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 effectiveness of WGS, including those in a randomized controlled trial setting.

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.

Landmark Peer-Reviewed Clinical Utility Studies & Randomized Control Trials

1.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 Dec 3;6(265):265ra168. PMID 25473036

- **Abstract:** "Neurodevelopmental disorders (NDDs) affect more than 3% of children and are attributable to single-gene mutations at more than 1000 loci. Traditional methods yield molecular diagnoses in less than one-half of children with NDD. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) can enable diagnosis of NDD, but their clinical and cost-effectiveness are unknown. One hundred families with 119 children affected by NDD received diagnostic WGS and/or WES of parent-child trios, wherein the sequencing approach was guided by acuity of illness. Forty-five percent received molecular diagnoses. An accelerated sequencing modality, rapid WGS, yielded diagnoses in 73% of families with acutely ill children (11 of 15). Forty percent of families with children with nonacute NDD, followed in ambulatory care clinics (34 of 85), received diagnoses: 33 by WES and 1 by staged WES then WGS. The cost of prior negative tests in the nonacute patients was $19,100 per family, suggesting sequencing to be cost-effective at up to $7640 per family. A change in clinical care or impression of the pathophysiology was reported in 49% of newly diagnosed families. If WES or WGS had been performed at symptom onset, genomic diagnoses may have been made 77 months earlier than occurred in this study. It is suggested that initial diagnostic evaluation of children with NDD should include trio WGS or WES, with extension of accelerated sequencing modalities to high-acuity patients."
- https://pubmed.ncbi.nlm.nih.gov/25473036/

2.Willig LK, Petrikin JE, Smith LD, et al. Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. Lancet Respir Med. 2015 May;3(5):377-87. PMID 25937001

- **Abstract:** "Background: Genetic disorders and congenital anomalies are the leading causes of infant mortality. Diagnosis of most genetic diseases in neonatal and paediatric intensive care units (NICU and PICU) is not sufficiently timely to guide acute clinical management. We used rapid whole-genome sequencing (STATseq) in a level 4 NICU and PICU to assess the rate and types of molecular diagnoses, and the prevalence, types, and effect of diagnoses that are likely to change medical management in critically ill infants.
- **Methods:** We did a retrospective comparison of STATseq and standard genetic testing in a case series from the NICU and PICU of a large children's hospital between Nov 11, 2011, and Oct 1, 2014. The participants were families with an infant younger than 4 months with an acute illness of suspected genetic cause. The intervention was STATseq of trios (both parents and their affected infant). The main measures were the diagnostic rate, time to diagnosis, and rate of change in management after standard genetic testing and STATseq.

- **Findings**: 20 (57%) of 35 infants were diagnosed with a genetic disease by use of STATseq and three (9%) of 32 by use of standard genetic testing (p=0·0002). Median time to genome analysis was 5 days (range 3-153) and median time to STATseq report was 23 days (5-912). 13 (65%) of 20 STATseq diagnoses were associated with de-novo mutations. Acute clinical usefulness was noted in 13 (65%) of 20 infants with a STATseq diagnosis, four (20%) had diagnoses with strongly favourable effects on management, and six (30%) were started on palliative care. 120-day mortality was 57% (12 of 21) in infants with a genetic diagnosis.
- **Interpretation**: In selected acutely ill infants, STATseq had a high rate of diagnosis of genetic disorders. Most diagnoses altered the management of infants in the NICU or PICU. The very high infant mortality rate indicates a substantial need for rapid genomic diagnoses to be allied with a novel framework for precision medicine for infants in NICU and PICU who are diagnosed with genetic diseases to improve outcomes."
- https://pubmed.ncbi.nlm.nih.gov/25937001/

3.Stavropoulos DJ, Merico D, Jobling R, et al. Whole Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Pediatric Medicine. NPJ Genom Med. 2016 Jan 13;1. PMID: 28567303

- **Abstract:** "The standard of care for first-tier clinical investigation of the etiology of congenital malformations and neurodevelopmental disorders is chromosome microarray analysis (CMA) for copy number variations (CNVs), often followed by gene(s)-specific sequencing searching for smaller insertion-deletions (indels) and single nucleotide variant (SNV) mutations. Whole genome sequencing (WGS) has the potential to capture all classes of genetic variation in one experiment; however, the diagnostic yield for mutation detection of WGS compared to CMA, and other tests, needs to be established. In a prospective study we utilized WGS and comprehensive medical annotation to assess 100 patients referred to a paediatric genetics service and compared the diagnostic yield versus standard genetic testing. WGS identified genetic variants meeting clinical diagnostic criteria in 34% of cases, representing a 4-fold increase in diagnostic rate over CMA (8%) (p-value = 1.42e-05) alone and >2-fold increase in CMA plus targeted gene sequencing (13%) (p-value = 0.0009). WGS identified all rare clinically significant CNVs that were detected by CMA. In 26 patients, WGS revealed indel and missense mutations presenting in a dominant (63%) or a recessive (37%) manner. We found four subjects with mutations in at least two genes associated with distinct genetic disorders, including two cases harboring a pathogenic CNV and SNV. When considering medically actionable secondary findings in addition to primary WGS findings, 38% of patients would benefit from genetic counseling. Clinical implementation of WGS as a primary test will provide a higher diagnostic yield than conventional genetic testing and potentially reduce the time required to reach a genetic diagnosis."
- https://pubmed.ncbi.nlm.nih.gov/28567303/

4.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/

5.Petrikin JE, Cakici JA, Clark MM, et al. The NSIGHT1-randomized controlled trial: rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. NPJ Genom Med. 2018 Feb 9;3:6. PMID: 29449963

- **Abstract:** “Genetic disorders are a leading cause of morbidity and mortality in infants in neonatal and pediatric intensive care units (NICU/PICU). While genomic sequencing is useful for genetic disease diagnosis, results are usually reported too late to guide inpatient management. We performed an investigator-initiated, partially blinded, pragmatic, randomized, controlled trial to test the hypothesis that rapid whole-genome sequencing (rWGS) increased the proportion of NICU/PICU infants receiving a genetic diagnosis within 28 days. The participants were families with infants aged <4 months in a regional NICU and PICU, with illnesses of unknown etiology. The intervention was trio rWGS. Enrollment from October 2014 to June 2016, and follow-up until November 2016. Of all, 26 female infants, 37 male infants, and 2 infants of undetermined sex were randomized to receive rWGS plus standard genetic tests (n = 32, cases) or standard genetic tests alone (n = 33, controls). The study was terminated early due to loss of equipoise: 73% (24) controls received genomic sequencing as standard tests, and 15% (five) controls underwent compassionate cross-over to receive rWGS. Nevertheless, intention to treat analysis showed the rate of genetic diagnosis within 28 days of enrollment (the primary end-point) to be higher in cases (31%, 10 of 32) than controls (3%, 1 of 33; difference, 28% [95% CI, 10-46%]; p = 0.003). Among infants enrolled in the first 25 days of life, the rate of neonatal diagnosis was higher in cases (32%, 7 of 22) than controls (0%, 0 of 23; difference, 32% [95% CI, 11-53%];p = 0.004). Median age at diagnosis (25 days [range 14-90] in cases vs. 130 days [range 37-451] in controls) and median time to diagnosis (13 days [range 1-84] in cases, vs. 107 days [range 21-429] in controls) were significantly less in cases than controls (p = 0.04). In conclusion, rWGS

increased the proportion of NICU/PICU infants who received timely diagnoses of genetic diseases."

- https://pubmed.ncbi.nlm.nih.gov/29449963/

6.Sanford EF, Clark MM, Farnaes L, et al. Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. Pediatr Crit Care Med. 2019 Nov;20(11):1007-1020. PMID: 31246743

- **Abstract:** "Objectives: Genetic disorders are a leading contributor to mortality in the neonatal ICU and PICU in the United States. Although individually rare, there are over 6,200 single-gene diseases, which may preclude a genetic diagnosis prior to ICU admission. Rapid whole genome sequencing is an emerging method of diagnosing genetic conditions in time to affect ICU management of neonates; however, its clinical utility has yet to be adequately demonstrated in critically ill children. This study evaluates next-generation sequencing in pediatric critical care.
- **Design**: Retrospective cohort study.
- **Setting**: Single-center PICU in a tertiary children's hospital.
- **Patients**: Children 4 months to 18 years admitted to the PICU who were nominated between July 2016 and May 2018.
- **Interventions:** Rapid whole genome sequencing with targeted phenotype-driven analysis was performed on patients and their parents, when parental samples were available.
- **Measurements and main results**: A molecular diagnosis was made by rapid whole genome sequencing in 17 of 38 children (45%). In four of the 17 patients (24%), the genetic diagnoses led to a change in management while in the PICU, including genome-informed changes in pharmacotherapy and transition to palliative care. Nine of the 17 diagnosed children (53%) had no dysmorphic features or developmental delay. Eighty-two percent of diagnoses affected the clinical management of the patient and/or family after PICU discharge, including avoidance of biopsy, administration of factor replacement, and surveillance for disorder-related sequelae.
- **Conclusions**: This study demonstrates a retrospective evaluation for undiagnosed genetic disease in the PICU and clinical utility of rapid whole genome sequencing in a portion of critically ill children. Further studies are needed to identify PICU patients who will benefit from rapid whole genome sequencing early in PICU admission when the underlying etiology is unclear."
- https://pubmed.ncbi.nlm.nih.gov/31246743/

7.**NICUSeq Study Group, Krantz ID, Medne L, et al. Effect of Whole-Genome Sequencing on the Clinical Management of Acutely Ill Infants With Suspected Genetic Disease: A**

Randomized Clinical Trial. JAMA Pediatr. 2021 Dec 1;175(12):1218-1226. Erratum in: JAMA Pediatr. 2021 Dec 1;175(12):1295. PMID: 34570182

- **Abstract:** “Importance: Whole-genome sequencing (WGS) shows promise as a first-line genetic test for acutely ill infants, but widespread adoption and implementation requires evidence of an effect on clinical management.
- **Objective**: To determine the effect of WGS on clinical management in a racially and ethnically diverse and geographically distributed population of acutely ill infants in the US.
- **Design, setting, and participants**: This randomized, time-delayed clinical trial enrolled participants from September 11, 2017, to April 30, 2019, with an observation period extending to July 2, 2019. The study was conducted at 5 US academic medical centers and affiliated children's hospitals. Participants included infants aged between 0 and 120 days who were admitted to an intensive care unit with a suspected genetic disease. Data were analyzed from January 14 to August 20, 2020.
- **Interventions**: Patients were randomized to receive clinical WGS results 15 days (early) or 60 days (delayed) after enrollment, with the observation period extending to 90 days. Usual care was continued throughout the study.
- **Main outcomes and measures**: The main outcome was the difference in the proportion of infants in the early and delayed groups who received a change of management (COM) 60 days after enrollment. Additional outcome measures included WGS diagnostic efficacy, within-group COM at 90 days, length of hospital stay, and mortality.
- **Results**: A total of 354 infants were randomized to the early (n = 176) or delayed (n = 178) arms. The mean participant age was 15 days (IQR, 7-32 days); 201 participants (56.8%) were boys; 19 (5.4%) were Asian; 47 (13.3%) were Black; 250 (70.6%) were White; and 38 (10.7%) were of other race. At 60 days, twice as many infants in the early group vs the delayed group received a COM (34 of 161 [21.1%; 95% CI, 15.1%-28.2%] vs 17 of 165 [10.3%; 95% CI, 6.1%-16.0%]; P = .009; odds ratio, 2.3; 95% CI, 1.22-4.32) and a molecular diagnosis (55 of 176 [31.0%; 95% CI, 24.5%-38.7%] vs 27 of 178 [15.0%; 95% CI, 10.2%-21.3%]; P < .001). At 90 days, the delayed group showed a doubling of COM (to 45 of 161 [28.0%; 95% CI, 21.2%-35.6%]) and diagnostic efficacy (to 56 of 178 [31.0%; 95% CI, 24.7%-38.8%]). The most frequent COMs across the observation window were subspecialty referrals (39 of 354; 11%), surgery or other invasive procedures (17 of 354; 4%), condition-specific medications (9 of 354; 2%), or other supportive alterations in medication (12 of 354; 3%). No differences in length of stay or survival were observed.
- **Conclusions and relevance**: In this randomized clinical trial, for acutely ill infants in an intensive care unit, introduction of WGS was associated with a significant increase in focused clinical management compared with usual care. Access to first-line WGS may reduce health care disparities by enabling diagnostic equity. These data support WGS adoption and implementation in this population.”
  https://pubmed.ncbi.nlm.nih.gov/34570182/

8.**Maron JL, Kingsmore S, Gelb BD, et al. Rapid Whole-Genomic Sequencing and a Targeted Neonatal Gene Panel in Infants With a Suspected Genetic Disorder. JAMA. 2023;330(2):161-169. doi:10.1001/jama.2023.9350**

- **Abstract:** "Importance: Genomic testing in infancy guides medical decisions and can improve health outcomes. However, it is unclear whether genomic sequencing or a targeted neonatal gene-sequencing test provides comparable molecular diagnostic yields and times to return of results.
- **Objective**: To compare outcomes of genomic sequencing with those of a targeted neonatal gene-sequencing test.
- **Design, setting, and participants**: The Genomic Medicine for Ill Neonates and Infants (GEMINI) study was a prospective, comparative, multicenter study of 400 hospitalized infants younger than 1 year of age (proband) and their parents, when available, suspected of having a genetic disorder. The study was conducted at 6 US hospitals from June 2019 to November 2021.
- **Exposure**: Enrolled participants underwent simultaneous testing with genomic sequencing and a targeted neonatal gene-sequencing test. Each laboratory performed an independent interpretation of variants guided by knowledge of the patient's phenotype and returned results to the clinical care team. Change in clinical management, therapies offered, and redirection of care was provided to families based on genetic findings from either platform.
- **Main outcomes and measures**: Primary end points were molecular diagnostic yield (participants with ≥1 pathogenic variant or variant of unknown significance), time to return of results, and clinical utility (changes in patient care).
- **Results**: A molecular diagnostic variant was identified in 51% of participants (n = 204; 297 variants identified with 134 being novel). Molecular diagnostic yield of genomic sequencing was 49% (95% CI, 44%-54%) vs 27% (95% CI, 23%-32%) with the targeted gene-sequencing test. Genomic sequencing did not report 19 variants found by the targeted neonatal gene-sequencing test; the targeted gene-sequencing test did not report 164 variants identified by genomic sequencing as diagnostic. Variants unidentified by the targeted genomic-sequencing test included structural variants longer than 1 kilobase (25.1%) and genes excluded from the test (24.6%) (McNemar odds ratio, 8.6 [95% CI, 5.4-14.7]). Variant interpretation by laboratories differed by 43%. Median time to return of results was 6.1 days for genomic sequencing and 4.2 days for the targeted genomic-sequencing test; for urgent cases (n = 107) the time was 3.3 days for genomic sequencing and 4.0 days for the targeted gene-sequencing test. Changes in clinical care affected 19% of participants, and 76% of clinicians viewed genomic testing as useful or very useful in clinical decision-making, irrespective of a diagnosis.
- **Conclusions and relevance**: The molecular diagnostic yield for genomic sequencing was higher than a targeted neonatal gene-sequencing test, but the time to return of routine results was slower. Interlaboratory variant interpretation contributes to differences in molecular diagnostic yield and may have important consequences for clinical management." https://pubmed.ncbi.nlm.nih.gov/37432431/