Rapid Genome Sequencing

Background

Rapid genome sequencing (rGS) involves sequencing of coding and noncoding regions of the nuclear and mitochondrial genome. Rapid analysis has an average turnaround time of less than 14 days, and typically less than 7 days. rGS has been proposed for diagnostic use in acutely-ill children 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 child, 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 children with a rare genetic condition can have a variety of health outcomes[1-17] including but not limited to:

- 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
- reducing the psychological and financial 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)
- allowing for more rapid molecular diagnosis than a sequential genetic testing approach
- informing genetic counseling for other living relatives (i.e., siblings), as well as recurrence risk counseling and prenatal diagnosis options for the family

Technical Information:

In GS, all intergenic and intragenic regions are sheared and sequenced. Advantages of GS can 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.[6,9,10,18-20]

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).[20-22]

The use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of ES/GS.[4,10,15,23] As part of a meta-analysis, five studies that conducted within-cohort comparisons of diagnostic utility of singleton and trio ES/GS found the pooled odds of diagnosis for trios was twice that of singletons ($P<0.0001$).[24]

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Periodic reanalysis of previously obtained genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication.[18] Reanalysis can be improved by thorough clinical reassessment and systematic reevaluation of the patient by the ordering provider.

Guidelines and Evidence:

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.[25,26]

The American College of Medical Genetics and Genomics (ACMG), has several relevant policy statements that offer guidance on the clinical application of ES/GS,[27,28] informed consent for ES/GS,[29] technical standards to ensure quality results and the interpretation and reporting of variants,[30] reporting of secondary findings in clinical ES/GS,[31,32] and re-analysis.[33]

The ACMG issued an evidence-based clinical practice guideline for the use of exome sequencing and genome sequencing (ES/GS) in 2021.[28] The guideline is a systematic evidence review based on peer-reviewed literature that supports the clinical utility of ES/GS as a first-tier or second-tier test for pediatric patients with multiple congenital anomalies with onset prior to age 1 year or developmental delay or intellectual disability with onset prior to 18 years, including impact on clinical management. ES/GS has a higher diagnostic yield compared with standard genetic testing, and may be more cost-effective when ordered earlier in the diagnostic evaluation.

In 2021, the ACMG Secondary Findings Working Group published an updated policy statement with recommendations for reporting of secondary findings in clinical ES and GS.[31] This policy statement provides guidance on consenting, scope of secondary finding reporting based on test type, and proposes a framework for annual updates to the secondary findings list. The goal of the secondary finding gene list is to provide guidance to clinical laboratories on which medically actionable genes unrelated to the indication for testing should be evaluated as part of clinical ES/GS.[32]

Recommendations for obtaining informed consent for clinical ES/GS, including secondary findings, have also been outlined by the ACMG.[29] A medical geneticist or genetic counselor should perform pre-test counseling and consent documentation.

The ACMG Laboratory Quality Assurance Committee issued points to consider in the reevaluation and reanalysis of genomic test results,[33] including general considerations, considerations for variant-level reevaluation and case-level reanalysis, and reporting. This statement also suggests considerations for reanalysis versus retesting using new methodologies, including:

- Time elapsed since the previous testing occurred
- Improvements in technology/chemistry (e.g., new methods for DNA capture and sequencing)
- Bioinformatics advancements
- New information regarding the genetic etiology of a condition
- Additional patient phenotypes or family history that developed in the interim

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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 diagnostic yield of GS depends on the individual's age, phenotype, previous workup, and inclusion of comparators. The average diagnostic yield of rGS in acutely-ill infants is 19-57%.[1-5,10-16] 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 and children suspected of having rare genetic disease includes numerous retrospective and prospective case series, and randomized controlled trials. 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. [1-17] An impact on medical management has also been clearly demonstrated in the setting of non-rapid GS. [6,34-36]

rGS has been shown to positively impact healthcare utilization through reduced lengths of stay and reduced professional and facility fees.[4,16,37-38]

Genetic counselors play a critical role in guiding testing strategy and assessing the utility of genetic testing in individuals with rare disease, as well as supporting informed consent. Practice guidelines outline the role of GCs in consent and result disclosure/interpretation for ES/GS.[29] Genetic counselors are trained to assess appropriate testing strategies and prevent order errors.[39,40] Genetic counselors can bridge access gap between medical geneticists and other specialists, ensuring appropriate utilization of genomic sequencing in individuals with rare disease.

Criteria:

Rapid genome sequencing (rGS) is considered medically necessary for the evaluation of acutely-ill individuals ≤ 21 years when ALL of the following criteria are met:

1. The etiology of the patient's features is not known and a genetic etiology is considered a likely explanation for the phenotype, based on one of the following, AND
    a) Multiple congenital abnormalities affecting unrelated organ systems, OR
    b) Epileptic encephalopathy, OR
    c) TWO of the following criteria are met:
        - abnormality affecting at minimum a single organ system
        - symptoms of a complex neurological condition (e.g., dystonia, hemiplegia, spasticity, epilepsy, hypotonia, myopathy, muscular dystrophy, global developmental delay, intellectual disability)
        - family history strongly suggestive of a genetic etiology, including consanguinity
        - laboratory findings suggestive of an inborn error of metabolism
        - abnormal response to standard therapy
2. Alternate etiologies have been considered and ruled out when possible (e.g., MRI abnormalities/brain malformations, environmental exposure, injury, infection, isolated prematurity), AND

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3. 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
4. Molecular results are predicted to impact health outcomes, including immediate impact on medical management.

Exclusions:

- rGS will not be covered in individuals with the following diagnoses:
  - Isolated Transient Neonatal Tachypnea
  - Isolated unconjugated hyperbilirubinemia
  - Isolated Hypoxic Ischemic Encephalopathy with clear precipitating event
  - Isolated meconium aspiration
  - Isolated prematurity
  - Infection/sepsis with normal response to therapy
- rGS is considered not medically necessary for the diagnosis of genetic conditions in individuals who do not meet the above criteria.

Other Considerations:

- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor is strongly recommended.
- Trio samples are preferred for rGS. Use of family trio samples in genomic sequencing analysis helps reduces the time to diagnosis, the rate of uncertain findings, and improves the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of rGS.
- Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. If available rapidly, re-analysis could be considered prior to rGS.

CPT Codes:

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
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)	0212U

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Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0213U

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Update details:

Clarified inclusion criteria, epileptic encephalopathy as stand-alone, age-limit changed, updated references, and overall policy re-format.