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Clinical Utility of Genomic Sequencing

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Abstract

Purpose of Review—Identifying pathogenic variation underlying pediatric developmental disease is critical for medical management, therapeutic development, and family planning. This review summarizes current genetic testing options along with their potential benefits and limitations. We also describe results from large-scale genomic sequencing projects in pediatric and neonatal populations with a focus on clinical utility.

Recent Findings—Recent advances in DNA sequencing technology have made genomic sequencing a feasible and effective testing option in a variety of clinical settings. These cutting-edge tests offer much promise to both medical providers and patients as it has been demonstrated to detect causal genetic variation in ~25% or more of previously unresolved cases. Efforts aimed at promoting data sharing across clinical genetics laboratories and systematic reanalysis of existing genomic sequencing data have further improved diagnostic rates and reduced the number of unsolved cases.

Summary—Genomic sequencing is a powerful and increasingly cost-effective alternative to current genetic tests and will continue to grow in clinical utility as more of the genome is understood and as analytical methods are improved. The evolution of genomic sequencing is changing the landscape of clinical testing and requires medical professionals who are adept at understanding and returning genomic results to patients.

Keywords

Genome sequencing; genetic testing; pediatrics; genetic diagnostics; rare disease

Introduction to Genomic Sequencing

Congenital malformations and other suspected genetic disorders are a leading cause of morbidity and mortality in children and infants.^{1,2} Understanding the precise genetic causes responsible for these disorders can guide therapeutic strategies, inform clinical management, and provide valuable counseling for families. However, finding such genetic causes is often

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complicated due to a high degree of genetic heterogeneity and a wide range of possible nonspecific clinical symptoms. Outside of the relatively few conditions with pathognomonic presentations and precisely defined molecular genetic etiologies, children suspected to have congenital disease often undergo a “diagnostic odyssey” characterized by numerous tests, both genetic and non-genetic, conducted over multiple years with little or no success. Recent advances in DNA sequencing technology are quickly changing the clinical genetics landscape by enabling research-based discovery of new genetic disorders and more efficient and comprehensive clinical detection of diagnostic genetic variation. Leading the charge of this rapid advancement are exome sequencing (ES), in which protein-coding gene exons (“the exome”) are captured and sequenced, and genome sequencing (GS) in which both coding and non-coding regions, including intronic and intergenic regulatory regions, are sequenced. Collectively referred to herein as “genomic sequencing,” the strength of this technology rests in its ability to offer an unbiased, base-pair level view of large fractions of a person’s genetic material compared to traditional array, single-gene, and gene-panel tests.

This article provides an overview of the increasing utility of genomic sequencing as a clinical diagnostic tool. Genome-driven diagnoses may in the short-term guide clinical treatment or management of phenotypes associated with rare disease, while at the same time potentially yielding beneficial medical information that will aid a patient throughout their lifetime.

Genomic Sequencing, Analysis, and Interpretation

Genomic sequencing involves a complex set of biochemical and bioinformatics processes that ultimately results in tens of thousands (in exomes) or millions of genetic variants (in genomes) that must be filtered down to a small number that can be manually curated and interpreted (Figure 1). Genomic sequencing begins with a biological sample, most often whole blood, from which DNA is isolated and then sheared, amplified and sequenced, typically by generating millions of “short” (i.e., 100-300 base-pairs) sequence reads that are aligned to the human reference assembly.³ Using bioinformatics tools, genetic variants are detected by identifying specific places where the observed sequence reads deviate from the reference genome. These variants are then annotated with information such as known functional effects or evolutionary histories that can be used to determine variant pathogenicity and medical relevance. Following annotation, variants can be computationally prioritized and reduced to a manageable number in a variety of ways. For example, one common strategy is to identify all variants that alter a protein (e.g., are missense or nonsense or at a splice junction), that are rare in the general population as defined in large variant databases,⁴⁻⁶ and that affect a gene flagged in the Online Mendelian Inheritance in Man catalog (OMIM, www.omim.org) as being disease-associated. After computational filtration and ranking, manual curation is done to determine if any detected variant contributes to the patient’s phenotype and is appropriate for return to the clinical team and, at their discretion, the patient.

While the American College of Medical Genetics and Genomics (ACMG) has published guidelines to standardize variant interpretation methods across clinical laboratories,⁷ this process remains challenging and results can vary between labs and over time. In many cases,

variants never before reported are identified and become variants of uncertain significance (VUS); those that are neither conclusively benign, nor conclusively pathogenic.⁷ This uncertainty sometimes results from a lack of understanding of how a given variant affects a given gene product, while uncertainty may also arise when the affected gene has no known association with disease.⁸ Interpretation of non-coding variation that may affect regulatory regions of the genome remains particularly difficult.⁹ However, a number of research approaches can be used to determine if a VUS is pathogenic, in particular aggregation of patients with similar phenotypes/variants¹⁰ and experimental validation.^{7,11-14}

As more genomes are sequenced and more high-throughput functional assays are developed, it is likely that variant interpretation will become more streamlined, accurate, and consistent.

Genomic Sequencing May End the “Diagnostic Odyssey”

Traditionally, a patient presenting with a suspected genetic disorder would undergo a sequential series of genetic tests (Table 1). Current ACMG guidelines recommend chromosomal microarray (CMA) as a first-line test for developmental disorders and congenital anomalies, although karyotyping has also been, and is, conducted to identify chromosomal aberrations (e.g. trisomy, etc.).^{15,16} CMA is effective for detecting copy number variants (CNVs; typically large deletion or duplications > 200 kb), with a diagnostic yield of ~10% or greater depending on patient phenotype.¹⁷⁻¹⁹ If no CNVs are identified, testing often proceeds with single gene or gene panel tests to detect smaller events, including single nucleotide variants (SNVs) and insertions/deletions (indels).^{15,16,20} Particularly if symptoms are non-specific, as is often the case with neurodevelopmental disorders, patients can undergo multiple tests without receiving a definitive molecular diagnosis. This “diagnostic odyssey” may not only be financially and emotionally draining, but potentially delay treatment and worsen outcomes.

Given its ability to survey most protein-coding genes at base-pair resolution with a single test, ES is an attractive alternative to traditional array and gene-based tests. However, due to its rapidly decreasing cost and potential to be even more comprehensive, many research studies and clinical labs have begun to use GS in place of ES. Despite this, there remains continued debate about choosing between ES and GS. Sequencing costs for GS are 1.5-3X more expensive than ES, and the vast majority of clinically interpretable, pathogenic mutations exist within coding regions of the genome typically captured by ES. In contrast, GS provides improved coverage in coding regions and allows for substantially greater sensitivity in CNV detection (in comparison to both CMA and ES), especially when it comes to identification of smaller CNV events (< 200 kb).²¹ Furthermore, there are a growing number of identified pathogenic variants that occur outside of annotated coding exons,^{9,22-25} and even though we do not fully understand the proportion of human disease that results from non-exonic variation, it is certain to explain a non-trivial fraction. However, contribution of non-coding variation to disease is likely smaller than that of highly-penetrant coding variation. As our functional understanding of non-coding regions continues to grow, uptake of GS by clinical labs is likely to become even more prevalent.²⁶

Large-scale genomic sequencing studies of pediatric populations suspected to have genetic disease report diagnostic yields ranging from 25 to 40% of cases, depending on the technology used and patient phenotype.^{19,20,27-31} Notably, this yield is substantially higher than CMA (~10-15%),¹⁹ the current frontline standard-of-care, and gene panel tests.³² As noted above, CMA and/or karyotype testing may be employed prior to genome sequencing to detect large deletion/duplication events or chromosomal abnormalities, as they can currently do so at reduced cost. “Trio sequencing,” in which both parents are sequenced along with the affected child, greatly aids interpretation and improves diagnostic yield by allowing rapid identification of *de novo*, causal variation and should be employed when possible.^{19,27,33} Given the advantages of genomic sequencing compared to current standard tests, it is likely to become a nearly universal frontline test for suspected genetic disorders in the near future.

It is important to note that at least twelve rare disorders (such as Beckwith-Wiedemann, Silver-Russell, Prader-Willi, and Angelman) result from variation (uniparental disomy, CNV, SNV, indel) or epimutation in genes located within imprinted regions of the genome. While ES/GS can certainly detect genetic variation at these loci, aberrant methylation cannot be detected via current genome sequencing technologies. Clinical suspicion of disease associated with imprinted genic regions requires methylation testing.^{34,35}

Genomic Sequencing: More Than a Diagnostic Tool

While identifying pathogenic variation is itself a desirable goal in order to end a patient’s diagnostic odyssey and provide reproductive counseling, a number of studies describe clinical management decisions that resulted from genomic sequencing. A recent meta-analysis of such decisions reported that clinical management was altered by ES in ~17% of cases and altered by GS in ~27% of cases.¹⁹ Examples include genomically guided decisions in palliative care, medication initiation/termination, and surgical care.³⁶⁻³⁸ Furthermore, cost analyses indicate genomic sequencing can provide an overall healthcare cost savings compared to traditional sequencing despite its relatively high upfront cost.^{37,39} One study from 2016 calculated a net savings of over \$128,000 (~\$3,000 per patient) as a result of rapid GS in a cohort of 42 NICU patients.³⁷

Due to the reduced need for an *a priori* clinical hypothesis and potential to guide clinical management, there is a growing argument for genomic sequencing to be used as an interventional tool for acutely ill infants as well as a routine part of newborn screening.^{37,38,40} The difficulty of diagnosis of suspected genetic disease in a neonatal setting is often greater than in pediatric or adult settings, as newborns are too young to display a full range of characteristic symptoms for many conditions. A recent study of ES in a neonatal setting was able to detect pathogenic variation related to childhood-onset disease in 15/159 newborns for a diagnostic rate of 9.4%. Of these cases in which pathogenic variation was identified, 10 findings were in ostensibly healthy babies (127 healthy babies in study), while 5 were from ill babies in the NICU (32 ill babies in study).⁴¹ Further, while at much higher cost, genomic sequencing can be performed quite rapidly, with testing, analysis, and results return in several days.³⁷ In general, these studies highlight the potential use of genomic

sequencing in both ill and healthy newborns, and suggests that sequencing may provide maximal benefit when performed earlier in life.

With Great Data Comes Great Responsibility

Genomic sequencing's ability to provide an unbiased look at nearly all of a person's DNA does not come without risks or potentially unintended consequences. Indeed, both ES and GS can yield incidental and secondary findings. Though often used interchangeably, incidental findings are medically relevant genetic results unintentionally observed during genomic analysis, while secondary findings are medically relevant results that are actively sought out, but are unrelated to the primary phenotypic motivation for performing genomic sequencing. Both can present difficult decisions for both clinicians and patients.

Consider a case in which a child with intractable epilepsy undergoes genomic sequencing. A mutation in a known epilepsy gene would be considered the primary finding as it is related to the phenotype which prompted sequencing. However, if during the analysis a known pathogenic variant in *PSEN1* is found, indicating a high risk for future onset of Alzheimer's disease, this could be considered a secondary finding if *PSEN1* variation was proactively analyzed, or an incidental finding if it was found as a by-product of searching for an epilepsy-associated variant. Whether secondary or incidental, such a finding is of medical relevance but is not related to the epilepsy that motivated sequencing. A related, but distinct, question is whether such a variant is "medically actionable". While the discussion of what constitutes actionability is ongoing, the ACMG has published a list of 59 genes (ACMG SFv2.0) for which they recommend return of secondary and incidental findings; examples include the genes *BRCA1* and *BRCA2*, associated with breast and ovarian cancer.⁴² Per ACMG's evaluation, the diseases associated with these 59 genes are considered actionable since there are standard clinical recommendations to prevent or mitigate their effects. *PSEN1*, in contrast, is not on this list given the lack of effective options for prevention of Alzheimer's. Within these "ACMG 59" genes, secondary findings have been reported in 1-3% of study participants, including in individuals for which a primary diagnosis was identified.^{43,44} Most participants in genomic sequencing studies (95-100%) prefer to receive secondary/incidental findings, especially if they are medically actionable.⁴⁵⁻⁵⁰ Factors influencing the desire to receive these results include the potential disease severity, risk of disease development (penetrance), medical actionability, and time until onset.⁵¹

Sequencing of pediatric patients presents additional challenges, particularly in regards to adult-onset disease, carrier status, and secondary findings in unaffected parents.⁵² This issue is highlighted in a recent case study in which a sequencing of an infant did not reveal a primary genetic cause for their condition, yet did reveal a maternally-inherited *BRCA2* mutation that elevates risk for breast and ovarian cancer.⁵³ A 3-generation family history taken at time of enrollment did not indicate a significant family history for cancer, and there was uncertainty regarding whether or not this result should be returned as the initial study protocol did not allow for return of adult-onset secondary findings. After discussion with the IRB, the family was given the option to receive this result, which they agreed to. Learning of the result prompted additional pertinent family history related to cancer, and eventually the mother received clinical follow-up in a cancer genetics clinic.

Moreover, incidental findings that result from genetic testing may also include discovery of consanguinity and/or non-paternity. These issues are often (and should be) addressed at time of consent for testing so that patients and families are aware that such information may be revealed. It is imperative that clinicians understand this potential as well, and that they are prepared to speak to patients and families in the event that these circumstances arise.

The psychosocial, ethical, and legal implications for the return of incidental and secondary findings remain an active field of study. However, there is no clear “one size fits all” paradigm for what results should be returned, who should return them, and to what extent patient preferences should be solicited. Regardless, clinicians should be aware of the potential for secondary findings in genomic testing, and communicate clearly with patients about such results and policies governing their return.

Reanalysis and Scalability: Genomic Sequences are Largely Static, Science is Not

An advantage of genomic sequencing data is its ability to grow in utility as science advances. Even if such data does not immediately yield a diagnostic result, it may potentially do so in the future. In fact, routine reanalysis over time has been shown to improve diagnostic rates by over 10%.⁵⁴⁻⁵⁶ Reasons for such improvement include publication of new disease-gene associations, improved bioinformatics tools, and data sharing using platforms such as GeneMatcher.^{10,57}

The ability to reanalyze genomic sequencing data highlights a need for iterative communication between researchers, clinicians, and families, as diagnoses can be made years after the initial sequencing and analysis has been performed. There also remains numerous practical questions about reanalysis such as, for example, how the genomic data is best stored, who should be given access for reanalysis, under what circumstances should reanalysis happen, and how to ensure that the data is appropriately tracked with a patient throughout their lifetime.

It is important to note that while reanalysis of old data in light of new information is clearly fruitful, newer sequencing technologies may in some cases justify resequencing and generation of new data. For example, Illumina currently hosts two different methods/platforms for conducting long-read DNA sequencing (10X Genomics and Pacific Biosciences).⁵⁸ Long-reads can be effective when trying to obtain coverage for regions that are of low complexity or are repetitive. Moreover, long-reads also facilitate determination of variant phase (useful for variation harbored within recessive disease genes) and better detection of structural variation. While reanalysis of older data will certainly remain relevant as scientific knowledge expands (i.e. new disease-gene associations), the medical genetics community must be cognizant of newer sequencing technologies and their potential for clinical utility.

Changing Genetics Landscape Requires Novel Skills

Compared to single-gene or gene panel testing, genomic sequencing reduces the necessity of identifying specific, candidate genetic conditions related to the patient's phenotype and, as such, may allow non-geneticist providers to more readily order tests. Furthermore, even for geneticists, the reports generated by genomic sequencing may use new, and often changing, types of evidence that may not be familiar to the ordering clinician, and new tools to aid in finding and evaluating pathogenicity of variation are constantly in development. It is also critical to note that the goal of a clinical sequencing lab is to find disease-associated variation, not to make diagnoses *per se*; while the presence of a particular variant can often point directly to a particular diagnosis, the latter requires clinical judgment that accounts for all information relevant to the patient and their condition. As such, understanding the complexities and limitations of genetic test results is crucial to ensure the information is used safely and effectively. ACMG and others have made efforts to provide education about how and when to order genome testing, the details of genetic testing reports, how to evaluate variant pathogenicity evidence, and how to communicate results to patients (www.ashg.org/education/csertoolkit).⁵⁹ It is critical for providers to have a basic understanding of genomic sequencing both to increase their confidence in the results they return to patients and to act appropriately given those results.

Conclusions and Outlook

With cost decreases and clinical utility increases, genomic sequencing will continue to replace our current suite of array and gene-based tests. Furthermore, there will likely be a point in the near future in which genomic sequencing is a routine part of newborn screening and is added to the medical record to be referenced as new health or pharmacogenetic concerns arise. Despite the advances in diagnostic yield due to genomic sequencing, ~50-65% of suspected genetic disease cases remain unsolved. Improvements in sequencing technology, bioinformatics tools, and variant interpretation, as well as increased biological understanding of the genome, will continue to increase yields. In addition to sequencing genomic DNA, complementary sequencing strategies such as RNA-seq are being piloted in clinical settings and have shown to provide a genetic resolution in ~36% of genomic sequencing-negative cases.⁶⁰ Demystifying these unresolved cases remains a primary goal of the research community and efforts to identify novel disease genes and new classes of pathogenic variation are ongoing.

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Key Points

Genome sequencing is of great clinical utility and has been demonstrated to be of benefit to both patients and medical providers

This review provides an overview of genome sequencing technology, and describes analysis and interpretation of genetic variation

Genome sequencing has great potential for ending the diagnostic odyssey for patients with rare disease

Genome sequencing has implications for clinical management as genetic testing results may guide provider decisions related to treatment and management of disease

The use of genome sequencing in clinical setting requires medical professionals who are adept at understanding and returning genomic results to patients

Figure 1. Genome sequencing workflow demonstrating processes necessary to go from a patient blood sample to medical intervention.

Table 1.

Description of genomic testing types, potential for diagnostic yield, detection capability, and advantages and disadvantages.

Test	Diagnostic Yield	Variation Detected	Major Advantages	Major Disadvantages
Single Gene or Gene Panel	~20% *	SNVs, indels	Accurate detection of SNVs and indels	Surveys selected genes; phenotype dependent
Chromosomal Microarray (CMA)	~10%	CNVs, SVs	Unbiased method for detecting CNVs and SVs	Does not detect SNVs/indels; low resolution for small CNVs
Whole Exome Sequencing (WES)	~25%	SNVs, indels	Unbiased survey of all coding regions	Low resolution for CNVs and SVs
Whole Genome Sequencing (WGS)	>25%	SNVs, indels, CNVs	Unbiased survey of coding and noncoding regions	High cost; interpretation of non-coding regions non-trivial

* Phenotype-driven, diagnostic yields vary across disorders