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Genetics Corner: Clinical Implementation and Improved Access of Whole-Genome Sequencing in the NICU: Learnings from a Virtual Educational Event

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Illumina, a genomic sequencing company (San Diego, CA), hosted a virtual educational event for neonatal providers interested in learning more about WGS and sharing best practices for attendees interested in driving legislation and reimbursement in their states. The event format allowed formal presentations and open discussion through roundtable sessions.

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An estimated 30-50% of neonatal and pediatric intensive care unit (NICU/PICU) admissions are secondary to birth defects or genetic conditions, which result in death in approximately 40% of neonates. (1-4) Whole-genome sequencing (WGS) in acutely ill infants has become essential in the neonatologists' toolkit. Over the past five years, published evidence has demonstrated the diagnostic, clinical, and economic utility of rapid WGS in the NICU setting. (5-10) The NICUSeq randomized-controlled trial, published last year, showed that a change in management is twice as likely when WGS is introduced as a first-tier test compared to infants who undergo usual care testing. (5) Genomic sequencing results that do not yield a diagnosis may also be medically actionable and add value to shared decision-making. (5-7,11)These findings support WGS adoption and implementation in acutely ill infants.

Even though the diagnostic yield is superior with WGS compared to standard testing in acutely ill infants, implementation as a first-tier test remains limited.(5,8-10) Several states, including California and Michigan, have worked towards legislation and Medicaid reimbursement to improve access. In addition to reimbursement limitations, there remains a gap in knowledge about WGS and comfort with clinical implementation. (12) The limited availability of geneticists and genetic counselors at many institutions may also preclude test utilization.

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Salient topics covered in this virtual event include clinical utility, management of WGS reports, result communication, economic utility, clinical implementation, and impact on precision medicine. Experts from Rady Children's Institute of Genomic Medicine (RCIGM), Helen DeVos Children's Hospital, HudsonAlpha Institute of Biotechnology, the University of California San Francisco (UCSF), and Illumina presented. Representatives from Project Baby programs in California, Michigan, and Minnesota shared different perspectives on their state successes. The event culminated in a discussion with a patient advocate, Amber Freed, Founder of SLC6A1 Connect, who has deep experience using her voice to raise money and drive meaningful change for rare diseases.

The following aims to summarize key takeaways from the different presentations.

Clinical utility – *Kristen Wigby, MD, Rady Children's Hospital*

- There is strong evidence that early diagnosis can have significant impacts on the management of acutely ill infants
- WGS may help distinguish between disorders with overlapping phenotypes or remove clinical bias in test selection
- Acutely ill infants or children may be good candidates for GS if:

- There is no unifying diagnosis, or a rapid diagnosis may inform medical management
- There is a suspected genetic disorder
- A diagnosis has not been confirmed previously despite an extensive workup, previous testing
- There is a history of multiple hospitalizations or prolonged stays

"First-line use of WGS in the NICU diagnostic workup is the most cost-effective approach and can bring potential savings to the payor, provider, and patient. (6,8,13)"

The current state of economic utility – *Audrey Ozuls, MBA, Illumina*

- Coverage of WGS, including rapid WGS, exists in several states across the US (see map)
- First-line use of WGS in the NICU diagnostic workup is the most cost-effective approach and can bring potential savings to the payor, provider, and patient. (6,8,13)

Experiences from Project Baby Programs in California, Michigan, and Minnesota - *Russell Nofsinger, Ph.D., Rady Children's Institute of Genomic Medicine; Andrea Scheurer-Monaghan, MD, Bronson Children's Hospital; Laura Appel, MS, Michigan Hospital Association; Jessica Aguilar, MHA, Sanford Health*https://www.mha.org/issues-advocacy/project-baby-deer/

- California: Project Baby Bear was a pilot project supported by a $2 million state appropriation and involved five hospitals throughout California. In total, 178 infants received rapid WGS with a diagnostic rate of 42%, and clinical management changes were noted in 31%. This project led to a legislative mandate and coverage of rapid WGS by Medi-Cal. (6)
- Michigan: Project Baby Deer was a collaboration between Michigan Health and Hospital Administration, Michigan clinical champions, and Rady Children's Institute for Genomic Medicine. Seven hospitals recruited 89 infants leading to a diagnosis in 39% and a change of management in 27%. This effort resulted in a net benefit totaling $252,938 and led to rWGS coverage through a 'carve out' payment by Michigan Medicaid.
- Minnesota: Project Baby Loon was initiated to emulate other projects' successes. In this instance, the Minnesota Sanford Children's Genomic Medicine Consortium formed by Sanford Health aimed to promote the implementation of precision medicine in pediatric practice. Before proposing a bill, their collaborative efforts led to the Minnesota Department of Human Services' decision to add coverage of rapid WGS to their Medical Assistance without additional research or legislative processes.

Successful Implementation - *Linda Franck, RN, PhD, FAAN, University of California San Francisco*

- Studies were performed as part of both the California and Michigan projects to assess knowledge, opinions and implementation barriers with rapid WGS
- Successful clinical implementation depends upon identifying champions, engaging all stakeholders, learning as a team, assessing interdepartmental relationships and unit culture, developing process maps, and defining metrics for success
- Tools were provided to map the clinical implementation process and assess team knowledge, attitudes and practices. (12,14)

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Managing the WGS Report – *Becky Milewski, MS, CGC, Illumina*

- WGS test reports can be long and overwhelming for some providers
- WGS is a phenotype-driven analysis, and all relevant phenotypic information must be provided to the lab
- There are several reasons a report may be negative, including lack of phenotypic presentation, limitations in WGS technology, or unknown/undiscovered genetic cause
- Clinicians should be aware of additional findings that may be reported, including secondary or incidental findings

Impact of WGS on Treatment – Caleb Bupp, MD, FACMG, Spectrum Health Helen DeVos Children's Hospital

- Acceleration of comprehensive WGS and downstream precision medicine tools have enabled improvements in rare disease diagnosis and clinical utility
- Findings from DNA sequencing can be combined with transcriptomics, proteomics, and epigenomics to help further define the underlying etiology and potential impact
- With knowledge of genomic pathways for rare diseases, new and existing treatments can be repurposed to treat rare and ultra-rare conditions

Result Communication – *Kelly East, MS, CGC, HudsonAlpha Institute of Biotechnology*

- SouthSeq evaluated first-tier WGS in NICUs across the Southeast. Non-genetic NICU providers were trained to disclose results(15)
- Error rates in result disclosure compared between non-ge-

netic providers and genetic counselors

- Non-genetic providers could return genomic results with no significant errors in 92% of cases. The most common significant errors were over-interpreted negative results, omitted critical information, and misquoted recurrence risk.
- With appropriate training, non-genetic providers can successfully manage WGS result disclosure.

" While solid evidence supports the utility of rapid WGS in acutely ill infants, under-utilization of testing for clinical indications demonstrates that challenges remain to realize the potential impact in this population. There is an interest to continue building pathways for adequate reimbursement and tools to support education and successful implementation."

Overall, this event sparked discussion among providers with variable experience implementing WGS. While solid evidence supports the utility of rapid WGS in acutely ill infants, under-utilization of testing for clinical indications demonstrates that challenges remain to realize the potential impact in this population. There is an interest to continue building pathways for adequate reimbursement and tools to support education and successful implementation.

For more information or to be included in email lists for future events, please email: hsnyder@illumina.com

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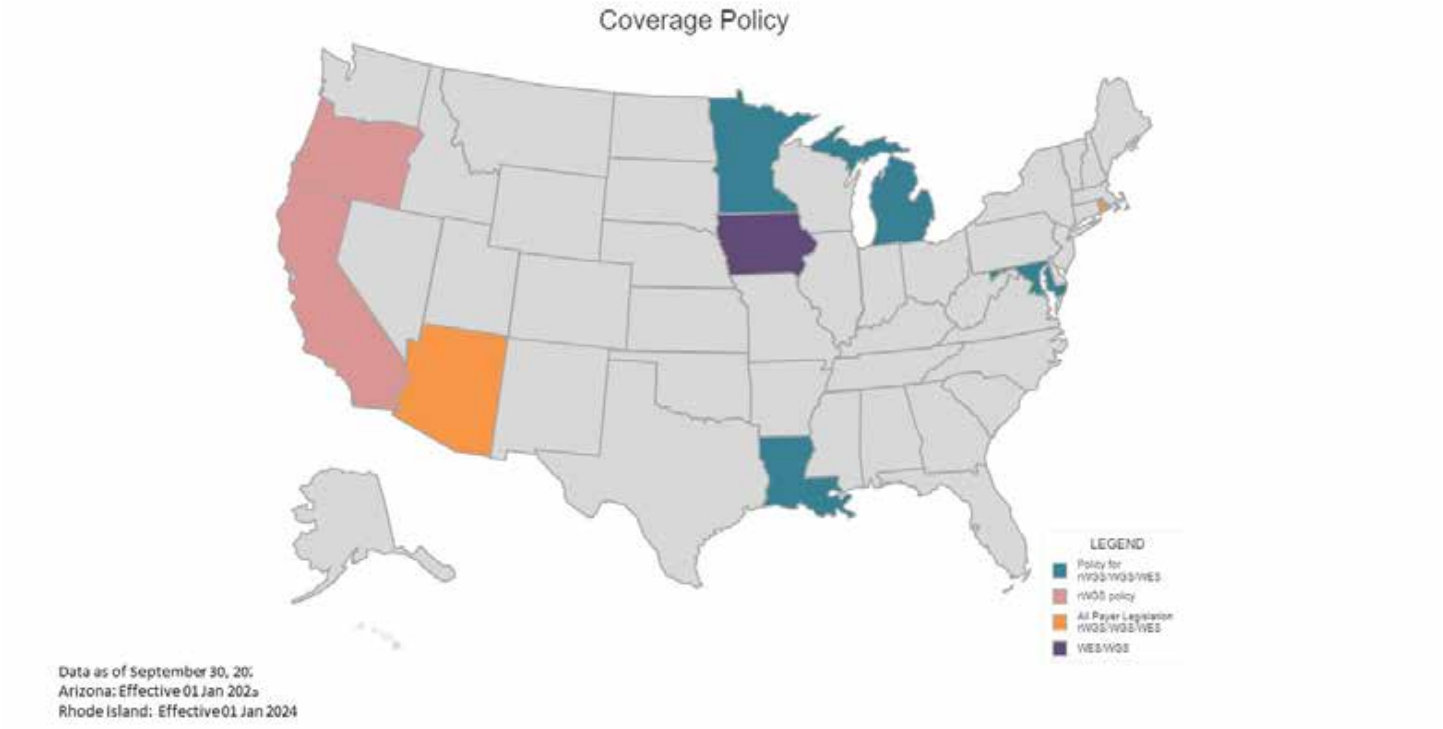

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