Shorten your diagnostic odyssey with a complete, IVDR-compliant chromosomal microarray solution

Children with developmental delay/intellectual disability (DD/ID) can have lifelong challenges, including various medical conditions as well as difficulties with physical movement, learning, and social interaction.

Establishing an underlying diagnosis early can better inform healthcare providers and families of prognosis, recurrence risk, and comorbidity information, all of which have implications beyond medical treatment. However, finding a diagnosis can be an arduous journey, and opportunities for taking early action are often lost during this "diagnostic odyssey."

When patient history and physical examination do not suggest an obvious syndrome, chromosomal microarray analysis (CMA) is recommended as a first-line test to aid in the diagnostic evaluation of ID by multiple medical societies, including:

- American Academy of Neurology (AAN) [1]
- Child Neurology Society (CNS) [1]
- American College of Medical Genetics and Genomics (ACMG) [2,3]
- European Society of Human Genetics (ESHG) [4]

Many medical society guidelines also recommend CMA as a replacement for traditional karyotyping and fluorescence *in situ* hybridization (FISH) because of its:

- Greater sensitivity
- Higher resolution
- Genome-wide capability
- Greater diagnostic yield

CytoScan Dx Test

The Applied Biosystems™ CytoScan™ Dx Test is an EU *In Vitro* Diagnostic Regulation (IVDR) 2017/746–compliant microarray solution. It is a whole-genome diagnostic test to aid clinicians in identifying the underlying genetic cause of developmental delay, intellectual disability, congenital anomalies, or dysmorphic features in children.

The complete, sample-to-insight, IVDR-compliant microarray analysis solution includes the Applied Biosystems™ CytoScan™ Dx Array, a reagent kit, the Applied Biosystems™ GeneChip™ System 3000Dx platform for array processing, and Applied Biosystems™ Chromosome Analysis Suite (ChAS) Dx Software.

Whole-genome coverage with the CytoScan Dx Array Designed for today and the future

The CytoScan Dx Array enables high-density whole-genome coverage to allow higher resolution than karyotyping and more comprehensive coverage than FISH.

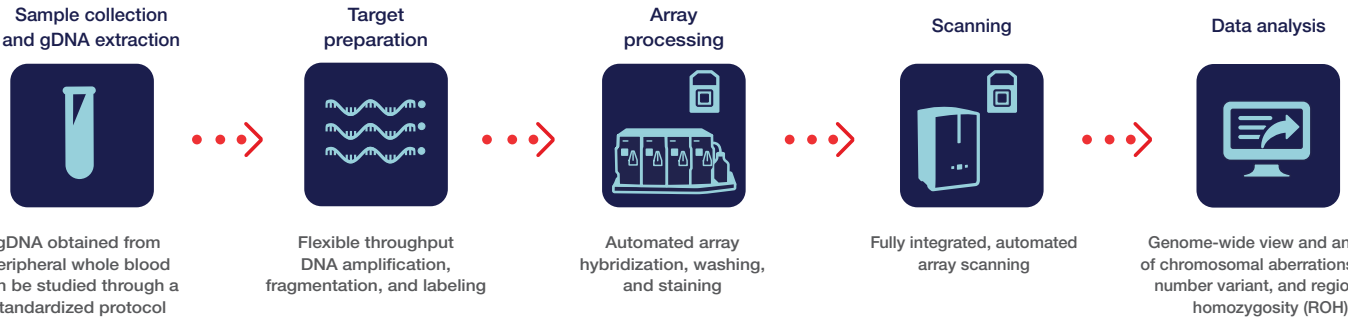
It includes 2.69 million markers for copy number (CN) analysis—750,000 bi-allelic single-nucleotide polymorphism (SNP) probes and 1.9 million nonpolymorphic markers—to provide coverage for a large majority of genes.

Intellectual disability might present itself as the only manifestation of a disease or may be associated with other manifestations causing a clinical syndrome [4]. Techniques like karyotyping, FISH, and array comparative genomic hybridization (aCGH) can potentially miss clinically relevant aberrations.

An incremental 13.8% diagnostic yield beyond traditional techniques is possible with the CytoScan Dx Array, allowing for accurate detection of numerous chromosomal variations of different types, sizes, and genomic locations.

In addition to identifying CN changes, the CytoScan Dx Array is capable of detecting allelic imbalances and copy-neutral aberrations (e.g., loss of heterozygosity (LOH)), which can be associated with uniparental disomy (UPD) or consanguinity, both of which may pose increased risk for autosomal recessive conditions.

The complete, IVDR-compliant, sample-to-insight microarray solution



CytoScan Dx Array specifications

Markers for copy number analysis	
Total number of markers	2,696,564
Number of nonpolymorphic markers	1,953,246
Number of SNP markers	743,318
Markers used for allele differences and B-allele frequency (BAF)	
Number of SNP markers	796,461
Performance specifications	
Genome build used for development	hg19
Recommended mass of input gDNA*	250 ng
Minimum resolution for losses	≥25 markers and 25 kb
Minimum resolution for gains	≥50 markers and 50 kb
Resolution for ROH	≥3 Mb
Mosaicism, limit of detection	≥20%

* 250 ng is optimal, but users have reported success using as little as 10 ng of starting DNA.

Marker distribution and spacing	
Number of autosomal markers	2,491,919
Number of pseudoautosomal markers	4,624
Number of intragenic markers	1,535,333
Number of intergenic markers	1,161,231
Average intragenic spacing (bp)	916
Average intergenic spacing (bp)	1,365
Average spacing (gene and nongene backbone, bp)	1,079
Percentage of genes having ≥25 markers/100 kb (hg19)	
Clinical genes and regions (ClinGen, OMIM® Morbid Map, and DECIPHER™) (5,148)	98.4%
ClinGen (1,172)	99.3%
OMIM morbid genes (4,388)	98.4%
DECIPHER genes (1,946)	99.0%
RefSeq genes (20,846)	96.7%

CytoScan Dx Array validation data

Study	Description
Accuracy	For the 132 samples, 163 CNVs were detected with historical karyotype or FISH and represented mostly large-size CNVs (mean size 25.1 Mbp, median size 11.2 Mbp, range 1.8–175.9 Mbp). The positive percent agreement between the CytoScan Dx Array and RPC was 91.4% (149/163; Wilson method 95% CI 86.1%–94.8%). Of the 14 missed aberrations, four were balanced translocations that are not detected by the CytoScan Dx Array, 3 CNVs were outside of the CytoScan Dx Array marker regions (two at the Y-ter and one in the acrocentric p-arm of chromosome 22), and 1 low-level mosaic was below the stated detection limit for the CytoScan Dx Array.
Clinical validity	In a multicenter retrospective-prospective study of 960 subjects, the CytoScan Dx Array identified 11.2 ± 4.1 (mean ± SD) CNVs per subject. Of 128 gDNA samples that were classified as pathogenic by the historical routine patient care, 82% were classified as pathogenic by clinicians using the CytoScan Dx Array. Of the 23 that were called pathogenic by historical methods and called VOUS or benign by the cytogeneticist interpreting the CytoScan Dx Array data, 92% agreed at the analytical level.
Limit of detection	DNA input for the CytoScan Dx Array is 250 ng, but input amounts as low as 10 ng still detect large chromosome aberrations.
Reproducibility	The CytoScan Dx Array was evaluated through a site-to-site study with 93 gDNA samples processed by 2 operators at each of 3 sites across 3 nonconsecutive time points. Each sample was run 9 times across the 3 time points and sites. Every CNV detected was analyzed for reproducibility across the 9 replicates by pairwise agreement for copy number state call. A pair of replicates was considered to agree if the CNVs overlapped by at least 50% of the CNV length and if the CNV states (gain/loss) were the same. Copy number gains and losses with 300 markers (~300 kbp) were 100% reproducible across the 9 replicates. For smaller CNVs, losses of 25–50 markers (25–50 kbp) were reproduced at 81% and gains of 50–75 markers (50–75 kbp) were reproduced at 75%. In the 93 samples, there were 481 ROH with sizes ≥3 Mbp that were called with 92.4% reproducibility.
Precision	With the high-density CytoScan Dx Array, endpoint precision had a mean CV of 5.3% across 914 CNV endpoints from 93 gDNA samples run at 3 sites 3 times (9 replicates).
Cross-contamination	gDNA samples with up to 20% contamination with another individual's DNA show good QC metrics and give good results with the CytoScan Dx Array.

CytoScan Dx Array validation data (continued)

Study	Description
Whole blood gDNA stability	The CytoScan Dx Array is validated for use with peripheral whole blood anticoagulated with heparin or EDTA. It has not been validated for any other specimen type. Institutional collection guidelines should be followed for the collection of peripheral blood specimens using EDTA or heparin as an anticoagulant. Testing has demonstrated that gDNA provided to the laboratory is stable per the following conditions: • Ambient (15 to 30°C), up to 6 weeks • Refrigerated (2 to 8°C), up to 3 months • Frozen (–25 to –15°C), up to 3 months, including up to 4 freeze-thaw cycles; or up to 6 months, including up to 2 freeze-thaw cycles • Ambient (15 to 30°C) for 2 weeks, then frozen (–25 to –15°C) up to 3 months, including up to 4 freeze-thaw cycles; or up to 6 months, including up to 2 freeze-thaw cycles • Refrigerated (2 to 8°C) for 2 weeks, then frozen (–25 to –15°C) up to 3 months, including up to 4 freeze-thaw cycles; or up to 6 months, including up to 2 freeze-thaw cycles
Interfering substances	Interference was evaluated using simulated aberrant samples (i.e., leukocyte-depleted blood spiked in with cells containing known aberrations) or normal blood samples spiked with conjugated and unconjugated bilirubin, triglycerides, and hemoglobin. No interference was observed with any of the tested substances.

GeneChip System 3000Dx

The power of intuitive design and automation

The GeneChip System 3000Dx v.2 is an advanced microarray platform for array processing that combines design improvements with high-resolution scanning and automation to dramatically improve efficiency in genetic analysis applications.

The system includes the GeneChip Fluidics Station 450Dx v.2 and the GeneChip Scanner 3000Dx v.2 with a preassembled Autoloader Dx Carousel, which, when used together, enable complete walk-away freedom for scanning your arrays. The GeneChip System 3000Dx v.2 fits easily into a benchtop environment. Its solid-state laser eliminates the need for an external laser power supply or a special cooling system under the bench.

The outstanding performance and enhanced capabilities of the GeneChip System 3000Dx v.2 offer accurate gridding and consistent scanner-to-scanner performance, helping to improve data integrity and data sharing between clinical researchers.

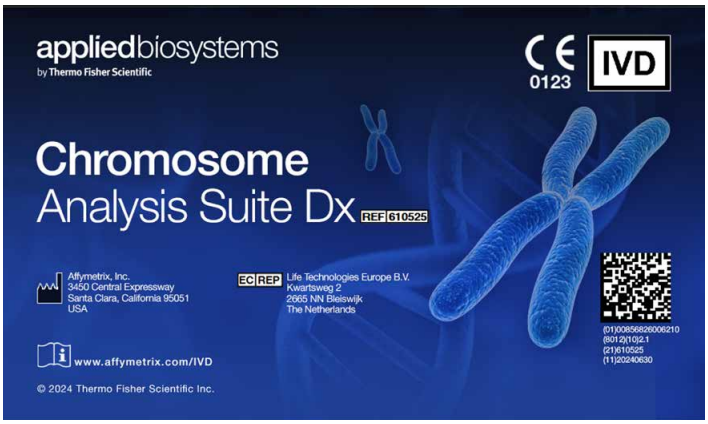
Highlights include:

- Compact size for better space utilization
- High-resolution scanning from 0.51 to 2.5 µm pixelations, automatically selected by array type
- Optimal image uniformity and collection efficiency across entire scan area with proprietary Applied Biosystems™ Flying Objective lens technology
- No laser drift and reduced scanner-to-scanner variability
- Automatic adjustment of residual arc correction and x-linearity
- The Autoloader Dx Carousel facilitates complete walk-away scanning of up to 48 arrays at a time

GeneChip System 3000Dx specifications

Feature	Description
Scan time	5–45 minutes per cartridge, depending on array type
Sensitivity	<0.5 chromophore equivalents/µm^2 (CPSM) at a signal-to-noise ratio of 2:1 at wavelengths appropriate to R-phycoerythrin
Excitation	532 nm, 10 mW maximum
Emission filters	570 nm longpass; 565 nm, 605 nm, 655 nm, and 705 nm longpass; 20 nm wide bandpass
Detector	Meshless photomultiplier tube, red enhanced
Displayed and saved dynamic range	16-bit (65, 535:1)
Software	GeneChip Data Collection Dx Software
Dimensions (W x D x H)	**GeneChip Scanner 3000Dx with preassembled Autoloader Dx Carousel**: 22.5 x 31 x 44.5 in. (57.2 x 78.7 x 113 cm) **GeneChip Fluidics Station 450Dx v.2**: 28 x 16.1 x 15.8 in. (71.1 x 41 x 40.2 cm)
	GeneChip Fluidics Station 450Dx v.2: 28 x 16.1 x 15.8 in. (71.1 x 41 x 40.2 cm)
Weight	**GeneChip Scanner 3000Dx with preassembled Autoloader Dx Carousel:** 105 lb (47.6 kg) **GeneChip Fluidics Station 450Dx v.2:** 80 lb (36.3 kg)
Power	Voltage: 100–240 V, current: 2-4 A, frequency: 50–60 Hz
Warranty	One-year limited coverage

Chromosome Analysis Suite (ChAS) Dx Software 2.1



Designed for cytogenetic analysis, ChAS Dx Software is an IVDR-compliant application for analysis and visualization of chromosomal aberrations across the genome that may include CN gain or loss, or LOH.

ChAS Dx Software provides tools to help you:

- Perform single-sample analysis of intensity data (.cel) files
- Analyze segment data at different levels of resolution
- View and export data that summarize chromosomal aberrations in table and graphical formats
- Customize and load your own annotations and regions for focused analysis
- Apply separate filters to the entire genome and user-specified regions of interest
- Perform detailed sample comparisons
- Directly access external databases (e.g., NCBI, UCSC Genome Browser, Ensembl, OMIM)
- Generate a results summary page containing copy number and LOH data
- Experience enhanced cybersecurity protection with ChAS DB administrator password change

Ordering information

Product	Description	Cat. No.
CytoScan Dx Assay Kit	1 kit	902420
CytoScan Dx Assay Training Kit	1 kit	902450
GeneChip System 3000Dx v.2	Includes: • GeneChip Scanner 3000Dx v.2 with preassembled GeneChip AutoLoader Dx Carousel • GeneChip Fluidics Station 450Dx v.2 • Workstation with GeneChip Data Collection Dx Software	00-0334
GeneChip Fluidics Station 450Dx v.2	Single station available to be purchased separately from the GeneChip System 3000Dx v.2	00-0335
FAS training	1.5-day on-site FAS training	000.882
FAS training	4-day on-site FAS training	000.883

References

1. Michelson DJ et al. (2011) Evidence report: genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 77(17):1629–1635.
2. Manning M et al. (2010) Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med* 12(11):742–745.
3. Manning M et al. (2020) Addendum: Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. *Genet Med* 22(12):2126.
4. Silva M et al. (2019) European guidelines for constitutional cytogenomic analysis. *Eur J Hum Genet* 27(1):1-16.
5. Miller DT et al. (2010) Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 86(5):749–764.
6. Chelly H et al. (2006) Genetics and pathophysiology of mental retardation. *Eur J Hum Genet* 14:701–713.
7. Pfundt R et al. (2016) Clinical performance of the CytoScan Dx Assay in diagnosing developmental delay/intellectual disability. *Genet Med* 18(2):168-73.

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