

Commercial

Medical Policy



Medical Policy Bulletin

Title:

Rapid Whole Exome Sequencing (rWES) and Rapid Whole Genome Sequencing (rWGS) for Diagnosis of Genetic Disorders

Policy #:

06.02.46

The Company makes decisions on coverage based on Policy Bulletins, benefit plan documents, and the member's medical history and condition. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Medical Policy Bulletin document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy Bulletin will be reviewed regularly and be updated as scientific and medical literature becomes available. For more information on how Medical Policy Bulletins are developed, go to the Policy Types and Descriptions section of this Medical Policy Web site.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's contract.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

Rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS), with trio testing when possible¹, are considered medically necessary and, therefore, covered for the evaluation of critically ill infants in neonatal or pediatric intensive care / critical care with a suspected genetic disorder of unknown etiology when BOTH of the following criteria are met:

1. At least one of the following criterion is met:
 1. Multiple congenital anomalies²;
 2. An abnormal laboratory test or clinical features suggests a genetic disease or complex metabolic phenotype³;
 3. An abnormal response to standard therapy for a major underlying condition;

2. None of the following criteria apply regarding the primary reason for admission to critical/intensive care:
 1. An infection with normal response to therapy;
 2. Isolated prematurity;
 3. Isolated unconjugated hyperbilirubinemia;
 4. Hypoxic Ischemic Encephalopathy;
 5. Confirmed genetic diagnosis explains illness;
 6. Isolated Transient Neonatal Tachypnea; or
 7. Nonviable neonates.

Further information and examples:

^{1,2,3} See Guidelines Section.

EXPERIMENTAL/INVESTIGATIONAL

Rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS) are considered experimental/investigational and, therefore, not covered for the diagnosis of genetic disorders in all other situations because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to, records from the physician's office, hospital, nursing home, home health agencies, therapies, other health care professionals, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request.

Guidelines

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, rWES and rWGS are covered under the medical benefits of the Company's products when the medical necessity criteria listed in this medical policy are met.

For rapid WES or WGS, the individual should be critically ill and in the NICU or PICU when the test is ordered but may be discharged before results are delivered.

Copy number variation (CNV) analysis should be performed in parallel with rWGS using chromosomal microarray analysis (CMA) or directly within rWGS if the test is validated for CNV analysis.

Further information and examples:

¹ The recommended option for testing when possible is testing of the child and both parents (trio testing), since trio testing increases the chance of finding a definitive diagnosis and reduces false-positive findings. Trio testing is preferred whenever possible but should not delay testing of a critically ill individual when rapid testing is medically necessary as outlined above. Testing of one available parent should be done if both are not immediately available and one or both parents can be done later if needed.

^{2 & 3} Examples of specific malformations highly suggestive of a genetic etiology, include but are not limited to any of the following:

- Choanal atresia
- Coloboma
- Hirschsprung disease
- Meconium ileus

Examples of an abnormal laboratory test suggesting a genetic disease or complex metabolic phenotype, include but are not limited to any of the following:

- Abnormal newborn screen
- Conjugated hyperbilirubinemia not due to total parental nutrition (TPN) cholestasis
- Hyperammonemia
- Lactic acidosis not due to poor perfusion &/or sepsis
- Refractory or severe hypoglycemia

Examples of clinical features suggesting a genetic disease include but are not limited to any of the following:

- Significant hypotonia; or
- Persistent seizures.
- Infant with high risk stratification on evaluation for a Brief Resolved Unexplained Event (BRUE) (see below)* with any of the following features:
 - Recurrent events without respiratory infection
 - Recurrent witnessed seizure like events
 - Required Cardiopulmonary Resuscitation (CPR)
 - Significantly abnormal chemistry including but not limited to electrolytes, bicarbonate or lactic acid, venous blood gas, glucose, or other tests that suggest an inborn error of metabolism
- Significantly abnormal electrocardiogram (ECG), including but not limited to possible channelopathies, arrhythmias, cardiomyopathies, myocarditis or structural heart disease
- Family history of:
 - Arrhythmia
 - BRUE in sibling
 - Developmental delay
 - Inborn error of metabolism or genetic disease
 - Long QT syndrome (LQTS)
 - Sudden unexplained death (including unexplained car accident or drowning) in first- or second-degree family members before age 35, and particularly as an infant

* Brief Resolved Unexplained Event (BRUE)

Brief Resolved Unexplained Event (BRUE) was previously known as Apparent Life Threatening Event (ALTE). In a practice guideline from the American Academy of Pediatrics (AAP), BRUE is defined as an event occurring in an infant younger than 1 year of age when the observer reports a sudden, brief (usually less than one minute), and now resolved episode of one or more of the following:

- Absent, decreased, or irregular breathing
- Altered level of responsiveness
- Cyanosis or pallor
- Marked change in tone (hyper- or hypotonia)

A BRUE is diagnosed only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination.

Description

Whole exome sequencing (WES) sequences the portion of the genome that contains protein-coding DNA, while whole genome sequencing (WGS) sequences both coding and noncoding regions of the genome. Whole exome sequencing and WGS have been proposed for use in patients presenting with disorders and anomalies not explained by a standard clinical workup. Potential candidates for WES and WGS include individuals who present with a broad spectrum of suspected genetic conditions. The median time for standard WGS is several weeks, and the turnaround time for WES may be in that range as well.

RAPID SEQUENCING

In the NSIGHT1 trial (Petrikin, 2018) rapid Whole Genome Sequencing (rWGS) provided time to provisional diagnosis by 10 days with time to final report of approximately 17 days although the trial required confirmatory testing of WGS results which lengthened the time to rWGS diagnosis by 7–10 days. The WGS was performed in ‘rapid run’ mode with a minimum depth of 90 Gb per genome and average depth of coverage of 40X.

In its 2021 guideline, American College of Medical Genetics (ACMG) defines rapid and ultrarapid testing as 6 to 15 days and 1 to 3 days, respectively.

rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS)

The purpose of rapid whole exome sequencing (rWES) or rapid whole genome sequencing (rWGS) in critically ill individuals with a suspected genetic disorder of unknown etiology is to establish a molecular diagnosis from either the coding or noncoding regions of the genome. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests;
- The clinical utility of a diagnosis has been established (e.g., by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes); and
- Establishing the diagnosis by genetic testing will end the clinical workup for other disorders.

The relevant population of interest for rWES & rWGS is critically ill infants presenting with any of a variety of disorders and anomalies suspected to have a genetic basis but not explained by a standard workup. For example, infants may have a phenotype that does not correspond with a specific disorder for which a genetic test targeting a specific gene is available. Specifically for critically ill infants, the population would also include individuals for whom specific diagnostic tests available for that phenotype are not accessible within a reasonable timeframe. Petrikin et al. (2018) identified critically ill infants that are appropriate for rapid testing as meeting the following inclusion criteria: multiple congenital anomalies; an abnormal laboratory test suggests a genetic disease or complex metabolic phenotype; an abnormal response to standard therapy for a major underlying condition; significant hypotonia; or persistent seizures. Exclusion criteria included: an infection with normal response to therapy; isolated prematurity; isolated unconjugated hyperbilirubinemia; Hypoxic Ischemic Encephalopathy; confirmed genetic diagnosis explains illness; Isolated Transient Neonatal Tachypnea; or nonviable neonates.

The most common cause of death in neonates in the United States is genetic disorders. Currently, critically ill neonates with suspected genetic diseases are frequently discharged or deceased without a diagnosis. There are thousands of rare genetic disorders. The presentation of many of these disorders in neonates may be nonspecific or differ from the presentation in older individuals and the disorder may produce secondary involvement of other systems due to the fragility of the neonate that obscures the primary pathology.

Treatment of suspected genetic diseases in critically ill infants is often empirical. Rapid diagnosis is critical for delivery of interventions that reduce morbidity and mortality in genetic diseases for which treatments exist. For many genetic diseases there is no effective treatment and timely diagnosis limits futile intensive care.

REVIEW OF RELIABLE EVIDENCE FOR rWES and rWGS

The use of rWES and rWGS, (with trio testing when possible), has been studied in critically ill children in multiple observational studies, both prospective and retrospective, and in three randomized controlled trials RCTs.

Petrikin et al. (2018) reported on the Prospective Randomized Trial of the Clinical Utility of Rapid Next Generation Sequencing in Acutely Ill Neonates (NSIGHT1; NCT02225522) RCT of rWGS to diagnose suspected genetic disorders in critically ill infants. In brief, NSIGHT1 was an investigator-initiated (funded by the National Human Genome Research Institute and Eunice Kennedy Shriver National Institute of Child Health and Human Development), blinded, and pragmatic trial comparing trio rWGS with standard genetic tests to standard genetic tests alone with a primary outcome of the proportion of NICU/pediatric intensive care unit (PICU) infants receiving a genetic diagnosis within 28 days. Parents of individuals and clinicians were unblinded after 10 days and compassionate cross-over to rWGS occurred in 5 control individuals. The study was designed to enroll 500 individuals in each group but was terminated early due to loss of equipoise on the part of study clinicians who began to regard standard tests alone as inferior to standard tests plus trio rWGS. Intention-to-treat analyses were reported, i.e., crossovers were included in the group to which they were randomized. The trial required confirmatory testing of WGS results, which lengthened the time to rWGS diagnosis by 7-10 days.

Kingsmore et al. (2019) reported early results of A Randomized, Blinded, Prospective Study of the Clinical Utility of Rapid Genomic Sequencing for Infants in the Acute-care Setting (NSIGHT2) trial. NSIGHT2 was a randomized, controlled, blinded trial of the effectiveness of rapid whole-genome or -exome sequencing (rWGS or rWES, respectively) in seriously ill infants with diseases of unknown etiology primarily from the NICU, pediatric intensive care unit (PICU), and cardiovascular intensive care unit (CVICU) at a single hospital in San Diego. Ninety-five infants were randomized to rWES and 94 to rWGS. In addition 24 infants who were gravely ill received ultrarapid whole-genome sequencing (urWGS). The initial Kingsmore et al (2019) publication included only the diagnostic outcomes. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). Although the urWGS was not part of the randomized portion of the study, the proportion diagnosed by urWGS was (11 of 24 [46%]) and time to result was a median of 4.6 days. The incremental diagnostic yield of reflexing to trio testing after inconclusive proband analysis was 0.7% (1 of 147). In 2020, Dimmock et al reported results of the primary endpoint of NSIGHT2: clinician perception that rWGS was useful and clinician-reported changes in management. Clinicians provided perceptions of the clinical utility of diagnostic genomic sequencing for 201 of 213 infants randomized (94%). In 154 (77%) infants, diagnostic genomic sequencing was perceived to be useful or very useful; perceptions of usefulness did not differ between infants who received rWES and rWGS, nor between ultra-rWGS and rWES/rWGS. Thirty-two (15%) of 207 clinician responses indicated that diagnostic genomic sequencing changed infant outcomes (by targeted treatments in 21 [10%] infants, avoidance of complications in 16 [8%], and institution of palliative care in 2 [1%] infants). Changes in outcome did not differ significantly between infants randomized to rWES and rWGS, although ultra rWGS was associated with a significantly higher rate of change in management than rWES/rWGS (63% vs. 23%; p=.0001).

In the NICUSeq RCT, Krantz et al. (2021) compared rWGS (test results returned in 15 days) to a delayed reporting group (WGS with test results returned in 60 days) in 354 infants admitted to an ICU with a suspected genetic disease at 5 sites in the United States. In 76% of cases, both parents were available for trio testing. Overall, 82 of 354 infants received a diagnosis (23%), with a higher yield in the 15-day group. The primary outcome was change in management, measured at day 60. Significantly more infants in the rWGS group had a change in management compared with the delayed arm (21.1% vs 10.3%; p=.009; odds ratio 2.3; 95% CI, 1.22 to 4.32). Changes in management included subspecialty referral (21 of 354, 6.0%), changes to medication (5 of 354, 1.4%), therapeutics specific to the primary genetic etiology (7 of 354; 2.0%) and surgical interventions (12 of 354; 3.4%). Survival and length of stay did not differ between the groups.

SUMMARY

One RCT comparing rWGS with standard genetic tests to diagnose suspected genetic disorders in critically ill infants was terminated early due to loss of equipoise. The rate of genetic diagnosis within 28 days of enrollment was higher for rWGS versus standard tests (31% vs. 3%; p=.003). Changes in management due to test results were reported in 41% vs. 21% (p=.11) of rWGS versus control patients; however, 73% of control subjects received broad genetic tests (eg, next-generation sequencing panel testing, WES, or WGS) as part of standard testing. A second RCT compared rWGS to rWES in seriously ill infants with diseases of unknown etiology from the neonatal intensive care unit, pediatric intensive care unit, and cardiovascular intensive care unit. The diagnostic yield of rWGS and rWES was similar (19% vs. 20%, respectively), as was time (days) to result (median, 11 vs. 11 days). The NICUSeq RCT compared rWGS (test results returned in 15 days) to a delayed reporting group

(WGS with test results returned in 60 days) in 354 infants admitted to an ICU with a suspected genetic disease. Diagnostic yield was higher in the rWGS group (31.0%; 95% CI 25.5% to 38.7% vs. 15.0%; 95% CI 10.2% to 21.3%). Additionally, significantly more infants in the rWGS group had a change in management compared with the delayed arm (21.1% vs. 10.3%; p=.009; odds ratio 2.3; 95% CI 1.22 to 4.32). Several retrospective and prospective studies including more than 800 critically ill infants and children in total have reported on diagnostic yield for rWGS or rWES. These studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60% for pathogenic or likely pathogenic variants. Studies have also reported associated changes in management for individuals receiving a diagnosis from rWGS or rWES, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS or rWES in critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

81415, 81416, 81417, 81425, 81426, 81427

THE FOLLOWING CODE REPRESENT RADY CHILDREN'S INSTITUTE FOR GENOMIC MEDICINE (RCIGM) RAPID WHOLE GENOME SEQUENCING

0094U

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

N/A

HCPCS Level II Code Number(s)

N/A

Revenue Code Number(s)

N/A

Cross Reference

Policy: 06.02.52ai: eviCore Lab Management (AmeriHealth)

Policy History

Revisions From 06.02.46:

02/21/2024	This policy has been reissued in accordance with the Company's annual review process.
11/01/2023	This policy has been reissued in accordance with the Company's annual review process.
01/01/2023	This new policy (# 06.02.46) has been developed to communicate Company's

policy position and criteria for rapid Whole Exome Sequencing (rWES) and rapid Whole Genome Sequencing (rWGS).

This policy is effective as of 01/01/2023.

Version Effective Date: 01/01/2023

Version Issued Date: 12/15/2022

Version Reissued Date: 02/21/2024