PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

PGxome (Whole Exome Sequencing) Version 1.0
Healthcare Provider Statement*

April 8, 2016

* Note: This Statement is required, and applies to all cases of Whole Exome Sequencing.

Patient's Name: _____ Date of Birth: _____
Family Member's Name: _____ Relationship: _____
Family Member's Name: _____ Relationship: _____
Family Member's Name: _____ Relationship: _____

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 Exome Sequencing (WES) test.

About PGxome

- This test involves the sequencing of thousands of genes at the same time, whereas many other genetic tests look at one gene or a cluster of genes. The way we test the exome is through a procedure called Next Generation Sequencing (NGS) technology. We confirm important results with another type of sequencing, called Sanger sequencing.
- We will need about one teaspoon of blood (3-5 mL of whole blood or DNA extracted from blood) from each family member 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 computer programs will help us filter the results. Our team of experts will then 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 is vital for interpretation of results. We require testing of the patient and two other family members (called a trio), preferably biological parents. If one or both biological parents are unavailable, sometimes siblings or other close relatives can be tested. Trio testing increases the chance of getting a conclusive result.
- 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.
- Separate reports will not be issued for family members.

Limitations

- Roughly 25% of patients will receive a diagnosis or suspected diagnosis from this testing (Yang et al. N Engl J Med. 2013 Oct 17;369(16):1502-11).
- This test targets most, but not all, of the coding part of the genes (called exons). All of the exons together is called the exome. The exome only covers approximately 1-2% of all the genetic material. However, testing the exome covers approximately 85% of disease-causing genetic variants (Majewski et al. 2011. J Med Genet. 48(9):580-9).
- Testing will detect single base pair changes or small deletions or duplications, but we are generally not able to detect other types of genetic changes (e.g. large deletions and duplications, rearrangements, inversions, deep intronic variants, methylation abnormalities, or repetitive sequence changes). We

generally do not have the ability to detect large deletions; however, we can detect gross homozygous or hemizygous deletions if the deletion spans 3 or more coding exons.
- This test may not provide detection of certain genes or specific exons of genes due to complicated technicalities (such as sequence characteristics or interfering pseudogenes).
- Because of the technicalities of WES, this test is not 100% sensitive and may not identify a disease-causing genetic variant associated with the patient's symptoms.
- Even if a disease-causing genetic variant associated with the patient's symptoms is identified, it may not allow for predictions regarding severity of the disease or prognosis.
- It is very important that your healthcare provider(s) provide us accurate family history and clinical information as that information is critical for result interpretation. Detailed clinical information (such as clinical features, a family pedigree, and results of prior testing) is required for testing to proceed.

Report Information
- We will generally only report results that may explain the patient's clinical features.
- In genes 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 significant (unknown if they cause disease) will be reported.
- In genes that are possibly associated with the patient's clinical features, only pathogenic variants and likely pathogenic will be reported.
- We may report other findings (aka "secondary 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 secondary findings for which medical treatment may prevent or minimize serious health problems are provided in the initial report unless the patient opts out.
- Family member information (i.e. parental genotype information) that helps us interpret the patient's result will be included in the patient's report.
- 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. 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 that perform WES 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. <u>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.</u>
    - 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 for additional secondary findings will only be reported if you OPT IN.
    - Genetic variants related to recessive carrier status, complex disease, pharmacogenetics, and mitochondrial disorders (excluding nuclear genes) 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, non-paternity), 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 WES data (such as a list of variants, OMIM list of genes analyzed, VCF files, and BED files with exome coverage information). 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.

Turn Around Time (TAT)

- Our maximum TAT for a report is 4 months. Most reports will be completed in 2-3 months.

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:** _____