CME OUTFITTERS

A NICU Clinician's Guide to Rapid Whole Genome Sequencing: Test Results, Communication, and Clinical Decision Making

This program has been supported by an independent educational grant from GeneDx, LLC.

JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, CME Outfitters LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Please note:

Audience questions and polling were integrated throughout the live webcast of this program.

CME OUTFITTERS

Rebecca J. Burke, MD, PhD

Assistant Professor of Pediatrics
Division of Neonatology and Medical Genetics
Penn State Health Milton S. Hershey School of Medicine
Hershey, Pennsylvania

CME OUTFITTERS

Wendy K. Chung, MD, PhD

Chief of Clinical Genetics
Kennedy Family Professor of Pediatrics (in Medicine)
Columbia University
New York, New York

CME OUTFITTERS

Michelle Fergus

Patient Caregiver Advocate
Orlando, Florida

CME OUTFITTERS

Learning Objectives

1. Implement a comprehensive, equitable approach to genetic testing in NICU settings to identify under-recognized genetic conditions.
2. Interpret genetic testing results in NICU settings to improve early referral and clinical management for patients and caregivers.
3. Develop an effective communication plan for the discussion of genetic results in the absence of genetic specialist support with caregivers in NICU settings.

Lived Experience with Genomic Testing

Perinatal and Infant Genetic Testing

	Genetics					Genomics	
Test	**Carrier Screening**	**Noninvasive Prenatal**	**Karyotyping**	**Chromosomal Microarray**	**Multigene Panel**	**Whole Exome Sequencing (WES)**	**Whole Genome Sequencing (WGS)**
Detects	Heterozygous carriership of autosomal recessive conditions	Common aneuploidies in fetal chromosomes	Number + overall structure of chromosomes	Smaller structural abnormalities vs karyotyping	Variants in multiple targeted genes	Protein coding variants in all 20,000 genes	Variants in all 20,000 genes
Pros	Informs family planning	Noninvasive sample of maternal serum Widely available	Chromosome overview including balanced rearrangements + mosaicisms	High sensitivity for small deletions/ duplications + uniparental disomy	Efficient test for genetic etiology of non-specific dx with phenotype overlap (e.g., epilepsy)	Comprehensive test for genetic etiology of completely non-specific dx Secondary findings	**Chromosomal microarray and WES in one test** Sensitive for trinucleotide repeats
Cons	Limited to targeted conditions/ mutations	Limited to common aneuploidies	Can miss smaller deletions/ duplications	Cannot detect balanced rearrangements	VUS Can miss deletions/ duplications Insurance/financial barriers	VUS + secondary findings Can miss deletions/duplications Phenotype driven Parents needed Insurance/financial barriers	Can miss mosaicisms

Dx, diagnosis; VUS, variants of uncertain significance.

Badeau M, et al. *Cochrane Database Syst Rev.* 2017;11(11):CD011767. Wallace SE, Bean LJH. Educational Materials—Genetic Testing: Current Approaches. In: Adam MP, et al. *GeneReviews* (Internet). Seattle, Washington: University of Washington–Seattle; 1993–2023.

CME OUTFITTERS

Audience Response

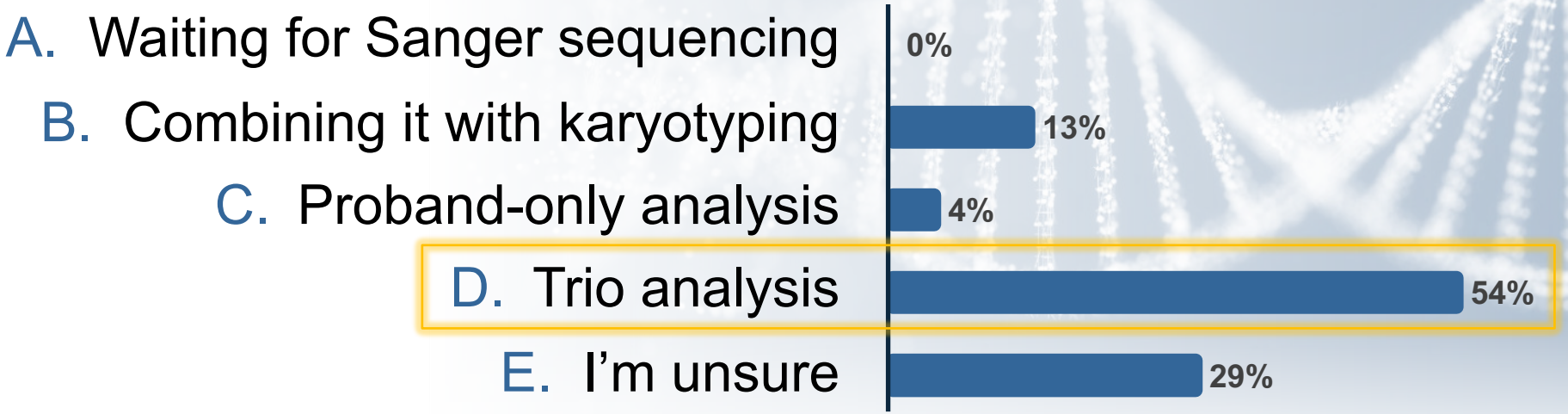
Which of the following can improve the diagnostic yield of genomic sequencing?

A. Waiting for Sanger sequencing
B. Combining it with karyotyping
C. Proband-only analysis
D. Trio analysis
E. I’m unsure

CME OUTFITTERS

Audience Response

Which of the following can improve the diagnostic yield of genomic sequencing?



CME OUTFITTERS

Diagnostic Yield of WES

WES of 3,040 consecutive cases at single clinical lab:

28.8% overall diagnostic yield

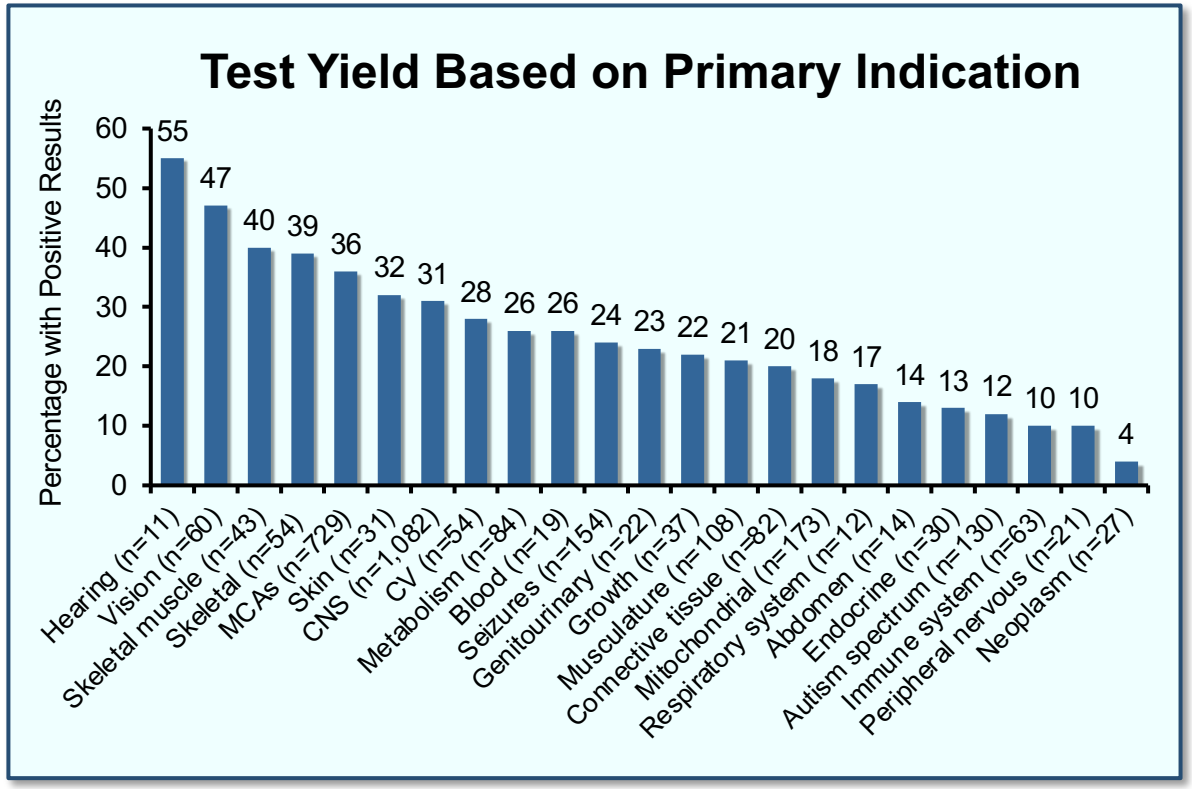
23.6% in proband-only cases

31% with WES trio

24.2% had candidate gene

25 cases had *dual diagnoses*

3 cases had *triple diagnoses*



MCA, multiple congenital anomaly; CNS, central nervous system; CV, cardiovascular.
Retterer K, et al. *Genet Med*. 2016;18(7):696–704.

CME OUTFITTERS

Rapid WGS (rWGS) in Critically Ill Infants

Genetic disorders are a leading cause of infant morbidity and mortality.

rWGS as a ***first-tier*** diagnostic test in critically ill infants:

- Improves diagnostic yields over conventional genetic testing
- Ends diagnostic odyssey before it begins
- Informs medical management
- Strengthens family decision making
- Reduces inpatient costs
- Is endorsed by the ACMG

ACMG, American College of Medical Genetics and Genomics.
Petrikin JE, et al. *Semin Perinatol*. 2015;39(8):623–631. Farnaes L, et al. *NPJ Genom Med*. 2018;3:10.
Wenger T, et al. *Genet Med*. 2022;24(3):S178. Manickam K, et al. *Genet Med*. 2021;23(11):2029–2037.

CME OUTFITTERS

rWGS in ICU Infants Pilot Protocol

Eligibility

Any infant with ≥2 of the following admitted to ICU	
Major structural anomaly	Intellectual disability/developmental delay
Dysmorphic facial features	Short stature, microcephaly, or weight <3%
Seizures/epilepsy	Organ failure (cardiac, pulmonary, renal, liver, immune)
Family history of similarly affected family member or consanguinity	

Additional Requirements
Both biological parents available
Blood samples for full trio
Patient expected to be admitted at time of results (TAT ~7 days)

Clinical Workflow

Eligibility Determination
1. NICU/PICU recommends rWGS
2. Genetics consult for rWGS request
3. Submit nomination/approval form
4. rWGS approved

Collection
1. Consent forms from family
2. 2 mL of blood from infant
3. 5 mL of blood from **both** parents
4. Basic medical and family history

Clinical Results
1. Send out trio consent + samples
2. Verbal results in ~7 days
3. Final written report in ~14 days
Secondary findings: patient decision

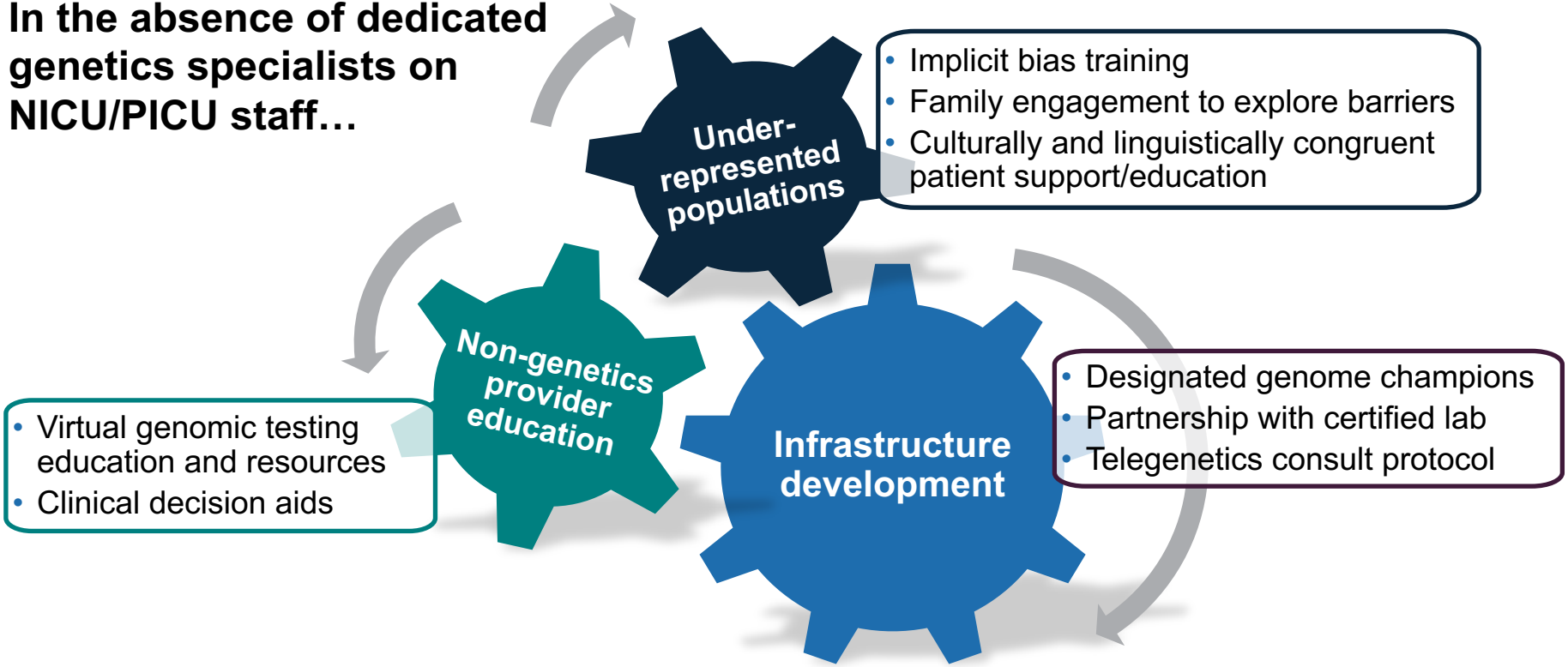
Outcomes since February 28, 2022: 36 of 42 requests completed; 33% with diagnostic results, 11% with VUS

ICU, intensive care unit; NICU, neonatal ICU; PICU, pediatric ICU; TAT, turnaround time.
Protocol and data provided courtesy of Chung WK.

CME OUTFITTERS

rWGS Implementation in NICU/PICU

In the absence of dedicated genetics specialists on NICU/PICU staff…



Raspa M, et al. *Interact J Med Res*. 2021;10(1):e23523. East KM, et al. *J Pers Med*. 2022;12(3):405. D'Gama AM, Agrawal PB. *J Perinatol*. 2023;1–5. Wojcik MH, et al. *J Perinatol*. 2023;43(2):248–252.

CME OUTFITTERS

CME OUTFITTERS

Faculty Panel Discussion

Overcoming Barriers to rWGS in Critically Ill Infants

Interpreting rWGS Results

Primary findings: gene(s) alterations directly related to the patient's symptoms or reason(s) for testing

Secondary findings: alterations that may be medically meaningful but unrelated to the reason for testing

Medically actionable: results used to alter treatment or surveillance of the patient

Variant classification: strength of a variant's association with disease

East K, et al. Guide to Interpreting Genomic Reports: A Genomics Toolkit. Clinical Sequencing Exploratory Research (CSER) Consortium. 2020. National Institutes of Health, National Human Genome Research Institute website. https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf.

CME OUTFITTERS

Patient Case: Diagnostic and Actionable

Infant phenotype:

Seizure, lethargy, hypertonia, small for gestational age, patent foramen ovale, weight loss, thrombocytopenia, anemia, metabolic acidosis, dehydration, subarachnoid hemorrhage, EEG abnormality, increased CSF lactate, hyponatremia, lactic acidosis, abdominal distention, concern for molybdenum cofactor deficiency, respiratory failure requiring assisted ventilation, feeding difficulties, meconium-stained amniotic fluid, sepsis, brain imaging abnormality.

rWGS test results: Primary findings identified

Gene (Transcript)	**Condition**	**Genomic Coordinates**	**Variant**	**Zygosity** (Inheritance)	**Classification**
CFTR (ENST00000003084)	Cystic fibrosis	7:117199644	c.1521_1523del p.Phe508del	Heterozygous (maternal)	Pathogenic
CFTR (ENST00000003084)	Cystic fibrosis	7:117227792	c.1585-1G>A	Heterozygous (paternal)	Pathogenic

EEG, electroencephalograph; CSF, cerebral spinal fluid.

Rady Children's Institute for Genomic Medicine. Clinician Toolbox. 2023. https://radygenomics.org/clinician-toolbox/.

Audience Response

The primary diagnosis identified by rWGS does not seem to explain all the patient's symptoms. What next steps should you take?

A. Assume the variants are secondary finding incorrectly labeled

B. Retest for molybdenum cofactor deficiency using WES

C. Investigate unifying etiologies

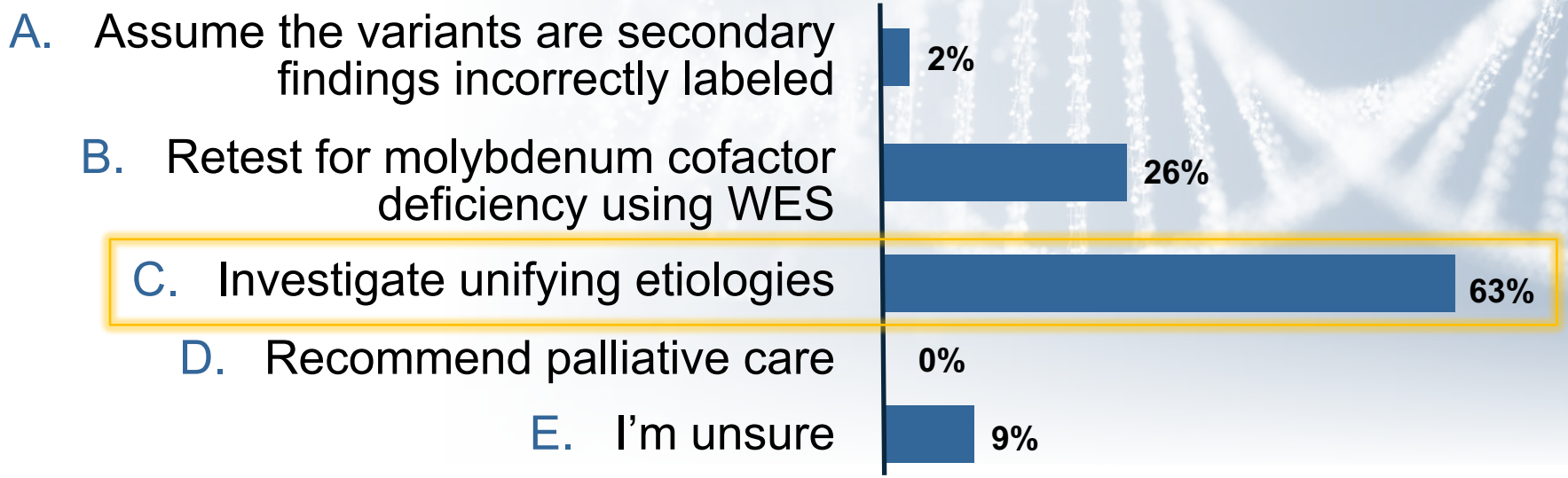
D. Recommend palliative care

E. I'm unsure

CME OUTFITTERS

Audience Response

The primary diagnosis identified by rWGS does not seem to explain all the patient's symptoms. What next steps should you take?



CME OUTFITTERS

Patient Case: Likely Pathogenic *de novo*

Gene	Variant	Condition	Inheritance	Classification
FOXF1	c.155 C>G p.S52C	Alveolar capillary dysplasia with misalignment of pulmonary veins	*de novo*	Likely pathogenic

Clinical indications:

- Severe hydronephrosis seen prenatally, s/p repair of posterior urethral valves after birth
- Developed pulmonary hypertension
- Transferred at 14 DOL for management of pulmonary hypertension
- Genetics evaluation at 16 DOL

Management implications:

- Care team investigated centers that may offer lung transplant and family decided to meet with a team from St. Louis
- Patient decompensated on the day of the meeting and the family elected to pursue comfort care

Final outcome: Patient passed away 2 days later at 8.5 weeks old

s/p, status post; DOL, days of life.

Patient Case: Maternal and *de novo* Variants

History of present illness:

- Ventricular septal defect diagnosed prenatally
- Rapid progression with biventricular cardiomyopathy and decreased systolic function at 1 month old
- Admitted for tachypnea and feeding difficulty → cardiomegaly dx on chest X-ray
- Paternal history of atrial septal defect
- Genetic evaluation at 5 weeks old

rWGS test results: **Primary findings identified**

Gene	Variant	Condition	Inheritance	Classification
MYBPC3	c.1227-13 G>A	HCM	*de novo*	Pathogenic
MYBPC3	c.1227-80 G>A	HCM	Maternal	Likely pathogenic

HCM, hypertrophic cardiomyopathy.

Audience Response

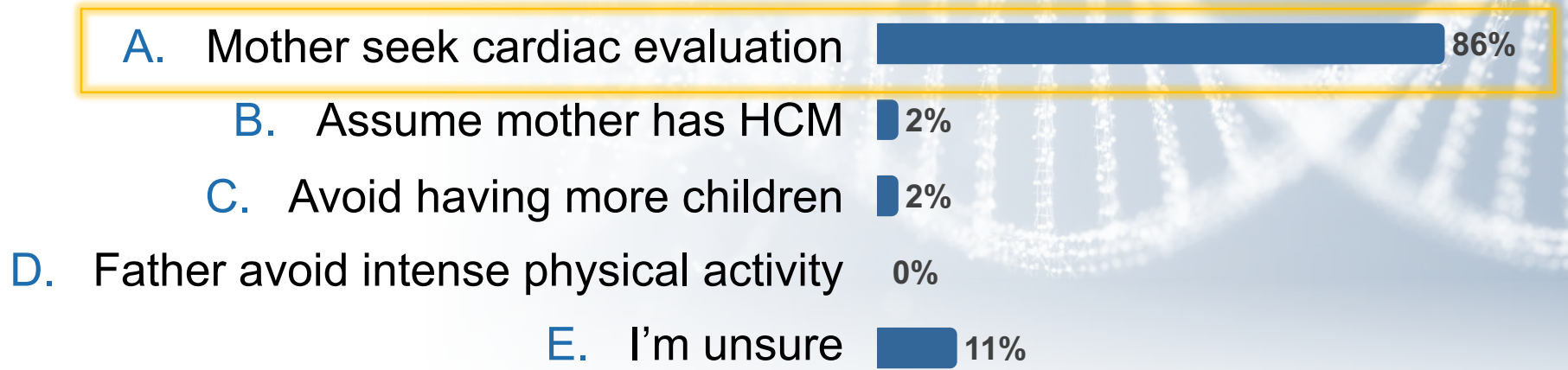
Other than the patient's care plan, what additional recommendation should you provide the family based on these results?

A. Mother seek cardiac evaluation
B. Assume mother has HCM
C. Avoid having more children
D. Father avoid intense physical activity
E. I'm unsure

CME OUTFITTERS

Audience Response

Other than the patient's care plan, what additional recommendation should you provide the family based on these results?



CME OUTFITTERS

rWGS Results: Patient Letter

Reason for testing:

Based on information provided to the research lab, the child has a history of heart muscle changes and a family history of a sibling with similar symptoms.

Gene	Transcript	Variant
RPL3L	NM_005061.3	c.1076_1080del CCGTG (p.Ala359Glyfs*4)
RPL3L	NM_005061.3	c.80G>A (p.Gly27Asp)

The information in the table is specific to your child. The “transcript” and “variant” describe the type and the specific location of your child’s gene change.

For more information:

- About CMD2D: https://omim.org/entry/619371
- For support related to CMD2D: https://rarediseases.org/rare-diseases/pediatric-cardiomyopathy/

Results related to the reason for testing (also called primary results):
Two genetic changes were found (also called a positive result)

Result

- The whole genome sequencing test found 2 changes in the *RPL3L* gene that together are likely the reason for most or all of your child’s symptoms.
- Changes in this gene have been seen in people with dilated cardiomyopathy 2D (CMD2D).
- People with CMD2D can have changes to their heart muscle and heart failure.

Chance That Family Members Could Have the Same Genetic Changes *(recurrence risk)*

- One of the genetic changes was found in his mother’s blood; the other genetic change was found in his father’s blood.
- *RPL3L* gene changes are thought to be recessive. This means that 2 gene changes together cause a problem.
- Having one genetic change in *RPL3L* does not cause CMD2D; one change means someone is a carrier for CMD2D.
- When 2 carriers of CMD2D have a child together, there is a 25% (1 in 4) chance with each pregnancy to have a child with CMD2D.

Future Care

- Your child’s doctors and nurses may talk with you about changes to your child’s care based on this result.
- Other genetic tests may be needed for your child based on his personal and family medical histories.
- Please continue to follow-up with your child’s healthcare providers to learn about new information, testing options, or research studies.
- Please see the end of this letter and the attached lab report for more specific information about these genetic changes.

Results NOT related to the reason for testing (also called secondary results):
No other genetic changes found (also called a negative result)

Keep in Mind

- In addition to looking for the reason for your child’s symptoms, this test looked at 73 other genes that can cause disease in the future.
- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.
- This does not mean your child will not develop a genetic disease in the future. Humans have more than 20,000 genes. There are many gene changes that may cause disease that the lab cannot find or understand.

East KM, et al. *J Pers Med*. 2022;12(3):405.

CME OUTFITTERS

Discussing Results with Patient Family

- **Stages**
  - Shock and awe—avoid information overload up front
  - Detailed discussion—ensure understanding that not every child will have every feature
  - Follow-up—provide options and revisit as needed
- **Multimodal Education**
  - Oral discussion—use interpreters if needed
  - Written materials—welcome packets, pamphlets, etc.
  - Virtual resources—videos, links, etc.
- **Care Team**
  - Introduce genetic and non-genetic providers, including social workers
  - Ensure parents and other family members/supporters are included
- **Community Support Groups**
  - Connect with vetted family groups and personal connection with another parent when possible

Courtesy of Chung WK.

CME OUTFITTERS

Genomic Sequencing Support Resources

- **American College of Medical Genetics and Genomics** (https://www.acmg.net/): interdisciplinary professional organization committed to advancing the practice of medical genetics
- **Guide to Interpreting Genomic Reports** (https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf): guide to genomic test results for non-genetics providers from the Clinical Sequencing Exploratory Research Consortium
- **iHOPE Network** (https://ihopenetwork.org/): philanthropic organization that provides rWGS for underserved patients and families
- **MedGen** (https://www.ncbi.nlm.nih.gov/medgen/): organized tools and information related to human medical genetics compiled from the Genetic Testing Registry, ClinGen, ClinVar, GeneReviews, Medical Genetics Summaries, and other comprehensive resources
- **National Center for Biotechnology Information** (https://www.ncbi.nlm.nih.gov/guide/genetics-medicine/): comprehensive list of medical genetics databases, tools, education, and more
- **National Coordinating Center for the Regional Genetics Network** (https://nccrcg.org/telegenetics/): HRSA-funded project to support patients and providers implementing and/or using telegenetics
- **National Human Genome Research Institute** (https://www.genome.gov/): NIH-funded project with virtual genomic education and resources for healthcare providers
- **National Organization for Rare Disorders** (https://rarediseases.org/): national nonprofit representing patients and families affected by rare disease
- **Online Mendelian Inheritance in Man** (https://www.omim.org/): online catalog of human genes and genetic disorders

CME OUTFITTERS

SMART Goals

- Equitably implement rWGS as a first-tier diagnostic test for critically ill infants with non-specific diagnoses of unknown etiology.
- Leverage partnerships with certified labs and/or telegenetics resources to facilitate timely access to genetics consults before, during, and after testing.
- Develop care plans based on rWGS test results and informed, empathetic, and multimodal discussion with family members.

CME OUTFITTERS

CME OUTFITTERS

Visit the **Virtual Education Hub**

Free resources and education to educate health care professionals and patients.

https://www.cmeoutfitters.com/practice/virtual-education-hub/

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Click on the *Request Credit* tab to complete the process and print your certificate.