

NICUXpress™ Panel

Description

The NICUXpress™ Panel offers analysis of 3,000+ genes associated with disorders impacting patients in the newborn to early childhood period of life. A verbal result, including pathogenic and/or likely pathogenic variants, is given within 7 calendar days after the start of testing and a written report including all potentially clinically relevant variants is issued within 2 weeks after the start of testing.

The NICUXpress Panel uses a trio approach that includes concurrent analysis of the affected proband and both parents, which increases the likelihood of identifying a definitive genetic explanation. Because of the rapid turnaround time (TAT) for the NICUXpress Panel, samples from the proband and both biological parents should be submitted at the same time, along with clinical information. This test is best suited for patients whose medical management may be altered by having a rapid molecular diagnosis. This test requires approval by GeneDx; email Xpress@GeneDx.com to discuss the case prior to sending in samples.

The clinical sensitivity of the NICUXpress Panel depends in part on the proband's clinical phenotype. Studies of ill infants undergoing exome/genome sequencing studies have reported identification of a molecular diagnosis in 20-58% of cases, with a higher yield for cases that specifically include other family members and have stricter clinical inclusion criteria (Willig et al., 2015; Meng et al., 2017; van Diemen et al., 2017; Clark et al., 2018; Petrikin et al., 2018; Kingsmore et al., 2019; Gubbels et al., 2020). If a trio is submitted for the NICUXpress Panel, the sensitivity may be comparable to trio-based exome sequencing as it includes a comprehensive list of genes previously associated with disorders impacting patients in the newborn to early childhood period of life.

Test Methods

An affected individual's received clinical records and prior genetic testing results will be reviewed prior to analysis. Using genomic DNA from the submitted specimen(s), the exonic regions and flanking splice junctions of the genome are sequenced by massively parallel (NextGen) sequencing with CNV calling (NGS-CNV) on an Illumina sequencing system with 100bp or greater paired-end reads. Reads are aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants and most deletions and duplications involving three or more coding exons in the targeted genes using a custom-developed analysis tool (Xome Analyzer). Reported variants are confirmed, if necessary, by an appropriate orthogonal method in the proband and, if submitted, in selected relatives. Sequence variants and copy number variants are reported according to the Human Genome Variation Society (HGVS) recommendations.

While the NICUXpress Panel captures and sequences the whole exome, analysis is targeted to the specific gene list for the NICUXpress Panel. The NICUXpress Panel gene list includes more than 3,000 genes. The list was developed by searching for genes in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) that are known to be associated with the following phenotypes: neurodevelopmental disorders, neuromuscular disorders, metabolic disorders, nuclear mitochondrial disorders, multiple congenital anomalies, congenital heart disease, neonatal sex development disorders, immunodeficiency disorders, congenital ichthyosis, and epidermolysis bullosa. Additionally, genes reported in patients referred to GeneDx for rapid exome or genome sequencing are included on the NICUXpress Panel. The gene list is systematically reviewed and updated as needed, at least quarterly. The current gene list is available on our website: (<https://www.genedx.com/test-catalog/medical-specialty/clinicalgenomics/>).

Results Reporting

The NICUXpress Panel is performed on the proband and the parental samples when submitted together for analysis. A single report will be issued for the affected individual in the family. A separate report will not be issued

for unaffected parents or other unaffected family members who may also have submitted a specimen for the purpose of allowing better interpretation of the results from the affected individual. If additional reports are requested for other affected family members, additional fees will apply.

The report issued for the affected proband will include reportable variants in genes that are associated with the proband's provided phenotype. Pathogenic and likely pathogenic variants in genes responsible for the reported phenotype of the patient will be reported; however, because this is a phenotype-driven test of a large number of genes, variants of uncertain significance (VUS) are not routinely reported, only at our discretion. Variants that are considered to be benign or likely benign will not be reported. As the NICUXpress Panel includes over 3,000 genes, the report will not include a comprehensive list of all observed variants.

In rare instances, this test may reveal a pathogenic variant that is not directly related to the test indication. For example, pathogenic variants in genes associated with an increased risk for cancer, cardiac abnormalities, or metabolic defects could be identified. In the event that an incidental finding is identified, this information will be disclosed to the ordering health care provider if it is likely to impact medical care. The absence of reportable incidental findings for any particular gene does not rule out the possibility of pathogenic variants in that gene.

Limitations

Some types of genetic disorders, such as those due to nucleotide repeat expansion/contraction, abnormal DNA methylation, and other mechanisms may not be detectable with this test. Additionally, small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be reliably detected.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the NICUXpress Panel may identify the presence of a variant in the sequence of an affected individual, but that we will not recognize it as the cause of disease due to insufficient knowledge about the gene and its function. Even if the NICUXpress Panel identifies the underlying genetic cause of a disorder in an affected individual, it is possible that such a diagnosis will not permit an accurate prediction of the prognosis or severity of the disease. While there is a possibility that identifying the genetic cause may help direct management and treatment of the disease, it is also possible that this knowledge will not change management or treatment

REFERENCES:

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3. van Diemen et al. (2017) Pediatrics 140 (4): (PMID: 28939701)
4. Clark et al. (2018) NPJ Genom Med 3 :16 (PMID: 30002876)
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6. Kingsmore et al. (2019) Am. J. Hum. Genet. 105 (4):719-733 (PMID: 31564432)
7. Gubbels et al. (2020) Genet. Med. 22 (4):736-744 (PMID: 31780822)