

CORRESPONDENCE



The post-diagnostics world: charting a path for pediatric genomic medicine in the twenty-first century

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Pediatric Research (2023) 93:457–459; <https://doi.org/10.1038/s41390-022-02144-2>

Genomic sequencing technologies, in particular next-generation sequencing (NGS), have transformed the pathway to diagnosis. Less than a decade ago, fewer than a third of patients with presumed monogenic genetic disorders were diagnosed, with many patients and families experiencing a “diagnostic odyssey” of prolonged clinical testing. Advances in DNA sequencing technology and bioinformatics, with clinical adoption of exome and genome sequencing as primary diagnostic tools, have led to a marked increase in diagnosis rates and new treatment opportunities for patients with diseases ranging from suspected genetic disorders to cancer. Diagnoses are now made in days to weeks instead of months to years. Genomic medicine, the use of genomic results to inform diagnosis, care, and treatment, is increasingly a clinical reality.

Nowhere is this adoption of genomic medicine more profoundly occurring than in pediatrics. Of the estimated ~7,500+ genetic disorders, the majority present in childhood, and the burden of pediatric hospitalizations are in children with complex diseases and in particular those with genetic disorders.¹ Genomic testing is used not only for diagnosis in monogenic disorders but also in determining treatment decisions in oncology² or in unraveling susceptibility for complex traits.³ In pediatrics, determining genetic etiology is key for diagnosis, which in turn drives clinical decision-making, management, treatment, family counseling, and outcomes. A rapid diagnosis takes on additional importance because some diseases can have precipitous decline; and for those disorders with treatment opportunity, early intervention is often essential for success of the therapy. These increases in diagnoses are providing biological insights into different phenotypes that have the same genetic cause; or conversely how single clinical disorders can be caused by different gene variants. Even for conditions where the contribution of genetics has been historically underemphasized, for example, infectious diseases, insights from genetic results can provide important insights. For example, for COVID-19, a genomic haplotype at chromosome 3p indicates high risk for respiratory involvement.⁴

The advances in early and rapid diagnosis are paralleled by accelerations in therapy development and delivery. These changes in clinical opportunity range from targeted treatment of genetic epilepsy variants (pyridoxine for *ALDH7* mutations); new drug development (mutation-specific CFTR modulators); viral gene replacement therapy (spinal muscular atrophy); and surveillance, cascade family testing, and immediate treatment in cancers (such as Li–Fraumeni syndrome).

These changes in diagnostic capability signal an inflection point for pediatric medicine, representing an opportunity for a “post-diagnostics” world. If the capability to rapidly, efficiently, and

equitably achieve a diagnosis is fully realized, this would be a paradigmatic shift. Diagnosis would become a standard first step—similar to the way vital signs are tested for a patient at their clinic visit. However, at this juncture, four major challenges, and how the field navigates them, will determine the success of this new era and will help define the future of pediatric medicine.

DIAGNOSTIC CEILING

Even with use of genome sequencing, diagnostic rates can be as low as 20–40%.^{5–7} Some molecular aspects contributing to the diagnostic ceiling are understood although not solved, including pleiotropy, variable disease penetrance, oligogenic and complex traits,⁸ and roles of epigenetic modifiers. There is still significant opportunity for advances in testing modalities. New approaches will need to consider yields of sequencing technologies, such as long-read sequencing, pairing DNA sequencing with RNA expression evaluation, and understanding disease-causal variants in non-coding regions of the genome (i.e., pathogenic variants in regulatory regions). Long-read sequencing can help resolve difficult-to-sequence regions and difficult-to-call variants (e.g., structural variants not detectable by short-read sequencing or microarrays), while RNA sequencing expands the “interpretable” genome space to intronic and non-coding regions. Furthermore, the potential for disease-causal variants in non-coding RNAs or synonymous variation in mRNA is largely unexplored.⁹ More studies into the contribution of somatic mutations for different diseases are needed, as novel findings of somatic causes for conditions such as Sturge–Weber syndrome or hemimegalencephaly have revealed their importance.¹⁰ Multigenic determinants of disease, and the role of inflammatory predispositions to disease, are also poorly understood. Larger collaborative efforts and deploying the use of more sophisticated clinical phenotype information is needed. Finally, potential for context-specific genetic variation necessitates studies of the interactions between germline DNA and inflammatory, microbiome, and environmental risks.

CLINICAL PHENOTYPE COMPREHENSION

With the massive expansion in clinical genetic testing, a gap is developing between testing results and correlation to disease. The dreaded variant of uncertain significance (VUS) leaves patient, family, and clinician in a limbo regarding the result and next steps. The cause(s) of variable disease penetrance is also poorly understood, for example, a variant with no phenotype in a parent, but severe disease in a child. Even with diseases that are extensively studied, identification of new variants in known disease genes poses a challenge. A further tension in the field is that of phenotyping- or genotyping-based grouping of patients. If patients and diseases are too widely split into different phenotype categories, there is missed opportunity to identify commonalities;

Received: 27 January 2022 Revised: 11 May 2022 Accepted: 20 May 2022
Published online: 11 June 2022

but conversely, grouping all patients with a mutation of a certain gene will risk oversimplifying diverse, distinct molecular mechanisms.

Improvements in bioinformatics and in modeling of disease (cell-based; animal models, etc.) are bridging some of the gap. Over a decade ago, the National Institutes of Health supported several initiatives to build capability of using model systems such as zebrafish to test variants. Now, there is an opportunity to build on the lessons learned from those initial programs, and also advances in technologies such as CRISPR, to fund new efforts in high-throughput testing of sequence variants and of disease model generation.

Further, collaborative efforts based on sharing of available genotype and clinical data, of cases and also of “unaffected” family members, could improve understanding of VUSs. There are likely >100,000 exome or genome sequencing tests performed among clinical and research laboratories every year, but the majority of this data is siloed in companies or academic centers. Coordinated efforts to share candidate variants and phenotypes, such as the Monarch Initiative or GeneMatcher, and expectation of participation by laboratories, scientists, and clinicians, should be encouraged.

EQUITY

There is a large gap between the opportunity for diagnosis and the rates of diagnosis in underrepresented minority patients, patients of lower socioeconomic status, and patients from parts of the world with no access to testing. Compounding this diagnosis gap is that many population groups are underrepresented in variant databases such as gnomAD, making determination of rare variant pathogenicity challenging in individuals not of Western European ancestry. These inequities in diagnosis will translate into a widening gap for treatment. Cultural differences in the understanding of disease and health, and of the relevance of genetic diagnosis, also need to be considered. For example, in the African-American community there are concerns not only about participation in medical and genetic research and lower rates of enrollment in studies but also that physicians may offer genetic testing at lower rates to minority patients.^{11,12}

There are opportunities to reduce these inequities, such as improved education and familiarity of healthcare providers in genetic testing technologies or expanding insurance requirements for coverage of testing. Efforts by NIH and other funding agencies to require inclusion of diverse racial, ethnic, and socioeconomic groups is also needed and appears to be gaining momentum. Another opportunity for improving equity would be to expand genetic testing into newborn screening (NBS). NBS in the U.S. is one of the most successful public health efforts of the twentieth century.¹³ Most NBS is based on mass spectroscopy, which limits the number and types of diseases that can be tested. NGS-based NBS has significant potential for broadening diagnoses; but there are major cost, technology, interpretation, and ethical challenges. For example, current NBS testing costs <\$100 per infant, but any NGS sequencing would be a tenfold increase in cost. An example of an ethical concern is that NGS NBS would identify infants who would develop Huntington’s disease during adulthood, but for which there is no treatment. Would families be informed of the diagnosis or not? Pilot trials of NGS use in NBS are technically promising,¹⁴ and studies include consideration of psychosocial effects.¹⁵

THERAPY LAG

With discovery of new diseases and more patients with diagnoses needing treatment, it is important to improve the process of therapy development and delivery. The pipeline to a new therapy can span decades, requiring huge financial investments and

navigating complicated regulatory requirements. With costs of some medicines in millions of dollars, this poses questions of balancing free-market healthcare with moral imperatives of treatment. Further, disadvantaged patients may not be able to access life-saving treatments. New paradigms need to be considered, such as trying to find shared pathways of pathophysiology, instead of working on distinct treatments for every disease. This strategy would condense patients with different rare diseases into common, molecularly targetable therapies of shared biochemical or genetic pathways. There is also opportunity to identify and share basic elements of certain therapies that could be used across multiple diseases. This would be situations such as viral gene therapy vectors that are pre-approved for human use by the Food and Drug Administration¹⁶ or approved chemical backbones for use in generating antisense oligonucleotides.

There are not easy solutions, but shared, inclusive decision-making may allow a path to be charted. For example, managing treatment costs, or which diseases to prioritize for therapy development, will ideally have input from patients, families, healthcare organizations, and pharma companies, as well as the government.

CONCLUSIONS

Pediatric medicine is poised at a threshold for a post-diagnostics world, but the success and outcomes are critically dependent on processes being implemented now. Perfecting diagnostic technology, understanding genetic variant to phenotype correlation, overcoming inequities, and translating diagnosis to therapy are key aspects for this transition. Concerted, coordinated partnerships of the public and government sectors, scientists and clinicians, and patients and families can build a new landscape for the health of children.

Joshua L. Bonkowsky^{1,2,✉}, Tomi Pastinen^{3,4} and Peter White^{5,6}
¹Division of Pediatric Neurology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA. ²Center for Personalized Medicine, Primary Children’s Hospital, Salt Lake City, UT, USA. ³Genomic Medicine Center, Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA. ⁴Children’s Mercy - Kansas City and Children’s Mercy Research Institute, Kansas City, MO, USA. ⁵The Steve and Cindy Rasmussen Institute for Genomic Medicine, Nationwide Children’s Hospital, Columbus, OH, USA. ⁶Department of Pediatrics, The Ohio State University School of Medicine, Columbus, OH, USA.
 ✉email: joshua.bonkowsky@hsc.utah.edu

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AUTHOR CONTRIBUTIONS

All authors conceived, contributed to intellectual content, revised drafts of the manuscript, and read and approved the final manuscript.

FUNDING

The authors report no funding for this study.

COMPETING INTERESTS

J.L.B.: consultant: Bluebird Bio, Calico, Neurogene, Passage Bio; Board of Directors: wFluidx; Stock: Orchard Therapeutics; royalties: Manson Publishing, BioMerieux (spouse); research support: NIH; Leukodystrophy Foundation; European Leukodystrophy Association. T.P.: no conflicts of interest. Research support: NIH, Ehlers Danlos Society, Canadian Institutes of Health Research. P.W.: no conflicts of interest. Research support: NIH, Additional Ventures Foundation.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Joshua L. Bonkowsky.

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