Finding Patients Through Genomic Sequencing

Holly L. Snyder, MS, LCGC

Senior Manager, Medical Affairs

illumina®

© 2022 Illumina, Inc. All rights reserved.

Disclosures and Disclaimers

I am an employee of and hold equity in Illumina.

Rare Disease

illumina®

Rare Disease and Pediatrics

~50%
of rare diseases impact children[1]

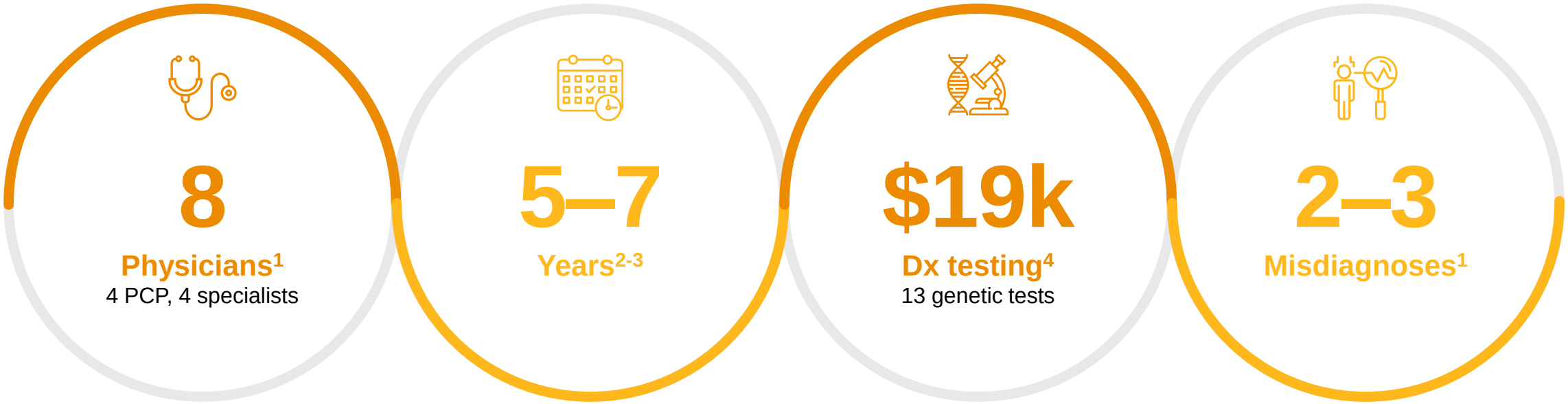
In the NICU, birth defects or genetic conditions attribute to[2–6]

~30%
of all admissions

Up to 40%
of all deaths

1. Bick D, Jones M, Taylor SL, et al. Journal of Medical Genetics. 2019.
2. Baxter SK, King MC. A Time to Sequence. JAMA Pediatr. 2017;171(12):e173435.
3. Weiner J, Sharma J, Lantos J, Kilbride H. How infants die in the neonatal intensive care unit: trends from 1999 through 2008. Arch Pediatr Adolesc Med. 2011;165(7):630-634
4. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. NCHS Data Brief. 2018(328):1-8. 39.
5. Arth AC, Tinker SC, Simeone RM, Ailes EC, Cragan JD, Grosse SD. Inpatient Hospitalization Costs Associated with Birth Defects Among Persons of All Ages - United States, 2013. MMWR Morb Mortal Wkly Rep. 2017;66(2):41-46.
6. Berry MA, Shah PS, Brouillette RT, Hellmann J. Predictors of mortality and length of stay for neonates admitted to children's hospital neonatal intensive care units. J Perinatol. 2008;28(4):297-302.

The Diagnostic Journey is Long, Costly and Imposes Significant Burden on the Healthcare System



Identifying all the known rare and ultrarare diseases can remain a challenge even for the most experienced clinical specialists.

1. Rare Disease Impact Report: Insights from patients and the medical community. https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf.
2. Global Commission. Ending the diagnostic odyssey for children with a rare disease. 2019. globalrarediseasecommission.com.
3. Posada de la Paz M, Taruscio D, Groft SC. Rare diseases epidemiology: Update and overview. 2nd edition. Chapter 2. Springer 2017. Cham, Switzerland.
4. Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med. 2014;6;265ra168.

RareX: Be Counted

Purpose

- Determine more accurate count of RD that resonates with communities
- Offer recommendations for RD communities

Findings

- RD Count
  - Conservative count of 10,867 RDs
    - 6,282 Orphanet + 2,065 OMIM + 2,520 OMIM with narrow match to Orphanet RD
  - 87% have a genetic or suspected genetic
  - Treatment options available for ~5%

https://rare-x.org/wp-content/uploads/2022/05/be-counted-052722-WEB.pdf

Comparison of WGS to Standard Testing

illumina®

Comparison of Genetic Testing

Single Gene Testing

Testing a single gene of interest

Targeted Sequencing

Testing a subset of genes related to a particular indication

Whole-Exome Sequencing

Testing the full exome

Whole-Genome Sequencing

Testing the full genome

WGS Provides the Most Comprehensive Analysis of Genomic Variants Among All Clinical Genomic Testing Methods

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

✓ Limited capabilities ✓ Capable

*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.

References: 1. 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. doi: 10.1038/gim.2017.119. Epub 2017 Aug 3. 2. Dolzhenko E, van Vugt JJFA, Shaw RJ, et al. Detection of long repeat expansions from PCR-free whole-genome sequence data. Genome Res. 2017;27(11):1895-1903. doi: 10.1101/gr.225672.117. 3. 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;32(8):1220–1222. http://doi.org/10.1093/bioinformatics/btv710.

The Value of Comprehensive Testing

Nearly 10% of molecularly diagnosed patients have multiple pathogenic variants

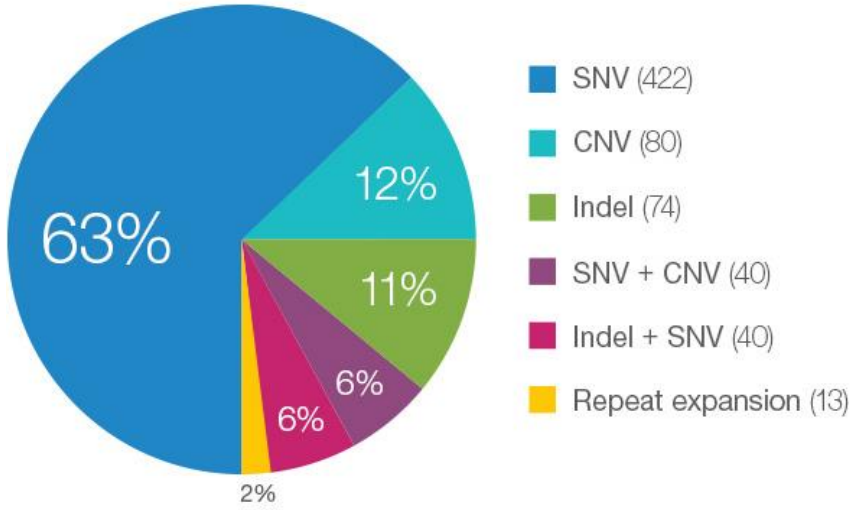
Significant diversity in pathogenic variation underlying genetic disease.

Multiple variant types identified in 5–12% of molecularly diagnosed cases.[1-3]

Demonstrates value of comprehensive approach.

Patient variant distribution

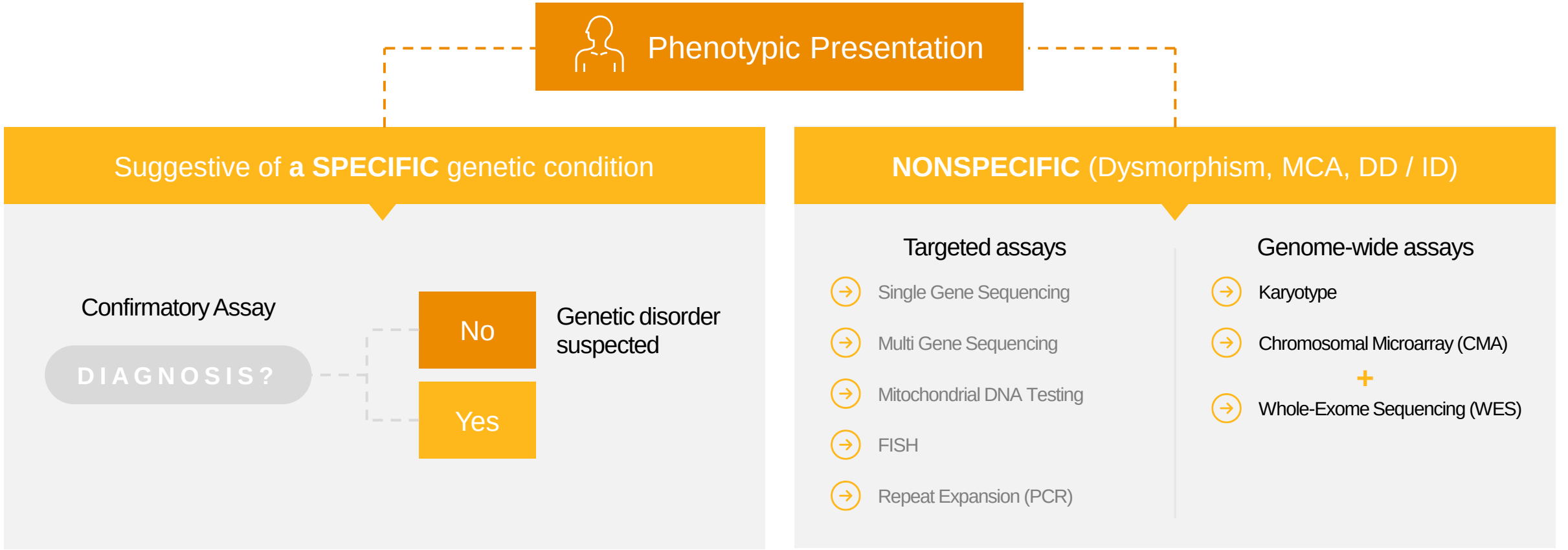
(N=699 patients)[3]



WGS testing performed in the Illumina Clinical Services Laboratory represents individuals enrolled in disease-specific clinical trials or as part of philanthropic efforts. As such, the percentage represented here may not be typical of that seen in a standard laboratory. This data is based on 669 total cases.

1. Posey et al. Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. New England Journal of Medicine. 2017.
2. Scoccia et al. Clinical whole-genome sequencing as a first-tier test at a resource-limited dysmorphology clinic in Mexico. NPJ Genome Med. 2019.
3. Data on file at Illumina Clinical Services Laboratory; patient cohort of 699.

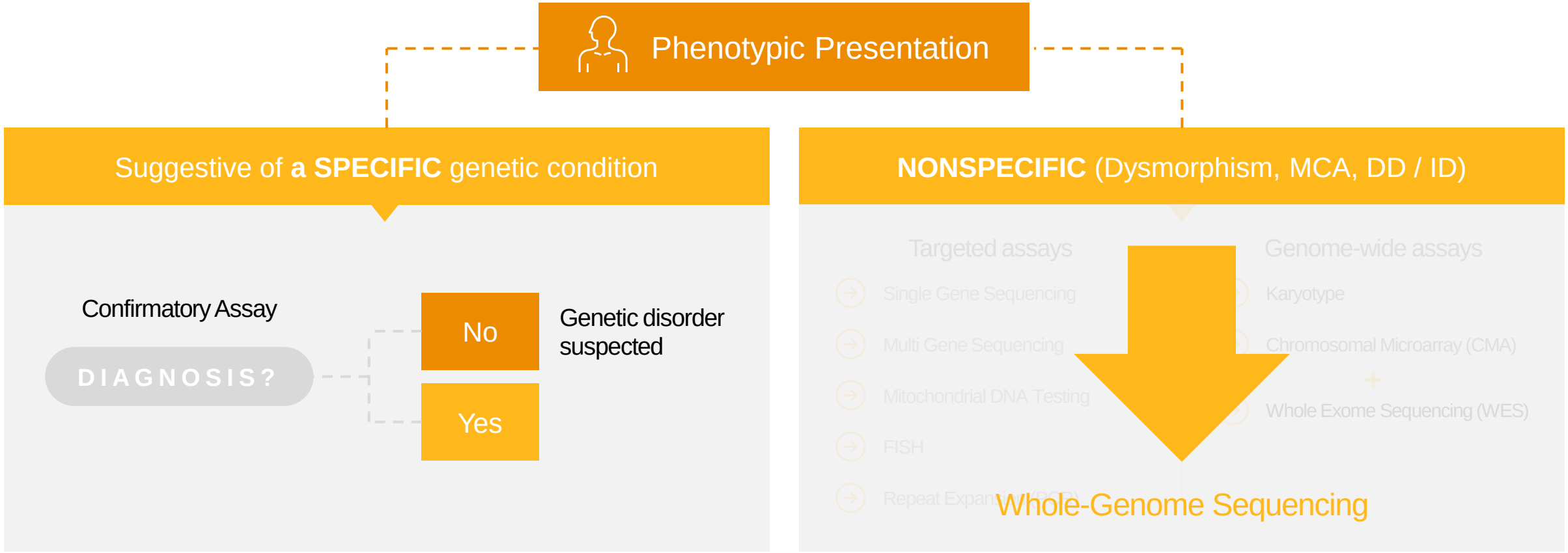
Rapid End to the Diagnostic Odyssey



MCA: Multiple congenital anomalies.
DD / ID: Development delay/intellectual disability.
FISH: Fluorescence in situ hybridization

Sun F, Oristaglio J, Levy SE, et al. Genetic testing for developmental disabilities, intellectual disability, and autism spectrum disorder. Technical Brief Number. 2015;23,(2):531.

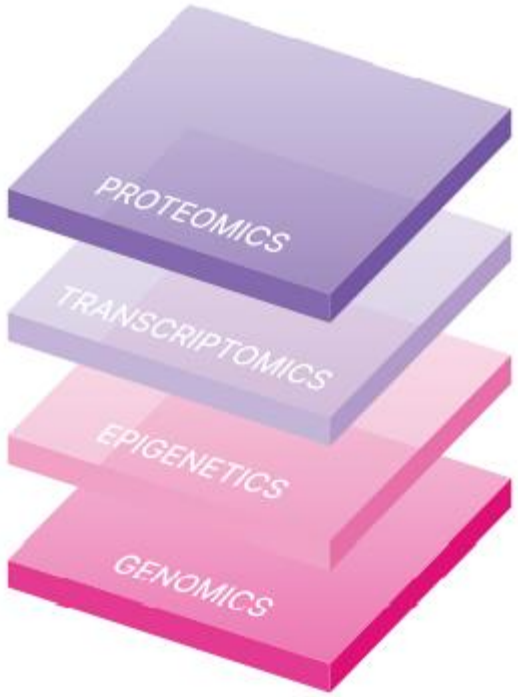
Rapid End to the Diagnostic Odyssey

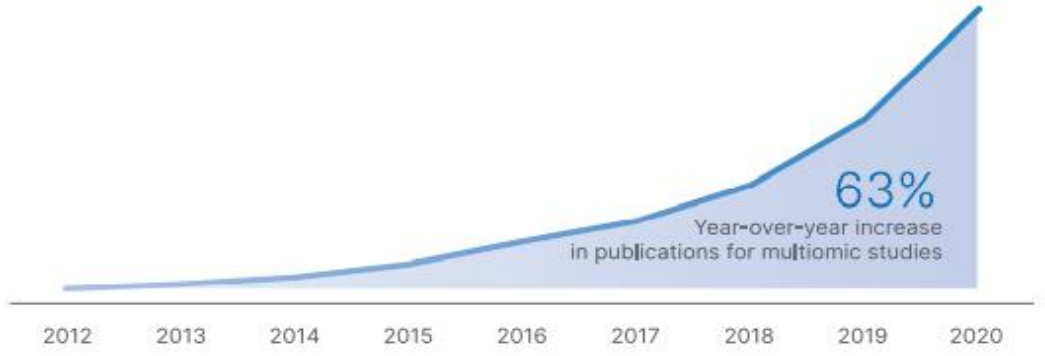


MCA: Multiple congenital anomalies.
DD / ID: Development delay/intellectual disability.
FISH: Fluorescence in situ hybridization

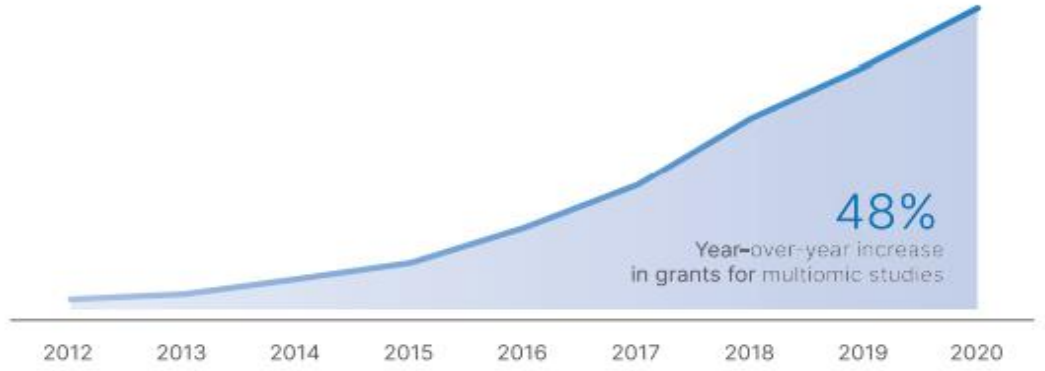
Sun F, Oristaglio J, Levy SE, et al. Genetic testing for developmental disabilities, intellectual disability, and autism spectrum disorder. Technical Brief Number. 2015;23,(2):531.

Multiomics





Multiomics publications on the rise—Since 2012, there has been a 63% average year-over-year increase in the number of publications featuring multiomic data.[1]



Grant funding growth for multiomics—Since 2012, there has been a 48% average year-over-year increase in the number of active or starting grants for multiomic studies.[1]

Utility Is Not One Thing

Clinical utility

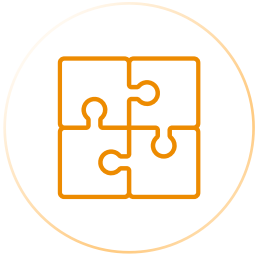
- **Impact of a result on medical decision-making**
- Comparison to other diagnostic tests
- Availability of effective interventions
- Avoidance of invasive testing and ineffective interventions
- Outcomes
- Physician behavior — medical error reduction

Personal utility

- Effect on future reproductive decisions
- **Impact on prognosis and direction of care**
- Impact on educational and rehabilitative services
- Cascade testing of relatives
- Satisfaction

Economic utility

- Costs of testing
- **Cost effectiveness**
- Utilization
- Risk reduction



System utility

- Services planning
- **Resource allocation**
- **Access to care**
- Efficiency of utilization
- Risk management
- Surveillance

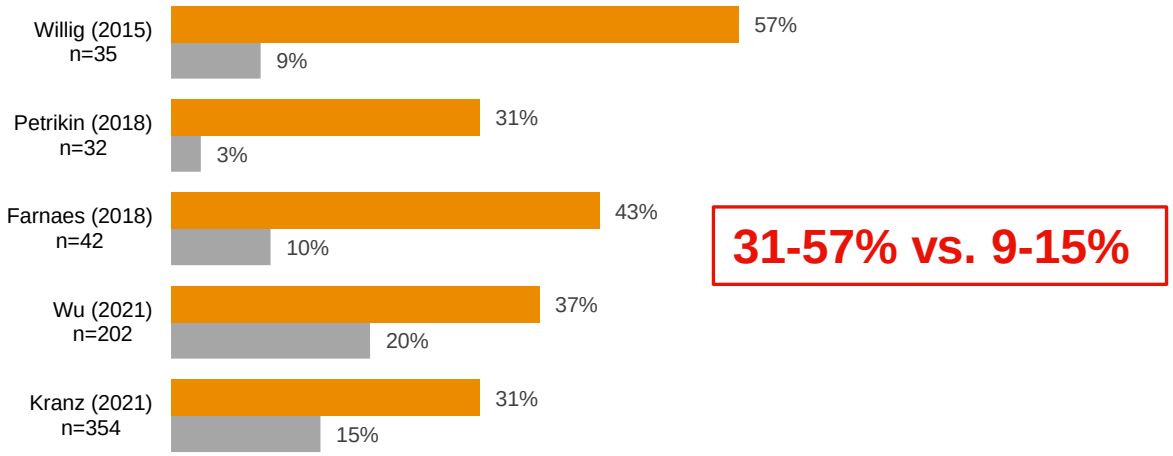
Supportive Evidence

illumina®

Rapid-WGS Has a Higher Diagnostic Yield Enabling Impact on Clinical Management of NICU / PICU Patients

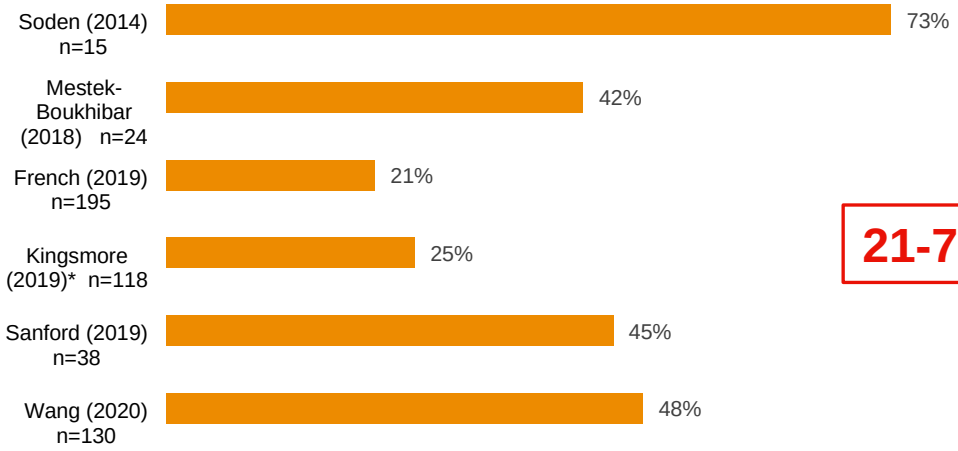
WGS Standard Tests

Dx yield from head-to-head comparison studies



31-57% vs. 9-15%

Dx yield from all other peer-reviewed publications



21-73%

A change in clinical management was reported across 8 of these studies.[2-5,8-11]

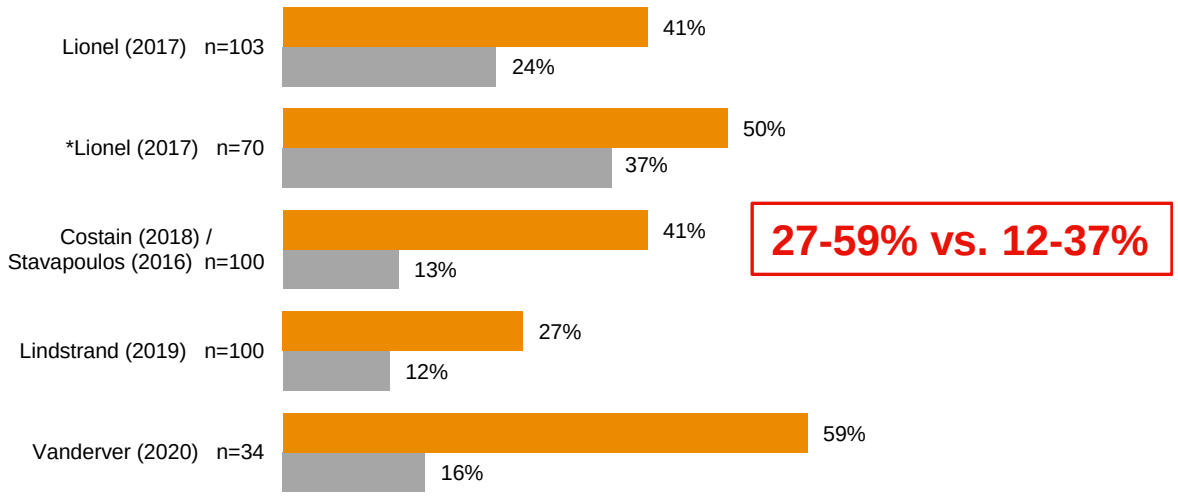
Note: Standard Tests may include CMA, FISH, karyotype ,targeted gene panels, microarrays, methylation, or other. In Kranz (2021), the comparison was between WGS early arm (15 days after enrollment) vs WGS delayed arm (60days after enrollment).
Cross-trial comparisons cannot be made given different study parameters/design.
WGS: whole-genome sequencing

References in slide notes; * Includes both rapid WGS and ultra rapid WGS.

Compared with Standard Approaches, WGS Has Higher Diagnostic Yields in Pediatric Outpatients

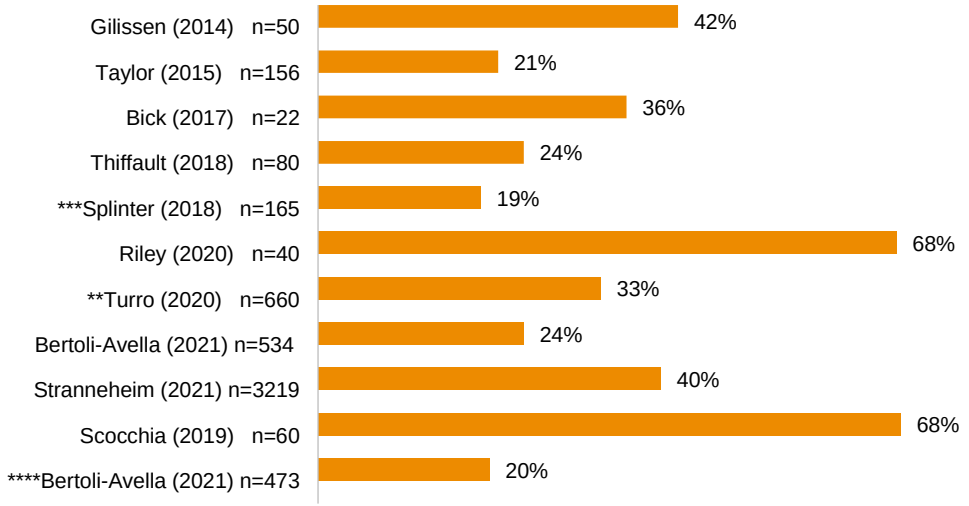
WGS Standard Tests

Dx yield from head-to-head comparison studies



27-59% vs. 12-37%

Dx yield from all other peer-reviewed publications



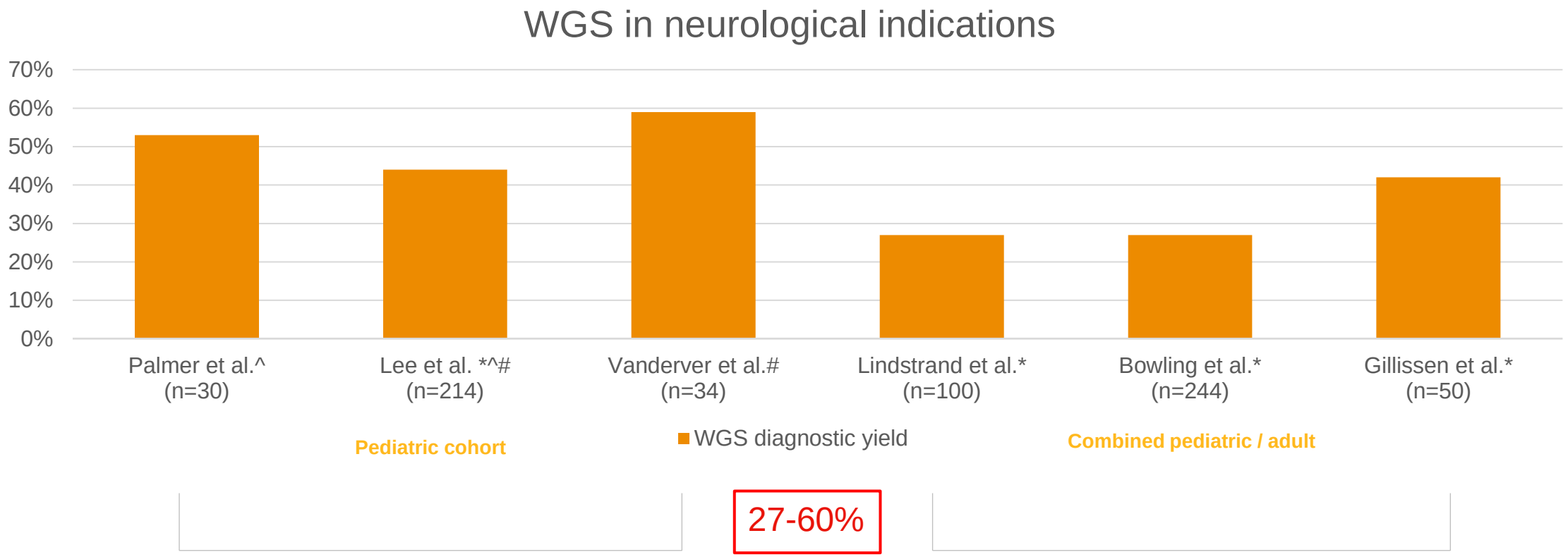
19-68%

A change in clinical management was reported in across 7 of these studies.[3,5,7,8,11,14,16]

Note: Standard Tests may include CMA, FISH, karyotype ,targeted gene panels, microarrays, methylation, or other. Cross-trial comparisons cannot be made given different study parameters / design
WGS: whole-genome sequencing

References in slide notes; *Subset of 70 patients with WGS and WES; **(Turro 2020) Neurodevelopmental disorders cohort; ***Note: in subset with negative WES, WGS diagnostic yield was 16% **** (Bertoli-Avella 2021) 83% of the sample at the age of testing are pediatric population (<16 years of age)

Whole-Genome Sequencing Demonstrates High Diagnostic Yield in Certain Neurological Indications



1. Studies may include combined adult and pediatric cohorts.
*Developmental delay/intellectual disability; ^Epilepsy; # Other neurologic disorders (eg. leukodystrophies, neuromuscular, movement).

Cost-effectiveness of ES/GS for children with rare disease

Modeled estimates of ES and GS compared to standard of care

Key Takeaway

First-line GS is cost-effective (CE) for diagnosing rare disease in infants. GS may be cost-effective in all children under certain assumptions. Standard of care testing prior to ES/GS increases cost without improving outcomes.

Method

- CE model incorporating costs, dx yield and quality-adjusted life years based on publicly available data and published evidence.
- Comparison of 7 test strategies over 10-years and lifetime (ie. 3 scenarios based on assumptions of disability/quality of life.
- Two cohorts of children with suspected genetic conditions analyzed: critically ill infants (<1 year) and all children (<18 years).

Findings

- Standard of care (SoC) testing had lowest cost over 10 years, but also the lowest dx yield.
- **First-line GS projected to increase costs & had higher dx yield** (~$15,048/added dx for infants and $27,349/added dx for all children).
- **First-line GS was most CE** (the lowest additional cost for each additional diagnosis) of the 6 strategies compared to SoC.
- Per probabilistic sensitivity analysis, first-line GS was the most CE approach at commonly accepted willingness to pay thresholds (how much society is willing to pay for a given outcome).
- **Reanalysis of ES or GS in undiagnosed children was considered CE** (good value for money)

Lavelle TA, Feng X, Keisler M, et al. Cost-effectiveness of exome and genome sequencing for children with rare and undiagnosed conditions . *Genet Med.*[published online ahead of print, 2022 Apr 8]. 2022;S1098-3600(22)00682-7. doi:10.1016/j.gim.2022.03.005

Health Economic Value of WGS in Rare Disease for Infants

Payer Perspective

Farnaes reported that rWGS reduced length of hospital stay by 124 days and resulted in a net savings of $804,200

- N=42 critically-ill infants in NICU

Dimmock reported that the GS testing in studied cohort cost $1.7 million, but led to $2.2–2.9 million cost savings in hospital costs and professional fees

- N=184 critically-ill infants

Lavelle reported, first-line GS may be the most cost-effective strategy for infants with rare conditions

- WGS is more cost-effective than WES in severally ill infants
- If used first WGS is cost-saving in severely ill infants compared to other common genetic testing in this population; CMA, WES, WES+CMA

Published September 5, 2022, Lindstrand et al, Genetics in Medicine

Our **findings strongly suggest** that **genome analysis outperforms** other testing strategies and **should replace traditional CMA and FMR1** analysis as a **first-line genetic test** in **individuals with ID/NDD. GS** is a **sensitive, time- and cost-effective** method that results in a confirmed molecular **diagnosis in 35% of all referred patients**.

Growing Coverage in the US and Globally

US

- As of December 2020, **commercial insurance plans in the US representing >16M lives have positive medical policies for rapid-WGS in the NICU/PICU**
  - Blue Shield of CA; Priority Health, Florida Blue, Horizon, Blue Cross Blue Shield Federal Employees Campaign, Capital Health Plan, Blue Cross of Idaho
- **11 state Medicaid** programs have payment rates posed for WGS

Asia

- **In Nov 2019**, **Australia's** Medical Services Advisory Committee (MSAC)—the official HTA body—issued a positive review for WES & WGS
- WES is reimbursed in **Japan** through the IRUD program

Europe, Middle East & Africa

- In the UK, **NHS England covers WES and WGS** in clinical routine for defined rare diseases and cancers. **Wales** has also commissioned the use of WGS in critically-ill children.
- Since 2021, **Germany reimburses WGS/WES** with no prior authorization requirement at the national level. In addition, major German health insurance companies also cover WES and WGS at a higher reimbursement level to allow for testing of patients and their parents ('trios').
- Other countries covering WES and WGS for patients with undiagnosed, suspected genetic diseases include **Switzerland, Denmark** and **Sweden**.
- Several countries, including but not limited to **Belgium, France, the Netherlands, Israel and Spain** are actively pursuing integration of WGS into clinical care and/or launching genomic initiatives that would include WGS for rare and undiagnosed disease

Societal Guidelines

illumina®

American College of Medical Genetics and Genomics Evidence-Based Guideline, 2021

Genetics inMedicine

www.nature.com/gim

ACMG PRACTICE GUIDELINE

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)

Kandamurugu Manickam[1,2], Monica R. McClain[3], Laurie A. Demmer[4], Sawona Biswas[5], Hutton M. Kearney[6], Jennifer Malinowski[7], Lauren J. Massingham[8,9], Danny Miller[10], Timothy W. Yu[11,12], Fuki M. Hisama[13] and ACMG Board of Directors[14✉]

Disclaimer: The ACMG has recruited expert panels, chosen for their scientific and clinical expertise, to develop evidence-based guidelines (EBG) for clinical practice. An EBG focuses on a specific scientific question and then describes recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options. ACMG EBGs are provided primarily as an educational resource for medical geneticists and other clinicians to help them provide quality medical services. They should not be considered inclusive of all relevant information on the topic reviewed.
Reliance on this EBG is completely voluntary and does not necessarily ensure a successful medical outcome. In determining the propriety of any specific procedure or test, the clinician should consider the best available evidence, and apply his or her own professional judgment, taking into account the needs, preferences and specific clinical circumstances presented by the individual patient. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this EBG. Clinicians are also advised to take notice of the date this EBG was published, and to consider other medical and scientific information that becomes available after that date.

PURPOSE: To develop an evidence-based clinical practice guideline for the use of exome and genome sequencing (ES/GS) in the care of pediatric patients with one or more congenital anomalies (CA) with onset prior to age 1 year or developmental delay (DD) or intellectual disability (ID) with onset prior to age 18 years.
METHODS: The Pediatric Exome/Genome Sequencing Evidence-Based Guideline Work Group ($n = 10$) used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence to decision (EtD) framework based on the recent American College of Medical Genetics and Genomics (ACMG) systematic review, and an Ontario Health Technology Assessment to develop and present evidence summaries and health-care recommendations. The document underwent extensive internal and external peer review, and public comment, before approval by the ACMG Board of Directors.
RESULTS: The 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 on family-focused and reproductive outcomes with relatively few harms. 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.
CONCLUSION: We strongly recommend that ES/GS be considered as a first- or second-tier test for patients with CA/DD/ID.

Genetics in Medicine; https://doi.org/10.1038/s41436-021-01242-6

INTRODUCTION

Congenital anomalies (CA), developmental delay (DD), and intellectual disability (ID) are among the most common indications for genetic referral in the pediatric population and comprise a heterogeneous group of conditions that can impact a child's physical, learning, or behavioral function. In contrast to early childhood mortality, which declined by 50% from 1990 to 2016, the prevalence of developmental disabilities was unchanged over the same period, according to the Global Burden of Diseases, Injuries and Risk Factors Study.[1] This study also reported on the worldwide prevalence and years lived with disability for six developmental disabilities: ID, epilepsy, autism spectrum disorder, attention deficit–hyperactivity disorder, and hearing and vision

[1]Division of Genetic and Genomic Medicine, Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH, USA. [2]The Ohio State University College of Medicine, Columbus, OH, USA. [3]Scientific and Strategic Affairs, Evidera | PPD, Waltham, MA, USA. [4]Division of Medical Genetics, Department of Pediatrics, Atrium Health's Levine Children's Hospital, Charlotte, NC, USA. [5]Division of Adult Genetics, Department of Pathology, University of California San Francisco, San Francisco, CA, USA. [6]Division of Laboratory Genetics and Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. [7]Write Inscite, LLC, South Salem, NY, USA. [8]Division of Medical Genetics, Department of Pediatrics, Hasbro Children's Hospital, Providence, RI, USA. [9]Alpert School of Medicine at Brown University, Providence, RI, USA. [10]MEPAN Foundation, Corte Madera, CA, USA. [11]Division of Genetics and Genomics, Boston Children's Hospital, Boston, MA, USA. [12]Harvard Medical School, Boston, MA, USA. [13]Division of Medical Genetics, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA. [14]American College of Medical Genetics and Genomics, Bethesda, MD, USA. ✉The Board of Directors of the American College of Medical Genetics and Genomics approved this evidence-based guideline on 24 May 2021. ✉email: documents@acmg.net

© The Author(s), under exclusive licence to the American College of Medical Genetics and Genomics 2021

SPRINGER NATURE

ACMG recommends exome/genome sequencing (ES / GS) as a first- or second-tier test in patients with 1 or more congenital anomalies prior to 1 year of age or intellectual disabilities / developmental delay prior to age 18.

ES / GS 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

Manickam, K., McClain, 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) https://doi.org/10.1038/s41436-021-01242-6

	ACMG* Practice Guideline	CMDA§ Expert Consensus	RACPβ Viewpoint	CCMG¥ Position Statement	ESHG# Recommendations
Date of Publication	July 2021[1]	June 2019[2]	February 2021[3]	May 2015[4]	May 2022[5]
Sequencing	WES/WGS	WGS	WES/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	Patients w/ suspicion of significant monogenic disease associated with high degree of genetic heterogeneity; specific genetic tests have failed to provide a diagnosis; cases when WES/WGS is a more cost-effective approach than available individual gene/gene panels	It is recommended to introduce WGS analysis in a diagnostic setting when it is a relevant improvement on quality, efficiency and/or diagnostic yield
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**	**Not specified**
Informed Consent and Pretest Counseling	Set expectations, review benefits/limitations/ harms of testing such as limited disease-known associations	Discuss purpose of test, test limitations, possible results, possibility of secondary findings; possibility of data reanalysis	Explain possible outcomes to manage patient/parent expectations, address potential for incidental (secondary) findings, address possibility of certain types of insurance discrimination	**Genetic counselling for the patient/ family should be undertaken and documented**. A list of what should be discussed during the informed consent process is included in the document.	**Pre-test genetic counseling should be performed prior to obtaining informed consent**. This counseling should be performed by a qualified expert (ie. clinician, genetic counselor).
Reevaluation/ Reanalysis	**Value in reanalysis**; frequency/strategy not specified	Not specified	In the event of a **variant of uncertain significance, recommend reanalysis in 18 months, up to twice after the initial test is performed**. Some situations warrant shorter reanalysis interval.	**Requests for re-analysis should be initiated by a ref. physician based on an established policy**; may involve **re-testing rather than re-analysis**, at discretion of laboratory. Further analysis of sequencing data through research may be an option.	**Reanalysis should be triggered by the clinician and not by the diagnostic laboratory**. Patients should be aware of and provide consent to reanalysis.

Pulled from CAP# M-GL-00364

Continued Efforts

What's Next in Evidence-Generation

Yield

- Indication-specific diagnostic yields
- Real-world evidence
- Multiomics (ie. RNAseq)
- Long-read sequencing

Utility

- Change of management
- Gene therapy/drug development
- Economic utility
- Personal utility

Implementation

- Demonstrating what's possible
- Workflow impacts
- Real-world implementation
- Education

iHope Global Network

Providing clinical whole-genome sequencing to patients in need

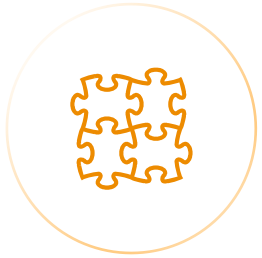
https://www.illumina.com/company/ihope.html

Challenges for Whole-Genome Sequencing Implementation

Areas of focus for future test adoption

Informatics

- Supporting evidence for validated algorithms
- Data storage bottlenecks



Interpretation

- Incidental findings, variants of unknown significance
- Periodic data reanalysis

Professional governance

- Recommendations and guidelines for use
- Evidence for clinical utility and health economic benefits

Access to testing

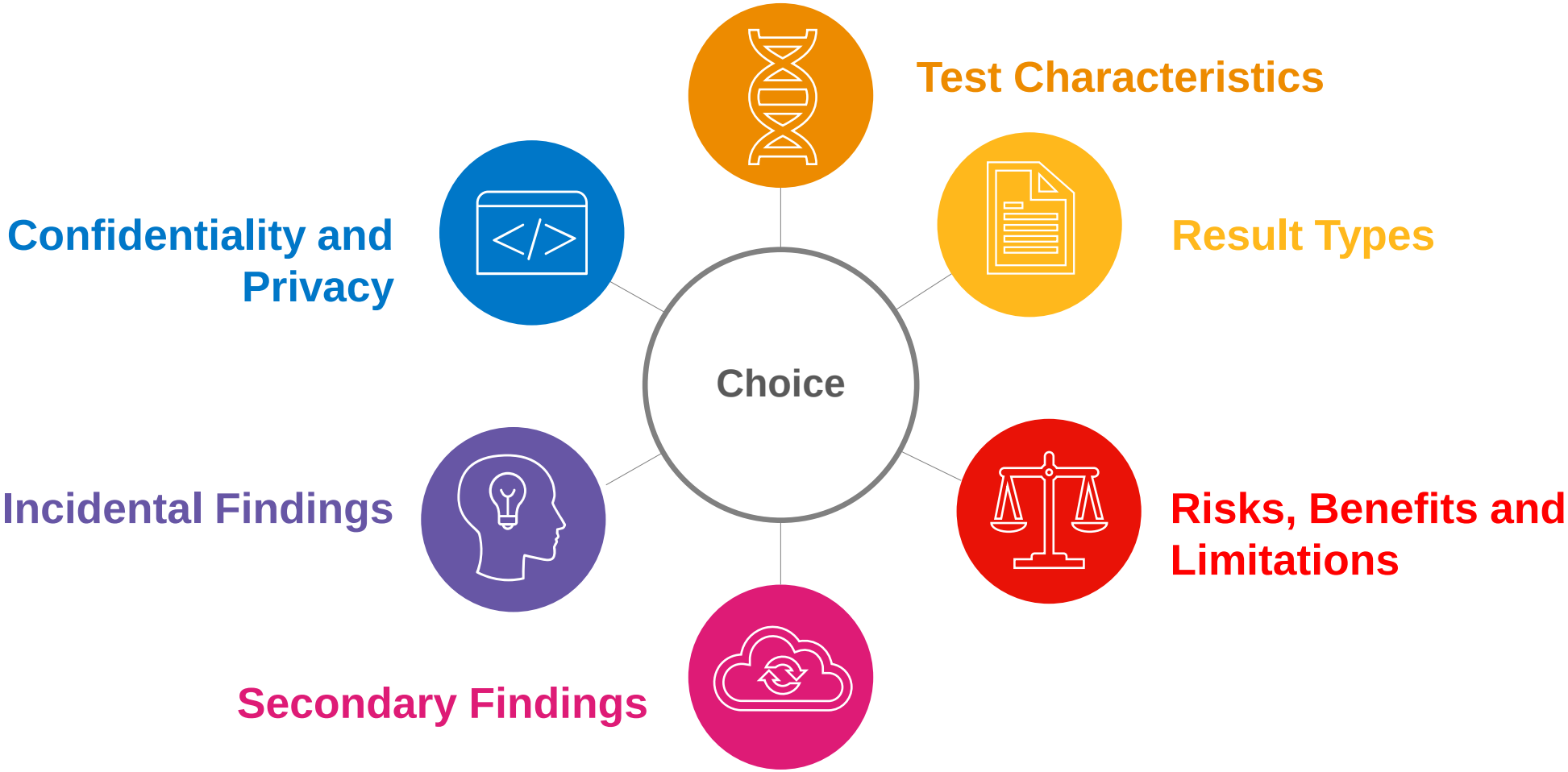
- Access to testing facility offering clinical WGS
- Equity of care
- Payer reimbursement

Thank you

illumina®

© 2022 Illumina, Inc. All rights reserved.

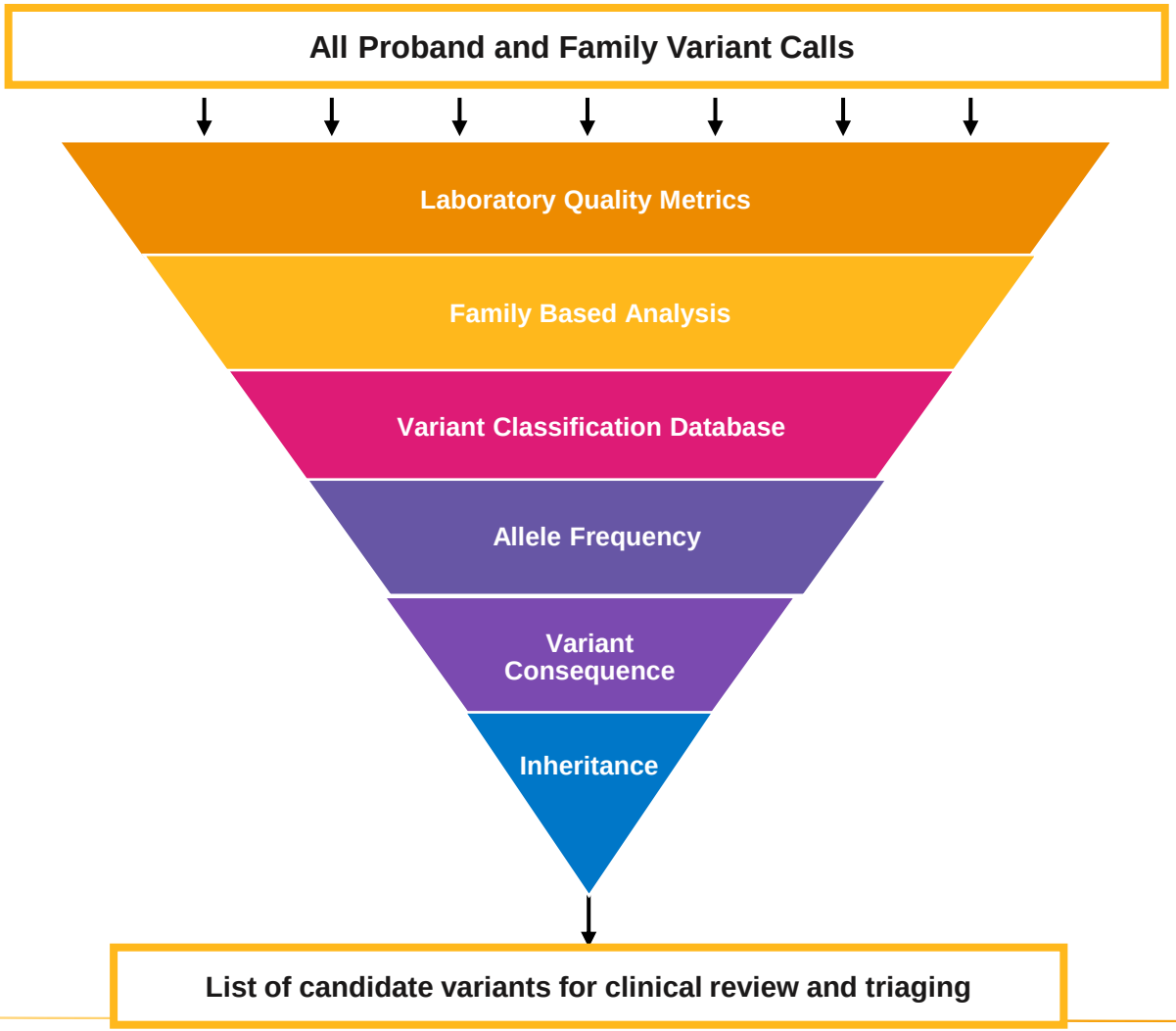
Pre-test Counseling for Genomic Sequencing



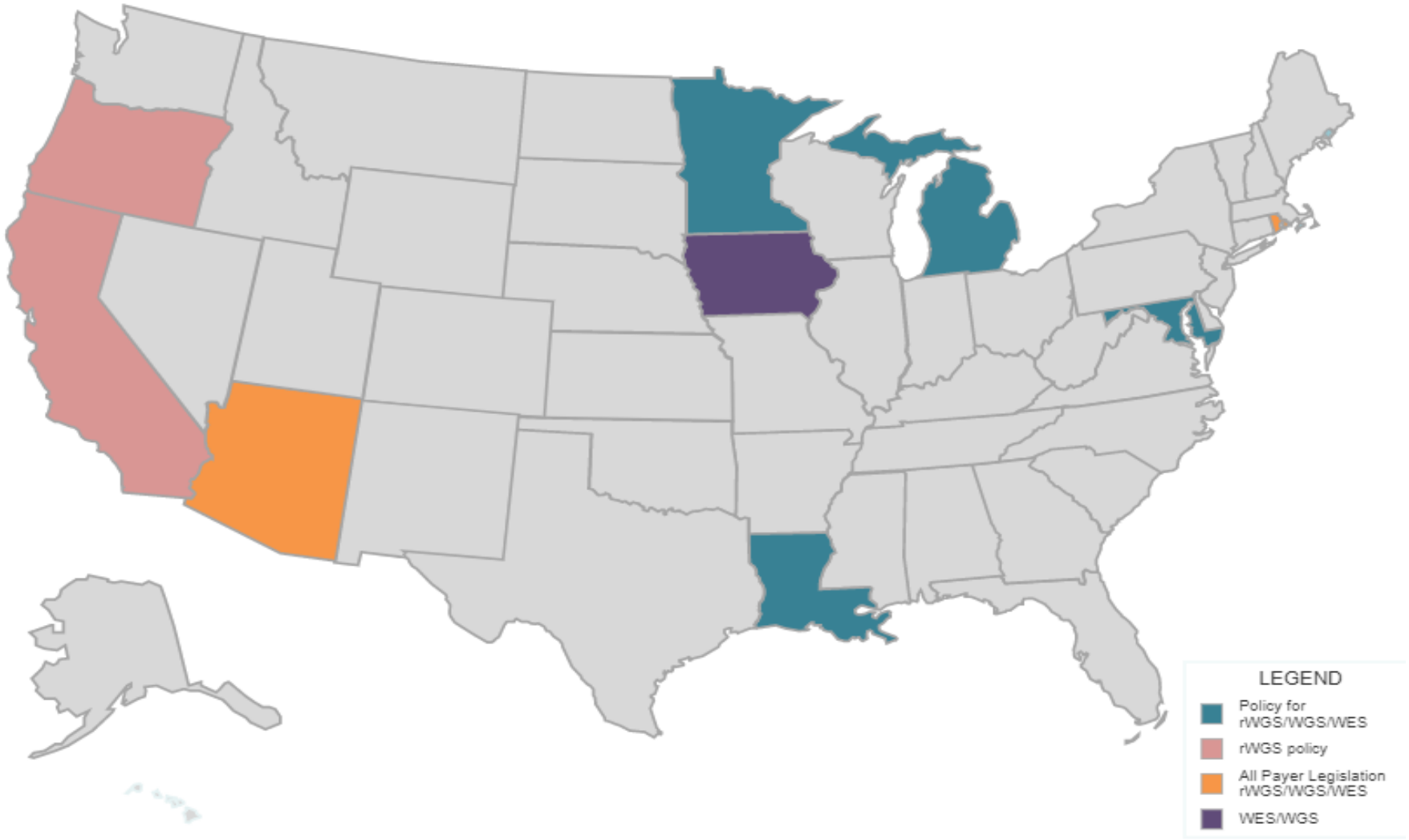
1. National Society of Genetic Counselors. Position Statement: Secondary and incidental findings in genetic testing. Adopted 2020. https://www.nsgc.org/p/bl/et/blogaid=30
2. ACOG Committee Opinion: Ethical Issues in Genetic Testing. Reaffirmed 2014. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2008/06/ethical-issues-in-genetic-testing
3. Roche, M. and Berg, J. Incidental Findings with Genetic Testing: Implications for Genetic Counseling Practice. *Curr Genet Med Rep.* 2015; 3(4):166-176. doi: 10.1007/s40142-015-0075-9

Variant Filtering, Triaging and Classification

Trio analysis



Coverage Policy



illumina®

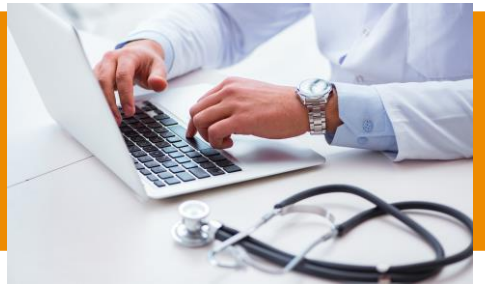
Data as of November 1, 2022
Arizona: Effective 01 Jan 2023
Rhode Island: Effective 01 Jan 2024

Systematic review of recommendations for reanalysis of next-generation sequencing data

Standardized guidelines for future studies relating to reanalysis

Key Takeaway

A meta-analysis of 29 articles determined that reanalysis of NGS data can improve diagnostic (dx) yield, yet there remains uncertainty regarding optimal timing for reanalysis. Recommendations are proposed for best practices in reanalysis and for minimum standards for future studies.



Method

- Systematic evidence review of publications from January 2007 to October 2021.
- Reanalysis defined as "bioinformatic examination of original sequencing data“ in undiagnosed patients.
- Primary outcome was proportion of cases without a molecular dx after initial sequencing that reached a dx after reanalysis.

Findings

- **29 studies** (9419 undiagnosed patients) met criteria for review and included reanalysis data from GS (n=3), ES (n=23) and GS/ES (n=3) studies.
- Overall pooled **dx yield from reanalysis was 10%**. Yields were higher when reanalysis occurred >24 months vs. those <24 months although this finding was not significant.
- **Updates in literature/databases** resulting in new gene discovery was most common reason for new diagnosis (62% of cases).
- Yield was significantly higher following reanalysis of ES data (11%) vs. GS data (4%) ($p<0.01$) and lowest in studies that limited reanalysis to known disease genes.

Dai P, Honda A, Ewans L, et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: A systematic review and meta-analysis. *Genet. Med. 2022*https://doi.org/10.1016/j.gim.2022.04.021