



**Informed Consent for Columbia Combined Genetic Panel (CCGP) for Children** Please read the following form carefully and discuss with your ordering physician/genetic counselor before signing consent.

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

**What is the Columbia Combined Genetic Panel (CCGP)?**

The Columbia Combined Panel is a genetic test that evaluates changes in your child's DNA that might be the cause of your child's clinical condition. A gene is an individual unit of DNA. Exons are the most important regions of the gene that provide the instructions for the body to make proteins and chemicals that allow it to function properly. Changes in genes, called mutations, can lead to disease. The Columbia Combined Panel tests for exons of many genes at the same time. The genes are chosen based on their known role in diseases that cause symptoms similar to your child's symptoms. Because this test examines a larger portion of the genetic material than traditional tests, it might discover the cause of disease in cases where other tests were inconclusive. Because the Columbia Combined Panel is more complicated than prior genetic testing your child may have had, the consent and ordering process must be thorough and will be done with the assistance of a genetic counselor and/or your doctor.

**How is the test done?**

Two tubes (two teaspoons) of blood will be collected from your child. Based on your family tree, your genetic counselor or doctor may also recommend that blood be drawn from two or more members of your family, such as the child's father or siblings, to help with interpretation of test results. The genes tested by the CCGP are part of the DNA in your child's blood cells. DNA from your child's blood is purified, and the exome sequence is obtained (or "read") using high throughput sequencing. The sequence obtained for the genes included in the CCGP is then searched for changes that are known or suspected to cause disease.

**How is this test interpreted?**

Once the DNA sequence of the exons of the genes of interest is read, the information obtained is analyzed for differences between your child's sequence and a reference ("normal") sequence. Everyone has places in their sequence that are different from the reference. These differences make us unique and usually do not cause medical problems. To determine whether the changes that are found are neutral, or can cause disease, the following steps are taken:

First, the variations in your child's sequence will be compared with a list of mutations that are known to cause medical problems in other people with symptoms similar to those seen in your child. Subsequently one will examine whether disruptive mutations not previously described are present in genes that are known to cause the type of disease your child has. Changes found will be compared to the changes seen in your selected family members with or without the disease (if available) to confirm that the changes are indeed the cause of your child's disease.

**2. The Primary Purpose of the test (why it is being performed).**

The test is being performed primarily to detect a genetic cause for your child's condition. The condition is \_\_\_\_\_ which causes \_\_\_\_\_.

**The test results may be complex, so you must obtain genetic counseling before signing this consent.**



### 3. 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 the healthcare provider who ordered the test.

1. Positive for disease-causing mutation(s): Your child may have one or more mutations that are known to cause a specific genetic condition in other individuals with symptoms similar to your child's symptoms. These mutations are interpreted as the cause of your child's symptoms.
2. No disease causing mutations or variants found: It is possible that the test will not find any genetic change that would explain your child's symptoms. This type of test result does not mean your child's condition is not genetic. The result would not take away whatever symptoms or current diagnoses doctors may have given your child.
3. Variant with uncertain significance: Sometimes the test will find a genetic variation that is predicted to be important, but has not been reported or seen before in people with your child's condition. Such a variant may or may not be causing your child's symptoms, but the lab will report it as a "variant of uncertain significance" if there is evidence strongly suggesting that it is related to your child's condition.

#### Are there any types of results that will not be given to me?

Yes, there are a few types of results that will not be included in the report your child's doctor gets.

1. Mutations that are not directly related to your child's condition (incidental findings) will not be reported.
2. We might use your relatives' samples to help us diagnose your child's condition, but we will not report results for these individuals. However, your child's genetic results might have implications for your relatives. It is important that you discuss these implications with your genetic counselor.
3. The DNA that will be tested on the sequencer will include genes that are not related to your child's condition. We will NOT analyze these genes. Therefore, results for these genes will NOT be available to you OR us, and will not be reported. If your doctor decides to test for the other genes in our large panel of genes, he/she will have to order another test.

#### What should I do if there is a positive result?

This is a test to identify a genetic cause of your child's clinical condition. If the test is positive for a genetic cause of your child's clinical condition, you may wish to consult your physician or have further genetic counseling or undergo further independent testing.

\_\_\_\_\_ (Initial) I understand that I have the option to seek further independent testing, and that I should obtain genetic counseling to help me understand the results.

#### Are there limitations to the testing?

Yes, there are several limitations to the Columbia Combined Genetic Panel:

1. The test is not able to detect mutations in genes that are not known to be associated with the symptoms that your child has.
2. The test report is generated based on current medical knowledge. A mutation that is not known to be the cause of a genetic condition today, may be shown to be disease-causing in a year or two. We do not generate updated reports for the test, unless we are requested to do so by the patient. There is a fee associated with providing an updated report.
3. The test is not currently validated to detect large-scale alterations in the DNA content of the patient's cells. These include losses or duplications of many genes. Another genetic test called a microarray is available for this purpose. It might be ordered by your child's physician before the CCGP testing.
4. The test may not be able to detect genetic disorders that are caused by expansion of repetitive regions of the genome. One example is Fragile X syndrome. If one of these conditions is suspected, your child's physician should order the appropriate test.



Internal Use Only CUMC MRN: \_\_\_\_\_ Acc #: \_\_\_\_\_

5. The test is not able to detect mutations in the part of the DNA that is not part of the exons, (the coding portion of the gene), such as parts of the DNA that help regulate gene function.
6. The test may detect findings of uncertain significance, which cannot be proven with complete certainty to be the cause of your child's condition (see types of results described above).
7. Finding a disease-causing mutation may not result in a treatment, cure, or a prognosis (knowledge about the way a disease is expected to progress).
8. Standard lab limitations caused by human error, such as sample contamination or sample mix-up, may occur but are unlikely.

\_\_\_\_\_ (Initial) I understand the limitations to CCGP

#### **4. When DNA testing detects the most common disease-causing changes in a gene, the test result is highly accurate.**

#### **5. Implications of positive and negative results for your diagnosis**

Predicting the results of CCGP in advance is not possible. Predicting in advance what the results will mean for your child's health is also not possible. This is due to the fact that 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 mutations responsible for your child's disease) will not change your child's diagnosis.

#### **6. Who will have access to the results?**

The results of the CCGP become a part of the patient's medical record. Test results are stored in the laboratory's computer records, and are normally automatically sent to computerized medical records of New York 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 the patient's 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 the patient's 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 the patient's care, the patient's current and future insurance carriers, after consent is obtained, and others specifically authorized by you or your authorized representative to gain access to your child's medical records.

\_\_\_\_\_ (Initial) I understand, that the results will be automatically transmitted to the patient's electronic medical records in the NYPH and Columbia University EMRs, and I do not object to this.

\_\_\_\_\_ (Initial) Please do not transmit any of the results to the Hospital's electronic medical records. I understand that the results *will* continue to be part of the laboratory's electronic information system. If the results are not entered in the Hospital or University's electronic medical records, future physicians may not have access to those results. I understand I must assume responsibility for informing my child's future physicians of these results, or for requesting that physicians contact the Columbia University Personalized Genomic Medicine Laboratory for these.

#### **7. How long are the CCGP results kept in the testing?**

The laboratory will keep the identified CCGP raw data for 5 years. The final report will be kept as long as possible, but at least 5 years. After this, the data from which the final report was generated will be de-identified, and will be stored in a database that does not include any names or other information that would link them back to your child. However, information about the type of disease and the type of symptoms associated with the genetic findings will be preserved. Because this is a new test, it is important to keep track of the types of variants and mutations that are being found to help us improve our diagnostic capabilities. Although your child would not directly benefit from this, others with similar conditions would. Please indicate your choice below.



\_\_\_\_\_ (Initial) I agree to the CCGP data being stored indefinitely in a de-identified way.

\_\_\_\_\_ (Initial) I do not want CCGP data being stored indefinitely even if it is de-identified.

**8. Statement that no additional tests will be performed on this sample, without specific, signed authorization by the patient/legal representative, and that after 60 days, unless consent is given, the sample will be destroyed.**

**How long are the samples kept in the lab?**

Blood and DNA samples are normally discarded after 60 days, following test completion, unless you provide us consent to store the DNA after testing is performed. Storing your child's sample may allow you to request testing in the future without having to obtain a new sample, or to participate in future research, should you wish to do so. If you would like the DNA to be stored after your child reaches the age of 18, the adult child (or legal representative) will have to request that the DNA continue to be stored after that period.

\_\_\_\_\_ (Initial) Please keep DNA used in testing my child indefinitely for future testing should I desire such testing, or should I want to participate in research in the future. I understand no additional genetic tests will be performed without my specific consent/instructions. If I decide to participate in research in the future, I will instruct the laboratory, and there will be a requirement of a separate IRB-approved consent. The DNA may be used only for quality control purposes, and I understand that there is no guarantee of its availability after 60 days.

\_\_\_\_\_ (Initial) Do not keep DNA used in testing my child associated with information that could identify my child, but you may use my child's de-identified DNA for quality control purposes or for research in which the identity cannot be traced back to my child or my family. I understand that any research using the de-identified DNA will require a specific IRB approval and oversight.

\_\_\_\_\_ (Initial) Please discard DNA and other biologic materials used in testing my child 60 days after all testing is completed.

**9. What are the risks of testing?**

1. Identification of familial relationships: CCGP may identify familial relationships other than those originally reported. For example, non-paternity (when the reported father of the child is not the biological father) or half sibling-ships (when siblings do not share the same father AND mother) would be detected. You may choose whether or not to be informed of this information, in case it is revealed during the testing.
2. Discrimination. The genetic non-discrimination law prevents insurance companies from using your child's 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 child's future ability to buy these forms of insurance or get the best insurance rates. 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.
3. Requirement for further testing: CCGP may identify genetic changes that may require additional testing to evaluate. This could result in anxiety, uncertainty, and additional expenses that may or may not be covered by your insurance.
4. Detection of untreatable conditions. CCGP may identify serious, untreatable genetic conditions. It can result in unexpected psychological trauma, both for you and your family. The detection of such a condition could also affect the health or health care needs of your child's siblings, or other close relatives.



Internal Use Only CUMC MRN: \_\_\_\_\_ Acc #: \_\_\_\_\_

## 10. Statement of Financial Responsibility

\_\_\_\_\_ (Initial) I understand that I, having requested testing to be performed, am responsible for the cost of this testing and will be required to pay for any/all of the test cost if health insurance does not reimburse the laboratory. In addition, if health insurance pays for the test, I understand that the laboratory is required to bill me for the co-pay or coinsurance that is required by my health plan.

## 11. CONSENT FOR CCGP TESTING

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

Signature of person being tested: \_\_\_\_\_ Date: \_\_\_\_\_

Signature of health care provider: \_\_\_\_\_ Date: \_\_\_\_\_



Internal Use Only CUMC MRN: \_\_\_\_\_ Acc #: \_\_\_\_\_

### 11a. Consent of family members submitting a sample for evaluation of patient's results.

I understand that I am submitting my blood sample to help evaluate the results obtained on the person being tested, and that results obtained from my sample will be used solely for this purpose. I will NOT be informed of any test results on my sample. If I request any test results, I will have to be tested separately. If questioned by an insurance carrier, I can state that I have not been tested for these conditions.

Name of Family Member: \_\_\_\_\_ Relationship to Person: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

---

I understand that I am submitting my blood sample to help evaluate the results obtained on the person being tested, and that results obtained from my sample will be used solely for this purpose. I will NOT be informed of any test results on my sample. If I request any test results, I will have to be tested separately. If questioned by an insurance carrier, I can state that I have not been tested for these conditions.

Name of Family Member: \_\_\_\_\_ Relationship to Patient: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

---

I understand that I am submitting my blood sample to help evaluate the results obtained on the person being tested, and that results obtained from my sample will be used solely for this purpose. I will NOT be informed of any test results on my sample. If I request any test results, I will have to be tested separately. If questioned by an insurance carrier, I can state that I have not been tested for these conditions.

Name of Family Member: \_\_\_\_\_ Relationship to Patient: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

---



**Notice to Health Care Practitioner:**

The above document is a consent form for the Columbia Combined Genetic Panel (CCGP) test, a targeted multigene test. Currently, the laboratory will only accept test requests after the patient/parent or legal guardian/next of kin has received genetic counseling from a genetic counselor, clinical geneticist, or neurogeneticist with experience in counseling patients for such a test. By NY State law, the patient/or authorized representative needs to be counseled about issues related to the current condition, implications of positive and negative test results, as well as other issue related to health insurance, and possible effects on life insurance. Please explain the above consent to the patient, or authorized representative/guardian, and obtain an informed consent.



## Description of high-throughput sequencing tests for genetic disorders offered by the Personalized Genomic Medicine Laboratory of Columbia University Medical Center

### Overview

The human genome contains in excess of 20000 protein coding genes. In a constantly updated encyclopedia of mendelian human disorders, OMIM, as of October 16, 2012, there are about 3600 phenotypes described in which the molecular basis of the disease is known. There is also an additional 3600 phenotypes listed that have no known molecular basis to date. The number of genes described on the site is past 14,000, and all these genes are thought to be relevant to human disease, although maybe only half of them have a confirmed role in one or more genetic disorders.

The current paradigm for genetic diagnosis rests on PCR and microarray-based detection of specific mutations of known significance and/or Sanger sequencing that allows detection of previously described, as well as novel mutations, in genes that have been well established to play a role in a specific disease. These methods work well for screening for specific mutations or for demonstration of mutations in a small number of genes, if the gene(s) to test can be largely ascertained based on the clinical phenotype. However, they fall short in cases where the phenotype and genotype correlation is not strong enough to efficiently guide the decision-making process as to what mutation in which gene should be tested for. In cases like congenital hearing loss in which over 100 loci have been implicated, it is often impossible to establish in what order to perform the review of genes linked to the phenotype. Even if a more logical phenotype based approach is available, like in the case of muscular dystrophies, the diagnostic odyssey is often too painful and expensive to undertake. Since genetic information is changing at a rapid pace, clinicians may be unaware of all known genes and, therefore, fail to order the appropriate tests. NGS allows for simultaneous sequencing of large number of genes that might carry mutations causing the symptoms of a patient at an affordable price. This prevents individual clinician bias in testing decisions and improves diagnostic success rate.

We offer four clinical NGS tests at the Personalized Genomic Medicine Laboratories at Columbia University Medical Center. These are full mitochondrial genome sequencing (MGS), the Columbia Combined Genetic Panel (CCGP), Whole Exome Sequencing (WES) and Whole Genome Sequencing (WGS) tests. The MGS and CCGP tests are for patients whose disease shows a very characteristic phenotype strongly associated with mutations in the mitochondrial genome, or in a few dozen candidate genes. The WES and WGS tests are to be used in situations where one cannot generate a credible list of candidate genes to be tested. These tests interrogate all coding regions or the entire genome, respectively. In addition to identifying known disease causing mutations and probable disease causing mutations in disease associated genes they can also identify entirely new private mutations in genes previously not linked to the disease. Confirmation of the disease causing nature of these novel mutations is based on segregation of the mutation in families and structural and functional characteristics of the mutation and the gene itself.

### Indication for testing

- The presence of a congenital developmental abnormality of presumed genetic origin



- Development of symptoms that suggest the presence of a genetic disorder with mitochondrial or Mendelian inheritance

### *Methodology*

- Hardware: Illumina sequencing instruments: MiSeq for MGS and CCGP tests and HiSeq2500 for WES and WGS tests.
- Capture reagents: We use PCR to capture the mitochondrial genome and Agilent Sureselect technology to capture the regions of interest (ROI) for the CCGP and WES studies. The WGS does not require capture, since the entire genome is sequenced.

### *Specimen requirements*

- All specimens should carry two independent identifiers.
- Blood > 300microliters, should be anti-coagulated, preferably with citrate or EDTA and should be less than a week old.
- Muscle biopsy specimens (>50mg) should be refrigerated from the time of biopsy to arrival to the lab.
- DNA should be greater than 10kb median length. We optimally need 3 micrograms of genomic DNA at concentrations 50-200ng/microliter.