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Leveraging PCORnet® to Advance Clinical Genetics and the Genomic Learning Health System

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Background: Scientific advances and cost efficiencies in genetics and genomics are expanding clinical application for prevention, diagnosis, and treatment.

Objective: PCORnet®, a research network that includes participation from 78 health systems nationally and is linked to more than 47 million unique patients with at least one encounter annually, can help (1) understand the ability of genetics/genomics to predict health outcomes, (2) identify diseases impacted by genetic/genomic factors, (3) evaluate pharmacogenomics' role in medication optimization, (4) evaluate emerging gene therapies, and (5) compare clinical genetic or genomic strategies within learning health systems to improve outcomes, while (6) facilitating patient and other partner engagement across these areas.

Main Arguments: The breadth of data accessible via PCORnet represents a unique opportunity to study relationships among genetic markers and clinical and exposome-based disease risk factors, particularly as more genomic data become available. The network's experience developing computable phenotypes for identifying specific diseases can be leveraged to evaluate the role of genetics/genomics in health. The PCORnet infrastructure can be used to identify patients with particular conditions for predictive modeling or comparative clinical effectiveness research using electronic health record data. The network can also recruit patients for observational cohorts or pragmatic clinical trials on pharmacogenomics or the return of genetic results, evaluation of emerging gene therapies, or embedded research into learning health systems to compare clinical genetics/genomics implementation approaches in health care. The partner engagement focus of the PCORnet® Network Partners can enrich research and improve health care delivery and outcomes. The rise of clinical genetics and genomics will profoundly impact health care in the next decade, and the PCORnet® Network Partners are primed to make a leading contribution in this area.

Key Words: genetics, genomics, comparative clinical effectiveness research, real-world evidence research, PCORnet

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A rapid increase in the relevance of genomics to patient care and a marked reduction in genetic testing costs have significantly expanded the use of clinical genetics for prevention, diagnosis, and targeted treatment.[1–5] Recent National Institutes of Health (NIH) initiatives have been studying new applications of clinical genomics and corresponding implementation strategies to increase patient and provider acceptability and uptake,[6] with initial results indicating a need to further study the role of both clinical

genomics (the study of a person's complete set of genes) and clinical genetics (the study of specific genes and their roles in inherited conditions)[7] for preventive care and individualized treatment strategies. For example, the Electronic Medical Records and Genomics (eMERGE) network[8] is investigating the use of genomic integrated risk assessments, combining polygenic risk scores, monogenic risk assessments, family history, and clinical data to predict an individual's risk for 11 common diseases.[9] The NIH Implementing Genomics in Practice (IGNITE) Network is supporting pragmatic clinical trials to study kidney disease risk and pharmacogenomics in different populations.[10–14] Most recently, the NIH has launched the Genomics-Enabled Learning Health System (gLHS) network to support the study of implementing genomics in routine clinical care.[15] The Patient-Centered Outcomes Research Institute® (PCORI®) has also contributed to this research base, including through comprehensive systematic reviews surveying available evidence on the use of genomic sequencing in cancer management[16] and gene therapies.[17]

PCORnet, a national research network supported by PCORI, engages 78 US health systems and is linked to longitudinal electronic health record (EHR) data on more than 47 million unique patients with at least one encounter in 2023 and a total of over 100 million patients with encounters over the past 15 years. PCORnet is funded by PCORI to support patient-centered research, including comparative clinical effectiveness research and pragmatic clinical research.[18,19] The network has a history of collaborating with researchers across the country with funding from the NIH, Centers for Disease Control and Prevention, PCORI, and others to conduct real-world data studies (eg, the PCORI ADAPTABLE study and the NIH PREVENTABLE study) that are national in scope. The PCORnet infrastructure is well suited to facilitate patient-centered research conducted by a wide range of academic and clinical scientists, where clinical genomics and clinical genetics either are the primary focus of the research or are relevant to understanding and improving multiple aspects of health and health care delivery.

OBJECTIVE

The broad and innovative PCORnet network is primed to help with: (1) understanding the potential of genetics/genomics information for predicting health outcomes; (2) identifying genetic diseases and diseases impacted by genomic factors; (3) evaluating pharmacogenomics' role to optimize medication treatments; (4) evaluating the emergence of gene therapies; and (5) comparing strategies of applying clinical genetics/genomics in learning health systems (LHS) to improve health outcomes, while (6) facilitating patient and other partner engagement in each of these areas. The focus on partner engagement in PCORnet helps ensure that the voices and experiences of patients, families, clinicians, health systems, researchers, funders, and other key partners are integrated into all PCORnet research, dissemination, and implementation. Engaging partners allows researchers to address important issues related to patient-centered value, data privacy, data confidentiality, ethics, scalability, and other areas. This article provides examples of existing work using PCORnet in genetics/genomics and discusses opportunities and challenges for leveraging PCORnet in multiple ways for future research in this area.

MAIN ARGUMENTS

Understanding the Potential of Genetics/Genomics Information for Predicting Health Outcomes

The breadth of data accessible via PCORnet across the United States represents a unique opportunity to study relationships among genetic, clinical, and exposome-based risk factors for disease, particularly as more discrete genetic data become available within the EHR and linked data sources. Currently, there are 78 health systems participating in PCORnet that have standardized their data to the PCORnet® Common Data Model (CDM)[20] (see Table 1 for key CDM variable categories). Data from sites participating in PCORnet undergo a quarterly refresh and data characterization to promote data quality undergo a quarterly refresh and data characterization to promote data quality. With appropriate regulatory approvals, CDM data can be linked to more comprehensive EHR data at each participating health system. With regulatory approvals, local health systems can evaluate unstructured EHR data using natural language processing, incorporate scanned reports (with optical imaging), and access other local EHR data that are often unavailable in national data sources. In addition, with regulatory approvals, data available through PCORnet can be linked to other data sources, including disease registries,[21] claims data,[22] geocoded data on environmental and social factors,[23] and other types of data.[24]

Data across the network can be evaluated through a distributed analytic model, a federated data model, or pooling data to a central enclave. This has the potential to allow for robust analyses to evaluate the relationship between genomic markers and health outcomes, with adjustment for many potential covariates. The large size and diversity of data accessible via PCORnet, with 47 million unique patients seen in the past year across many different types of health systems nationwide,[19] provide an important, unique, and heterogeneous sample for analysis, with great potential for understanding the ability of genetics/genomics to predict health outcomes.

A major challenge to examining the relationship between clinical genetics/genomics and health outcomes using PCORnet is the lack of robust, standardized genomic information.[25] While genetic testing is increasingly incorporated into patient care, informatics solutions for integrating these tests into the EHR have not kept pace.[25] Ideally, genetic test results would be stored in a searchable, standardized format and seamlessly shared across systems, much like other laboratory test results.[26] These tests could then be standardized into the PCORnet®

TABLE 1. PCORnet® Common Data Model (https://pcornet.org/data/common-data-model/)

Current standard CDM elements across all sites	Evolving CDM elements with variable accessibility
Demographics and geocoding of patient addresses	Clinical observations (eg, pulmonary function tests, immunizations, echocardiology results)
Vital Signs (eg, weight, height, blood pressure)	Local tumor registry data
Diagnoses (eg, ICD codes)	Patient-reported outcomes and patient-generated health data
Procedures (eg, CPT/HCPCS and ICD)	Social determinants of health
Medications (ordered, administered, patient-reported, and some dispensing)	Genomic or clinical genetic data
Laboratory results	Unstructured data (extracted with NLP, ML/AI)
Encounter and provider details	Linked claims data or other exposome data

CDM, similar to how LOINC codes are used to incorporate common lab tests.[27] However, in practice, the genetic test results are often stored in the EHR as scanned, nonmachine-readable documents.[28,29] The lack of structured, standardized data limits the possibility of using PCORnet to track trends in clinical genetic testing, identify inefficiencies, and repurpose data for research on rare genetic variants and diseases. Future efforts should focus on expanding the availability of standardized genetic information in the EHR and data warehouses and improving linkage with genetic testing companies to access their electronic genetic data.

Identifying Genetic Diseases and Diseases Impacted by Genomic Factors

The PCORnet® Network Partners have a long history of developing computable phenotypes for identifying both common and rare diseases that can be leveraged for evaluating the role of genetics and genomics in these conditions.[27,30–32] The PCORnet infrastructure can be used to identify patients with specific conditions both for secondary data studies and for contact and cohort/trial enrollment. Studies using PCORnet data infrastructure have identified study cohorts with hypertension, diabetes, neuroendocrine tumors, congenital heart disease, sickle cell anemia, pediatric kidney diseases, and other conditions.[18,19] The PCORnet infrastructure allows for EHR linkage for chart review to more thoroughly evaluate computable phenotypes' positive predictive value. Many sites have opt-out recruitment approaches, facilitating the electronic identification of particular conditions, followed by direct contact for potential recruitment. The network's large size is especially helpful in studying rare diseases with genetic components, including those requiring genomic analyses. Rare disease investigation is a current emphasis for PCORI and the PCORnet® Network Partners. The network can support comparative clinical effectiveness research focused on comparing different diagnosis or treatment approaches to specific rare diseases or genetic conditions.

Major challenges to identifying diseases with genetic or genomic components using PCORnet include heterogeneity in how genomic results are returned to the EHR and integrated into disease registries. When necessary, the PCORnet infrastructure can potentially be used to link in results from genomic testing vendors or disease registries, but this increases technical complexity and costs. Institutional governance barriers may also hinder linking data available through PCORnet with disease-centric centers controlling access to some registries and genomic test results. Collaboration between a variety of researchers and PCORnet® Network Partners is a powerful tool to address these issues and expand access to standardized data.

Evaluating the Role of Pharmacogenomics to Optimize Medication Treatments

Although pharmacogenomics is increasingly used to guide medication therapy[21] and the potential patient benefit of knowledge about gene–drug interactions is clear, significant evidence and implementation gaps remain.[33,34] Despite promising indications regarding patient benefit, few studies have investigated pharmacogenomics' role in improving patient-centered outcomes versus usual care.[34] In this area, PCORnet can be used to conduct comparative clinical effectiveness research using existing EHR data and to perform pragmatic clinical trials.

PCORI has funded a small number of initiatives on the role of pharmacogenomics in medication optimization, and there is enormous potential for further PCORnet contributions. For example, the complexity of pharmacogenetics makes effectively communicating results to patients and physicians challenging, and PCORnet could be used for comparative clinical effectiveness trials of different communication approaches to understand optimal approaches to improving patient understanding and consequent results for health outcomes. Secondly, variability in pharmacogenomic data across populations requires large, diverse cohorts such as those seen in PCORnet to ensure generalizability. Third, pharmacogenetic interventions are primarily relevant with initial drug exposure, which requires specific timing relative to prescription; this can be optimized with PCORnet. Finally, the impact of the interplay of genomic, genetic, pharmacokinetic or pharmacodynamic, environmental, and lifestyle factors on drug response suggests pharmacogenomic interventions should be integrated with other risks, which is enabled by the expanding availability of multiple covariates, including many socioecological factors, in the PCORnet® CDM.

Evaluating the Emergence of Gene Therapies

PCORnet can be used to evaluate the role of gene

therapies as they become part of usual care. A recent PCORnet query identified over 10,000 instances of gene therapy use at one of 72 responding health systems from January 2016 through June 2024. Over 60% of use appeared to be for cancer. The most common cancer therapies were axicabtagene ciloleucel (relapsed or refractory large B-cell lymphoma, n = 2797) and tisagenlecleucel (refractory B-cell precursor acute lymphoblastic leukemia, n = 1062). The most common noncancer therapies were nusinersen (n = 2082) and onasemnogene abeparvovec (n = 277) for spinal muscular atrophy, and vutrisiran (n = 485) and patisiran (n = 478) for hereditary transthyretin-mediated amyloidosis.[35] With increasing approvals for gene therapies in recent years, these numbers will likely grow. Notably, many sites participating in PCORnet have successfully integrated North American Association of Central Cancer Registries tumor registry data to support cancer research, which improves the ability to confirm cancer diagnoses and provides other information useful to researchers.

Small sample size for certain emerging gene therapies is a substantial challenge, and accruing sufficient numbers for conclusive studies may take some time. Another challenge, specific to cancer research, is that existing registries tend to be weak in identifying treatment resistance/recurrence, which may pose challenges to studying treatments for refractory/relapsed cancer. Chart review, which is possible by PCORnet® Network Partners, may be beneficial for capturing staging/severity at initiation of these treatments.

Comparing Strategies of Clinical Genetics and Genomics in the LHS to Improve Health Outcomes

Learning health systems systematically integrate internal data and experience with external evidence and put that knowledge into practice.[36] Without implementation science and an LHS approach, genetic and genomic discoveries may fail to be translated into practice for improved patient and population health.[37] PCORnet, in alliance with the PCORI/Agency for Healthcare Research and Quality (AHRQ)-funded Learning Health System Embedded Scientist Training and Research (LHS E-STaR) Centers,[38] the PCORI Health Systems Implementation Initiative (HSII),[39] and the NIH-funded gLHS network, offers the opportunity to embed comparative effectiveness and implementation research directly into health systems to advance clinical genetics and genomics. The gLHS network "aims to identify and advance approaches for integrating genomic information into existing learning health systems" and to translate genomic evidence "quickly and directly into improvements in medical care," with specific attention to under-resourced settings.[40] All 3 of these programs include sites participating in PCORnet and present exciting opportunities for collaboration both within and outside core networks. For example, the gLHS network is developing a series of implementation studies to close the evidence–practice gaps in the clinical use of genetic testing. The initial projects focus on the lack of guideline-recommended genetic testing to detect hereditary syndromes among patients with cardiomyopathy or certain cancers. As the network selects implementation strategies to increase genetic testing, there is specific attention to gathering input from partners outside the core sites that have less mature genetic testing and return infrastructure or that serve different populations of patients. This collaborative engagement is expected to result in implementation guides and protocols that will be broadly applicable and adaptable to a range of clinical settings.

Focusing on Partner Engagement in Clinical Genetics/Genomics Research

Clinical genetics/genomics research should engage patients and other community members, health care providers, health system leaders, researchers, disease-focused organizations, payers, and other partners at all stages—from idea generation to study implementation to evaluation and dissemination/implementation. The need for partner engagement is relevant for each of the topics outlined above concerning genetics/genomics research. A wide range of research partners (ie, clinicians, patients and patient advocates, payers, and policymakers) have raised concerns regarding the potential for suboptimal delivery of clinical genetics/genomics as the field continues to grow, with underserved and rural patient populations being less likely to benefit from these emerging technologies.[16] Engagement of a broad array of partners is crucial to empower communities and build (or rebuild) trust, encourage clinician uptake of genetics/genomics approaches, and identify system-level approaches for intervention and scalability.[41,42] Meaningful partner engagement in genetics/genomics research also helps ensure patient value, data privacy, and ethical practice.[40,43,44]

The engagement of a broad array of partners is a cornerstone of PCORI-funded research. Foundational expectations for partnership include broad representation, early and ongoing engagement, appropriately funding engagement and partner compensation, building capacity for engagement, including partners in decision-making, and continually reviewing engagement policies and practices.[45] Over the last decade, PCORI has demonstrated sustained commitment to engagement in clinical genomics, funding several initiatives to build coalitions to advance the field, as well as studies focusing on partner engagement to improve the patient relevance and optimal delivery of care in clinical genomics. The high standards for engagement of the PCORnet® Network Partners are reflected in mechanisms throughout the network to ensure meaningful engagement[46] and have been well documented.[47–50]

CONCLUSION

PCORnet is a uniquely useful resource for investigators engaged in health and health care research. Areas where PCORnet is particularly valuable for patient-centered advancements in clinical genetics and clinical genomics include understanding the ability of genetics/

genomics to predict health outcomes, identifying genetic diseases and diseases impacted by genomic factors, evaluating the role of pharmacogenomics to optimize medication treatments, evaluating the emergence of gene therapies, comparing strategies of clinical genetics and genomics in the LHS to improve health outcomes, and focusing on partner engagement to ensure the inclusion of many different voices in clinical genetics/genomics research.

The potential contributions of the PCORnet infrastructure to comparative clinical effectiveness research, including randomized controlled trials examining meaningful patient health outcomes, which are still rare in clinical genetics/genomics research,[16] present particularly exciting opportunities. Over the next year, sites participating in PCORnet should expand efforts to run data queries to characterize genetic conditions, genetic tests, and genetic treatments and develop specific research priorities in this field. Further work is needed to more consistently incorporate genomic test results into structured data and the PCORnet® CDM and improve the efficiency of this research.

Researchers active in this and associated fields, whether focusing on clinical genetics/genomics or incorporating related information to address broader questions in health services or clinical research, can benefit greatly from the resources available through PCORnet. Research can be advanced by PCORnet® Network Partner engagement with clinical genetics/genomics experts and researchers as well as organizations representing patients and families affected by conditions that are inherited or for which genetic or genomic testing could strongly influence diagnostic and treatment decisions. We hope this article will serve, in part, as an invitation to these groups to increasingly engage in meaningful collaborations with PCORnet® Network Partners to enhance understanding of the multifaceted influence of genetics and genomics on health and health care on a national scale. The rapid rise of clinical genomics will have a profound impact on health care over the next decade, and PCORnet will be invaluable in optimizing related improvements to individual and population health.

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