510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

k163367

B. Purpose for Submission:

New device

C. Measurand:

Genome-wide chromosomal copy number variations

D. Type of Test:

Chromosomal Microarray

E. Applicant:

Agilent Technologies, Inc.

F. Proprietary and Established Names:

Agilent GenetiSure Dx Postnatal Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.5920

2. Classification:

   Class II (special controls)

3. Product code:

   PFX -- System, Microarray-based, genome-wide, postnatal chromosomal abnormality detection

4. Panel:

   Immunology

H. Intended Use:

1. Intended use(s):

   GenetiSure Dx Postnatal Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) and copy-neutral loss of heterozygosity (cnLOH) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. GenetiSure Dx Postnatal Assay is intended for the detection of CNVs and cnLOH associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the SureScan Dx Microarray Scanner System and analyzed by CytoDx Software.

   This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

2. Indication(s) for use:

   Same as Intended use above.

3. Special conditions for use statement(s):

   For prescription use.

4. Special instrument requirements:
   SureScan Dx Microarray Scanner with CytoDx 1.0 software.

I. Device Description:

The GenetiSure Dx Postnatal Assay consists of the following components:

1. Six 4 x 180K Microarray slides capable of running 4 assays per slide and Gasket slides which hold the samples during hybridization to the microarrays

2. Reagents and Columns (materials supplied separately)
   a) GenetiSure Dx DNA Labeling Kit contains sufficient two-color labeling reaction contains Random Primers and the Exo(-) Klenow fragment to differentially label DNA, enzymes, nucleotides, columns, and human reference DNA for the six 4x180K microarray slides included with the GenetiSure Dx Postnatal Assay.
   b) GenetiSure Dx Hybridization Kit contains hybridization buffer and blocking agent used for hybridization to the microarrau
   c) GenetiSure Dx Wash Buffer Set- The kit contains wash buffers for washing unhybridized labeled DNA from the microarrays.

d) GenetiSure Dx Cot-1 Human DNA - The kit contains a solution of fractionated human DNA that has been enriched for repetitive sequences.

3. CytoDx 1.0 Software- CytoDx Software performs feature extraction, CNV and cnLOH identification and reporting on the microarray TIF images generated by the SureScan Dx Microarray Scanner.

J. Substantial Equivalence Information:

1. Predicate device name:

   Affymetrix CytoScan Dx Assay

2. Predicate device 510(k) number:

   DEN130018

4. Comparison with predicate:

SIMILARITIES		
Item	**Device** **GenetiSure Dx Postnatal Assay**	**Predicate** **Affymetrix CytoScan Dx Assay**
Indications for Use	GenetiSure Dx Postnatal Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) and copy-neutral loss of heterozygosity (cnLOH) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. GenetiSure Dx Postnatal Assay is intended for the detection of CNVs and cnLOH associated with developmental delay, intellectual disability, congenital anomalies, dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate.	CytoScan® Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate.

Indications for Use, continued	Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the SureScan Dx Microarray Scanner System and analyzed by CytoDx Software.	Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the GeneChip® System 3000Dx and analyzed by Chromosome Analysis Suite Dx Software (ChAS Dx Software).
Limitation of Indications for Use	This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.	This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.
Sample Type	EDTA-anticoagulated Peripheral whole blood	Same.
Technology	Microarray for comparative genomic hybridization	Same.
Quality Controls	In-process QC checks, external controls and array QC metrics are used to monitor and assess the quality of results.	Same.

DIFFERENCES		
Item	**Device** **GenetiSure Dx Postnatal Assay**	**Predicate** **Affymetrix CytoScan Dx Assay**
Array Format	60-mer probes Four microarrays on a single 1”x 3” glass slide	25-mer oligos Individual microarrays housed in a GeneChip cartridge
Method of Array Manufacture	On slide (in-situ) synthesis of probes using ink-jet printing	On-wafer synthesis of probes using photolithography

DNA Fragmentation/ Labeling	Fragmented DNA is directly labelled with fluorescent dye (Cy3 and Cy5) before hybridization. Data is produced in two intensity channels which are then compared to generate a LogRatio	Fragmented DNA is PCR amplified and then labelled with biotin before hybridization. Single channel data is produced which is later compared to an in silico reference to produce a LogRatio.
Hybridization	Cohybridization of labeled sample and reference for direct on-array comparison	Hybridization of single labeled sample which is compared to an in silico reference.
Washing / Staining of Microarrays	Manual washing process in accordance with instruction for the validated diagnostic assay	Automated processing with FS450Dx fluidics station for both washing and staining steps
Instrument	SureScan Dx Microarray Scanner	GeneChip System 3000Dx Scanner

K. Standard/Guidance Document Referenced:

- CLSI EP07-A2 Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition.
- CLSI EP12-A2 User Protocol for Evaluation of Qualitative Test Performance.
- EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.
- CLSI MM13-A Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods; Approved Guideline.
- CLSI MM21 Genomic Copy Number Microarrays for Constitutional Genetic and Oncology Applications –First Edition.

L. Test Principle:

The GenetiSure Dx Postnatal Assay uses array comparative genomic hybridization (aCGH) and single nucleotide polymorphism (SNP) technology (referred to as CGH +SNP microarray) to detect chromosomal imbalances in genomic DNA (gDNA) isolated from 200µL of EDTA-anticoagulated peripheral blood using the QIAamp DSP DNA Blood Mini kit. The gDNA is quantified and 0.5 µg (500ng) is processed in parallel with 0.5 µg of sex-matched reference DNA included in the GenetiSure Dx DNA Labeling Kit. gDNA is disgested with restriction enzymes and labeled with fluorescent dyes in the Labeling Kit. The subject samples is labeled with cyanine 5 (Cy5) dye and the sex-matched reference samples is labeled with cyanine 3 (Cy3) dye. Sex-matched reference DNAs are used for data normalization and aberration detection on a per test sample basis. Labeled samples are co-hybridized onto a single GenetiSure Dx microarray using the reagents in the GenetiSure Dx Hybridization Kit, and Hybridization Chamber Kit. The in situ hybridization technique allows detection and mapping of DNA sequence copy differences between the two differentially labeled genomic DNAs (subject/test sample and a reference sample).

The microarray contains complementary nucleic acid sequences synthesized in situ on a microarray slide: approximately 107,000 probes for CNV analysis, and approximately 59,000 bi-allelic SNP probes. The CNV probes are distributed across the entire genome with a higher density of probes in regions designated by the International Standards for Cytogenomic Arrays (ISCA) consortium to be of clinical interest.

The relative amount of the hybridized target sequences is computed by the Analytics module, based on the relative intensities of the fluorophores in the patient and reference samples hybridized to each of the probe sequences. After hybridization and subsequent washing with the GenetiSure Dx Wash Buffer Set, the microarrays are scanned by SureScan Microarray Scanner. The scanner generated image is processed using the Agilent CytoDx Software, and the image data are converted to numeric data using the Feature Extraction module of the software. Internal control probes on each array are used to calculate array quality metrics and assess the quality of the data. Additional array QC metrics are employed to detect for potential anomolies. Locations of copy number variation (CNVs) and copy-neutral loss of heterozygosity (cnLOH) in the DNA segments of the subject sample genome are identified. The aberrations identified in a patient sample by the CytoDx algorithms can be viewed from the Triage View screen of the CytoDx software. The reported CNVs and cnLOH are interpreted by a Board Certified Cytogeneticist, Molecular Geneticist, Molecular Pathologist, or similarly qualified clinician who has been trained to identify the clinically relevant CNVs, determine clinical significance, and report out these findings.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Two reproducibility studies were conducted. The first was a site-to-site reproducibility study, and the second was a between-lot reproducibility study.

Study 1. Site-to-site reproducibility:
A reproducibility study was performed with 48 genomic DNA samples purified from cell lines representing a range of aberrations detected (gains, losses and copy neutral loss of heterozygosity (cnLOH)). Each sample was tested at 3 sites by 2 operators in triplicate across 3 non-consecutive weeks for a total of 18 replicates (3x2 x 3). The entire study was performed using one lot of reagents including each of the following: Qiagen DSP extraction kits, GenetiSure Dx Complete DNA Labeling kit, microarrays, gaskets, Oligo aCGH/ChIP-on-chip Hybridization Kit, Cot 1 DNA, Oligo aCGH/ChIP-on-chip Wash Buffer 1, Oligo aCGH/ChIP-on-chip Wash Buffer 2, and SureScan Dx Microarray Scanner.

The aberrations met the following criteria: common syndromes (i.e., known syndromic regions), analytically challenging regions, claimed minimal resolution, varying aberration size ranges, and genomic coverage of aberrations. Multiple samples had multiple aberrations spanning multiple criteria. Test sample selection criteria encompassed aberrations expected to be found in normal whole blood

samples.

For a given test sample (n=48), each aberration identified, regardless of expected pathogenicity, in each of the 18 replicates was reported. A total of 325 unique aberrations (87 gains, 193 losses, and 45 cnLOH) were detected from the 48 gDNA samples across their replicates. These aberrations were distributed across all 24 chromosomes in the human genome, with a collective coverage of 41.8% (16.7% for gains, 11.3% for losses, 22.4% for gains or losses, and 27.7% for cnLOH).

All individual aberrations reported were compared to their respective replicates (18 replicates for each aberration) by pairwise replicate analysis (PRA), requiring at least 50% overlap of chromosomal coordinates for confirmation. The aberrations reported across the replicate arrays, for a given sample, were first divided into specific "unique" aberration groups, each representing a specified genomic range with a specified aberration type (gain, loss, or cnLOH). Individual replicates for a unique aberration were then evaluated using pairwise analyses:

- For replicates i and j, where $i \neq j$, an aberration found in replicate i was considered pairwise confirmed if it had $\geq 50\%$ overlap with an aberration found in replicate j.
- If either or both replicates i or j had a gap, the gap region was considered as not being in agreement for the overlap calculation; no gap filling or segment joining was performed.
- The replicates must have the same copy number state (i.e., gain or loss) to be confirmed.
- An alternative, more stringent 80% overlap criteria was also assessed.

Percent Pairwise Replicate Agreement was calculated across all replicates and also individually by variable type (site, operator, test sample, processing week, probe size, length (kb) and aberration type such as gain, loss, or LOH). Additional breakpoint/endpoint agreement was assessed

The following statistics are reported: positive percent agreement (PPV), call rate, percent overlap, length, percent coefficient of variance (% CV), median percent absolute endpoint deviation, and standard deviation (SD) for both left and right endpoints.

The results demonstrated that when comparing all replicates of all test samples across all days, sites, and operators, using a 50% aberration overlap criterion, the overall pairwise replicate agreement across all CNVs was 85.0% (Table 1). Pairwise replicate agreement across the various kb (length) bins ranged from 75.9% to 100%. For copy number gains, the overall agreement was 85.7%; for losses, the overall agreement was 84.6%. For cnLOH, the overall pairwise replicate agreement was 89.1%. Applying a more stringent 80% overlap criterion produced overall agreements of 82.3% for CNVs, 84.4% for gain, 81.3% for losses, and 87.9% for LOH. When assessing specifically the agreement between replicates for positive aberration calls by PPA analysis, the agreement was 89.3% for all copy number calls and 92.7% for

LOH using the 50% overlap criterion. Call rate averaged 78.1% for CNVs, and 74.9% for cnLOH. The results are shown in Table 1.

Table 1. Reproducibility of Aberrations Categorized by Size (in kb) and Type Based on Call Rate, Pairwise Agreement between Replicates and Positive Percent Agreement (PPA) for Two Criteria (50% and 80% Overlap) in All Regions in the Site-to-Site Study.

Aberration Type	Aberration Range (kb)	# Aberrations	Call Rate (%)	Pairwise Replicate Agreement (%)		PPA (%)	
				50% Overlap	80% Overlap	50% Overlap	80% Overlap
GAIN	**10 - 50**	5	51.2	82.5	82.5	82.9	82.9
	50 - 100	3	68.7	96.3	96.3	97.3	97.3
	100 - 200	13	50.5	79.9	79.8	80.1	80.0
	200 - 500	26	82.7	86.3	84.6	91.5	89.4
	500 - 1000	9	79.7	80.2	78.9	87.6	86.0
	1000 - 2000	7	72.1	90.7	82.8	92.4	81.6
	2000 - 5000	11	65.1	75.9	75.9	79.7	79.7
	5000 +	13	93.2	98.4	98.4	99.1	99.1
	Total	87	73.8	85.7	84.4	89.9	88.2
LOSS	**10 - 50**	14	51.6	76.8	76.1	77.6	76.2
	50 - 100	2	100.0	100.0	89.5	100.0	89.5
	100 - 200	23	81.4	82.3	78.1	88.1	82.9
	200 - 500	31	82.6	81.8	75.5	86.3	78.7
	500 - 1000	55	72.8	81.2	76.2	85.2	78.5
	1000 - 2000	30	83.3	86.4	85.9	91.5	91.0
	2000 - 5000	18	88.9	87.4	85.1	89.9	87.3
	5000 +	20	100.0	100.0	100.0	100.0	100.0
	Total	193	80.1	84.6	81.3	89.0	84.8
ALL CNVs	**Total**	280	78.1	85.0	82.3	89.3	85.8
cnLOH	**5000 - 10000**	21	50.6	77.1	76.8	77.4	76.8
	10000 - 20000	11	91.5	99.0	96.4	99.4	96.7
	20000 +	13	100.0	100.0	98.4	100.0	98.4
	Total	45	74.9	89.1	87.9	92.7	91.1

When results were grouped into various bins by the number of probes in an aberration, rather than length in kb, using the 50% overlap criterion, the overall pairwise replicate agreement was similar to the above: 86.2% for CNVs (ranging from 70.6% to 100%), 86.1% for gains alone, 86.3% for losses alone, and 89.1% for LOH. Using the 80% overlap criterion, overall agreements were 84.6% for CNVs, 85.3% for gains, 84.2% for losses, and 88.4% for LOH. PPA for the 50% overlap

criterion was 90.9% and 92.7% for CNVs and cnLOH, respectively. Call rate averaged 78.1% for CNVs, and 74.9% for cnLOH. The results are shown below in 2.

Table 2. Reproducibility of Aberrations Categorized by Probe Number and Type Based on Call Rate, Pairwise Agreement between Replicates and PPA for Two Criteria (50% and 80% Overlap) in All Regions in the Site-to-Site Study.

Aberration Type	Aberration Range (# Probes)	# Aberrations	Call Rate (%)	Pairwise Replicate Agreement (%)		PPA (%)	
				50% Overlap	80% Overlap	50% Overlap	80% Overlap
GAIN	5 - 7	11	38.0	76.5	76.5	69.0	69.0
	7 - 10	15	54.1	70.6	69.4	72.8	70.6
	10 - 15	23	87.9	89.4	88.3	94.0	92.7
	15 - 20	11	66.5	82.4	79.9	86.8	83.1
	20 - 30	9	89.6	97.5	97.5	97.9	97.9
	30 - 100	3	70.3	93.0	93.0	95.0	95.0
	100 - 500	3	72.3	90.2	90.2	93.2	93.2
	500 +	12	100.0	100.0	100.0	100.0	100.0
	Total	87	73.8	86.1	85.3	90.5	89.4
LOSS	5 - 7	36	61.1	76.6	75.6	80.9	79.1
	7 - 10	39	65.5	77.6	75.4	82.8	79.6
	10 - 15	42	81.9	85.5	81.0	90.5	85.0
	15 - 20	18	96.9	95.9	94.0	97.6	95.7
	20 - 30	16	87.5	89.1	85.7	91.6	87.9
	30 - 100	10	92.2	93.2	92.9	96.3	96.0
	100 - 500	17	100.0	100.0	100.0	100.0	100.0
	500 +	15	100.0	100.0	100.0	100.0	100.0
	Total	193	80.1	86.3	84.2	91.1	88.5
ALL CNVs	Total	280	78.1	86.2	84.6	90.9	88.8
cnLOH	100 to 200	25	54.8	80.3	80.3	82.0	82.0
	200 to 500	13	100.0	100.0	97.7	100.0	97.7
	> 500	7	100.0	100.0	100.0	100.0	100.0
	Total	45	74.9	89.1	88.4	92.7	91.8

For endpoint analysis, only those CNVs detected and with the same copy number state (gain/loss) were assessed for endpoint agreement (i.e., 'no calls' in replicates could not be included). Endpoint agreement is assessed by median % absolute endpoint deviation, standard deviation of left endpoint, and standard deviation of right endpoint. For copy number aberrations (CNVs), the Median % Absolute Endpoint Deviation was 3% (mean) when analyzed by both probe number and size (in kb) (Table 3 and 4). For cnLOH calls, the Median % Absolute Endpoint Deviation was 1% (mean) for both analyses. In addition, the average % overlap for all pairwise confirmed aberration was 82.1% (by probe number) and 80.8% (by size) for CNVs, and 84.7% (by probe number) and 84.5% (by size) for cnLOH calls.

Table 3. Reproducibility of Aberration Breakpoints by Probe Number

Aberration Type	Aberration Range (# Probes)	N	% CV Aberration Length	Average % Overlap	% Median Absolute Endpoint Deviation (x100)	SD Left Endpoint (# Probes)	SD Right Endpoint (# Probes)
			Mean (Min, Median, Max)		Mean (Min, Median, Max)		
GAIN	5 - 7	11	3.0 (0.0, 0.0, 11.7)	51.9	0.01 (0.00, 0.00, 0.13)	0.1 (0.0, 0.0, 0.6)	0.1 (0.0, 0.0, 0.5)
	7 - 10	15	9.0 (0.0, 6.5, 35.4)	55.1	0.05 (0.00, 0.00, 0.31)	0.5 (0.0, 0.4, 2.0)	0.5 (0.0, 0.0, 2.9)
	10 - 15	23	5.1 (0.0, 4.5, 19.0)	86.6	0.01 (0.00, 0.00, 0.08)	0.4 (0.0, 0.2, 2.7)	0.2 (0.0, 0.0, 1.5)
	15 - 20	11	5.0 (0.0, 3.0, 17.0)	74.8	0.02 (0.00, 0.00, 0.11)	0.8 (0.0, 0.4, 2.8)	0.1 (0.0, 0.0, 0.5)
	20 - 30	9	3.5 (0.0, 1.5, 19.5)	96.5	0.01 (0.00, 0.00, 0.05)	0.8 (0.0, 0.0, 5.1)	0.4 (0.0, 0.3, 1.7)
	30 - 100	3	0.9 (0.0, 1.3, 1.4)	90.2	0.00 (0.00, 0.00, 0.01)	0.1 (0.0, 0.0, 0.3)	0.3 (0.0, 0.5, 0.5)
	100 - 500	3	0.1 (0.0, 0.2, 0.2)	87.3	0.00 (0.00, 0.00, 0.00)	0.2 (0.0, 0.0, 0.5)	0.0 (0.0, 0.0, 0.0)
	500 +	12	0.1 (0.0, 0.1, 0.3)	99.9	0.00 (0.00, 0.00, 0.00)	1.0 (0.0, 0.5, 3.6)	0.8 (0.0, 0.2, 3.2)
	Total	87	4.3 (0.0, 2.4, 35.4)	81.4	0.02 (0.00, 0.00, 0.31)	0.5 (0.0, 0.3, 5.1)	0.3 (0.0, 0.0, 3.2)
LOSS	5 - 7	36	6.9 (0.0, 7.4, 21.1)	65.2	0.03 (0.00, 0.00, 0.20)	0.1 (0.0, 0.0, 1.1)	0.4 (0.0, 0.3, 1.5)
	7 - 10	39	6.6 (0.0, 4.5, 28.6)	68.2	0.02 (0.00, 0.00, 0.22)	0.1 (0.0, 0.0, 0.9)	0.5 (0.0, 0.3, 2.2)
	10 - 15	42	9.0 (0.0, 3.6, 66.1)	81.0	0.05 (0.00, 0.00, 0.60)	0.8 (0.0, 0.0, 6.8)	0.5 (0.0, 0.3, 3.0)
	15 - 20	18	7.4 (0.0, 1.7, 53.6)	93.2	0.10 (0.00, 0.00, 1.42)	1.2 (0.0, 0.1, 9.4)	0.7 (0.0, 0.2, 9.8)
	20 - 30	16	8.5 (0.0, 0.4, 47.3)	87.7	0.01 (0.00, 0.00, 0.18)	1.4 (0.0, 0.1, 6.9)	0.7 (0.0, 0.0, 5.1)
	30 - 100	10	3.9 (0.0, 0.3, 24.0)	92.1	0.01 (0.00, 0.00, 0.04)	0.1 (0.0, 0.0, 1.0)	1.2 (0.0, 0.0, 8.9)
	100 - 500	17	0.3 (0.0, 0.1, 1.3)	99.9	0.00 (0.00, 0.00, 0.00)	0.3 (0.0, 0.0, 2.6)	0.2 (0.0, 0.2, 0.4)
	500 +	15	0.1 (0.0, 0.1, 0.2)	100.0	0.00 (0.00, 0.00, 0.00)	0.3 (0.0, 0.0, 3.7)	0.3 (0.0, 0.0, 1.1)
	Total	193	6.2 (0.0, 1.3, 66.1)	82.4	0.03 (0.00, 0.00, 1.42)	0.5 (0.0, 0.0, 9.4)	0.5 (0.0, 0.0, 9.8)
ALL CNVs	Total	280	5.6 (0.0, 1.9, 66.1)	82.1	0.03 (0.00, 0.00, 1.42)	0.5 (0.0, 0.0, 9.4)	0.4 (0.0, 0.0, 9.8)
cnLOH	100 - 200	25	4.8 (0.0, 4.8, 13.4)	67.8	0.01 (0.00, 0.00, 0.11)	4.7 (0.0, 0.3, 25.6)	3.5 (0.0, 0.5, 17.2)
	200 - 500	13	7.0 (4.1, 6.1, 12.5)	98.2	0.00 (0.00, 0.00, 0.02)	9.7 (0.0, 5.7, 32.3)	8.0 (0.0, 2.9, 28.4)
	> 500	7	6.0 (4.1, 5.4, 9.6)	98.6	0.01 (0.00, 0.00, 0.04)	32.2 (1.1, 36.4, 74.8)	9.3 (0.0, 2.6, 42.9)
	Total	45	5.6 (0.0, 5.4, 13.4)	84.7	0.01 (0.00, 0.00, 0.11)	10.4 (0.0, 3.0, 74.8)	5.7 (0.0, 0.9, 42.9)

Table 4. Reproducibility of Aberration Breakpoints by Size (kb)

Aberration Type	Aberration Range (kb)	N	% CV Aberration Length	Average % Overlap	% Median Absolute Endpoint Deviation (x100)	SD Left Endpoint (# Probes)	SD Right Endpoint (# Probes)
			Mean (Min, Median, Max)		Mean (Min, Median, Max)		
GAIN	20 - 50	6	4.2 (0.0, 0.0, 14.7)	65.5	0.00 (0.00, 0.00, 0.00)	1.0 (0.0, 0.0, 3.5)	0.0 (0.0, 0.0, 0.0)
	50 - 100	6	8.1 (0.0, 5.0, 27.3)	80.5	0.01 (0.00, 0.00, 0.03)	5.2 (0.0, 0.7, 21.9)	1.5 (0.0, 0.0, 5.4)
	100 - 200	16	4.0 (0.0, 0.0, 26.5)	67.8	0.00 (0.00, 0.00, 0.00)	2.5 (0.0, 0.0, 36.2)	3.6 (0.0, 0.0, 25.1)
	200 - 500	30	5.5 (0.0, 0.0, 73.9)	72.3	0.02 (0.00, 0.00, 0.36)	11.2 (0.0, 0.0, 264.8)	11.6 (0.0, 0.0, 120.1)
	500 - 1000	6	6.3 (0.0, 0.6, 23.6)	69.0	0.00 (0.00, 0.00, 0.01)	40.6 (0.0, 4.1, 136.6)	1.3 (0.0, 0.0, 7.9)
	1000 - 2000	4	3.2 (0.0, 1.7, 9.5)	74.4	0.01 (0.00, 0.00, 0.02)	9.9 (0.0, 0.0, 39.7)	48.7 (0.0, 7.9, 178.8)
	2000 - 5000	18	3.0 (0.0, 0.6, 37.3)	88.1	0.00 (0.00, 0.00, 0.06)	54.7 (0.0, 4.7, 751.3)	18.8 (0.0, 0.0, 145.9)
	5000 +	17	0.1 (0.0, 0.1, 0.5)	99.9	0.00 (0.00, 0.00, 0.00)	28.5 (0.0, 11.1, 162.5)	6.0 (0.0, 0.0, 48.2)
	Total	103	4.0 (0.0, 0.1, 73.9)	80.7	0.01 (0.00, 0.00, 0.36)	21.0 (0.0, 0.0, 751.3)	10.3 (0.0, 0.0, 178.8)
LOSS	10 - 50	20	4.0 (0.0, 0.0, 35.0)	74.6	0.00 (0.00, 0.00, 0.00)	0.0 (0.0, 0.0, 0.3)	0.9 (0.0, 0.0, 7.9)
	50 - 100	4	5.4 (0.0, 4.7, 12.1)	88.1	0.00 (0.00, 0.00, 0.00)	4.9 (0.0, 4.6, 10.2)	0.0 (0.0, 0.0, 0.0)
	100 - 200	33	9.1 (0.0, 0.0, 187.7)	89.9	0.00 (0.00, 0.00, 0.11)	11.9 (0.0, 0.0, 257.0)	2.2 (0.0, 0.0, 27.6)
	200 - 500	24	3.6 (0.0, 0.0, 31.5)	83.8	0.02 (0.00, 0.00, 0.35)	4.2 (0.0, 0.0, 45.1)	9.5 (0.0, 0.0, 111.8)
	500 - 1000	31	9.8 (0.0, 2.1, 45.6)	86.5	0.00 (0.00, 0.00, 0.07)	30.0 (0.0, 0.0, 259.4)	44.5 (0.0, 0.0, 223.5)
	1000 - 2000	15	2.1 (0.0, 0.0, 22.1)	93.7	0.00 (0.00, 0.00, 0.02)	15.7 (0.0, 0.0, 235.5)	10.4 (0.0, 0.0, 64.6)
	2000 - 5000	6	3.5 (0.0, 0.1, 17.9)	98.2	0.00 (0.00, 0.00, 0.00)	11.0 (0.0, 0.0, 66.1)	10.9 (0.0, 0.0, 60.1)
	5000 +	33	1.1 (0.0, 0.0, 15.8)	98.8	0.00 (0.00, 0.00, 0.04)	20.3 (0.0, 0.0, 216.8)	60.0 (0.0, 0.0, 870.1)
	Total	166	5.3 (0.0, 0.0, 187.7)	89.3	0.00 (0.00, 0.00, 0.35)	14.5 (0.0, 0.0, 259.4)	23.5 (0.0, 0.0, 870.1)
ALL CNVs	Total	269	4.8 (0.0, 0.0, 187.7)	86.3	0.01 (0.00, 0.00, 0.36)	17.0 (0.0, 0.0, 751.3)	18.4 (0.0, 0.0, 870.1)
cnLOH	5000 - 10000	23	3.5 (0.0, 1.7, 17.7)	63.6	0.01 (0.00, 0.00, 0.11)	132.6 (0.0, 4.2, 1637.7)	206.1 (0.0, 92.4, 938.9)
	10000 - 20000	18	9.8 (0.0, 8.4, 27.5)	80.1	0.02 (0.00, 0.00, 0.17)	791.8 (0.0, 890.2, 2038.5)	536.4 (0.0, 33.9, 2487.3)
	20000 +	5	1.7 (0.4, 1.7, 3.0)	91.3	0.00 (0.00, 0.00, 0.01)	554.6 (14.3, 262.4, 1819)	172.3 (15.4, 86.9, 631.1)
	Total	46	5.7 (0.0, 2.3, 27.5)	73.7	0.01 (0.00, 0.00, 0.17)	436.4 (0.0, 107.3, 2038.5)	331.7 (0.0, 76.6, 2487.3)

A second supplemental study was conducted to increase the number of samples and representative CNV regions to align with the predicate evaluation using a panel of 48 genomic DNA encompassing a wide variety of chromosomal aberrations of interest. A total of 315 unique aberrations (103 CN gains, 166 CN losses, and 46 cnLOH) were detected from the 48 gDNA samples. These aberrations were distributed across all 24 chromosomes in the human genome, with collective genome coverage of 42.0% (18.6% for CN gains, 11.6% for CN losses, 27.1% for all CNVs, and 18.4% for cnLOH).

A total of nine (9) replicates for each sample in the diverse 48 aberrant gDNA panel were processed by multiple operators using combinations of three (3) reagent lots and three (3) scanner instruments, across three (3) processing weeks at a single site, for a total of 432 data points. The study spanned across 3 weeks (runs, or sample processing batches).

Individual aberrations called within each processed test sample were compared to their respective replicates (9 replicates for each aberration representing 3x3 reagent lot/scanner combinations) by pairwise replicate analysis (PRA), requiring at least 50% overlap of chromosomal coordinates for confirmation (agreement). Agreement was assessed separately for small copy number variants (CNVs, 5-20 probes contained within the aberration), larger CNVs (>20 probes), or cnLOH regions. The results demonstrate that the pre-defined acceptance criteria were met for each category with a pairwise replicate agreement of 83.33%, 98.39%, and 80.80%, respectively. Results were similar when using a more stringent 80% overlap criterion for pairwise replicate agreement. In addition, no substantial differences were observed when the pairwise replicate agreement was assessed separately for inter-lot vs. intra-lot replicate pairs, or for inter-scanner vs. intra-scanner replicate pairs.

Study 2. Lot-to-Lot reproducibility:

A lot-to-lot reproducibility study was conducted using first a set of 6 samples and then a second set of 48 samples containing a range of chromosomal aberrations (gains, losses, and cnLOH). Samples were processed by one (1) operator, using combinations of three (3) reagent lots analyzed on three (3) scanner instruments across five (5) processing weeks at a single site. Aberrations were distributed across most of the 24 chromosomes in the human genome, with the exception of chromosomes 7, 17, 19, and 20. Data analysis methods were the same as those used in the site-to-site reproducibility study.

Individual aberrations called within each processed test sample were compared to their respective replicates (9 replicates for each aberration, representing 3x3 reagent-lot/scanner combinations) by pairwise replicate analysis (PRA), requiring at least 50% overlap of chromosomal coordinates for confirmation. Agreement was assessed separately for small copy number variants (CNVs, 5-20 probes contained within the aberration), larger CNVs (>20 probes), or cnLOH regions. The results demonstrate that the pre-defined acceptance criteria were met for each category with a pairwise

replicate agreement of 83.33%, 98.39%, and 80.80%, respectively. Results were similar when using a more stringent 80% overlap criteria for pairwise replicate agreement. In addition, no substantial differences were observed when the pairwise replicate agreement was assessed separately for inter-lot vs. intra-lot replicate pairs, or for inter-scanner vs. intra-scanner replicate pairs.

Data were further refined by size, probe number, aberration type, and study variable (e.g. reagent lot, scanner, processing week). Alternative metrics of positive percent agreement, call rate, and breakpoint accuracy/endpoint deviation were conducted and consistent with data observed in the site-to-site reproducibility.
he results demonstrated that when comparing all replicates of all test samples across all lots, scanners, and weeks, using a 50% aberration overlap criteria, the overall pairwise replicate agreement across all sizes of copy number gains and losses was 89.0%. Pairwise replicate agreement across the various kb bins ranged from 76.9% to 100%. For copy number gains, the overall agreement was 85.4%; for copy number losses, the overall agreement was 91.3%. For cnLOH, the overall pairwise replicate agreement was 80.8%. Applying a more stringent 80% overlap criteria produced overall agreements of 87.2% for all CNVs (gains or losses) combined, 84.0% for CN gains, 89.2% for CN losses, and 76.0% for cnLOH.

When assessing specifically the agreement between replicates for positive aberration calls by PPA analysis, the agreement was 93.0% for all copy number calls and 87.3% for cnLOH using the 50% overlap criteria. Call rate averaged 83.0% for CNVs, and 75.6% for cnLOH.

DNA extraction precision:

A panel of twenty-four (24) samples was tested by each operator. The gDNA from the samples was extracted using the same lot of the QIAamp DSP DNA Blood Mini kit, at one site, in duplicate, by 3 operators, on 3 separate days, for a total of 432 extractions (3 operators x 3 days x 2 duplicates x 24 samples). Each of the three operators labelled a set of 48 extracted samples (24 different samples x 2 extractions) per week for 3 weeks for a total of 144 test results run per operator over the course of the study. The extracted gDNA replicates were tested in the GenetiSure Dx Postnatal Assay in 3 weeks, each corresponding to a specific day of extraction.

A total of 160 unique aberrations (65 gains, 79 losses, and 16 cnLOH) were detected from the 24 gDNA samples across their replicates. These aberrations were distributed across all chromosomes in the human genome with the exception of Chr17 and Chr20, with a collective coverage of 25.1% (13.8% for gains, 8.8% for losses, 16.6% for gains or losses, and 8.9% for cnLOH). Primary analysis was performed using pairwise comparison of aberration results on each of the 18 replicates (3 operators x 3 days x 2 duplicates) for each sample. An aberration was considered confirmed if at least 50% of the region of aberration overlapped between the replicates being compared.

The individual Pairwise Replicate Agreement % values stratified by week or operator

were similar to each other and the overall agreement averages 82.17% for CNVs called by 5-20 probes, 98.47% for CNVs called by >20 probes, and 81.15% for cnLOH, which further supports that similar assay performance can be expected from different extractions, personnel, days, and samples.

b. Linearity/assay reportable range:

N/A

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Array and Reagent Stability:

Stability studies were performed to demonstrate the stability of the GenetiSure Dx Postnatal Assay and reagents (controls were included in the evaluation). Stability testing consisted of four different arms of the study:

- Shelf Life: testing after storage of assay components under recommended conditions at defined intervals after manufacturing.
- Multi-use testing: testing after components of the assay that are stored at -15°C to -25°C are subject to different numbers of freeze/thaw cycles.
- Transport: Similar to Shelf life testing, but assay components were subject to a transportation simulation prior to storage at recommended conditions.
- In-use testing: testing after different components of the assay are stored for various times after preparation or testing where reaction intermediates are stored for various times.

A leukocyte-depleted whole blood sample spiked in with human B-lymphocyte cell with known genotype, a whole blood from an anonymous male donor, and the Agilent male reference DNA combined with Agilent female reference DNA were used with a minimum of 2 replicates at a minimum of 4 time points in the study.

The final stability was determined based on the time point prior to that at which the 95% confidence interval of any of the QC metrics first overlaps with the acceptance criteria. Interim stability is defined based on the maximum duration for which the 95% confidence intervals for all QC metrics do not overlap with the acceptance criteria.

Results of the study to date indicate that all tested conditions pass all metrics under all conditions tested, supporting a shelf life of the assay components of 12 months. In addition, multi-use and in-use testing support the tested conditions of the assay:

All reagents should be stored in the dark. The stability claims are as follows:

- 8x freeze/thaw for Labeling Kit components;
- 16x freeze/thaw or 120 days' storage at -15°C to -25°C for reconstituted 10x Blocking Agent;

- 16x freeze/thaw for Cot-1 DNA;
- 60 days' storage of an open microarray package under specified conditions;
- 30 days' storage of the digested gDNA or labeled DNA reaction intermediates at -15°C to -25°C.

Whole Blood Stability

To determine the stability of whole blood specimens prior to gDNA isolation, 24 whole blood specimens, 12 male and 12 female, were obtained from a blood bank and gDNA was isolated from the specimens at 1, 3, 7, and 10 days after initial collection.

A list of aberrations for each sample extracted on Days 3, 7 and 10 were reported and compared with the 'Day 1' list for the same sample. An aberration from the 'Day 1' sample was considered confirmed in the stored samples if the test result identifies a region of aberration that overlaps the 'Day 1' region by at least 50%. Blood was considered stable when stored for a given time when 75% of small gain/loss aberrations, called by 5-20 copy number probes, and 90% of the larger gain/loss aberrations, called by >20 probes, were confirmed.

An additional analysis was also performed using an 80% overlap criterion. The results of both the 50% and 80% overlap analysis methods demonstrated that whole blood specimens may be stored for up to 10 days at 2–8ºC prior to gDNA isolation. Samples stored for this period of time and processed with the GenetiSure Dx Postnatal Assay produced acceptable results.

d. Detection limit:

DNA input:
The amount of genomic DNA recommended for testing per samples with the GenetiSure Dx Postnatal Assay is 500ng. To determine the performance of the assay across a range of genomic DNA input concentrations, 24 gDNA samples with known chromosomal aberrations were tested. These DNA samples were tested in the assay using 2 lots of reagents across a range of varied DNA input levels from 0.125 µg (125 ng) to 1 µg (1000 ng), with 0.5 µg (500 ng) as the recommended input quantity (standard).

The study assessed the impact of various gDNA input on aberration calling and determined the upper and lower limits of detection (ULOD and LLOD) of the assay by comparing the percentage of aberrations confirmed at each non-standard DNA input level against pre-defined acceptance criteria. The study data, and supplemental data generated under similar study conditions, support a conservative LLOD at 375 ng and a common ULOD at 1000 ng for both copy number and cnLOH aberrations. For copy number aberrations only, the LLOD could be further reduced to 250 ng. Data from this study support the use of 500 ng as the recommended input amount.

Mosaicism:
To determine the level of mosaicism reliably detected by the GenetiSure Dx Postnatal Assay, 24 aberrant cell line DNAs containing known copy number changes were mixed with a reference background DNA in different percentages to mimic various levels of mosaicism. 12 male and 12 female DNA samples, each with at least 4 previously identified aberrations, were each mixed with sex-matched reference DNA in the following ratios: 1:0, 9:1, 3:1, 1:1; 1:3, 1:9, and 0:1.

Large copy number aberrations could be reliably detected when present in a 50% or greater admixture. Some aberrations were correctly identified at lower than a 50% level, but the sensitivity of detection was reduced. Results were similar for both gains and losses. Smaller aberrations could not be reliability detected in any of the admixtures.

e. Analytical specificity:

Interfering Substances:
To assess the impact of interfering substances on the GenetiSure Dx Postnatal Assay, a study evaluating the impact of hemoglobin, conjugated bilirubin, unconjugated bilirubin and triglycerides (triolein) spiked into whole blood prior to gDNA isolation was conducted. Blood drawn from 12 phenotypically normal males and 12 phenotypically normal females was used in the testing. The list of aberrations for each sample containing a given interferent was reported and compared with the 'non-adulterated control' list for the same sample. An aberration was considered confirmed if the test result identified a region of aberration that overlaps between the sample and control by at least 50%. The test was considered robust to a given interferent when 75% of the gains/losses in the 5-20 probe category and 90% of the gains/losses in the >20 probe category in the 'non-adulterated control' were confirmed. No interference was observed with any of the tested conditions. The results of the study met the acceptance criteria.

Cross-Contamination:
To determine the effect of potential gDNA carry-over from 1 array to the next when processing multiple arrays, 2 male and 2 female gDNA samples from cell lines, each with distinctive sets of known chromosomal aberrations, were tested across multiple microarray slides under conditions that would either allow or prevent detection of cross contamination between the adjacent arrays on the slides. Four (4) microarray slides served as the "non-contaminated condition" with four replicates of the same sample placed on each of the four arrays of the slides. Six (6) slides served as a test for "potential cross-contamination" that could occur between adjacent arrays within a single slide during the hybridization set–up or overnight incubation. For these slides, the sample replicates were alternated on the slide with sample replicates from a different sample. The CNV and cnLOH aberration results from the "potential cross-contamination" microarray slides were compared to the aberration results from the "non-contaminated condition" microarray slides, using a 50% overlap criterion, to determine if detectable cross contamination had occurred on the test slides.

Additionally, gasket related cross-contamination was evaluated by use of three (3) different lots of gasket slides. No suspected cross contamination was detected.

f. Assay cut-off:

N/A

2. Comparison studies:

a. Accuracy — comparison to orthogonal methods:

Accuracy of the GenetiSure Dx Postnatal Assay results was assessed by comparing the CNVs identified by GenetiSure Dx Postnatal Assay to the results obtained using comparator microarray methods. A total of 556 out of 626 samples were eligible for testing based. Samples were excluded based on pre-specified exclusion criteria (e.g., lack of informed consent, lack of sufficient gDNA). The sample panel consisted of 451 aberrant genomic DNA (gDNA) samples derived from established commercial cell lines, 76 archived clinical gDNA samples isolated from whole blood specimens of anonymized patients, 5 globally recognized syndrome reference panel gDNA samples, and 24 fresh blood-derived gDNA samples extracted from whole blood of phenotypically normal subjects. The samples were selected to maximize the variation across the genome with consideration for gain and loss segments of various sizes/number of probes, chromosomal representation, CNV regions in genic and non-genic regions, and in telomeric and centromeric regions. A total of 2187 CNV regions covered 91% of the genome and were more prevalent in non-telomeric/non-centromeric regions than in telomeric/centromeric (1337 regions vs 1130 regions). A total of 21% (534 out of 2187 regions) of the CNVs had high (>45%) GC content.

Due to the lack of an applicable universal comparator, two independent (non-Agilent) commercially available microarray based assays analytically validated for copy number detection were employed to assist accuracy assessment of CNV aberrations and resolve discrepancies. The samples were tested with the GenetiSure Dx Postnatal Assay using standard procedures in a designated Agilent laboratory.

Three methods were used to analyze the data (Figure 1). Method 1 and Method 2 compared Agilent results with the two platform results each separately. Method 3 generated a composite dataset by consolidating results from these two platforms. A description of the differences between the methods is shown in Figure 1 and Table 5. The main differences were in the definition of comparator and overlap.

A target Agilent aberration was deemed “confirmed” if a minimum of percent overlap was found with comparator aberration call(s) of the same type (gain, loss, or cnLOH). Method 1 and 2 used 50% overlap, and method 3 used a 65% overlap criterion. All eligible Agilent aberrations were assessed. If an Agilent CNV aberration could not be “confirmed” by a microarray-based comparator, another analytically validated method was employed to adjudicate the results. To avoid bias in the assessment, an additional

5% randomly selected “confirmed” CNV aberrations (separately selected for CNVs>20 probes and CNVs with 5-20 probes) were also included in the discrepancy resolution testing. Other CNVs directly subject to a third method confirmation included those selected from normal whole blood samples near the limit of resolution.

Figure1. Methods to assess the accuracy

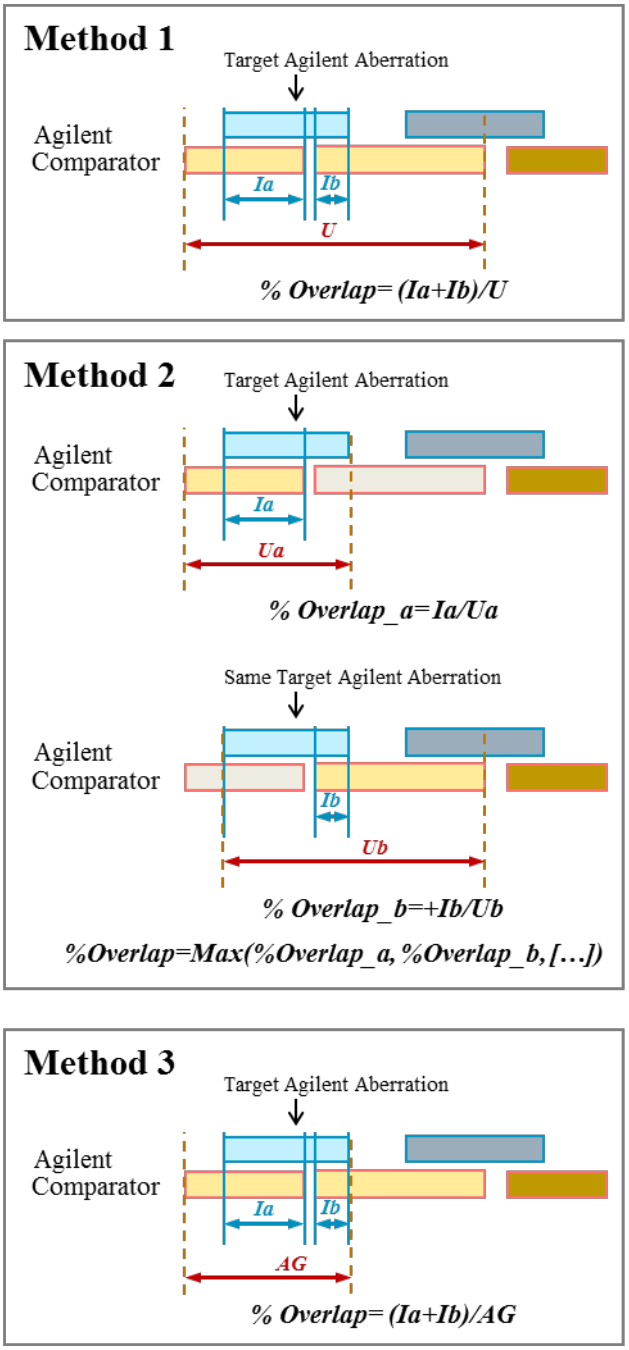

Table 5. Comparison of Assessment Criteria

	Comparator applicable to		Calculation of Overlap %			Minimum Overlap % considered as "confirmed"
	Cell line Samples	Clinical lab Samples	Numerator	Denominator	How to treat Multiple comparator aberrations overlapping a single Agilent aberration	
Method 1	Comparator platform 1 and 2 compared separately	Comparator platform 1 only (same for all criteria)	Length of overlap summed	Union (merged length) of the Agilent aberration and overlapping comparator aberrations(s)	All overlaps considered together	50%
Method 2			Length of overlap itemized	Union (merged length) of the Agilent aberration and one overlapping comparator aberrations	Each overlap considered separately, one at a time. The maximum % overlap was chosen to assess confirmation	
Method 3	Composite Data set		Length of overlap summed	Length of the Agilent aberration	All overlaps considered together	65%

The results are analyzed as confirmation rate/ false positive rate and are summarized for each method either including indeterminate CNVs as unconfirmed (referred to as scheme a) or excluding indeterminate CNVs (referred to as scheme b). The data in each table is stratified by copy number state, size (kb) or probe number, and genomic region (Tables 6-17). The results were generally consistent across all methods but differed dependent on probe vs size and whether indeterminate CNVs were included or excluded: gains ranged

In addition, refined aberration size binning either by probe number or length in kilobases (kb) was carried out in the accuracy evaluation. 25/26, or 96.2% confirmation rate near the resolution limit for CNV detection was confirmed using the aforementioned qPCR technology on selected small CNVs detected in normal whole blood-derived samples. Alternative assessment criteria for aberration confirmation (agreement) were also performed and produced comparable results. Breakpoint accuracy was evaluated on confirmed aberrations. Breakpoint agreement with comparators were 91.0% for CNVs and 91.4% for cnLOH.

Table 6. Accuracy based on number of probes
(Method 1, Scheme a: Including Indeterminate CNVs as "not confirmed")

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
Gain	5-7	48	38	79.2% (65.7%, 88.3%)	20.8% (11.7%, 34.3%)
	7-10	101	85	84.2% (75.8%, 90.0%)	15.8% (10.0%, 24.2%)
	10-15	197	152	77.2% (70.8%, 82.5%)	22.8% (17.5%, 29.2%)
	15-20	101	83	82.2% (73.6%, 88.4%)	17.8% (11.6%, 26.4%)
	20-50	148	104	70.3% (62.5%, 77.0%)	29.7% (23.0%, 37.5%)
	50-500	82	64	78.0% (67.9%, 85.6%)	22.0% (14.4%, 32.1%)
	500 +	169	166	98.2% (94.9%, 99.4%)	1.8% (0.6%, 5.1%)
	Total	**846**	**692**	**81.8% (79.1%, 84.3%)**	**18.2% (15.7%, 20.9%)**
Loss	5-7	216	196	90.7% (86.1%, 93.9%)	9.3% (6.1%, 13.9%)
	7-10	202	165	81.7% (75.8%, 86.4%)	18.3% (13.6%, 24.2%)
	10-15	257	216	84.0% (79.1%, 88.0%)	16.0% (12.0%, 20.9%)
	15-20	125	90	72.0% (63.6%, 79.1%)	28.0% (20.9%, 36.4%)
	20-50	130	95	73.1% (64.9%, 80.0%)	26.9% (20.0%, 35.1%)
	50-500	225	217	96.4% (93.1%, 98.2%)	3.6% (1.8%, 6.9%)
	500 +	186	180	96.8% (93.1%, 98.5%)	3.2% (1.5%, 6.9%)
	Total	**1341**	**1159**	**86.4% (84.5%, 88.2%)**	**13.6% (11.8%, 15.5%)**
All CNVs		2187	1851	**84.6% (83.1%, 86.1%)**	**15.4% (13.9%, 16.9%)**
cnLOH	100-200	132	94	71.2% (63.0%, 78.2%)	28.8% (21.8%, 37.0%)
	200-500	102	96	94.1% (87.8%, 97.3%)	5.9% (2.7%, 12.2%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	**292**	**248**	**84.9% (80.4%, 88.6%)**	**15.1% (11.4%, 19.6%)**

Table 7. Accuracy based on number of probes
(Method 1, Scheme b: Excluding Indeterminate CNVs)

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
Gain	5-7	43	38	88.4% (75.5%, 94.9%)	11.6% (5.1%, 24.5%)
	7-10	91	85	93.4% (86.4%, 96.9%)	6.6% (3.1%, 13.6%)
	10-15	175	152	86.9% (81.1%, 91.1%)	13.1% (8.9%, 18.9%)
	15-20	91	83	91.2% (83.6%, 95.5%)	8.8% (4.5%, 16.4%)
	20-50	124	104	83.9% (76.4%, 89.3%)	16.1% (10.7%, 23.6%)
	50-500	72	64	88.9% (79.6%, 94.3%)	11.1% (5.7%, 20.4%)
	500 +	169	166	98.2% (94.9%, 99.4%)	1.8% (0.6%, 5.1%)
	Total	**765**	**692**	**90.5% (88.2%, 92.3%)**	**9.5% (7.7%, 11.8%)**
Loss	5-7	197	196	99.5% (97.2%, 99.9%)	0.5% (0.1%, 2.8%)
	7-10	183	165	90.2% (85.0%, 93.7%)	9.8% (6.3%, 15.0%)
	10-15	231	216	93.5% (89.6%, 96.0%)	6.5% (4.0%, 10.4%)
	15-20	102	90	88.2% (80.6%, 93.1%)	11.8% (6.9%, 19.4%)
	20-50	114	95	83.3% (75.4%, 89.1%)	16.7% (10.9%, 24.6%)
	50-500	222	217	97.7% (94.8%, 99.0%)	2.3% (1.0%, 5.2%)
	500 +	184	180	97.8% (94.5%, 99.2%)	2.2% (0.8%, 5.5%)
	Total	**1233**	**1159**	**94.0% (92.5%, 95.2%)**	**6.0% (4.8%, 7.5%)**
All CNVs		1998	1851	**92.6% (91.4%, 93.7%)**	**7.4% (6.3%, 8.6%)**
cnLOH	100-200	132	94	71.2% (63.0%, 78.2%)	28.8% (21.8%, 37.0%)
	200-500	99	96	97.0% (91.5%, 99.0%)	3.0% (1.0%, 8.5%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	**289**	**248**	**85.8% (81.3%, 89.4%)**	**14.2% (10.6%, 18.7%)**

Table 8. Accuracy based on CNV size (kb)
(schemes a and b) (Method 1, Including Indeterminate CNVs as "Not Confirmed")

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
Gain	20-100	69	37	53.6% (42.0%, 64.9%)	46.4% (35.1%, 58.0%)
	100-200	94	75	79.8% (70.6%, 86.7%)	20.2% (13.3%, 29.4%)
	200-300	136	120	88.2% (81.7%, 92.6%)	11.8% (7.4%, 18.3%)
	300-500	123	92	74.8% (66.5%, 81.6%)	25.2% (18.4%, 33.5%)
	500-1,000	90	70	77.8% (68.2%, 85.1%)	22.2% (14.9%, 31.8%)
	1000-10,000	168	136	81.0% (74.3%, 86.2%)	19.0% (13.8%, 25.7%)
	10,000 +	166	162	97.6% (94.0%, 99.1%)	2.4% (0.9%, 6.0%)
	Total	**846**	**692**	**81.8% (79.1%, 84.3%)**	**18.2% (15.7%, 20.9%)**
Loss	10-100	88	59	67.0% (56.7%, 76.0%)	33.0% (24.0%, 43.3%)
	100-200	207	180	87.0% (81.7%, 90.9%)	13.0% (9.1%, 18.3%)
	200-300	129	114	88.4% (81.7%, 92.8%)	11.6% (7.2%, 18.3%)
	300-500	116	103	88.8% (81.8%, 93.3%)	11.2% (6.7%, 18.2%)
	500-1,000	209	164	78.5% (72.4%, 83.5%)	21.5% (16.5%, 27.6%)
	1000-10,000	398	351	88.2% (84.6%, 91.0%)	11.8% (9.0%, 15.4%)
	10,000 +	194	188	96.9% (93.4%, 98.6%)	3.1% (1.4%, 6.6%)
	Total	**1341**	**1159**	**86.4% (84.5%, 88.2%)**	**13.6% (11.8%, 15.5%)**
All CNVs		**2187**	**1851**	**84.6% (83.1%, 86.1%)**	**15.4% (13.9%, 16.9%)**
cnLOH	5,000-10,000	93	61	65.6% (55.5%, 74.5%)	34.4% (25.5%, 44.5%)
	10,000-20,000	94	84	89.4% (81.5%, 94.1%)	10.6% (5.9%, 18.5%)
	20,000 +	105	103	98.1% (93.3%, 99.5%)	1.9% (0.5%, 6.7%)
	Total	**292**	**248**	**84.9% (80.4%, 88.6%)**	**15.1% (11.4%, 19.6%)**

Table 9. Accuracy based on CNV size (kb)
(Method 1, Scheme b: including Excluding CNVs)

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
Gain	5-7	43	38	88.4% (75.5%, 94.9%)	11.6% (5.1%, 24.5%)
	7-10	91	85	93.4% (86.4%, 96.9%)	6.6% (3.1%, 13.6%)
	10-15	175	152	86.9% (81.1%, 91.1%)	13.1% (8.9%, 18.9%)
	15-20	91	83	91.2% (83.6%, 95.5%)	8.8% (4.5%, 16.4%)
	20-50	124	104	83.9% (76.4%, 89.3%)	16.1% (10.7%, 23.6%)
	50-500	72	64	88.9% (79.6%, 94.3%)	11.1% (5.7%, 20.4%)
	500 +	169	166	98.2% (94.9%, 99.4%)	1.8% (0.6%, 5.1%)
	Total	**765**	**692**	**90.5% (88.2%, 92.3%)**	**9.5% (7.7%, 11.8%)**
Loss	5-7	197	196	99.5% (97.2%, 99.9%)	0.5% (0.1%, 2.8%)
	7-10	183	165	90.2% (85.0%, 93.7%)	9.8% (6.3%, 15.0%)
	10-15	231	216	93.5% (89.6%, 96.0%)	6.5% (4.0%, 10.4%)
	15-20	102	90	88.2% (80.6%, 93.1%)	11.8% (6.9%, 19.4%)
	20-50	114	95	83.3% (75.4%, 89.1%)	16.7% (10.9%, 24.6%)
	50-500	222	217	97.7% (94.8%, 99.0%)	2.3% (1.0%, 5.2%)
	500 +	184	180	97.8% (94.5%, 99.2%)	2.2% (0.8%, 5.5%)
	Total	**1233**	**1159**	**94.0% (92.5%, 95.2%)**	**6.0% (4.8%, 7.5%)**
All CNVs		**1998**	**1851**	**92.6% (91.4%, 93.7%)**	**7.4% (6.3%, 8.6%)**
cnLOH	100-200	132	94	71.2% (63.0%, 78.2%)	28.8% (21.8%, 37.0%)
	200-500	99	96	97.0% (91.5%, 99.0%)	3.0% (1.0%, 8.5%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	**289**	**248**	**85.8% (81.3%, 89.4%)**	**14.2% (10.6%, 18.7%)**

Table 10. Accuracy based on number of probes
(Method 2, Scheme a: Excluding Indeterminate CNVs)

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	20-100	69	37	53.6% (42.0%, 64.9%)	46.4% (35.1%, 58.0%)
	100-200	94	75	79.8% (70.6%, 86.7%)	20.2% (13.3%, 29.4%)
	200-300	136	120	88.2% (81.7%, 92.6%)	11.8% (7.4%, 18.3%)
	300-500	123	92	74.8% (66.5%, 81.6%)	25.2% (18.4%, 33.5%)
	500-1,000	90	70	77.8% (68.2%, 85.1%)	22.2% (14.9%, 31.8%)
	1000-10,000	168	136	81.0% (74.3%, 86.2%)	19.0% (13.8%, 25.7%)
	10,000 +	166	162	97.6% (94.0%, 99.1%)	2.4% (0.9%, 6.0%)
	Total	846	692	81.8% (79.1%, 84.3%)	18.2% (15.7%, 20.9%)
LOSS	10-100	88	59	67.0% (56.7%, 76.0%)	33.0% (24.0%, 43.3%)
	100-200	207	180	87.0% (81.7%, 90.9%)	13.0% (9.1%, 18.3%)
	200-300	129	114	88.4% (81.7%, 92.8%)	11.6% (7.2%, 18.3%)
	300-500	116	103	88.8% (81.8%, 93.3%)	11.2% (6.7%, 18.2%)
	500-1,000	209	164	78.5% (72.4%, 83.5%)	21.5% (16.5%, 27.6%)
	1000-10,000	398	351	88.2% (84.6%, 91.0%)	11.8% (9.0%, 15.4%)
	10,000 +	194	188	96.9% (93.4%, 98.6%)	3.1% (1.4%, 6.6%)
	Total	1341	1159	86.4% (84.5%, 88.2%)	13.6% (11.8%, 15.5%)
ALL CNVs		2187	1851	84.6% (83.1%, 86.1%)	15.4% (13.9%, 16.9%)
cnLOH	5,000-10,000	93	61	65.6% (55.5%, 74.5%)	34.4% (25.5%, 44.5%)
	10,000-20,000	94	84	89.4% (81.5%, 94.1%)	10.6% (5.9%, 18.5%)
	20,000 +	105	103	98.1% (93.3%, 99.5%)	1.9% (0.5%, 6.7%)
	Total	292	248	84.9% (80.4%, 88.6%)	15.1% (11.4%, 19.6%)

* The number of aberrations analyzed in each range bin, including indeterminate CNVs as "not confirmed".

Table 11. Accuracy based on number of probes
(Method 2, Scheme b: including Indeterminate CNVs as "Not Confirmed")

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	5-7	48	38	79.2% (65.7%, 88.3%)	20.8% (11.7%, 34.3%)
	7-10	101	85	84.2% (75.8%, 90.0%)	15.8% (10.0%, 24.2%)
	10-15	197	151	76.6% (70.3%, 82.0%)	23.4% (18.0%, 29.7%)
	15-20	101	83	82.2% (73.6%, 88.4%)	17.8% (11.6%, 26.4%)
	20-50	148	104	70.3% (62.5%, 77.0%)	29.7% (23.0%, 37.5%)
	50-500	82	57	69.5% (58.9%, 78.4%)	30.5% (21.6%, 41.1%)
	500 +	169	119	70.4% (63.1%, 76.8%)	29.6% (23.2%, 36.9%)
	Total	846	637	75.3% (72.3%, 78.1%)	24.7% (21.9%, 27.7%)
LOSS	5-7	216	200	92.6% (88.3%, 95.4%)	7.4% (4.6%, 11.7%)
	7-10	202	165	81.7% (75.8%, 86.4%)	18.3% (13.6%, 24.2%)
	10-15	257	215	83.7% (78.6%, 87.7%)	16.3% (12.3%, 21.4%)
	15-20	125	89	71.2% (62.7%, 78.4%)	28.8% (21.6%, 37.3%)
	20-50	130	95	73.1% (64.9%, 80.0%)	26.9% (20.0%, 35.1%)
	50-500	225	212	94.2% (90.4%, 96.6%)	5.8% (3.4%, 9.6%)
	500 +	186	176	94.6% (90.4%, 97.1%)	5.4% (2.9%, 9.6%)
	Total	1341	1152	85.9% (83.9%, 87.7%)	14.1% (12.3%, 16.1%)
ALL CNVs		2187	1789	81.8% (80.1%, 83.4%)	18.2% (16.6%, 19.9%)
cnLOH	100-200	132	94	71.2% (63.0%, 78.2%)	28.8% (21.8%, 37.0%)
	200-500	102	95	93.1% (86.5%, 96.6%)	6.9% (3.4%, 13.5%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	292	247	84.6% (80.0%, 88.3%)	15.4% (11.7%, 20.0%)

* The number of aberrations analyzed in each range bin, including indeterminate CNVs as "not confirmed".

Table 12. Accuracy based on CNV size (kb)
(Method 2, Scheme a: Excluding Indeterminate CNVs)

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	20-100	53	37	69.8% (56.5%, 80.5%)	30.2% (19.5%, 43.5%)
	100-200	87	75	86.2% (77.4%, 91.9%)	13.8% (8.1%, 22.6%)
	200-300	123	120	97.6% (93.1%, 99.2%)	2.4% (0.8%, 6.9%)
	300-500	107	92	86.0% (78.2%, 91.3%)	14.0% (8.7%, 21.8%)
	500-1,000	75	68	90.7% (82.0%, 95.4%)	9.3% (4.6%, 18.0%)
	1000-10,000	145	128	88.3% (82.0%, 92.5%)	11.7% (7.5%, 18.0%)
	10,000 +	120	117	97.5% (92.9%, 99.1%)	2.5% (0.9%, 7.1%)
	Total	710	637	89.7% (87.3%, 91.7%)	10.3% (8.3%, 12.7%)
LOSS	10-100	76	59	77.6% (67.1%, 85.5%)	22.4% (14.5%, 32.9%)
	100-200	191	184	96.3% (92.6%, 98.2%)	3.7% (1.8%, 7.4%)
	200-300	115	114	99.1% (95.2%, 99.8%)	0.9% (0.2%, 4.8%)
	300-500	103	101	98.1% (93.2%, 99.5%)	1.9% (0.5%, 6.8%)
	500-1,000	179	164	91.6% (86.6%, 94.9%)	8.4% (5.1%, 13.4%)
	1000-10,000	378	350	92.6% (89.5%, 94.8%)	7.4% (5.2%, 10.5%)
	10,000 +	184	180	97.8% (94.5%, 99.2%)	2.2% (0.8%, 5.5%)
	Total	1226	1152	94.0% (92.5%, 95.2%)	6.0% (4.8%, 7.5%)
ALL CNVs		1936	1789	92.4% (91.1%, 93.5%)	7.6% (6.5%, 8.9%)
cnLOH	5,000-10,000	93	61	65.6% (55.5%, 74.5%)	34.4% (25.5%, 44.5%)
	10,000-20,000	92	83	90.2% (82.4%, 94.8%)	9.8% (5.2%, 17.6%)
	20,000 +	104	103	99.0% (94.8%, 99.8%)	1.0% (0.2%, 5.2%)
	Total	289	247	85.5% (80.9%, 89.1%)	14.5% (10.9%, 19.1%)

* The number of aberrations analyzed in each range bin, excluding indeterminate CNVs

Table 13. Accuracy based on CNV size (kb)
(Method 2, Scheme b: including Indeterminate CNVs as "Not Confirmed")

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	20-100	69	37	53.6% (42.0%, 64.9%)	46.4% (35.1%, 58.0%)
	100-200	94	75	79.8% (70.6%, 86.7%)	20.2% (13.3%, 29.4%)
	200-300	136	120	88.2% (81.7%, 92.6%)	11.8% (7.4%, 18.3%)
	300-500	123	92	74.8% (66.5%, 81.6%)	25.2% (18.4%, 33.5%)
	500-1,000	90	68	75.6% (65.8%, 83.3%)	24.4% (16.7%, 34.2%)
	1000-10,000	168	128	76.2% (69.2%, 82.0%)	23.8% (18.0%, 30.8%)
	10,000 +	166	117	70.5% (63.1%, 76.9%)	29.5% (23.1%, 36.9%)
	Total	846	637	75.3% (72.3%, 78.1%)	24.7% (21.9%, 27.7%)
LOSS	10-100	88	59	67.0% (56.7%, 76.0%)	33.0% (24.0%, 43.3%)
	100-200	207	184	88.9% (83.9%, 92.5%)	11.1% (7.5%, 16.1%)
	200-300	129	114	88.4% (81.7%, 92.8%)	11.6% (7.2%, 18.3%)
	300-500	116	101	87.1% (79.8%, 92.0%)	12.9% (8.0%, 20.2%)
	500-1,000	209	164	78.5% (72.4%, 83.5%)	21.5% (16.5%, 27.6%)
	1000-10,000	398	350	87.9% (84.4%, 90.8%)	12.1% (9.2%, 15.6%)
	10,000 +	194	180	92.8% (88.3%, 95.7%)	7.2% (4.3%, 11.7%)
	Total	1341	1152	85.9% (83.9%, 87.7%)	14.1% (12.3%, 16.1%)
ALL CNVs		2187	1789	81.8% (80.1%, 83.4%)	18.2% (16.6%, 19.9%)
cnLOH	5,000-10,000	93	61	65.6% (55.5%, 74.5%)	34.4% (25.5%, 44.5%)
	10,000-20,000	94	83	88.3% (80.2%, 93.3%)	11.7% (6.7%, 19.8%)
	20,000 +	105	103	98.1% (93.3%, 99.5%)	1.9% (0.5%, 6.7%)
	Total	292	247	84.6% (80.0%, 88.3%)	15.4% (11.7%, 20.0%)

* The number of aberrations analyzed in each range bin, including indeterminate CNVs as "not confirmed".

Table 14. Accuracy based on number of probes
(Method 3, Scheme a: Excluding Indeterminate CNVs)

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)**	FPR*** (95% CI)
GAIN	5-7	44	39	88.6% (76.0%, 95.0%)	11.4% (5.0%, 24.0%)
	7-10	97	91	93.8% (87.2%, 97.1%)	6.2% (2.9%, 12.8%)
	10-15	188	165	87.8% (82.3%, 91.7%)	12.2% (8.3%, 17.7%)
	15-20	91	83	91.2% (83.6%, 95.5%)	8.8% (4.5%, 16.4%)
	20-50	127	107	84.3% (76.9%, 89.6%)	15.7% (10.4%, 23.1%)
	50-500	78	70	89.7% (81.0%, 94.7%)	10.3% (5.3%, 19.0%)
	500 +	169	166	98.2% (94.9%, 99.4%)	1.8% (0.6%, 5.1%)
	Total	**794**	**721**	**90.8% (88.6%, 92.6%)**	**9.2% (7.4%, 11.4%)**
LOSS	5-7	212	211	99.5% (97.4%, 99.9%)	0.5% (0.1%, 2.6%)
	7-10	187	169	90.4% (85.3%, 93.8%)	9.6% (6.2%, 14.7%)
	10-15	244	229	93.9% (90.1%, 96.2%)	6.1% (3.8%, 9.9%)
	15-20	107	95	88.8% (81.4%, 93.5%)	11.2% (6.5%, 18.6%)
	20-50	122	103	84.4% (77.0%, 89.8%)	15.6% (10.2%, 23.0%)
	50-500	225	220	97.8% (94.9%, 99.0%)	2.2% (1.0%, 5.1%)
	500 +	184	180	97.8% (94.5%, 99.2%)	2.2% (0.8%, 5.5%)
	Total	**1281**	**1207**	**94.2% (92.8%, 95.4%)**	**5.8% (4.6%, 7.2%)**
All CNVs		2075	1928	92.9% (91.7%, 93.9%)	7.1% (6.1%, 8.3%)
cnLOH	100-200	132	106	80.3% (72.7%, 86.2%)	19.7% (13.8%, 27.3%)
	200-500	102	99	97.1% (91.7%, 99.0%)	2.9% (1.0%, 8.3%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	**292**	**263**	**90.1% (86.1%, 93.0%)**	**9.9% (7.0%, 13.9%)**

* The number of aberrations analyzed in each range bin, excluding indeterminate CNVs

** Confirmation Rate = TP/(TP+FP), equivalent to "# Confirmed / Sample Size (N)". It can also be referred to as "% Agreement" or "Positive Predictive Value (PPV)". 95% CI calculated using the Wilson score method. Applicable to other tables in this report.

*** FPR (False Positive Rate) = Pr (Aberration "Not Confirmed" | Aberration detected by the GenetiSure Dx Postnatal Assay) in this context is "1-Agreement (Confirmation Rate)" rather than the conventional concept of "1-specificity". Applicable to other tables in this report.

Table 15. Accuracy based on number of probes w
(Method 3, Scheme b: including Indeterminate CNVs)

TYPE	Aberration Range (# of Probes)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	5-7	48	39	81.3% (68.1%, 89.8%)	18.7% (10.2%, 31.9%)
	7-10	101	91	90.1% (82.7%, 94.5%)	9.9% (5.5%, 17.3%)
	10-15	197	165	83.8% (78.0%, 88.3%)	16.2% (11.7%, 22.0%)
	15-20	101	83	82.2% (73.6%, 88.4%)	17.8% (11.6%, 26.4%)
	20-50	148	107	72.3% (64.6%, 78.9%)	27.7% (21.1%, 35.4%)
	50-500	82	70	85.4% (76.1%, 91.4%)	14.6% (8.6%, 23.9%)
	500 +	169	166	98.2% (94.9%, 99.4%)	1.8% (0.6%, 5.1%)
	Total	**846**	**721**	**85.2% (82.7%, 87.5%)**	**14.8% (12.5%, 17.3%)**
LOSS	5-7	216	211	97.7% (94.7%, 99.0%)	2.3% (1.0%, 5.3%)
	7-10	202	169	83.7% (77.9%, 88.1%)	16.3% (11.9%, 22.1%)
	10-15	257	229	89.1% (84.7%, 92.4%)	10.9% (7.6%, 15.3%)
	15-20	125	95	76.0% (67.8%, 82.6%)	24.0% (17.4%, 32.2%)
	20-50	130	103	79.2% (71.5%, 85.3%)	20.8% (14.7%, 28.5%)
	50-500	225	220	97.8% (94.9%, 99.0%)	2.2% (1.0%, 5.1%)
	500 +	186	180	96.8% (93.1%, 98.5%)	3.2% (1.5%, 6.9%)
	Total	**1341**	**1207**	**90.0% (88.3%, 91.5%)**	**10.0% (8.5%, 11.7%)**
All CNVs		**2187**	**1928**	**88.2% (86.7%, 89.4%)**	**11.8% (10.6%, 13.3%)**
cnLOH	100-200	132	106	80.3% (72.7%, 86.2%)	19.7% (13.8%, 27.3%)
	200-500	102	99	97.1% (91.7%, 99.0%)	2.9% (1.0%, 8.3%)
	500 +	58	58	100.0% (93.8%, 100.0%)	0.0% (0.0%, 6.2%)
	Total	**292**	**263**	**90.1% (86.1%, 93.0%)**	**9.9% (7.0%, 13.9%)**

* The number of aberrations analyzed in each range bin, including indeterminate CNVs as “not confirmed”.

Table 16. Accuracy based on CNV size (kb)
(Method 3, Scheme a: Excluding Indeterminate CNVs)

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	20-100	57	41	71.9% (59.2%, 81.9%)	28.1% (18.1%, 40.8%)
	100-200	89	77	86.5% (77.9%, 92.1%)	13.5% (7.9%, 22.1%)
	200-300	131	128	97.7% (93.5%, 99.2%)	2.3% (0.8%, 6.5%)
	300-500	112	97	86.6% (79.1%, 91.7%)	13.4% (8.3%, 20.9%)
	500-1,000	84	77	91.7% (83.8%, 95.9%)	8.3% (4.1%, 16.2%)
	1000-10,000	155	138	89.0% (83.1%, 93.0%)	11.0% (7.0%, 16.9%)
	10,000 +	166	163	98.2% (94.8%, 99.4%)	1.8% (0.6%, 5.2%)
	Total	794	721	90.8% (88.6%, 92.6%)	9.2% (7.4%, 11.4%)
LOSS	10-100	82	65	79.3% (69.3%, 86.6%)	20.7% (13.4%, 30.7%)
	100-200	204	197	96.6% (93.1%, 98.3%)	3.4% (1.7%, 6.9%)
	200-300	121	120	99.2% (95.5%, 99.9%)	0.8% (0.1%, 4.5%)
	300-500	112	110	98.2% (93.7%, 99.5%)	1.8% (0.5%, 6.3%)
	500-1,000	185	170	91.9% (87.1%, 95.0%)	8.1% (5.0%, 12.9%)
	1000-10,000	385	357	92.7% (89.7%, 94.9%)	7.3% (5.1%, 10.3%)
	10,000 +	192	188	97.9% (94.8%, 99.2%)	2.1% (0.8%, 5.2%)
	Total	1281	1207	94.2% (92.8%, 95.4%)	5.8% (4.6%, 7.2%)
All CNVs		2075	1928	92.9% (91.7%, 93.9%)	7.1% (6.1%, 8.3%)
cnLOH	5,000-10,000	93	70	75.3% (65.6%, 82.9%)	24.7% (17.1%, 34.4%)
	10,000-20,000	94	89	94.7% (88.1%, 97.7%)	5.3% (2.3%, 11.9%)
	20,000 +	105	104	99.0% (94.8%, 99.8%)	1.0% (0.2%, 5.2%)
	Total	292	263	90.1% (86.1%, 93.0%)	9.9% (7.0%, 13.9%)

* The number of aberrations analyzed in each range bin, excluding indeterminate CNVs

Table 17. Accuracy base don CNV size (kb)
(Method 3, Scheme b: including Indeterminate CNVs as "Not Confirmed")

TYPE	Aberration Range (kb)	Sample Size (N)*	# Confirmed	Confirmation Rate (95% CI)	FPR (95% CI)
GAIN	20-100	69	41	59.4% (47.6%, 70.2%)	40.6% (29.8%, 52.4%)
	100-200	94	77	81.9% (72.9%, 88.4%)	18.1% (11.6%, 27.1%)
	200-300	136	128	94.1% (88.8%, 97.0%)	5.9% (3.0%, 11.2%)
	300-500	123	97	78.9% (70.8%, 85.1%)	21.1% (14.9%, 29.2%)
	500-1,000	90	77	85.6% (76.8%, 91.4%)	14.4% (8.6%, 23.2%)
	1000-10,000	168	138	82.1% (75.7%, 87.2%)	17.9% (12.8%, 24.3%)
	10,000 +	166	163	98.2% (94.8%, 99.4%)	1.8% (0.6%, 5.2%)
	Total	846	721	85.2% (82.7%, 87.5%)	14.8% (12.5%, 17.3%)
LOSS	10-100	88	65	73.9% (63.8%, 81.9%)	26.1% (18.1%, 36.2%)
	100-200	207	197	95.2% (91.3%, 97.4%)	4.8% (2.6%, 8.7%)
	200-300	129	120	93.0% (87.3%, 96.3%)	7.0% (3.7%, 12.7%)
	300-500	116	110	94.8% (89.2%, 97.6%)	5.2% (2.4%, 10.8%)
	500-1,000	209	170	81.3% (75.5%, 86.0%)	18.7% (14.0%, 24.5%)
	1000-10,000	398	357	89.7% (86.3%, 92.3%)	10.3% (7.7%, 13.7%)
	10,000 +	194	188	96.9% (93.4%, 98.6%)	3.1% (1.4%, 6.6%)
	Total	1341	1207	90.0% (88.3%, 91.5%)	10.0% (8.5%, 11.7%)
All CNVs		2187	1928	88.2% (86.7%, 89.4%)	11.8% (10.6%, 13.3%)
cnLOH	5,000-10,000	93	70	75.3% (65.6%, 82.9%)	24.7% (17.1%, 34.4%)
	10,000-20,000	94	89	94.7% (88.1%, 97.7%)	5.3% (2.3%, 11.9%)
	20,000 +	105	104	99.0% (94.8%, 99.8%)	1.0% (0.2%, 5.2%)
	Total	292	263	90.1% (86.1%, 93.0%)	9.9% (7.0%, 13.9%)

* The number of aberrations analyzed in each range bin, including indeterminate CNVs as "not confirmed".

The endpoint agreements were also analyzed. Agreements using Method 1 are shown in Table 18-.19. All three methods were found to have similar results (data not shown).

Table 18. Endpoint Agreement for Method 1 Based: comparator platform 1 Only; Binning by Number of Probes; Start/Stop Breakpoints Combined

TYPE	Aberration Range (# of Probes)	Breakpoints N	Breakpoint Agreement N	Breakpoint Agreement % (95% CI)
GAIN	5-7	48	47	97.9% (89.1%, 99.6%)
	7-10	126	116	92.1% (86.0%, 95.6%)
	10-15	258	223	86.4% (81.7%, 90.1%)
	15-20	110	88	80.0% (71.6%, 86.4%)
	20-50	128	115	89.8% (83.4%, 94.0%)
	50-500	124	104	83.9% (76.4%, 89.3%)
	500 +	296	258	87.2% (82.9%, 90.5%)
	Total	**1090**	**951**	**87.2% (85.1%, 89.1%)**
LOSS	5-7	236	234	99.2% (97.0%, 99.8%)
	7-10	124	117	94.4% (88.8%, 97.2%)
	10-15	116	89	76.7% (68.3%, 83.5%)
	15-20	84	69	82.1% (72.6%, 88.9%)
	20-50	138	110	79.7% (72.2%, 85.6%)
	50-500	420	382	91.0% (87.8%, 93.3%)
	500 +	350	283	80.9% (76.4%, 84.6%)
	Total	**1468**	**1284**	**87.5% (85.7%, 89.1%)**
All CNVs		2558	2235	87.4% (86.0%, 88.6%)
cnLOH	100-200	188	176	93.6% (89.2%, 96.3%)
	200-500	194	176	90.7% (85.8%, 94.1%)
	500 +	116	104	89.7% (82.8%, 94.0%)
	Total	**498**	**456**	**91.6% (88.8%, 93.7%)**

Table 19. Endpoint Agreement for Method 1 Based: comparator platform 2 Only; Binning by Number of Probes; Start/Stop Breakpoints Combined

TYPE	Aberration Range (# of Probes)	Breakpoints N	Breakpoint Agreement N	Breakpoint Agreement % (95% CI)
GAIN	5-7	38	37	97.4% (86.5%, 99.5%)
	7-10	124	120	96.8% (92.0%, 98.7%)
	10-15	242	204	84.3% (79.2%, 88.3%)
	15-20	58	49	84.5% (73.1%, 91.6%)
	20-50	156	140	89.7% (84.0%, 93.6%)
	50-500	140	119	85.0% (78.2%, 90.0%)
	500 +	306	261	85.3% (80.9%, 88.8%)
	Total	**1064**	**930**	**87.4% (85.3%, 89.3%)**
LOSS	5-7	254	247	97.2% (94.4%, 98.7%)
	7-10	124	121	97.6% (93.1%, 99.2%)
	10-15	138	117	84.8% (77.9%, 89.8%)
	15-20	72	63	87.5% (77.9%, 93.3%)
	20-50	160	153	95.6% (91.2%, 97.9%)
	50-500	426	398	93.4% (90.7%, 95.4%)
	500 +	352	324	92.0% (88.7%, 94.4%)
	Total	**1526**	**1423**	**93.3% (91.9%, 94.4%)**
All CNVs		2590	2353	90.8% (89.7%, 91.9%)
cnLOH	100-200	188	174	92.6% (87.9%, 95.5%)
	200-500	196	176	89.8% (84.8%, 93.3%)
	500 +	116	104	89.7% (82.8%, 94.0%)
	Total	**500**	**454**	**90.8% (87.9%, 93.0%)**

b. Matrix comparison:

Not applicable. The device is for use with EDTA anticoagulated peripheral blood only.

3. Clinical Studies:

a. Clinical Sensitivity:

A retrospective clinical study was performed to characterize the clinical performance characteristics of GenetiSure Dx Postnatal Assay for the purpose of reporting the pathogenic detection rate (potential diagnostic yield) of the assay. A total of 800 gDNA samples from patients suspected of having pathogenic aberrations (SPA

samples) were collected from 3 regionally distinct clinical institutions that offer postnatal array testing for the detection of chromosomal abnormalities. One hundred (100) samples from phenotypically normal individuals were also processed using the GenetiSure Dx Postnatal Assay and were used to assess the aberrations that might be expected to be found in a normal (non-patient) population. The aberrations detected in each sample, for all nine hundred (900) samples, were interpreted by one of four cytogeneticists as Benign, Likely Benign, Variant Of Unknown Significance (VOUS), Likely Pathogenic, or Pathogenic.

The interpretations of the calls were in agreement if the cytogeneticists at both the CNC Test processing site and at the collection site determined an aberration to be of the same pathogenicity.

The test results, per sample, were compared to historical array data from the respective collection site, which were generated using the methods established at each laboratory. All reported Pathogenic and Likely Pathogenic copy number variants (CNVs), gains and losses, were subject to confirmation by alternative methods. Confirmation methods used at the collection sites were selected by the sites based on the assays availability as well as the nature of the aberration being confirmed. The methods used included one or more of the following:

a. G-banded karyotyping
b. Fluorescence *in situ* hybridization (FISH)
c. Multiplex Ligation-dependent Probe Amplification (MLPA)
d. Quantitative Polymerase Chain Reaction (qPCR)
e. Non-Agilent Comparative Genomic Hybridization oligonucleotide microarrays (molecular karyotyping)

The diagnostic yield based on the subset evaluated with the GenetiSure Dx Postnatal Assay, when considering only copy number aberrations, was 15%. This increased to 20% when cnLOH aberrations were also considered.

Table 20. Diagnostic Yield by Collection Site (95% CI)

Collection Site	Number of Samples	Collection Site: Number of Pathogenic Calls	Collection Site: Diagnostic Yield	GenetiSure Dx Postnatal Assay: Number of Pathogenic Calls	GenetiSure Dx Postnatal Assay: Diagnostic Yield
Copy Number Aberrations Only					
Site 1	257	29	11% (8.0%, 15.7%)	39	15% (11.3%, 20.1%)
Site 2	313	35	11% (8.2%, 15.2%)	33	11% (7.6%, 14.4%)
Site 3	230	48	21% (16.1%, 26.6%)	45	20% (15.0%, 25.2%)
TOTAL	800	112	14% (11.8%, 16.6%)	117	15% (12.3%, 17.2%)

All Aberrations (Copy Number and cnLOH)					
Site 1	257	29	11% (8.0%, 15.7%)	48	19% (14.4%, 23.9%)
Site 2	313	39	12% (9.2%, 16.6%)	60	19% (15.2%, 23.9%)
Site 3	230	48	21% (16.1%, 26.6%)	51	22% (17.3%, 28.0%)
TOTAL	800	116	15% (12.2%, 17.1%)	159	20% (17.3, 22.8%)

Results of the PPA and NPA analysis are presented considering only copy number aberrations (Table 21) or considering both copy number and cnLOH aberrations (Table 22). For the copy number aberration only analysis, samples with pathogenic cnLOH aberrations were considered as non-pathogenic, unless they also included a pathogenic copy number aberration.

Table 11. Comparison of Sample Classification between the Collection Site and the GenetiSure Dx Postnatal Assay, Considering only Copy Number Aberrations

		Collection Site Aberration Interpretation					
		Pathogenic Interpretation		Non-Pathogenic Interpretation			
GenetiSure Dx Postnatal Assay Interpretation		**Pathogenic**	**Likely Pathogenic**	**VOUS**	**Likely Benign[1]**	**Normal[2]**	**Total**
Pathogenic Interpretation	**Pathogenic**	56	14	9	0	3	82
	Likely Pathogenic	12	4	11	0	8	35
Non-Pathogenic Interpretation	**VOUS**	5	8	35	0	32	80
	Normal[2]	6	7	80	1	509	603
Total		79	33	135	1	552	800
PPA[3]		86/112 = 76.8% (95%CI=68.2% – 83.6%)					
NPA[4]		657/688 = 95.5% (95%CI=93.7% – 96.8%)					

[1]One Site 2 sample was presented with the interpretation on Likely Benign.
[2]Samples from the GenetiSure Dx Postnatal Assay or Site 1 with either only Benign or Likely Benign aberrations, or samples without aberrations are classified as "Normal". Site 3 and Site 2 provided sample classification of "Normal".
[3]Positive Percent Agreement (PPA): Percent [(Agilent GenetiSure Dx Postnatal Assay = Pathogenic & Collection site classification = Pathogenic)/(Collection site classification = Pathogenic)]
[4]Negative Percent Agreement (NPA): Percent [(Agilent GenetiSure Dx Postnatal Assay = Non-pathogenic & Collection site classification = Non-Pathogenic)/(Collection site classification = Non-Pathogenic)]

When considering only copy number aberrations in the sample classification, PPA was 76.8% and NPA was 95.5%. In total, 26 samples which were determined to have Pathogenic or Likely Pathogenic copy number aberrations by the collection sites were reported as non-pathogenic by the GenetiSure Dx Postnatal Assay. Most of these

aberrations were either detected by GenetiSure Dx Postnatal Assay, but interpreted differently by the cytogeneticist, or below the detection limit of the Assay.

Table 22. Comparison of Sample Classification between the Collection Site and the GenetiSure Dx Postnatal Assay, Considering Copy Number and cnLOH Aberrations

		Collection Site Aberration Interpretation					
		Pathogenic Interpretation		Non-Pathogenic Interpretation			
GenetiSure Dx Postnatal Assay Interpretation		**Pathogenic**	**Likely Pathogenic**	**VOUS**	**Likely Benign[1]**	**Normal[2]**	**Total**
Pathogenic Interpretation	**Pathogenic**	56	14	9	0	3	82
	Likely Pathogenic	14	5	23	0	35	77
Non-Pathogenic Interpretation	**VOUS**	5	10	59	0	46	120
	Normal[2]	7	5	74	1	434	521
Total		82	34	165	1	518	800
PPA[3]		89/116 = 76.7% (95%CI=68.3%-83.5%)					
NPA[4]		614/684 = 89.8% (95%CI=87.3%-91.8%)					

[1]One Site 2 sample was presented with the interpretation on Likely Benign.
[2]Samples from the GenetiSure Dx Postnatal Assay or Site 1 with either only Benign or Likely Benign aberrations, or samples without aberrations are classified as "Normal". Site 3 and Site 2 provided sample classification of "Normal".
[3]Positive Percent Agreement (PPA): Percent [(Agilent GenetiSure Dx Postnatal Assay = Pathogenic & Collection site classification = Pathogenic)/(Collection site classification = Pathogenic)]
[4]Negative Percent Agreement (NPA): Percent [(Agilent GenetiSure Dx Postnatal Assay = Non-pathogenic & Collection site classification = Non-Pathogenic)/(Collection site classification = Non-Pathogenic)]

When considering all aberrations, PPA remained similar at 76.7%, and NPA dropped to 89.8%, which is consistent with the higher diagnostic yield for the GenetiSure Dx Postnatal Assay when considering all aberrations. Twenty-seven (27) samples were called as Pathogenic at the collection sites and non-pathogenic by the GenetiSure Dx Postnatal Assay.

When likely pathogenic and likely benign are considered as VOUS, the agreements are shown in Table 23.

Table 23. Using three categories of interpretation to compare Sample Classification between the Collection Site and the GenetiSure Dx Postnatal Assay Considering only Copy Number Aberrations

Interpretation based on GenetiSure Dx classification		Pathogenic	Diagnosis at CollectionSite Non-Pathogenic		Total
			VOUS	Benign	
Pathogenic*		56	23	3	72
Non-Pathogenic*	**VOUS***	17	58	40	115
	Benign*	6	88	509	603
Total		79	169	552	800

Positive Percent Agreement: Pr(GeneticSure Dx = pathogenic |Diagnosis at Collection Site classification = pathogenic): 56/79 = 70.9% (95%CI 59.4-80.3%)

Negative Percent Agreement: Pr(GeneticSure Dx = non-pathogenic Diagnosis at Collection Site classification = non-pathogenic): 695/721 = 96.4% (95%CI 94.5-97.6%)

Agilent reviewed the pathogenic and likely pathogenic calls from the GenetiSure Dx Postnatal assay clinical study samples and gathered clinical syndrome information based on Agilent results. In total, 36 distinct syndromes were identified which encompassed 73 cases from the clinical study sample set (Table 24). However, there was no clinical syndrome information requested from the original clinical sample collection sites. Therefore the syndrome agreements have not been established for GenetiSure Dx Postnatal assay.

Table 24: Syndromes detected with the GenetiSure Dx Postnatal Assay

Syndrome	Number of Cases
10q26 Deletion Syndrome	1
13q Deletion Syndrome	1
15q11.2 Deletion Syndrome	5
15q13.3 Microdeletion Syndrome	1
15q25 Deletion Syndrome	1
16p11.2 Microdeletion	1
16p11.2 Microduplication	2
16p12.1 Deletion Syndrome	1
16p13.11 Microdeletion	2
16p13.11 Microduplication neurocognitive disorder susceptibility locus	3
1q21.1 Deletion Syndrome	2
1q21.1 Duplication Syndrome	2
22q11.2 Duplication Syndrome	3
2q37 Deletion Syndrome	4
3q29 Deletion Syndrome	1

7q11.23 Duplication Syndrome	1
8p23.1 Microdeletion/CDH syndrome	1
8p23.1 Microduplication	1
Angelman/Prader-Willi Syndrome	6
Charcot-Marie-Tooth Neuropathy, Type 1a	1
DiGeorge Syndrome	7
Distal 22q11.2 Deletion Syndrome	1
Downs Syndrome/Trisomy 21	6
Ichthyosis, X-Linked/ STS Deficiency	1
Isodicentric Chromosome 15 Syndrome	1
Jacobsen/ 11q Deletion	1
Klinefelter Syndrome	4
Mental Retardation-Hypotonic Facies Syndrome, X-Linked/ Smith-Fineman-Myers	1
Neuropathy, Hereditary, With Liability to Pressure Palsies; HNPP	1
Sotos Syndrome-1/ 5q35 Deletion Syndrome	1
Triple X Syndrome	2
Trisomy 9 mosaicism	1
Turner Syndrome	1
Williams-Beuren Syndrome	2
Xq26.3 Duplication Syndrome	1
Other	2
Total	**73**

*b. Clinical specificity**:***

See above

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off**:**

N/A

5. Expected values/Reference range:

The prevalence of CNVs in patient populations depends on risk factors such as age, gender, presence of symptoms, and family history. A blinded study was conducted to assess the potential impact of the GenetiSure Dx Assay CNV results on interpretation using 100 phenotypically normal individual samples in the clinical specimen evaluation described above. The results showed that 8 samples with aberrations were interpreted as

Likely Pathogenic or Pathogenic by GenetiSure Dx Postnatal Assay by the cytogeneticist. Of the 8 samples with Pathogenic or Likely Pathogenic aberrations reported, 2 of those were cnLOH aberrations reported as Likely Pathogenic. These samples were not confirmed by an independent method. The other six 6 samples contained copy number changes, for which 5 were confirmed by qPCR. One (1) of the copy number changes, a 100 kb gain on Chromosome 22, was not confirmed by qPCR.

N. Instrument Name:

The GenetiSure Dx is for use on the SureScan Dx Microarray Scanner. The instrument was reviewed.

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes _____ or No __x_____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No __x_____

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes __x_____ or No _____

3. Specimen Identification:

   Each GenetiSure Dx microarray is identified based on the slide barcode with the array position appended (e.g., 1_1, 1_2). Users associate the specimen ID with the microarray identifier using a Sample Attribute File. The device software uses the association in the Sample Attribute File to identify the specimens.

4. Specimen Sampling and Handling:

   Specimens are processed according to GenetiSure Dx Postnatal assay instructions.

5. Calibration:

   Installation and calibration are performed by Agilent trained service personnel. No user

calibration is required.

6. Quality Control:

   Internal control probes on each array are used to calculate array QC metrics and assess the quality of data. As external controls, Agilent Male and Agilent Female reference DNA (provided with the Labeling Kit) are sex-matched, processed alongside, and co-hybridized with each test sample. These reference DNAs are used for data normalization and aberration detection on a per test sample basis, and to aid in troubleshooting, if necessary.

   The following QC checks are required to assure reliable results:

   1) Sample input: only samples with sufficient amount of gDNA obtained by DNA extraction/purification procedures proceed to labeling: minimum of 500 ng is required.
   2) Labeling/In-Process QC: only samples passing DNA yield and specific activity measurements proceed to array hybridization. The required amount of fluorescently labeled DNA obtained after labeling/purification procedures is 8-15 µg, and the specific activity, i.e. the amount of dye (Cy3 or Cy5) incorporated into DNA after labeling and purification is 20-45 pmol Cy3 dye/µg of DNA or 20-40 pmol Cy5 dye/µg of DNA.
   3) Array QC metrics: The software uses the signal from probes on the microarray to perform a series of data verifications that detect laboratory processing anomalies. These include automated grid finding, probe-to-probe noise, signal-to-noise ratios and SNP call rates. Only arrays passing the QC metrics proceed to analysis. If the assay fails any of the array QC metrics, the software will generate a report for review of the QC metrics, but "sign-off" will not be allowed for the report.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Testing was performed on a representative cohort of microarrays across multiple operators and multiple instruments.

Two classes of biological microarrays were run as part of the representative cohort, Gene Expression Microarrays (RNA) and CGH+SNP Microarrays (DNA). Testing was performed across 24 discrete samplings points using two operators and three instruments.

Data was collected from each scan of the cohort yielding 96 CHG+SNP microarray measurements and 192 GE microarray measurements.

For the GE cohort, the total precision of the signal intensity was estimated using a general nested analysis of variance.

A subset of the 10 x 35 E1A spike-in control probes (in vitro synthesized, polyadenylated transcripts) that are detectable in all the scans were used in the gene

expression microarray analysis of the signal intensity.

With 10 probes being used, the number of results expected was 134,400 (2 slides x 10 probes x 35 replicates x 8 arrays x 4 days x 6 times).

The acceptance criteria were that the upper bound of the 1-sided 95% confidence interval on the coefficient of variation using the total standard deviation from the model must be less than 15%.

GE Signals	N	Mean	Upper Bound of 1-sided 95% CI of VC using McKay's Procedure
gBG Sub Signal	134,400	3.19	4.32
rBG Sub Signal	134,400	3.09	4.82

For the CGH+SNP cohort, the components of variance that pertain to multiple operators, scanners, slides, days, arrays and probes, were assessed using a general nested analysis of variance on the data.

The six-hundred (600) probes that are replicated were used in the CGH+SNP microarray analysis of the log-ratios. The number of results expected was 576,000 (2 slides x 600 probes x 5 replicates x 4 arrays x 4 days x 6 times).

The acceptance criterion was set that the upper bound of a 1-sided 95% confidence interval of the sum of the standard deviations from the model associated with the scanner, operator and day components must be less than 0.06.

Component	Variance Component Estimate	Std Dev	Degrees of Freedom	1-sided 95% CI
Day	1.896e-6	0.00138	3	N/A
Scanner	2.037e-7	0.00045	2	N/A
Ooperator	0	0	1	N/A
Day × Scanner	1.267e-7	0.00036	6	N/A
Day × Operator	2.844e-9	0.00005	3	N/A
Scanner × Operator	1.789e-9	0.00004	2	N/A
Residual	0.000819	0.0286	570,007	N/A
Sum of Day, Operator and Scanner	2.10e-06	0.00145	4	0.0042
Sum of Day, Operator, Scanner, and Residual	0.000821	0.0287	281,446	0.03

Instrument Uniformity was assessed across a population of 106 instruments using a chemically coated uniformity chip divided into a set of O(145,000) 100 μm2 virtual features [squares] (20x20 pixels, 5μm pixel size: 10,000 μm2). Both local and global uniformity were assessed.

Each virtual feature was assigned an independent red and green signal level value, based upon the mean signal level of the 400 pixels that comprise the virtual feature.

The signal level values of each virtual feature were stored as arrays of positional data, and used to compute the global and local uniformity metrics for the scanner under test.

Performance Specification	N	Spec	Min	Max	Mean	Median	STDEV
Red Global Uniformity Ratio (%)	106	≤ 5%	1.60%	4.20%	2.95%	2.90%	0.0056
Red Local Uniformity Ratio (%)	106	≤ 5%	0.40%	1.50%	0.85%	0.70%	0.0026
Green Global Uniformity Ratio (%)	106	≤ 5%	1.90%	4.90%	3.43%	3.40%	0.0069
Green Local Uniformity Ratio (%)	106	≤ 5%	0.30%	1.70%	0.73%	0.50%	0.0044

The IEC safety protocols and documentation and found it to be adequate. The SureScan Dx Microarray Scanner complies with the emissions limits for Class A, Group 1 equipment specified in CISPR 11/EN5011 as required in IEC 61326-1 for Class A equipment. It complies with the immunity levels required in IEC 61326-2-6 for a non-controlled, electromagnetic environment. This equipment is not intended for use in residential or industrial environment.

Standard	
EMC	IEC 61326-1:2012 / EN 61326-1:2013
	IEC 61326-2-6:2012 / EN 61326-2-6:2013
	CISPR 11:2009 / EN 55011:2009 - Group 1 Class A
	Australia/New Zealand: AS/NZS CISPR 11:2004
	Canada ICES-001:2004 / NMB-001:2004
Safety	IEC 61010-1:2001 / EN 61010-1:2001
	IEC 61010-2-101:2002 / EN 61010-2-101:2002
	Canada: CSA C22.2 No. 61010-1-04
	USA: UL Std. No. 61010-1 (2nd Edition)
Other	EN 50581:2012

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.