

# STAKEHOLDER COMMITTEE ON GENOME SEQUENCING ANALYSIS FOR A-BOMB SURVIVORS' CHILDREN

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### 1. INTRODUCTION

In 1945, the atomic bombs dropped on Hiroshima and Nagasaki resulted in a great number of deaths. The A-bomb survivors lived the rest of their lives with health problems and concerns over them. The children of A-bomb survivors are also living with concerns over possible genetic effects of radiation exposure as well as other related difficulties.

The Atomic Bomb Casualty Commission (ABCC), the Radiation Effects Research Foundation's (RERF) predecessor organization, was established in 1947, and research concerning the A-bomb survivors and their children began. In 1975, ABCC was re-launched as RERF, a joint Japan-U.S. operation. However, the past criticism of ABCC, that is "Only do the tests but not the medical treatments," is still being carried on by RERF.

Under such circumstances, the reality of the health effects of radiation revealed among the A-bomb survivors has become the basis of the radiation protection system, protecting the people around the world from radiation health risks. As for the genetic effects on A-bomb survivors' children, the study began with the health examinations of the newborns in 1948, and the follow-up studies conducted to date, such as epidemiological and clinical analyses of diseases, have shown no apparent health problems. However, concerns over potential heritable effects of radiation have been shared by A-bomb survivors and their children as well as many people of Hiroshima and Nagasaki and across the world.

The A-bomb survivors are now reaching advanced ages, some of their children are already in their 70s. This means that time is limited to convey the truth about any heritable radiation effects to A-bomb survivors who are concerned about their children's health.

In the 21st century, genomic DNA sequencing technology has made a great progress. And now, we are living in the era where the reality of naturally occurring and chemically induced sequence changes can be detected. Under these circumstances, RERF has publicly disclosed its plan to use genomic DNA sequencing to analyze genetic effects in addition to analyses based on the epidemiological and clinical studies RERF has conducted thus far.

Since the genomic DNA sequencing analysis will be able to detect all changes in the DNA sequence. Therefore, it has the potential to yield important outcomes leading to a degree of conclusiveness about the extent of heritable effects of A-bomb radiation, which has been an issue of concern. On the other hand, because the study will have such a large societal impact, RERF has a social responsibility to establish a thorough implementation system and to explain the significance of the study in a way that is attentive to the feelings of A-bomb survivors and their children who have faced difficulties concerning genetic effects.

In light of the above, RERF established the Stakeholder Committee on Genome Sequencing Analysis for A-bomb Survivors' Children consisting of the A-bomb survivors, their children, and outside experts in order to receive to a wide variety of comments and opinions from the community before implementing the proposed study. The committee chair and vice-chair were responsible for preparing this document to introduce the contents of the committee's discussions and offer seven pieces of advice to RERF.

## **2. ESTABLISHMENT OF THE STAKEHOLDER COMMITTEE**

RERF established the Stakeholder Committee on Usage of RERF's Stored Biosamples in 2018 to promote the use of the preserved biosamples it has collected.

RERF's proposed study of the genetic effects of A-bomb radiation shares some of the issues discussed in the Stakeholder Committee on Usage of RERF's Stored Biosamples in terms of the analysis of stored samples. However, this study will have an enormous social impact. Furthermore, the fact that analyses of DNA sequences, the ultimate personal information, will be performed means that RERF's strict compliance with Japan's ethical guidelines is sought after. Above all, as this is a study targeting A-bomb survivors and their children, individuals for whom special consideration should be granted, more consideration than stipulated in the Japanese ethical guidelines for genome studies is necessary. In addition, the children of A-bomb survivors and their parents are unlikely to derive any benefits from this study, and since they participate in this study out of the goodness of their hearts, this study must not cause any social disadvantages to them.

Considering the above, in August 2021, the Stakeholder Committee on Genome Sequencing Analysis for A-bomb Survivors' Children was newly established, consisting of 14 members, including A-bomb survivors with children, children of A-bomb survivors whose parents are A-bomb survivors, and related persons in Hiroshima and Nagasaki to listen to their opinions, and started discussions.

## **3. PROGRESS OF THE COMMITTEE MEETINGS**

The committee met five times, but since many of the members who are children of A-bomb survivors were busy with their work lives, and it was difficult to coordinate their schedules. Therefore, the first through third meetings were held in two sessions, resulting in a total of eight sessions.

- First meeting : August 21, 2021, and August 25, 2021
- Second meeting : October 7, 2021, and October 9, 2021
- Third meeting : November 6, 2021, and November 17, 2021
- Fourth meeting : February 6, 2022
- Fifth meeting : April 9, 2022

#### **4. OUTLINE OF MEETINGS**

At the first meeting of this committee, RERF's previous studies on the genetic effects of A-bomb radiation were introduced, followed by an introduction of the advice of the Stakeholder Committee on Usage of RERF's Stored Biosamples that was established in 2018. The purpose and methodology of the planned study of DNA sequencing of A-bomb survivors' children were then explained. In the subsequent four meetings, issues that had to be addressed in the course of the study were presented, and the committee members asked questions and commented on the issues, which were summarized by the chair. The following is a summary of the advice received based on these discussions.

#### **5. TOPICS AND ADVICE**

##### **TOPIC 1: TRUST IN RERF**

Trust is the cornerstone of all research involving humans. At the Stakeholder Committee on Usage of RERF's Stored Biosamples, a discussion related to trust was also held. Given that the current study will have a significant impact on the study participants, who are A-bomb survivors and children, "trust in RERF" was the first issue addressed in the discussion.

##### **ADVICE**

- The trust of A-bomb survivors and their children is the backbone of all RERF research, and undoubtedly, it is of paramount importance that RERF secures it. The trust of the communities in Hiroshima and Nagasaki, where they reside, is also invaluable. RERF should spare no effort in gaining trust.
- It is imperative to make this study accessible to the local community. Therefore, public relations and public awareness activities should be performed through several channels, such as through newspapers, television, public lectures, dialogues, and online distribution.

##### **TOPIC 2: SIGNIFICANCE OF THE STUDY FOR A-BOMB SURVIVORS AND THEIR CHILDREN**

RERF's Articles of Incorporation state "its objectives shall be to conduct research and studies for peaceful purposes on medical effects of radiation and associated diseases in humans, with a view to contributing to maintenance of the health and welfare of the atomic-bomb survivors and to enhancement of the health of all humankind." How this study will be received by A-bomb survivors and their children is deeply intertwined with the welfare mentioned in the Articles of Incorporation, and thus is a topic for this committee to address.

##### **ADVICE**

- In light of the scientific and social importance of this study, and the fact that it also carries significance for A-bomb survivors and their children, as well as for the local community, this study should be prepared for deliberately and conducted promptly. RERF should proceed with the research immediately, prepare carefully, and make every effort to produce results while the A-bomb survivors are still alive and before their children reach ages where they are likely to develop cancers.

- As a public interest incorporated foundation, RERF should remain neutral on issues that have the potential to become political. All RERF's research is rooted in the support of the A-bomb survivors and their children and also relies on the unseen cooperation of the people of Hiroshima and Nagasaki. RERF needs to understand the earnest antinuclear aspirations of these communities as it conducts its research.

### TOPIC 3: MANAGEMENT OF GENOME DATA AND SAMPLES

There are the national guidelines for the management of data and samples related to the human genome, and this issue was also discussed at the Stakeholder Committee on Usage of RERF's Stored Biosamples meetings. However, since genetic effects will be studied this time, the committee members who are both A-bomb survivors and their children were once again asked to provide their opinions on this issue.

#### ADVICE

- Based on rigorous adherence to Japanese national guidelines for the management of genomic data, RERF should follow the advice of the Stakeholder Committee on Usage of RERF's Stored Biosamples and document its own guidelines and charter for the handling of genomic data on A-bomb survivors and their children.

### Topic 4: DISCLOSURE OF GENOMIC DATA AND SECONDARY USE

In addition to technological breakthroughs, progress in 21st-century genome research is driven by a culture of sharing that has emerged in this field. In other words, the genomic information obtained from studies is published in papers, and the primary data are registered in public repositories so that they can be analyzed by researchers around the world, which has led to rapid progress in the field of genome research. On the other hand, as discussed in the previous section, genomic information is under strict legal controls and RERF must take into account the special nature of research involving A-bomb survivors and their children, who must be protected ethically. The committee members discussed this complex issue of disclosure and secondary use of genomic information in this study, which is based on a complex balance of disclosure and sharing, legal controls, and the needs of A-bomb survivors and their children.

#### ADVICE

- It is understandable that the disclosure of genome data is often required for the publication of scientific papers both to verify the study findings and because it is expected from human genome databases that contribute to the health and welfare of humankind. It is preferable that the content of the controlled disclosure should be acceptable to everyone. However, RERF needs to examine the nature of this controlled access. RERF should take responsibility to ensure that international research collaborations are limited to those it leads.
- A management framework is needed to ensure that data leakage and the use of personal information do not occur. In particular, RERF should consider measures to prevent the leakage of data overseas, as several members of the committee commented.
- RERF is obligated to explain the significance of the research and interpretation of the results to the public before publishing papers and disclosing controlled genomic data to the public. In other words, the results must be disseminated from Hiroshima and Nagasaki. Cooperation with the mass media should also be sought after.
- The term "genomic mutation" should be avoided, and analysis of "genomic alterations" should be used.

### Topic 5: DISCLOSURE OF INFORMATION TO STUDY PARTICIPANTS

How to disclose the results of genome sequencing analysis performed for research purposes to the people concerned is an issue that requires examination from several angles. Above all,

this study involving A-bomb survivors and their children requires sensitive handling. Therefore, the committee discussed this important issue.

#### ADVICE

It is important to return information on mutations found by chance in the course of the study to participants when it will lead to the promotion of their health. However, the disclosure of genetic information should be done in such a way that the preference of the study participant is respected to the greatest extent possible.

#### Topic 6: OBTAINING INFORMED CONSENT FOR THE STUDY

Informed consent for research involving humans is standard practice in today's scientific community. There are numerous cases in obtaining such informed consent, depending on the status of the participant. In the research conducted at RERF, the acquisition of informed consent and the trust addressed at the beginning of this advice are the cornerstones of all research given the history of the past. The committee members discussed this important issue.

#### ADVICE

- The consent form must cover content that is necessary comprehensively yet be of an appropriate volume so people of advanced ages can concentrate on listening to it.
- The consent form should follow the new guidelines, and the opinions of experts in genome ethics should be sought after. The role of RERF's IRB will be significant.
- Legal representatives, standards for determining them, and opt-out\* methods all need to be defined. (\*Notifying the study participants of relevant information or making such information readily accessible to them and ensuring that they have the opportunity to refuse.)
- RERF needs to carefully determine how it should contact participants and its specific approach.
- Public relations activities and communication to the media are necessary to ensure that the participants and the public understand the above process.

#### Advice 7. CONCLUSIONS

- We hope that this study's findings will bring closure to the studies on the genetic effects of radiation that have been ongoing since the 1950s. That would not only bring comfort to A-bomb survivors and their children, who have faced hardships with regard to the genetic effects of radiation but would also have a great impact on the welfare and health of present and future generations living under the risk of radiation exposure.
- At the same time, the considerable level of community interest in the study might occasionally lead to needless friction. Accordingly, in order to implement this study, we request that RERF establish a thorough framework that is attentive to A-bomb survivors and their children at all stages of the process, with reference to the comments from this committee: From preliminary explanations through the implementation of the study and the publication and return of results.
- It is the responsibility of RERF to communicate factual information on the genetic effects of radiation not only to A-bomb survivors, their children, and the local community but also to the public as a whole through all possible channels.