

Rapid Genome Sequencing

Procedure(s) addressed by this policy:	Procedure Code(s)
Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))	81426
Re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)	81427
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCI GM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U

What is Rapid Genome Sequencing?

- Rapid genome sequencing (rGS) involves sequencing of coding and noncoding regions of the nuclear and mitochondrial genome. Preliminary positive results should be returned in <7 days and a final report delivered in <14 days.
- rGS has been proposed for diagnostic use in acutely-ill infants who present with complex phenotypes suspicious for a rare genetic condition, who cannot be diagnosed by standard clinical evaluation rapidly, or when features suggest a broad differential diagnosis that would require evaluation by multiple genetic tests.
- When used as a first-tier test in the acutely-ill infant, rGS can identify a genetic diagnosis efficiently, which has clinical utility in changing acute medical or surgical management and improving outcomes.
- Identifying a molecularly confirmed diagnosis in a timely manner for acutely-ill infants with a rare genetic condition can have a variety of health outcomes¹⁻⁹, including but not limited to:
 1. guiding prognosis and improving clinical decision-making via
 - application of specific treatments, as well as withholding of contraindicated treatments for certain rare genetic conditions
 - planning or avoidance of surgical interventions
 - surveillance for comorbidities
 - initiation of palliative care
 2. reducing the financial & psychological impact of diagnostic uncertainty and the diagnostic odyssey (e.g., eliminating lower-yield testing and additional screening testing that may later be proven unnecessary once a diagnosis is achieved)
 3. allowing for more rapid molecular diagnosis than a sequential genetic testing approach
 4. informing genetic counseling for other living relatives (i.e., siblings), as well as recurrence risk counseling and prenatal diagnosis options for the family

- Periodic reanalysis of previously obtained genome sequence has the potential for additional diagnostic yield because of constant expansions of existing variant databases, as well as periodic novel gene discovery and publication.¹⁰

Technical Information:

- In GS, all intergenic and intragenic regions are sheared and sequenced. Advantages of GS include eliminating the need for a capture step (increased efficiency, minimizes PCR-based artifacts), uniformity of coverage, including GC-rich regions, and the ability to detect variants that may be missed by exome sequencing (ES), such as copy-number variants (CNV), mid-size insertions and deletions (ca. 10-500 bp), nucleotide repeat expansion mutations, deeper intronic mutations, structural variants (e.g., translocations, inversions), and variants that result in methylation defects and uniparental disomy.^{7,9,11-14}
- Addition of CNV calling to small variant calling pipelines can improve diagnostic efficacy and efficiency in patients with rare genetic disease. As such, GS can be used as a unified testing platform, in place of combined or sequential exome sequencing and chromosomal microarray (CMA).¹⁵

Guidelines and Evidence:

- No specific evidence-based U.S. testing guidelines were identified.
- The standard approach to the diagnostic evaluation of an individual suspected of having a rare genetic condition may include combinations of imaging, biochemical, and electrophysiologic evaluations, which can help guide a molecular testing approach including CMA, single-gene analysis, a targeted gene panel, or exome/genome sequencing.^{16,17}
- The American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup that developed standard terminology for describing sequence variants identified by genomic sequencing. The guidelines describe criteria for classifying sequence variants into five categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign) based on criteria using typical types of variant evidence (e.g., population data, computational data, functional data, segregation data).^{18,19}
- The American College of Medical Genetics has three relevant policy statements that offer guidance on: 1) the clinical application of whole exome and whole genome testing,²⁰ 2) informed consent for genome/exome sequencing,²¹ and 3) reporting of incidental findings in clinical exome and genome sequencing.^{22,23}
- GS and rGS are powerful diagnostic tools for individuals with rare genetic conditions in which the specific genetic etiology is unclear or unidentified by standard clinical evaluation. The average diagnostic yield of rGS in acutely-ill infants is 21-73%.¹⁻⁶ In one rGS study, 4% of cases received a dual molecular diagnosis contributing to a complex phenotype, including two individuals with a pathogenic CNV and single nucleotide

variant (i.e., two significant findings associated with non-overlapping clinical presentations).⁷

- Evidence for the clinical utility of rGS in acutely-ill infants suspected of having rare genetic disease includes numerous retrospective and prospective case series, and one randomized controlled trial, with an impact on medical management described in 31-65% of individuals.¹⁻⁶ Relevant outcomes include improved clinical decision-making (e.g., initiation of specific treatments, withholding of contraindicated treatments, changes to surveillance, changes in reproductive decision making) and resource utilization.^{6,24} Further evidence of clinical utility of GS is demonstrated in the setting of non-rapid GS, with an impact on medical management in >48% of individuals.^{7,8,25,26}
- The use of family trio rGS reduces the time to diagnosis, the rate of uncertain findings, and adds to the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of rGS.^{6,27,28}
- rGS has been shown to positively impact healthcare utilization through reduced lengths of stay and reduced professional and facility fees.⁴

Criteria:

Rapid Genome Sequencing (rGS):

- Rapid genome sequencing (rGS) is considered medically necessary for the evaluation of acutely-ill infants ≤ 12 months of age when ALL of the following criteria are met:
 1. The patient and patient's family history have been evaluated by a Board-Certified or Board-Eligible Medical Geneticist, or an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), AND
 2. The etiology of the infant's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on EITHER of the following, AND
 - a) multiple congenital abnormalities affecting unrelated organ systems
 - b) TWO of the following criteria are met:
 - abnormality affecting at minimum a single organ system
 - encephalopathy
 - symptoms of a complex neurodevelopmental disorder (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia)
 - family history strongly suggestive of a genetic etiology, including consanguinity
 - laboratory findings suggestive of an inborn error of metabolism
 - abnormal response to therapy
 3. Alternate etiologies have been considered and ruled out when possible (e.g., environmental exposure, injury, infection, isolated prematurity), AND
 4. Clinical presentation does not fit a well-described syndrome for which rapid single-gene or targeted panel testing is available, AND

5. rGS is more efficient and economical than the separate single-gene tests or panels that would be recommended based on the differential diagnosis (e.g., genetic conditions that demonstrate a high degree of genetic heterogeneity), AND
6. A diagnosis cannot be made in a timely manner by standard clinical evaluation, excluding invasive procedures such as muscle biopsy, AND
7. Predicted impact on health outcomes, including immediate impact on medical management based on the molecular results, AND
8. Pre- and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor

Exclusions and Other Considerations:

- Trio samples are preferred for rGS
- rGS will not be covered if ES has already been completed.
- rGS will not be covered in acutely-ill infants with the following diagnoses:
 - Isolated Transient Neonatal Tachypnea
 - Isolated unconjugated hyperbilirubinemia
 - Isolated Hypoxic Ischemic Encephalopathy with clear precipitating event
 - Isolated meconium aspiration
- rGS is considered experimental/investigational for the diagnosis of genetic disorders in individuals >12 months of age who do not meet the above criteria.
- rGS is considered experimental/investigational for screening for genetic disorders in asymptomatic or pre-symptomatic individuals.

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