



## Test Information Sheet

### GenomeDx version 3.0:

#### High-resolution whole-genome cytogenetic array CGH with a custom 105,000 oligonucleotide probe design for detecting copy number changes (including genomic deletion/duplication syndromes)

**Also known as:** Chromosomal microarray analysis (CMA); oligonucleotide array comparative genomic hybridization, array CGH

**Clinical utility of this service:** GeneDx provides whole-genome cytogenetic oligonucleotide array CGH testing, the next generation of chromosomal analysis methodology in the molecular era. In one assay the entire genome is evaluated for chromosomal aneuploidy and for intrachromosomal duplications and deletions. Abnormal copy number can often be associated with pediatric and adult genetic disorders. The sensitivity of GenomeDx is substantially higher than conventional cytogenetic testing and BAC-based array CGH because this array design includes high-density oligonucleotide probe coverage at disease-associated and gene-dense regions to better define the boundaries of chromosomal rearrangements and to show which genes lie within rearranged genomic regions. Array CGH can detect disease-associated copy number changes in 5%-17% of individuals with mental retardation and/or developmental problems, even when a karyotype is normal (deVries et al., 2005; Shaffer et al., 2006; Krepischi-Santos et al., 2006). In addition, 6-7% of individuals with nonsyndromic autism and as many as 27% of individuals with autism spectrum disorders in conjunction with additional congenital anomalies carry copy number aberrations detectable by whole-genome array CGH (Marshall et al., 2008; Jacquemont et al., 2006). Abnormal findings have been detected in 25% of over 5,000 array CGH cases tested at GeneDx using designs v1.0 – v3.0.

#### **Applications of GenomeDx v3.0 whole-genome oligonucleotide array CGH:**

- As a **primary screening test** for the diagnosis of persons with unexplained dysmorphic features, birth defects, unexplained mental retardation/developmental delay, multiple congenital anomalies, seizures or any suspicion of genomic imbalance
- As a **primary screening test** for the diagnosis of persons with autism spectrum disorder
- As a **complementary or replacement test** for **FISH and BAC-based microarray analysis** when a deletion or duplication syndrome (contiguous or single-gene) is suspected or to precisely determine the breakpoints of chromosomal rearrangements that were previously detected with conventional cytogenetic methods and BAC arrays
- As a superior **alternative to subtelomere FISH** in persons with developmental disabilities/mental retardation
- As a **complementary diagnostic test** in a **Mendelian disorder** due to functional loss of one allele (haploinsufficiency), specifically when sequence analysis fails to identify a causative mutation and a whole-gene deletion is suspected.

#### **Test limitations:**

- GenomeDx v.3.0 oligonucleotide array CGH **cannot** detect the following abnormalities:
  - Balanced chromosomal rearrangements, such as inversions, balanced insertions, and reciprocal translocations
  - Polyploidy
  - Genomic alterations in regions that are not represented on the microarray
  - Low-level mosaicism (<20-25%)
  - Rearrangements in repeat sequences (e.g., short arms of acrocentric chromosomes and heterochromatic regions)
- Normal findings at a specific locus do not rule out the diagnosis of a genetic disorder associated with that locus since another abnormality may be present but undetectable by this cytogenetic array design. Specifically, Mendelian disorders predominantly caused by small DNA mutations (point mutations, small intragenic deletions or insertion) are better diagnosed by methods such as DNA sequencing or by ultra-high-resolution array CGH (ExonArrayDx).
- Test results are often complex and interpretation may be confounded by the detection of copy number variants (CNV) that may be present in the general population.

#### **Test method, array design, and clinical sensitivity:**

The GenomeDx v.3.0 array was developed and its performance verified by GeneDx. This test is based on a form of comparative genomic hybridization using an oligonucleotide DNA microarray containing 105,000 oligonucleotide probes designed from human genome build hg18. Probes are specifically selected to achieve an average coverage of 1 probe per 37 kb across the non-repetitive sequence of the human genome. In addition, >150 clinically significant chromosomal loci, subtelomeric and pericentromeric regions, and the entire X chromosome carry an average coverage of 1 probe every 9-17 kb. Specific dosage-sensitive genes contain ultra-high probe density (300bp-1 kb resolution). The GenomeDx array can detect deletions or duplications that are  $\geq 50$  kb in targeted regions (associated with contiguous gene deletion/duplication syndromes), and  $\geq 200$  kb in other areas of the genome. Data analysis is performed with Genomic Workbench software v5.0 (Agilent). Significant genomic imbalances are compared to an external database of copy number changes found in the general population (Database of Genomic Variants; <http://projects.tcag.ca/variation>) as well as to

an internal database. When necessary, copy number changes are confirmed by FISH, quantitative PCR analysis (CopyDx), and/or array CGH with another design (15K or 60K). In some cases, interpretation of results depends on whether the copy number change is inherited or *de novo*, and analysis of parental samples is useful for accurate and rapid interpretation of the proband's test results. The GenomeDx array design is updated continually and optimized based on performance evaluation and newly published CNV and disease locus data.

The GenomeDx array can reliably detect aneuploidy and genomic deletions or duplications of  $\geq 200$  kb. The clinical utility of GenomeDx analysis to test for a specific disorder, syndrome, or malformation depends on the proportion of cases that are caused by deletions and duplications versus other types of mutations. For known deletion/duplication syndromes, such as Cri-du-Chat or DiGeorge/VCF, the detection rate is very high (>90%), while it may be low (1-2%) in single-gene disorders such as Coffin-Lowry syndrome. Overall, 5-17% of individuals who exhibit clinical symptoms suggestive of a genomic disorder but demonstrate a normal karyotype have an abnormal result using BAC array CGH (Shaffer & Bejjani, 2006). The sensitivity of oligonucleotide probe-based array CGH is significantly greater: in over 5,000 cases analyzed by oligonucleotide array CGH at GeneDx using v.1.0 (44k), v2.0 (105K), and v3.0 (105k), the frequency of reportable findings was 25% (positive findings accounted for 18% and novel, previously unreported findings of uncertain clinical significance accounted for 7%). For patients with autism or autism spectrum disorders, we expect to identify genomic copy number changes in approximately 6-27% (Marshall et al., 2008; Jacquemont et al., 2006).

**Specimen Requirements and Shipping/Handling:**

- **Blood:** One tube of 1-3ml blood in EDTA (and one tube of 1-3ml blood in heparin for FISH, if necessary). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated up to 7 days prior to shipping.
- **Buccal brushes:** Buccal brush specimens are **NOT SUITABLE** for array CGH analysis.
- **Extracted DNA:** High-quality DNA preparations are requested. A **minimum amount of 5 micrograms DNA**, with a **concentration of at least 50 ng/ul** (50 nanograms per microliter) is required.

**Parental testing policy:**

GeneDx recommends parental testing in cases in which the patient is found to have a genomic imbalance. Parental analysis is used to evaluate the inheritance of an abnormality (familial or *de novo*) and may also clarify the clinical significance of the patient's results. GeneDx offers free parental analysis in cases in which parental testing can be useful to interpret a result of unclear clinical significance in the patient. When a patient has a clinically well-characterized genomic imbalance and parental testing is indicated (e.g., to determine if a microdeletion is inherited) or if testing is standard of care to determine recurrence risk and for genetic counseling (e.g., to rule out a balanced chromosomal rearrangement in a parent), FISH or targeted array CGH (FISHonChipDx) testing is available for an additional cost, as shown below. Turn-around time for an updated report including parental or relatives' results is 4-6 weeks.

**Required Forms:**

- Molecular cytogenetics sample submission (requisition) form available online at [www.genedx.com](http://www.genedx.com)
- Payment options / Institutional billing information (last page of submission form PDF)

**Price: Fees are subject to change without notice:**

Test #910: GenomeDx whole-genome oligonucleotide probe array CGH, including confirmation of abnormal results and parental testing when necessary = \$ 1595

**Testing of other family members:**

- Test #336: Follow-up testing for known deletion/duplication by FISH = \$555
- Test #337: Follow-up testing for known deletion/duplication by targeted array CGH (FISHonChipDx) = \$650
- Test #905: Follow-up testing for known familial deletion/duplication by qPCR = \$500

**Turn-Around Time for GenomeDx:** 14-28 days, depending on complexity of results.

**Relevant CPT codes:**

<b>GenomeDx array CGH</b>	<b>FISHonChipDx array CGH</b>	<b>FISH</b>	<b>qPCR</b>
83891 x 1 unit	88230 x 2 units	88230 x 1 unit	83891 x 2 units
88271 x 81 units	88271 x 2 units	88271 x 2 units	83898 x 8 units
88291 x 1 unit	88283 x 2 units	88283 x 1 unit	83892 x 2 units
	88273 x 4 units	88273 x 4 units	83912 x 2 units
	88291 x 2 units	88291 x 2 units	
<b>TOTAL = \$1595</b>	<b>TOTAL = \$650</b>	<b>TOTAL = \$555</b>	<b>TOTAL = \$ 500</b>

**ICD9 codes will depend on the clinical diagnosis.**

**References:** (1) de Vries BB, et al. *Am J Hum Genet* 77(4):606-16, 2005. (2) Shaffer LG et al. *J Pediatr* 149(1):98-102, 2006. (3) Krepischi-Santos AC et al., *Cytogenet Genome Res* 115(3-4):254-61, 2006. (4) Shaffer & Bejjani. *Cytogenet Genome Res* 115(3-4):303-9, 2006. (5) Marshall et al., *Am J Hum Genet* 82:477-488, 2008. (6) Jacquemont et al., *J Med Genet* 43:843-849, 2006.