Stakeholder Consensus on return of biospecimens donated to and raw genomic data generated from the National Clinical Trials, PRISM and ZERO2.

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This Consensus Document was developed using the Delphi Methodology which ran from November 2021 to November 2022 with contributions from the following stakeholders:Kathy Tucker; David Ziegler; Mark Cowley; Noemi Fuentes Boalnos; Toby Trahair; Camron Ebzery; Chelsea Mayoh; Matthew O'Connor; Rishi S Kotecha; Di Milnes; Catherine Speechly; Andrew Gifford; Jane Nielsen; Marion Mateos: Andrew Wood; Mark Pinese; Ashleigh Sullivan; Bhavna Padhye; Judy Kirk; Vanessa Tyrrell and representatives from Australian Families for Genomics; Rare Voices Australia; Li Fraumeni Syndrome Association Australia & New Zealand; Neuroblastoma Australia; and ZERO Childhood Cancer Parents Consultation Group.

Purpose of the Consensus Document

Participating in the Zero Childhood Cancer Precision Medicine Program (ZERO) National Clinical Trials, PRISM and ZERO2 (together referred to as 'trials') requires donation of a biospecimen from which a raw genomic sequence is generated. The raw genomic data is then analysed by the research team and the interpreted findings (if any) reported to the requesting clinician to be shared with the participant or the parent/guardian if the participant is under 18 years.

It is recognised that:

- While the ZERO2 research team conducting the trials, are custodians of the biospecimens and the raw genomic data generated, the adult/young person (AYA) participants and parents/guardians on behalf of their child have an interest in accessing both the biospecimen and the raw genomic data after receiving the report of the research findings of both the tumour and non-cancerous samples.
- Raw genomic data on its own cannot inform clinical decision-making nor answer questions in a research setting, but its subsequent analysis and interpretation may have great value.

The document is in two parts: (1) the policy underpinning meeting the request for return of the biospecimens and raw genomic data by AYA participants, parents/guardians on behalf of their child and/or parent participants; and (2) the process developed to implement such return.

PART 1 POLICY FOR RETURN

Scope

Biospecimens

Biospecimens are defined as tissue removed from the participant, including both tumour and non-tumour tissue. The tissue may be in one or more of several forms: fresh human tissue, fresh frozen tissue, formalin fixed tissue (prior to processing), formalin fixed paraffin embedded tissue, nucleic acid (DNA or RNA) isolated from tissue (such as blood or skin) or collected (such as urine).

Raw genomic data

For the purposes of this Consensus document, raw genomic data is obtained from the genomic sequencing of a biospecimen and is genomic sequence reads without **annotation or interpretation** (Schickhardt et al 2020) in the form of a FASTQ file(s).

Assumptions underpinning the policy

- It is aimed to have an INITIAL REPORT of the interpretation of the findings of changes in the DNA sequence from the tumour and non-tumour biospecimens for some cancers sent to the clinician by 4 weeks after receipt of the samples. The germline report and the report of all genomic findings from ZERO2 are aimed to be returned within a timeframe of 8 weeks (FINAL REPORT).
- After receiving the initial (where applicable) and then final reports of the interpretation of the analysis of the DNA by the ZERO research team, the clinician will provide a copy of both reports to the participant/parent/guardian without delay.
- If the AYA participant/parent/guardian then wishes to have the biospecimens and/or raw genomic data returned to them they will be returned without delay, following the process outlined in Part 2.
- Cultural understanding of genomic data is respected, including the cultural understanding of those who identify as Aboriginal and/or Torres Strait Island, Māori or other indigenous peoples. if the participant or parent/guardian (and/or their families), so directs, a dialogue and collaboration with leaders of the relevant indigenous people with whom they identify, should form part of the process to return of the biospecimens and raw genomic data.

Background

There is ethical complexity and diverse perspectives on the return of raw genomic data. There are recognised concerns, such as the utility of the data itself, the potential for harm arising from third party interpretation and the possibility of unnecessary interventions based on such information.

Worldwide from both public and academic sectors, there is a general shift on ethical grounds, underpinned by duty of care, to the provision of raw genomic data to research participants, if requested, (Beauvais et al 2021; Middleton et al, 2015; Lunshof et al, 2014).

In recognition of the complexity, the Global Alliance for Genomics Health, Ageing and Dementia task team (Thorogood 2018) published recommendations guiding ethical access to raw genomic data and in Europe, the EURAT consortium has developed a process for return of raw genomic data (Winkler et al., 2020). In Australia guidance has been provided by Nielsen et al, 2022, whose recommendations have informed this policy.

Ethical considerations (Thorogood et al, 2018; Schickhardt et al, 2020; Chad et al, 2021)

- *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 future 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*

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 of child participants 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 may 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.

- *Non-maleficence*

While the participant/parent/guardian is the sole owner of the biospecimens and/or raw data, and therefore takes responsibility for their future use, it is important that awareness is raised of potential harms generated from both tumour and non-tumour (germline) samples and data. These include (but are not limited to):

  - Risk to a child's privacy if the raw genomic data was then shared inappropriately;);
  - Misinterpretation of the data by external researchers/clinicians or third-party interpretative services;
  - The potential for a cascade of (possibly unnecessary) health interventions following a re-interpretation of the raw data, for example by a third party service;
  - Future potential genetic discrimination such as from life insurers; and
  - The identification of a 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*

Participants who are recruited to ZERO2 anticipate that genomic information may contribute to the diagnosis and management of their cancer. Their data will also contribute to translational research in Australia and around the world including the utility of genomic sequencing as a diagnostic test compared with standard of care testing. In reciprocity for this contribution to research raw genomic data should be returned to research participants who request it.

- *Responsibility*

Once biospecimens/raw genomic data have been returned to AYA participants, parents/guardians on behalf of their child, ZERO2 loses control over how it is used and shared by them, and the recipient take responsibility for its future use. If interpretation of the raw data reveals medically actionable findings, this has potential implications for the participants' genetic relatives, giving rise to a moral obligation to consider their right to know/ not to know, which may not be mediated with the expertise of healthcare professionals.

PART 2 APPLYING THE POLICY

Requests for return of raw genomic data will be received from AYA participants or parents/guardians on behalf of their child or from their clinician or parent participants. There may be many reasons for such requests underpinned by a range of complexities.

This policy assumes a default provision of biospecimens and/or raw genomic data when a request is made. All requests for return of biospecimens and/or raw genomic data (whether made by AYA participants, parents/guardians or the clinician) will be considered by the Data Access Committee of ZERO2 (comprising clinicians, scientists and other health care professionals) and the participant's enrolled healthcare provider. The aim of such review is to oversee the operation of this policy.

The process

The process of the return of biospecimens and/or raw genomic data for parents/guardians on behalf of their child, AYA participants and parent participants who wish to have access to their/their child's biospecimens and/or raw genomic data is informed by discussion reported by Beauvais et al (2021), Thorogood et al (2018), Schickhardt et al (2020), Chad et al (2021) and recommendations proposed by Nielsen et al (2022).

The ZERO2 Patient Information Sheet (PIS) and consent form states that following the issuing of the reports of the analysed genomic data, a process for return of biospecimens and raw genomic data to the participant/parent/guardian is in place and that requests should be discussed with their treating clinician or the site ZERO2 Study team.

Process Steps 1 & 2

1. This Policy and Process document will be provided to all enrolled healthcare providers who can then provide it to AYA participants/parents/guardians where an enquiry is made regarding return of the biospecimen(s) and/or raw genomic data. The healthcare provider or the participant/parent/guardian on behalf of the child participant notifies the site ZERO2 Study team using the contact details on the consent form.

2. As soon as possible after a request is received, the AYA participant/parent/guardian are offered a meeting (by telephone or videolink) with the study genetic counsellor. The participant/parent/guardian can request for their clinician to attend. The meeting is to gain an understanding of the basis for their request; to understand and document how the participant/parent/guardian wishes or intends to use the biospecimens and/or raw genomic data; and to consider how the request may best be facilitated. The role of the study genetic counsellor is to ensure all views are heard and considered.

Prior to the meeting, a leaflet outlining the issues below will be provided (emailed or hard copy) to guide the discussion:

- The types of biospecimens that may be available for return
- The general characteristics of raw genomic data
- The potential benefits and risks of analysis of raw genomic data external to the ZERO2 Study and the implications of its use, including issues regarding privacy and data handling, and potential implications for genetic relatives. While clinical expertise and counselling support form an integral part of minimizing any potential harm, these will not be provided as a routine part of the return of raw data.
- Where the participant/parent/guardian intends sharing the data with another research organisation for re-analysis purposes, applications for access will be managed through the Data Access Committee of ZERO2.
- Use and limitations of Third-Party Interpretation Services and any treatment recommendations arising.
- There is no guarantee that clinical recommendations from external researchers/clinicians or third-party interpretative services arising from subsequent analysis of the raw data will be able to be tested, actioned or implemented.
- Where the request for return 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.

Process Steps 3-8

3. A summary of the meeting is provided to the participant/parent /guardian and to the clinician by the genetic counsellor who met with the participant/parent/guardian.
4. If after review of the summary, the participant/parent/guardian still wishes to request the biospecimens and/or raw genomic data, they complete the application/consent form which includes acknowledgement of their understanding of the potential benefits and risks.
5. The release raw genomic data consent form delineates that:
   - The data is generated for research purposes and should not be used for clinical interpretation or decision- making without medical advice. Confirmatory testing in a NATA accredited laboratory is recommended prior to reliance on the data for clinical purposes.
   - 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.
   - Responsibility by the participant/parent/guardian is accepted for subsequent uses of the data.
   - The ease of identifiability of genomic data is understood.
6. In regard to return of biospecimens, the type and availability of the samples will guide the discussion. Also, when enrolling in ZERO2, consent may have been given to storage of the samples for future research. The discussion will therefore address whether all samples will be returned or whether some will be retained by the research group.
7. The site ZERO2 Program Management Team receipts the completed application/consent and circulates it to the Data Access Committee of ZERO. All communications will come out of the ZERO@ccia.org.au shared mailbox.
8. When the signed consent form is received by the Data Access Committee
   a) Arrangements will be made to transfer the biospecimens and/or raw genomic data as soon as possible.
   b) The data will be provided as a FASTQ file(s) that enables the ability to reconstruct the individual's genome and will be transferred using an appropriate delivery mode for data tracking and security processes.
   c) The data will be accompanied by the consent form signed by the site ZERO2 Program Management Team leader and the parent/guardian/participant.
9. Notification of the release is sent to the site ZERO2 Program Management Team who will report annually on the requests to the ZERO2 research management committee. All documentation will be stored in the child/young person's electronic medical record.

References

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REQUESTING RETURN OF TISSUE SAMPLES AND/OR THE GENOMIC DATA GENERATED BY ZERO2 FROM YOUR/YOUR CHILD'S TISSUE SAMPLES

The research teams of the National Clinical Trials, PRISM and ZERO2, work in partnership with participating families. This partnership aims to achieve better outcomes through precision medicine for all children and young people with cancer, now and into the future.

Precision medicine involves checking your/child's DNA to look for changes that may guide treatment and future healthcare.

Checking the DNA

The first step is collecting samples of your/your child's tumour and non-cancer cells (referred to as 'biospecimens') to obtain the DNA. All the genes in their DNA makes up their genome.

When DNA is obtained from a participant's biospecimen, a genomic test cuts the DNA into fragments. Each fragment is a long string of these DNA letters.

Computer systems are then used to order the DNA letters into the sequence found in each of the genes. This genomic sequence (a string of DNA letters) is called *raw genomic data.*

What happens next?

Raw genomic data on its own cannot inform clinical decision-making nor answer questions in a research setting, but its subsequent analysis and interpretation may be invaluable.

So, a team of ZERO2 research scientists analyse this raw genomic data by "reading" the information contained in the string of DNA letters. Changes in the information in the genes (if any) from that usually seen are discussed with clinical and genetic experts to interpret what the changes mean.

The findings help guide treatment and inform your/your child's future healthcare are then reported to your/your child's doctor to share with you.

The timeframe to produce the final report is within 8 weeks of the biospecimens arriving at the laboratory.

The team recognises that, after receiving the report of the ZERO2 findings, you may wish to access your child's raw genomic data and/or the biospecimens from which it was generated.

What if I want my/my child's raw genomic data and biospecimens

In the spirit of partnership,

- the research teams are custodians of participants' donated biospecimens and the raw genomic data generated.
- parent(s)/guardian(s) of a participant < 18 years old, and participants > 18 years old may have an interest in accessing their/their child's donated biospecimens and the raw genomic data.

The information in this document has been provided to assist in providing that access.

What do I have to do?

If you want access to your/your child's raw genomic data and/or biospecimens, please ask your/your child's clinician or contact the ZERO2 Study Team (schn-zero2@health.nsw.gov.au).

Once a formal request is made, a meeting with you and the study genetic counsellor will be organised. If you request, your/your child's clinician can be present. The meeting will be by Telehealth (telephone or video link).

While there is no barrier to returning the biospecimens and/or providing the raw genomic data, the purpose of the meeting is to understand why the request is being made and to consider the potential outcomes. Your/your child's clinician will be updated with a summary of the discussion.

It is also to ensure that decisions are made in your/your child's best interest. For example, if your child is under 18 years, their capacity to decide whether they wish to receive their raw genomic data needs to be assessed. As far as possible, they need to be included in the decision. Where your child is not involved, you will need to tell them in the future that you have the raw genomic data and how it has been used.

- ***Possible reasons for requesting the raw genomic data and/or biospecimens.***

These include (but are not limited to):

1. To upload the raw data to an online portal to share with others conducting precision medicine research. This may not help you or your child directly but may contribute to future international research and improve outcomes for other families.

2. To have the data re-analysed by another research group, or a commercial laboratory based overseas ('third-party interpretative services'). This is done in the hope that the group/lab may be able to identify gene changes not found by the ZERO research team, and that these results may help guide your/your child's cancer treatment. They may also be used to understand whether other family members are at risk of having a genetic predisposition to cancer.

3. Requests for the biospecimens may be made to provide other research groups the opportunity to create their own raw genomic data.

- ***Potential outcomes and considerations***

There are several potential outcomes and considerations to take into account before requesting raw genomic data.

1. The re-analysis identifies a gene change relevant to your/your child's cancer.

Potential cancer treatment and/or clinical recommendations may be made as a result of re-analysis. However, there is no guarantee that these recommendations will be able to be acted upon by your clinical service. The recommended drug may not be available in Australia.

There is also the possibility that the meaning of the gene change is misinterpreted. This can mean that a lot of (possibly unnecessary) health checks will be done.

It is important to consider what support will be available to you after the re-analysis to help to understand what the results mean for you/your child and for other genetic (blood) relatives.

If the data is checked by another group and identifies something new that wasn't found by the ZERO2 study, this would need to be confirmed by an Australian clinically accredited laboratory before any changes are made to the medical care of you/your child/your relatives.

In some cases, confirmation testing might not be recommended and would not lead to a change in medical care.

2. The re-analysis identifies a gene change related to a condition other than cancer. It may mean that you/your child have an increased chance of developing that condition.

The condition may have no treatment, such as an adult-onset neurological or dementia condition. If the raw data is from a child, analysis for such conditions is generally considered unethical practice. The findings may also lead to future potential genetic discrimination, such as by companies who provide life insurance.

If the condition does have available treatments or prevention options, it is important to make relatives aware of this information.

3. There may be risks to your/your child's privacy and data security. This can occur if the raw data is shared inappropriately, either by the online portals or the third-party interpretive services.

4. If the data is being provided to another research group, it may be that a formal agreement to share findings is already in place with them. If not, such an agreement could be put in place.

The next steps

After a meeting has been held, a summary will be provided to you and your/your child's clinician by the study genetic counsellor. This gives you the chance to decide how or if you want to proceed.

If you do wish to proceed, you will need to complete the application/consent form. This includes agreeing that you understand the potential outcomes.

Regarding return of biospecimens, the type and availability of the samples will guide the discussion. Also, when enrolling in ZERO2, consent may have been given to storage of the samples for future research. The discussion will therefore address whether all samples will be returned or whether some will be retained by the research group.

The consent form is then sent to the site ZERO2 Program Management Team. They will provide it to the Data Access Committee of ZERO2.

Arrangements will then be made to transfer the data and/or biospecimens to you along with your signed consent form. The mode and format of transferring the data is different depending on the type of request that is being made. An appropriate delivery mode for data tracking and security processes will be used.

[Insert Site Logo]

RETURN OF RAW GENOMIC DATA AND/OR BIOSPECIMENS CONSENT FORM

Parent/Guardian consenting on behalf of participant or participant

Principal Investigator	[Insert site PI name]
Associate Investigators	[Add details]
Site Name	[Add details]

Declaration by Parent/Guardian/Adult Participant

I understand that:

- There are potential benefits and risks associated with accessing raw genomic data and/or biospecimens, including the chance of false positive and false negative findings arising from re-analysis.
- The data is generated for research purposes and should not be used for clinical interpretation or decision-making without medical advice. Confirmatory testing in a NATA accredited laboratory (or equivalent) is recommended prior to reliance on the data for clinical purposes.
- There is no obligation on the treating clinician to act on any therapeutic recommendations arising from analysis by a third party.
- There is no warranty of data accuracy and ZERO2 are not liable for any direct, consequential, indirect, or any other harm caused from analysis or other use of the data/biospecimens.
- The raw genomic data (and any data generated using the biospecimens) contains sensitive information regarding both my child/me and genetic (blood) relatives. It is possible to identify my child/me from raw genomic data. Protections regarding data security, privacy, and misuse, by third parties with whom the data is shared cannot be guaranteed.
- The information that can be generated from the raw genomic data/biospecimens may pose psychological difficulties for my child/me, my family, and society.
- The data will be provided as a FASTQ file(s) and will be transferred using an appropriate delivery mode and format dependent on the nature of the request.
- My request for return of biospecimens will depend on the type and availability of the samples. I understand that there may be insufficient, or no sample left for third party analysis. When enrolling in ZERO2, consent may have been given to storage of the samples for future research. I will be able to decide whether all samples will be returned or whether some will be retained by ZERO2.
- Arrangements will be made to transfer the raw genomic data and/or biospecimens as soon as possible following completion of this consent form.
- If I intend on sharing the data and/or biospecimens directly with another research group/organisation for re-analysis purposes, wherever feasible, this may be facilitated by the Data Access Committee of ZERO2 without the need for the information to be released to me.

I agree that:

- I am giving consent for the return of my child’s/my raw genomic data and/or biospecimens to me. A summary of the discussion with the study genetic counsellor will be provided to me and my child’s/my treating clinician.
- I have been given the opportunity to discuss my request with the study genetic counsellor and at my request, my child’s/my treating clinician. I have been informed of the potential benefits and risks of my request, and I have been provided with this information in written format. I have been given the opportunity to ask questions and am satisfied with the answers.

- I take responsibility for the data protection, handling, and any outcomes arising from use of the data upon release.

Consent for Return of Raw Genomic Data

☐ I do ☐ I do not consent to the transfer of my child’s/my raw genomic data generated by their participation in ZERO2 to me.

Consent for Return of Biospecimens

☐ I do ☐ I do not consent to the return of my child’s/my available biospecimens that were collected as part of ZERO2 participation.

Name of Participant (please print)	Signature of Participant	Date
______________________________	______________________	__________
Name of Parent/Guardian (please print)	Signature of Parent/Guardian	Date
______________________________	______________________	__________
Name of Interpreter/Witness, if required (please print)	Signature of Interpreter/Witness	Date
______________________________	______________________	__________

Declaration by person performing the informed consent discussion

I have given a verbal explanation of the process for return of raw genomic data and/or biospecimens, its potential benefits and risks, and I believe that the participant/parent/guardian has understood that explanation.

______________________________	______________________	__________
Name (please print)	Signature	Date

Note: All parties signing the consent section must date their own signature.