BAYLOR GENETICS

ONE AND DONE: UTILIZING WES AND WGS TO END THE DIAGNOSTIC ODYSSEY

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TSGC 2024

AGENDA

- WES & WGS Overview
- Data
- Test Options
- Case Examples
- Q&A

CONFLICT OF INTEREST

- Currently an employee of Baylor Genetics

Learning Objectives

Illustrate the benefits and limitations of Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS)

Examine the utility of comprehensive and rapid testing using clinical case scenarios

// BAYLOR GENETICS' WES & WGS

WHOLE EXOME SEQUENCING (WES)

WES is a comprehensive genetic testing solution to analyze all exons (protein-coding sections within genes) within the human genome. Most genetic conditions are caused by variants found within the exons.

ANALYSIS:

- Detection of sequence variants, e.g., single nucleotide variants (SNVs) and indels
- Detection of copy number variants (CNVs) > 3 exons and homozygous copy number changes of any size

WHOLE GENOME SEQUENCING (WGS)

WGS is the most comprehensive genetic testing solution and analyzes 98% of the genome, covering both the protein-coding exons and non-coding regions of the genome.

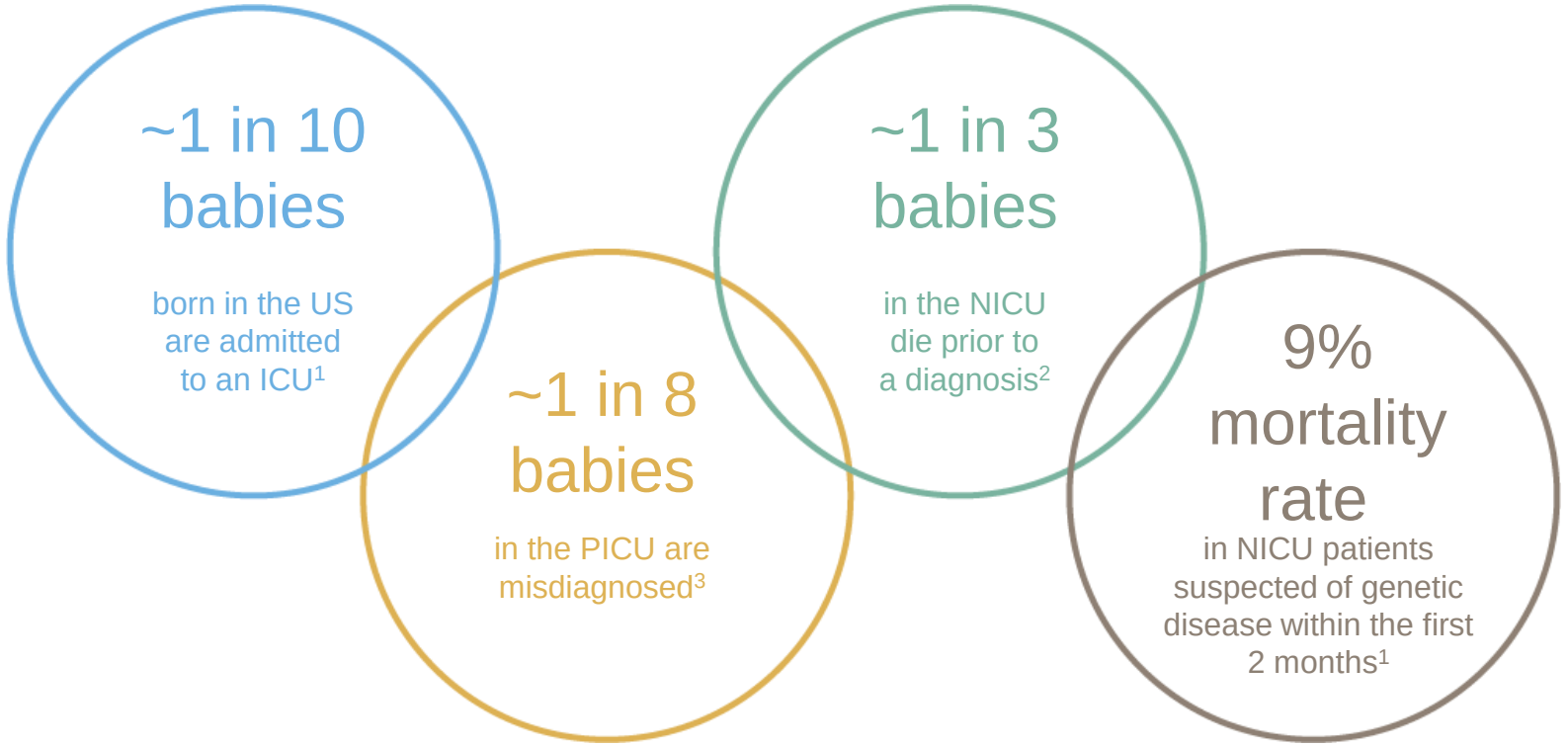
ANALYSIS:

Genome-wide detection of SNVs, indels, CNVs, regions of homozygosity (ROH), and short tandem repeats:

- Clinically significant exonic, intronic, and regulatory variants are reported
- Clinically significant CNVs
- Uniparental disomy (UPD) reported in trio cases only
- Short tandem repeat (STR) detection in 28 genes
- Detection of mitochondrial DNA (mtDNA) variants


Why Choose WES or WGS?

// DIAGNOSIS GAPS IN NEONATAL CARE

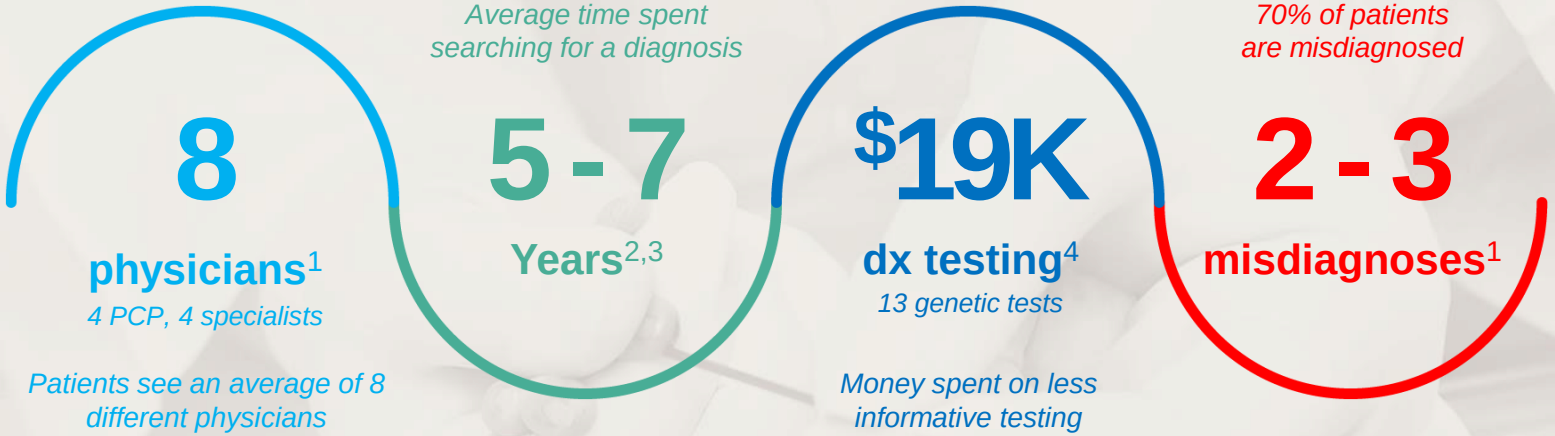


Babies and Families Confront Key Challenges

- Infants with genetic disorders account for 30 – 50% of neonatal and infant deaths.[3]
- Lack of an accurate diagnosis leads to longer hospital stays, and poor outcomes in up to 40% of patients.[4]
- Patients and families face fatigue, frustration, and financial costs forcing many to abandon the search for a diagnosis.[5,6]

1. Association Between Neonatal Intensive Care Unit Admission Rates and Illness Acuity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833518/
2. Genetic Disorders and Mortality in Infancy and Early Childhood: Delayed Diagnoses and Missed Opportunities https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6185816/
3. Finding Diagnostic Errors in Children Admitted to the PICU https://pubmed.ncbi.nlm.nih.gov/28125548/
4. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care, https://pubmed.ncbi.nlm.nih.gov/34089648/
5. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2654887
6. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. https://ojrd.biomedcentral.com/articles/10.1186/s13023-022-02358-x

// THE DIAGNOSTIC ODYSSEY IS LONG AND CHALLENGING



DELAYED DIAGNOSIS IS DETRIMENTAL FOR THE PATIENT, THE FAMILY, THE PROVIDERS, AND THE PAYERS.

The Diagnostic Odyssey

The diagnostic odyssey involves patients, their families, and clinicians.

Patients must see multiple specialists, undergo extensive testing, while receiving no or conflicting clinical diagnoses.[5]

This odyssey also leads patients and families to face fatigue, frustration, and significant financial costs forcing many to abandon the search for a diagnosis before one can be made.[6,7]

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.
5. Neurol Genet. 2018 Apr; 4(2): e230.
6. PLoS One. 2017; 12(2): e0172532.
7. Orphanet Journal of Rare Diseases volume 17, Article number: 233 (2022)

// COMPLEX CONDITIONS DEMAND COMPREHENSIVE GENETIC ANALYSIS

Neuromuscular

600+ genes

have been associated with neuromuscular disease[1]

~63%

of patients with neuromuscular disorders received a molecular diagnosis via genome sequencing[2]

NDD & Epilepsy

900+ genes

have been associated with developmental and epileptic encephalopathies[3]

Up to 40%

of epilepsy in children is genetic in origin[4,5]

NDD & ID, ASD, CA

1500+ genes

have been associated with neurodevelopmental disorders such as intellectual disability and autism spectrum disorder[6]

~35%

overall diagnostic yield of exome sequencing in patients with neurodevelopmental disorders[7]

Genetic Testing Can Help End the Diagnostic Odyssey

- **~30 million** people in the United States, or **1 in 10** people, suffer from one of the 7,000+ known rare diseases
- Children represent **~50% of those impacted** by rare disease
- Rare diseases are often misdiagnosed or remain undiagnosed because **symptoms not obvious**
- WGS/WES, with the highest diagnostic yield, and other genetic tests, can help provide answers to help inform care plans and **end the diagnostic odyssey**

Sources

1. Ng, K. W. P., Chin, H. L., Chin, A. X. Y., & Goh, D. L. (2022). Using gene panels in the diagnosis of neuromuscular disorders: A mini-review. *Frontiers in neurology*, *13*, 997551. https://doi.org/10.3389/fneur.2022.997551; 2. Lee, H. F., Chi, C. S., & Tsai, C. R. (2021). Diagnostic yield and treatment impact of whole-genome sequencing in paediatric neurological disorders. Developmental medicine and child neurology, 63(8), 934–938. https://doi.org/10.1111/dmcn.14722; 3. Oliver, K. L., Scheffer, I. E., Bennett, M. F., Grinton, B. E., Bahlo, M., & Berkovic, S. F. (2023). Genes4Epilepsy: An epilepsy gene resource. Epilepsia, 64(5), 1368–1375. https://doi.org/10.1111/epi.17547; 4. Zhang, D., Liu, X., & Deng, X. (2017). Genetic basis of pediatric epilepsy syndromes. Experimental and therapeutic medicine, 13(5), 2129–2133. https://doi.org/10.3892/etm.2017.4267; 5. Joseph D Symonds, Sameer M Zuberi, Kirsty Stewart, Ailsa McLellan, Mary O'Regan, Stewart MacLeod, Alice Jollands, Shelagh Joss, Martin Kirkpatrick, Andreas Brunklaus, Daniela T Pilz, Jay Shetty, Liam Dorris, Ishaq Abu-Arafeh, Jamie Andrew, Philip Brink, Mary Callaghan, Jamie Cruden, Louise A Diver, Christine Findlay, Sarah Gardiner, Rosemary Grattan, Bethan Lang, Jane MacDonnell, Jean McKnight, Calum A Morrison, Lesley Nairn, Meghan M Slean, Elma Stephen, Alan Webb, Angela Vincent, Margaret Wilson, Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort, Brain, Volume 142, Issue 8, August 2019, Pages 2303–2318, https://doi.org/10.1093/brain/awz195 ; 6. Leblond, C. S., Le, T. L., Malesys, S., Cliquet, F., Tabet, A. C., Delorme, R., Rolland, T., & Bourgeron, T. (2021). Operative list of genes associated with autism and neurodevelopmental disorders based on database review. Molecular and cellular neurosciences, 113, 103623. https://doi.org/10.1016/j.mcn.2021.103623; 7. Srivastava, S., Love-Nichols, J. A., Dies, K. A., Ledbetter, D. H., Martin, C. L., Chung, W. K., Firth, H. V., Frazier, T., Hansen, R. L., Prock, L., Brunner, H., Hoang, N., Scherer, S. W., Sahin, M., Miller, D. T., & NDD Exome Scoping Review Work Group (2019). Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genetics in medicine : official journal of the American College of Medical Genetics, 21(11), 2413–2421. https://doi.org/10.1038/s41436-019-0554-6

// THE GENETIC TESTING LANDSCAPE IS QUICKLY EVOLVING

An increasing number of studies demonstrate the clinical utility of genetic testing

Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability

Anna Lindstrand [1 2], Marlene Ek [1 2], Malin Kvarnung [1 2], Britt-Marie Anderlid [1 2], Erik Björck [1 2], Jonas Carlsten [1 2], Jesper Eisfeldt [1 2 3], Giedre Grigelioniene [1 2], Peter Gustavsson [1 2], Anna Hammarsjö [1 2], Hafdís T. Helgadóttir [1 2], Maritta Hellström-Pigg [1 2], Ekaterina Kuchinskaya [1 2], Kristina Lage, Helena Malm

Clinical utility of multigene analysis in over 25,000 patients with neuromuscular disorders

Thomas L Winder [1], Christopher A Tan [1], Sarah Klemm [1], Hannah White [1], Jody M Westbrook [1], James Z Wang [1], Swaroop Aradhya

Hum Genet. 2014 Mar;133(3):331-45. doi: 10.1007/s00439-013-1381-5. Epub 2013 Oct 24.

Next generation sequencing–based molecular diagnosis of retinitis pigmentosa: identification of a novel genotype–phenotype correlation and clinical refinements

Feng Wang [1], Hui Wang, Han-Fang Tuan, Duy H Nguyen, Vincent Sun, Vafa Keser, Sara J Bowne, Lori S Sullivan, Hongrong Luo, Ling Zhao, Xia Wang, Jacques E Zaneveld, Jason S Salvo, Sorath Siddiqui, Louise Mao, Dianna K Wheaton, David G Birch, Kari E Branham, John R Heckenlively, Cindy Wen, Ken Flagg, Henry Ferreyra, Jacqueline Pei, Ayesha Khan, Huanan Ren, Keqing Wang, Irma Lopez, Raheel Qamar, Juan C Zenteno, Raul Ayala-Ramirez, Beatriz Buentello-Volante, Qing Fu, David A Simpson, Yumei Li, Ruifang Sui, Giuliana Silvestri, Stephen P Daiger, Robert K Koenekoop, Kang Zhang, Rui Chen

Mol Genet Genomic Med. 2022 Apr; 10(4): e1892. PMCID: PMC9000935
Published online 2022 Mar 5. doi: 10.1002/mgg3.1892 PMID: 35247231

Genome sequencing reveals novel noncoding variants in *PLA2G6* and *LMNB1* causing progressive neurologic disease

Nicholas Borja, [1] Stephanie Bivona, [1] Lé Shon Peart, [1] Brittany Johnson, [1] Joanna Gonzalez, [1] Deborah Barbouth, [1] Henry Moore, [2]

Hum Mutat. 2011 Dec;32(12):1450-9. doi: 10.1002/humu.21587. Epub 2011 Sep 23.

Whole-exome sequencing identifies ALMS1, IQCB1, CNGA3, and MYO7A mutations in patients with Leber congenital amaurosis

Xia Wang [1], Hui Wang, Ming Cao, Zhe Li, Xianfeng Chen, Claire Patenia, Athurva Gore, Emad B Abboud, Ali A A, Donna Muzny, Richard

Genet Med. Author manuscript; available in PMC 2016 Apr 1. PMCID: PMC4385427
Published in final edited form as: NIHMSID: NIHMS641971
Genet Med. 2015 Apr; 17(4): 262–270. PMID: 25474345
Published online 2014 Dec 4. doi: 10.1038/gim.2014.174

Comprehensive analysis of Stargardt macular dystrophy patients reveals new genotype-phenotype correlations and unexpected diagnostic revisions

Jacques Zaneveld,[1,2] Sorath Siddiqui,[5] Huajin Li,[6] Xia Wang,[1,2] Hui Wang,[1,2] Keqing Wang,[2] Hui Li,[6] Huanan Ren,[5] Irma Lopez,[5] Allison Dorfman,[5] Ayesha Khan,[5] Feng Wang,[1,2] Jason Salvo,[1,4] Violet Gelowani,[2] Yumei Li,[1,2] Ruifang Sui,[6] Robert Koenekoop,[5] and Rui Chen[1,2,3,4,*]

// OVERVIEW

ACMG recommends **WES/WGS as a first-/second-tier test** for patients with **congenital anomalies**, **developmental delays**, and **intellectual disability**[1]. **Coverage** by **commercial payors** is **improving**.

COVERAGE

Most commercial payors cover exome for a wide range of conditions when patients meet clinical criteria

- Cigna and UHC, 2 of the largest national payors, now also covering outpatient WGS

Most State Medicaid programs cover WES

GUIDELINES

- ACMG
- AANEM
- AES
- NSGC

1. Manickam, K., McClain, M. R., Demmer, L. A., Biswas, S., Kearney, H. M., Malinowski, J., Massingham, L. J., Miller, D., Yu, T. W., Hisama, F. M., & ACMG Board of Directors (2021). 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). Genetics in medicine : official journal of the American College of Medical Genetics, 23(11), 2029–2037. https://doi.org/10.1038/s41436-021-01242-6

// MEANINGFUL IMPACT OF A GENETIC DIAGNOSIS

Medical Care

32% of affected individuals had changes in medical care[1]

Cost Savings

~ $12k-15k per child on average[1]

Length of Hospitalization

457 to 592 days were avoided[1]

Families Want Answers

3 out of 4 families want answers and are in favor of diagnostic tests[2*]

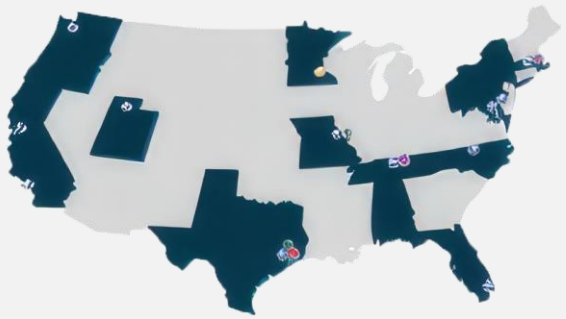
**75% of those who decided cited insurance issues*

1. Am J Hum Genet 2021 Jul 1; 108(7): 1231–1238.; **2.** Child Neurology Foundation 2020 Assessment Survey Summary
2. Rare Disease Impact Report: Insights from patients and the medical community. https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf.
3. Global Commission. Ending the diagnostic odyssey for children with a rare disease. 2019. globalrarediseasecommission.com.
4. Posada de la Paz M, Taruscio D, Groft SC. Rare diseases epidemiology: Update and overview. 2nd edition. Chapter 2. Springer 2017. Cham, Switzerland.
5. 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.
6. Neurol Genet. 2018 Apr; 4(2): e230.
7. PLoS One. 2017; 12(2): e0172532.
8. Orphanet Journal of Rare Diseases volume 17, Article number: 233 (2022)


Let’s Look at Some Data

// BAYLOR GENETICS EXPERTISE

Baylor Genetics is the sole sequencing core partner for the Undiagnosed Diseases Network (UDN), funded by National Institutes of Health



2,220	2,199	676
• participants evaluated or ~1 every other day	• participants with exome and/or genome sequencing	• 30% of participants diagnosed

- UDN leverages Baylor Genetics expertise with Whole Genome and Exome Sequencing, and unique capabilities to deliver answers for patients with ultra-rare diseases
- Providing data-driven information and insights to improve health outcomes

Undiagnosed Diseases Network

COLLABORATING ON COMPLEX CASES

- 10-year partnership
- 13 sites at top U.S. children's hospitals and 10 diagnostic centers of excellence
- Working with clinical and research experts to solve the most challenging cases

*Facts and figures were last updated by the UDN on July 7, 2023

// DIAGNOSTIC RATE

The diagnostic rate for WES/WGS is 30 – 50%

The diagnostic rate depends on the type of test (e.g., proband v. trio, rapid vs. standard) & clinical indication

// CLINICAL EXOME SEQUENCING UNCOVERS A HIGH FREQUENCY OF MENDELIAN DISORDERS IN INFANTS WITH STROKE: A RETROSPECTIVE ANALYSIS

- We conducted a retrospective analysis of WES cases with the clinical indication of stroke
  - 124 individuals, ages 10 days to 69 years
  - 8.9% received a molecular diagnosis
  - This included 25% of infants <1 year old at diagnosis
- Identified syndromes predisposing to stroke included: *COL4A1*-related brain small vessel disease, homocystinuria caused by *CBS* mutation, *POLG*-related disorders, *TTC19*-linked mitochondrial disease, and *RNASEH2A* associated Aicardi-Goutieres syndrome.
- Pathogenic variants were found in genes rarely associated with stroke: *NSD1, PKHD1, HRAS, ATP13A2*.

This study demonstrates the utility of exome sequencing for diagnosing the genetic etiology of stroke, especially for children <1 year of age

// NOT JUST ONE: THE UTILITY OF WHOLE GENOME SEQUENCING FOR MAKING A DUAL MOLECULAR DIAGNOSIS

- We conducted a retrospective analysis of WGS cases and identified reportable multilocus findings in 48 cases:
  - 13 with dual molecular diagnoses (pathogenic/ likely pathogenic)
  - 24 with one diagnosis along with reportable findings in another locus
  - 7 with one molecular diagnosis and one reportable variant in an autosomal recessive (AR) locus
  - 4 with one molecular diagnosis and an actionable secondary finding.This included 25% of infants <1 year old at diagnosis
- Clinical indications for dual diagnoses included MCA (n=10), DD/ID (n=4), seizures (n=3), and failure to thrive (n=1).
- All 13 cases with dual diagnoses involved at least one autosomal dominant (AD) gene
- CNVs contributed to high impact findings in 8/13
- Of the 8 trios available, de novo findings accounted for at least one of the diagnostic variants in 7 trios

This study demonstrates the utility of WGS in providing reportable multi-locus findings and optimizing the diagnosis of patients with complex phenotypes

What Are the Different Test Options?

// TESTING FOR YOUR CRITICALLY-ILL PATIENTS

Baylor genetics specializes in Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) – comprehensive precision diagnostic tests for actionable treatment guidance

Both tests offer

- Written results in **3 weeks***
- ~**38% diagnostic yield** for genome sequencing vs 21% for standard genetic testing including CMA, single gene testing, and panels[1]
- Variant interpretation aided by concurrent, trio-based analysis
- Sample types accepted: Blood, Cord Blood, Cultured Cells, Extracted DNA, Buccal Swabs, and Saliva

Clear results that change patient outcomes

- Identifying treatment options
- Adjustments in medical management
- Providing patients with additional clinical trial eligibility and research opportunities
- Informing family planning decisions
- Recommended as a first-tier test to provide the greatest chance to reach a diagnosis

Opt-in selections

- ACMG Secondary Findings
- Other medically actionable incidental findings known to be associated with disease but not known to be associated with the patient's phenotype
- Potential clinically significant findings in genes with no known disease associations

*TAT dependent on sample type. Please call client services at 1-800-411-4636 for further information

1. Manickam, K., McClain, M. R., Demmer, L. A., Biswas, S., Kearney, H. M., Malinowski, J., Massingham, L. J., Miller, D., Yu, T. W., Hisama, F. M., & ACMG Board of Directors (2021). 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). Genetics in medicine : official journal of the American College of Medical Genetics, 23(11), 2029–2037. https://doi.org/10.1038/s41436-021-01242-6

// RAPID TESTING FOR YOUR CRITICALLY-ILL PATIENTS

Rapid Whole Genome Sequencing (WGS) and Rapid Whole Exome Sequencing (WES) can expedite the diagnostic process and provide time-sensitive treatment guidance

Both tests offer

- Written results starting at **5 days***
- ~**38% diagnostic yield** for genome sequencing vs 21% for standard genetic testing including CMA, single gene testing, and panels[1]
- Variant interpretation aided by concurrent, trio-based analysis
- Sample types accepted: Blood, Cord Blood, Cultured Cells, Extracted DNA, Buccal Swabs, and Saliva

Clear results that change patient outcomes

- Identifying treatment options
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- Providing patients with additional clinical trial eligibility and research opportunities
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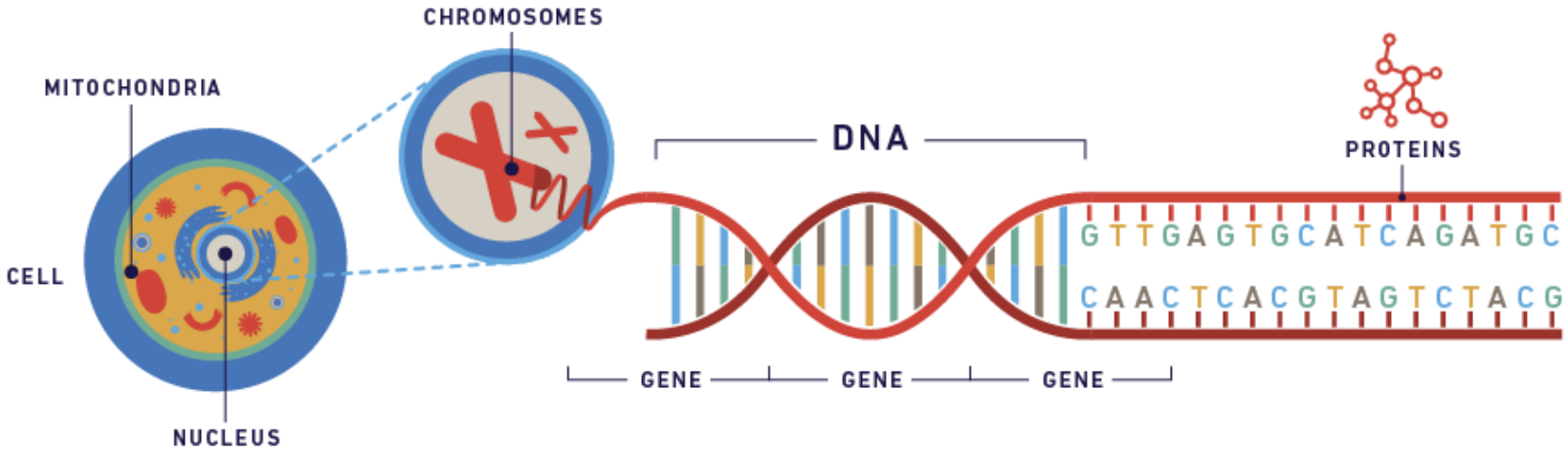
1. Manickam, K., McClain, M. R., Demmer, L. A., Biswas, S., Kearney, H. M., Malinowski, J., Massingham, L. J., Miller, D., Yu, T. W., Hisama, F. M., & ACMG Board of Directors (2021). Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). Genetics in medicine : official journal of the American College of Medical Genetics, 23(11), 2029–2037. https://doi.org/10.1038/s41436-021-01242-6

03/26/2024

// OUR UNIQUE MULTI-OMICS APPROACH



Tests at Mitochondrial Level	Tests at Chromosome Level	Tests at DNA/RNA Level	Tests at Analyte Level (Amino Acids, Proteins, Metabolites)
• Ex. MitoNGS℠ (Mitochondrial Genome Analysis)	• Ex. Chromosome Microarray Analysis (CMA)	• Ex. Whole Exome Sequencing (WES) • Whole Genome Sequencing (WGS) • WES/WGS reanalysis available	• Ex. Global Metabolomic Assisted Pathway Screen (Global MAPS®)

Case Examples

// 1. TRIO WES IDENTIFIES DE NOVO FINDING

Clinical indication: The case involves a newborn identified as small for gestational age, prenatally diagnosed with oligohydramnios, tetralogy of Fallot, pulmonary atresia, and unilateral urinary tract dilation. The differential for this condition includes many genes.

Previous Genetic Testing: No diagnostic testing occurred during pregnancy. Prenatal cell-free DNA screening for Trisomy 21, Trisomy 18, Trisomy 13, 22q11.2 deletion syndrome, and sex chromosome aneuploidies showed low risk for these conditions.

Genetic Testing: Trio Whole Exome Sequencing (WES)

Results: WES revealed a de novo likely pathogenic variant in the *NOTCH2* gene associated with Alagille syndrome.

Implications: Alagille syndrome manifests with various features, including bile duct abnormalities, cholestasis, cardiac defects, skeletal abnormalities, eye abnormalities, characteristic facial features, renal abnormalities, growth failure, developmental delay, enlarged liver, and vascular abnormalities. Despite presenting in 1:30,000-1:50,000 births, the condition is considered underdiagnosed due to significant clinical variability. WES results enabled multidisciplinary care, addressing potential features not immediately apparent in a newborn.

Parents were tested and found negative for the *NOTCH2* variant. This information determined a low recurrence risk for the parents to have another child affected by Alagille syndrome.

// 2. RAPID WHOLE GENOME SEQUENCING FINDS A DIAGNOSIS OUTSIDE THE DIFFERENTIAL

Clinical indication: The patient is a 2-month-old female admitted to the Pediatric Intensive Care Unit (PICU) with feeding difficulty, lethargy, fever, concern for sepsis, and seizures. The clinical indication for testing was broad, and included 22q11.2 deletion syndrome, 15q duplication syndrome, Angelman syndrome, GLUT1 deficiency, and Dravet syndrome.

Previous Genetic Testing: No prior genetic testing was performed.

Genetic Testing: Rapid Trio Whole Genome Sequencing (rWGS)

Results: rWGS identified compound heterozygous pathogenic and likely pathogenic variants in the *COQ5* gene, consistent with a diagnosis of Primary Coenzyme Q10 Deficiency 9.

Implications: This condition follows autosomal recessive inheritance and is characterized by cerebellar ataxia, cerebellar atrophy in the first decade of life, and additional symptoms such as seizures, intellectual disability, hypertrophic cardiomyopathy, and kidney dysfunction. Patients with Primary Coenzyme Q10 Deficiency 9 may benefit from treatment with coenzyme Q10 supplementation. The confirmation of this diagnosis through genetic testing enables the healthcare team to initiate personalized treatment and supportive therapies tailored to the specific needs of the patient.

Both parents were identified as carriers of the condition. This finding provides information on the reproductive risk for any future pregnancies.

Primary coenzyme Q10 deficiency 9 was not a condition considered by the providers in the differential diagnosis; using Rapid WGS as a first line test allowed the patient to receive optimal care in a timely manner. For this patient, the clinically actionable result was life changing.

// 3. WHOLE GENOME SEQUENCING PROVIDES A DIAGNOSIS AND CLARIFIES PREVIOUS TESTING THROUGH ANOTHER LABORATORY

Clinical indication: The patient is an 11-year-old female presenting with juvenile myoclonic seizures, bilateral tonic-clonic seizures, ataxia, torticollis, tremors, muscle fibrillation, hemangioma, and abnormalities observed on EEG.

Previous Genetic Testing: Prior genetic testing included an epilepsy panel examining over 1000 genes, resulting in a non-diagnostic outcome with three variants of uncertain significance.

Genetic Testing: Trio Whole Genome Sequencing (WGS) to comprehensively assess the nuclear and mitochondrial genome

Results: Trio WGS identified a homozygous pathogenic CCCCGCCCCGCG (dodecamer) repeat expansion with repeat number >50 in the *CSTB* gene, consistent with a diagnosis of progressive myoclonic epilepsy type 1 (EPM1)

Implications: EPM1 follows autosomal recessive inheritance and typically manifests in childhood or adolescence with myoclonus, tonic-clonic seizures, ataxia, and poor coordination.

A precise diagnosis allows for the implementation or avoidance of specific treatments. For EPM1, valproic acid and clonazepam can effectively treat myoclonus and reduce seizure frequency, while drugs like phenytoin and sodium channel blockers should be avoided due to adverse effects.

Both parents were identified as carriers, carrying the heterozygous repeat number >40 in *CSTB*. This finding provides information on the reproductive risk for any future pregnancies.

This case underscores the importance of comprehensive genetic testing, especially in complex cases where traditional panels may overlook relevant disorders.

Questions

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APPENDIX

// BLUEPRINT – CUSTOMIZABLE NGS PANEL WHEN WES OR WGS ARE NOT AVAILABLE

Baylor Genetics' BluePrint panel (test code 1300) is a customizable panel that enables healthcare providers to analyze up to 1000 genes for a customized approach to patient care.

It assesses the exonic regions of selected genes to identify the rare DNA changes that cause or contribute to your patient's medical condition.

Build your own panel via the Baylor Genetics Ordering Portal*

- Enter your desired list of genes
- Search for genes using approved HGNC symbols
- Save your custom gene list for future orders

Order the BluePrint Panel to Get Answers

- For patients with a clinical history strongly suggestive of an underlying genetic cause
- For patients for which an existing gene panel does not meet the diagnostic needs

Test Features

- Analyze up to 1,000 genes in a single panel
- Convenient ordering via the Baylor Genetics Ordering Portal*
- TAT: 3 weeks
- Flexible sample types: blood, gDNA, cultured skin fibroblast, buccal swab, saliva

Variant Detection

Performed on a whole exome backbone and at an average read depth of 120x for robust detection of:

- Single nucleotide variants (SNVs)
- Insertions/deletions
- Copy number variants (CNVs)

*Please note that at this time, we are only accepting online orders for the BluePrint Panel .
If you have any questions regarding the online ordering portal, please contact our client services team at 1-800-411-4636 or email us at help@baylorgenetics.com.

// COMMON INDICATIONS FOR EXOME SEQUENCING IN ICU

HPO term	Count (n = 278)	Percentage
Abnormal Facial Shape	96	34.5%
Malformation Of The Heart And Great Vessels	85	30.6%
Muscular Hypotonia	42	15.1%
Seizures	35	12.6%
Intrauterine Growth Restriction	31	11.2%
Abnormality Of The Skeletal System	23	8.27%
Ventricular Septal Defect	21	7.55%
Microcephaly	20	7.19%
Feeding Difficulties	20	7.19%
Abnormality Of The Genital System	17	6.12%

Source
1. Meng, L., Pammi, M., Saronwala, A., Magoulas, P., Ghazi, A. R., Vetrini, F., Zhang, J., He, W., Dharmadhikari, A. V., Qu, C., Ward, P., Braxton, A., Narayanan, S., Ge, X., Tokita, M. J., Santiago-Sim, T., Dai, H., Chiang, T., Smith, H., Azamian, M. S., … Lalani, S. R. (2017). Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. JAMA pediatrics, 171(12), e173438. https://doi.org/10.1001/jamapediatrics.2017.3438

// TANDEM REPEAT DISORDERS

Gene	STR	Disease
NOTCH2NLC	GGC	Neuronal intranuclear inclusion disease [MIM:603472]; Tremor, hereditary essential, 6 [MIM:618866]
ATN1	CAG (Gln)	Dentatorubral-pallidoluysian atrophy [MIM:125370]
DIP2B	CGG	Intellectual Disability, FRA12A type [MIM:136630]
ATXN2	CAG (Gln)	Spinocerebellar ataxia 2 [MIM:183090]
ATXN8OS	CTA/G	Spinocerebellar ataxia 8 [MIM:608768]
PABPN1	GCN (Ala)	Oculopharyngeal muscular dystrophy [MIM:164300]
ATXN3	CAG (Gln)	Machado-Joseph disease [MIM:109150]
JPH3	CTG (Ala)	Huntington disease-like 2 [MIM:606438]
TCF4	CTG or CAG	Corneal dystrophy, Fuchs endothelial, 3 [MIM:613267]
CACNA1A	CAG (Gln)	Spinocerebellar ataxia 6 [MIM:183086]
DMPK	CTG	Myotonic dystrophy 1 [MIM:160900]
GLS	GCA	Global developmental delay, progressive ataxia, and elevated glutamine [MIM:618412]
NOP56	GGCCTG	Spinocerebellar ataxia 36 [MIM:614153]
CSTB	CCCCGCCCCGCG	Epilepsy, progressive myoclonic 1A (Unverricht and Lundborg)[MIM:254800]
ATXN10	ATTCT	Spinocerebellar ataxia 10 [MIM:603516]
ATXN7	CAG (Gln)	Spinocerebellar ataxia 7 [MIM:164500]
CNBP	CCTG	Myotonic dystrophy 2 [MIM:602668]
HTT	CAG (Gln)	Huntington disease [MIM:143100]
RFC1	AARRG	Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome [MIM:614575]
PHOX2B	GCN (Ala)	Central hypoventilation syndrome, congenital, with or without Hirschsprung disease [MIM:209880]
PPP2R2B	CAG	Spinocerebellar ataxia 12 [MIM:604326]
ATXN1	CAG (Gln)	Spinocerebellar ataxia 1 [MIM:164400]
TBP	CAG or CAA (Gln)	Spinocerebellar ataxia 17 [MIM:607136]
C9orf72	GGGGCC	Frontotemporal dementia and/or amyotrophic lateral sclerosis 1 [MIM:105550]
FXN	GAA	Friedreich ataxia [MIM:229300]
AR	CAG (Gln)	Spinal and bulbar muscular atrophy of Kennedy [MIM:313200]
FMR1	CGG	Fragile X syndrome [MIM:300624]; Fragile X tremor/ataxia syndrome [MIM:300623]; Premature ovarian failure 1 [MIM:311360]
AFF2	CCG	Intellectual developmental disorder, X-linked 109 [MIM:309548]

// CMA
COST EFFECTIVE TEST FOR MULTIPLE CONDITIONS

Baylor Genetics has expertise with CMA and has analyzed over 100,000 microarrays

Overview	Chromosomal Microarray Analysis (CMA) detects genome-wide copy number variants (CNV) associated with genetic diseases, unlocking diagnoses to both common chromosomal conditions and severe genetic disorders. With its unparalleled ability to detect these variants, CMA offers a unique advantage over other types of genetic tests such as karyotype or NGS-based tests. TC8665 CMA-HR+SNP Screen BENEFITS • Maximum sensitivity for detection of gains and losses • Exon-by-exon coverage of over 5,000 clinically relevant genes • Whole genome backbone resolution in average is approximately 30 kb per probe • 60,000 SNP probes used for the detection of AOH associated with UPD or consanguinity LIMITATIONS • AOH less than 10 Mb in size may not be reported • The uniparental heterodisomy detection rate is not currently known for this assay
Turnaround Time	14 days
Sample types	• Blood, extracted DNA, cultured skin fibroblasts, buccal swabs

Old Slides

LEARNING OBJECTIVES

- Illustrate the benefits and limitations of WES and WGS
- Examine the utility of comprehensive and rapid testing using clinical case scenarios

// EXPAND YOUR DIAGNOSTIC YIELD BY ADDING COMPANION TESTING

WGS, WES, and NGS panels can be bundled with additional tests for a more comprehensive analysis.

Companion Testing	Rational	WGS	WES	NGS Panels
Global Metabolomic Assisted Pathway Screen (Global MAPS™) Test Codes: 4900, 4901 • TAT: 21 days	• Helps diagnose inborn errors of metabolism. When ordered in combination with exome and genome it can also help clarify variants of uncertain significance[1]	✓	✓	✓
Chromosomal Microarray Analysis (CMA) - HR + SNP Screen • Test Codes: 8665, 8655 • TAT: 14 days	• Screens for copy number variations with exon by exon coverage of >5,000 genes to detect conditions caused by deletions and duplication such as 22Q11.2 Deletion syndrome	CNV analysis included in our WGS	✓	✓
Comprehensive mtDNA Analysis • Test Code: 2055 • TAT: 28 –56 days*	• Examines mitochondrial DNA for single nucleotide and copy number changes to aid in the diagnosis of mitochondrial conditions such as Leigh Syndrome or Complex Deficiency.	mtDNA analysis included in our WGS	✓	✓

*TAT dependent on sample type. Please call client services at 1-800-411-4636 for further information

1. Alaimo et al., Genetics in Medicine. 2020