University of North Carolina-Chapel Hill
Assent Form 2: Assent to Research Genomic Sequencing
Adolescent Subjects ages 15-17
Biomedical Form

IRB Study # 17-1806
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Title of Study: North Carolina Clinical Genomic Evaluation by Next-gen Exome Sequencing, phase 2 (NCGENES 2)
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As part of the NCGENES 2 research study, you and your parents have been randomized to have the option for them to consent for you to have *research* genomic sequencing. We will also ask for your assent for this testing. This form explains research genomic sequencing testing and your options. You will be given a copy of this assent form. You should ask the researchers or research staff any questions you have about this research study at any time.

Why is this test being offered to NCGENES participants?
We are offering research genomic sequencing to learn whether using it changes a child's future medical care. We think it could do this by helping us diagnose genetic conditions faster than we can with other kinds of tests.

When a child has a condition that might have a genetic cause, special tests called "genetic tests" might find that cause. One kind of genetic test is called "genomic sequencing." To help you understand why this test might find the cause of a condition, it is helpful to know what genes are and what they do.

Our genes are like an instruction book that tells our bodies how to grow and develop. Genes are in almost every cell in our body. They are made of DNA, which uses four "letters" (A, C, T, and G) to encode information. The order of these letters is called the DNA's "sequence." Genomic sequencing is a way to look at the sequence of the DNA that makes up our ~20,000 genes.

Just like how the order of the words in a sentence tells you what the sentence means, the sequence of our DNA tells our cells which proteins to make and how to make them. Those proteins, along with our environment, affect how our bodies work. Genetic differences, or "variants," are part of what make each person unique. Almost all of our genetic variants are

harmless, but some can affect the way our bodies grow and develop. Genomic sequencing is a way to find genetic variants in DNA that explain why a person has a medical condition.

What will happen if you agree to have research genomic sequencing?
We will ask you to read and sign this assent form and will ask your parents to sign a consent form to allow us to get blood or saliva samples from you for research genomic sequencing.

If your parents sign the consent form and you sign this assent form, a phlebotomist at UNC Hospitals will draw two tubes of blood (~6 ml or 1-2 teaspoons) from you. Dr. Jonathan S. Berg and his colleagues will use this blood to do the research genomic sequencing. Part of the blood sample will be sent to the Medical Genetics Laboratory at UNC Hospitals It will be used to confirm positive or uncertain research results using established clinical testing procedures. If the blood sample does not provide usable data, we may ask to collect another blood sample or a saliva sample taken by a cheek swab.

What kinds of results might be found by genomic sequencing?
Genomic sequencing looks for genetic variants. Since we have over 3 billion "letters" of DNA, there are millions of differences in the DNA sequences or DNA letters between people. Almost all these differences, called "variants," are harmless but some can affect the way our bodies grow and develop. These variants might give us information about the medical condition that made you eligible for this study. This type of genetic information is called a ***diagnostic result***. There are three possible diagnostic results that you might learn from your research genomic sequencing:

1. Positive result: This type of result means that sequencing found one or more genetic variants that explain your condition. It may help your doctor understand how to treat your condition but it may not lead to specific treatments or prevention.

2. Uncertain result: This type of result means that sequencing found one or more variants that *might* explain your condition but the clinical meaning is *not* known for certain. This type of result usually does *not* result in a change in how your condition is treated.

3. Negative result: This type of result means that sequencing did *not* find any variants that could explain your condition. It is important to remember that genomic sequencing may not find all genetic variants that cause a condition. Scientists are still trying to learn the genetic causes of many health conditions. Therefore, a negative result does *not* mean that your condition is not genetic. It only means that genomic sequencing did not find an explanation.

What is the difference between research genomic sequencing and clinical genomic sequencing?
Clinical genomic sequencing is done in a special clinical laboratory to provide information for clinical care. The laboratory must pass certain tests such as being CLIA certified meaning it meets the federal regulatory standards for clinical laboratory testing, to show that the genomic sequencing results are accurate and reliable. A research laboratory does not have to meet these requirements.

For this reason, if research genomic sequencing finds one or more gene variants that explains or might explain your condition, these will be confirmed in the Molecular Genetics Laboratory, a clinical laboratory at UNC Hospitals. If confirmed, the results will be discussed with you and your parents. We will also make healthcare recommendations for your and possibly other family members.

You and your parents will be given one or more clinical laboratory reports that summarizes the clinically confirmed results. These reports will become part of your UNC medical record so that other health care providers involved in your care can be aware of this information.

It is not possible to confirm "negative" results from research genomic sequencing. It is not certain how often research genomic sequencing will miss gene variants that clinical genomic sequencing would have found. If your research genomic sequencing does not find any variants that explain or might explain your condition, you and your parents will be given a "research report" that summarizes the limitations of this testing. This report is not eligible to go into your medical record.

Rarely, genomic sequencing will find variants that are ***not*** related to the medical condition that made you eligible for this study, but that ***are*** related to ***other*** medical conditions. These variants are rare and we expect to find them in fewer than 5% or 5 of every 100 children in this study.

- These variants suggest that you currently have a serious medical condition **that can be treated** OR that you are at high risk for a future medical problem **that can likely be prevented**. These are called ***medically actionable secondary findings***.

- When these variants are confirmed by the Molecular Genetics Laboratory, we will discuss them with you and your parents. We will give you and your parents a clinical laboratory report with these results and they will become part of your UNC medical record. It is recommended that this information be reported whenever genomic sequencing is done. However, if you and your parents do not want this analysis to be performed when your genome is sequenced, you can indicate this decision at the end of this form.

Do you request the analysis of genes that could provide medially actionable information that is unrelated to your child's current condition?

_____I do wish to request this analysis _____ I do **NOT** wish to request this analysis

Most variants found by genomic sequencing have nothing to do with why you have a condition. We call these variants harmless or "benign" and we will not report them.

Your results, whether positive, negative or uncertain will be discussed with you and your parents. Your family may be asked to make another appointment to discuss your diagnostic results and, if you and your parents have consented to having these analyzed, any medically actionable secondary findings.

There are a few other things you should know about this study:

- If we find uncertain results in your genomic sequencing, they might be better understood if we test other family members to see if they have the same variant or variants. If we test family members, we will only look for the presence or absence of the specific variant(s) identified in your sample. If family members are offered this testing they will be asked to sign a consent form.

- If we find either a diagnostic result that clearly explains your condition or a medically actionable secondary finding, we may ask to test family members to determine the best way to provide them with medical care. This testing would not be part of this research study but may be obtained through a clinical appointment with a genetic specialist.

- Information about the genetic causes of health is changing. As a result, we plan to re-study your genetic information as part of this research study to determine whether there are any changes in the interpretation of your results. If there is new information important for your health, we will contact you.

What will happen to my blood sample?

We will label your blood sample with a unique study participant identifier (ID) and not your personal identifying information. Part of the blood sample will be sent to the UNC Biospecimen Processing Facility for DNA extraction and storage. A portion of this DNA sample will be transferred to the laboratory of Dr. Jonathan S. Berg for research genomic sequencing. Although research using these DNA samples will continue for an undetermined period of time, the study team may choose to destroy your uniquely coded research sample when the study is complete. The other part of the blood sample will be sent to the UNC McClendon Laboratories Molecular Genetics Laboratory for DNA extraction and storage. These samples will be used to confirm genetic variants found by genomic sequencing and to do quality control testing.

Who owns the samples?

Any blood, body fluids, tissue samples, or genomic sequencing data obtained in this study become the exclusive property of the University of North Carolina at Chapel Hill. The researchers may keep, preserve, or dispose of these samples, and they may use them for research that may result in commercial applications. There are *no* plans to compensate you or your parents for any future commercial use of these coded samples.

Research is designed to benefit society by gaining new knowledge. There is some chance you will benefit from having genomic sequencing if we find variants that explain your condition. Your participation will help us understanding how to use this test with patients and help us find out if using it improves a person's future medical care.

What are the possible benefits to you?

Research is designed to benefit society by gaining new knowledge. There is some chance you will benefit from having genomic sequencing if we find variants that explain your condition.

Your participation will help us understanding how to use this test with patients and help us find out if using it improves a person's future medical care.

What are the possible risks or discomforts involved with participation in this study?
We think that the risks to collecting the samples are low. An experienced technician in a phlebotomy laboratory will obtain your blood. If needed, cheek swabs will be done by a trained clinical staff member.

We also think that the foreseeable risks of storing your genetic material are low.

We think that the risks to your privacy and confidentiality are low. There is a small chance that someone may find out things about you (for example, that you have a genetic variant that increases your risk for a certain disease). We have safeguards to protect information while it is stored and used for research. These privacy protections are listed under the section "How will your privacy be protected." Genomic test results that are placed in the medical record have the same privacy protections as any other medical information located there.

Genetic testing can provide information about how health or illness is passed on within your family. This knowledge may affect your and/or your parents' emotional well-being. The results will be explained to you and you will receive genetic counseling to help you understand their meaning and implications for family members.

There may also be uncommon or previously unknown risks. You should report any concerns to the researchers listed on the first page of this form.

What if we learn new things or information during the study?
You will be given any new information gained during the study that might affect your medical care or your or your parent's willingness to continue participating in the study.

Will there be any cost to you for this research testing?
Neither you nor your parents will be charged for the genomic sequencing performed during your participation in the study.

Will you receive anything for your participation?
We will not pay you or your parents for consenting for your sample to be obtained.

How will your privacy be protected?
We may share DNA samples or genomic sequencing data with researchers at UNC or other institutions who are not a part of this study. Research studies may be done at many places at the same time. Your personal identifying information will *not* be included with these data or samples and will *not* be sent to other researchers who are not a part of this study.

Your samples will be uniquely coded with an ID number. We will keep the link between your participant ID number and your personal identifying information in a secured database with access restricted to certain study personnel. We will store paper study documents in a locked

filing cabinet in a locked office. We may store information from your medical records in the secured database.

Neither you nor your parents will be identified in any report or publication about the research findings using your data. Although we will make every effort to keep research records private, there may be times when federal or state law requires us to disclose records, including personal information. This is very unlikely. However, if disclosure is ever required, the University of North Carolina at Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, the information could be reviewed by representatives of the University, research sponsors, or government agencies for purposes such as quality control or safety.

You might be concerned about risk to privacy and confidentiality resulting in discrimination because of your genetic information. A Federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against someone based on their genetic information. GINA does *not* protect people against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does *not* protect people against discrimination based on an already-diagnosed genetic condition or disease.

Can you withdraw your consent for research testing?
Yes. You can withdraw your consent at any time, without penalty. If you decide that you no longer wish to have genomic sequencing, contact the researchers on the front page of this form.

Any genomic results that were confirmed by the Molecular Genetics Laboratory at UNC will remain a permanent part of your medical record. Any research analyses that are complete or in progress at the time you request to stop your participation will continue to be used as part of the study. If you end your participation, any remaining samples will be destroyed.

What will happen if you are injured by this research testing?

All research involves a chance that something bad might happen to participants. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from having your specimen collected. The University of North Carolina at Chapel Hill has *not* set aside funds to pay for any such reactions or injuries, or for the related medical care. However, by signing this form, you do *not* give up any of your or your parent's legal rights.

The IRB reviews all research on human volunteers to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at 919-966-3113 or by e-mail to IRB_subjects@unc.edu.

Optional Consent for Storing Biological Specimens and Related Study Data with Identifying Information After This Study Ends:

In the future, after this study is over, researchers may identify new questions that might be answered with the use of your study specimen (DNA) and related data. The specimen and related data from the NCGENES will be stored in what we call a "repository" or "data bank". Related specimen data includes things like the DNA variants or differences in DNA sequence. Some of these variants may be normal while other variants may explain a health condition. We will store this information with only a code or number that does not identify you. We will not share data that has your name or personal identifying information on it. We will keep a list that can link your identity to the code or number that is labeled on your information, but we will not share this link with anyone outside of the study team. When you turn 18 years old, we will remove the link so your information will be completely de-identified, that is no longer linkable to your identity.

It is unlikely that you will directly benefit from these future studies. Future studies that use the specimen or specimen-related data from this repository or data bank may help us develop new tests and answer important questions. For example, it may provide information that can be used to explain certain health conditions and to test for them.

The risks to the use of your study specimen are similar to the risks described above. Sometimes people are concerned that people may find out things about them (for example that the variants in their genes make them more susceptible to a certain disease). The use of the repository or data bank to store the specimens and data has protections to prevent this from happening. Researchers who use the specimen or data will not have access to the link between the data and your identity. There will be no cost to you for the storage and use of the data for research purposes. At any point after the study ends you can decide that you want to withdraw your data from the data bank. To do this, you or your parents should contact the researcher whose name is listed on the front of this consent form.

Do you agree to the use of your data in future studies after NCGENES?

_____ I agree to this use _____ I do **NOT** agree to this use

Title of Study: North Carolina Clinical Genomic Evaluation by Next-gen Exome Sequencing, phase 2 (NCGENES 2) **Principal Investigators**: Jonathan S. Berg, MD, PhD, Bradford Powell, MD, PhD, Christine Rini, PhD.

Participant's Agreement:

I have read the information provided above. I have asked all the questions I have at the present time. I voluntarily agree to have research genomic sequencing as part of the NCGENES 2 study.

_____ _____

Your signature, if you agree to have research genomic sequencing Date

_____

Your printed name, if you agree to be in the study

Signature of Research Team Member Obtaining Assent	Date
Printed Name of Research Team Member	