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# Ethical, legal and social implications of human genome studies in radiation research: a workshop report for studies on atomic bomb survivors at the Radiation Effects Research Foundation

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**ABSTRACT**

The Radiation Effects Research Foundation (RERF) is the primary organization in Japan dedicated to studying the health consequences of the Hiroshima and Nagasaki atomic bombings in World War II. In December 2020, RERF held a virtual international workshop on the ethical, legal and social implications (ELSI) of genome studies. In this workshop, the ELSI considerations of future human genome studies on radiation research including atomic bomb survivors and their families were discussed. Since genome sequencing (GS) is now practical and affordable, RERF now plans GS of parents/child trios to examine genetic effects of atomic bomb radiation. As such studies may engender some novel risks and benefits, ethics review and engagement with families (including consent) need to be considered. These include protection of individual privacy, use of samples from deceased prior participants, return of results to the participants, public sharing of genome data and advance science and social welfare. Specifically with regard to social welfare, the results of such studies may have implications for public and government decision-making regarding social benefits of victims and other important questions. Based on these broad-ranging discussions we have developed the following concepts to guide this work: "trust," "compromise" and "relationship building," inclusive of the concerned stakeholders, scientific aims and Japanese society at large. We conclude that in order to realize, establish and maintain these concepts, it is essential to put procedures into place to ensure the successful, consensus-based implementation of the RERF studies.

**Keywords:** genome study ethical, legal and social implications (ELSI); human biosamples; genome sequencing (GS); atomic bomb survivors; informed consent; community engagement

## INTRODUCTION

Human specimens are used in many biomedical studies of radiation effects. In the past, cells from normal humans or from DNA-repair-deficient patients registered in a cell bank have been used. Samples from individuals undergoing accidental or radiotherapy-associated exposure have also been employed. In recent years, studies that aim to elucidate the molecular mechanisms of radiation damage or evaluate associated disease risks have employed genome analysis because it is a broad and robust assay of genomic integrity and it is comprehensive in its ability to assess the complete mutational landscape of the cell. As these studies are mostly based on the use of human samples, considering the ethical implications is essential. A remarkable example is the study of atomic bomb survivors that has been conducted at the Radiation Effects Research Foundation (RERF) for over 70 years. Genome studies using biosamples from the survivors of the Hiroshima/Nagasaki bombings have been important in radiation genetics as well as in cancer and noncancer diseases. Thus, there has been a long-standing and robust science of radiation effects on genomic integrity in the past several decades.

These questions have come into focus as considerations for genome sequencing (GS) of atomic bomb survivors by RERF are raised. To address these, a workshop was held by RERF in December 2020, on the ethical, legal and social implications (ELSI) of potential future genome studies on the offspring of survivors of the bombings. We selected the key problems to be solved and discussed how RERF should move forward with American and Japanese ELSI experts. The participants were comprised of the authors of this article and other RERF scientists and staff.

RERF and its predecessor, the Atomic Bomb Casualty Commission (ABCC), have been studying the potential genetic effects of atomic bomb radiation since soon after the bombings (i.e., for over 70 years) The study was based on the hypothesis that parental spermatogonia or oocyte radiation exposure would induce heritable mutations in the offspring of the survivors. The evolution of these studies mirrors advances in the field of human genetics, from phenotypic and pedigree analysis, through cytogenetics and then single gene molecular biology. It began with the investigation of congenital anomalies (malformations of the offspring) for the first decade, followed by cytogenetic examinations beginning in 1965. DNA from peripheral lymphocytes of the offspring were subjected to analyses of mutation rates of specific gene loci beginning in 1985, in parallel with clinical and epidemiological investigations of offspring throughout the periods [1–3]. Overall, to date, these studies have failed to demonstrate apparent genetic effects in the offspring.

For parents/child genome studies, 1000 family trios (two parents, at least one a survivor and children) were selected from the 77 000 offspring cohort. In an era where GS has become practical, RERF genetic studies have been proposed to identify de novo or new mutations in the offspring by comparing the parents' and children's entire genome sequences. Blood samples that could be useful for this study from this sub-cohort were collected beginning in 1985 after obtaining simple oral consent; written informed consent was obtained from the same individuals since 1994, and the informed consent form was revised according to the guidelines for genome study in Japan after 2001. However, the informed consent did not include the concept of entire GS or a policy on disclosure of results. Hence, this workshop explored the ELSI of the genome study plan.

## ELSI CONSIDERATIONS FOR THE PROPOSED GENOMIC STUDY ON THE ATOMIC BOMB SURVIVORS AND THEIR CHILDREN

The study subjects are atomic bomb survivors and their children. It is critical to recognize that they are neither volunteers for medical research nor patients in hospitals but rather the victims of atomic bombing during WWII, who were unfortunately exposed to varying doses of radiation. Therefore, the studies on them have an aspect of victim research.

Atomic bomb survivors have experienced significant discrimination. For example, a rumor circulated that the survivors could not have normal babies due to the radiation, which resulted in marriage discrimination against young women. This has remained a stigma in citizens' subconscious awareness. Indeed, old memories awoke when some of the offspring recalled their experiences surrounding marriage and job-seeking [4]. Thus, it is essential to take into consideration the cultural and social dimensions of these individual's experiences as survivors or descendants of survivors.

The current aims of the study are to investigate the genetic effects of atomic bomb radiation across the genome by determining radiation-associated mutations and their relationship, if any, to the radiation exposure. Estimating the genetic risk of radiation exposure could be scientifically beneficial to all humankind. This is the responsibility of RERF and radiation scientists, and the results will enhance public health services.

However, there are important issues that must be addressed: For example: (i) how to share the individual genome study results (i.e., genomic sequence alterations between parents and children, regardless of parental radiation exposure) with offspring; (ii) how to explain the genetic risk of radiation; (iii) how to disclose the genome data; and (iv) how to protect ultimate privacy, such as individual genome sequences tagged with radiation dose and health information. Above all issues need to be considered for individual- and aggregate-bases, respectively. The Japanese guidelines for genome studies designate such data as "non-anonymizable; special-care required [for] personal information." It also declares the need to obtain re-consent by explaining the procedures used to address the above-mentioned issues. However, since many atomic bomb survivors have now died and many of those still alive are now over 80 years of age and may find genome studies difficult to understand, it is necessary to obtain re-consent from legally acceptable representatives or through an alternative procedure. The RERF stakeholder committee for the use of stored biosamples released their advice in October 2020, after two years of discussions. The advice consists of seven points [5]:

Stakeholder committee's advice on the usage of RERF's stored biosamples

(1) Establish a relationship of trust with the atomic bomb (A-bomb) survivors, improving the provision of information and disclosing research results at individual—and community-bases.
(2) Enhance the provision of information to A-bomb survivors in general and the general public.

(3) Find ways to exclude military research when conducting collaborative research with foreign countries.
(4) Develop RERF own guidelines or charter for the provision of biological samples for research.
(5) Strive to provide donors with adequate explanations when obtaining consent and finding possible solutions to the use of biological samples of the deceased survivors.
(6) Carefully explain the research procedures, extent and method of returning genome analysis results and establishing a system of genetic counseling and follow-up.
(7) Conduct research while considering the sensitivities of A-bomb survivors who have long aspired for peace.

## JAPANESE LAWS AND GUIDELINES

In Japan, there are guidelines and laws involving the ELSI of genome studies. These consist of the Japanese Ethical Guidelines for Human Genome/Gene Analysis Research, the Outline of Ethical Guidelines for Medical and Health Research Involving Human Subjects and the Act on Protection of Personal Information. Genome studies on atomic bomb survivors must be conducted in accordance with these guidelines and rules. The genome study guidelines describe the necessary procedures for both newly collected and stored biosamples [6]. It is a primary principle, when using stored samples, to obtain re-consent. However, if the donors are already deceased or have no contact information, the guidelines allow the use of such samples if they are anonymized. Since GS data intrinsically cannot be anonymized, the guidelines suggest an alternative which requires the following two conditions: (i) that the investigators provide the donors and their families with the information about the research protocol, sharing it with the public through the use of the Internet and other approaches (Section 14, Chapter 5), and (ii) that the investigators verify whether the preexisting informed consent from the deceased donors conceptually includes the content of the new informed consent, ensuring that this new consent is reasonably interpreted in the context of the old one. This alternative procedure will satisfy the minimum requirements, but it has been suggested that there is a need to go beyond this, for mutual understanding of these studies through a dialog with survivors, offspring and associated communities, including the general public. This indicates the importance of community engagement beyond individual subjects in the ELSI of genome research. While the participants of the RERF genome cohort are limited, the study results have implications for the survivors' offspring who reside throughout Japan, numbering between an estimated 300 000 and 500 000 people. A procedure to facilitate dialog with the offspring is needed. Indeed, "trust" and "relationship building" are becoming important factors among the subjects, stakeholders and researchers. This is also the case when it comes to the disclosure of results.

## GENETIC COUNSELING; CONSIDERING SOCIETAL PERCEPTIONS OF SURVIVORS

RERF epidemiological and clinical studies have continuously reported lack of findings regarding health effects on the offspring; however even now, survivors' offspring occasionally ask their genetic counselors whether their health will be all right in the future or how their children will be. This happens not only in Hiroshima and Nagasaki, but all over Japan. As shown by such questioning, there remains an incorrect perception within Japanese society that there are adverse health effects on the offspring of survivors, despite the RERF's findings to the contrary. Even worse, some people believe that the ABCC, the predecessor of RERF, hid data on the adverse health and genetic effects of the radiation. The "Storyteller" campaign, which is now very familiar in Japanese, contributes to telling citizens a frightening story of atomic bombs and the insanity of the war based on their experiences. On the other hand, science-based information on the relationship between radiation doses and health effects on survivors as well as the lack, to date, of demonstrable health effects in the survivors' offspring, are not well known in society. Though the effect of high dose exposure was serious, it was apparently different at low and especially at very low doses. RERF needs to continuously communicate to Japanese society about the dose-dependent effects, as well as study results of genetic effects. Japanese society's fears of radiation from an atomic bomb resurfaced with the radionuclide contamination resulting from the Fukushima nuclear power plant disaster in 2011. Indeed, some people felt suspicious about why local governments provide free health examinations to the offspring of A-bomb survivors, fearing that there may still be genetic effects in offspring. Since Japanese are sensitive regarding the concept of heredity, "radiation" and "genetics" have a negative synergy for survivors and their offspring. Even though research has shown that there appears to be no genetic effects (i.e., genetic phenotypes) in offspring—whose average age is over 60-years-old [1–3]—even 75 years after the bombing, some of the offspring have asked RERF to conduct a complete personal genome analysis to confirm that there are no negative health effects. Thus, it is clear that there are both concerns about and a desire for genome analysis in individuals affected by the atomic bomb radiation.

## RETURN OF GENOME STUDY RESULTS

When human GS became practicable, the return of results to individuals became a challenge. The return of genetic testing results has been debated and discussed widely. Some of the challenges of returning individual gene testing results are amplified in genome and exome sequencing, because of the sheer numbers of variants present in each person. The ClinSeq® Project, initiated by the National Institutes of Health (NIH) of the USA in 2006, set out to analyze the associations between genotype and phenotype, genome-wide and for any and all potential genetic traits [7]. ClinSeq® pioneered the return of clinically actionable results, which contributed to the justification for the American College of Medical Genetics and Genomics (ACMG) policy that causative variants in 59 designated genes should be routinely disclosed to individuals, regardless of the indication for the sequencing, for the health benefits of the individuals [8]. There is a general agreement by genetics professionals that this is limited to highly penetrant conditions that have severe health consequences, are otherwise challenging to diagnose, and for which medical intervention can mitigate the risk of that disease. Many other categories of genetic diseases are not included in this policy nor are variants of uncertain significance, likely benign and benign variants. The concept of secondary findings variant return is conceived as a minimum obligation to a sequenced individual—these recommendations do not proscribe disclosure of additional variants. Mutations involving unknown gene function, which are

impossible to clinically interpret, may confuse the patients and possibly should not be returned. As well, the RERF study must, to the best of its ability, distinguish normal, spontaneous mutations from those that are radiogenic.

In the ClinSeq® Project and in many other studies, it has been repeatedly demonstrated that recipients of genetic test results, even those with negative health implications, can be initially distressed, but return to their pre-test emotional baseline within three to six months. Surprisingly, this also includes variants of uncertain significance and genetic risk results for untreatable neurocognitive disorders [9]. It is important to note that these studies show a return to baseline—not to normal. Of course, measurable levels of emotional distress are common in the population, and therefore those receiving genetic test results must have access to expert genetic counseling services to allow the return of results and address their emotional needs.

It is also essential that the policies for the return of genomic sequencing results which are formulated by research projects conform to relevant regulations, ethics guidelines and quality control [10].

## GENOME DATA DISCLOSURE

### RERF study

Genome sequences will be compared between parents and children, and possible associations between de novo mutations in offspring and parental radiation doses will be discussed in a manuscript after the completion of the trio GS project. In a genome study, it is frequently requested that the original sequencing data be disclosed simultaneously with a manuscript publication. This is based on the idea that human genomic data should be shared widely among qualified researchers in order to contribute to knowledge and general welfare. In Japan, most genome data are submitted to the National Bioscience Database Center (NBDC) through the DNA Data Bank of Japan (DDBJ) [11]. However, to date, the survivors' research data remain strictly limited to RERF—so that only collaborators who are approved through an internal review can access them. Careful considerations are necessary for the data disclosure because deposited data may be used without RERF oversight and collaboration. RERF's current policy requires re-consent of the donors for deposition into databases by anonymizing and modifying the data to prevent the identification of individuals; this is not applicable to genome data (because it cannot be anonymized), but the accompanying information, such as radiation doses, could be rounded to reduce re-identification risks. RERF restricts the usage of deposited data only to the promotion of health, medical care and welfare by prohibiting re-distributions; it also strictly prohibits usage for military purposes. However, the problem remains that it is difficult to judge the range that is covered by military research, and that RERF cannot control the limitation of data use once it is deposited. Therefore, the current position of RERF is to share survivors' genome data only through an internal mechanism, and to deposit it into database for restricted use only when a scientific journal requests the data deposition as per submission rules. However, this policy needs to be revised in discussion with atomic bomb survivors and their offspring.

### National databases in Japan

BioBank Japan (BBJ) was established in 2003 as a research resource organization that collects DNA, serum and clinical information from over 200 000 patients nationwide [12]. Their DNA sequence information can be obtained through the NBDC. In the early years, research protocol proposals were strictly reviewed by the NBDC committee since informed consent was not uniformly practiced, and many Japanese did not have a good understanding of genetic studies. For these reasons, genome data from patients have limited accompanying information (e.g., simply disease name). Broad consent, including an ambiguous explanation of the study purpose, was applied in early consent forms. However, this has gradually evolved over 20 years to specify the research purpose of genetic studies. Changes in research proposals are announced to the participants at the hospitals and on their homepages, simultaneously offering an opt-out opportunity. Data users are strictly forbidden to contact patients. The BBJ's current concern is whether the occasional changes of research protocols effectively reach patients, and that they do not know whether the approval of sample use comes from the patients' consent or from the decisions of institutional review board. Thus, the BBJ aims to build a decision-making system regarding sample use by improving informed consent and accompanying descriptions with the participation of patients. RERF genome data will also be deposited in the NBDC. In such cases, both the survivors' and offspring's data will receive treatment similar to that of other research participants and patients.

## ETHICAL CONSIDERATIONS ON THE STUDIES OF ATOMIC BOMB SURVIVORS

Studies on atomic bomb survivors have a characteristic of victim research, which investigates previously experienced damage and its continuing effects as retrospective and ongoing data acquisition. This is different from typical prospective clinical investigations, where participants are informed of the potential benefits, burdens and harms and asked for their consent prior to the study. Atomic bombs have caused severe physical and psychological damage to survivors, thereby decreasing their quality of life. Propelled by rapidly evolving genomic technology, the RERF has an increasing awareness of and commitment to ELSI issues among survivors. In order for studies to proceed, they should be scientifically and socially important, and special considerations are necessary to obtain survivors/offspring support and cooperation regarding additional potential burdens of newly proposed studies. Many Japanese people are unaware that research on the survivors remain in progress, but this does not mean that they are unconcerned; they know that there was once a campaign for the return of survivors' tissue specimens and medical records from the USA. Studies of radiation effects on survivors should be based on the accumulated documentation of their experience. Future studies must show how the potential benefits outweigh burdens and risks of harm.

In this workshop, the ELSI of other victim research were briefly introduced for comparison: one study focused on the victims of the Fukushima nuclear power plant disaster during a large earthquake/tsunami, and the other was a genome study of Ainu people residing in Hokkaido, Japan. In Fukushima, resident health data in areas contaminated by radionuclides were initially only available in the Fukushima community, but these data later became available for further scientific use. However, the prefectural government is now planning a review

**Table 1. Potential outcomes of RERF trio genome studies**

| | Elevated mutation rate | No elevated rate |
|---|---|---|
| Study done | Affirm adverse effect | Refute adverse effect |
| Study not done | Adverse effect present but not recognized | Adverse effect absent but not demonstrated |

system of the research protocol and manuscript draft in order to avoid negative effects on residents. With respect to the Ainu case, which involves an ethnic minority group in Japan, three Japanese academic associations, Anthropological Society of Nippon, Japanese Archaeological Association and Japanese Society of Cultural Anthropology, are planning a preliminary review system, in consultation with the Ainu people, for research using biosamples and associated burial accessories. While both cases require further discussion, they are indeed noteworthy. Studies on atomic bomb survivors are conducted not only by RERF but also by other organizations and universities, so the ELSI issues should be addressed among the institutions. Nationwide cooperation regarding survivor research, including that of the survivors and stakeholders, will also be necessary to address the challenges and develop robust and appropriate policies and guidelines going forward.

## DISCUSSIONS FOR FUTURE STUDIES

Genetic studies of atomic bomb radiation have been conducted for over 70 years. At present, the GS of survivor parents and their offspring (i.e., the trios) is being planned. RERF has prepared for the genome analysis of the selected trios since 1985, and after 35 years, GS has become widely available and affordable. In reviewing the history of RERF research, in 1965—10 years after discovering the number of human chromosomes to be 46—RERF cytogenetics studies on the trios were initiated. Around 1985, 10 years after the primitive DNA analysis (e.g., Southern blotting) became available, RERF initiated DNA analysis on the trios. Subsequently, 10 years after the completion of the Human Genome Project, the GS of the trios planning began. However, the ELSI of the project has not caught up with the rapid progress in genome science. The ELSI of genome studies of individuals appears to be coming of age in Japan, but there remains much work to be done within society—critically there is an increasing need for community engagement. In the USA, community-based participatory research (CBPR), where donors and stakeholders participate in preparing research protocols, has been a useful approach to obtain mutual trust [13]. The RERF trio genome study could receive social recognition for obtaining "community engagement" if society accepts that the study results are made through a collaborative partnership between RERF and donors, and that the results would be useful for human welfare for its contribution to radiation genetic risk studies. The ultimate goal would be social understandings for the survivor genome study. Informed consent needs to have an active function that shows respect to donors, builds mutual trust, and produces valuable research results through a transparent study process [14]. However, informed consent does not address all of the challenges. The study needs to be supported by all processes, such as informed consent and other social processes built among the people involved.

There are four potential outcomes of RERF trio genome studies. These can be grouped according to the assumption of whether or not the mutation rate is increased by parental germ cell radiation exposure, and whether or not the study plan was put into practice (Table 1). The outcomes are as follows:

(1) The GS data demonstrate increased mutation rates in the offspring. The result indicates possible radiation-genetic effects on offspring population, which may cause a painful situation. However, since the dose response of mutation found a lower limit of risk, this, in turn, relieves society.
(2) The GS data show no increase in mutation rate, which relieves both the survivors and offspring. Society is also relieved of the negative feeling surrounding radiation, with respect to heritable genetic risks.
(3) There was no execution of GS. As a result, we never know the genetic effects of atomic bomb radiation, if any, and society's fear of radiation remains. In the future, RERF may be criticized for not taking responsibility, although they had shown plenty of data regarding no phenotypic alterations in their epidemiological and clinical studies.
(4) There was no execution of GS. Both survivors and offspring are not relieved of their fear of radiation, even though there were no effects shown from prior studies. Society does not change, and no new ideas emerge.

We expect the actual data of genetic effects to be in between negative and positive since all survivor/offspring data from RERF epidemiological and clinical studies thus far suggest no phenotypic changes in offspring; however, experimental animal studies have indicated an increase in small Indels and relatively large structural changes in the genome of pups at higher doses of parental exposure [15,16]. Taken together, it is expected that a few changes in the DNA sequence will be detected in the genome of offspring, but it will be too little to affect the essential genes and make phenotypic changes. The planned whole genome analysis project would reveal the actual results. If predicted results are shown, the risk from such changes would be quantitatively small in contrast to the well-recognized spontaneous mutation rate on the order of 100 de novo mutations per genome per generation. Therefore, it is important to share the implications of the research results with society—which may eventually lead to community understanding and support. The result of trio GS may affect not only the children of atomic bomb survivors but also those affected by Chernobyl and Fukushima.

The result of trio GS may affect the future of all survivors' offspring, comprising between 300 000 to 500 000 people all over Japan. Community engagement may be an important and useful approach, based on the above discussion. Considering all discussion throughout the workshop, the ELSI of the trio genome study is a matter of "trust," "compromise," and "relationship building" with stakeholders and societies.

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## CONFLICT OF INTEREST

There is no conflict of interest.

## PRESENTATION AT A CONFERENCE

Workshop summary.

## ADDITIONAL NOTE

After drafting the current article, the results of GS of Chernobyl trios were published [17]. They reported no apparent changes observed in the offspring born to exposed parents.

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