

DRAFT Medical Coverage Policy | Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders



EFFECTIVE DATE: 01 | 01 | 2024

POLICY LAST UPDATED: 09 | 06 | 2023

OVERVIEW

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 patients who present with a broad spectrum of suspected genetic conditions.

The following test(s) are addressed in this policy:

- Genomic Unity® Exome Plus Analysis – Proband (Variantyx, Inc.) CPT code 0214U
- Genomic Unity® Exome Plus Analysis – Comparator (Variantyx, Inc.) CPT code 0215U

For CPT codes 81415, 81416, 81417, 81425, 81426 and 81427, please refer to the Genetic Testing Services policy listed in the Related Policies section below.

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Genomic Unity® Exome Plus Analysis – Proband (CPT code 0214U) and Genomic Unity® Exome Plus Analysis – Comparator (CPT code 0215U)

Standard whole exome sequencing, with trio testing when possible (see guidelines below*), may be considered **medically necessary** for the evaluation of unexplained congenital or neurodevelopmental disorders in children when ALL of the following criteria are met:

1. Documentation that the individual has been evaluated by a clinician with expertise in clinical genetics, including at minimum a family history and phenotype description, and counseled about the potential risks of genetic testing.
2. There is potential for a change in management and clinical outcome for the individual being tested.
3. A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (eg, chromosomal microarray analysis and/or targeted single-gene testing), **OR** when previous genetic testing has failed to yield a diagnosis, and the affected individual is faced with invasive procedures or testing as the next diagnostic step (eg, muscle biopsy).

Rapid whole exome sequencing or rapid whole genome sequencing, with trio testing when possible (see guidelines below*), may be considered **medically necessary** for the evaluation of critically ill infants in neonatal or pediatric intensive care with a suspected genetic disorder of unknown etiology when BOTH of the following criteria are met:

1. At least one of the following criteria is met:
 - a. Multiple congenital anomalies (see Policy Guidelines);
 - b. An abnormal laboratory test or clinical features suggests a genetic disease or complex metabolic phenotype (see Policy Guidelines);
 - c. An abnormal response to standard therapy for a major underlying condition.
2. None of the following criteria apply regarding the reason for admission to intensive care:
 - a. An infection with normal response to therapy;

- b. Isolated prematurity;
- c. Isolated unconjugated hyperbilirubinemia;
- d. Hypoxic Ischemic Encephalopathy;
- e. Confirmed genetic diagnosis explains illness;
- f. Isolated Transient Neonatal Tachypnea; or
- g. Nonviable neonates.

**Trio Testing*

The recommended option for testing when possible is testing of the child and both parents (trio testing). 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 indicated. 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.

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products for the following Proprietary Laboratory Analyses (PLA) tests:

- Genomic Unity® Exome Plus Analysis – Proband CPT code 0214U
- Genomic Unity® Exome Plus Analysis – Comparator CPT code 0215U

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following Proprietary Laboratory Analyses (PLA) tests may be considered medically necessary when the medical criteria above have been met:

- Genomic Unity® Exome Plus Analysis – Proband CPT code 0214U
- Genomic Unity® Exome Plus Analysis – Comparator CPT code 0215U

The following are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine that the technology results in an improvement in the net health outcomes:

- Whole exome sequencing for the diagnosis of genetic disorders in all other situations.
- Repeat whole exome sequencing for the diagnosis of genetic disorders, including re-analysis of previous test results
- Whole genome sequencing for the diagnosis of genetic disorders in all other situations.
- Whole exome sequencing and whole genome sequencing for screening for genetic disorders.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable benefits/coverage.

BACKGROUND

Whole Exome Sequencing and Whole Genome Sequencing

Whole exome sequencing (WES) is targeted next-generation sequencing (NGS) of the subset of the human genome that contains functionally important sequences of protein-coding DNA, while whole genome sequencing (WGS) uses NGS techniques to sequence 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 patients who present with a broad spectrum of suspected genetic conditions.

Given the variety of disorders and management approaches, there are a variety of potential health outcomes from a definitive diagnosis. In general, the outcomes of a molecular genetic diagnosis include (1) impacting the search for a diagnosis, (2) informing follow-up that can benefit a child by reducing morbidity, and (3) affecting reproductive planning for parents and potentially the affected patient.

The standard diagnostic workup for patients with suspected Mendelian disorders may include combinations of radiographic, electrophysiologic, biochemical, biopsy, and targeted genetic evaluations.¹ The search for a diagnosis may thus become a time-consuming and expensive process.

Whole Exome Sequencing and Whole Genome Sequencing Technology

Whole exome sequencing or WGS using NGS technology can facilitate obtaining a genetic diagnosis in patients efficiently. Whole exome sequencing is limited to most of the protein-coding sequence of an individual (≈85%), is composed of about 20,000 genes and 180,000 exons (protein-coding segments of a gene), and constitutes approximately 1% of the genome. It is believed that the exome contains about 85% of heritable disease-causing variants. Whole exome sequencing has the advantage of speed and efficiency relative to Sanger sequencing of multiple genes. Whole exome sequencing shares some limitations with Sanger sequencing. For example, it will not identify the following: intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications; or rearrangements within genes, nucleotide repeats, or epigenetic changes. Whole genome sequencing uses techniques similar to WES but includes noncoding regions. Whole genome sequencing has a greater ability to detect large deletions or duplications in protein-coding regions compared with WES but requires greater data analytics.

Technical aspects of WES and WGS are evolving, including the development of databases such as the National Institutes of Health's ClinVar database (<http://www.ncbi.nlm.nih.gov/clinvar/>) to catalog variants, uneven sequencing coverage, gaps in exon capture before sequencing, and difficulties with narrowing the large initial number of variants to manageable numbers without losing likely candidate disease-associated variants. The variability contributed by the different platforms and procedures used by different clinical laboratories offering exome sequencing as a clinical service is unknown.

In 2013, the American College of Medical Genetics and Genomics, Association for Molecular Pathology, and College of American Pathologists convened a workgroup to standardize terminology for describing sequence

variants. In 2015, guidelines developed by this workgroup describe criteria for classifying pathogenic and benign sequence variants based on 5 categories of data: pathogenic, likely pathogenic, uncertain significance, likely benign, and benign.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Whole exome sequencing or WGS tests as a clinical service are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive whole exome sequencing (WES) with trio testing when possible, the evidence includes large case series and within-subject comparisons. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by a standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. One comparative study found a 44% increase in yield compared with standard testing strategies. Many of the studies have also reported changes in patient management, including medication changes, discontinuation of or additional testing, ending the diagnostic odyssey, and family planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WES with trio testing when possible, the evidence includes small case series and prospective research studies. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. There is an increasing number of reports evaluating the use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allow reanalysis as new genes are linked to the patient phenotype. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage with uncertainty about changes in patient management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have previously received WES who receive repeat WES, including re-analysis of previous test results, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. There is no direct evidence of clinical utility. In a meta-analysis of nonrandomized studies, re-analysis of WES data resulted in an 11% increase in diagnostic yield (95% confidence interval (CI), 8% to 14%) in individuals who were previously undiagnosed via WES. Three nonrandomized studies published after the meta-analysis had findings consistent with the meta-analysis. Conclusions were limited by heterogeneity across individual studies and a lack of detailed reporting on reasons for new diagnoses, changes in management based on new diagnoses, and the frequency of the identification of variants of uncertain significance (VUS). Therefore, a chain of evidence for clinical utility cannot be established. Additionally, the optimal timing of re-analysis has not been established, and there are no clear guidelines on what factors should prompt the decision to repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup or WES who receive whole genome sequencing (WGS) with trio testing when possible, the evidence includes nonrandomized studies and a systematic review. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. In studies of children with congenital anomalies and developmental delays of unknown etiology following standard clinical workup, the yield of WGS has ranged between 20% and 40%. A majority of studies described methods for interpretation of WGS indicating that only pathogenic or likely pathogenic variants were included in the diagnostic yield and that VUS were frequently not reported. In a systematic review, the pooled (9 studies, N=648) diagnostic yield of WGS was 40% (95% CI, 32% to 49%). Although the diagnostic yield of WGS is at least as high as WES in individuals without a diagnosis following standard clinical workup, it is unclear if the additional yield results in actionable clinical management changes that improve health outcomes. Further, while reporting practices of VUS found on exome and genome sequencing vary across laboratories, WGS results in the identification of more VUS than WES. The clinical implications of this difference are uncertain as more VUS findings can be seen as potential for future VUS reclassification allowing a diagnosis. However, most VUS do not relate to the patient phenotype, the occurrence of medical mismanagement and patient stress based on misinterpretation of VUS is not well defined, and provider reluctance to interpret VUS information lessen the value of additional VUS identification by WGS. As such, higher yield and higher VUS from WGS currently have limited clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are children with a suspected genetic disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WGS with trio testing when possible, the evidence includes case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. Whole genome sequencing has also been studied in other genetic conditions with yield ranging from 9% to 55%. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WGS as well as information regarding meaningful changes in management for these disorders is at an early stage. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid WGS (rWGS) or rapid WES (rWES) with trio testing when possible, the evidence includes randomized controlled trials (RCTs) and case series. Relevant outcomes are test validity, functional outcomes, changes in reproductive decision making, and resource utilization. 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% ($p=.11$) of rWGS versus 21% of 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 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 intensive care unit 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 patient management for patients 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

For CPT codes 81415, 81416, 81417, 81425, 81426 and 81427, please refer to the Genetic Testing Services policy listed in the Related Policies section below.

The following CPT code(s) are covered for Medicare Advantage Plans and Commercial Products when medical criteria above are met:

This code can be used for Genomic Unity® Exome Plus Analysis – Proband (Variantyx, Inc.)

0214U 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

This code can be used for Genomic Unity® Exome Plus Analysis – Comparator (Variantyx, Inc.)

0215U 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, each comparator exome (eg, parent, sibling)

RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

Proprietary Laboratory Analyses (PLA)

PUBLISHED

Provider Update, November 2023

REFERENCES

1. Dixon-Salazar TJ, Silhavy JL, Udpa N, et al. Exome sequencing can improve diagnosis and alter patient management. *Sci Transl Med.* Jun 13 2012; 4(138): 138ra78. PMID 22700954
2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med.* May 2015; 17(5): 405-24. PMID 25741868
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Special Report: Exome Sequencing for Clinical Diagnosis of Patients with Suspected Genetic Disorders. TEC Assessments. 2013; Volume 28: Tab 3.
4. Smith HS, Swint JM, Lalani SR, et al. Clinical Application of Genome and Exome Sequencing as a Diagnostic Tool for Pediatric Patients: a Scoping Review of the Literature. *Genet Med.* Jan 2019; 21(1): 3-16. PMID 29760485
5. Vissers LELM, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med.* Sep 2017; 19(9): 1055-1063. PMID 28333917
6. Córdoba M, Rodríguez-Quiroga SA, Vega PA, et al. Whole exome sequencing in neurogenetic odysseys: An effective, cost- and time-saving diagnostic approach. *PLoS One.* 2018; 13(2): e0191228. PMID 29389947
7. Powis Z, Farwell Hagman KD, Speare V, et al. Exome sequencing in neonates: diagnostic rates, characteristics, and time to diagnosis. *Genet Med.* Nov 2018; 20(11): 1468-1471. PMID 29565416
8. Tsuchida N, Nakashima M, Kato M, et al. Detection of copy number variations in epilepsy using exome data. *Clin Genet.* Mar 2018; 93(3): 577-587. PMID 28940419
9. Evers C, Staufner C, Granzow M, et al. Impact of clinical exomes in neurodevelopmental and neurometabolic disorders. *Mol Genet Metab.* Aug 2017; 121(4): 297-307. PMID 28688840

10. Nolan D, Carlson M. Whole Exome Sequencing in Pediatric Neurology Patients: Clinical Implications and Estimated Cost Analysis. *J Child Neurol.* Jun 2016; 31(7): 887-94. PMID 26863999
11. Allen NM, Conroy J, Shahwan A, et al. Unexplained early onset epileptic encephalopathy: Exome screening and phenotype expansion. *Epilepsia.* Jan 2016; 57(1): e12-7. PMID 26648591
12. Stark Z, Lunke S, Brett GR, et al. Meeting the challenges of implementing rapid genomic testing in acute pediatric care. *Genet Med.* Dec 2018; 20(12): 1554-1563. PMID 29543227
13. Tarailo-Graovac M, Shyr C, Ross CJ, et al. Exome Sequencing and the Management of Neurometabolic Disorders. *N Engl J Med.* Jun 09 2016; 374(23): 2246-55. PMID 27276562
14. Farwell KD, Shahmirzadi L, El-Khechen D, et al. Enhanced utility of family-centered diagnostic exome sequencing with inheritance model-based analysis: results from 500 unselected families with undiagnosed genetic conditions. *Genet Med.* Jul 2015; 17(7): 578-86. PMID 25356970
15. Yang Y, Muzny DM, Xia F, et al. Molecular findings among patients referred for clinical whole-exome sequencing. *JAMA.* Nov 12 2014; 312(18): 1870-9. PMID 25326635
16. Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA.* Nov 12 2014; 312(18): 1880-7. PMID 25326637
17. Iglesias A, Anyane-Yeboah K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* Dec 2014; 16(12): 922-31. PMID 24901346
18. 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.* Dec 03 2014; 6(265): 265ra168. PMID 25473036
19. Srivastava S, Cohen JS, Vernon H, et al. Clinical whole exome sequencing in child neurology practice. *Ann Neurol.* Oct 2014; 76(4): 473-83. PMID 25131622
20. Yang Y, Muzny DM, Reid JG, et al. Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med.* Oct 17 2013; 369(16): 1502-11. PMID 24088041
21. Kwong AK, Tsang MH, Fung JL, et al. Exome sequencing in paediatric patients with movement disorders. *Orphanet J Rare Dis.* Jan 15 2021; 16(1): 32. PMID 33446253
22. Gileles-Hillel A, Mor-Shaked H, Shoseyov D, et al. Whole-exome sequencing accuracy in the diagnosis of primary ciliary dyskinesia. *ERJ Open Res.* Oct 2020; 6(4). PMID 33447612
23. Kim SY, Jang SS, Kim H, et al. Genetic diagnosis of infantile-onset epilepsy in the clinic: Application of whole-exome sequencing following epilepsy gene panel testing. *Clin Genet.* Mar 2021; 99(3): 418-424. PMID 33349918
24. Hauer NN, Popp B, Schoeller E, et al. Clinical relevance of systematic phenotyping and exome sequencing in patients with short stature. *Genet Med.* Jun 2018; 20(6): 630-638. PMID 29758562
25. Rossi M, El-Khechen D, Black MH, et al. Outcomes of Diagnostic Exome Sequencing in Patients With Diagnosed or Suspected Autism Spectrum Disorders. *Pediatr Neurol.* May 2017; 70: 34-43.e2. PMID 28330790
26. Walsh M, Bell KM, Chong B, et al. Diagnostic and cost utility of whole exome sequencing in peripheral neuropathy. *Ann Clin Transl Neurol.* May 2017; 4(5): 318-325. PMID 28491899
27. Miller KA, Twigg SR, McGowan SJ, et al. Diagnostic value of exome and whole genome sequencing in craniosynostosis. *J Med Genet.* Apr 2017; 54(4): 260-268. PMID 27884935
28. Posey JE, Rosenfeld JA, James RA, et al. Molecular diagnostic experience of whole-exome sequencing in adult patients. *Genet Med.* Jul 2016; 18(7): 678-85. PMID 26633545
29. Ghaoui R, Cooper ST, Lek M, et al. Use of Whole-Exome Sequencing for Diagnosis of Limb-Girdle Muscular Dystrophy: Outcomes and Lessons Learned. *JAMA Neurol.* Dec 2015; 72(12): 1424-32. PMID 26436962
30. Valencia CA, Husami A, Holle J, et al. Clinical Impact and Cost-Effectiveness of Whole Exome Sequencing as a Diagnostic Tool: A Pediatric Center's Experience. *Front Pediatr.* 2015; 3: 67. PMID 26284228
31. Wortmann SB, Koolen DA, Smeitink JA, et al. Whole exome sequencing of suspected mitochondrial patients in clinical practice. *J Inher Metab Dis.* May 2015; 38(3): 437-43. PMID 25735936
32. Neveling K, Feenstra I, Gilissen C, et al. A post-hoc comparison of the utility of sanger sequencing and exome sequencing for the diagnosis of heterogeneous diseases. *Hum Mutat.* Dec 2013; 34(12): 1721-6. PMID 24123792
33. Dai P, Honda A, Ewans L, et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: A systematic review and meta-analysis. *Genet Med.* Aug 2022; 24(8): 1618-1629. PMID 35550369

34. Ewans LJ, Minoche AE, Schofield D, et al. Whole exome and genome sequencing in mendelian disorders: a diagnostic and health economic analysis. *Eur J Hum Genet.* Oct 2022; 30(10): 1121-1131. PMID 35970915
35. Halfmeyer I, Bartolomeus T, Popp B, et al. Approach to Cohort-Wide Re-Analysis of Exome Data in 1000 Individuals with Neurodevelopmental Disorders. *Genes (Basel).* Dec 22 2022; 14(1). PMID 36672771
36. Sun Y, Peng J, Liang D, et al. Genome sequencing demonstrates high diagnostic yield in children with undiagnosed global developmental delay/intellectual disability: A prospective study. *Hum Mutat.* May 2022; 43(5): 568-581. PMID 35143101
37. Lionel AC, Costain G, Monfared N, et al. Improved diagnostic yield compared with targeted gene sequencing panels suggests a role for whole-genome sequencing as a first-tier genetic test. *Genet Med.* Apr 2018; 20(4): 435-443. PMID 28771251
38. Costain G, Jobling R, Walker S, et al. Periodic reanalysis of whole-genome sequencing data enhances the diagnostic advantage over standard clinical genetic testing. *Eur J Hum Genet.* May 2018; 26(5): 740-744. PMID 29453418
39. Stavropoulos DJ, Merico D, Jobling R, et al. Whole Genome Sequencing Expands Diagnostic Utility and Improves Clinical Management in Pediatric Medicine. *NPJ Genom Med.* Jan 13 2016; 1: 15012-. PMID 28567303
40. Hiatt SM, Amaral MD, Bowling KM, et al. Systematic reanalysis of genomic data improves quality of variant interpretation. *Clin Genet.* Jul 2018; 94(1): 174-178. PMID 29652076
41. Bowling KM, Thompson ML, Amaral MD, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. *Genome Med.* May 30 2017; 9(1): 43. PMID 28554332
42. Gilissen C, Hehir-Kwa JY, Thung DT, et al. Genome sequencing identifies major causes of severe intellectual disability. *Nature.* Jul 17 2014; 511(7509): 344-7. PMID 24896178
43. Lindstrand A, Ek M, Kvarnung M, et al. Genome sequencing is a sensitive first-line test to diagnose individuals with intellectual disability. *Genet Med.* Nov 2022; 24(11): 2296-2307. PMID 36066546
44. van der Sanden BPGH, Schobers G, Corominas Galbany J, et al. The performance of genome sequencing as a first-tier test for neurodevelopmental disorders. *Eur J Hum Genet.* Jan 2023; 31(1): 81-88. PMID 36114283
45. Vandersluis S, Li CM, Cheng L, et al. Genome-Wide Sequencing for Unexplained Developmental Disabilities or Multiple Congenital Anomalies: A Health Technology Assessment. *Ont Health Technol Assess Ser.* 2020; 20(11): 1-178. PMID 32194879
46. Costain G, Walker S, Marano M, et al. Genome Sequencing as a Diagnostic Test in Children With Unexplained Medical Complexity. *JAMA Netw Open.* Sep 01 2020; 3(9): e2018109. PMID 32960281
47. Thiffault I, Farrow E, Zellmer L, et al. Clinical genome sequencing in an unbiased pediatric cohort. *Genet Med.* Feb 2019; 21(2): 303-310. PMID 30008475
48. Alfares A, Aloraini T, Subaie LA, et al. Whole-genome sequencing offers additional but limited clinical utility compared with reanalysis of whole-exome sequencing. *Genet Med.* Nov 2018; 20(11): 1328-1333. PMID 29565419
49. Carss KJ, Arno G, Erwood M, et al. Comprehensive Rare Variant Analysis via Whole-Genome Sequencing to Determine the Molecular Pathology of Inherited Retinal Disease. *Am J Hum Genet.* Jan 05 2017; 100(1): 75-90. PMID 28041643
50. Ellingford JM, Barton S, Bhaskar S, et al. Whole Genome Sequencing Increases Molecular Diagnostic Yield Compared with Current Diagnostic Testing for Inherited Retinal Disease. *Ophthalmology.* May 2016; 123(5): 1143-50. PMID 26872967
51. Taylor JC, Martin HC, Lise S, et al. Factors influencing success of clinical genome sequencing across a broad spectrum of disorders. *Nat Genet.* Jul 2015; 47(7): 717-726. PMID 25985138
52. Yuen RK, Thiruvahindrapuram B, Merico D, et al. Whole-genome sequencing of quartet families with autism spectrum disorder. *Nat Med.* Feb 2015; 21(2): 185-91. PMID 25621899
53. 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; 3: 6. PMID 29449963
54. Manickam K, McClain MR, Demmer LA, et al. Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: an evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* Nov 2021; 23(11): 2029-2037. PMID 34211152
55. Wu ET, Hwu WL, Chien YH, et al. Critical Trio Exome Benefits In-Time Decision-Making for Pediatric Patients With Severe Illnesses. *Pediatr Crit Care Med.* Nov 2019; 20(11): 1021-1026. PMID 31261230

56. Elliott AM, du Souich C, Lehman A, et al. RAPIDOMICS: rapid genome-wide sequencing in a neonatal intensive care unit—successes and challenges. *Eur J Pediatr.* Aug 2019; 178(8): 1207-1218. PMID 31172278
57. Gubbels CS, VanNoy GE, Madden JA, et al. Prospective, phenotype-driven selection of critically ill neonates for rapid exome sequencing is associated with high diagnostic yield. *Genet Med.* Apr 2020; 22(4): 736-744. PMID 31780822
58. Meng L, Pammi M, Saronwala A, et al. Use of Exome Sequencing for Infants in Intensive Care Units: Ascertainment of Severe Single-Gene Disorders and Effect on Medical Management. *JAMA Pediatr.* Dec 04 2017; 171(12): e173438. PMID 28973083
59. French CE, Delon I, Dolling H, et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Med.* May 2019; 45(5): 627-636. PMID 30847515
60. Sanford EF, Clark MM, Farnaes L, et al. Rapid Whole Genome Sequencing Has Clinical Utility in Children in the PICU. *Pediatr Crit Care Med.* Nov 2019; 20(11): 1007-1020. PMID 31246743
61. Hauser NS, Solomon BD, Vilboux T, et al. Experience with genomic sequencing in pediatric patients with congenital cardiac defects in a large community hospital. *Mol Genet Genomic Med.* Mar 2018; 6(2): 200-212. PMID 29368431
62. Farnaes L, Hildreth A, Sweeney NM, et al. Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *NPJ Genom Med.* 2018; 3: 10. PMID 29644095
63. Mestek-Boukhibar L, Clement E, Jones WD, et al. Rapid Paediatric Sequencing (RaPS): comprehensive real-life workflow for rapid diagnosis of critically ill children. *J Med Genet.* Nov 2018; 55(11): 721-728. PMID 30049826
64. van Diemen CC, Kerstjens-Frederikse WS, Bergman KA, et al. Rapid Targeted Genomics in Critically Ill Newborns. *Pediatrics.* Oct 2017; 140(4). PMID 28939701
65. 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.* May 2015; 3(5): 377-87. PMID 25937001
66. Kingsmore SF, Cakici JA, Clark MM, et al. A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. *Am J Hum Genet.* Oct 03 2019; 105(4): 719-733. PMID 31564432
67. Dimmock DP, Clark MM, Gaughran M, et al. An RCT of Rapid Genomic Sequencing among Seriously Ill Infants Results in High Clinical Utility, Changes in Management, and Low Perceived Harm. *Am J Hum Genet.* Nov 05 2020; 107(5): 942-952. PMID 33157007
68. Krantz ID, Medne L, Weatherly JM, 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.* Dec 01 2021; 175(12): 1218-1226. PMID 34570182
69. Narayanaswami P, Weiss M, Selcen D, et al. Evidence-based guideline summary: diagnosis and treatment of limb-girdle and distal dystrophies: report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular Electrodiagnostic Medicine. *Neurology.* Oct 14 2014; 83(16): 1453-63. PMID 25313375

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