Resources on Whole Genome Sequencing

The Genomic Answers for Children's Health (GACH) Alliance has put together several compilations of studies and resources on whole genome sequencing (WGS). This document focuses on studies that demonstrate the efficacy of WGS in real-world settings.

About the GACH Alliance

The GACH Alliance is a diverse group of health care stakeholders committed to expanding access to WGS and helping to end the diagnostic odyssey. Our mission is to ensure that any child with a rare disease or suspected genetic disorder who is enrolled in Medicaid has timely access to genomic sequencing, especially whole genome sequencing. We also seek to ensure that patients and their families have the opportunity to share the sequencing results with medical researchers, to help aid in the discovery and development of new treatments for rare diseases.

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Clinical Demonstration Projects – Real-World Evidence Studies

1.Dimmock DC S, Waldman B, Benson W, et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. Am J Hum Genetics. 2021;108:1-8. PMID: 34089648

- **Abstract:** "Genetic disorders are a leading contributor to mortality in neonatal and pediatric intensive care units (ICUs). Rapid whole-genome sequencing (rWGS)-based rapid precision medicine (RPM) is an intervention that has demonstrated improved clinical outcomes and reduced costs of care. However, the feasibility of broad clinical deployment has not been established. The objective of this study was to implement RPM based on rWGS and evaluate the clinical and economic impact of this implementation as a first line diagnostic test in the California Medicaid (Medi-Cal) program. Project Baby Bear was a payor funded, prospective, real-world quality improvement project in the regional ICUs of five tertiary care children's hospitals. Participation was limited to acutely ill Medi-Cal beneficiaries who were admitted November 2018 to May 2020, were <1 year old and within one week of hospitalization, or had just developed an abnormal response to therapy. The whole cohort received RPM. There were two prespecified primary outcomes-changes in medical care reported by physicians and changes in the cost of care. The majority of infants were from underserved populations. Of 184 infants enrolled, 74 (40%) received a diagnosis by rWGS that explained their admission in a median time of 3 days. In 58 (32%) affected individuals, rWGS led to changes in medical care. Testing and precision medicine cost $1.7 million and led to $2.2-2.9 million cost savings. rWGS-based RPM had clinical utility and reduced net health care expenditures for infants in regional ICUs. rWGS should be considered early in ICU admission when the underlying etiology is unclear." https://pubmed.ncbi.nlm.nih.gov/34089648/

2.Project Baby Bear: Final Report. https://radygenomics.org/wp-content/uploads/2021/04/PBB-Final-_Report_07.14.20.pdf
Executive Summary: "In a pilot study implemented across the State of California, five clinical sites have demonstrated that a rapid precision medicine program for critically ill Medi-Cal babies improves clinical outcomes, improves the experience of care for families and clinicians, and reduces net healthcare expenditures. Over the course of this demonstration pilot ("Project Baby Bear") a single, comprehensive tool historically employed only as a last resort proved it could serve as the standard of care for testing sick babies early in their hospitalizations. Rapid whole genome sequencing (rWGS) yielded vital information that changed the decisions families and clinicians made, and ultimately saved lives and resources." https://radygenomics.org/wp-content/uploads/2021/04/PBB-Final-Report_07.14.20.pdf

3.Bowling KM, Thompson ML, Finnila CR, et al. Genome sequencing as a first-line diagnostic test for hospitalized infants. Genet Med. 2022 Apr;24(4):851-861. doi: 10.1016/j.gim.2021.11.020.

- **Abstract:** "Purpose: SouthSeq is a translational research study that undertook genome sequencing (GS) for infants with symptoms suggestive of a genetic disorder. Recruitment targeted racial/ethnic minorities and rural, medically underserved areas in

the Southeastern United States, which are historically underrepresented in genomic medicine research.

- **Methods**: GS and analysis were performed for 367 infants to detect disease-causal variation concurrent with standard of care evaluation and testing.
- **Results**: Definitive diagnostic (DD) or likely diagnostic (LD) genetic findings were identified in 30% of infants, and 14% of infants harbored an uncertain result. Only 43% of DD/LD findings were identified via concurrent clinical genetic testing, suggesting that GS testing is better for obtaining early genetic diagnosis. We also identified phenotypes that correlate with the likelihood of receiving a DD/LD finding, such as craniofacial, ophthalmologic, auditory, skin, and hair abnormalities. We did not observe any differences in diagnostic rates between racial/ethnic groups.
- **Conclusion**: We describe one of the largest-to-date GS cohorts of ill infants, enriched for African American and rural patients. Our results show the utility of GS because it provides early-in-life detection of clinically relevant genetic variations not detected by current clinical genetic testing, particularly for infants exhibiting certain phenotypic features." https://www.gimjournal.org/article/S1098-3600(21)05400-9/pdf

4.Bupp CP, Ames EG, Arenchild MK, Caylor S, Dimmock DP, Fakhoury JD, Karna P, Lehman A, Meghea CI, Misra V, Nolan DA, O'Shea J, Sharangpani A, Franck LS, Scheurer-Monaghan A. Breaking Barriers to Rapid Whole Genome Sequencing in Pediatrics: Michigan's Project Baby Deer. *Children*. 2023; 10(1):106.
https://doi.org/10.3390/children10010106

- **Abstract:** "The integration of precision medicine in the care of hospitalized children is ever evolving. However, access to new genomic diagnostics such as rapid whole genome sequencing (rWGS) is hindered by barriers in implementation. Michigan's Project Baby Deer (PBD) is a multi-center collaborative effort that sought to break down barriers to access by offering rWGS to critically ill neonatal and pediatric inpatients in Michigan. The clinical champion team used a standardized approach with inclusion and exclusion criteria, shared learning, and quality improvement evaluation of the project's impact on the clinical outcomes and economics of inpatient rWGS. Hospitals, including those without on-site geneticists or genetic counselors, noted positive clinical impacts, accelerating time to definitive treatment for project patients. Between 95–214 hospital days were avoided, net savings of $4155 per patient, and family experience of care was improved. The project spurred policy advancement when Michigan became the first state in the United States to have a Medicaid policy with carve-out payment to hospitals for rWGS testing. This state project demonstrates how front-line clinician champions can directly improve access to new technology for pediatric patients and serves as a roadmap for expanding clinical implementation of evidence-based precision medicine technologies."
  https://pdfs.semanticscholar.org/bc53/f8307cf4de0a8b4f368a15fcf4e54bb5a8a8.pdf