PREVENTION GENETICS

DISEASE PREVENTION THROUGH GENETIC TESTING

PGxome (Whole Exome Sequencing) Health Screen
Healthcare Provider Statement

November 21, 2016

This Statement is required, and applies to Whole Exome Sequencing tests for carrier and/or predisposition screening.

Patient's Name: _____ **Date of Birth:** _____

The following information should be used as a guide to provide informed consent to the patient. We require that the consenting healthcare provider sign below. Testing must be ordered by a qualified healthcare provider.

Purpose

- The purpose of this test is to provide pan-ethnic carrier screening for autosomal recessive disorders or X-linked recessive disorders (in females) using a Whole Exome Sequencing (WES) test. In addition, patients have the option of also receiving genetic variants that predispose to autosomal or X-linked dominant disorders or X-linked recessive disorders (in males).

About PGxome Test

- This test involves the sequencing of thousands of genes at the same time, whereas many other genetic tests look at only one gene or a small group of genes. The way we perform the exome test is through a procedure called Next Generation Sequencing (NGS). 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 such a blood specimen) from the patient to perform testing.
- Results of the test will be presented in an individualized, written report that will be transmitted to the patient's healthcare provider(s).
- In accordance with current professional guidelines (Borry et al. 2006. Eur J Hum Genet 14(2):133-8; NSGC Position Statement 2012; Ross et al. 2013 Genet Med 15(3):234-245), we do *not* recommend carrier testing for minors (under the age of 18 years). For minors, we recommend that carrier testing be postponed until the age of 18 years. In rare cases, we will consider special requests for PGxome carrier testing of minors.
- For additional information about this test, see the PGxome Health Screen Test Description on the PreventionGenetics web site (https://www.preventiongenetics.com/ClinicalTesting/TestCategory/PGxome.php)

Report Information

- Genetic variants are defined as the differences between the patient's DNA and the human reference DNA. We will report all Pathogenic and Likely Pathogenic recessive sequence variants (Richards et al. 2015 Genet Med 17:405-424) within genes that are currently known to be clinically relevant for carrier status in autosomal recessive disorders or X-linked recessive disorders (in females). Variants in genes that are not currently known to be clinically relevant will not be reported.
- Some individuals may have two Pathogenic or Likely Pathogenic genetic variants (compound heterozygous or homozygous) in a gene that causes an autosomal recessive disorder. Even if the patient may not be obviously affected by the disorder, this finding could lead to a diagnosis. If we identify this, we will include it in the patient's test report as it also indicates a positive carrier status.

- The patient will also very likely have many recessive variants that are of Uncertain significance. We will retain lists of these Uncertain variants at PreventionGenetics, but will not include them in the test report.
- 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, and are provided in the report if the patient opts in (see bottom of first page of Test Requisition Form).
- New research results are continually improving our ability to interpret the WES results. An ordering healthcare provider can request a reinterpretation from us.

Issuing the Report

- Results will be sent directly to the ordering healthcare provider(s) and NOT to the patient.
- We recommend genetic counseling and/or clinical genetics consultation before and after testing is completed.
- Patients have the right to receive a copy of their test report. They may obtain a copy from their healthcare provider(s) or if a signed patient authorization form (available upon request) is received, from PreventionGenetics.

Secondary Findings

- In a small fraction of patients, WES will reveal one or more additional genetic variants which are dominantly inherited (or X-linked recessive) and which could be important to the patient's health. These include for example variants predisposing the patient to cancer or heart disease. These are termed secondary findings. The patient may or may not wish to be informed of secondary findings.
- The patient has two choices about which secondary findings are reported (see bottom of first page of Test Requisition Form). *Please consider the following carefully.*
    - The American College of Medical Genetics and Genomics recommends that all labs performing WES report pathogenic variants in 59 genes that cause certain, mostly dominantly inherited disorders (Kalia et al. 2016. Genet Med. Advance online publication. doi:10.1038/gim.2016.190). These disorders are treatable and/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. Since the main indication for this test is carrier testing, <u>we will NOT report Pathogenic or Likely Pathogenic variants in these genes (ACMG 59 Genes) unless the patient OPTS IN.</u>
    - Genes involved in other dominantly-inherited disorders are not included on the ACMG list of 59 genes because treatment or prevention may not be effective (examples: Amendola et al. 2015. Genome Res 25(3):305-315; Dorschner et al. 2013. Am J Hum Genet 93(4):631-640). Some of these disorders are very serious, leading to death. Some people may want to know about these genes for planning purposes while others may prefer not to know. Many of these conditions have adult onset. Since the main indication for this test is carrier testing, <u>we will NOT report Pathogenic or Likely Pathogenic variants in these genes (Other Predispositions/Diagnoses) unless the patient OPTS IN.</u>
    - Genetic variants related to complex disease, pharmacogenetics, and mitochondrial disorders (excluding nuclear genes) will not be reported at this time.
    - Genetic variants in genes not currently known to be involved in human disease will not be reported.

Data

- PreventionGenetics will store the patient's sequence data. This will permit reanalysis and reinterpretation of the data in the future. Upon physician request, PreventionGenetics will perform, without additional charge, one reanalysis and reinterpretation of the data within three years of the date on the original test report. Thereafter, reanalysis and reinterpretation may be requested, but a fee will be charged for this service.
- PreventionGenetics recommends that DNA sequence information from this test also be stored in the patient's electronic medical record. This will best benefit the patient and family members. Upon request, PreventionGenetics will provide WES data such as a list of sequence variants, a list of genes analyzed,

and .bed files with coverage information. PreventionGenetics does not supply software for data review and interpretation.

Risks

- Blood draw risks include 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 Federal Genetic Information Non-discrimination Act (GINA) prohibits the use of genetic information for discrimination in health insurance and employment.

Limitations

- This test targets most, but not all, of the coding parts of our genes (called exons). All of the exons together is called the exome. The exome only covers approximately 1.5% of all the genetic material. However, testing the exome covers the vast majority of genetic variants which cause single gene (or Mendelian) disorders.
- Interpretation of the test results is limited by the information that is currently available. Better interpretation should be possible in the future as more data and knowledge about human genetics are accumulated.
- 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).
- This test will not provide detection of certain genes or specific exons of genes due to complicated technicalities (such as sequence characteristics or interfering pseudogenes). Because of these technicalities, *this test is not 100% sensitive* and *will not identify all disease-causing genetic variants associated with a positive carrier status or predisposition to genetic disorders.*
- Even if a disease-causing genetic variant associated with a positive carrier status is identified in the patient, it may not allow for accurate predictions regarding severity of the disease or prognosis for future children.
- Additional limitations to this test will be provided in the Supplementary material included with the test report.

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)

- The maximum TAT for our exome test is 45 days.

I have provided informed consent to my patient. My patient has had the opportunity to ask questions. Please indicate patient preferences for secondary findings on the Test Requisition Form.

Healthcare Provider's Name: _____

Healthcare Provider's Signature: _____Date: _____

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Office use only

3800 S. Business Park Ave
Marshfield, WI 54449
Phone: 715-387-0484
Fax: 715-384-3661

PGxome Health Screen Test Requisition Form

(revised 12/30/2016)

- The primary purpose of this test is for carrier and disease susceptibility screening. For diagnosis purposes, please use our Diagnostic PGxome Test Requisition Form.
- Test information is available from our web site.
- Testing must be ordered by a qualified healthcare provider.

Ordering Checklist (required):

- ☐ Patient specimen
- ☐ Healthcare Provider Statement
- ☐ Relevant medical and family health history information, if available

Person Completing Form	*Contact Information (phone or email)*	*Date of Request*

Patient Information

Patient's Last (Family) Name	*First Name*	*MI*	*Date of Birth:* Month Day Year

Patient ID Code	*Date Collected:* Month Day Year	*Sex:* ☐ Male ☐ Female ☐ Other

Specimen Source: ☐ *Whole blood* ☐ *Extracted DNA Source:* ☐ *Cultured Cells Source:* ☐ *Tissue Source:* ☐ *Other:*

GeoAncestry/Ethnicity

Relevant Clinical/Medical Information

Testing related to an ongoing pregnancy? ☐ Yes ☐ No	*Has the patient's relative been tested at PreventionGenetics?* ☐ Yes ☐ No *If yes, provide name & DOB:*	*Has either patient or partner been tested previously at PreventionGenetics?* ☐ Yes ☐ No *If yes, PG ID#(s):*	*Has patient had a blood transfusion within the last month?* ☐ Yes ☐ No *If yes, provide type & date:*	*Has patient had a bone marrow transplant?* ☐ Yes ☐ No

Other relevant medical and/or family health history information:

Test Selection

✓ ***Test Code 4000: PGxome Health Screen***

Secondary (Additional) Findings

Testing may reveal other genetic information unrelated to carrier testing. These are termed secondary findings. **Details can be found in the PGxome Health Screen Healthcare Provider Statement (required). Options for reporting of secondary findings are to be marked below. If left blank, carrier status only will be reported.**

☐ **OPT IN: ACMG 59 GENES**

☐ **OPT IN: OTHER PREDISPOSITIONS/DIAGNOSES**

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Provider/Laboratory Contact Information

- **Our preferred method of report transmission is secure email (via ZixCorp). Please provide an email address when possible.**
- **If you have additional specific reporting requests, please indicate them below.**

Provider Information			
Institution			
Address (please include city, state, country & postal code)			
Requesting Physician (First, Last, Degree)		***Requesting Genetic Counselor (First, Last, Degree)***	
Phone Number	***NPI#:***	***Phone Number***	***NPI#***
Email		***Email***	
Test Reporting Instructions *Our preferred method of report transmission is email (via ZixCorp)*		**Test Reporting Instructions** *Our preferred method of report transmission is email (via ZixCorp)*	
Secure Email (via ZixCorp): ☐ *use above*		***Secure Email (via ZixCorp):*** ☐ *use above*	
☐ ***DO NOT use ZixCorp. Instead, send email via ShareFile.***		☐ ***DO NOT use ZixCorp. Instead, send email via ShareFile.***	
☐ ***DO NOT email results. Instead, send via fax (provide fax #):***		☐ ***DO NOT email results. Instead, send via fax (provide fax #):***	

Sendout Laboratory (Complete only if report needed)	**Other**
Laboratory & Contact Person	***Contact Name***
Address	***Address***
Phone Number	***Phone Number***
Email	***Email***
Test Reporting Instructions *Our preferred method of report transmission is email (via ZixCorp)*	**Test Reporting Instructions** *Our preferred method of report transmission is email (via ZixCorp)*
Secure Email (via ZixCorp): ☐ *use above*	***Secure Email (via ZixCorp):*** ☐ *use above*
☐ ***DO NOT use ZixCorp. Instead, send email via ShareFile.***	☐ ***DO NOT use ZixCorp. Instead, send email via ShareFile.***
☐ ***DO NOT email results. Instead, send via fax (provide fax #):***	☐ ***DO NOT email results. Instead, send via fax (provide fax #):***

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Billing Instructions

1. Please choose one of the three billing options:

- ☐ Institutional
- ☐ Individual
- ☐ Insurance

2. Provide all information for the selected option only

Note: Patient testing will be delayed until all of the billing requirements have been met. Please print clearly. If Individual/Insurance billing information is incomplete, the Institution will be billed. Tests that are cancelled while in progress will be billed for the amount of work completed up to that point. If the patient's specimen is collected in New York, a New York State Non-Permitted Laboratory Test Request approval letter (see web site) must be included before testing will proceed.

1. Institutional Billing (Preferred)

Billing Institution		***PO Number***
Contact	***Phone Number(s)***	***Email***
Address		
City	***State***	***Zip***
Email Invoice **Email Address:**	***Copy of Test Report(s) for Billing*** ☐ **Secure Email (via ZixCorp):** ☐ **Other (please specify):**	

2. Individual Billing

Responsible Party's Name (Must be 18 years or older)	***Phone Number(s)***	***Email***
Address		
City	***State***	***Zip***

ACCEPTANCE OF FINANCIAL RESPONSIBILITY FOR GENETIC TESTING

Note: PreventionGenetics cannot proceed with testing of the specimen without a signature below.

My signature below indicates that I accept financial responsibility for all fees associated with this genetic testing order.

_____	_____	_____
Signature of Responsible Party	***Printed Name of Responsible Party***	***Date***

COMPLETE THE FOLLOWING FOR CREDIT CARD PAYMENT

Credit Card # / (VISA, Discover, or Mastercard only)	***Expiration Date***	***3-Digit Security Code***

My signature below authorizes PreventionGenetics to charge my credit card for services for which I am responsible.

Signature: ***Date:***

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Billing Instructions

3. Insurance Billing

We will file an insurance claim on behalf of the patient with any commercial insurance company. However, the claim will be submitted as an "out of network" service provider. We are in network (contracted provider) with a limited number of insurance plans (see website). The patient is responsible for any portion of the test fee not covered by the insurance company for any reason including, but not limited to, co-payments, co-insurance, unmet deductibles, or non-covered services.

Responsible Party's Name (Must be 18)	*Phone Number(s)*	*Email*

Responsible Party Address

City *State* *Zip*

Policyholder Name (Required)	*Please indicate the type of insurance: (Circle One)* *Private / Medicare / WI Medicaid** **We only accept WI Medicaid*	*Primary Insurance Company Name (Required)*

Insurance Company Address- Claims

City *State* *Zip*

ICD-10 Codes (Required)	*Policy ID#*	*Group #*	*Authorization #*

Please attach the following:

Note: PreventionGenetics cannot proceed with testing of the specimen until all information is received.

- ☐ *NPI # of Requesting Physician _____*
- ☐ *Medicare – signed ABN Form completed IN FULL*
- ☐ *Copy of both sides of Insurance Card*
- ☐ *Authorization number or letter of agreement from insurance company (if available). If not included, we will routinely perform pre-verification prior to initiating testing & will relay information to ordering provider.*
- ☐ *Letter of Medical Necessity*
- ☐ *Relevant Medical Records*
- ☐ *NY Non-permitted lab approval letter (if specimen collected in NY)*
- ☐ *Share results of benefits investigation with patient directly via email provided above or FAX# _____*

AUTHORIZATION TO ASSIGN BENEFITS AND ACCEPT FINANCIAL RESPONSIBILITY FOR MY ACCOUNT

Note: PreventionGenetics cannot proceed with testing of the specimen without a signature below.

I authorize PreventionGenetics to release information received including, without limitation, medical information, which includes laboratory test results, such as genetic tests results, to my health plan/insurance carrier and its authorized representatives. I further authorize insurance payments directly to PreventionGenetics for the services rendered. I understand my health plan/insurance/Medicare/Medicaid carrier may not approve and reimburse my medical genetic services in full due to usual and customary rate limits, benefit exclusions, coverage limits, lack of authorization, medical necessity or otherwise. I understand I am financially responsible for fees not paid in full by my insurer, co-payments, and policy deductibles except where my liability is limited by contract or State and Federal law. I agree to help PreventionGenetics resolve any insurance claim issues.

_____ _____ _____

Signature of Patient or Guardian *Printed Name of Patient or Guardian* *Date*

Credit Card # / (VISA, Discover, or Mastercard only)	*Expiration Date*	*3- Digit Security Code*

My signature below authorizes PreventionGenetics to charge my credit card for services for which I am responsible upon completion of insurance processing.

Signature: ***Date:***

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Specimen and Shipping Instructions

Specimen Requirements

WHOLE BLOOD: Collect 3-5 ml of whole blood in EDTA (purple top tube) or ACD (yellow top tube), minimum 1 ml for small infants.

DNA: Send in screw cap tube at least 10 µg of purified DNA at a concentration of at least 100 µg/ml (indicate concentration on tube label) for exome only.

SALIVA, CELL CULTURE, & FRESH, FROZEN TISSUE: Please contact us.

Shipping/Handling Instructions

Please label all specimen containers with the patient's name, date of birth and/or ID number. At least two identifiers should be listed on specimen containers. We accept specimen deliveries Monday-Saturday for all specimen types except cell cultures. Cell culture deliveries are routinely accepted Monday-Thursday and require advance notice of arrival. If a Friday delivery is necessary please contact us to make arrangements. Holiday schedules will be posted on our home page at least one week prior to major holidays.

BLOOD: Do not freeze. During hot weather, include a frozen ice pack in the shipping container. Place a paper towel or other thin material between the ice pack and the blood tube. In cold weather include an unfrozen ice pack in the shipping container as insulation. At room temperature, blood specimen is stable for up to 48 hours. If refrigerated, blood specimen is stable for up to one week.

DNA: DNA may be shipped at room temperature. Label the tube with the composition of the solute, DNA concentration as well as the patient's name, date of birth, and/or ID number. We only accept genomic DNA for testing. We do NOT accept products of whole genome amplification reactions or other amplification reactions.

CELL CULTURES: We are NOT able to culture cells. Send confluent flasks of cultured cells in insulated, shatterproof container overnight.

Address	Testing Kits
Diagnostic Lab PreventionGenetics 3800 S. Business Park Ave. Marshfield, WI 54449 USA	Clinical testing kits with prepaid return shipping are now available for our U.S. clients. We are able to provide Clinical Testing Kits to our international clients without the return postage at this time. To order kits, submit requests through our Electronic Order Form on our web site or contact our Client Service Representatives at 715-387-0484, ext. 0.

DNA Genotyping Panel

For quality control purposes, the PreventionGenetics DNA Genotyping Panel is performed on all clinical specimens. Genotyping results are ***not*** included in test reports.

DNA Banking

DNA Banking has a reduced price of $98 for patients if clinical testing is also being performed with us. For DNA Banking, see our DNA Banking Process and DNA Banking Forms. For questions related to DNA Banking, contact our DNA Banking Director at 715-387-0484, ext. 151 or email dnabanking@preventiongenetics.com.

Contact Us

For additional questions or concerns, please contact our Client Service Representatives at 715-387-0484, ext. 0 or our Genetic Counseling Team at ext. 208 or clinicaldnatesting@preventiongenetics.com.