# NewbornDx™ Advanced Sequencing Evaluation

**Test Codes:** 2052 (Proband); 2053 (Family Member)

**Specimen Requirements:** Preferred: 2 mL room-temperature whole blood (lavender-top tube); 1 mL minimum
OR
5 room-temperature dried blood spots (PerkinElmer 226 Spot Saver Card or equivalent); 2 spots minimum

Alternative acceptable specimen type (family members only): 1 tube room-temperature saliva (Oragene OGD-500); no eating, drinking, smoking, gum chewing 30 minutes before collection

**CPT Code*:** 81443 for test code 2052 or 2053

## CLINICAL USE

- Diagnose genetic disorder(s) in symptomatic newborns

## CLINICAL BACKGROUND

Congenital disorders account for 20% to 34% of neonatal deaths.[1,2] Timely diagnosis of these disorders is especially important in newborns, as appropriate management can prevent mortality and lifelong morbidity. However, diagnosis can be difficult and protracted, because symptoms can be nonspecific or overlap with complications related to prematurity. Furthermore, traditional serial testing for specific mutations or single genes can contribute to an extended diagnostic odyssey.

Next-generation sequencing (NGS) allows testing of thousands of genes at the same time and can be used to diagnose disorders in neonatal intensive care units (NICUs). Rates of diagnosis vary based on study populations and the method of detection, which include whole-genome sequencing (WGS), whole-exome sequencing (WES), and panels of targeted genes; WGS and WES are better studied than gene panels. Studies in intensive care units (ICUs) in the United States show that these approaches yield a diagnosis in 37% to 57% of cases and affect patient management in 52% to 94% of patients who receive a diagnosis.[3-5] The speed that NGS potentially offers over traditional serial testing should be balanced with the likelihood of incidental findings (ie, variants of unknown clinical significance [VUS] or pathogenic variants associated with a disorder that has not yet presented clinically during the newborn period).

One approach to reducing the likelihood of incidental findings, and thus improving variant interpretation, is to limit the number of relevant genes tested by using a panel instead of WES or WGS. Small studies on the use of NGS panels in US or Canadian ICUs (neonatal or pediatric) reported diagnosis rates of 40% to 50%.[6,7] The panels included over 4,500 genes that are associated with or relevant to disorders. The disorders were not specific for newborns,[7,8] and one of the studies noted that removing 2,000 genes to focus on genes related to neonatal disorders would not reduce yield.[7] A panel can also improve analytical sensitivity and specificity by increasing sequence coverage, and improve the ability to interpret results by limiting clinical context.[9]

Another approach to improving variant interpretation is to test family members of the patient. The American College of Medical Genetics and Genomics (ACMG) indicates that testing parents or other family members can improve interpretation of sequencing results.[9] Such testing can help establish when a variant is de novo, co-segregates with a disorder in the family, or occurs in trans with a pathogenic variant of a recessive disorder. Potential dominant disorders can also be discounted if variants appear in healthy relatives. Thus, testing the patient and the patient's parents, referred to as "trio" testing, can benefit interpretation[9]; testing other family members can help if one or both parents are unavailable.

Athena Diagnostics offers the NewbornDx™ Advanced Sequencing Evaluation, Proband (test code 2052) for newborns; the test is intended to complement traditional clinical and diagnostic testing in neonates at high risk. The same test is offered for family members (test code 2053) to assist with interpretation. The panel examines 1,722 genes related to recessive, dominant, and X-linked disorders that can present during the neonatal period and early infancy. The disorders span many categories, including metabolic, endocrine, immunodeficiency, developmental delay, neurologic, and congenital disorders.

## INDIVIDUALS SUITABLE FOR TESTING

- Test code 2052: Newborns admitted to the NICU who have symptoms or clinical findings that suggest a likely biochemical or genetic etiology
- Test code 2052: Infants or children with early-onset symptoms that suggest a likely biochemical or genetic etiology
- Test code 2053: Parents or family members of newborns, infants, or children with symptoms that suggest a likely biochemical or genetic etiology

## METHOD

Next-generation sequencing of 1,722 genes involved in genetic and or biochemical conditions that can present in the newborn period or early infancy.

- Genomic DNA libraries are created by hybrid-capture using a custom-targeted panel. Libraries are sequenced to ~300X mean targeted coverage and local base coverage quality of ~99% at 20X.
- Reference genome alignment (hg37), variant calling, and quality control are performed using a bioinformatics pipeline developed at Athena Diagnostics.
- Variant annotation and phenotypic filtering are performed using the Fabric Genomics Opal Platform.
- Initial classification of variants is performed by scientist(s) on the Athena Insight™ team; variant and clinical interpretation is performed by board-certified geneticists.

## REFERENCE RANGE

Not detected

## INTERPRETIVE INFORMATION

Detection of a pathogenic variant is consistent with a diagnosis of, or predisposition to develop, the condition associated with the variant. Results from the panel are reviewed in the context of the patient's reported clinical features; genetic variants that could be associated with the features are included in the report with recommendations that would help confirm or rule out their relevance.

A negative result does not rule out a genetic condition. The method does not detect mosaicism, variants in regions of the gene not analyzed (eg, promoter, 5' and 3' untranslated regions, introns, or regions with consistently low coverage), or copy-number variants (deletions or duplications). The method also does not analyze potential variants with allelic frequencies below 20%. Some gene regions are more susceptible to low coverage and/or reduced accuracy (eg, sequences with exceptionally high or low GC content, repetitive sequences, sequences having a high degree of similarity with other regions).

This test may identify genetic variants that cause childhood-onset disorders not related to the patient's current symptoms. These variants will only be reported if the individual or guardian has opted-in to receive such findings. Genetic variants associated with late-onset disorders or conditions that cannot be treated will not be reported. Parents of the individuals being tested may discover that they are at an increased risk for being diagnosed with or predisposed to developing hereditary conditions.

All results should be interpreted in the context of clinical findings, relevant history, and other laboratory data. The classification and interpretation of the variant(s) identified reflect the current state of Athena Diagnostics' understanding at the time of the report. Inquiry regarding potential changes to the classification of the variant is strongly recommended prior to making any clinical decisions. For questions regarding variant classification updates or additional assistance, please call the Athena Diagnostics at 1.800.394.4493 to speak to a genetic counselor or board-certified geneticist, or visit AthenaDiagnostics.com/athenainsight.

### References


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* The CPT code provided is based on AMA guidelines and is for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

This test was developed and its analytical performance characteristics have been determined by Athena Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.