Return of WGS Results in Paediatric Research:

Sample Consent Clauses

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VIEWPOINT

Return of whole-genome sequencing results in paediatric research: a statement of the P^{3}G international paediatrics platform

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Keywords: Paediatric research; whole-genome sequencing; best interests of the child

Whole-genome sequencing (WGS) reveals the genome of an individual including both rare mutations and genes that

EXISTING GUIDANCE

General criteria

At a general level, publically accessible lay

the child's best interests should guide decision making.[6]

The release of WGS information is also complicated by the fact that children mature as they grow older and thus become more autonomous in their decision-making abilities. The mechanism for recognizing this in the research context is requiring assent from the child according to the degree and level of his or her maturity.[7] This is how the child can be involved and engaged in the decision-making process.[8,9]

Generally, professional guidance on the communication of genetic information has favoured waiting until the child is capable of understanding its nature and consequences, including familial consequences. Accordingly, at maturity, a child could decide to undergo genetic testing or not. But today, with the arrival of WGS, we are faced with the issues of which WGS results should be communicated (or not) before the child reaches the age of majority as well as the familial consequences.

Specific criteria

The 2005 European *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*[10] states

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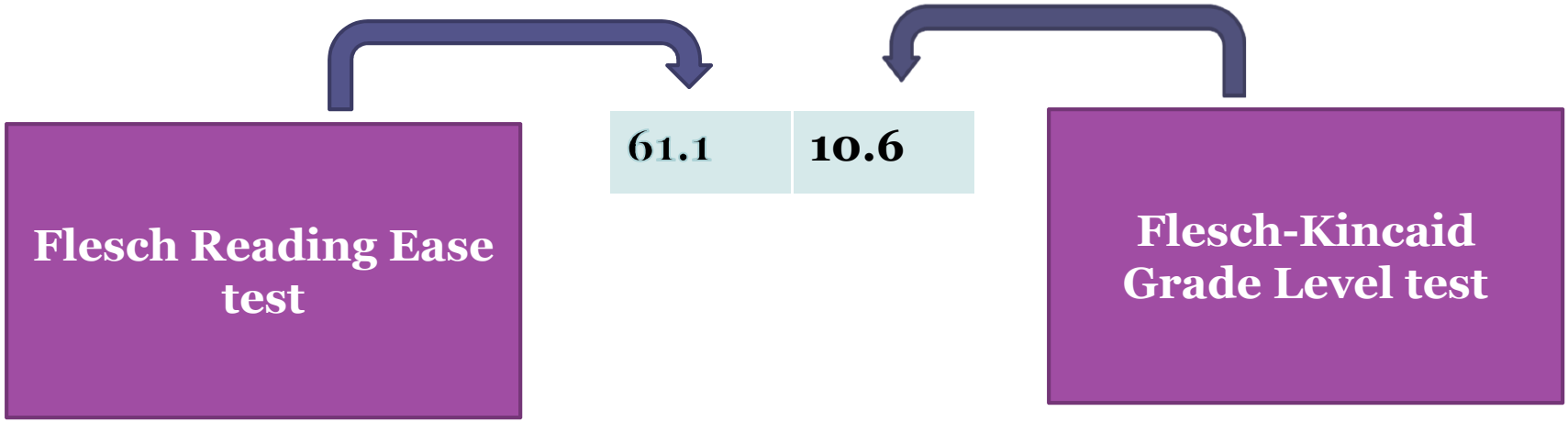
Assessing Readability

Readability Statistics (Microsoft Word)



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Recommendation 1: The issue of the possible return (or not) of WGS results should be discussed during the informed consent process

Reporting of genetic variants: We expect to find thousands of genetic variants in your child's DNA. We will sort the variants into groups based on how they may affect your child's health. Some of your child's variants also may be important for your own health, since genetic information is passed on from parents to children. Any of your child's variants that we report to you as medically important will be filed in your child's medical record. (cont'd)

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What we will tell you about a variant will depend on what kind of variant it is. The different groups of variants and how we will report them to you are discussed below:

1. *Harmful genetic variants (mutations) associated with your child's condition:* We will tell you if the genetic analysis identifies a genetic variant believed to be a cause of your child's condition…
2. *Other genetic variants*: We will not inform you of any genetic variants that are thought to be harmless or whose impact on health is either minor or unknown at the time of our analysis. We also will not give you a copy of your child's complete genome sequence. We will not place any of this information into your child's medical records.

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We may not release certain types of results, including:

- Inconclusive or uncertain incidental findings,
- Results that cause a difference in response to medication or a minor increased risk for common adult onset diseases, such as heart disease or Alzheimer's disease,
- Results that do not have associated health problems, such as baldness,
- Results related to incidental findings in family members, or
- Other results that the study team determines are inappropriate to release, such as those restricted by patents or regulations.

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You will receive access to a personally- controlled health record (PCHR). Through the PCHR, you/your child will be able to review your/your child's research data and, in the future, genetic test results. We have not yet created an organized way for you to view your/your child's genetic research data. In the future, you/your child will have the option of viewing your/your child's genetic test results through the PCHR after signing a separate consent form. If you/your child do not have a personal email account and/or access to the internet, we will help you set up an email account and locate places within Children's Hospital and in the community where you can use a computer to log-in to you/your child's PCHR. (cont'd)

Recommendation 1: The issue of the possible return (or not) of WGS results should be discussed during the informed consent process

(cont'd)

The messages delivered by the system are meant to provide you with study information and results. They are not meant to replace the information and support that can be given in a clinical appointment with a genetic counselor, geneticist, and/or other clinicians. A member of the study staff may suggest a clinical appointment with a physician, genetic counselor or other health care provider so that you/your child may receive further assistance in understanding and using the study information.

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You and your child will not be told about your child's individual research results.

The results are only for research purposes and will be stored in the [biobank name]. You and your child will not be told of the results of any research tests performed nor any personal information resulting from the analysis of your child's sample. No information about genes or inheritance will be reported to you or your doctor. Research results are often preliminary, inconclusive, and not necessarily valid for use by your physician in the management of your child's healthcare.

48.7	11.0

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If a researcher finds that the results obtained from the genetic testing performed on your samples may be useful for your health care, you will be contacted and given the choice to learn the test results. At this time, you will be given general information on the potential risks, benefits, and costs of choosing to learn the test results. The risks of learning genetic test results may include emotional upset, insurance or job discrimination, and/or family conflicts from learning unknown information about your parents or blood relatives. No test results will be put into your medical record unless you choose to learn the results of the testing. Sometimes results should be released only through a genetic counselor who can help explain the possible risks and benefits of learning this information.

43.9	13.6

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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 doctor or your other healthcare provider who ordered the test.

1. Positive for disease-causing mutation(s): You may have one or more mutation or mutations known to cause disease consistent with your symptoms and would be interpreted as the cause of your symptoms. (cont'd)

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2. No disease causing mutation(s) found: It is possible that the test will not find any genetic change that could explain your symptoms. This type of test result does not mean your condition is not genetic. The result would not take away whatever current diagnoses doctors may have given for your condition. (cont'd)

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3. Variant with uncertain significance: Sometimes the test will find a genetic change that is predicted to be important, but has not been seen before in people with your condition. The genetic change may or may not be the cause of your symptoms. The lab would report it as a "variant with uncertain significance" if there is evidence strongly suggesting that it is related to your condition. (cont'd)

50.2	10.5

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4. "Incidental findings": These are test results that are not related to the symptoms for which the test was ordered. They might indicate that you have another previously undiagnosed, potentially serious condition. Some of these diseases might manifest later during your lifetime and knowing about them might help to prevent development of serious medical conditions. A list of such conditions is provided below. You may decide whether or not you want to be alerted to the presence of these conditions…[provide list] (cont'd)

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Please state whether you want to be informed about incidental findings causing the conditions listed.

____(Initial) I would like to learn of incidental findings in my child's WGS related to the conditions listed.

____(Initial) I would NOT like to learn of incidental findings in my child's WGS related to the conditions listed.

50.2	10.5

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Recommendation 2: During the consent/assent process, the child or adolescent's views should be solicited and given due weight and consideration in accordance with her or her age and maturity

Once you/your child turns 13 years of age you/your child can receive a separate login to access the PCHR. This means parents/guardians and participating children aged 13 years and older will have the ability to see and receive the same information as part of this study. You/your parent/legal guardian will have to sign a permission form allowing us to create a separate login for you/your child once you/your child turns 13 years of age.

Once you/your child turns 18 years of age, you/your child will have the ability to decide to discontinue parental access to your/their PCHR record.WGS related to the conditions listed.

55.6	12.2

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Recommendation 2: During the consent/assent process, the child or adolescent's views should be solicited and given due weight and consideration in accordance with her or her age and maturity

The study genetic counselor and/or health care provider (doctor or nurse) will discuss these findings with you and/or your child (depending on your child's capacity to understand this information).

Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

Will I be told individual results from the testing?

In general, you will not be told individual results.

However, it is possible that researchers may find a result that could be important to your/your child's health. If you say that you want to be told about these results, there is a process for providing them. A doctor at [site name] who understands the results will try to contact you to discuss the result. During this process, it is possible that your insurance company may also learn the result.

67.2	7.5

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Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

If we find information by chance that relates to another condition or conditions, besides the one under study, and it is life threatening or very serious and there is treatment available, we will re-contact you unless you indicate you do not wish to be contacted. For this reason, it is important to advise our department of a change in phone number or address if you move as we do not have the resources to track participants.

Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

If a researcher discovers a research result that may be important, the result will be reviewed by a board called the Informed Cohort Oversight Board (ICOB). The ICOB is a group of scientists, physicians, genetic counselors and other health professionals that is completely separate from the investigators of this research project. The ICOB will decide if it is important to inform participants such as you/your child of study findings and how to best inform participants of those results. When deciding this, the ICOB will look at the accuracy and health importance of the research finding in addition to other factors. This means that not all research results will be given to participants including yourself/your child. (cont'd)

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Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

(cont'd)

If the ICOB decides it is important to send out a message to you/your child, a message explaining the finding will be sent anonymously to your/your child's PCHR. You will have to log into your/your child's PCHR account to view the message. The message will include the name and contact information for a member of the study staff who will be available to answer questions regarding any messages that have been sent to you/your child.

Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

Incidental findings: It is important that you understand that although we may be sequencing you/your child's entire genome, we will not be reviewing all of this information in detail. However, there is a chance we may uncover health information (information we were not looking for) which would directly impact the care of you/your child during childhood (this is what we refer to as "incidental findings"). If the study identifies such information, the study doctor will inform you/your child. Should this happen, repeat testing might be recommended to confirm any research results and the benefits and risks as well as possible inconveniences will be discussed with you/your child.

42.4	11.0

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Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

In the course of this research study, unexpected findings that are outside the scope of our research objectives could be discovered. Where these findings have been interpreted as a very high risk of a serious, treatable or preventable condition, they will be returned to you. If you so wish, we will communicate these findings to you with the help of your child's physician.

56.6	10.5

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Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

Incidental medically actionable variants: Although our analysis will focus on the genes that may contribute to your child's condition, we will be screening all of the DNA obtained from your child's blood sample (i.e. your child's whole genome). As a results, 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 or family member(s). We call variants that have a high chance for a serious health problem and for which treatment and/or screening is available: *incidental medically actionable variant(s)*. (cont'd)

30.0	16.5

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Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

We will only talk with you about those medically actionable variants that we think are likely to have a major effect on health. In addition, whether we report a medically actionable variant to you depends on which kind of variant it is, as described below: (cont'd)

Recommendation 3: WGS results that are scientifically valid, clinically useful, and reveal conditions that are preventable and actionable during childhood should be offered

a) *Incidental variants that are medically actionable in childhood*: These variants are associated with conditions for which treatment and/or screening can be started during childhood. Because these variants could affect your child's health before s/he becomes an adult we will *always* discuss these variants with you (and your child, depending on capacity to understand this information). We will then work with you, your child, and your pediatrician/family physician to ensure that you are referred to the appropriate specialists for follow-up of these variants…

30.7	16.0

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Recommendation 4: Mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult

There are certain conditions that do not develop until the adult years (>18 years of age). It is standard of care not to offer genetic testing to children for these adult onset disorders until they have reached 18 years of age and have decided they would like to know this information. Therefore, we will NOT send any messages about adult-onset disorders to you/your child and we will NOT allow access to the genetic data that corresponds to any adult-onset disorder until you/your child reaches the age of 18 years.

Recommendation 4: Mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult

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. Some changes in genes might make a person *slightly* more likely to develop a type of common condition that happens in adults, such as diabetes or heart disease. Because these changes are not well understood, they are not looked at in detail or included in the report. (cont'd)

56.2	**11.6**

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Recommendation 4: Mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult

(cont'd)

2. Some changes in genes might make a person *much* more likely to develop a type of condition that happens in adults, such as Alzheimer's disease. However, these changes do not guarantee that the condition will develop in a given individual, and even though the increased risk is known, no action can be taken to modify it.

Recommendation 4: Mutations that predispose the child to develop an adult-onset disorder, even if accidentally discovered in the research process, generally should not be returned. This allows the child to make his or her own decision about receiving the results as an adult

Incidental findings (not medically actionable in adulthood): It is possible that we will find variants in genes associated with adult-onset conditions that are *not considered to be medically actionable* (e.g. Alzheimer's disease or Huntington disease). We will not return this information about your child. Neither will we place this information into your child's medical records. When your child is old enough to decide if they want this information, s/he will likely be able to obtain it independently through updated genetic testing.

Recommendation 5: Questions, which should arise rarely, of whether the child would benefit on balance, from disclosure because of the potential benefit to the family from knowing about a highly-penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis

Genome sequencing can also reveal information that may not affect your child's health right now but it may be helpful to know later in life because of the risk of developing a serious but preventable and treatable disease later on. If a child has one of these kinds of mutations, he or she probably inherited it from a parent. Therefore parents and other family members might want to be screened. However, some people do not want to know this kind of information. Please initial below whether you would like this type of genetic information to be included in your child's sequencing report: (cont'd)

52.3	11.2

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Recommendation 5: Questions, which should arise rarely, of whether the child would benefit on balance, from disclosure because of the potential benefit to the family from knowing about a highly-penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis

(cont'd)

- Yes _____ I would like to receive information about whether my child has inherited any mutations that indicate that they are a carrier of a genetic disorder.
- No_____I would not like to receive this information and do not want it included in my child's sequencing report.

Recommendation 5: Questions, which should arise rarely, of whether the child would benefit on balance, from disclosure because of the potential benefit to the family from knowing about a highly-penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis

What is the potential impact to my family if my child takes part?

If the research discloses that one of your child's family members may be at risk of a life-threatening or serious illness for which treatment is available or pending, this information may, with the prior approval of the Ethics Committee, be offered by the study doctor to the family member, even if you as the participant's parent/guardian do not consent to this.

32.3	9.3

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Recommendation 5: Questions, which should arise rarely, of whether the child would benefit on balance, from disclosure because of the potential benefit to the family from knowing about a highly-penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis

Incidental variants that are medically 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 do not 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. You may want to know about variants associated with certain adult conditions and not others, therefore we will ask you to tell us which groups of conditions you wish to learn about and which you do not. (cont'd)

77.0	**4.9**

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Recommendation 5: Questions, which should arise rarely, of whether the child would benefit on balance, from disclosure because of the potential benefit to the family from knowing about a highly-penetrant gene they may have that poses serious risk to health and that is preventable or treatable, should be assessed on a case-by-case basis

☐ Yes, I do want to learn about variants associated with adult conditions. We will ask you to tell us which groups of conditions 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 … for a list of the groups of conditions.

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

77.0	4.9

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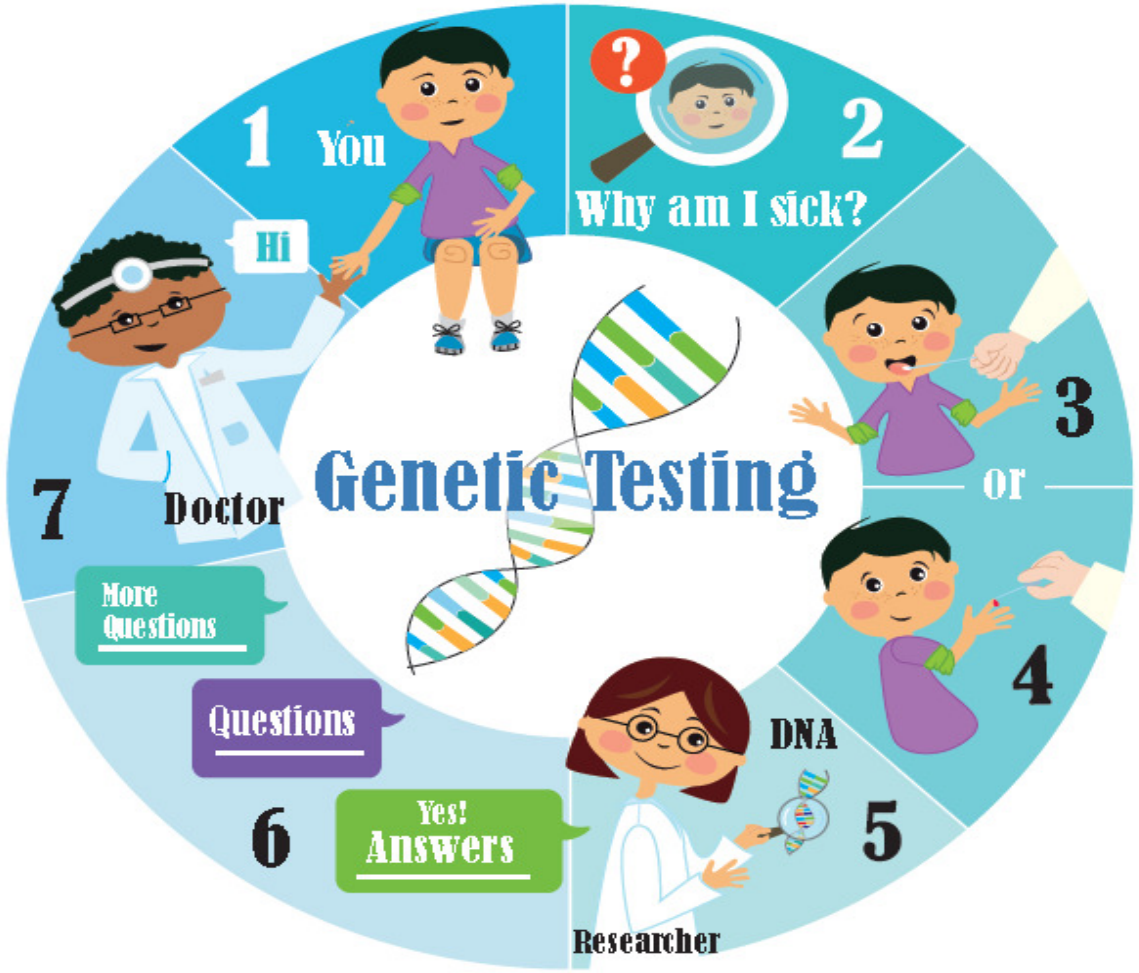

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