



Test Information Sheet

ExonArrayDx

Gene-specific array CGH analysis for detecting partial or full gene deletions or duplications

Also known as: Molecular array; high-resolution oligonucleotide array comparative genomic hybridization

The ExonArrayDx employs a GeneDx-designed oligonucleotide microarray constructed for comparative genomic hybridization (oligo aCGH) to identify deletions or duplications within or encompassing the entire targeted gene. This array targets more than 375 clinically significant genes, which can be ordered individually or as part of a clinically defined panel. The sensitivity of ExonArrayDx is substantially higher than that of conventional testing by quantitative PCR (qPCR) or by multiplex ligation-dependent probe assay (MLPA) because it utilizes many more probes strategically positioned in all exons of a given target gene. The utility of high-resolution array CGH for single gene analysis has been demonstrated in multiple studies.¹⁻⁶

This test is expected to provide additional sensitivity in genetic testing for a large number of pediatric and adult genetic disorders. This is particularly important for disorders that arise due to loss of function of one allele (haploinsufficiency) or for disorders in which a substantial proportion of mutations are intragenic deletions. For example, small deletions are frequently identified within the STK11 gene in patients with Peutz-Jeghers syndrome. In addition, testing for partial or complete gene deletions is extremely valuable in cases in which there is a strong suspicion of a particular recessive disorder and only one mutation is identified by sequence analysis. One example of this is an inherited metabolic disorder in which a specific enzyme defect can be identified. In both of these examples, as well as others, a highly robust assay to examine each exon is very useful. Intragenic deletions or duplications can have consequences similar to some single-nucleotide mutations due to alteration of a sequence from which a protein is produced.

*GeneDx offers sequence analysis for a large number of metabolic and other recessive disorders. If sequencing is done at GeneDx and only one mutation has been identified in a patient, GeneDx will perform ExonArrayDx analysis to exclude a deletion of the second allele **at no extra cost**.*

Applications of ExonArrayDx:

- As a diagnostic test for a specific disorder that results from haploinsufficiency for a clinically significant gene
- As a diagnostic test for an autosomal recessive disorder when sequencing or another test identifies only a single mutation
- As a diagnostic test for X-linked gene deletions or duplications associated with mental retardation (XLMR genes)
- As a confirmation test for an imbalance of a chromosomal region that contains a dosage-sensitive gene that is present on the ExonArrayDx microarray

Test method and sensitivity:

ExonArrayDx detects deletions or duplications as small as 150-300 bp. Results are compared to the HGMD database and may be confirmed by qPCR, MLPA or another array. In cases where interpretation of results depends on whether the deletion or duplication is inherited or *de novo*, analysis of parental samples is useful for accurate interpretation of the proband's results. ExonArrayDx probes represent the current genome build (hg19) and analysis of array data is performed using DNA Analytics software (Agilent Technologies). The array design is updated continually and optimized based on its performance and on newly published gene information. The technical sensitivity of ExonArrayDx analysis for a specific disorder, syndrome, or malformation depends on the proportion of cases that are typically caused by such genomic alterations versus other types of mutations. For disorders that are commonly caused by intragenic deletions/duplications, such as Peutz-Jeghers syndrome (STK11) or Gorlin syndrome (PTCH), the deletion rate may be as high as 30%. It may be lower in other disorders such as Cowden syndrome (10-13%) or very low (1-2% or less) in conditions like CHARGE syndrome, X-linked Chondrodysplasia Punctata, and many other Mendelian disorders.

Test limitations:

- ExonArrayDx is **not** appropriate for detecting the following abnormalities:
 - Deletions or duplications of a single nucleotide (point mutations) or a stretch of nucleotides <100 bp
 - Mutations in genes or intragenic regions that are not represented on the microarray
 - Small promoter or 3' deletions or duplications (except the PTEN gene)
 - Deletions or duplications in genes that have pseudogene copies in the genome
 - Large unbalanced chromosomal rearrangements (GenomeDx array is appropriate)

- Normal findings at a specific gene locus do not rule out the diagnosis of a genetic disorder associated with this gene as another genetic abnormality may be present but undetectable by ExonArrayDx. Specifically, Mendelian disorders that are predominantly caused by small DNA mutations (point mutations or <100bp intragenic deletions or insertion) are better diagnosed by other molecular methods, such as DNA sequencing.
- Test results are often complex and interpretation may be confounded by polymorphisms in the general population.

Specimen Requirements and Shipping/Handling:

- *Blood:* A single tube with 1-3 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- *Buccal brushes:* CANNOT BE ACCEPTED for ExonArrayDx
- *Extracted DNA:* A minimum amount of 5 micrograms of high-quality DNA with a concentration of at least 50 ng/μl (50 nanograms per microliter).

Required Forms:

- ExonArrayDx sample submission form – including the informed consent and payment options / institutional billing page

Prices: (*Fees are subject to change without notice:*)

Test #906: ExonArrayDx for 1 gene	\$ 500
Test #907: ExonArrayDx for 2 genes	\$1000
Test #908: ExonArrayDx for 3 genes or a gene panel (up to 10 genes)	\$1500

Testing includes confirmation of abnormal results.

Turn-Around Time: Approximately 3-4 weeks, depending on complexity of results.

CPT codes:

<i>ExonArrayDx for a single gene Test #906</i>	<i>ExonArrayDx for 2 genes Test #907</i>	<i>ExonArrayDx for 3-10 genes Test #908</i>
83891 x 2 units = \$ 12	83891 x 4 units = \$ 24	83891 x 6 units = \$ 36
88386 x 1 units = \$ 488	88386 x 2 units = \$ 976	88386 x 3 units = \$ 1464
TOTAL = \$500	TOTAL = \$1000	TOTAL = \$1500

ICD9 codes will depend on the clinical diagnosis.

References: (1) del Gaudio D et al. Hum Mutat 29:1100-1107, 2008 (2) Saillour Y et al. Hum Mutat 29:1083-1090, 2008, (3) Staaf J et al. Hum Mutat 29:555-564, 2008 (4) Hegde MR et al. Hum Mutat 29:1091-1099, 2008 (5) Wong LJ et al. Clin Chem 54:1141-1148, 2008 (6) Dhami P et al. Am J Hum Genet 76:750-762, 2005.