Changing Paradigms

Genomics-Driven Treatment for Patients with Rare Disease

August 2021

INTEGRITY
Content Consulting

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Key Takeaways

- Rare genetic disease is actually common, when considered collectively
- The path to an accurate rare genetic disease diagnosis is winding, lengthy, and costly, to both the health care system and the patient
- Genomic testing technologies like exome sequencing and genome sequencing are valuable tools to improve the diagnostic yield, medical management, and clinical outcomes for patients with rare genetic diseases
- Treatment and medical management options for patients with rare genetic diseases are growing
- 2021 evidence-based guidelines strongly recommend exome sequencing and genome sequencing for pediatric patients with clinical indications at specific ages (e.g. multiple congenital anomalies, developmental delay, intellectual disability)
- Understanding a genetic diagnosis unlocks opportunities to offer appropriate disease-targeting and prognosis-based care, optimizing health care resources

Introduction

Approximately 2%-6.2% of the worldwide population is affected by rare disease; the number of diseases that meet this definition is rising as more are identified.[1,2,3,4,5] The exact prevalence of patients with rare genetic disease is not well established, but recent analyses of the Orphanet database estimate that 70%-80% of rare diseases are exclusively genetic, or have significant genetic forms that account for at least 10% of patients with the disorder.[2,5] As of January 2021 6,077 rare diseases are annotated within the Orphanet database.[6] **Genetic diseases are not rare when considered collectively.**

Patients with complex rare genetic diseases follow a long and circuitous road to diagnosis, with several diagnostic approaches and evaluations that typically begin in childhood. **For patients with rare disease, the average length of time from when a disease is first suspected to when a correct diagnosis is reached is 5-8 years.[7,8]** This is a time- and resource-intensive process, with an average diagnostic workup cost reported in the range of $5,000-$8,000 USD for children with suspected genetic diseases.[9,10,11,12,13,14]

Advances in genomic testing technology, such as next-generation sequencing (NGS), further the ability to diagnose genetic diseases. **Genomic testing technologies like exome sequencing (ES) and genome sequencing (GS) improve diagnostic yield, lead to changes in medical management, and identify novel genetic diseases.[15,16,17,18,19,20,29] Payers are increasingly covering these testing technologies for appropriate patients.**[55,57]

Genomics-driven treatments are not limited to orphan pharmaceutical drugs that may only benefit a single patient or family.

Historically, treatment of genetic diseases has been reactive, managing symptoms known to occur within a diagnosis. Patients with an absent or delayed diagnosis experience significant disease burden or even death as they wait for treatment that depends on a diagnosis. **Many of these patients are critically ill and hospitalized; up to 40% of deaths in the neonatal intensive care unit (NICU) are attributable to birth defects or a genetic condition.[21,22,23,24,25,26]**

Once a genetic disease mechanism is understood, appropriate treatment and management can attempt to proactively address symptoms and prognosis. **As diagnostic rates rise and timeframes shrink, treatments are increasingly available for patients with rare genetic disorders, unlocking options for prompt and appropriate clinical management.[10,27,28,29]** Genomics-driven treatments are not limited to orphan pharmaceutical drugs that may only benefit a single patient or family. Treatment and management measures also include dietary recommendations, enzyme replacement therapy, medications, hematopoietic stem cell transplant, as well as being able to offer palliative care or avoid unnecessary procedures.[30,31] **ES and GS are important diagnostic tools that boost opportunities for available treatment and management for patients with rare genetic diseases.**

Current Diagnostics in Rare Genetic Disease

Historical approaches to a genetic diagnosis are iterative, typically leading to a lengthy and costly diagnostic journey. (see Figure 1).[7,8,10,32] Rare genetic disease patients often need consultations with multiple specialists, each conducting evaluations to reach a unifying diagnosis. As this occur, patients can experience significant morbidity and mortality.[15,33]

Figure 1. Diagnostic Journey Statistics for Rare Disease

8	Physicians[32]
5–8	Years[7,8]
2–3	Misdiagnoses[32]
$19k	Diagnostic testing[10]

Even the most experienced clinical specialists cannot reliably recognize all the known rare and ultra-rare genetic diseases.

Phenotype-driven genetic testing typically has a low diagnostic rate for patients with rare pediatric diseases, such as 10% with chromosomal microarray (CMA).[20,34] NGS is a scalable testing technology that can be used to identify disease-causing variants in a single gene, subset of genes, or the entire exome (ES) or genome (GS). ES and GS are effective in identifying a genetic diagnosis in patients with phenotypically heterogeneous features[29,35,36,37,38,39,40] and critically ill neonates.[13,41,42,43] An advantage of using a GS-based approach is that it allows for detection of a more comprehensive set of variant types than WES, including copy number variants (CNVs), repeat expansions and structural variants.[44,45,46,47,48] Over the past 5 years, numerous peer-reviewed studies have been published including over 6,000 patients, collectively demonstrating the high diagnostic yield of GS and resultant changes to medical management.[16,38,39,40,42,43,49]

A 2020 Blue Cross and Blue Shield Association Evidence Street health technology assessment (HTA) found, "Rapid ES and rapid GS meet the definition of medical necessity for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when criteria are met."[50] Rady Children's Hospital Project Baby Bear found clinicians caring for infant NICU patients to have more confidence in treatment decisions following rapid GS results, as compared to standard of care.[51]

The cost of DNA sequencing is shrinking[52], making payers consider costs of testing and the diagnostic odyssey to the health care system. For example, a 2020 Ontario HTA

Ending the search for a diagnosis stops the need for more tests and evaluations, saving short- and long-term time, cost, and burden to the health care system and patients.

concluded that if the cost of GS is equivalent or lower than ES and CMA together, GS becomes an equivalent or dominant strategy.[53]

ES and GS shift the diagnostic approach from an iterative one that can loop back onto itself, to a single approach. This offers clinical utility on its own as a part of the patient care paradigm. Preventing a diagnostic odyssey or ending the search for a diagnosis stops the need for more tests and evaluations, saving short- and long-term time, cost, and burden to the health care system and patients. A molecular diagnosis also opens the door to appropriate disease treatment, management, and follow-up.[20,30,54]

In July 2021, the American College of Medical Genetics and Genomics (ACMG) published an evidence-based guideline strongly recommending ES and GS for pediatric patients with one or more congenital anomalies (CA) with onset prior to age one; or developmental delay (DD) or intellectual disability (ID) with onset prior to age 18. The guideline highlighted that the peer-reviewed published literature, "...supports the clinical utility and desirable effects of ES/GS on active and long-term clinical management of patients with CA/DD/ID..." and that, "compared with standard genetic testing, ES/GS has a higher diagnostic yield and may be more cost-effective when ordered early in the diagnostic evaluation."[68]

U.S. Coverage and Utilization of Genomic Testing

About 10,000 unique genetic tests are available in the market as of 2020.[55,56] In terms of total payer spend on genetic testing, the majority (~86%) is on single gene tests and represents only limited spend.[55]

A 2020 study showed that U.S. payer coverage policies for genomic tests are growing over time.[57] ES and GS showed particular payer coverage growth in 2020 (see Figure 2).[55]

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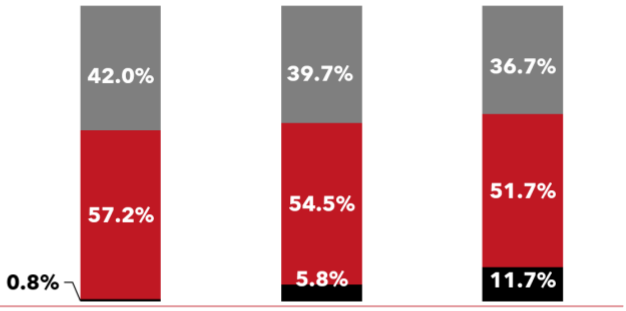
Despite favorable coverage policies, testing utilization rates are not consistent across U.S. states and higher utilization rates do not always correlate with favorable coverage policies.[57] ES utilization rates observed in claims data are lower than expected for the population size of members eligible for ES.[57]

This suggested under-utilization of genomic testing that is medically appropriate and covered by payers. Other barriers to genomic testing utilization remain and need to be further investigated.

Figure 2. Exome and Genome Sequencing Coverage By Category*
Percentage of Total Insured Lives[55]



	End Q1 2019	End Q1 2020	End Q1 2021**
Total Insured Lives	**257MM**	**257MM**	**240MM**
ES & GS Covered	2MM	15MM	28MM
Only ES Covered	147MM	140MM	124MM
Not Covered	108MM	102MM	88MM

* Represents coverage in rare disease only. Presently, 16.1MM of these GS covered lives only cover rapid GS (with explicit inpatient setting requirement). 131MM of these covered lives also have explicit coverage for ES comparison testing (trios); no policies explicitly exclude trios. Total insured lives excludes Medicare.

** 2021 data not directly comparable with 2019/20. Updated covered lives data used for 2021. Total insured lives fell due to reduction in double-counting, loss of coverage in the population, shift towards out-of-scope coverage types. 2019/20 managed Medicaid coverage based only on state Medicaid policy. 2021 Medicaid coverage based on whichever was more generous in a member's state Medicaid policy and the commercial policy of their managed care organization (MCO).

Evolution of Disease Management and Treatment

Historically, with few treatments available for patients with rare genetic diseases, some questioned the need for a long search for a specific genetic diagnosis. However, treatment and management paradigms for patients with rare genetic diseases are shifting and growing over time, from supportive care to anticipatory management based on a genetic diagnosis.

Supportive Care (1902-present)

Supportive treatment and care likely predate when alkaptonuria was discovered in 1902 as the first inborn error of metabolism.[58] These aim to alleviate symptoms as they arise, but do not directly address the underlying disease mechanism. Treatments may be identical to someone with a non-genetic cause for the same medical issue. Examples include cochlear implants for a deaf patient, an implantable defibrillator for an inherited arrhythmia syndrome, or chelation treatment for iron overload disorders.[30,59]

Treating Symptoms Related to Disease Pathology (1954-present)

These treatments target symptoms due to the underlying disease pathology. An early example is a nutritional formula and dietary recommendations for patients with phenylketonuria (PKU), which first became available in 1954.[60] Recent examples include enzyme replacement therapy (ERT) for lysosomal storage disorders like Gaucher disease and Fabry disease, as well as immunoglobulin therapy for inherited immunodeficiencies.[30,61,62]

Directly Treating the Disease Mechanism (2017-present)

Growing understanding of genetic disease mechanisms has now shifted treatment paradigms, to where these directly target the mechanism to prevent or slow disease progression. An example is gene therapy, approved by the U.S. Food & Drug Administration (FDA) for *RPE65*-related Leber congenital amaurosis in 2017.[63] Gene therapy is also FDA-approved for spinal muscular atrophy type 1[64] and others are in clinical trials for different genetic diseases. Another example of disease-targeting treatment is hematopoietic stem cell transplantation, appropriate for immunodeficiencies, inherited blood disorders, and storage disorders.[30]

While broad statements like, "95% of all rare diseases do not have a single FDA approved drug treatment"[7] are common and may be true, they don't capture the full picture. It is a misconception that treatments for patients diagnosed with specific rare genetic disease are limited to expensive FDA-approved therapies. Orphan drugs indicated for a small number of patients are only one example of rare disease treatments. Others may be relatively inexpensive and non-prescription options that treat symptoms related to a disease pathology, such as supplements like minerals, vitamins, sugars, and other natural products.[30] The need for these treatments is only identified once an accurate molecular diagnosis is reached.

Clinicians have a growing number of treatments to evaluate and manage for patients with a growing number of known genetic diseases, with information often fragmented in multiple locations. Resources are becoming available to help. A 2020 publication described an online database (Rx-genes.com) that allows users to search for available treatments linked to a genetic diagnosis, based on English language medical literature.[30] Treatments are broken into categories, with the approximate number of relevant genetic diseases at the time of the publication (see Table 1).[30]

Table 1. Examples of Treatment Types and Genetic Diseases, as listed in Rx-genes.com[30]

Treatment type	Number of relevant genetic diseases	Example
Medications, vaccinations, blood products	328	Complement factor deficiency (various types)
Supplements	175	Congenital adrenal hyperplasia
Hematopoietic stem cell transplantation	157	Sickle cell disease
Dietary management	95	Phenylketonuria
Immunoglobulin therapy	42	Agammaglobulinemia (various types)
Procedures	36	Prophylactic oophorectomy (guidelines recommend offering to individuals with ovaries for *BRCA1/2*-associated hereditary breast and ovarian cancer)
Enzyme replacement therapy	28	Gaucher disease, type 1
Solid organ transplantation	18	Primary hyperoxaluria, type 2
Gene therapy	4	Spinal muscular atrophy, type 1

Many diseases found within the database necessitate several treatments due to the involvement of numerous organ systems in a single genetic diagnosis. A concrete example of this is in the care for patients with epilepsy. Current diagnostic approaches are frequently associated with long delays, leading to sub-optimal care. However, NGS-based tests, such as ES and GS, identify more underlying molecular diagnoses. Treatment is becoming linked to the molecular cause, for example avoid valproic acid in patients with pathogenic variants in *POLG* (associated with Alpers-Huttenlocher and *POLG*-related disorders).[65] In another example, knowing a patient has pathogenic variants in *GAMT* or *GATM* can reveal the need for oral creatine supplementation.[66]

Using the example of Project Baby Bear at Rady Children's Hospital, in which critically ill infants underwent rapid GS, this enabled clinicians to shorten length of hospital stays by discharging babies sooner and reducing the number of procedures they underwent.[51] This led to:

- 513 fewer days in the hospital
- 11 fewer major surgeries
- 16 fewer invasive diagnostic tests
- $2.5 million in health care savings

As genomic testing like ES and GS diagnose more patients with rare genetic disease, a prognosis-based approach to care can begin to be implemented. For example, critically ill neonates may be offered pediatric palliative care instead of continued interventions in the NICU based on their molecular diagnosis. This can provide relief from ongoing symptoms, medical interventions, as well as the emotional toll on the patient and family.[67] These can deliver short-term and long-term benefits to the health care system as well.

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Conclusion

Rare genetic diseases represent a large underrecognized burden in our population. In particular, the well-characterized diagnostic odysseys that many patients and families face are associated with high costs and poor outcomes. A more comprehensive diagnostic approach earlier in the care paradigm can lead to better outcomes and lower costs. For critically ill patients in intensive care, rapid GS early during hospitalization can facilitate a timely diagnosis and lead to changes in management and improved outcomes. More comprehensive genetic testing technologies can also allow for better management, allowing for health care resources to be appropriately delivered to those who need it most.

The diagnostic yield of GS is expected to increase the understanding of rare genetic disease. This will also unlock opportunities to disease-specific treatment, interventions, and avoidance of

a protracted diagnostic process. The number of disease-targeting treatments is rising, beyond orphan drug treatments, allowing for the paradigm of care to shift for patients with genetic disease. This can move from managing patients reactively to aiming treatment directly at the disease mechanism, allowing for disease progression to be slowed or stopped altogether. All of this will benefit the patient, payer, and health care system in the short-term and long-term by informing immediate and future care decisions.

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Acknowledgements

Illumina, Inc. provided funding to help develop this document. Deepti Babu, Founder of Integrity Content Consulting (www.integritycontentforyou.com), led the authorship in collaboration with Trish Brown, Brock Schroeder, Daisy Du, and Ashley Arthur.

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