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 cost-effectiveness and cost-efficacy of utilizing WGS for rare diseases.

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.

To learn more about the Alliance, contact Josh Trent at josh.trent@leavittpartners.com, Clay Alspach at clay.alspach@leavittpartners.com, Melissa Pfaff at melissa.pfaff@leavittpartners.com, or Tanner Fliss at tanner.fliss@leavittpartners.com. Visit our website at gachalliance.org.

Cost-Effectiveness and Cost-Efficacy of Genome Sequencing for Rare Disease

1.Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. NPJ Genom Med. 2018 Apr 4;3:10. PMID: 29644095

- **Abstract:** "Genetic disorders are a leading cause of morbidity and mortality in infants. Rapid whole-genome sequencing (rWGS) can diagnose genetic disorders in time to change acute medical or surgical management (clinical utility) and improve outcomes in acutely ill infants. We report a retrospective cohort study of acutely ill inpatient infants in a regional children's hospital from July 2016-March 2017. Forty-two families received rWGS for etiologic diagnosis of genetic disorders. Probands also received standard genetic testing as clinically indicated. Primary end-points were rate of diagnosis, clinical utility, and healthcare utilization. The latter was modelled in six infants by comparing actual utilization with matched historical controls and/or counterfactual utilization had rWGS been performed at different time points. The diagnostic sensitivity of rWGS was 43% (eighteen of 42 infants) and 10% (four of 42 infants) for standard genetic tests (P = .0005). The rate of clinical utility of rWGS (31%, thirteen of 42 infants) was significantly greater than for standard genetic tests (2%, one of 42; P = .0015). Eleven (26%) infants with diagnostic rWGS avoided morbidity, one had a 43% reduction in likelihood of mortality, and one started palliative care. In six of the eleven infants, the changes in management reduced inpatient cost by $800,000-$2,000,000. These findings replicate a prior study of the clinical utility of rWGS in acutely ill inpatient infants, and demonstrate improved outcomes and net healthcare savings. rWGS merits consideration as a first tier test in this setting." https://pubmed.ncbi.nlm.nih.gov/29644095/

2.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/

3.Incerti D, Xu XM, Chou JW, et al. Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases. Genet Med. January 2022. 24(1): 109-118. PMID: 34906478 4.

- **Abstract:** "Purpose: To estimate the cost-effectiveness of genome sequencing (GS) for diagnosing critically ill infants and noncritically ill pediatric patients (children) with suspected rare genetic diseases from a United States health sector perspective.
- **Methods**: A decision-analytic model was developed to simulate the diagnostic trajectory of patients. Parameter estimates were derived from a targeted literature review and meta-analysis. The model simulated clinical and economic outcomes associated with 3 diagnostic pathways: (1) standard diagnostic care, (2) GS, and (3) standard diagnostic care followed by GS.
- **Results**: For children, costs of GS ($7284) were similar to that of standard care ($7355) and lower than that of standard care followed by GS pathways ($12,030). In critically ill infants, when cost estimates were based on the length of stay in the neonatal intensive care unit, the lowest cost pathway was GS ($209,472). When only diagnostic test costs were included, the cost per diagnosis was $17,940 for standard, $17,019 for GS, and $20,255 for standard care followed by GS.
- **Conclusion**: The results of this economic model suggest that GS may be cost neutral or possibly cost saving as a first line diagnostic tool for children and critically ill infants." https://pubmed.ncbi.nlm.nih.gov/34906478/

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

5.Lavelle TA, Feng X, Keisler M, et al. Cost-effectiveness of exome and genome sequencing for children with rare and undiagnosed conditions [published correction appears in Genet Med. 2022 Nov;24(11):2415-2417]. Genet Med. 2022;24(6):1349-1361. doi:10.1016/j.gim.2022.03.005

- **Abstract:** "Purpose: This study aimed to estimate the cost-effectiveness of exome sequencing (ES) and genome sequencing (GS) for children.
- **Methods**: We modeled costs, diagnoses, and quality-adjusted life years (QALYs) for diagnostic strategies for critically ill infants (aged <1 year) and children (aged <18 years) with suspected genetic conditions: (1) standard of care (SOC) testing, (2) ES, (3) GS, (4) SOC followed by ES, (5) SOC followed by GS, (6) ES followed by GS, and (7) SOC followed by ES followed by GS. We calculated the 10-year incremental cost per additional diagnosis, and lifetime incremental cost per QALY gained, from a health care perspective.
- **Results**: First-line GS costs $15,048 per diagnosis vs SOC for infants and $27,349 per diagnosis for children. If GS is unavailable, ES represents the next most efficient option compared with SOC ($15,543 per diagnosis for infants and $28,822 per diagnosis for children). Other strategies provided the same or fewer diagnoses at a higher incremental cost per diagnosis. Lifetime results depend on the patient's assumed long-term prognosis after diagnosis. For infants, GS ranged from cost-saving (vs all alternatives) to $18,877 per QALY (vs SOC). For children, GS (vs SOC) ranged from $119,705 to $490,047 per QALY.
- **Conclusion**: First-line GS may be the most cost-effective strategy for diagnosing infants with suspected genetic conditions. For all children, GS may be cost-effective under certain assumptions. ES is nearly as efficient as GS and hence is a viable option when GS is unavailable." https://pubmed.ncbi.nlm.nih.gov/35396982/

6.Sanford Kobayashi EF, Dimmock DP. Better and faster is cheaper. Human Mutation. Published online June 27, 2022. doi:10.1002/humu.24422

- **Abstract:** "The rapid pace of advancement in genomic sequencing technology has recently reached a new milestone, with a record-setting time to molecular diagnosis of a mere 8 h. The catalyst behind this achievement is the accumulation of evidence indicating that quicker results more often make an impact on patient care and lead to healthcare cost savings. Herein, we review the diagnostic and clinical utility of rapid whole genome and rapid whole exome sequencing, the associated reduction in healthcare costs, and the relationship between these outcome measures and time-to-diagnosis." https://onlinelibrary.wiley.com/doi/10.1002/humu.24422

7.Sanford Kobayashi E, Waldman B, Engorn BM, et al. Cost efficacy of rapid whole genome sequencing in the pediatric intensive care unit. Front Pediatr. 2021 9:809536. PMID: 35141181

- **Abstract:** "The diagnostic and clinical utility of rapid whole genome sequencing (rWGS) for critically ill children in the intensive care unit (ICU) has been substantiated by multiple studies, but comprehensive cost-effectiveness evaluation of rWGS in the ICU outside of the neonatal age group is lacking. In this study, we examined cost data retrospectively for a cohort of 38 children in a regional pediatric ICU (PICU) who received rWGS. We identified seven of 17 patients who received molecular diagnoses by rWGS and had resultant changes in clinical management with sufficient clarity to permit cost and quality adjusted life years (QALY) modeling. Cost of PICU care was estimated to be reduced by $184,846 and a total of 12.1 QALYs were gained among these seven patients. The total cost of rWGS for patients and families for the entire cohort (38 probands) was $239,400. Thus, the net cost of rWGS was $54,554, representing $4,509 per QALY gained. This quantitative, retrospective examination of healthcare utilization associated with rWGS-informed medicine interventions in the PICU revealed approximately one-third of a QALY gained per patient tested at a cost per QALY that was approximately one-tenth of that typically sought for cost-effective new medical interventions. This evidence suggests that performance of rWGS as a first-tier test in selected PICU children with diseases of unknown etiology is associated with acceptable cost-per-QALY gained." https://pubmed.ncbi.nlm.nih.gov/35141181/

8. Moore C, et al. An Economic Analysis of the Value of Genetic Testing. World Economic Forum Brief. 2021 Sept.

- **Summary:** A document that highlights advancement in genetic testing in three major areas: rare disease, cancer and population health. It describes how genetic testing as a treatment pathway in the future that will save time, resources as well as the use of carrier screening in diagnosis to screen whether an individual is a carrier for certain disorders. https://www3.weforum.org/docs/WEF_An_Economic_Analysis_of_the_Value_of_Genetic_Testing_2021.pdf

9. Vrijenhoek et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. European Journal of Human Genetics (2018) 26:1566–1571. https://doi.org/10.1038/s41431-018-0203-6

- **Abstract:** "Clinical application of whole-exome and whole-genome sequencing (WES and WGS) has led to an increasing interest in how it could drive healthcare decisions. As with any healthcare innovation, implementation of next-generation sequencing in the clinic raises questions on affordability and costing impact for society as a whole. We retrospectively analyzed medical records of 370 patients with ID who had undergone WES at various stages of their diagnostic trajectory. We collected all medical interventions performed on these patients at the University Medical Center Utrecht (UMCU), Utrecht, the Netherlands. We categorized the patients according to their WES-based preliminary diagnosis ("yes", "no", and "uncertain"), and assessed the per-patient healthcare activities and corresponding costs before (pre) and after (post) genetic

diagnosis. The WES-specific diagnostic yield among the 370 patients was 35% (128 patients). Pre-WES costs were €7.225 on average. Highest average costs were observed for laboratory-based tests, including genetics, followed by consults. Compared to pre-WES costs, the post-WES costs were on average 80% lower per patient, irrespective of the WES-based diagnostic outcome. Application of WES results in a considerable reduction of healthcare costs, not just in current settings, but even more so when applied earlier in the diagnostic trajectory (genetics-first). In such context, WES may replace less cost-effective traditional technologies without compromising the diagnostic yield. Moreover, WES appears to harbor an intrinsic "end-of-trajectory" effect; regardless of the diagnosis, downstream medical interventions decrease substantially in both number and costs." https://pubmed.ncbi.nlm.nih.gov/29959382/

10.Palmer et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: Evidence of clinical utility and cost effectiveness.
https://pubmed.ncbi.nlm.nih.gov/29314763/

- **Abstract:** "Background: Epileptic encephalopathies are a devastating group of neurological conditions in which etiological diagnosis can alter management and clinical outcome. Exome sequencing and gene panel testing can improve diagnostic yield but there is no cost-effectiveness analysis of their use or consensus on how to best integrate these tests into clinical diagnostic pathways.
- **Methods**: We conducted a retrospective cost-effectiveness study comparing trio exome sequencing with a standard diagnostic approach, for a well-phenotyped cohort of 32 patients with epileptic encephalopathy, who remained undiagnosed after "first-tier" testing. Sensitivity analysis was included with a range of commercial exome and multigene panels.
- **Results**: The diagnostic yield was higher for the exome sequencing (16/32; 50%) than the standard arm (2/32; 6.2%). The trio exome sequencing pathway was cost-effective compared to the standard diagnostic pathway with a cost saving of AU$5,236 (95% confidence intervals $2,482; $9,784) per additional diagnosis; the standard pathway cost approximately 10 times more per diagnosis. Sensitivity analysis demonstrated that the majority of commercial exome sequencing and multigene panels studied were also cost-effective. The clinical utility of all diagnoses was reported.
- **Conclusion**: Our study supports the integration of exome sequencing and gene panel testing into the diagnostic pathway for epileptic encephalopathy, both in terms of cost effectiveness and clinical utility. We propose a diagnostic pathway that integrates initial rapid screening for treatable causes and comprehensive genomic screening. This study has important implications for health policy and public funding for epileptic encephalopathy and other neurological conditions."
  https://onlinelibrary.wiley.com/doi/10.1002/mgg3.355

11. Runheim H, et al. The cost-effectiveness of whole genome sequencing in neurodevelopmental disorders. Sci Rep 13, 6904 (2023).
https://www.nature.com/articles/s41598-023-33787-8

- **Abstract:** "Whole genome sequencing (WGS) has the potential to be a comprehensive genetic test, especially relevant for individuals with neurodevelopmental disorders, syndromes and congenital malformations. However, the cost consequences of using whole genome sequencing as a first-line genetic test for these individuals are not well understood. The study objective was to compare the healthcare costs and diagnostic yield when WGS is performed as the first-line test instead of chromosomal microarray analysis (CMA). Two cohorts were analyzed retrospectively using register data, cohort CMA (418 patients referred for CMA at the department of Clinical Genetics, Karolinska University Hospital, during 2015) and cohort WGS (89 patients included in a WGS-first prospective study in 2017). The analysis compared healthcare consumption over a 2-year period after referral for genetic testing, the diagnostic yield over a 2- and 3-year period after referral was also compiled. The mean healthcare cost per patient in cohort WGS was $2,339 lower compared to cohort CMA ($ − 2339, 95% CI − 12,238–7561; P = 0.64) including higher costs for genetic investigations ($1065, 95% CI 834–1295; P < 0.001) and lower costs for outpatient care ($ − 2330, 95% CI − 3992 to (− 669); P = 0.006). The diagnostic yield was 23% higher for cohort WGS (cohort CMA 20.1%, cohort WGS 24.7%) (0.046, 95% CI − 0.053–0.145; P = 0.36). WGS as a first-line diagnostic test for individuals with neurodevelopmental disorders is associated with statistically non-significant lower costs and higher diagnostic yield compared with CMA. This indicates that prioritizing WGS over CMA in health care decision making will yield positive expected outcomes as well as showing a need for further research." https://www.nature.com/articles/s41598-023-33787-8