

Cytogenetic array CGH testing for copy number abnormalities

Routine chromosomal analysis for constitutional developmental disorders is shifting from G-banded karyotype analysis to DNA microarray-based comparative genomic hybridization (array CGH) as a first-tier test (Miller D et al., 2010). The clinical sensitivity of whole-genome array CGH in patients with developmental delay, mental retardation, and/or congenital anomalies is at least 10% higher than that associated with karyotyping and subtelomere FISH. Array CGH can detect pathogenic copy number changes in up to 15% of individuals with mental retardation and developmental delay when the karyotype is normal (Fan YS et al, 2007). In addition, 7% of individuals with nonsyndromic autism and as many as 27% of individuals with autism spectrum disorders and additional congenital anomalies carry copy number changes detectable by array CGH (Marshall et al., 2008). GeneDx offers the options below for postnatal array CGH testing. (*For prenatal array CGH testing, please visit www.genedx.com/site/prenatal.*)

Array type	Whole-genome postnatal array CGH (GenomeDx v4)	Targeted postnatal array CGH (FISHonChipDx v1)
Description of array	This is a state of the art platform for constitutional cytogenetic analysis. In one assay the entire genome is evaluated for chromosomal aneuploidy and for intrachromosomal duplications and deletions.	This array offers an economical first-pass genome scan and a superior alternative to subtelomere FISH or microdeletion syndrome testing. This array targets 65 known microdeletion/duplication syndromes and interstitial imbalances >2 Mb
Number of probes	180,000	15,000
Resolution	35 kb probe spacing across the entire genome and 5-20 kb spacing in >150 microdeletion/duplication syndrome and subtelomeric regions	450 kb spacing across the entire genome and 50 kb probe spacing at 65 microdeletion/duplication syndrome and subtelomeric regions
Test indications:	<ul style="list-style-type: none"> • Primary screening test for diagnosis of persons with dysmorphic features, birth defects, mental retardation/developmental delay, autism spectrum disorder, multiple congenital anomalies, seizures or any suspicion of genomic imbalance • Determine breakpoints of chromosomal rearrangements previously detected by conventional cytogenetic methods and BAC arrays 	<ul style="list-style-type: none"> • Suspected common microdeletion/duplication syndrome • Replacement test for subtelomere FISH panel • First-pass genome scan in patients with mental retardation and a normal karyotype • Confirmation of certain karyotypes with large (>2 Mb) intrachromosomal rearrangements
Sample type	1-3 ml blood in EDTA	1-3 ml blood in EDTA
Turn-around-time	3 weeks	2 weeks
Parental testing	<ul style="list-style-type: none"> • Free if array result of uncertain significance is reported, or if parental samples are available at time of proband's confirmation testing. • If finding in proband has known clinical significance, parental testing offered for an additional cost to determine inheritance. 	<ul style="list-style-type: none"> • Positive array findings in the proband are expected to be clinically significant and parental analysis is typically not needed for interpretation of results. • Where parental testing is standard of care (e.g., to rule out balanced translocation), that testing is available for an additional cost.

Test method and sensitivity:

The GenomeDx v.4 array detects copy number changes as small as 15-250 kb, depending on genomic location. The FISHonChipDx targeted array detects copy number changes as small as 250 kb in targeted regions and more than 1.5 Mb in the rest of the genome. Technical sensitivity is greater than 95% for both arrays at the described size ranges. Array findings are compared to a database of copy number changes found in the normal population (Database of Genomic Variants), another database hosted by the International Standard Cytogenetic Array (ISCA) consortium at NCBI/NIH, and to an internal GeneDx database. FISH, quantitative PCR, or another array may be used to confirm copy number changes. In those cases where interpretation of results depends on whether the copy number change is inherited or *de novo*, analysis of parental samples is essential for accurate interpretation.

Test limitations:

- Array CGH **cannot** detect balanced chromosomal rearrangements (inversions, balanced insertions, and balanced 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), and mutations of single or small stretches of nucleotides (point mutations, indels, etc.).
- 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.
- 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.

Specimen Requirements and Shipping/Handling:

- **Blood:** One tube of 1-3 ml blood in EDTA for array and one tube of 1-3 ml blood in heparin for FISH. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens in EDTA may be refrigerated up to 7 days prior to shipping.
- **Buccal brushes:** Cannot be accepted for array CGH analysis.
- **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).

Parental testing policy:

GeneDx recommends parental testing when a 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 when parental testing can be useful to interpret a result of unclear 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 form is available online at www.genedx.com/site/genomedx.
- Payment options / Institutional billing information (last page of submission form PDF)

Testing of other family members:

Test #336: Follow-up testing for known deletion/duplication by FISH = \$555

Test #9051: Follow-up testing (or family member testing) for known deletion/duplication by targeted array CGH = \$500

Test #905: Follow-up testing for known familial deletion/duplication by qPCR = \$500

Relevant CPT Codes, Prices and Turn-Around Times (Fees are subject to change without notice):

Whole-genome array CGH (GenomeDx v4) Test #910	Targeted postnatal array CGH (FISHonChipDx v1) Test #337	FISH Test #336	qPCR Test # 905	Targeted array CGH for known familial del/dup Test# 9051
83891 x 1 unit	83891 x 1 unit	88230 x 1 unit	83891 x 2 units	83891 x 1 unit
88271 x 81 units	88271 x 65 units	88271 x 2 units	83898 x 8 units	88271 x 45 units
88291 x 1 unit	88291 x 1 unit	88283 x 1 unit	83892 x 2 units	88291 x 1 unit
		88273 x 4 units	83912 x 2 units	
		88291 x 2 units		
TOTAL= \$1595	TOTAL= \$650	TOTAL= \$555	TOTAL= \$ 500	Total= \$500
Turn-around time: 2-4 weeks	Turn-around time: 2 weeks	Turn-around time: 3-4 weeks	Turn-around time: 4-6 weeks	Turn-around time: 3-4 weeks

ICD9 codes will depend on the clinical diagnosis.

References: Miller D et al. Am J Hum Genet. In press, May 2010. Fan YS et al. Hum Mut 28:1124-1132, 2007. Marshall CR et al. Am J Hum Genet 82:477-488, 2008