CNNH
The Center for Neurological and Neurodevelopmental Health®

CNNH NeuroGenomics Program Peer-to-Peer Service Consent/Information Form

WHO WE ARE

The Center for Neurological and Neurodevel-opmental Health (CNNH) is an innovative patient- and family-centered "Specialty Care Medical Home®" providing a comprehensive array of assessment, treatment and support services (https://cnnh.org). We are based in Southern New Jersey/Philadelphia Area with the main location in Voorhees, NJ.

NeuroGenomics is a new service provided by CNNH in order to more fully integrate genetic information into the care of patients with neurological and neurodevelopmental disorders. Our Director, Richard G. Boles, M.D. is an international expert in the innovative use of genetic testing to improve patient care.

PURPOSE OF THIS SERVICE

Genetic testing is extremely complicated, and very few physicians can fully understand the information provided, or how to apply that information in your or your dependent child's medical care in order to improve treatment outcomes. For these reasons, your physician has recommended our service.

GENETIC TESTING

Your physician has ordered genetic testing for you/your child. Genetic testing is a very powerful method that may help your doctor identify a diagnosis and/or establish a treatment plan. Upon ordering genetic testing, your physician should have discussed with you the benefits, risks, and limitations of the specific testing ordered, and you should have had an opportunity to have your questions answered. If this is not the case, please contact your physician. Furthermore, the present document does not explain what genetic testing is, how it works, or the limitations that are specific to each test and laboratory. For that information, please consult the consent form from the laboratory that is performing the testing, or speak directly to that laboratory and/or your physician.

WHAT WILL HAPPEN IN THIS SERVICE?

1. Clinical information, including physician note(s) and the genetic testing report, will be forwarded to CNNH before the telephone appointment for our review.
2. Your physician and an M.D. geneticist from CNNH will discuss the case by telephone ("Peer-to-Peer"), including:
    a. Clinical information.
    b. Genetic findings.
    c. Compare the two to determine what genetic findings are likely or possibly related to health and disease in you/your child.
    d. Any further testing that may be suggested, genetic or otherwise.
    e. Any changes to patient care that may be suggested, including possible changes to diet, supplements, medications, lifestyle, etc.
3. A brief summary of the call and the full recording will be provided to your physician.
4. Your physician will discuss the relevant findings with you as part of your ongoing medical care.

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LEVELS OF SERVICE

Focused and Standard Peer-to-Peer Services: The information on the official report(s) from the genetic testing laboratory will be discussed with your physician during the conversation. The difference between the Focused and Standard levels of service is determined by the number and/or complexity of the report(s). For example, three or more reports, or any number of reports that includes exome, determines the Standard service.

Comprehensive Peer-to-Peer Service:
In addition to the above, your physician will be provided a re-analysis of the raw sequence data provided by the genetic testing laboratory. The aim in this re-analysis is to identify sequence variants that are NOT on the official report by the laboratory, but of which your physician and the CNNH geneticist after discussion believe might have implications to your/your child's health and/or medical care. This service is explained in more detail later in this document.

WHAT IS NOT PART OF THIS SERVICE

No physician-patient relationship is provided or implied by your/your child's and/or your physician's participation in this program, regardless of how payment for these services is arranged, or the presence of a brief summary of the call and full recording provided by CNNH. Please note that:

1. Discussion of any findings is between you and your physician(s). Please do not contact CNNH with questions.
2. Arrangements for any follow-up testing and payment thereof is to be arranged with your physician(s), and not with CNNH.
3. Any changes to patient management, including testing or medications, done as a result of any level of this Service is between you and your physician(s). The CNNH geneticist may discuss options during the Peer-to-Peer, but which of these options to bring to your attention for potential implementation is up to your physician.
4. Some cases are complex and your physician may want to have an additional Peer-to-Peer discussion, which can be arranged, for example to ask a few questions. However, the Peer-to-Peer system is not designed for ongoing care management. In some cases, a referral to a geneticist may be appropriate.

INCIDENTAL FINDINGS

Genetic testing is designed to determine causes or factors underlying your/your child's illness, in order words finding that are relevant to the reason why testing was performed. However, sometimes the genetic results indicate findings that are likely unrelated to the reason that testing was performed. These so called "incidental findings" can include, but are not limited to, the following:

1. The presence of another condition that you/your child may have.
2. An increased risk to develop certain conditions, for example certain cancers, and heart or brain disease.
3. An increased risk related to certain drugs. For example, that a given drug, if taken, may lead to toxic blood levels, severe bleeding, or even sudden death.
4. Bullets 1 to 3 above could also apply to one or more relatives if they carry the same genetic change(s).
5. Genetic "blood" relationship between the parents may be identified by testing.
6. Non-paternity may be identified by testing if parental samples are

provided.

When you were originally consented for genetic testing, you should have been given the opportunity to "opt-out" of receiving information on incidental findings. If you continue to wish to opt-out, or if you change your mind, please contact your physician so that incidental findings will not be discussed. However, even if you do opt out, you will be told about cross-over findings that may be relevant to the disease being tested, as well as relevant to other issues. For example, sequence variants in some genes can predispose (increase the risk) towards migraine, seizures, and abnormal heart rhythms. If your child has migraine, you will also learn about potential risks for seizures and abnormal heart rhythms.

LIMITATIONS

1. A negative test result does not rule out all genetic causes for disease. It is still possible that your/your child's symptoms have an underlying genetic cause or risk factors that the technology used was unable to detect, that we do not understand, or that is in the vast amounts of little-understood DNA outside of exome. In addition, if a panel was performed, the cause or risk factors may simply be outside of the area sequenced.
2. Some results are of uncertain clinical significance, meaning that while they may be related to disease, they may also be harmless changes unrelated to disease.
3. Genetics determines risk for disease, but cannot state whether disease will in fact occur, or the severity of disease, with certainty as knowledge is incomplete and the environment is also important.
4. This test is not meant to evaluate for carrier status related to reproduction. Most individuals are apparent carriers for a great number of the genes sequenced by exome, and with rare exceptions we do not pursue or confirm this data.
5. Sequencing assays such as exome have poor sensitivity to detect large gene deletions or duplications. The appropriate test for detection of these larger variants is a chromosomal microarray (CMA). Upon request and arrangement, our Service can help your physician to understand the meaning and implications of a CMA result as well.

TESTING IN OTHER FAMILY MEMBERS AND GENETIC COUNSELING

In certain situations, the genetic testing of relatives may be of help in understanding the meaning of genetic findings in you/your child. Common examples of some of these situations include the testing of:

1. Additional individuals in the same family who are affected.
2. Parents, to see if a variant is *de novo* (a new mutation absent in both parents), and thus very likely to be disease related.

In these and in some other situations, we may recommend that genetic testing be performed on one or more relatives.

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of

genetic disorders to help them make informed medical and personal decisions. Genetic counseling is beyond the knowledge and skill of most physicians. Some genetic counseling-related information, such as the risk of another child being born in your family with the same condition, may be discussed during the Peer-to-Peer discussion, and maybe forwarded to you by your physician. However, this Service is NOT a substitute for genetic counseling.

PARENTAL/TRIOME SEQUENCING

In some cases, DNA is obtained from the patient and both parents. The exome/WES sequences from these three individuals is called a "triome". Triome sequencing offers several advances over simply sequencing the patient, but the primary advantage is the identification of *de novo* variants. Triome sequencing is often used in patients with neurodevelopmental disorders, epilepsy, and/or birth defects.

The purpose of triome sequencing is to better understand the sequence results in the patient. Triome sequencing is NOT intended to identify genetic disease or risks is the parents, most of which will not be identified. Of course, triome sequencing will identify a parent as having a disease-causing variant if both the patient and a parent share the variant.

RISKS OF DISCRIMINATION

The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits health insurance plans and employers from discrimination based on genetic information, including the results of genetic testing. However, such genetic testing may result in life insurance, disability insurance and/or long-term care insurance discrimination that is not prohibited by law.

WRITTEN DOCUMENTATION

The three levels of service do NOT constitute a clinical evaluation as the history obtained is focused on understanding the report/sequences, not obtained directly from the patient or family, not associated with a physical examination, and there are no direct questions asked by the patient or family. No physician-patient relationship is created or implied. Your physician is fully responsible for any diagnoses or management (e.g. treatment) plans that arise from the Peer-to-Peer discussion. Thus, no written note will be provided for the medical chart.

However, a brief summary will be provided to your physician that documents that this service took place, and some of the genes, mechanisms, conditions, and/or management considerations that were under discussion. In addition, the discussion will be taped and a copy provided to your physician. Ask your physician if you wish to obtain copies of the brief summary and/or recording.

INNOVATIVE & FUNCTIONAL INTERPRETATION

The term "functional" when applied to disease means different things to different people, but in this Service this term refers to any condition that results from the abnormal function of cells, tissues, and organs, and not the abnormal structure of cells, tissues, and organs. Autism, seizures, pain, nausea, fatigue, dysautonomia, depression, and anxiety are all functional signs and symptoms that often arise from functional disease. In this usage, the term "functional" does not infer that it is fictitious, non-organic, or any

other term to suggest that disease is not "real". Functional signs, symptoms, and disease are one of the main focuses at CNNH, and in particular at the CNNH NeuroGenomics Program. Dr. Boles, our Director, has spent the last quarter century searching the DNA for changes related to functional disease, with the primary motivation that an in-depth biological understanding can lead to improved therapies.

The medical world sometimes appears to be divided between extreme "allopathic" providers that use pharmaceutical agents exclusively and extreme "alternative" providers who consider all prescription drugs to be toxic. At CNNH, we are moderate, "integrated" care providers who recommend what we believe is best for each patient. We are conformable with recommending drug therapy as well as interventions often considered to be "alternative", such as diet, nutritional supplements, exercise, good sleep hygiene, stress reduction, acupuncture, plant-based treatments, biofeedback, and sensory therapies. In particular, Dr. Boles trained at two of the "ivory towers" of allopathy, Yale and UCLA, yet worked for over 20 years as a biochemical geneticist (metabolic specialist) at Children's Hospital Los Angeles, which made him very familiar and conformable with nutritional interventions.

The CNNH NeuroGenomic Program is designed to help physicians better able to understand genetic testing in order to unlock the substantial power of this tool for improving patient care. We use an integrated mind-set, bringing the best of allopathic and functional medicine perspectives, using science- or evidence-based information whenever possible. Thus, in addition to explaining what the DNA sequencing indicate with a high-degree of certainty, we will also discuss what the sequences appear to be suggesting, but cannot prove at this time. The goal is to identify low-risk (e.g. "safe") therapeutic options that are consistent with the patient's disease and the genetic information.

INFORMATION SHEET

Focused and Standard Peer-to-Peer Services: For these levels of this Service, this document is for your information only, and no signature or return is required. You can skip all of the following pages.

Comprehensive Peer-to-Peer Service:
For this level of Service, this document contains the first pages of a legal consent form that you are required to sign and forward to your physician (see the last page). Please read the remaining pages as they apply to you.

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CNNH NeuroGenomics Program

Comprehensive Level of Service Consent Form, Continued

SUMMARY

If your physician orders this highest level of our Service, in addition to the above, an extensive re-analysis of the raw sequence data will be performed and discussed with your physician.

PURPOSE OF THIS SERVICE

To identify sequence variants that are NOT on the official report by the laboratory, but in which your physician and the CNNH geneticist believe might have implications to you/your child's health and/or medical care.

WHAT WILL HAPPEN IN THIS LEVEL OF SERVICE?

1. Every aspect of the preceding pages applies to this level of the Service as well.
2. The genetic testing laboratory will be asked to forward their raw sequence data in an electronic format. Each testing laboratory has a different procedure:
    a. You may need to complete and/or sign a request form. If so, this form (or the hyperlink to the form on the laboratory's website) will be provided to you.
    b. You may be required to pay a small fee to the testing laboratory to cover their costs (e.g. for the flash drive).
    c. The electronic sequence may be sent electronically (Internet) or by mail (flash drive).
    d. The above may be sent to your physician or directly to our Service. If sent to your physician, his/her office will forward the sequence to us.
3. The electronic sequence data will be forwarded for a special computerized analysis. Currently, this is performed at GeneSaavy in the Seattle Area. The results will be electronically transmitted to CNNH.
4. An M.D. geneticist from CNNH will analyze the sequences, with the primary aim of identifying variants that might be treatable.
5. The M.D. geneticist will discuss the findings with your physician during the "Peer-to-Peer" telephone call.

WHY YOU SHOULD CONSIDER THIS SERVICE

Clinical genetics laboratories and the official reports they provide are limited to the standards set by the American College of Medical Genetics (ACMG). These standards are excellent for determining which variants are the likely cause of disease in many settings. However, they suffer from the following limitations:

1. Most laboratories do NOT report findings that MIGHT be disease related, even if there is a possible therapy.
2. Your physician likely knows your/your child's issues in much further depth that what the laboratory can understand by reading the information provided to them. Laboratories rarely discuss the findings directly with the physician in order to determine which variants fit and which do not, but we will.
3. ACMG standard are designed for

monogenic disease, which is disease caused by a variant in one gene. Most human disease is polygenic, which means that disease is influenced by risk factors consisting of variants in more than one gene.

   a. In particular, functional (e.g. pain, fatigue, GI dysmotility, dysauto-nomia, depression) and neuro-developmental (e.g. autism, ADHD) disorders are generally thought to be polygenic.

4. Most geneticists and genetic counselors that interpret the sequence data for laboratories are trained in a strict allopathic manner, with little to no training in functional medicine.

For all of the above reasons, sequence variants related to disease are likely to be missed by the laboratory and NOT listed on the reports. A re-analysis of the raw sequence is needed in order to identify them, and this is what the Comprehensive level of the Service is designed to accomplish.

WHAT ARE YOU LIKELY TO FIND IN THE RE-ANALYSIS?

Some genetics testing laboratories, but not all, will list variants that are of unclear connection with disease if they believe that they may be disease related. These variants are termed as Variants of Uncertain Significance (VUS). On the extensive sequence re-analysis as part of the Comprehensive Service, many additional VUSs will be identified that may or may not be disease related.

During the Peer-to-Peer telephone discussion, your physician and the CNNH MD geneticist will discuss these VUSs to determine which ones appear to be a good "fit" for your/your child's disease. Those variants that are potentially treatable or that inform on treatment choices are of particular interest and are discussed in detail. The goal is to identify candidate variants that suggest low-risk therapies which may be of help in treating the disease and/or improving symptoms. Your physician will discuss with you any options that he/she believes are reasonable in you/your child based on an assessment of risks and benefits.

Every case is different, but our experience to date suggest that one to several such candidate variants are identified in the average patient. While treatment directed at these candidates is successful in many patients, in many other patients it is not. Sequence re-analysis is NOT a guarantee of clinical success.

REQUEST TO OPT-OUT OF RECEIVING INCIDENTAL FINDINGS:

Despite the focus being on the primary illness, sequence re-analysis as part of the Comprehensive Service is likely to identify one or more potential incidental findings NOT listed on the official report from the testing laboratory. Some of the types of incidental findings were listed earlier in this document.

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Please initial one of the below choices:

____ I wish to receive ALL results that my physician and/or the CNNH MD geneticist believe may be directly related to my/my child's health.

____ I do NOT wish to receive the above results that my physician and/or the CNNH MD geneticist believe are likely not directly related to the reason for which testing was performed.

By signing below, I give consent for re-analysis of my/my child's genetic testing results in the Comprehensive level of this Service as discussed in this document. I have read this document, had the opportunity to ask questions to my physician, and wish to proceed with the Service.

Patient's name: _____
Please print

Legal signature: _____
Patient if over age 18, otherwise parent/guardian

Print name: _____
Person signing form if parent/guardian

Date signed: _____