Autism/ID *Xpanded*® Panel
A targeted test for monogenic causes of autism spectrum disorder and/or intellectual disability using a trio approach

Clinical Features:

Autism spectrum disorders and intellectual disability (intellectual developmental disorder) are clinically and genetically heterogeneous. Approximately 2.8% of children have an autism spectrum disorder (ASD), characterized by deficits in social interaction, impaired communication, repetitive behavior, and restricted interests and activities beginning in the first few years of life.[1] Autism spectrum disorder includes several clinically defined conditions, of which pervasive developmental disorder-not otherwise specified (PDD-NOS), Asperger syndrome, and autistic disorder ('classic' autism) are the most common. Approximately 1-3% of individuals have intellectual disability (ID), which is typically associated with an IQ of 70 or below and deficits in adaptive functioning, communication, and/or social skills with an onset before 18 years of age.[2] Autism spectrum disorder and ID are often co-morbid disorders; over half of children with autism also have intellectual disability. Young children may also be diagnosed with global development delay (DD), which is defined as significant delay in two or more developmental domains (gross or fine motor, speech/language, cognitive, social/personal, etc.) in children younger than five years. The prevalence is estimated to be 1-3%, similar to that of ID.[3]

The cause of ASD and/or ID can be difficult to discern as there are many genes known to cause these neurodevelopmental disorders. Moreover, new genes known to cause ASD and ID are being discovered regularly, making it challenging for clinical laboratories to keep traditional testing panels updated. Additionally, interpretation of the clinical significance of variants in these newly discovered genes is often difficult in the absence of parental testing to clarify which variants are de novo or inherited.

The Autism/ID *Xpanded*®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 for ASD and/or ID. Depending on the family structure, family history, and the availability of both parents, other family members of the affected individual may be evaluated in conjunction with the proband. Please contact GeneDx for prior approval when both parents are not available to submit samples for the Autism/ID *Xpanded*® Panel. The Autism/ID *Xpanded*® Panel is based on whole exome capture (WEC), Next Generation sequencing (NGS), and targeted analysis of a comprehensive list of genes currently associated with ASD and/or ID. The design of the panel allows for a comprehensive, dynamic gene list that is updated regularly to ensure inclusion of genes recently associated with ASD and/or ID.

Inheritance Pattern/Genetics:

The etiology of ASD is complex, including multiple genetic, epigenetic, and environmental factors. Approximately 30-40% of individuals with ASD and approximately 20% of individuals with ID have an identifiable genetic cause, often a chromosomal abnormality.[4-5] It has been suggested that, if a specific underlying genetic syndrome is not suspected (e.g. Fragile X syndrome, Rett syndrome), array comparative genomic hybridization (aCGH) be considered as a first-tier test for individuals with an ASD or ID.[4-5] However, recent studies have demonstrated that exome sequencing has even higher diagnostic yields for these affected individuals. Multiple studies have reported a high frequency of de novo variants in ASD and ID,

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highlighting the importance of a trio approach, including the affected proband and both parents when performing genetic testing for these phenotypes.[6-10] Many patients with autism spectrum disorder experience co-occurring conditions for which guidelines recommend exome sequencing as a first-line test. The American College of Medical Genetics and Genomics recommends exome or genome sequencing as a first-line test for individuals with developmental delay, intellectual disability, and/or congenital anomalies.[16] Additionally, the National Society of Genetic Counselors recommends exome or genome sequencing as a first-line test for all individuals with unexplained epilepsy, and this guideline is endorsed by the American Epilepsy Society.[17] For more information about ordering exome sequencing, see test code 561a XomeDx Trio, https://providers/genedx.com/tests/details/xomedx-trio-882. In some cases, confirmation of the molecular genetic cause of ASD and/or ID may have implications for treatment, management, and eligibility for needed services.[11]

Test Methods:

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions are enriched for most genes of the human genome using a proprietary capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. Data are filtered and analyzed to identify sequence variants and most deletions and duplications involving three or more coding exons. Smaller deletions or duplications may not be reliably identified. Reported clinically significant variants are confirmed by an appropriate orthogonal method in the proband and, if submitted, in selected relatives as necessary. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. Reportable variants include pathogenic variants and likely pathogenic variants. Variants of uncertain significance, likely benign and benign variants, if present, are not routinely reported. A list of additional variants not included in the report is available upon request.

Please note that while the Autism/ID *Xpanded*®Panel captures and sequences the whole exome, analysis is targeted to the specific phenotype-driven gene list for this panel. The Autism/ID *Xpanded*®Panel gene list includes 2300+ genes. The list was developed by searching for genes associated with autism spectrum disorder and/or intellectual disability in multiple sources, including OMIM, HGMD, and Human Phenotype Ontology (HPO) terms. This list undergoes continual review and curation by GeneDx experts. During this review, genes are added to the list using GeneDx data from clinical exome sequencing done on patients reported to have ASD/ID. Additionally, genes may be removed from the panel if they are found to be weakly or questionably associated with ASD/ID. In rare situations, genes are removed from the panel if they are expected to be low yield for this phenotype but contain an inherent high risk for incidental findings. The current gene list is available on our website. *Xpanded*®panel gene lists are regularly updated/improved using evidence from the literature and from GeneDx data from clinical exome sequencing done on patients with autism spectrum disorder and/or intellectual disability. Rarely, during this internal evaluation, a positive finding in a gene not on this *Xpanded*®gene list may be uncovered. If this happens, an updated report will be issued.

Result Reporting:

The Autism/ID *Xpanded*®Panel is performed on the proband and the parental samples (and/or additional relatives) when submitted together for analysis. A single report will be issued on the affected proband in the family. A separate report will not be issued for unaffected parents or other 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 that is issued for the affected individual will include reportable variants in genes that have been previously associated with autism and/or ID in the published or emerging literature. Pathogenic/likely pathogenic variants in genes responsible for the 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 Autism/ID *Xpanded*®Panel includes 2300+ genes, the report will not include a comprehensive list of all observed variants. If desired, clinicians can request a separate file containing a list of identified variants that will be provided upon completion of testing.

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.[12] The absence of reportable incidental findings for any particular gene does not rule out the possibility of pathogenic variants in that gene.

Test Sensitivity:

The clinical sensitivity of the Autism/ID *Xpanded*®Panel depends in part on the patient's clinical phenotype. Previous exome sequencing studies have reported identification of a definitive pathogenic variant in 14-33% of individuals who have neurodevelopmental phenotypes such as ASD, ID and developmental delay.[6-10, 13-15] However, the clinical sensitivity of analysis of the genes on the panel depends on the clinical phenotype. It has been demonstrated that the yield of exome sequencing is higher with a Trio approach compared to a Proband-only approach.[9]

The sensitivity of this test is expected to be comparable to trio-based exome sequencing since it uses a trio approach to test a comprehensive list of genes previously associated with ASD and/or ID. The clinical sensitivity is expected to be significantly lower for singleton testing when only the affected proband is tested.

The average coverage of all genes on the panel is greater than 98% at 10X (with a depth of 10 or more reads). The coverage of each gene on the panel for a specific patient may vary, and the actual coverage for each gene is included in the final report.

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. For example, the CGG repeat expansions in *FMR1* causing fragile X syndrome, the polyalanine repeat expansions in *ARX*, and abnormal methylation of *UBE3A* causing Angelman syndrome would not be detectable by this Autism/ID *Xpanded*®Panel.

The scientific knowledge available about the function of all genes in the human genome is incomplete at this time. It is possible that the Autism/ID *Xpanded*®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 their disease due to insufficient knowledge about the gene and its function. Even if the Autism/ID *Xpanded*®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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