

**Whole-Genome Chromosomal Microarray (CMA-ISCA)  
Healthcare Provider Statement\***

April 8, 2016

\* Note: This Statement is required, and applies to all cases of Whole-Genome Chromosomal Microarray testing.

Patient's Name: \_\_\_\_\_ Date of Birth: \_\_\_\_\_

The following information should be used to as a guide to provide informed consent to the patient and/or patient's family. We require that the consenting healthcare provider sign below.

**Purpose**

- The purpose is to find the underlying genetic cause for the patient's health condition using a Whole-Genome Chromosomal Microarray test.

**About CMA-ISCA**

- This test involves comparing a patient's genomic DNA with a gender-matched reference genomic DNA to detect small copy number gains (duplications) and losses (deletions) on all 46 chromosomes in a single test. PreventionGenetics' CMA-ISCA v1.0 (Whole-genome chromosomal microarray) contains ~110,000 distinct comparative genomic hybridization (CGH) probes distributed across the entire genome with a median probe spacing of ~25 kb, and ~59,000 single nucleotide polymorphism (SNP) probes resulting in ~5-10 Mb resolution detection of chromosomal regions with absence of heterozygosity (AOH). The CGH probes consist of the entire ISCA (International Standards for Cytogenomic Arrays: <https://www.iscaconsortium.org/>) Consortium 8x60K version probe set and an additional 60,000 backbone probes. This includes high-density coverage of ~500 targeted regions with the spacing of 5 kb per probe or at least 20 probes per gene region. These targeted regions include telomere and unique centromere FISH clone regions, microdeletion/duplication regions, genes of known haploinsufficiency, and X-linked mental retardation regions.
- We will need about one teaspoon of blood (3-5 mL of whole blood or DNA extracted from blood) from the patient to perform testing. In some instances, a second specimen may be requested.
- Based on the information given by the healthcare provider(s) about symptoms and family history, our team of experts will study the results and create an individualized report that will be given to the patient's healthcare provider(s).

**Family Testing**

- Testing of family members may be necessary for interpretation of unclear results. PreventionGenetics' policy for CMA is to provide free complimentary parental studies by FISH for copy number results of unknown significance, and for which the parental studies may clarify the clinical significance. Parental studies may be performed by FISH analysis for regions that are large enough (>0.5 Mb for deletions, and >1 Mb for duplications), and for which commercial FISH probes are available.
- Parental samples will only be tested for the regions of interest detected in their child.
- It is very important that family genetic relationships are correctly stated because issues such as undisclosed adoption or uncertain paternity can confuse test results. If you are aware of any such issues in the family, they should be discussed confidentially with your genetic counselor or ordering physician.

**Limitations**

- CMA can only detect gross genomic copy number imbalances and long regions of AOH in the nuclear genome. It cannot detect balanced chromosomal rearrangements such as inversions, balanced insertions, and reciprocal translocations.

- CMA cannot detect:
  - Genomic copy number changes in the regions of the genome not represented on the microarray (including regions with repeat sequences such as segmental duplications, repeat sequences in the short arms of acrocentric chromosomes, and heterochromatic regions)
  - Low levels of mosaicism for regions <10-15 Mb in size (although, it can reliably detect mosaicism as low as 25% for whole chromosome or whole chromosomal arm imbalances)
  - Point mutations and small insertions/deletions (indels)
  - Minimal detectable CNV size may be 500bp in targeted regions
  - Complete uniparental heterodisomy for the entire chromosome (it can only detect uniparental isodisomy and segmental heterodisomy)
  - Imbalances in the mitochondrial genome
  - CMA cannot detect imbalances when mosaicism for reciprocal CNVs exist. For example, when mosaicism for 46,XX, 45,X and 47XXX exist in approximate equal proportions, CMA will fail to detect the presence of the clinically significant 45,X line.
- Failure to detect an alteration at a specific locus does not rule out the diagnosis of a genetic disorder associated with that locus. Other abnormalities may be present that are undetectable by the microarray design.
- Failure to detect evidence of UPD does not exclude the clinical diagnosis of an imprinted associated disorder. For example complete heterodisomy that is seen in ~21-29% of UPD15 will show no evidence of recombination, leading to 8% of the individuals with Prader-Willi syndrome being missed by CMA alone

### Report Information

- We will generally only report results that may explain the patient's clinical features.
- In regions that are believed to be associated with the patient's clinical features, pathogenic variants (known to cause disease), likely pathogenic variants (probably cause disease), and variants of uncertain significance (unknown if they cause disease) will be reported.
- In regions that are possibly associated with the patient's clinical features, only pathogenic variants and likely pathogenic will be reported.
- Long contiguous region of AOH will be reported if they occur on a chromosome/chromosomal region associated with UPD.
- Multiple regions of AOH on several chromosomes will be reported only if it cumulatively exceeds 2% of the genome.
- We may report secondary findings (aka "incidental findings" - see below) depending on the patient's preference. These secondary findings may have an important impact on health but are often unrelated to the patient's clinical features. Some additional findings for which medical treatment may prevent or minimize serious health problems are provided in the initial report unless the patient opts out.
- We recommend that the patient stay in touch with their healthcare provider(s) to discuss any updated information regarding results and our interpretation. An ordering healthcare provider can request a re-interpretation from us by contacting our laboratory.

### Issuing the Report

- Results will be sent to the ordering healthcare provider(s) and NOT to the patient/family directly.
- We strongly recommend genetic counseling and/or clinical genetics consultation before and after testing is completed.
- If the patient/family wishes to receive a copy of results directly after review with their healthcare provider(s), a signed patient authorization must be sent to us. Patient authorization forms are available upon request.

### Secondary Findings

- Testing might reveal information unrelated to the patient's clinical features. These are termed secondary findings (aka "incidental" findings). The patient undergoing testing may or may not wish to be informed of these potential secondary findings.

- The patient and/or patient's family will have a choice on which types of secondary findings are reported. *Please consider the following carefully.*
  - We follow recommendations by the American College of Medical Genetics and Genomics, who recommend that all labs report pathogenic variants in 56 genes that cause certain inherited disorders (Green et al. 2013. Genet Med 15(7):565-574). These disorders may cause serious health problems that are treatable or preventable. Included on this list are some cancer predisposition conditions, heart conditions associated with sudden death, and conditions that could result in severe health consequences if surgery is performed with certain anesthetics. We will standardly report pathogenic or likely pathogenic variants in these genes unless you OPT OUT. These findings will be included in the patient's report.
  - Some genetic conditions are associated with a known disease which may be serious (leading to disability or death) but are not included on the list of 56 genes because treatment or prevention may not be effective. Some people may want to know about these genes for planning purposes while others may prefer not to know. Since many of these conditions have adult onset, testing for children is usually delayed until they can make their own decision. Pathogenic or likely pathogenic variants affecting genes other than the ACMG-56 will only be reported if you OPT IN.
  - Genetic variants related to recessive carrier status will not be reported.
  - Genetic variants in genes not currently known to be associated with human disease will not be reported.
- If we learn that family relationships are not as expected (for example, if the cumulative total of regions of AOH suggests a close [i.e. first or second degree] relationship between the patient's parents), this information will be relayed to the healthcare provider(s) for discussion, but will not be included in the patient's report.

**Data**

- Upon request, PreventionGenetics can provide CMA data. This data will be provided once testing is completed and a final report has been released. PreventionGenetics does not supply software for data review and interpretation.

**Risks**

- Blood draws can have risks associated including bruising and bleeding. There is also a small chance that you may get an infection, have excess bleeding, become dizzy, or faint from the blood draw.
- Learning about test results can be stressful and upsetting.
- The patient and/or patient's family may have concerns about genetic discrimination, including health insurance, life insurance, employment and long-term disability. These should be addressed according to federal and state laws. The Genetic Information Non-discrimination Act (GINA) prohibits the use of genetic information for discrimination in health insurance and employment.

**Confidentiality**

- We take confidentiality and patient privacy very seriously. We follow confidentiality laws related to protected health information and are a CAP and CLIA certified laboratory.

**Turnaround Time (TAT)**

- Most tests are completed within 20 days.

I have provided informed consent to my patient and/or patient's family using the above consent form. My patient and/or patient's family has had the opportunity to ask questions. Please indicate family preferences for secondary findings on page one of the CMA-ISCA/PGxome Test Requisition Form.

**Healthcare Provider's Name:** \_\_\_\_\_

**Healthcare Provider's Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_