Whole-genome sequencing for rare disease diagnosis

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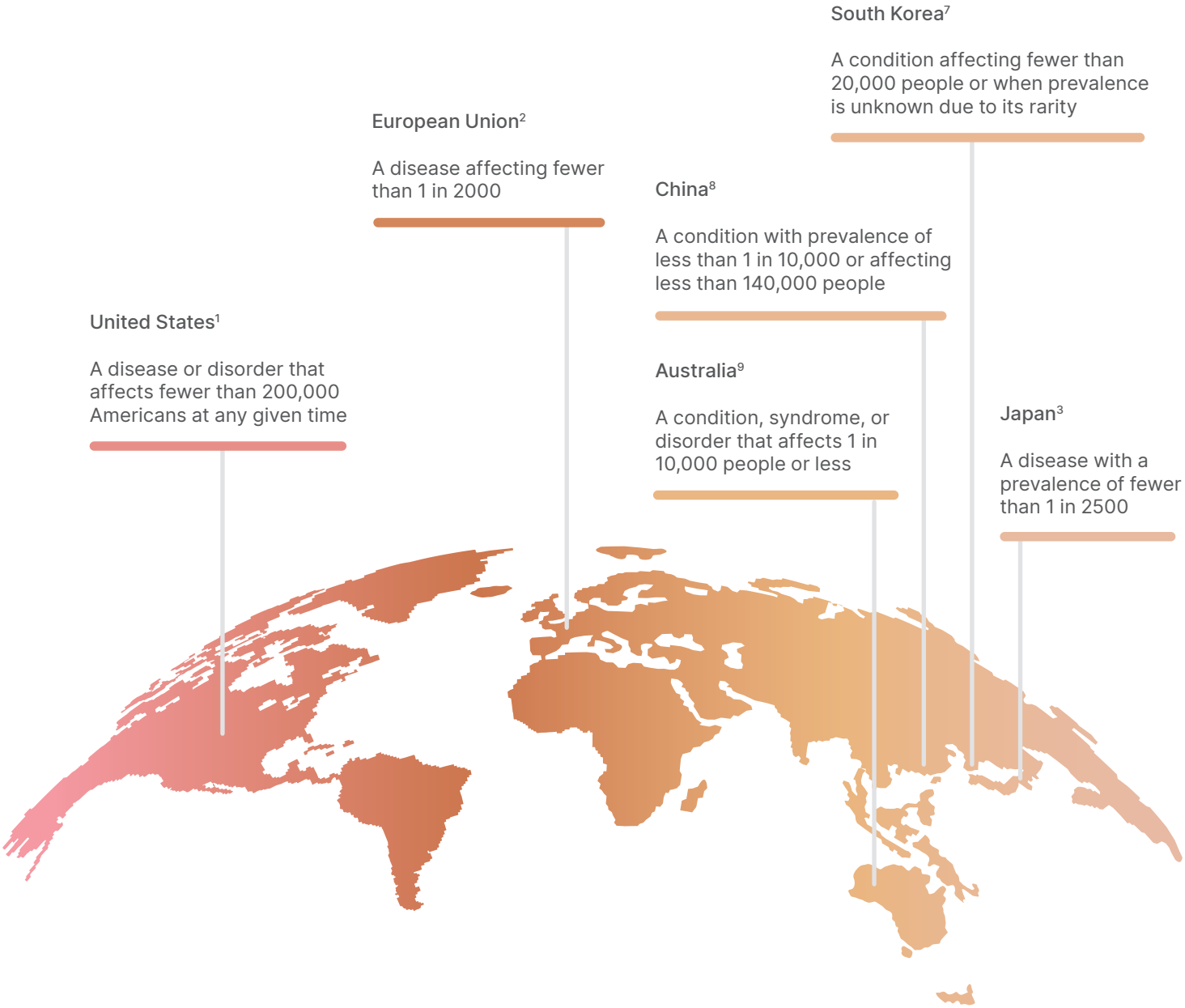
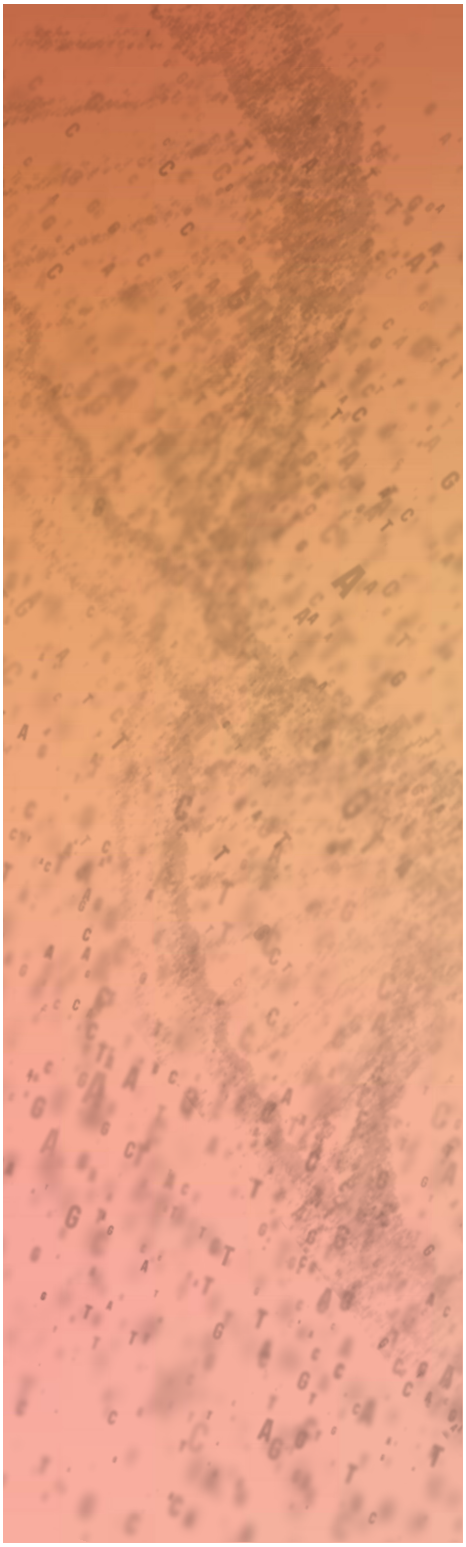
The patient journeys in this book are from individuals and patient advocates that work with Illumina. The Illumina Global Patient Advocacy team works with patients, families, carers, and the groups that represent them in order to build evidence and advocate for the positive impact of genomics utilization. Their stories are a testimonial of the potential impacts and benefits genomics can have on disease. One person's experience is not predictive of results in all disease cases, which may differ based on a variety of factors. Results in other cases may vary.

Rare disease diagnosis

Impact of rare disease globally

A rare disease affects only a small group of individuals. Yet, the term small is relative. In the United States, a rare disease is defined as affecting fewer than 200,000 Americans.[1] In Europe, a disease is considered rare when it affects fewer than 1 in 2000 individuals.[2] A disease with a prevalence of 1 in 2500 counts as rare in Japan.[3] With as many as 7000 known rare diseases and many yet to be discovered, these small groups add up.[4] Collectively, 2%–6% of the global population (nearly 300 million people) are affected by a rare disease.[4-6]





Unfortunately, many individuals affected by rare disease are likely to go undiagnosed, misdiagnosed, and untreated without access to reliable and accurate clinical tools.[10] Children account for approximately 50% of patients affected by rare diseases and 30% of these children will not reach their fifth birthday.[11,12]

On average, the long search for a rare disease diagnosis—the "diagnostic odyssey":

- May involve multiple tests
- Includes up to eight physicians[13,14]
- Takes five to seven years[13-16]
- Results in two to three misdiagnoses[10,14]

Up to

80%

of rare diseases are genetic or have a genetic component.[4,5,12,14]

Understanding the genomics of rare disease can help doctors pinpoint the cause of undiagnosed disorders and help families avoid years of hospital visits and unnecessary tests. Comprehensive genomic analysis using next-generation sequencing (NGS) increases the potential of uncovering an underlying etiology in patients.[12,17,18] It offers the highest likelihood of rare disease diagnosis[19,20] and a faster path to ending the diagnostic odyssey.[19]

The value of genomics for rare disease diagnosis

Genomics is driving a fundamental shift in rare disease diagnosis, from symptom analysis to molecular etiology assessment. Understanding the biological basis of disease can lead to better care and targeted treatment, with predictable, evidence-based outcomes. Molecular diagnosis in rare disease genomics can provide an opportunity for precision medicine.

Molecular diagnosis of rare disease is a critical step that can benefit patients, their families, physicians, and other care providers. According to the American College of Medical Genetics and Genomics (ACMG), the identification of the genetic etiology of an individual's disease has utility for the patient, their family, and society at large.[21]

Identifying the genetic cause of an individual's disease can:

Prevent additional unnecessary testing

Lead to the development of new therapies and management strategies

Enable informed family planning

Provide opportunities for psychosocial support via disease support groups[5,22,23]

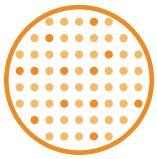
Limitations of iterative testing

What you may be missing with current testing applications

There are many ways to investigate the genetic cause of disease, yielding varying results. Traditional methods for genetic analysis are limited in the type of variants they detect and the amount of genome coverage they provide, reducing their potential utility.

Single-gene tests can identify variants or changes in a single gene. Single-gene tests are typically used to confirm or exclude a condition where there is a clear phenotype or family history.

Multigene panels focus on a selection of genes that are typically associated with an indicative phenotype. Multigene panels may not allow for examination of new and emerging targets.



Chromosomal microarrays (CMAs) are designed to detect copy number variants (CNV). CMAs analyze < 0.01% of the genome, missing opportunities to find underlying genetic causes for disease.[24]

Whole-exome sequencing (WES) sequences the protein coding regions of genes that account for around 2% of the genome, leaving 98% unexplored. WES has limited capability to detect CNVs or structural variants (SV), and fails to detect repeat expansions or paralogs.[25-33]

Often, these focused methods are chosen as first-line tests based on phenotype. Historical guidance from societies associates specific clinical presentations with certain variant types. For example, because cases of multiple congenital anomalies are commonly associated with aneuploidy and other CNVs, CMAs are frequently used as a first-line test.[34] Similarly, multigene targeted NGS panels may be used for patients with conditions, such as epilepsy, that are associated with single nucleotide variants (SNVs) or small insertions–deletions (indels) in multiple genes.[35]

However, with many rare diseases the phenotype can be unclear and complex.[36] Inconclusive results from initial tests can prompt more genetic tests. This iterative testing places additional burdens on an already stressed healthcare system, requires multiple patient samples, adds complexity to test ordering, and increases the cost and time to answer.

A single comprehensive test that sequences the whole genome can provide more information and be completed more quickly than multiple, iterative tests.[37] Whole-genome sequencing (WGS) offers comprehensive genome coverage to maximize testing efficiency and speed to a diagnosis.

The most comprehensive test for rare disease

WGS provides the most comprehensive analysis of genomic variants among all clinical genomic testing methods.[25,27,29,38] WGS examines the entire genome and has the capability to assess variants in both coding and noncoding regions of the genome.[25,27,29,30,33,39,40] Importantly, WGS can detect multiple variant types in a single assay, which improves testing efficiency for rare disease cases of heterogeneous etiologies.[25-27,29,30,33,39,40]

Advantages of WGS

- Get to a diagnosis faster, with lower costs[25,41]
- Find actionable answers, even when a negative result is returned[17]
- Enable more personalized care management than other genomic tests[42]
- Obtain a comprehensive view across the genome, including coding and noncoding regions[25]
- Detect a diverse range of variants in a single assay[25-27,29,30,33,39,40,43]

Variant types detected using WGS compared to standard testing

	Sanger*	Targeted NGS*	PCR*	CMA*	WES*	WGS*
Single nucleotide variants (SNVs)[25]	●	●	●		●	●
Insertions–deletions (Indels)	●	●	●	◖	●	●
Copy number variants (CNVs)[25,26]		◖	●	●	◖	●
Repeat expansions[29-32]			◖			●
Structural variants (SVs)[27,28]				◖	◖	●
Mitochondrial[25]	●	●			●	●
Paralogs[33]	●		●		◖	●

◖ Limited capabilities ● Capable

*Variant detection may vary depending on particular laboratory and performance limits of validated variant types. Detection of repeat expansions by PCR is typically limited to single-gene analysis, compared to multigene capabilities for WGS. Improvements to SV variant callers and increased success with long-read whole-genome approaches suggest fully capable SV insights from WGS.
NGS = next-generation sequencing, PCR = polymerase chain reaction

WGS captures CNVs with greater resolution than CMA.[25,40,44,45] WGS also captures some variants in exomes with greater accuracy than WES.[25,44,46-48] Because WGS provides better coverage and higher yield across the genome, including GC-rich regions, the European Society for Human Genetics (ESHG) guidelines recommend use of WGS, even if only the exome or specific genes are examined bioinformatically.[49]

Many rare disease diagnoses found with WGS would have been missed by WES, including those caused by repeat expansions or mutations in noncoding regions.[29-32,46,47,50]

PATIENT JOURNEY

Carson and Chase and their 6-year diagnostic odyssey[51]

YEAR 1 - Parents noticed movement issues with Carson in first few months

YEAR 2 - Carson diagnosed with cerebral palsy (CP)

YEAR 3 - Chase was born with similar symptoms, calling CP diagnosis into question

▶ **WATCH THEIR STORY**

YEAR 4 - Negative whole-exome sequencing

YEAR 5 - Whole-genome sequencing identified a rare mitochondrial disease resulting in a diagnosis of MEPAN syndrome

6 years

WGS offers the highest likelihood of finding a diagnosis for rare genetic disease

WGS for rare disease has the power to help health care providers diagnose genetic diseases quickly, helping families avoid long diagnostic odysseys. The goal of WGS is to provide a diagnosis with a single test versus multistep iterative testing.

In critically ill infants and in a pediatric outpatient setting, WGS has been shown to have a superior diagnostic yield compared to standard testing and significant evidence of improved clinical management. Combined data from 37 studies comprising 20,068 children found an 8.3× increase in diagnostic yield with WES/WGS compared to CMA.[19]

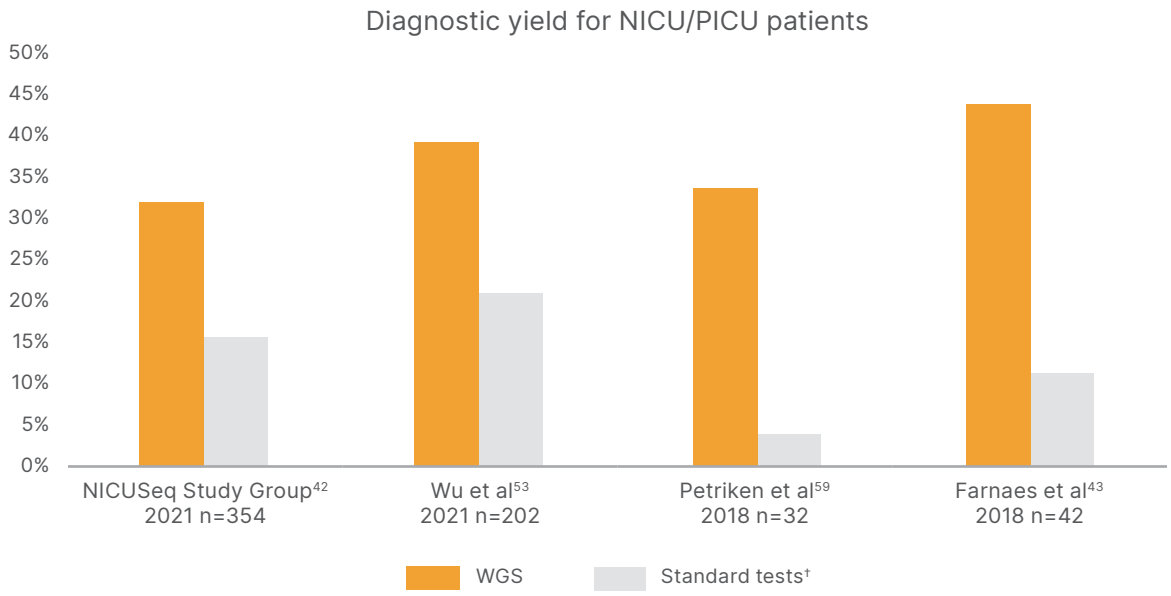
Higher diagnostic yield

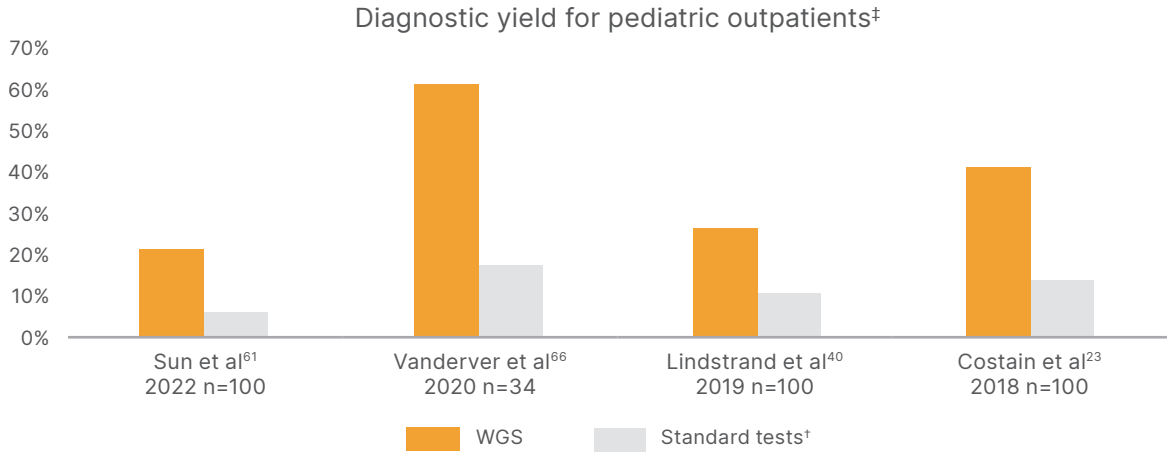
Clinical performance and utility of WGS has been demonstrated by over 40 peer-reviewed published studies in neonatal or pediatric patients with suspected genetic disease. Together, these reports include more than 9000 patients from around the world.[23,25,32,40-44,46,48,50,52-83]

Highlighted here are eight studies that performed head-to-head comparison of WGS to standard tests.† Four of these studies looked at diagnostic yield for patients in neonatal or pediatric intensive care units (NICU/PICU)[42,43,53,59] and four looked at yield in pediatric outpatients.[23,40,61,66] In both settings, WGS yielded a higher percentage of diagnoses than standard approaches and made a clear impact on clinical management.

† Standard tests may include CMA, fluorescence *in situ* hybridization (FISH), karyotype, targeted gene panels, microarrays, methylation, WES, or other.

WGS has been shown to improve diagnostic yield in both critical care and outpatient settings





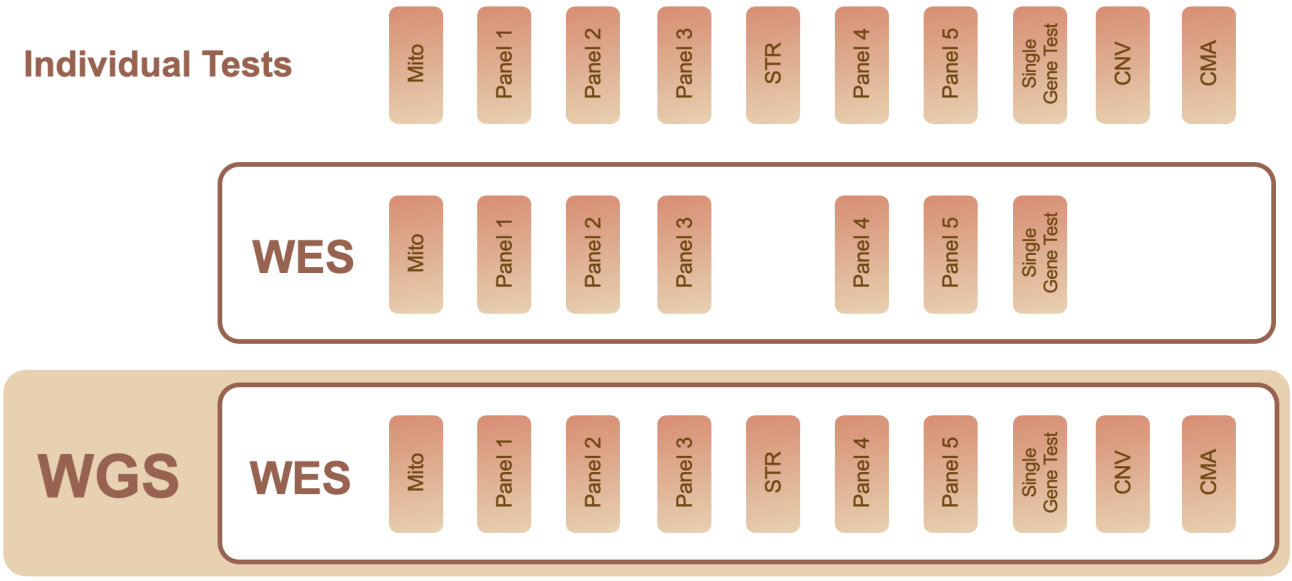
† Standard tests may include CMA, FISH, karyotype, targeted gene panels, microarrays, methylation, WES, or other. Cross-trial comparisons cannot be made given different study parameters/design.
‡ Indications may vary across studies.

One test to replace many

WGS may offer the greatest success in finding a diagnosis in rare disease. A single, comprehensive WGS test can provide more information and be completed more quickly than multiple, iterative tests. In addition, WGS data can be stored and reanalyzed as new gene–disease associations are discovered.

In patients with dysmorphism, multiple congenital anomalies, developmental delay, or intellectual disability, the phenotypic presentation often does not suggest a specific genetic condition. In these cases, the standard diagnostic workflow can involve many rounds of targeted genetic assays and/or genome-wide approaches. A workflow that integrates WGS as a first- or second-tier test greatly improves testing efficiency and has the potential to bring a rapid end to the diagnostic odyssey.[37,86]

Consolidate single tests to a comprehensive genomic backbone



For many rare diseases, faster speed to diagnosis can be critical. For example, infantile encephalopathy is associated with over a thousand genetic diseases, which are difficult to distinguish clinically. Some of these diseases have unique, effective treatments that, when given promptly, can prevent permanent neurologic injury or death.[84]

your diagnostic potential

"In situations where there is not the luxury of waiting, I see it as a moral imperative and an obligation for us to do everything possible in these cases to get to an answer as quickly as possible."

Luca Brunelli, MD, PhD
Neonatologist
University of Utah Health

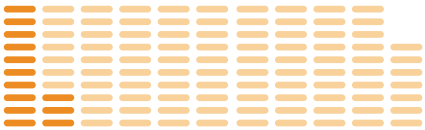
Advances in genomic testing are leading to answers faster than ever before

Studies show that WGS can save years on the time from symptom onset to diagnosis compared to standard genetic testing.[59,76] In a large, randomized controlled trial, the median time to diagnosis in NICU/PICU patients was 13 days with WGS, compared to 107 days with standard testing.[59]

WGS can provide answers faster than standard testing[§]

Acutely ill NICU infants:
Time to diagnosis using WGS vs standard genetic tests in the NICU

Rapid WGS = 13 days
Standard testing = 107 days



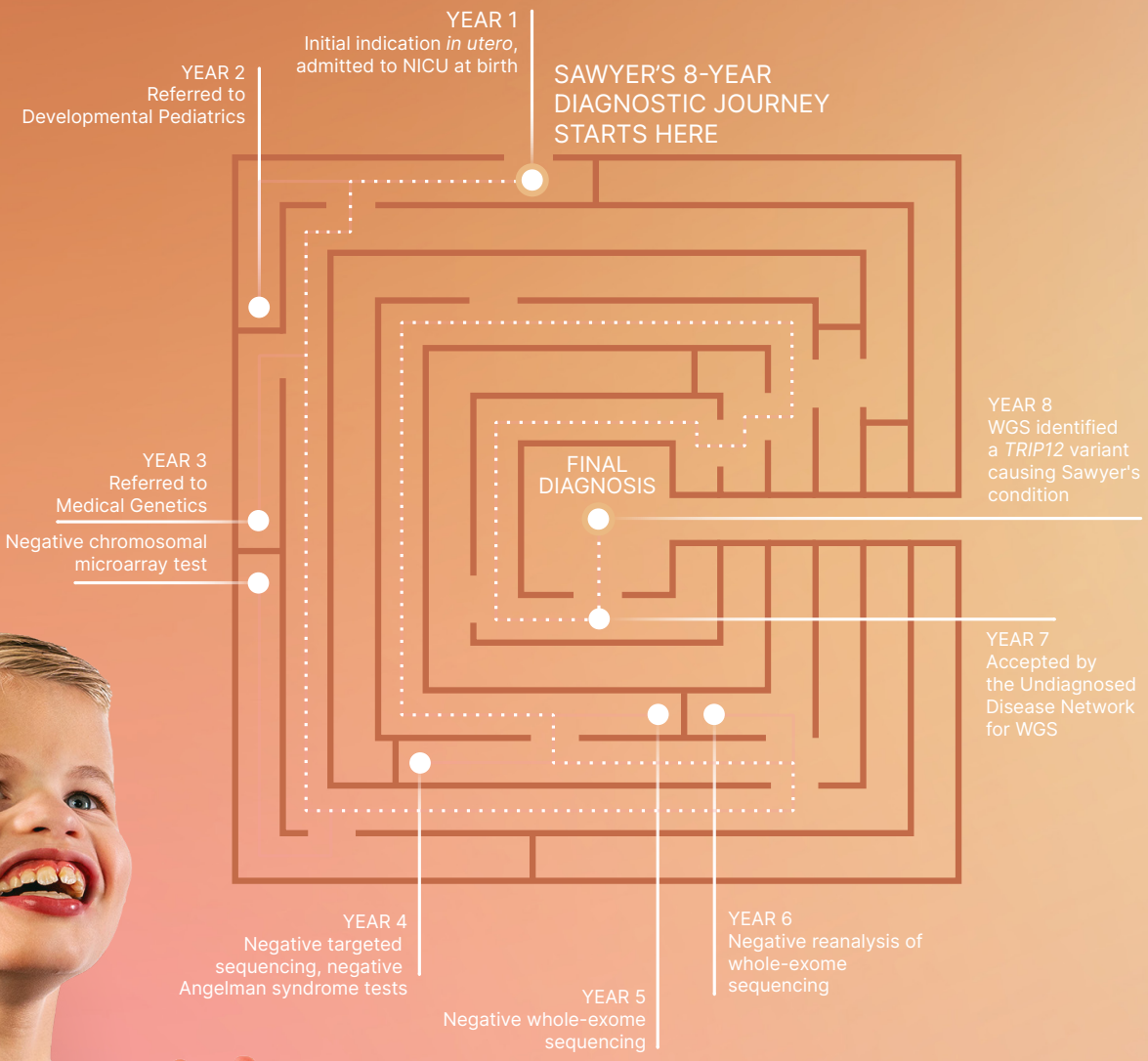
Pediatric patients:
Average time to diagnosis using WGS vs standard genetic tests in pediatric patients

WGS = 1.3 months
Standard testing = 77 months

[§] Standard tests may include: CMA, FISH, karyotype, targeted gene panels, WES, methylation studies, and gene detection or duplication assays.

PATIENT JOURNEY

Sawyer was on an 8-year diagnostic odyssey before his family found an answer with WGS.[85]



WATCH HIS STORY

Rapid and ultra-rapid WGS protocols are further speeding the path to rare genetic disease diagnosis in acutely ill infants and allowing earlier intervention that may improve outcomes.[43,54,57,58,84,86,87]

PATIENT JOURNEY

Sebastiana's rapid diagnosis with WGS

- Sebastiana, a newborn girl with persistent seizures, was dependent on feeding tubes to survive. Diagnostic workups, including brain MRI, yielded no results.
- Rapid WGS** zeroed in on Sebastiana's exact diagnosis within four days: a novel *de novo KCNQ2* mutation associated with Ohtahara syndrome.
- Her medication was changed immediately, her seizures were controlled, and she was discharged home on Christmas day. Since then, Sebastiana has continued to grow and delighted her parents and doctors with her progress.[88]

**In the NICU and PICU, rapid WGS and ultra-rapid WGS are often used because of their rapid turnaround time given the critical nature of the patients. Ultra-rapid WGS has a median turnaround time of 2.2 days; rapid WGS has a median turnaround time of 3.2 days; 3–14 days turnaround time is routinely achievable.

Understanding a WGS report

Although WGS reports may vary from lab to lab, the content that is included tends to be similar across reports. Here are terminology and guidance on the key information to focus on in a WGS report.

Results

	What may be included	What to look for
+ Positive	Identification of pathogenic or likely pathogenic variant that may fully or partially explain the patient's phenotype	• Whether variant fully or partially explains phenotype • Inheritance pattern • Supporting evidence used to classify variants
- Negative	No variants identified that explain the patient's phenotype	N/A
VUS	Variant identified that is of uncertain significance in relation to the patient's phenotype	• If a VUS is reported, what supporting evidence was used to classify it as such?
Other	May include secondary, incidental, or other findings	• What additional findings were identified and are they relevant to the patient's phenotype or medical management?

Pathogenic variant
Well-established as a cause of the patient's disease

Likely pathogenic variant
Considered a probable cause of the patient's disease

Variant of uncertain significance (VUS)
No or very little evidence to confidently support or rule out pathogenicity

Likely benign variant
Not likely to be the cause of the tested disease

Benign variant
Common polymorphism, not considered to be the cause of the tested disease

Clinical management

A diagnosis can be life-changing

When WGS is implemented early in the diagnostic pathway, it has the potential to offer life-changing options to patients and their families.[84]

Changes to care my include:

- Pharmacotherapy
- Referral to specialists
- Access to precision medicine–based approaches
- Avoidance of unnecessary procedures or treatments
- Informed reproductive risk counseling for parents and other family members

PATIENT JOURNEY

Cocktail treatment for Shubao[89]

Shubao suffers from hypertonia, which stiffens his muscles making it difficult to move, eat, or sleep. CMA and WES testing and visits to medical specialists failed to find his genetic anomaly. Finally, WGS showed he had lactic acidosis from a mutation in his *PDHX* gene. Doctors developed a cocktail treatment for Shubao and he showed almost immediate improvement. His muscles relaxed, he slept more, and he started eating.

WATCH THE VIDEO

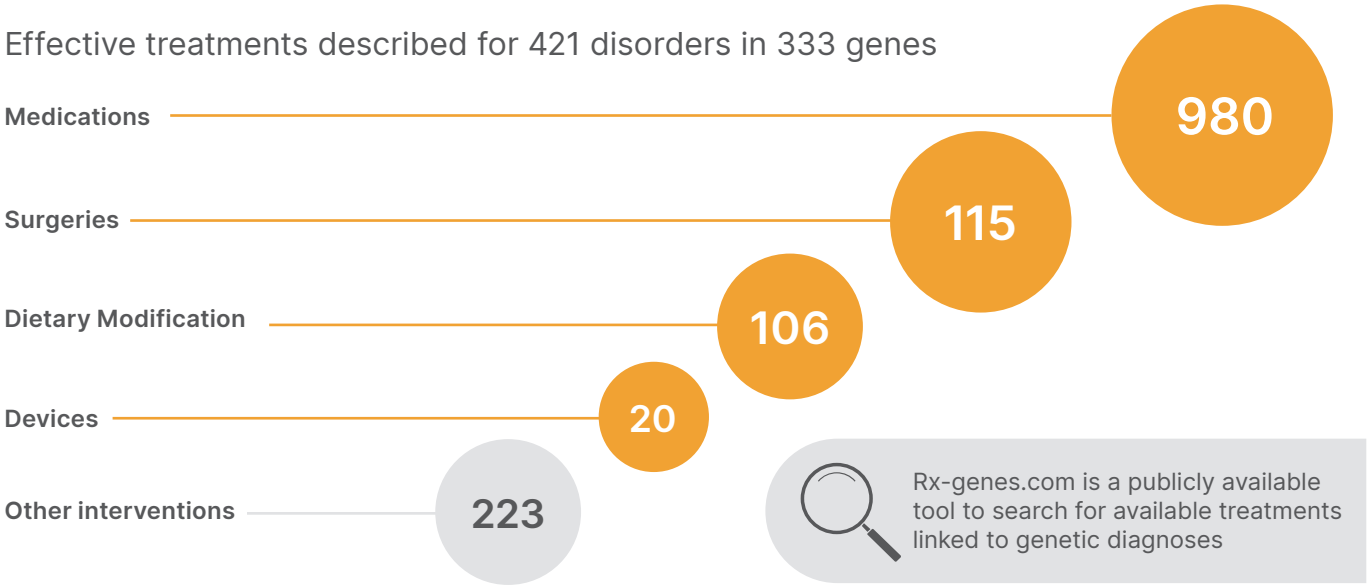
WGS has been shown to impact clinical management in both critical care and outpatient settings

	Study	Year	Location	Change in clinical management††
NICU/PICU patients	Suzuki et al[52]	2022	Japan	49% New treatment or therapeutic options, specialty referrals, avoidance of invasive testing, and palliative care
	Dimmock et al[54]	2021	United States	32% Change in surgical procedures, medication, diet, and length of hospital course
	NICUSeq Study Group[42]	2021	United States	31% Subspecialty referral, palliative care, medication changes
	Wang et al[56]	2021	China	43% Therapeutic strategy change, including transplant, diet, or medication change
	Wu et al[53]	2021	China	21% Targeted treatments or specialty referrals
	Sanford et al[58]	2019	United States	76%‡‡ Genome-informed changes in pharmacotherapy and transition to palliative care
	French et al[41]	2019	United Kingdom	70% Modification of treatments and care pathways and/or informing palliative care decisions
	Mestek-Boukhibar et al[60]	2018	United Kingdom	30% Counseling on prognosis, avoidance of unnecessary investigations, and informed recurrence risk
	Farnaes et al[43]	2018	United States	31% Avoidance of invasive test and/or transplant, reducing patient costs by $800,000–$2,000,000
	Petrikin et al[59]	2018	United States	31% Consideration of acute precision intervention in time for critically ill patients
Pediatric outpatients	Sun et al[61]	2022	China	43% Identification of targeted treatments, cessation of unnecessary treatment, and considerations for family planning
	Lee et al[72]	2021	Taiwan	23% Immediate changes in treatment strategies after undergoing WGS
	Beuschel et al[69]	2021	United States	60% Changes to medication, avoidance of additional testing, palliative care
	100,000 Genomes Project[46]	2021	United Kingdom	25% Immediate implications for clinical decision making
	Scocchia et al[67]	2019	Mexico	49% Referrals to specialists, avoidance of invasive muscle biopsies, additional clinical investigations, genetic counseling, and palliative care

†† Percentage is based on those with a positive WGS result.
‡‡ 24% for rapid WGS during PICU stay, 82% for rapid WGS after discharge.

Treatment options for genetic diseases

Specific and effective treatments are available for many rare genetic diseases. Orphan drugs indicated for a small number of patients are just one example of rare disease treatments.[90] Other options may be special diets or supplements to treat symptoms related to disease pathology. WGS-enabled diagnoses can lead to a growing number of effective interventions in acute care settings.



Support for precision medicine

There are tools to help health care providers easily search for available treatments that are linked to a genetic diagnosis. The following online resources are continuously updated to synthesize the published treatment literature and provide guidance and practical information for front-line physicians.[86]

- **Rx-genes.com** is an online compendium of over 633 treatable genetic disorders[91]
- **Genome-to-Treatment (GTRx™)** is a virtual automated system for immediate clinical management of childhood genetic diseases[90]

PATIENT JOURNEY

Gene therapy trial for Fitz[93]

As a newborn, Fitz was diagnosed with severe combined immunodeficiency (SCID). Rapid WGS identified his specific mutation in under three days and matched him with a gene therapy clinical trial. The treatment succeeded in creating a functioning immune system for Fitz and he is growing up healthy.

WATCH THE VIDEO

Patient selection

WGS addresses unmet needs among specific patient groups

WGS is especially helpful to provide faster answers for patients with immature phenotypes or those with heterogeneous symptoms.[94] The purpose of using WGS is to avoid the anchoring bias of a phenotype-based approach to diagnosis.

WGS may be considered clinically useful when:[12,49,73,95]

- The patient's phenotype does not clearly identify a specific disease with an established single-gene or multigene panel, or the patient has phenotypic characteristics outside of, or in addition to, what has been established for the disease
- A definitive diagnosis cannot be made based on standard clinical work up
- A definitive diagnosis will have clinical utility (improvement in net health outcomes); for example:
  1. establishing the diagnosis by genetic testing will end the clinical workup for other disorders
  2. a definitive diagnosis will lead to changes in clinical management or changes in surveillance
  3. the diagnosis leads to changes in reproductive decision-making for parents

Specifically, WGS may be indicated for pediatric patients who have multiple congenital anomalies, early onset epileptic encephalopathies, moderate-to-severe intellectual disability, global developmental delay, or other phenotypes that do not clearly point to any specific disease.[12,49,73,95]

WGS for neurological indications

WGS demonstrates high diagnostic yield for multiple neurological indications, including developmental delay, intellectual disability, epilepsy, and neuromuscular conditions. A wide range of studies have established WGS diagnostic yield for neurological conditions to range from 25% to almost 60%.[36,40,48,61,62,66,72,74,75]

	Year	Study size	Location	Diagnostic yield
French et al[62]	2022	122	United Kingdom	45%
Sun et al[61]	2022	100	China	21%
Palmer et al[36]	2021	30	Australia	63%
Lee et al[72]	2021	214	Taiwan	44%
Souche et al[48a]	2020	660	United Kingdom	33%
Vanderver et al[66]	2020	34	Worldwide	59%
Lindstrand et al[40*]	2019	100	Sweden	27%
Bowling et al[74*]	2017	244	United States	25%

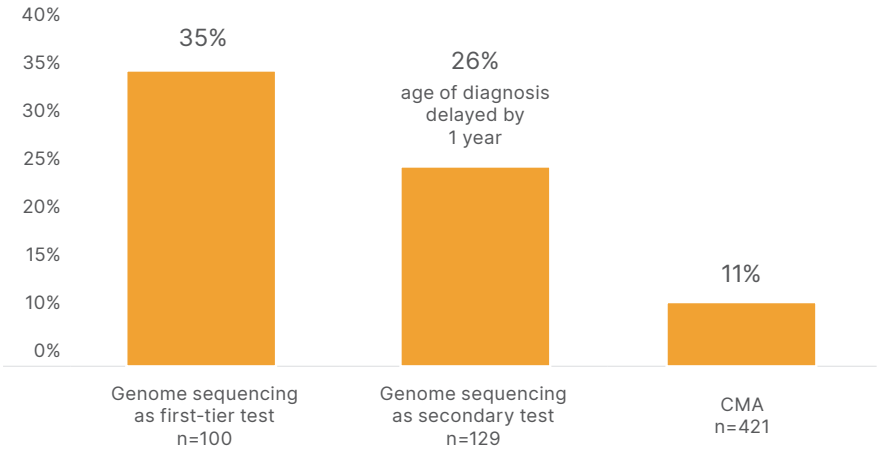
a. Studies combined pediatric and adult cohorts.

WGS is a highly effective first-tier test for unexplained intellectual disability or developmental delay (ID/DD)[55,76,97,98]

Intellectual disability affects around 1%–3% of the population with around three per thousand being of the severe form.[96] Severe intellectual disability often has a genetic etiology and WGS has proven an effective diagnostic first-tier test for these patients, with higher diagnostic yield compared to traditional testing methods.[96]

Emerging evidence for WGS as a first-tier test

Improved diagnostic yield for intellectual disability[71]

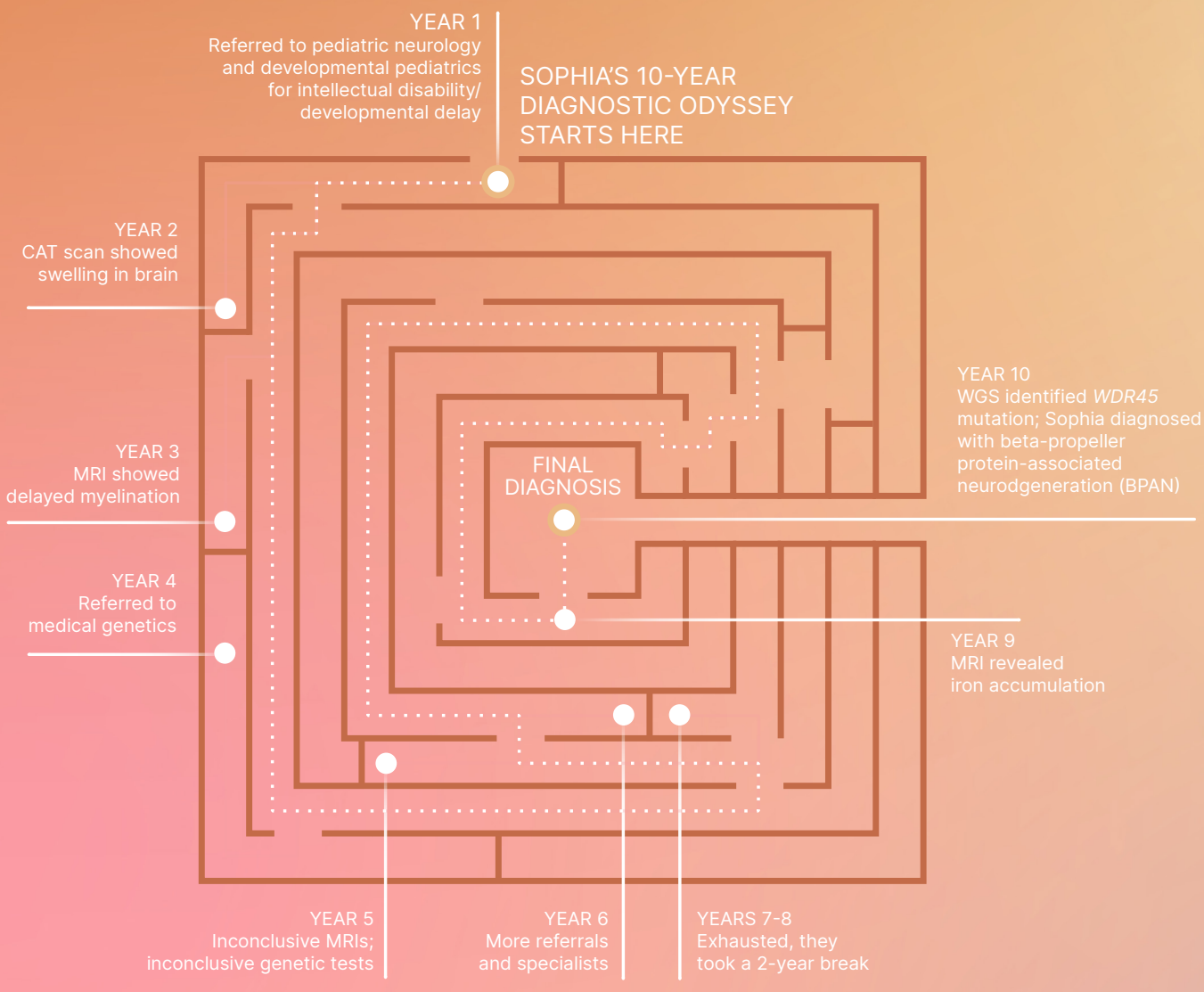


PATIENT JOURNEY

Sophia's 10-year diagnostic odyssey[99]

The long search for a diagnosis was so fatiguing for Sophia and her family that they almost gave up. Learn how they found not only an answer, but a community.

WATCH HER STORY



"Clinical WGS has turned out to be a true game changer in the rare disease space." Stranneheim et al, 2021[63]

WGS in clinical practice

The promise of WGS to improve diagnosis and management of rare disease is being validated in clinical practice and recognized by societies. ACMG and ESHG guidelines advocate genome sequencing when it can improve testing quality, efficiency, or diagnostic yield.[49,100] With inclusion in national healthcare systems[46,63] and increasing evidence of economic value when used as a first-tier test,[54,87,101] WGS appears to be on the path toward standard of care.

The Genomic Medicine Center Karolinska-Rare Diseases (GMCK-RD) in Sweden demonstrated a successful approach to integrating WGS into the management of rare disease in a clinical setting. Out of 3219 rare disease patients over four years, 40% (1285/3219) received a molecular diagnosis with WGS. Variants in 754 different genes were reported. The medical center stated that clinical WGS has turned out to be a true game changer in the rare disease space.[63]

Society endorsements

In 2021, ACMG released guidance recommending the use of WES or WGS as first- or second-tier tests in patients with one or more congenital anomalies prior to one year of age or intellectual disabilities/developmental delay prior to eighteen years of age.[17] The ACMG guideline states that genome-wide sequencing leads to:

- Increased diagnostic yield in rare disease
- Awareness of broad spectrum of genetic variants
- Improved patient outcomes
- Expanded treatment and management
- Access to support networks for patients and families[17]

Medical societies across the world also recommend genome-wide sequencing as a first- or second-tier diagnostic test for rare disease.[17,49,102,103]

Society statements on genome-wide sequencing for rare disease diagnosis

	ACMG[17] American College of Medical Genetics and Genomics	CMDA[102] Chinese Medical Doctor Association, Medical Genetics Branch	RACP[103] Royal Australasian College of Physicians, Paediatric and Child Health Division	ESHG[49] European Society of Human Genetics
Date of latest publication	July 2021	June 2019	February 2021	May 2022
Sequencing type	WES/WGS	WGS	WES/WGS	WGS
Eligible patients	Patients with one or more congenital anomalies prior to one year of age OR with intellectual disability with onset prior to age 18	Non-specific phenotype associated with intellectual disability and/or developmental delay; multiple congenital anomalies Clear clinical diagnosis associated with high level of genetic heterogeneity Previously negative WES or CMA	Any child < 10 years with: facial dysmorphism AND ≥ 1 congenital structural anomaly; OR global developmental delay/ intellectual disability (moderate to severe); Test must be requested by clinical geneticist OR pediatrician following consultation with clinical geneticist	It is recommended to introduce WGS analysis in a diagnostic setting when it is a relevant improvement on quality, efficiency and/or diagnostic yield

ESHG recommendations for WGS in diagnostics for rare diseases

Guidelines released by ESHG in 2022 recommend WGS analysis in diagnostic settings when it is a relevant improvement on quality, efficiency, and/or diagnostic yield.[49] The ESHG acknowledges that WGS offers a "potential overall benefit for the patient" and that when used as a first-tier test, "the extra sequencing costs may be compensated by the fact that fewer additional tests will be required."[49]

The ESHG guidelines also outline best practices for when clinicians are ordering WGS testing:

- Describing the patient phenotype (including negative criteria) in standardized terms and data formats is necessary for interpretation of variants
- Clinicians should provide genetic counseling—conducted by a qualified clinical expert—and obtain informed consent prior to clinical WGS
- Requests for reanalysis of WGS data should be triggered by the referring physician, with patient consent

> "WES and gene panels have been commonly used in a diagnostic setting for many years. WGS can be recommended based on increased quality and diagnostic yield. For instance, WGS allows the detection of SNVs and CNVs outside the exome, and provides a better coverage of coding regions than WES."
>
> Stranneheim et al 2022[49]

WGS is cost-effective when used as a first-tier test

The Center for the Evaluation of Value and Risk in Health (CEVR) at Tufts Medical Center in Massachusetts examined the cost-effectiveness of exome and genome sequencing for infants and children with rare and undiagnosed conditions.[101] This rigorous study compared standard-of-care genetic testing to seven possible diagnostic pathways, including first-tier WES, first-tier WGS, and combinations of WES and/or WGS after standard care. Cost-effectiveness analysis compared cost and clinical and quality-of-life impact of different modalities. First-tier WGS was considered the most cost-effective approach, producing the lowest cost per diagnosis and potentially the lowest cost per quality-adjusted years of life.[101] All other strategies led to the same or fewer diagnoses at a higher cost per diagnosis. CEVR found that standard-of-care testing before WES or WGS increases costs without improving outcomes.[101]

A similar study in Australia evaluated the cost associated with providing rapid genomic results in pediatric critical care vs reduction in health care costs.[87] This prospective study analyzed real-world hospital data for 40 critically ill infants with suspected genetic disease and different genetic testing approaches. Early rapid WGS was the most cost-effective strategy with an estimated savings of $800,000 to $2 million per 100 patients tested. The study authors found that reducing the time to diagnosis led to significant economic and personal benefits, and they recommended changing clinical practice to expedite WGS test initiation.[87]

Continuing to establish the cost-effectiveness of WGS in clinical practice is needed across the globe. The following special projects were designed to evaluate the clinical and economic effects of rapid WGS for critically ill children. These pioneering initiatives are generating evidence of clinical utility and economic benefits that will make it easier for other institutions to follow.

Project Baby Bear[54]

Rapid WGS for 184 newborns in NICUs in California

Saved an average of $12K to $15K per child's genome sequenced, compared with the $9K per child cost of the procedure, for around $1.2 million net savings

Baby Lion study[108,109]

Rapid WGS for 100 children in NICU/PICU and parents (trios) in Germany

Ongoing study to demonstrate the positive impact of earlier diagnosis and targeted treatment

Project Baby Manatee[105]

Rapid WGS for 50 critically ill babies and children in Florida

Reported a return on investment of $2.88 million

Project Baby Deer[106,107]

Five hospitals across Michigan offering rapid WGS to newborns and children up to 18 years

- Decreased hospital stays for NICU patients, which led Michigan to be the first state to mandate Medicare coverage of rapid WGS
- Clinical utility research is ongoing

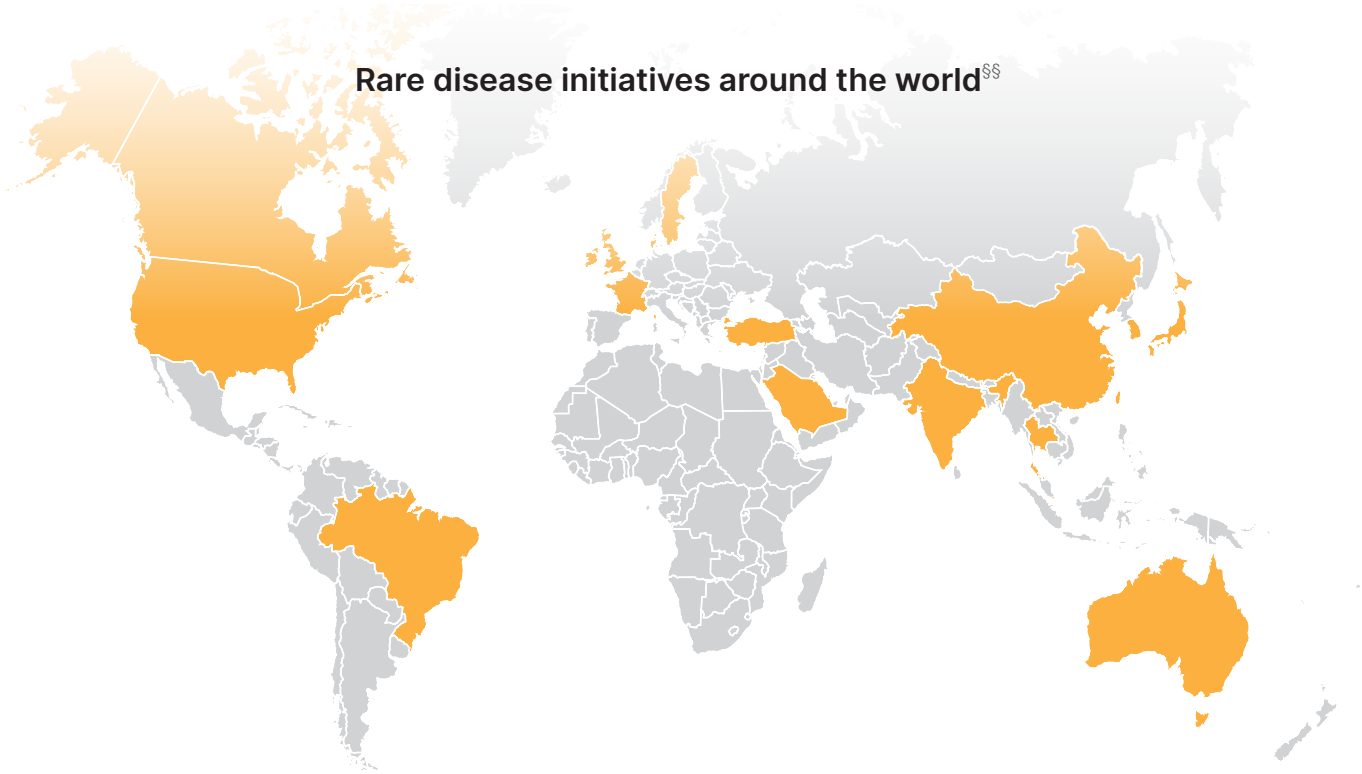
Baby Bambi[110]

Pilot study to offer rapid WGS to NICU patients across hospitals in Israel

- Evaluating workflow and feasibility of implementing WGS-based diagnostics into routine care
- Clinical utility research is ongoing

Global access to genomic sequencing for rare disease

Improving care for rare disease is a global mission. Nations and health systems across Europe, North America, and East Asia are increasing coverage for WGS and WES as they recognize the value of genome sequencing for rare disease diagnosis.[111] Special initiatives like the 100,000 genomes projects in the United Kingdom and Singapore are committed to expand knowledge about the role of genomics in rare disease.[46,48,112]



United Kingdom

The UK has set an example for the world with the 100,000 Genomes Project to study the role of genomics in rare disease and cancer.[46,48] The Wales Infants and Children's Genome Service (WINGS) and the National Health Service (NHS) in Wales were the first to offer rapid WGS as a diagnostic service for acutely unwell children.[113] Since 2019, the NHS in England covers WGS as a routine diagnostic test for over 30 different clinical presentations. For patients with specific disorders, such as intellectual disability, WGS is a first-line test in the NHS.[114]

Canada

In 2020, the Ontario Health Technology Assessment (HTA) Series concluded that genome-wide sequencing (including WES and WGS) has a higher diagnostic yield than standard genetic testing (CMA, targeted single-gene tests, or gene panels) and can prompt changes to some medications or treatments and referrals to specialists. The HTA also stated that genome-wide sequencing could be a cost-effective strategy when used after standard testing to diagnose people with unexplained developmental disabilities or multiple congenital anomalies and could also lead to cost savings when used earlier in the diagnostic pathway. Patients and families consistently noted a benefit from seeking a diagnosis through genetic testing.[18]

§§ Not all countries with rare disease initiatives are detailed here. Information current as of January 2023.

United States

The Blue Cross Blue Shield Association (BCBSA) technology assessment was positive for rapid WGS in the NICU/PICU. Based on critical review of peer-reviewed, published evidence, the BCBSA technical assessment body determined that WGS results in a "meaningful improvement in the net health outcome."[115] Since 2020, Blue Shield of California has covered rapid WGS for sick children up to age 18. Medicaid programs in Michigan and California were the first to cover rapid WGS for critically ill infants up to age one.

Japan

From 2015 to 2021, the Initiative on Rare and Undiagnosed Disease (IRUD) program led to final diagnoses in 2247 out of 5136 pedigrees (43%) and identified over a thousand novel pathogenic variants in 657 known genes.[116] The 100K national WGS project is ongoing. About 2500 cases of analysis are planned for the 2022 fiscal year for intractable disease, which covers monogenetic, multifactorial, and difficult-to-diagnose diseases.

Korea

The second pilot in National Project of Bio Big Data project will analyze the genetic makeup of 12,500 donated DNA samples from Korean patients living with a rare disease. The effort will work towards establishing a national digital library on health and genome data by 2028.[117]

China

In 2019, China launched the Newborn Genome Project to conduct rapid WGS for 200 NICU patients and compare diagnosis rates vs traditional detection methods. The project is also assessing diagnosis time, prognosis improvement, and hospitalization turnaround time to provide feasible recommendations for the application of rapid WGS in the NICU.[118]

Singapore

In 2022, Singapore announced the Precision Health Research Singapore (PRECISE) program to sequence 100,000 genomes of Singaporean participants and gather deep insights into key genetic, social, environmental, and other factors associated with disease.[112]

Australia

In 2019, the Medical Services Advisory Committee (MSAC) supported the inclusion of trio testing with WES or WGS for affected patients with dysmorphic facial appearance and one or more major structural congenital anomalies; or intellectual disability or global developmental delay of at least moderate severity to be determined by a specialist pediatrician.[119]

Germany

In 2021, Germany began reimbursing WGS/WES with no prior authorization requirement at the national level. In addition, major German health insurance companies cover WES and WGS at a higher reimbursement level to allow for testing of patients and their parents (trios).

Other countries that cover WES and WGS for patients with undiagnosed, suspected genetic diseases include Switzerland, Denmark, and Sweden. Several countries, including Belgium, France, the Netherlands, Israel, and Spain are actively pursuing integration of WGS into clinical care for certain indications and/or launching genomic initiatives that would include WGS for rare and undiagnosed disease.

Improving human health by unlocking the power of the genome

Ending the diagnostic odyssey through collaboration and innovation

Illumina strives to make genomics available to the many, not the few. As part of that commitment, Illumina sponsors several collaborations and programs to increase adoption and access to WGS for rare disease diagnosis.

Supporting the journey to the implementation of WGS

Illumina is creating a network of sites across Europe and the Middle East to connect and collaborate as they work to implement genomic sequencing in the intensive care setting. The working group includes 45 participants from 22 institutions across Belgium, Czech Republic, France, Germany, Israel, Italy, the Netherlands, Norway, Saudi Arabia, Spain, Sweden, UAE-Abu Dhabi, UAE-Dubai, and the United Kingdom. Participants share experiences, enabling discussion on technical aspects, resources needed, and clinical considerations such as referral criteria, results reports, and patient follow-up.

Dr Ahmad Abou Tayoun (pictured on the cover) is director of the Genomics Centre at Al Jalila Children's Specialty Hospital in Dubai and a member of the working group. Dr Abou Tayoun and colleagues published a study on rapid WGS for critically ill infants from genetically underrepresented populations. Trio WGS analysis was completed within 37 hours, which provided fast and precise diagnostic findings in three out of five patients and aided in devising better management plans for them in the intensive care setting.[120] For example, one patient was diagnosed with Pallister-Killian syndrome. Another was found to have pathogenic variants in the *LIPA* gene and became a candidate for an FDA-approved enzyme replacement therapy. Even the data for the two infants without a diagnosis could present a research opportunity for gene discovery, which may lead to a diagnosis in the future.[121]

Regarding the clinical utility of rapid WGS, Dr Abou Tayoun says, "Although it looks slightly more expensive than traditional testing, it has its value. It's quick, and there's no unnecessary diagnostic workup or inefficient treatment."[121]

The Medical Genome Initiative

The Medical Genome Initiative is a consortium of nine equal participating member institutions with the joint mission to expand access to high-quality WGS for rare disease diagnosis. These thought-leader institutions coordinate projects to develop and publish common laboratory and clinical best practices.[122] The Medical Genome Initiative also seeks to align the clinical research community on endpoints for measuring WGS clinical and economic utility. Illumina participates as a scientific contributor, administrator, and sponsor.

Illumina iHope™ program and iHope Genetic Health program

The iHope program is a philanthropic initiative launched by Illumina to make WGS accessible to underserved families with children facing rare and undiagnosed genetic diseases. This program collaborates directly with pediatric health care providers, organizations, and academic institutions to identify patients appropriate for testing. iHope Genetic Health, a program governed, managed, and operated by the nonprofit Genetic Alliance, expands the Illumina iHope program to make WGS broadly accessible to low- and middle-income communities around the world, with more than one-third of funds being allocated to patients in Africa.[123,124]

A promising future for all

Whole-genome sequencing has great potential to deliver precise molecular diagnoses and alter future medical management in many patient populations, including those with rare and undiagnosed genetic disease. WGS can provide pharmacogenomic data to inform individualized drug selection and/or dosing adjustment.[125] As use of WGS grows and that data is shared, more genotype–phenotype associations are being established and information of the pathogenicity of variants will become more certain, and reanalysis of genomes will yield new diagnoses.[49,126]

WGS is already in use and showing positive results in critical care units across the globe[41,42,52,53,56-60,76,70-128] and is recommended by the ACMG and ESHG.[17,49] With its improved diagnostic performance and faster time to answer, WGS holds the promise of helping patients and their families end an odyssey of inconclusive testing and unnecessary medical interventions—or prevent one altogether—and focus on care management.

Learn from others using whole-genome sequencing for rare disease diagnostics

Learn more about rare disease genomics

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