innovation meeting of the US Food and Drug Administration. An FDA qualification opinion indicates that a biomarker is well understood, demonstrates robust and reproducible assay performance when measured, and produces clinically meaningful results across a broad range of assays, populations, and settings.

Multiplex assay platforms, such as liquid chromatography–mass spectrometry, demonstrate high potential for BioGenomic Precision Medicine because they facilitate biomarker panels. These enable the molecular phenotyping central to precision medicine, providing rich datasets for drug development and clinical management. However, navigating the relationships between diverse assay datasets is challenging. Integration of transcriptomic, proteomic, and metabolomic data in the context of gene-function knowledge holds promise but requires careful consideration of phenotypic relevance and support for predictive uses. These issues have been illustrated for neurodegenerative diseases. In addition, evidence from psychiatric disorders (where genome-wide association studies have identified hundreds of common risk variants) must be integrated with knowledge of rare variants uncovered by high-coverage whole-exome sequencing. Ultimately, analysis of the full spectrum of genomic variation in well-characterised cohorts should enable a more integrated understanding of etiology, susceptibility, and clinical management.

Assay / platform (from paper)	Primary readouts (what it captures)
Whole-genome sequencing (WGS)	SNVs, structural variants, CNVs, chromothripsis, somatic mutations
Whole-exome sequencing (WES)	Protein-coding variants (SNVs/indels), some CNVs
Transcriptome (RNA-seq)	Aberrant splicing, fusion transcripts, expression changes

III. NEURO DISORDERS: GENOMIC INSIGHTS AND THERAPEUTIC STRATEGIES

Delving into genome-wide studies of neurodegenerative diseases reveals the most extensive catalogue of genetic risk factors known to date; thus, connecting them with pathogenic processes forms the basis of targeted therapies, all explored in the context of patient stratification for treatment allocation and therapeutic endpoints. Over the past decade, neurodevelopmental disorders have attracted tremendous interest because the underlying Mendelian genes are being discovered at an unprecedented level, the penetrance and expressivity of associated mutations determined, and genotype–phenotype correlations established. With these advances comes the prospect of precision interventions, most importantly with regard to prevention.

Causative genes for monogenic neurodegenerative diseases have been identified, and the exploration of gene-modulating strategies including RNA silencing, viral vector-based delivery of the antisense-transcript or protein, and gene-editing technology is underway. Among complex neurodegenerative disorders, functionally enriched polygenic risk scores have been developed and applied to cohort studies; risk-modifying genes, more penetrant mutations, and disease courses with excess cerebrospinal fluid pathology have also been discovered. For Alzheimer's disease, neurofibrillary changes have been proposed as a better precision endpoint than clinical stage. These genome-driven insights promise to transform the landscape of drug development and testing.

A. Neurodegenerative Diseases

Genes associated with neurodegenerative diseases have been validated as risk factors for pharmacological treatment. Therapies targeting amyloid-beta deposition are now tested in presymptomatic cases shown to have amyloid accumulation; similarly, anticontamination approaches in carriers of GBA mutations; and antisense oligonucleotides for SOD1 mutations—opening avenues for tailored interventions. Efforts are ongoing to classify patients according to protein-induced toxicity, aiming to recruit those exhibiting a distinct biomarker signature. Finally, polygenic risk scores linking neurodegeneration and synaptic processes may inform trial design.

Disease-modifying therapies for Alzheimer's disease and frontotemporal dementia target amyloid-beta and tau protein alterations and are being assessed in presymptomatic patients. In Huntington's disease, neurotoxicities from the mutant huntingtin protein are being addressed (e.g.

silencing); and SOD1 mutations in amyotrophic lateral sclerosis offer an additional opportunity for antisense oligonucleotide intervention. For spinocerebellar ataxias caused by polyglutamine expansion, PROTAC and other modalities to degrade the toxic protein are anticipated. Colocalisation of synaptic and neurodevelopmental genes supports a synaptic basis for neurodegeneration, and polygenic risk scores provide a statistical classifier independent of rare variants.

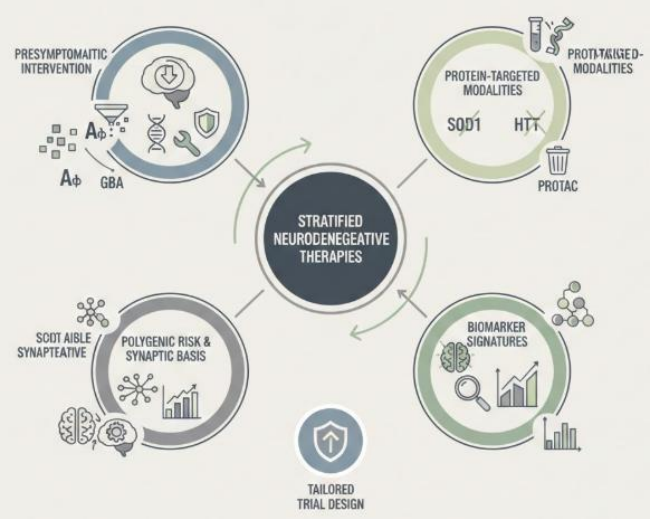


Fig 2: Genomic Stratification and Proteostatic Interventions: A Precision Framework for Presymptomatic Neurodegeneration

B. Neurodevelopmental and Psychiatric Conditions

Identified de novo mutations and rare sequence variants in neurodevelopmental and psychiatric disorders (neurodevelopmental and psychiatric conditions") represent the full range of protein-coding genome alterations with specific and clear-aided penetrance. These findings open new avenues for precise interventions in specific groups of patients at the critical period of life. The recent discovery of genetic factors associated with pato-genes in most of these disorders, high-metric correlation, the construction of large-scale risk associated with gene-sign readers and modulators, and further validation in cell functional services pave the way for potential neurodevelopmental and psychiatric genetic screening to predict the predisposition of specific individuals or cohorts toward a particular neurodevelopmental and psychiatric disorder. Moreover, the gene-phenotype correlation is also guiding adaptive interventions and stratified formulations. Specific Brain Biomedicine-Glial Cell Biomedicine-Psychometric with the Drug Based on Pathological Changes provides baseline support for intervention in the reproductive period.

Neurodevelopmental and psychiatric disorders are highly heterogeneous in presentation and development, showed by patients with episodes of de novo mutations, rare and low-frequency mutations due to recent introduction of large mutation burden, leading to disturbed intra- or extra-brain cellular and synaptic apparatus during the early neurodevelopmental stage, or the slowly accumulated genetic risk factors influenced by various risk contributors during the developmental or adult stage. Emerging evidence has demonstrated that these alterations can emerge from the full spectrum of protein-coding genome variations contributing positively or negatively. Nevertheless, their penetrance ranges from seldom to definitely causing the disorder, which thus offer both opportunities and challenges for diagnosis and possible intervention.

IV. KIDNEY DISORDERS: GENOMIC PERSPECTIVES AND PRECISION TREATMENTS

Genetic discoveries over the past two decades have highlighted the complexity of kidney disorders, paving the way for targeted therapies. Genomewide association studies (GWAS) have identified many genetic loci associated with complex kidney disorders, including chronic kidney disease and glomerular and tubular diseases. Even if the risk at each locus per se is not large enough for a specific prevention strategy, such accumulation of genetic predisposition may facilitate deterioration of kidney function. Those at high risk may also harbor unique kidney lesions that can be treated individually through their respective pathways. Such heterogeneity should be considered in the treatment strategy of these complex kidney disorders. Genes causing monogenic kidney diseases, especially in syndromic forms, have rapidly widened the pool of potential therapeutic targets, and genotype-specific treatment strategies have burgeoned. Modulators to compensate for dysfunctional gene products with no therapeutic options are coming into reach.

For monogenic kidney diseases, mutation-level information is necessary for effective precision medicine. Studies on modifying effects, either from supervised or unsupervised approaches, can complement the understanding of complex diseases and inform kidney care. Beyond establishing Risk Stratification and Treatment Access for Kidney Disease, an integrated bio-genomic approach targeting cross-organ connections can enhance clinical efficiency and treatment strategy for other organ systems.

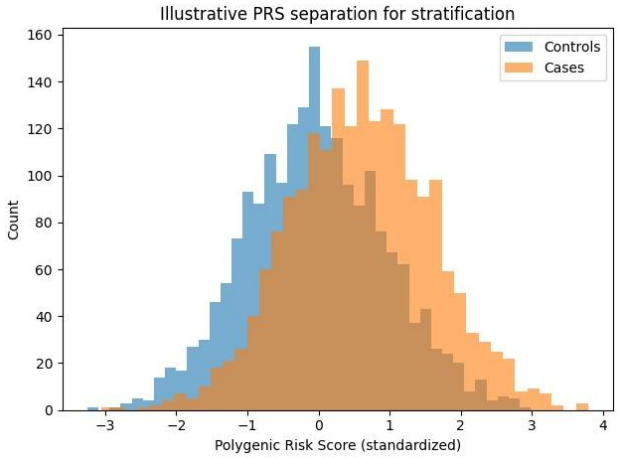
A. Monogenic Kidney Diseases

Monogenic Kidney Diseases: Causative Genes, Genotype-Phenotype Links, and Gene-Based Therapies or Modulation Approaches

Monogenic kidney diseases encompass Mendelian syndromes caused by mutations in single genes, each significantly affecting a specific protein, organelle, or cellular pathway while displaying substantial internal variability. Identified genetic defects have led to increasingly effective genotype-targeted therapies, particularly in syndromes like Alport syndrome. These syndromes also serve as critical models for unraveling distal segments of the renal tubular system, guiding clinical approaches for rare yet pathogenic alterations. The function of these pathways has been investigated using heterologous expression systems, animal models, and non-renal tissues, ultimately leading to targeted, non-gene replacement strategies.

Alport syndrome, characterized by frequent hematuria, progressive renal failure, sensorineural hearing loss, and ocular abnormalities, results from mutations in COL4A3, COL4A4, or COL4A5 encoding type IV collagen chains. Following pioneering studies demonstrating its nature as a monogenic recessive disease, utilizing all available therapeutic approaches for the 'classical' form of the disease, offers the unique challenge of developing specific and potentially curative treatments. Completion of transcatheter aortic valve-in-valve therapy in an elderly female patient with end-stage aortic stenosis, a challenging approach for complex

aortic anatomies and for patients at high risk for open-heart surgery, supports safety and feasibility.



Equation B) GWAS effect size → PRS weights (why β_i appears)

Step 1 — GWAS per-variant regression. For each SNP i, GWAS estimates an effect $\hat{\beta}_i$ from:

$$\text{logit}(p) = \alpha + \beta_i G_i + \gamma^\top C$$

where C are covariates (sex, ancestry PCs, etc.).

Step 2 — Likelihood for n independent subjects. Let $p_j = \Pr(Y_j = 1)$. Then logistic likelihood:

$$L(\beta_i) = \prod_{j=1}^{n} p_j^{Y_j} \left(1 - p_j\right)^{1-Y_j}$$

Step 3 — Log-likelihood.

$$\ell(\beta_i) = \sum_{j=1}^{n} \left[Y_j \ln p_j + \left(1 - Y_j\right) \ln\left(1 - p_j\right)\right]$$

Step 4 — MLE yields $\hat{\beta}_i$.
Numerical optimization (Newton–Raphson / IRLS) solves:

$$\frac{\partial \ell}{\partial \beta_i} = 0$$

and returns $\hat{\beta}_i$, which becomes the PRS weight in:

$$\text{PRS} = \sum_i \hat{\beta}_i \, G_i$$

Step 5 — Relation to odds ratio (OR).
For a one-allele increase in G_i,

$$\text{OR}_i = \exp(\beta_i) \quad \Rightarrow \quad \beta_i = \ln(\text{OR}_i)$$

B. Complex Glomerular and Tubular Disorders

A polygenic component contributes to the risk for several glomerulopathies and tubulopathies, and there is potential for modifier effects acting on Mendelian disorders within these organ systems. Future studies integrating genome-wide association data with functional analyses of risk variants could help identify potential new pharmacological targets for complex kidney diseases. Such targets may also provide candidate pathways for therapeutic modulation of monogenic glomerular and tubular disorders, opening the possibility of personalized intervention strategies. Collaboration between specialists equipped to assess genomic variation in these kidney disorders will facilitate a tailored clinical approach.

Investigations of the genetic architecture of syndromes affecting renal tubules and glomeruli have revealed that, in addition to the known bona fide Mendelian causes, a polygenic component also contributes to severity and susceptibility. This polygenic risk may, in some instances, influence the expressivity of monogenic causes. It is anticipated that the integration of genome-wide association study results with appropriate functional analyses will aid the identification of novel pharmacological targets. Such targets may also facilitate candidate-gene approaches for therapeutic modulation of complex kidney diseases.

V. INTEGRATED BIOGENOMIC APPROACHES IN NEURO-KIDNEY SYNDROMES

Neuro-Kidney Syndromes are genetically diverse multisystemic diseases characterized by neuronal and kidney dysfunction due to alterations in development, maintenance, and/or training of excitation-inhibition balance, nutrient homeostasis, and/or immune response. Pathogenic mutations share common key signaling pathways and networks, including calcium and immune response pathways. Recent studies identified specific molecular variants, which, associated with neurodevelopmental or psychiatric disorders, have been proposed as biomarkers of risk for the development of renal diseases. For some, biomarkers of specific categories of disorders and their possible consequences in other organs, including the kidney, have been identified. A panel of neurodevelopmental and psychiatric biomarkers is underway to validate possible consequences in the kidney.

Insights into the genetic architecture of neurodevelopmental and psychiatric disorders offer exciting prospects for the identification of disease-modifier variants that can guide individual treatment selection. Expanding genetically guided kidney therapeutic approaches into neurodevelopmental and psychiatric disorders is an attractive option that requires further investigation. These two-way translation avenues can facilitate the development of a clinical panel encompassing pathology-associated biomarkers with neurodevelopmental, neuropsychiatric, and kidney-relevant implications. The integration of proof-of-concept experimental evidence holds the potential to establish an ad hoc clinical panel to support decision-making in different specialties.

A. Shared Molecular Pathways

A degenerative neurological disorder might be caused by defective neurotransmission in the circuits that're directly involved in the modulation of renal homeostasis. Alternatively, alterations in renal function could influence signaling processing within the central nervous system, ultimately leading to neurodegenerative manifestations. Certainly, there exist well-documented neuro–kidney axes, since the kidney is responsive to circulating factors produced in the brain that influence renal vascular resistance, sodium balance and homeostasis, and blood pressure. The full extent of the cross-talk has yet to be systematically explored, given the complexity of the kidney and nervous system and the

various contributing and associated factors.

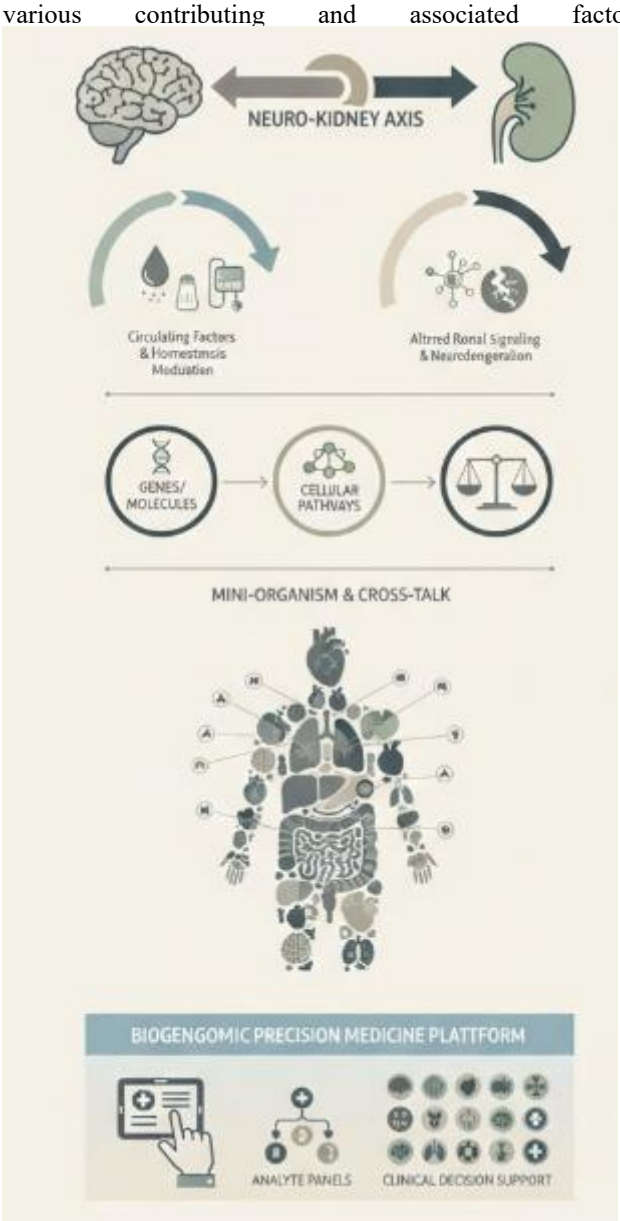


Fig 3: Deciphering the Neuro–Kidney Axis: A Biogenomic Precision Medicine Framework for Systemic Cross-Talk and Multi-Organ Clinical Decision Support

Determining whether the same genes, molecules or cellular pathways in different organs exert similar or inverse effects in terms of complex diseases would facilitate the prediction of risks, chances and outcomes on a person-to-person basis. In fact, it would be even more appropriate to consider every individual as a mini–organism, connected to others primarily by blood circulation, and whichever biomolecules are present in blood can be considered additional signals for the numerous peripheral organs, including the other organ responses. This form of connection can be strengthened with a panel of analytes that are reflectively present in the biological fluids of every organ involved in specific conditions; on the contrary, a panel with at least one candidate per organ for which the expression is reflective only in that organ and the pathophysiological function is known would not possess the broader communicative nature over an organism. Tailoring the BioGenomic Precision Medicine approach to these considerations could serve as an additional platform for clinical decisions across different fields of medicine.

B. Cross-Dpecialty Biomarker Panels

Cross-disciplinary biomarker panels. Multi-omic science has revealed individual and milieu-specific alterations of multiple systems, including neurodevelopmental, neurodegenerative, kidney, muscular, and immune systems, in diverse multi-system disorders. Therefore, evidence-based integrated panels of molecular biomarkers with cross-disciplinary significance could facilitate early diagnosis, predict disease severity, optimize treatment options, and evaluate prognosis and treatment response. The results of individual analyses can be synthesized to predict risks of diseases affecting other systems, supporting referrals to cross-specialty clinics and timely monitoring.

Standardized reference panels of genes/pathways implicated in neuro and kidney pathology across disorders would enhance personalized medicine approaches. Neuro/kidney multi-omics datasets can define “organdominant” pathways whose alterations accelerate damages in other systems. For instance, the activation of kidney-accelerating pathways in patients with Alzheimer disease may modify its clinical profile and could therefore be included in the secondary monitoring protocol. A gene expression signature for systemic lupus erythematosus has demonstrated biological relevance in kidney and central nervous system diseases and validated predictive value for disease onset and progression. Consequently, future multi-omics studies of both early-onset and late-onset neuro/kidney disorders, such as Alzheimer disease or kidney cancer, should implement the proposed strategy in order to develop multi-omic biomarker panels with organ-crossing significance that support individual outcomes and clinical decision-making strategies.

VI. CLINICAL TRANSLATION AND IMPLEMENTATION

Beyond BioGenomic Precision Medicine discovery, e.g., novel or expanded biomarkers and therapeutic targets, new knowledge must adequately comply with the translational framework bootstrapped by international collaborative consortia that currently facilitate healthcare delivery. A prudent approach is to identify and emphasize specific components of implementation. Healthcare infrastructure that promotes the integration of new knowledge and clinical translation and implementation data governance that stewards collection, maintenance, and sharing of multi-omic data are at least as fundamental as the discoveries themselves.

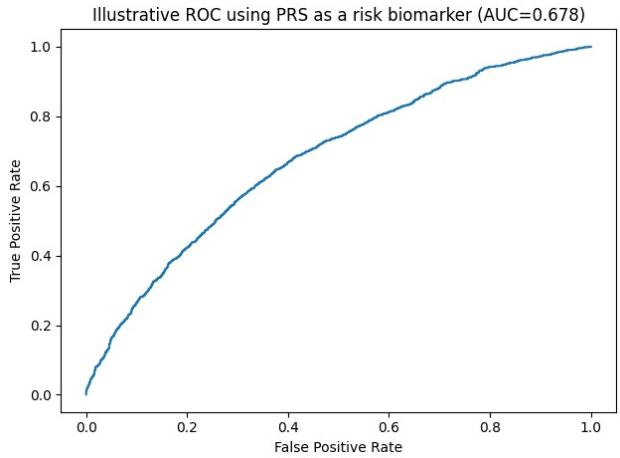
Sequencing studies generate vast, discordant datasets posing challenges to their design and management. To ameliorate these difficulties, the genomics community is adopting Fair principles: making data Findable, Accessible, Interoperable, and Reusable for a wider range of users. Rigorous attention to Data Governance, ensuring appropriate collection, maintenance, and sharing of patient data, together with processing pipelines, will not only support detection of CNS and urinary tract pathologies, but also empower the application of previously established techniques in other specialties, with consequent gains for clinical decision support systems.

A. Healthcare Infrastructure and Data Governance

BioGenomic Precision Medicine in Neuro and Kidney Disorders: present a concise scholarly abstract-oriented overview with an objective tone, outlining aims, methods, and key implications; emphasize evidence-based framing and formal structure.

Implementing the outlined BioGenomic Precision Medicine concepts requires advances at the healthcare and clinical trial levels. Integrated healthcare encompassing these new approaches demands improved infrastructure. Well-functioning, well-governed local and international healthcare systems are not only required to handle the ever-growing amount of data produced and to support BioGenomic Precision Medicine through clinical studies but also to contribute to a broad cohort effect that will eventually benefit every patient.

Although cross-institution, cross-nation, or cross-continent cooperation across healthcare systems is key to large cohort studies involving a large number of patients with rare diseases, the actual data collected for these studies can only be generated distally in the local healthcare centers. The need for the data collected for a special purpose to also be of use for surrounding healthcare systems and for BioGenomic Precision Medicine applications beyond that special purpose is therefore paramount. Well-structured and well-governed healthcare systems and their interconnectivity are critical for ensuring that healthcare will not focus its efforts into a single and well-defined BioGenomic Precision Medicine pathway but will remain a vast open road for all forms of precision medicine. Such a system can boost discovery beyond BioGenomic Precision Medicine to create a healthcare system that enriches every patient's experience.



Equation C) Biomarker evaluation equations (sensitivity/specificity → PPV/NPV)

Let:

- Sensitivity $Se = \Pr(T = 1 \mid D = 1)$
- Specificity $Sp = \Pr(T = 0 \mid D = 0)$
- Prevalence $\pi = \Pr(D = 1)$

Step 1 — Write PPV by Bayes' theorem.

$$\mathrm{PPV} = \Pr(D = 1 \mid T = 1) = \frac{\Pr(T = 1 \mid D = 1)\Pr(D = 1)}{\Pr(T = 1)}$$

Step 2 — Expand $\Pr(T = 1)$ using total probability.

$$\Pr(T = 1) = \Pr(T = 1 \mid D = 1)\Pr(D = 1) + \Pr(T = 1 \mid D = 0)\Pr(D = 0)$$

But $\Pr(T = 1 \mid D = 0) = 1 - Sp$ and $\Pr(D = 0) = 1 - \pi$. So:

$$\Pr(T = 1) = Se \cdot \pi + (1 - Sp) \cdot (1 - \pi)$$

Step 3 — Substitute back to get PPV.

$$\boxed{\mathrm{PPV} = \frac{Se \cdot \pi}{Se \cdot \pi + (1 - Sp) \cdot (1 - \pi)}}$$

Step 4 — Similarly derive NPV.

$$\mathrm{NPV} = \Pr(D = 0 \mid T = 0) = \frac{Sp \cdot (1 - \pi)}{Sp \cdot (1 - \pi) + (1 - Se) \cdot \pi}$$

B. Clinical Trial Design for Genomic Therapies

Clinical trials underpin genomic discoveries, yet require distinctive adaptations. Therapeutics targeting neuro and kidney disorders can feasibly revert, stabilize, or mitigate disease in specific cohorts defined by mutation type, penetrance, or organ activity. Comprehensive effect-size estimation has thus far achieved clinical translation for only a subset of genetically induced neuro and kidney diseases. Malformation-causing mutations supplied rich interventional insight in rare conditions, but applying similar principles is impractical in common sporadic disorders, more amenable to prevention via polygenic risk evaluation. Research involving multilocus assessments, pathogenicity-clarifying functional assays, and multispecialty management can facilitate therapeutic stratification, including adverse-modifier curation.

Therapeutic-approval design for genomic therapy requires newly identified genetic causes, ideal subcohort-matching selection, genotype–phenotype correspondence, relevant primary and secondary biomarkers, synthetic-lethal networks, signal-transduction inhibition and modulation, and translational-consideration connections. Precision endpoints optimized for well-powered studies promote treatment consistency and regulatory acceptance. As these requirements emerge, opportunities to incorporate gene-modifying or -reparative agents into onco-syndrome frameworks multiply.

Biomarker category	Illustrative weight
Diagnostic	1
Prognostic	1
Predictive	1
Therapeutic/Pharmacologic	1
Pharmacodynamic	1
Safety	1

VII. CONCLUSION

The work presents an overview of BioGenomic Precision Medicine, a novel concept that aims to optimize patient care by considering disease and treatment biomarkers yielded by

genomics technology. Information gleaned from whole-genome or whole-exome sequencing of patients plays a critical role in guiding precision medicine strategies for various diseases, particularly neuro and kidney disorders.

Evidence is accumulating on the potential of genetic insights to classify patients and direct decisions for preventive, lifestyle, therapeutic, and medical interventions. Patient stratification significantly enhances the prediction of drug response and treatment endpoints. Despite these advances, scaling genomics for BioGenomic Precision Medicine remains challenging. Genomic and associated data must be managed as open public goods; AI and cloud innovations enable new discoveries for binding targets and precision medicines. Testing hypotheses on genetically altered model systems is crucial, yet gene-based and drug-modulating strategies are also viable. Accelerated developments in BioGenomic Precision Medicine are warranted for neuro degenerative diseases, kidney disorders, syndromic conditions, and other heritable diseases for which treatment endpoints are determined by renal failure or geological state.

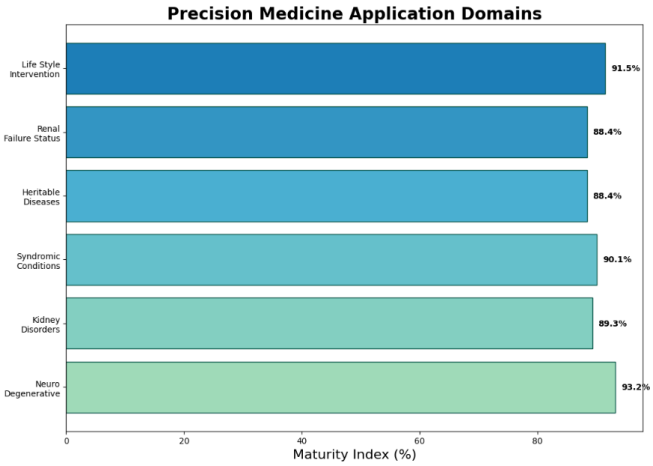


Fig 4: Precision Medicine Application Domains

A. Summary of Findings and Future Directions

Evidence from genomic technologies and analyses of rare variants has cataloged pathogenic genes and elucidated biological mechanisms for a range of neuro and kidney disorders. These developments have informed molecularly targeted therapies, enabling RNA- or DNA-based gene correction, protein replacement, and specific pharmacological modulation of disorder-associated pathways in animal models or patients. A corollary effect on clinical trial design has been the increasing relevance of genetic information in endophenotype stratification, therapeutic response prediction, clinical trial success prediction, and prospective ethics.

Advancing therapeutic development and implementation requires prioritization of available enabling evidence. In addition to facilitating targeted treatments in specific well-defined disorders, genomic-region-centered approaches may also provide a basis for stratified therapies in broadly-defined indications, such as those using anti-amyloid and anti-synuclein agents in Alzheimer disease. Future research efforts should also focus on populating polygenic risk-associated neurodevelopmental and psychiatric loci with penetrating variants supported by functional assays. These advances would subsequently enable a second wave of targeted therapeutic development in these disorders, aimed at reversing excess risk rather than restoring normal function. Beyond the identification of therapeutic options, the intellectual-sequence-principle should be applied to rapidly and comprehensively evaluate adaptive-trial-operational implications.

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