Modified Delphi survey to inform the Return of Raw Genomic Data Policy and protocol

Thank you for agreeing to participate in this expert review (Delphi technique – McKenna, 1994) of the ZERO2 Return of Raw Genomic Data Policy and protocol. Both your time and input are greatly appreciated.

A policy regarding the return of raw genomic data defined as the uninterpreted genomic sequence reads before annotation and analysis obtained from the genomic sequencing (either somatic or germline) of a tissue sample from participants enrolled in ZERO2 is required as noted in the NHMRC Guidelines for the Ethically Defensible Plan. Any such policy needs to describe the process for how the data would be returned.

In order to receive feedback from a drafted policy and protocol, it is anticipated that there will be three rounds of consultation.

- **Round 1 (this Round)**: you will be asked to comment on the content that has been drafted for its relevance and clarity as well as provide other content that you think needs to be added. The round will be open for one week for comment.
- The feedback will be analysed, and the content modified according to a recommended 80% consensus level. Where statements in the content receive 80% consensus support, for both relevance and clarity, they will be accepted for the final policy/protocol draft.
- **Round 2:** if there is <80% for either relevance or clarity for any statement within the content, the statement will be amended/removed, and that part of the content will be presented back to the group for review. You will be asked to review any new or amended statements for relevance and clarity. You will be provided with the Round 1 relevance and clarity results, feedback received, and the original and amended statements. Where feedback is minor, you will be presented with a summary; if complex, you will be presented with expert comments to consider. If an amendment is made, the rationale will be provided.
- **Round 3:** Review of any remaining statements where >80% consensus had not been reached. If consensus is not reached, another round of these statements may be required.

The draft document is available here to download as a pdf version of the draft document which is in 2 parts: The Policy (1) and the Process (2).

Below is a link to the Survey and a code to use to enter.

We will also be asking you for limited demographic data including your area of expertise.

Each statement will be a screenshot so you cannot amend it but there is a place for comments and suggested changes. You will be asked to state your level of agreement in terms of clarity and relevance on a 5-pont Likert scale form strongly agree to strongly disagree as well as exploring other views.

Part 1 – the policy

Scope

For the purposes of this policy, raw genomic data is defined as the uninterpreted genomic sequence reads before annotation and analysis obtained from the genomic sequencing (either somatic or germline) of a tissue sample from participants enrolled in ZERO2. Biospecimens are any tissue/blood samples provided by participants: children/adolescents and young adults (AYAs) and their biological parents; and, where requested, family members.

Note that a related policy has been developed for the return of biospecimens (see xxxxxx)

Please state the extent to which you agree or disagree with the following statements

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The scope of the policy as described is clear					
The scope of the policy as described is relevant					
It is appropriate ot develop a separate related policy for the return of the biospecimens					

Please comment if you have selected strongly disagreed or disagreed	
Are there any changes to the wording of the Scope that you would make?	

Premises underpinning the policy

- Recognition by the ZERO Childhood Cancer Program, specifically for the ZERO2 trial, that the biospecimens and generated raw data belongs to each participant.
- Aboriginal and Torres Strait Islander cultural understanding of genomic data is respected. Where relevant, at the request of the patient or parents, dialogue and collaboration with Aboriginal and/or Torres Strait Islander leaders should form part of the process to return raw data.
- Raw genomic data is assumed to have undergone robust sample and data management before it is released.
- Raw data has no clinical value in the absence of further analysis.

Please state the extent to which you agree or disagree with the following statements

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The premises underpinning the policy as described are clear					
The premises underpinning the policy as described are relevant					

Please comment if you have selected strongly disagreed or disagreed with any of the above	
Are there any additional premises that should be included?	
Are there any changes to the wording of the premises underpinning the policy that you would make?	

Background

Internationally, support for enabling access to raw genomic data for individuals has been expressed by both public and academic sectors, underpinned by the moral imperative. For example, Thorgood (2018) provided recommendations to enable access for individuals who request their raw genomic data proposed by a task force of the Global Alliance for Genomics and Health. This position is aligned with another recent legal and ethical analysis suggesting patients and research subjects should have access to their raw data, provided there are no compelling moral reasons to override such a request. The General Data Protection Regulation in Europe has also been interpreted to provide a right to access raw genomic data.

In Australia, the Australian Genomics research group has a policy of not returning genomic raw data to participants in their clinical flagship projects, citing ethical and legal issues. There would seem to be no legal right to receive raw data in Australia. The Privacy Act 1988 (Cth) and state and territory laws provide a right to receive sensitive health data upon request, however, there is some uncertainty about whether this applies to raw data as it does not readily identify an individual without further analysis. Further, in the research context, the National Statement on Ethical Conduct in Human Research 2007 (updated 2018) acknowledges that researchers are not expected to return raw genomic data to participants. In a clinical setting healthcare professionals owe a duty of care to their patients, and although this has not yet been tested in the courts, this duty is unlikely to extend to provision of raw data, and a claim in negligence would thus not provide a remedy where raw data has not been provided upon request.

Nevertheless, a small number of requests for the raw data of individual child participants in PRISM were received from parents and the data was provided by the ZERO program, on an *ad hoc* basis, based on the ethical imperative (Appendix 1). These requests are likely to increase in number as enrolment eligibility expands with ZERO2. Therefore, irrespective of the legal position, it is essential that a policy that maps a framework underpinned by a partnership between participants/parents, clinicians and study team members be developed to support responses to future requests.

Please state the extent to which you agree or disagree with the following statements

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The background to the policy as described is clear					
The background to the policy as described is relevant					

Please comment if you have selected strongly disagreed or disagreed with any of the above	
Are there any changes to the wording of the Background that you would make?	

Ethical considerations

Respect for autonomy

The return of raw genomic data respects the autonomy of participants in ZERO2, and the personal meaning and value that genomic information has for them. However, the autonomy of the child also needs to be considered so that any potential outcome of the return is in line with 'the best interests of the child'.

Beneficence/clinical utility

There are potential benefits that accrue in returning raw data, including the option for further use and interpretation, thus providing hope to parents of very ill children. Parents may have a purpose for the raw data, such as uploading the child's data to an online portal for data sharing purposes, and so the request for raw data would be unconnected with benefitting their child, but for contributing to future research for improved outcomes for other families. Although this would unlikely be of direct benefit for their child, acts of altruism may help families cope with or make meaning from their child's cancer diagnosis. This may also be of particular significance in the case of a deceased child.

Minimising the potential for harm

We recognise that there are potential harms from returning raw genomic data, both germline and somatic, including (but not limited to) risk to a child's privacy if the raw data was then shared inappropriately, interrogation of regions of the child's germline genome that is generally considered unethical in minors (for example, the HTT gene for Huntington's disease), misinterpretation of raw data by external researchers/clinicians or third-party interpretative services, and the identification of a potential drug treatment not available in Australia. The proposed process for return of raw data aims to mitigate the potential harms arising in these circumstances.

Reciprocity

Individuals who are recruited to ZERO2 anticipate that targeted therapies and/or a causative cancer predisposition syndrome will be identified for them. Their data will also contribute to translational research in Australia and around the world. Raw genomic data should be returned to those who request it, in reciprocity for their contribution to research.

Responsibility to genetic relatives

The interpretation of the raw data has potential implications for the participants' genetic relatives. These relatives will need to be made aware by the participant/parent that they have the data that may reveal medically actionable findings and determine if their relatives wish to know this information.

Schickhardt et al (2020) summarise the above considerations that

a) "data subjects (research participants and parents) have a right to receive their genomic raw data;

b) the right must be respected in a substantial way that helps data subjects to make an informed use of their right and released data;

c) concerns relating to the data subjects themselves, researchers, physicians and relatives should be addressed through an information process and do not justify a refusal to release genomic raw data."

Please state the extent to which you agree or disagree with the following statements

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The descriptions of the ethical considerations listed as described are clear					
The descriptions of the ethical considerations listed as described are relevant					
There are no other ethical considerations that require listing and descriptions					

Please comment if you have selected strongly disagreed or disagreed with any of the above	
Are there any changes to the wording of each of the ethical considerations that you would make?	

Applying the policy

This policy assumes a default right of a participant aged 16 and over (or if younger, their parents) enrolled in ZERO2, to access their raw genomic data when they make a request, or if a clinician makes a request on their behalf. Any exceptions to such provision will be transparent, justified, and developed by a specially constituted panel comprising the child's treating oncologist and the relevant study team, which would then be submitted to the local HREC for approval. The reasons for refusal include that access compromises a primary objective of the ZERO2 study or resources are not available to enable the data transfer.

Requests for return of raw genomic data will likely be most often received from participants or their parents/guardians or from clinicians on their behalf. There may be many reasons for such requests: further interpretation and/or sharing with other researchers to provide a second opinion or enable access to another clinical trial; to be kept for future use; or simply to have it just because they consider it 'belongs' to them.

Noting the complexity of reasons underpinning requests, decisions on whether to return data will continue to be made on a case-by-case basis, in partnership with the study team and treating clinicians, with a focus on the best interest of the child or the family where a child has died.

Please state the extent to which you agree or disagree with the following statements

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of the rationale for applying the policy is clear					
The description of the rationale for applying the policy is is relevant					

Please comment if you have selected strongly disagreed or disagreed with any of the above	
Are there any changes to the wording of the the rationale for applying the policy that you would make?	

Part 2 – The Process

The process of the return of raw genomic data is informed by recommendations proposed by Thorgood et al (2018), Schickhardt et al (2020) and Chad et al (2021).
There are three different groups who may request access to a participant's raw genomic data:

1. AYA participants, parents/guardians on behalf of their child and parent participants
2. Researchers
3. Clinicians

Are there any other references that could be used to inform the process?	
Are there any other groups that may wish to access the raw genomic data?	

1. AYA participants, parents/guardians on behalf of their child and parent participants wish to have access to their/their child's raw data (Figure 1).

The Patient Information Sheet (PIS) states that a process for potential return of raw genomic data is in place and requests should be discussed with their treating oncologist. The consent form also requires agreement that the participants/parents understands this process. The provision of request for return of raw genomic data is clearly separated on the consent form from the consent to receive individual cancer-related findings (or other medically actionable incidental findings) from the analysis of the data undertaken in the ZERO2 project.

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description that the request for the raw data is separated in the PIS and consent forms for participation in ZERO2 is clear.					
The description that the request for the raw data is separated in the PIS and consent forms for participation in ZERO2 is relevant					

Please comment if you have selected strongly disagreed or disagreed with the statement	

Process Steps 1 & 2

1. The treating clinician notifies the study team of the request.
2. The participant/parent/guardian are offered a meeting (online or in person) with the clinician and a study genetic counsellor to gain a basic understanding of the basis for their request and how the raw data is intended to be used. The following issues to be discussed include:
   - The reasons why release of raw data is requested
   - The general characteristics of raw genomic data
   - The relative benefits and harms of analysis of raw genomic data external to the ZERO2 Study and the implications of its use
   - Where the data is to be shared with another research organisation for re-analysis purposes, all efforts, where possible, to facilitate this by collaborative research agreement will be taken. Where a collaborative research agreement is not possible, thorough discussion regarding the potential benefits and risks of sharing data with external parties will be discussed with participants/parents, including issues regarding privacy and data handling
   - Use and limitations of Third-Party Interpretation Services and any treatment recommendations arising
   - The potential implications of the release of raw genomic data for genetic relatives
   - Where the request is from a parent of a child under 16 years, the capacity of the child to decide whether they wish to receive their raw genomic data will be assessed but discussions should, as far as possible, include the child. Where that child is not involved, discussion will address the obligation on the parent/guardian in the future to disclose to the child that they have the raw data and how it has been used

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of the issues that need to be discussed in Step 2 are clear.					
The issues that need to be discussed in Step 2 are relevant					

Please comment if you have selected strongly disagreed or disagreed with the issues identified that need to be discussed	
Are there any other suggestions you have for these steps?	

Process Steps 3-6

3. A summary of the meeting is provided to the participant/parent /guardian and to the clinician by the genetic counsellor.
4. If after review of the summary, the participant/parent/guardian still wishes to request the raw data, the application form will be provided by the Study Team.
5. The Study Team receipts the completed application and circulates it to a specifically constituted meeting of the treating clinician, other clinicians and geneticists with expertise in deliberating ethical dilemmas involving germline and somatic genomic data. All communications will come out of the ZERO@ccia.org.au shared mailbox
6. Notification of the decision is sent to the Study leads, the HREC responsible for ZERO2 ethics, and CCI legal for ratification.

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of Steps 3-6 are clear.					
The process described in Steps 3-6 are relevant					

Please comment if you have selected strongly disagreed or disagreed with the processes in Steps 3-6	
Are there any other suggestions you have for these steps?	

Process Steps 7 & 8

7. If endorsed, the release of raw data consent form is provided to the participant/parent/guardian clearly articulating
   - The data is research generated and should not be used for clinical interpretation or decision-making without medical advice and confirmatory testing in a NATA accredited laboratory
   - There is no warranty of data accuracy and ZERO2 are not liable for harm caused from analysis or other use of the data
   - There is no obligation on the treating clinician to act on any therapeutic recommendations arising from analysis by a Third Party

   When that endorsement is received
   a) Arrangements will be made to transfer the data, free of charge. Raw genomic data will be returned in the same way for all participants.
   b) The data will be provided on a hard drive in a standard format that enables the ability to reconstruct the individual's genome and will be transferred using appropriate data tracking and security processes.
   c) The data will be accompanied by the standard letter to the participant/parent/guardian (Appendix 2)

8. If declined, the rationale for the decision is provided to the participant/parent/guardian in a letter from the Study Leads.

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of Steps 7 & 8 are clear.					
The process described in Steps 7 & 8 are relevant					

Please comment if you have selected strongly disagreed or disagreed with the processes in Steps 7 & 8	
Are there any other suggestions you have for these steps?	

Figure 1 (see pdf)

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
Figure 1 captures the **current version as presented** of the process					

Please comment if you have selected strongly disagreed or disagreed with Figure 1 capturing the **current version as presented** of the process	

2. A clinician wishes to provide access to a participant's raw data to another research group

1. The treating clinician notifies the participant/parent/guardian of the intention to request the participant's raw genomic data and provides the rationale for analysis by another research group.
2. If the participant/parent/guardian agrees, the application form will be provided by the Study Team.
3. The Study Team receipts the completed application and circulates it to a specifically constituted meeting of the treating clinician, other clinicians and geneticists with expertise in deliberating ethical dilemmas involving germline and somatic genomic data. All communications will come out of the ZERO@ccia.org.au shared mailbox
4. Notification of the decision is sent to the Study leads, the HREC responsible for ZERO2 ethics, and CCI legal for ratification.
5. If endorsed, a collaborative research agreement (CRA) will be sought with the research group
6. Once a CRA has been established, the release of raw data consent form is provided to the clinician that clearly articulates
   - The data is research generated and should not be used for clinical interpretation or decision-making without medical advice and confirmatory testing in a NATA accredited laboratory
   - There is no warranty of data accuracy and ZERO2 are not liable for harm caused from analysis or other use of the data

   When that consent is received
   a) Arrangements will be made to transfer the data, free of charge.
   b) The data will be provided on a hard drive in a standard format that enables the ability to reconstruct the individual's genome and will be transferred using appropriate data tracking and security processes.
   c) The data will be accompanied by the standard letter to requestor (Appendix 2)
7. If declined, the rationale for the decision is provided to the clinician in a letter from the Study Leads.

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of Steps 1-7 are clear.					
The process described in Steps 1-7 are relevant					

Please comment if you have selected strongly disagreed or disagreed with the processes in Steps 1-7	
Are there any other suggestions you have for these steps?	

Group 3. A clinician wishes to provide a participant's raw data to another research group to advide on treatment

1. The treating clinician notifies the participant/parent/guardian of the intention to request the participant's raw genomic data and provides the rationale for analysis by another research group.
2. If the participant/parent/guardian agrees, the application form will be provided by the Study Team.
3. The Study Team receipts the completed application and circulates it to a specifically constituted meeting of the treating clinician, other clinicians and geneticists with expertise in deliberating ethical dilemmas involving germline and somatic genomic data. All communications will come out of the ZERO@ccia.org.au shared mailbox
4. Notification of the decision is sent to the Study leads, the HREC responsible for ZERO2 ethics, and CCI legal for ratification.
5. If endorsed, the release of raw data consent form is provided to the clinician that clearly articulates
   - The data is research generated and should not be used for clinical interpretation or decision-making without medical advice and confirmatory testing in a NATA accredited laboratory
   - There is no warranty of data accuracy and ZERO2 are not liable for harm caused from analysis or other use of the data

   When that consent is received
   a) Arrangements will be made to transfer the data, free of charge.
   b) The data will be provided on a hard drive in a standard format that enables the ability to reconstruct the individual's genome and will be transferred using appropriate data tracking and security processes.
   c) The data will be accompanied by the standard letter to requestor (Appendix 2)
6. If declined, the rationale for the decision is provided to the clinician in a letter from the Study Leads.

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The description of Steps 1-6 are clear.					
The process described in Steps 1-6 are relevant					

Please comment if you have selected strongly disagreed or disagreed with the processes in Steps 1-6	
Are there any other suggestions you have for these steps?	

Appendix 2 (Standard letter accompanying data)

Dear ___,

Thank you for your request for access to the genetic data for _____ held by CCIA on behalf of Zero Childhood Cancer. We would like to take this opportunity to thank you for your generosity in agreeing to participate in the program and send our condolences at _____'s passing.

I am pleased to confirm that CCIA is permitted to provide the data to you. We do need to note, however, that CCIA cannot give any warranties, or make any representations of any kind in relation to the data. By accessing your _____'s genetic data, you can, by all means, undertake your own independent analysis of the data. However, CCIA may not be able to ensure that any conclusion you reach from this analysis is correct. We also cannot assume liability for any loss, damage or harm which may arise from any analysis or interpretation of _____'s genetic data.

We thank you again for your request, and CCIA is glad to be of assistance Should you have any more questions or concerns, please do not hesitate to contact us.

Kind Regards,

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
Appenix 2 captures the **current version as presented** of the process					

Please comment if you have selected strongly disagreed or disagreed with Appenix 2 capturing the **current version as presented** of the process	