SickKids
THE HOSPITAL FOR SICK CHILDREN
Research Ethics Board

Research Consent Form for Parents of a non-capable child – Genetic Analysis

Title of Research Project:
The SickKids Genome Clinic: Developing and evaluating clinical uses of Whole Genome Sequencing

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Introduction

Dr. _____ has referred you and your child to us as a potential participant in a research study at the Hospital for Sick Children. This consent describes the study and what it means to participate. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at SickKids, or with family, friends, or your personal physician or other health professional.

Purpose of Research

The goal of this study is to learn how to best use a new kind of genetic test, whole genome sequencing, in clinical care and in research. The word genome is used to describe all of the genetic material inside our cells, including the thousands of genes that contain instructions for how our bodies develop, grow and function. You are being invited to provide a biological sample to facilitate interpretation of your child's DNA sequencing results.

Genes are made up of many individual building blocks (bases) of DNA (deoxyribonucleic acid), strung together in specific sequences. Genes are linked to one another with additional DNA sequences. DNA sequences can vary slightly from one person to another. These differences in DNA sequence are called variants. Variants are what make each individual's genome unique.

Variants range greatly in size. The most common variants affect only a single base of DNA, while rare, very large variants can affect millions of bases. Large variants are called copy number variants Variants are usually harmless, but even small variants can sometimes prevent a gene from working properly. These harmful variants are usually called mutations, and they can cause genetic disorders Other genetic disorders can be caused by having too many or too few copies of one or more genes, due to the presence of a harmful copy number variant.

Current genetic testing typi ally involves either a) a detailed examination of one gene or a few genes at a time, or b) a genome wide search for copy number variants. A new kind of genetic test, called whole genome sequencing, allows us to test DNA from an individual and find variations in DNA sequence and in gene copy number for thousands of their genes at the same time. Some of these gene variants may have important health implications for your child and for your family, while others may not.

In this study we will use whole genome sequencing to dentify variants in DNA from your child. We expect to find thousands of variants, most of which will be harmless. We will look for those few variants that could affect your child's health; these variants could also impact the health of your family members. We expect to find 4 types of medically important variants using whole genome sequencing:

1) Harmful variants that affect genes that we already know play a role in your child's disorder. These are the genetic variants that standard genetic testing usually looks for. We want to learn if whole genome sequencing is better than standard genetic testing for identifying these variants.

2) Harmful variants that affect genes that might be associated with your ch ld's disorder. We have yet to identify all of the genes that can cause genetic disorders. Finding and studying these harmful variants could lead to our discovering new genes that could be the cause of your child's disorder. This new knowledge may be important in clarifying the diagnosis of your child's disorder, improving our understanding of the condition, and in designing new treatments.

3) Gene variants that are not directly involved in causing your child's disorder but may affect his/her response to drug therapy. Knowing these variants could help us develop better treatments that are specifically tailored to your child.

4) Variants that may affect your child's or your family's risk to develop conditions unrelated to your child's disorder. We call these incidental variants (see below). We want to learn how often these occur, how best to deal with them, and if knowing about them in advance can allow us to lessen their impact on health.

Description of the Research:

This is a five year research project, requiring at least a one year commitment on the part of participants. As many as 200 individuals and their parents may be recruited to this study in the first year. Participants will be seen for three to five 60-120 minute appointments at the genome clinic during the course of one year and may be contacted several times in the subsequent four years to receive additional information discovered by the clinic or, if they have consented to be contacted, to participate in related research projects.

Genetic Analyses: A small blood sample (5-10 ml or 1-2 teaspoons) will be taken from you by a trained health care professional. DNA and RNA will be isolated from the cells in the blood and used for geneti testing.

You should know that:

1. The DNA and RNA samples from the blood and the test results obtained from analyzing the DNA will be securely stored indefinitely for research unless and until you (or your child once he/she is able to consent) tell us otherwise.

2. We will not sequence all of your DNA. However, if genome sequencing identifies a potentially important genetic variant in your child, we may test the samples from both biological parents (if available) using other targeted methods to help us interpret the variant. Checking parents for the same var ant(s) found in a child often helps us understand the potential significance of any variant. We may also test your RNA sample, as examining RNA can sometimes help us determine if a genetic variant affects the function of a gene.

Reporting of genetic variants:
If a medically significant variant is identified in your child, you sample may be tested by other targeted methods to facilitate interpretation of your child's DNA sequencing results. Since genetic information is passed on from parents to child en, some of the variants identified in your child may also be important for your own health.

As previously stated, we will not sequence all of your DNA. However, if genome sequencing identifies a potentially important genetic variant in your child, your sample will be tested by targeted methods for the same variant. We may then report this information to you. What we will tell you about one of your own variants will depend on what kind of variant it is and the groups of disorders you wish to learn about. We will only talk with you about those medically actionable variants that we think are likely to have a major effect on health. Any of your own variants that we report to you as medically important will be filed in your medical records. We will also provide this information to your primary care physician if you wish.

Here we will focus on the types of variants we may identify in your own DNA when we are examining your genome for medically important variants found in your child:

1. *Harmful genetic variants (mutations) associated with your child's condition:* We will tell you if our genetic analysis identifies a genetic variant in your DNA that we believe contributes to your child's condition. The study genetic counselor and/or health care provider (doctor or nurse) will discuss these findings with you).

2. *Pharmacogenetic variants:* These are genetic variants that influence how effective or toxic a medication or drug therapy can be. We will tell you if the genetic analysis identifies a variant in your DNA that we first found in your child's DNA and that could have a major effect on responses to drug treatments.

3. *Incidental medically actionable variants:* Although our analysis will focus on the genes that may contribute to your child's disorder, we will be screening all of the DNA obtained from your child's blood sample (i.e. your child's whole genome). As a result, there is a possibility that we will uncover genetic variants associated with a high chance of developing a serious condition that is not related to your child's current condition. For some of these findings, seeing a medical specialist could be helpful as there might be specific health recommendations for your child, yourself, or family member(s). Variants that have a high chance for a serious health problem and for which treatment and/or screening is available a e called *incidental medically actionable variant(s).*

   We will only talk w th you about those medically actionable variants that we think are likely to have a major effect on your health. In addition, whether we tell you about a medically actionable va iant found in your own DNA depends on which kind of variant it is, as described below:

   Incidental variants that are medic lly actionable in adulthood: These are variants associated with disorders for which treatment and/or screening is not available until adulthood. Because the conditions associated with these variants don't require any intervention during childhood you can choose if you want to receive information about these variants. Because many of these variants are passed on from parent to child, identification of one of these variants in your child could have implications for your health as well. In the Genome Clinic Consent tha you previously reviewed, we asked whether you want to know about your child s genomic variants that are associated with adult conditions. We are now asking what you want to know about your own variants that are associated with adult cond tions.

   ☐ Yes, I do want to learn about my own variants that are associated with adult conditions and first discovered in my child. We will ask you to tell us which groups of disorders you wish to learn about and which you do not. We will ask you again about your choices when we have test results to tell you. See Appendix I for a list of the groups of disorders.

   ☐ No, I do not want to learn about my own variants that are associated with adult conditions.

4. *Carrier status:* Humans have two copies of most of our genes - one copy from our mother and one copy from our father. Having a second copy of a gene can protect us

against many harmful genetic variants (mutations), because the presence of a working copy of the same gene frequently prevents these variants from causing disease. Genetic disorders are called "recessive" if they only occur when there is no normal copy of a gene to perform the work that the disease-causing variant cannot do. For recessive disorders, individuals who carry a mutation in one copy of a pair of genes are said to be a "carrier" of that disorder. Carriers are usually healthy. However, their children can be at increased risk to have that specific genetic disorder.

Because there are thousands of different recessive conditions almost everyone is a carrier of at least one of these conditions. As a result, we expect that some of the va iants we find in your child's DNA will be carrier mutations for a recessive condition. In the Genome Clinic Consent that you previously reviewed, we asked whether you want to know about your child's carrier mutations. We are now asking what you want to know about carrier mutations we might discover in your own DNA.

If you dec de that you wish to learn about your own carrier mutations, we ask that you tell us which groups of disorders you wish to learn about and which you do not. We will ask you again about your choices when we have test results to tell you. See Appendix I for a list of the groups of disorders.

☐ Yes, I do want to be informed of my own carrier mutations.

☐ No, I do not want to be informed of my own carrier mutations.

If we report that you have a medically significant variant or carrier mutation, we will work with you and your family physician to ensure that you are referred to the appropriate specialists for follow-up of these variants.

It is important to know that we will not examine the vast majority of your genomic variants. Rather we will only examine your DNA for those few variants that we found in your child and we think might be medically important. We will not return information about variants that are not medically actionable. We will also not inform you of any genetic variants that are thought to be harmless or whose impact on health is either minor or unknown a the time of our analysis. We also will not give you a copy of your genomic sequence. We will not place any of this information into your medical records at SickKids.

Medical Records: We may need to obtain your medical records to aid in analysis of potentially significant variants identified in you and/or your child and to ensure appropriate medical management related to such variants. We will ask your permission to access your medical records if necessary.

Future studies: We will likely contact you in the future for several reasons:

1. Members of our research team will attempt to re-contact you if, as part of this research project, we re-analyze your DNA and RNA at a future date and identify additional genetic variants that:
   (i) May be incidental variants *medically actionable in adulthood* (If you agree that you want to know about this type of variant.)

(v)May be variants associated with being a carrier for an autosomal recessive condition (If you agree that you want to know about this type of variant.)

Opt out:
☐ Please do **not** contact me to tell me about additional genetic variants that you find when you re-analyze my DNA and RNA.

2. You may also be contacted by us in the future for additional clinical information so that we can learn if your health has changed.

Op out:
☐ Please do **not** contact me in the future to request additional clinical information about heal h.

3. You may be re-contacted and invited to participate in follow-up research to get your feedback on this consent process, how genetic information was communicated with you, and how learning about your family's genetic variants might have affected your life and that of your child. We will provide you with additional information about that research study and a separate consent form when we contact you.

Opt out:
☐ Please do **not** contact me in the future to invite me to participate in the follow-up study.

Please keep your contact information up to date so we may contact you for the reasons outlined above.

Other Research Studies:
If you agree, your DNA sequence information and clinical information about you (phenotypic information) may be used for other research projects after personal information that would identify you has been removed. Your participation in any such additional research would be in addition to your participation in this project and is vo untary You may opt-out of participating in these additional research studies by indicating your choice below

☐ I give my permission for my DNA sample, RNA sample, sequence information and clinical information to be used for other research projects.

_____ _____

Printed Name of Participant Participant's signa ure & date

☐ I do **no**t give my permission for my DNA sample, RNA sample, sequence information and clinical information to be used for other research projects.

Potential Harms:
I understand that whole genome sequencing is a new technology and the potential psychological and social risks of participating and receiving genomic information are not fully known at this time. For example, some people find it upsetting to learn about the genetic cause of their child's disorder or about other incidental gene variants.

Because parents and children can share genetic variants, the discovery of harmful variants in your child's genome may lead to identifying the same variants in your own genome. It may be upsetting to learn that you or other members of your family share harmful genetic variants with your child.

The interpretation of your gene changes will depend in part on family information you will have provided. If the gene changes in you do not match up with your family information, it may be that the genetic test is faulty, or that the family information that you gave was not fully accurate. For example, this might happen if the child is adopted, or if the biological father is different from the apparent father (known as non-paternity).

There may be a small amount of bleeding when blood is taken from a vein and there may be slight discomfort and bruising or redness that will usually disappear in a few days. A cream (EMLA) to numb the puncture area will be made available upon request.

Potential Benefits to your child and your family

You and your family may or may not benefit from participating in this study.

It is possible that we will be able to identify the genetic cause of the genetic condition in your family. If published in the scientific literature, these research findings may one day allow a commercial company to develop a test or a treatment for your condition. Neither you nor the Consortium will benefit financially from the development of these types of tests or treatments. You will not incur any costs nor will you be paid to participate in this research.

However, one goal of this study is to help improve our ability to find the genetic cause of the disorder in your family which may potentially help with medical care or treatment. Clinically validated research results will be provided to you. Gene ic counselling will be offered to you to help you understand these results. Any Incidental findings which are medically actionable in adulthood and variants indicating carrier status may be communicated to you depending on your choice. You may also change your mind about this choice in future. This information may directly impact your and other family members' health care.

Our current genetic knowledge is imperfect but improving at a rapid pace. If you do not receive any medically actionable results at this time, this does not mean that none are present. Also, not all genetic changes leading to health problems have been discovered as yet. If you have any health concerns you should still seek medical care just as you would without the results of genome sequencing. We would ask that you contact us with new, significant health information. Lastly, genetic testing approaches are also improving at a rapid pace and newer genome testing options may be offered to you in future.

Potential Benefits to Society

Although you may not benefit directly from this study, results from the study may benefit other patients in the future.

Confidentiality

We will respect your privacy. No information about your identity will be given to anyone outside of the study investigators or be published without your permission, unless required by law. For

example, if you have an illness that could spread to others, if you or someone else talks about suicide (killing themselves), or if the court orders us to give them the study papers.

SickKids Clinical Research Monitors, or members of the research team may see your health record to check on the study. By signing this consent form, you agree to let these people look at your records. We will put a copy of this research consent form in your patient health record and give you a copy as well.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (including the individuals described above) will have access to the data. Published study results will not reveal your identity.

The data collected from you will be kept strictly confidential. Confidentiality will be maintained at all times by assigning number codes rather than names to the DNA and RNA samples. The code will be kept in ocked files and available only to study investigators. No information that reveals your identity will be released or published without your consent.

If you agree, the DNA and RNA samples from your blood and your genome sequence will be stored indefinitely with the number codes (unless otherwise indicated), so future genetic research studies can be conducted which may or may not be related to your child's condition.

If you apply for insurance and provide written consent, the information in your medical records, including the results of any clinically validated genetic testing obtained through this research study, will be available to the company.

Reimbursement:
You will not be paid for participating in this study.

Participation:
If you choose to take part in this study you can withdraw from the study at any time. If you choose to withdraw from this study you will have the option to prevent any future use of your sequence, DNA sample, RNA sample, and clinical data in this project. You cannot request that your data be removed from any analyses performed prior to the request for withdrawal. The care your child receives at SickKids unrelated to this study will not be affected in any way whether you take part in this study or not.

During this study we may create new tests, new medicines, or other things that may be worth some money. Although we may make money from these findings, we will not give you any of this money now or in the future.

If you become ill or are harmed because of study participation, we will treat you for free. Your signing this consent form does not interfere with your legal rights in any way. The staff of the study, any people who gave money for the study, or the hospital are still responsible, legally and professionally, for what they do.

Sponsorship:
This study is being led by Drs. Stephen Meyn and Peter Ray at The Hospital for Sick Children. The major funder of this research is the Centre for Genetic Medicine at SickKids. In addition, Complete Genomics is providing some of the study's whole genome sequencing for no charge.

Conflict of Interest
Dr. Stephen Meyn, Dr. Peter Ray, Dr. Sarah Bowdin and the other research team members have no obvious conflict of interest to declare.

CONSENT
I have read pages 1 to 10 of this form and Appendix I.

By s gning this form, I agree that:

1) You have explained this study to me. You have answered all my questions.
2) You have explained the possible harms and benefits (if any) of this study.
3) I know what I could do instead of taking part in this study. We understand that I have the right to refuse to take part in the study. I also have the right to withdraw from the study at any time. My decision about taking part in the study will not affect my child's health care at Sick Kids.
4) I am free now, and in the future to ask questions about the study.
5) I have been told that my medical records will be kept private except as described to me.
6) I understand that no information about me or my child will be given to anyone or be published without first asking our permission.
7) I agree, or consent, that I_____ may take part in this study.

_____	_____
Printed Name of Participant	Part cipant's signature & date
_____	_____
Printed Name of person who explained consent	Signature of Person who explained consent & date
_____	_____
Printed Witness' name (if the participant does not read English)	Witness' signature & date

If you have any questions about this study, please call Nasim Monfared, a genetic counsellor involved in this research, at 416-813-7654 ext. x202054

If you have questions about your rights as a subject in a study or injuries during a study, please call the Research Ethics Manager at 416-813-5718.

REAFFIRMATION/WITHDRAWAL OF CONSENT

I contacted the participant on by [ ] phone, [ ] E-mail, or [ ] in person.

At that time they agreed to:

[ ] continue to participate in the study [ ] withdraw from the study

Comments

_____ _____ _____ _____

Printed Name f person who explained consent Signature of person who explained consent & date

Appendix I – Initial Preferences for Return of Genomic Results:

Incidental Variants that are *Medically Actionable in Adulthood*

These genetic variants are not related to your child's current condition but they carry a high risk of developing a serious disorder for which treatment and/or screening is not available until adulthood. We have divided these disorders into five groups in the table below. Please indicate your choices regarding learning about your own incidental variants that are medically actionable in adulthood. We will ask you to confirm these choices when we have test results to tell you.

Type of In idental Variant	**I want to know these results**	**I do *not* want to these results**	**I haven't decided yet**
Risk for cancer	☐	☐	☐
Risk for heart disease and related diso ders	☐	☐	☐
Risk for neurologic condi ions	☐	☐	☐
Risk for other chronic condition	☐	☐	☐
Risk for mental health diso ders	☐	☐	☐

Some parents are particularly interested in learning (or not learning) about their own risk for incidental variants that carry a risk for a specific disorder that is actionable in adulthood. If there are any of these disorders that are of spec al concern to you, please list them below, along with whether or not you want to learn about their variants.

Incidental Variants associated with spec fic dise listed below:	**I want to know these results**	**I do *not* want to these results**
1.	☐	☐
2.	☐	☐
3.	☐	☐
4.	☐	☐
5.	☐	☐

Incidental Variants that Indicate *Carrier Status*

"Carriers" are individuals who carry a mutation in one copy of a pair of genes associated with recessive genetic disorders. Carriers are usually healthy. However, thei children and other family members can be at increased risk to have that specific genetic disorder.

Please indicate below your choice regarding learning about carrier mutations in your DNA. We will ask you to confirm your choice when we have test results to tell you.

Type of Carrier Status Variant	**I want to know these results**	**I do *not* want to these results**	**I haven't decided yet**
Risk for cancer	☐	☐	☐
Risk for heart disease and related conditions	☐	☐	☐
Risk for neurologic conditions	☐	☐	☐
Risk for other chronic conditions	☐	☐	☐
Risk for mental health conditions	☐	☐	☐

Printed Name of Parent/Legal Guardian

Parent/Legal Guardian's signature & date

Printed Name of person who explained consent & date

Signature of Person who explained consent

Printed Witness' name

Witness' signature & date