

Whole-Genome Sequencing

A collection of recent publications addressing performance, utility, and implementation in a clinical setting



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INTRODUCTION

There are an estimated 6–7,000 distinct diseases that meet the definition of rare disease—a number that is growing as new diseases are identified. Epidemiologic studies have estimated that approximately 2 – 6.2% of the population worldwide is affected by rare disease.¹⁻⁵ Recent literature estimates that between 70 – 80% of rare diseases are either exclusively genetic or have genetic subtypes.^{1,3-4,6} Thus, although individual genetic diseases are rare, in aggregate they are quite common.

Current standard of care diagnostic approaches are frequently associated with long diagnostic odysseys, leading to sub-optimal care. However, as understanding of the genetic etiology of diseases has grown, the ability to impact care management (including targeted treatments and other precision approaches guided by molecular diagnosis) for many genetic diseases has increased dramatically.⁷⁻¹¹ Obtaining a molecular diagnosis in a timely fashion is critical, as early intervention can change the course of disease progress, prevent morbidity, and improve outcomes in many cases. In addition, a confirmed molecular diagnosis can allow for disease-specific follow-up/ preventative recommendations, referral to subspecialty services, change in aggressiveness of treatment plan, referral to palliative care, and reproductive counseling for families.^{12,13}

Many publications have demonstrated that whole-genome sequencing (WGS) has technical advantages over other genetic testing applications and can provide a diagnosis with a single test versus multi-step iterative testing. The goal of WGS is to provide the most comprehensive analysis of the human genome to increase the likelihood of a molecular diagnosis in less time compared to standard testing practices.

Goal of Publication Overview

This publication overview highlights relevant publications that show WGS is the most comprehensive test for detecting multiple variant types in a single assay and can provide a genetic diagnosis faster than current genetic testing approaches in acutely ill infants and undiagnosed pediatric outpatients with rare diseases with suspected genetic etiology. The overview also lists publications which demonstrate that clinical implementation of WGS can lead to both clinical utility and cost savings.¹⁴⁻²⁰ Finally, clinical guidelines, society statements, and links to additional resources are provided.

TECHNICAL COMPARISON OF WGS TO OTHER MOLECULAR DIAGNOSTIC TESTS

Genetic disease can be caused by many different variant types including:

- Single nucleotide variants (SNVs): single base pair change which can disrupt a gene
- Insertions and deletions (indels): genetic material is lost or gained on a small scale (< 1000 base pairs)
- Copy number variants (CNVs): a gain or loss of genetic material on a larger scale (>1000 base pairs) that can cause simple duplications, deletions or more complex rearrangements
- Structural variants (SVs): copy-neutral changes such as an inversion or balanced translocation
- Short tandem repeats (STRs): repeated DNA sequences, also known as repeat expansions
- Paralogs: class of homologous genes resulting from gene duplication

The contribution of pathogenic variant types to various rare genetic diseases is shown in Table 1.

Table 1: Examples of contribution of variant types of rare genetic diseases¹³

Clinical Indication	Causal Pathogenic variant types
Multiple congenital anomalies	CNV (most common), SNV, SV, Mitochondrial, STR (rarely)
Early onset or intractable epilepsy	SNV (most common), all other variant types
Intellectual disability (moderate to severe) / Global developmental delay	All variant types
Inborn errors of metabolism	SNV and Indels (most common), Mitochondrial
Musculoskeletal disorders, including neuromuscular, skeletal dysplasia and abnormal growth, and connective tissue disorders	SNV, Indel, Mitochondrial, STR; less commonly CNV and SV

*Note: this list is not intended to be comprehensive.

Additional Reading

Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med.* 2018. Nov;20(11):1328-1333.

Chen X, Sanchis-Juan A, French CE, et al. Spinal muscular atrophy diagnosis and carrier screening from genome sequencing data. *Genet Med.* 2020 May;22(5):945-953.

Chen X, Schulz-Trieglaff O, Shaw R, et al. Manta: rapid detection of structural variants and indels for germline and cancer sequencing applications. *Bioinformatics.* 2016 Apr 15;32(8):1220-2.

Dolzhenko E, van Vugt JJ, Shaw RJ, Bekritsky, et al. Detection of long repeat expansions from PCR-free whole-genome sequence data. *Genome Res.* 2017 Nov;27(11):1895-1903.

Gross A, Ajay SS, Rajan V, et al. Copy number variants in clinical WGS: deployment and interpretation for rare and undiagnosed disease. *Genetic Med.* 2019;21(5):1121-1130.

Ibanez K, Polke J, Hagelstrom T, et al. Whole genome sequencing for diagnosis of neurologic repeat expansion disorders. *bioRxiv.* bioRxiv 2020.11.06.371716.

Lindstrand A, Eisfeldt J, Pettersson M, et al. From cytogenetics to cytogenomics: whole genomes sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. *Genome Med.* 2019 Nov 7;11(1):68.


Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med.* 2018 Apr;20(4):435-443.

Sanghvi RV, Buhay CJ, Powell, V et al. Characterizing reduced coverage regions through comparison of exome and genome sequencing data across 10 centers. *Genet Med.* 2018 Aug;20(8):855-866.


There are numerous technologies used to evaluate patients with suspected genetic disease and each technology varies in its ability to detect different variant types. Notably, WGS sequences both the coding and noncoding regions of the genome allowing for the most comprehensive variant analysis [i.e., SNVs, indels, CNVs, repeat expansions, mitochondrial variants, and paralogs (i.e.. spinal muscular atrophy)] compared to standard testing methodologies (Table 2).

Table 2. Genetic testing approaches and variant detection

	Sanger*	Targeted NGS*	PCR*	CMA*	WES*	WGS*
SNVs	✓	✓	✓		✓	✓
Indels	✓	✓	✓	✓	✓	✓
CNVs		✓	✓	✓	✓	✓
Repeat Expansions			✓			✓
Structural Variants				✓	✓	✓
Mitochondrial	✓	✓			✓	✓
Paralogs	✓		✓			✓



Capable



Limited capabilities

*Variant detection may vary depending on laboratory and test offering

CMA=chromosomal microarray; CNV=copy number variant; FISH=fluorescence in situ hybridization; Indel=small insertion/deletion; NGS=next-generation sequencing; PCR=polymerase chain reaction; SNV=single nucleotide variant; WES=whole-exome sequencing; WGS=whole-genome sequencing.

WGS IN AN ACUTE CARE SETTING

For critically ill infants, a rapid diagnosis can be vital for timely and appropriate medical intervention. The following publications highlight evidence demonstrating diagnostic yield and changes in clinical management triggered by a WGS diagnosis in acutely ill infants.

Key Publications

Effect of whole genome sequencing on the clinical management of acutely ill infants with suspected genetic disease: the NICUSeq Randomized Time-Delayed Trial.

Krantz ID, Medne L, Weatherly JM, et al. Am J Med Genet A. 2021 Aug 5. Sep 27:e213496. Epub ahead of print.

A randomized-controlled, time-delayed trial was conducted across five US institutions comprising a racial, ethnic and geographically diverse study cohort. Whole-genome sequencing (WGS) was performed in 354 infants randomized to receive results at 15 days (Early arm, n=176) or 60 days (Delayed arm, n=178) after enrollment. When compared to usual care (UC) testing at 60 days, WGS demonstrated a two-fold higher diagnostic yield (31% vs. 15%; $p < 0.001$). Management changes were significantly higher in patients in the Early arm vs. the Delayed arm (21% vs. 10%; $p = 0.009$). The most frequent changes in management were subspecialty referrals, alterations in medication, surgery, or other invasive procedures. For acutely ill infants in an intensive care unit, WGS was associated with a significant increase in focused clinical management compared to UC, supporting WGS adoption as a first-line test in this population.

Application of full-spectrum rapid clinical genome sequencing improves diagnostic rate and clinical outcomes in critically ill infants in the China Neonatal Genomes Project.

Wu B, Kang W, Wang Y, et al. Crit Care Med. 2021 Oct 1;49(10):1674-1683

Critically ill infants (n = 202) were recruited from 13 China Neonatal Genomes Project hospitals which spans 10 provinces. In a direct comparison to proband-only clinical exome sequencing (PoCES), trio-rapid WGS provided higher diagnostic yield in a shorter period time (20.3% vs 36.6%; 7 vs 20 days, respectively). The study also demonstrated the clinical actionability of trio-rapid WGS as 21.6% of those receiving a diagnosis experienced a change in clinical management and 32.4% were referred to a new subspecialist.



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Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care.

Dimmock D, Caylor S, Waldman B, et al. *Am J Hum Genet.* 2021 Jul 1;108(7):1231-1238.

Rapid WGS was performed on 184 critically ill infants with Medi-Cal recruited from five children's hospitals across the state of California. Outcomes were evaluated using a healthcare provider questionnaire and modeled processes to estimate clinical management changes and the economic impact on the hospitals. A total of 74/184 (40%) of infants received a diagnosis and 32% experienced at least one change in medical care. Changes in management and/or cost savings were not limited to only those receiving a diagnosis as negative results also resulted in clinical management modifications. Cost savings was calculated based on a smaller cohort of 31 infants whose length of stay was impacted by rWGS results. Considering the cost of rWGS for the entire cohort, the average cost savings was \$2549-6294 per child. The authors concluded that rapid WGS can be deployed as a first-tier test in the NICU.

The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants.

Petrikina JE, Cakici JA, Clark MM, et al. *NPJ Genom Med.* 2018 Feb 9;3:6.

Rapid WGS plus standard clinical testing yielded a higher genetic diagnosis rate and shorter time to diagnosis compared to standard clinical testing alone. In this partially blinded, randomized controlled trial, 65 infants (<4 months of age) with highly variable phenotypes had rapid WGS to determine diagnosis at 28 days post enrollment. Median time to diagnosis with WGS was 13 days vs. 107 days with standard clinical testing and median day of life at diagnosis was 25 days with WGS vs. 130 days with standard genetic testing. This study was terminated early due to equipoise and the growing inclusion of NGS in standard clinical testing strategies.

Additional Reading

Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. *Am J Hum Genet.* 2019 Oct 3;105(4):719-733.

Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med.* 2018 Apr 4;3:10.

Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing: comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet.* 2018 Nov;55(11):721-728.

Sanford EF, Clark MM, Farnaes L, et al. Rapid whole genome sequencing has clinical utility in children in the PICU. *Ped Crit Care Med.* 2019 Nov;20(11):1007-1020.

van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. *Pediatrics.* 2017;140(4).

Willig LK, Petrikina JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015 May;3(5):377-87.

WGS IN A PEDIATRIC OUTPATIENT SETTING

For pediatric outpatients, an early diagnosis can prevent a long, expensive diagnostic odyssey. Diagnostic delays can result in significant health and financial burdens including missed opportunities for critical intervention (e.g., specialist visits), unnecessary procedures and treatments, and an emotional toll on families. Recent evidence has demonstrated that WGS has high diagnostic and clinical utility when used as first-tier test in pediatric outpatients with suspected genetic disease.

Key Publication Summaries

Integration of whole genome sequencing into a healthcare setting: high diagnostic rates across multiple clinical entities in 3219 rare disease patients.

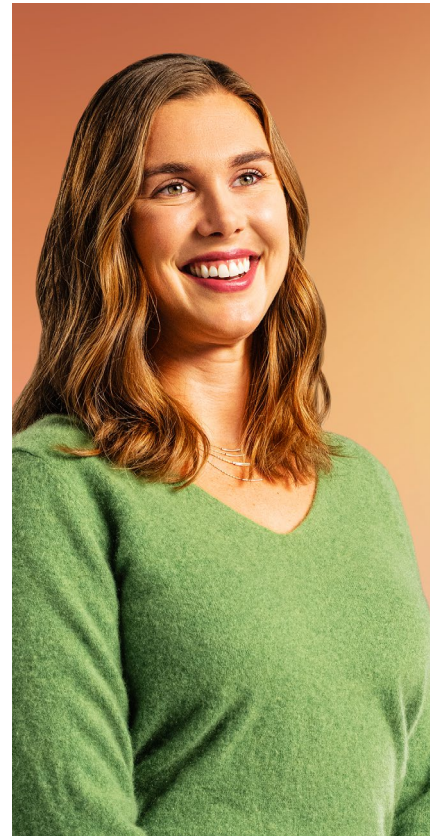
Stranneheim H, Lagerstedt-Robinson K, Magnusson M, et al. *Genome Med.* 2021 Mar 17;13(1):40.

An approach combining first-tier clinical WGS and multidisciplinary expertise led to the successful integration of genomics into the management of rare disease. Rare disease patients (n = 3219) were recruited over 4-year period. Initial analysis was performed using disease-specific panels or an OMIM morbid gene panel based on phenotype. In the absence of molecular finding, additional analysis including a research WGS was offered. The overall diagnostic yield 40% (1285/3219) and variants were identified in 754 different genes. Variant analysis evolved over the course of the study to include all variant types currently detectable by WGS. The authors remarked that clinical WGS has “turned out to be a true game changer in the rare disease space”.

Clinical whole genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico.

Scocchia A, Wigby KM, Masser-Frye D, et al. *NPJ Genom Med.* 2019 Feb 14;4:5.

In a resource-limited setting, WGS achieved a wide range of diagnoses and impacted patient care. WGS was provided to 60 children suspected of having a genetic condition. Indications included 77% with suspected pattern of malformation and 23% with primary neurological presentation. The diagnostic rate of WGS was 68.3% (76.1% in primary malformation subgroup vs. 42.9% in primary neurological group) and a change in clinical management was



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reported in 48.8% of all cases, including 6 of 19 without a diagnosis. Post-test genetic counseling was modified for 81.7% of the entire cohort.

Diagnostic yield and treatment impact of whole-genome sequencing in paediatric neurological disorders.

Lee HF, Chi CS, Tsai CR. *Dev Med Child Neurol.* 2021 Aug;63(8):934-938.

A study cohort of 214 pediatric patients with various neurologic disorders received WGS. Specific indications included, epilepsy (120), neurodevelopmental disorders (73), movement disorders (13) and neuromuscular conditions (8). The overall diagnostic yield was 43.9% (94/214) with the highest yield in patients with neuromuscular conditions (62.5%) followed by epilepsy (47.5%). Of those diagnosed via WGS, 23.4% experienced a change in medical management.

Genome sequencing as a diagnostic test in children with unexplained medical complexity.

Costain G, Walker S, Marano M, et al. *JAMA Netw Open.* 2020 Sep 1;3(9):e2018109.

This prospective study evaluated the analytical and clinical validity of WGS as a first-tier test compared to conventional genetic testing in a cohort of 49 children with medical complexity. The median number of conventional genetic tests was four per proband (1-13) including chromosomal microarray (n=48) and WES (n=33). WGS at 36x detected 100% of variants detected by the other tests (n=124) with an overall diagnostic yield of 30.6% (15/49), including the discovery of three new genetic conditions. Clinical implications were noted in 12 patients, including an immediate medical management change in seven. The authors conclude that WGS has a role as a first-tier test in children with medical complexity.

100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care — Preliminary Report

100,000 Genomes Project Pilot Investigators, Smedley D, Smith KR, et al. *N Engl J Med.* 2021 Nov 11;385(20):1868-1880.

This pilot study cohort of 4660 participants (all ages) from 2183 families who received WGS uncovered new diagnoses across a broad range of rare diseases, many of which had impacts on clinical decision making for patients and families. It was led by Genomics England and Queen Mary University of London in partnership with National Institute of Health Research (NIHR) BioResource. WGS led to a diagnosis for 25% of the participants who previously had no diagnosis from prior standard testing. Of the new diagnoses, 14% were found in regions of the genome that would be missed by other tests.

Additional Reading

Bertoli-Avella AM, Beetz C, Ameziane N, et al. Successful application of genome sequencing in a diagnostic setting: 1007 index cases from a clinically heterogeneous cohort. *Eur J Hum Genet.* 2021 Jan;29(1):141-153.

Bhatia NS, Lim JY, Bonnard C, et al. Singapore Undiagnosed Disease Program: Genomic analysis aids diagnosis and clinical management. *Arch Dis Child.* 2021 Jan;106(1):31-37.

Lindstrand A, Eisfeldt J, Pettersson M, et al. From cytogenetics to cytogenomics: whole genomes sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. *Genome Med.* 2019 Nov 7;11(1):68.

Splinter K, Adams DR, Bacino CA, et al. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. *N Engl J Med.* 2018 Nov 29;379(22):2131-2139.

CLINICAL GUIDELINES AND PROFESSIONAL SOCIETY STATEMENTS

Professional organizations such as the American College of Medical Genetics and Genomics (ACMG), Chinese Medical Doctor's Association, Royal Australasian College of Physicians, and Canadian College of Medical Genetics have issued guidelines and viewpoints regarding clinical implementation of WGS in certain patient populations. Considerations are listed in the table below.

Table 3: Summary of societal publications specific to WES and/or WGS

	ACMG*	CMDA [§]	RACP [®]	CCMG [¥]
Date of latest publication	July 2021 ²¹	June 2019 ²²	February 2021 ²³	May 2015 ²⁴
Publication Type	Practice Guideline	Expert Consensus	Viewpoint	Position Statement
Sequencing Type	WES/WGS	WGS	WES/WGS	WES/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	Patients with suspicion of a significant monogenic disease associated with a high degree of genetic heterogeneity; patients where specific genetic tests have failed to provide a diagnosis; when WES/WGS is a more cost-effective approach than available individual gene or gene panel testing
Tier	First or second tier test	First or second tier test	Second tier: Negative routine blood tests if indicated, negative CMA required	First or second tier test
Secondary Findings	Patient can opt out with informed consent	Patient can opt out with informed consent	Referred to as Incidental Findings; Authors do not endorse the intentional clinical analysis of disease genes not related to primary indication.	Referred to as Incidental Findings; Recommend cautious approach with opt-in/opt-out. CCMG does not endorse the intentional clinical analysis of disease genes unrelated to the primary indication.

ACMG: American College of Medical Genetics and Genomics

CMDA: Chinese Medical Doctor Association, Medical Genetics Branch

RACP: Royal Australasian College of Physicians, Paediatrics and Child Health Division

CCMG: Canadian College of Medical Genetics

META-ANALYSES AND SYSTEMATIC EVIDENCE REVIEWS

Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment.

Ontario Health Technology Assessment Series, 2020 Mar 6;20(11):1-178.

A systematic literature review was conducted as part of a recent Ontario Health Technology Assessment of the clinical utility of genome-wide sequencing for individuals with unexplained developmental delay or multiple congenital anomalies. They found that compared to standard of care genetic testing, ES+GS had higher diagnostic yield and demonstrated clinical utility. A primary economic evaluation of ES + GS was conducted using a discrete choice simulation. The authors concluded that the use of genome-wide sequencing as a first-or second-tier test could save cost and improve diagnostic yield.

Systematic evidence-based review: outcomes from exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability.

Malinowski J, Miller DT, Demmer L, et al. Genet Med. 2020 Jun;22(6):986-1004.

This review compiled primary literature from 2007 to 2019 to evaluate the utility of exome/ genome sequencing (ES/GS) in patients with congenital anomalies, developmental delay or intellectual disability (CA/DD/ID). After review of 7178 publications, 167 met criteria for evaluation including 36 with >20 patients. For the studies with larger sample sizes, utility was evaluated following ES and/or GS (ES= 27; GS = 7; ES/GS = 2) with a range in sample size from 22-278. Ninety-five percent of studies reported a change in clinical management including changes in medication, procedures, specialist referrals, redirection of care and clinical trial opportunities. More than half of patients experienced a reported clinical impact related to an ES/GS diagnosis and more than half of studies with >20 patients identified an impact on family planning or reproductive decision-making. There was a paucity of data describing improved morbidity and mortality; however, there was sufficient, indirect evidence of the clinical and personal utility of ES/GS in patients with CA/DD/ID. The committee concluded that there is a need for a more formal framework to evaluate outcomes for ES/GS. This review was used to guide the development of an evidence-based guideline.



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Additional Reading

Bick D, Jones M, Taylor SL, et al. Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. *Journal of Medical Genetics*. 2019 Dec;56(12):783-791.

Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected diseases. *NPJ Genom Med*. 2018 Jul 9;3:16.

Shickh S, Mighton C, Uleryk E, et al. The clinical utility of exome and genome sequencing across clinical indications: a systematic review. *Hum Genet*. 2021 Oct;140(10):1403-1416.

RESOURCES

As the body of evidence supporting first-tier WGS continues to grow, it is important that resources and tools are made available to healthcare providers, laboratories, patients and payers to support implementation. The following is a list of globally-recognized resources available to the public. While this list is not exhaustive, it may serve as a guide for those looking for additional support.

1. The Medical Genome Initiative: www.medgenomeinitiative.org: Consortium of leading research and healthcare organizations. Goals of the initiative are to develop and publish best practices for clinical implementation of WGS.
2. Clinical Sequencing for Rare Disease online short course through Precision Medicine Advisors: <https://precision-medicine-academy.thinkific.com/courses/Rare-disease>: Online course developed to provide healthcare providers with high level overview of WGS and demonstration of its potential use in the diagnosis and management of patients.
3. Rady Children's Institute of Genomic Medicine Precision Medicine Grand Rounds: <https://radygenomics.org/rpm-grand-rounds/>: Monthly live and on-demand digital seminars aimed at clinicians with an interest in how WGS can improve patient management.
4. ClinGen – Clinical Genome Resources: www.clinicalgenome.org: Resource dedicated to building database of clinically relevant genes and variants.
5. Genomics England: <https://www.genomicsengland.co.uk/understanding-genomics/>: Delivering the 100,000 genomes project with aim to benefit patients by ethical implementation of WGS into clinical practice.
6. Australian Genomics Health Alliance: <https://www.australiangenomics.org.au/>: National collaboration with aim to translate genomics into real world value for patients.

BIBLIOGRAPHY

1. Wakap, S, Lambert DM, Orly A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet.* 2020 Feb;28(2):165-173.
2. Walker et al. The collective impact of rare diseases in Western Australia: an estimate using a population-based cohort. *Genet Med.* 2017 May;19(5):546-552.
3. Ferreira CR. The Burden of Rare Diseases. *American Journal of Medical Genetics.* 2019 Jun;179(6):885-892.
4. Bick D, Jones M, Taylor SL, et al. Case for genome sequencing in infants and children with rare, undiagnosed or genetic diseases. *Journal of Medical Genetics.* 2019 Dec;56(12):783-791.
5. Posada De La Paz, M. et al. Rare Diseases Epidemiology: Update and Overview. *Advances in Experimental Medicine and Biology.* 2017; 1031:589-604.
6. Eurodis Rare Diseases Europe. About rare diseases. <https://www.eurodis.org/content/what-rare-disease>. Updated June 14, 2019. Accessed March 27, 2020.
7. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med.* 2018 Apr 4;3:10.
8. Scocchia A, Wigby KM, Masser-Frye D, et al. Clinical whole genome sequencing as a first tier test at a resource-limited dysmorphology clinic in Mexico. *NPJ Genom Med.* 2019 Feb 14;4:5.
9. Splinter K, Adams DR, Bacino CA, et al. Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease. *N Engl J Med.* 2018 Nov 29;379(22):2131-2139.
10. Sanford et al. Rapid whole genome sequencing has clinical utility in children in the PICU. *Ped Crit Care Med.* 2019 Nov;20(11):1007-1020.
11. Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *Lancet Respir Med.* 2015;3(5):377-387.
12. Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected diseases. *NPJ Genom Med.* 2018 Jul 9;3:16.
13. Wright C, FitzPatrick, D, Firth H. Paediatric genomics: diagnosing rare disease in children. *Nat Rev Genet.* 2018 May;19(5):253-268.
14. Chen X, Sanchis-Juan A, French CE, et al. Spinal muscular atrophy diagnosis and carrier screening from genome sequencing data. *Genet Med.* 2020 May;22(5):945-953.
15. Chen X, Schulz-Trieglaff O, Shaw R, et al. Manta: rapid detection of structural variants and indels for germline and cancer sequencing applications. *Bioinformatics.* 2016 Apr 15;32(8):1220-2.
16. Dolzhenko E, van Vugt JJ, Shaw RJ, Bekritsky, et al. Detection of long repeat expansions from PCR-free whole-genome sequence data. *Genome Res.* 2017 Nov;27(11):1895-1903.
17. Gross A, Ajay SS, Rajan V, et al. Copy number variants in clinical WGS: deployment and interpretation for rare and undiagnosed disease. *Genetic Med.* 2019;21(5):1121-1130.
18. Lelieveld SH, Spielmann M, Mundlos S, Veltman JA, Gilissen C. Comparison of Exome and Genome Sequencing Technologies for the Complete Capture of Protein-Coding Regions. *Hum Mutat.* 2015 Aug;36(8):815-22.
19. Lindstrand A, Eisfeldt J, Pettersson M, et al. From cytogenetics to cytogenomics: whole genomes sequencing as a first-line test comprehensively captures the diverse spectrum of disease-causing genetic variation underlying intellectual disability. *Genome Med.* 2019 Nov;11(1):68.
20. Sanghvi RV, Buhay CJ, Powell, V et al. Characterizing reduced coverage regions through comparison of exome and genome sequencing data across 10 centers. *Genet Med.* 2018 Aug;20(8):855-866.
21. Manickham K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2021 Nov;23(11):2029-2037.
22. Chinese Medical Doctor Association Medical Genetics Branch. Expert consensus on the clinical application of whole-genome sequencing in the detection of genetic diseases. *Chinese Journal of Pediatrics.* 2019, 57(6): 419-423.
23. Sachdev R, Field M, Baynam GS, et al. Paediatric genomic testing: Navigating medicare rebatable genomic testing. *J Paediatr Child Health.* 2021 Apr;57(4):477-483.
24. Boycott K, Hartley T, Adam S, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *J Med Genet* 2015;52: 431-437.

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