COLUMBIA | PRECISION GENOMICS LABORATORY

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Columbia Preventive Genomic Screen (CPGS)

Notice to Health Care Practitioner:

The following document is a consent form for clinical whole exome sequencing for screening for genetic variants relevant to health in an adult. Currently, the laboratory will only accept test requests after the patient has received genetic counseling from a health care provider for such a test. An informed consent form, signed by the patient (or by his/her authorized representative), as well as by the person obtaining consent should be submitted with each specimen.

Summary for Patient:

What is the Columbia Preventive Genomic Screen (CPGS)?

CPGS is genetic test that uses exome sequencing (ES) technology to search through the most important part of a person's entire genetic material, called the "exome", for DNA variation that can cause disease or have other important effects on health. Instructions in the exome tell our bodies how to function properly; abnormalities of this information can lead to disease. CPGS is performed on a blood or buccal sample. DNA is purified from the sample, the exome sequenced is obtained from the DNA, and then the exome is analyzed to identify certain types of clinically relevant changes.

What Information Might Be Learned from This Testing?

The purpose of this test is to provide a comprehensive interpretation of your exome, in order to identify genetic changes relevant to your health. Everyone has variations in their exome, however most variants do not cause medical problems. An expert will analyze the variants found through CPGS, and only those variants that definitely or likely to cause disease, indicate an increased risk for disease, indicate that you are a carrier for a genetic condition, or indicate how you may respond to certain drugs will be reported. There are many variants where the relationship to disease is unclear, or that have been reported to have only small effects on disease risk. Because these types of results do not provide clinically relevant information, they will not be reported through this testing.

How Do I Obtain CPGS Testing?

Because CPGS is a very detailed type of genetic test that can reveal information on risks for many different types of diseases, you will need to meet with your healthcare provider to discuss the test in detail. You also have the option to receive genetic counseling prior to signing the consent form. The testing takes about 3 months to complete. When results are available, your provider will schedule a consultation to review the results with you in detail. Your medical team will need to evaluate these in light of your medical and family history.

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Informed Consent – Columbia Preventive Genomic Screen

1. The nature of the test and how it will be performed:

What is the Columbia Preventive Genomic Screen?

A number of genes in the human genome confer very high risk of preventable diseases when mutated. It has been estimated that about 1% of the adult population is predisposed to a serious hereditary condition that may be preventable or treated more successfully through early diagnosis (PMID: 26540154). Genomic information can help individuals and their health care providers proactively make important health management decisions. The Columbia Preventive Genomic Screen (CPGS) uses exome sequencing (ES) technology to screen for genetic variants relevant to health in adults who are looking for insights and information about their genetic make-up.

CPGS is genetic test that searches through the most important part of a person's entire genetic material, called the exome, for DNA variation that can cause disease. Instructions in the exome tell our cells how to function properly. Abnormalities of this information can lead to disease. Because CPGS is more complicated than other genetic tests, the consent and ordering process must be thorough and should be done with the assistance of a healthcare provider familiar with the test.

What is the primary purpose of the test?

The test is being performed to provide a comprehensive interpretation of your exome, in order to identify genetic changes relevant to your health.

How is the test performed?

One tube (one teaspoon) of blood or a buccal swab sample will be collected from you. DNA from your sample is purified, then the exome sequence is obtained (or "read").

Once the exome is read, the information obtained is analyzed for differences between your exome sequence and a reference ("normal") sequence. Everyone has places in their exome that differ from the reference, which typically do not cause medical problems. To determine whether the changes that are found are benign, or can cause disease,

1- We compare the variations in your exome to a list of genetic changes that are known to cause medical problems in people
2- We examine known disease-causing genes for mutations that are definitely disruptive
3- The mutations are evaluated by an expert to indicate if they are truly likely to either cause disease or contribute to it
4- Only those variants that are definitely or likely to cause disease, indicate an increased risk for disease, indicate that you are a carrier for a genetic condition, or indicate how you might respond to certain drugs will be reported. There are many variants that might be disease causing or that might contribute to a disease. These will *not* be reported.

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2. What kinds of results may be obtained, what is their significance for health, and what should you do after receiving the results?

What kind of results may be reported?

There are several different kinds of results that may be reported. All results will go directly to your physician or other healthcare provider who ordered the test.

1. Variants causing conditions/diseases which are clinically actionable: You may have one or more genetic variation(s) that are known to cause a specific genetic condition. If found to have this type of result, there would be some type of clinical intervention or monitoring that could reduce the risk of developing the associated disease. Please consult the latest version of the American College of Medical Genetics (ACMG) Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing guidelines for an up-to-date list of genes and conditions reported in this category.

2. Variants causing single-gene heritable disorders: Diseases in this category may include conditions for which there is no intervention or treatment that can reduce the risk.

3. Variants indicating carrier status for known recessive conditions: Recessive conditions are those where a person must have variants in both copies of a gene to develop the disease. A person who has a variant in only one copy of the gene is a carrier, meaning they are not at risk for the disease themselves, but could be at risk to have a child with the condition.

4. Risk alleles: these are variants that have been associated with a slight or moderate increased risk for common diseases, such as blood clotting disorders or late-onset Alzheimer's disease. Please refer to the last page of this consent form for a list of risk alleles that would be reported.

5. Pharmacogenomic screening: Variants in this category are known to affect how a person responds to certain medications. They do not indicate a risk for disease, but provide information on the effectiveness of a certain medication or suggested dosage in an individual. Please refer to the last page of this consent form for a list of pharmacogenomic variants that would be reported.

What do I do with the results?

This is a test to identify genetic changes that may cause disease, indicate an increased risk for disease, indicate a possibility of passing on a disease to your children, or indicate how you might respond to certain drugs. We recommend reviewing your report with your ordering provider, who will need to evaluate these in light of your medical and family history. In addition to risk of future illnesses, or conditions that might run in your family, the results might help your physician understand the cause of any existing conditions, which may (or may not) help your physician alter management of existing conditions.

Predicting the results of CPGS in advance is not possible. Predicting exactly what the results will mean for your health is also not possible. This is because many genes are tested and many different positive results can be obtained. Each of these different results will have potentially different implications. A negative result (not finding variants) does not rule out disease and will not change your health status.

Genetic counseling and further testing might be recommended based on the results of this test.

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3. Limitations and risks

What are the limitations of the test?

1. At the current time, the test does not interrogate 100% of the exome. CPGS is not able to detect mutations in the 99% of the DNA that is not part of the exome, including parts of the DNA that help regulate gene function. Therefore, there is a possibility that there could be a mutation or variation that is associated with a condition that is not picked up by CPGS.

2. The CPGS report is generated based on current medical knowledge. A genetic variant that is not known to be the cause of a genetic condition today may be shown to be disease-causing in the future. CPGS will not report findings of uncertain significance, which cannot be proven with complete certainty to be disease-causing. Your physician may request re-analysis and ask for an updated report for a fee.

3. CPGS may not be able to detect genetic disorders that are caused by variants not detected by exome sequencing, such as expansion of repetitive regions, copy number changes in the DNA, variants in the mitochondrial DNA, or methylation abnormalities. If one of these conditions is suspected, your physician should order the appropriate test.

4. Please be aware that we do not report out on changes for diseases where the genetic correlation is not well understood, such as diabetes and hypertension.

What are the risks of the test?

1. Finding a disease-causing mutation may not result in a treatment, cure, or a prognosis (knowledge about how a disease is expected to progress). CPGS may identify serious, untreatable genetic conditions. It can result in unexpected psychological trauma, both for you and for your family. The detection of such a condition could also affect the health or health care needs of your siblings, children, or other close relatives.

2. Standard laboratory limitations caused by human error, such as sample contamination or sample mix-up, may occur but are unlikely.

3. In the United States: The genetic non-discrimination law prevents insurance companies from using your genetic information to deny health insurance coverage. However, the law does not cover life insurance, disability insurance or long-term care insurance. The detection of an incidental condition may affect your future ability to obtain these forms of insurance. By New York State Law, your consent is required for the release of these results to insurance companies. However, you may be required to release this information to the insurance companies for your contract with them to be valid.

4. CPGS may identify genetic changes that may require additional testing to be completely evaluated. This could result in anxiety, uncertainty, and additional expenses that may or may not be covered by your insurance, and may or may not provide additional useful information.

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4. Who will have access to the results?

The results of CPGS will become a part of your medical record. Test results are stored in the laboratory's computer records, and are automatically sent to computerized medical records of NewYork Presbyterian Hospital and Columbia University. If you do not want these results to be sent to these records, you must inform us about this. Unless you tell us not to transmit them, the results will become part of your electronic medical record. Even if they do not become part of the electronic medical record, the results may be made available to individuals/organizations with legal access to your medical record, on a strict "need-to-know" basis. Those with legal access include, but are not limited to, the physicians and nursing staff directly involved in your care, your current and future insurance carriers, and others specifically authorized by you or your authorized representative.

Columbia University, NewYork-Presbyterian and Weill Cornell Medicine and their related entities participate in an Organized Health Care Arrangement (OHCA). This allows us to share health information to carry out treatment, payment and our joint health care operations, including integrated information system management, health information exchange, financial and billing services, insurance services, insurance, quality improvement, and risk management activities. Organizations that will follow this Notice include Columbia University, NewYork-Presbyterian sites, Weill Cornell Medicine and their related entities.

I understand that the results will be automatically transmitted to my electronic medical records in the NYPH and Columbia University EMRs. I will email the laboratory at PGLsupport@cumc.columbia.edu if I do not consent to the transmission of my results to the hospital or university electronic medical record as describe above. I understand that the results will continue to be part of the laboratory's electronic information system. If test results are not entered into my hospital or university electronic medical records, future physicians may not have access to those results. I understand that I must assume responsibility for informing my future physicians about findings of CPGS that may affect my healthcare.

4. What else could happen to my genetic data?

In accordance with CLIA, CAP, and CLEP guidelines, the laboratory will keep the identified CPGS raw data in the lab for at least 7 years. The final report will be kept as long as possible, at least 7 years. You consent to the sharing of your de-identified health history and genetic variants through publication, presentation at scientific meetings, and through NIH-funded databases such as ClinVar or ClinGen. You understand that although you may not personally benefit from this, the sharing of data might accelerate medical research and help other families. If you do not consent to the sharing of your data as described above, please email the laboratory at PGLsupport@cumc.columbia.edu. You have the option of allowing your coded data to be used for research purposes. Please indicate your choice below:

_____ (Initial) I consent to the use of my genomic data for research purposes. Additional written consent is required for any research study that may involve return of results.

5. Sample Retention

_____(Initial) I consent to the use of my specimen for genetic research studies and/or to be used for quality assurance, assay development and validation. Additional written consent is required for any research study that

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may involve return of results. The duration of the retention of my sample will depend on the individual research study. By not initialing here, my sample will be destroyed not more than 60 days after completion of testing.

6. Consent for CPGS testing

All of the above has been explained to me, to my satisfaction, and my signature below attests to the same.

Person being tested:

Print Name:_____Signature:_____ Date: _____

Health care provider obtaining consent:

Print Name:_____Signature:_____ Date: _____

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Risks Alleles Reported as part of CPGS:

Gene	Coordinates (hg19)	RefSeq	Allele	RefSeq ID	Common Name
F5	Chr1: 169519049	NM_000130.4	c.1601G>A; p.Arg534Gln	rs6025	Factor V Leiden
SERPINC1	Chr1: 173883881	NM_000488.3	c.218C>T; p.Pro73Leu	rs121909551	AT Basel
F2	Chr11: 46761055	NM_000506.4	c.*97G>A; p.?	rs1799963	Prothrombin G20210A
APOE	Chr19: 45411941	NM_000041.4	c.388T>C; p.Cys130Arg	rs429358	Apo-E4
APC	Chr5: 112175211	NM_000038.6	c.3920T>A; p.Ile1307Lys	rs1801155	N/A
HFE	Chr6: 26093141	NM_000410.3	c.845G>A; p.Cys282Tyr	rs1800562	N/A

Pharmacogenomic Alleles Reported as part of CPGS:

Gene	Coordinates (hg19)	Allele	RefSeq ID	Drug (Indication)
CYP2C19	Chr10: 96541616 Chr10: 96540410 Chr10: 96521657	*2 *3 *17	rs4244285 rs4986893 rs12248560	Clopidogrel (Anti-coagulation)
CYP2C9	Chr10: 96702047 Chr10: 96741053	*2 *3	rs1799853 rs1057910	Warfarin (Anti-coagulation)
VKORC1	Chr16: 31107689	-1639G>A	rs9923231	
SLCO1B1	Chr12: 21331549	c.521T>C	rs4149056	Simvastatin (Hyperlipidemia)