# **FY2025** Plans of Activities

## I. Plans of Major Activities

RERF research activities prioritize the evaluation of radiation-related long-term health effects in atomic bomb survivors, and possible transgenerational effects of parental radiation exposure on their children. RERF is grateful for the dedicated support and cooperation of the atomic bomb survivors and their children. Ongoing plans for long-term follow up of epidemiologic studies of atomic bomb survivors and their children to assess risk of cancer and non-cancer disease have been largely covered under research achievements. Here, we provide highlights of new research plans and selected plans of note.

#### 1. Research Projects Examining A-bomb Survivors Health

#### **1.1 Radiation and Cancer**

- Cancer incidence study series 1958-2009 (RPs 1-75, 18-61): A summary paper on radiation-related risks of cancer incidence, describing main results from the series of site-specific incidence papers for the follow-up period 1958–2009, is expected to be completed and published in 2025. The summary paper will provide a comprehensive overview of the latest cancer incidence data, including some sites (e.g., thyroid) of high interest that were not included in the site-specific papers. Joint endpoint analysis will be used to evaluate radiation risks for families of physiologically related cancers, and to assess within-cancer family heterogeneity of radiation effects.
- Updated Life Span Study (LSS) report on mortality from cancer and non-cancer disease (*RP 1-75*): Analysis and publication of LSS Report 15 on mortality among atomic bomb survivors (1950–2019) will be of the highest priority over the next several years. The updated mortality report, which will include an additional follow-up of 16 years from the last mortality report (Report 14), provides more information on mortality among those who were young at the time of bombing, and will be key to understanding the nature of the curvature of the dose-response relationship shown in Report 14 and the latest comprehensive cancer incidence study (Grant et al. *Radiat Res*, 2017). The analysis will also provide additional information on non-cancer diseases such as cardiovascular diseases for which suggestive increased risks were observed in Report 14. Following the publication of overall mortality risks, detailed analyses are planned for major subgroups such as cancer and diseases of the circulatory system.
- Updated Life Span Study (LSS) report on cancer incidence, 1958-2019 (RPs 1-75, 18-61): The new analysis of cancer incidence in atomic bomb survivors, incorporating an additional 10 years of follow-up (through 2019), has been launched with high priority. In recent years, new cancers have been observed mainly in individuals who were younger than 20 years of age at the time of the bombings. The distribution of observed cancer types differs by calendar time due to aging of the subjects, changes in risk factors (viral infections, lifestyle, reproductive factors, etc.), and improved diagnostic techniques over the 60-year follow-up period. Modeling for radiation-associated risk estimation will be improved by taking these factors into account, as well as by using revised J45 estimates of organ dose of radiation, and updated migration rates based on contact information for AHS. In addition to an analysis of all solid cancers, more detailed analyses will be conducted and published separately for specific sites of interest.

- Completion of site-specific cancer studies with pathological reviews in the LSS cohort: With changing classification of disease and sub-types over time, very few studies can provide radiation risk estimates applying standardized diagnostic criteria based on pathological review of cases collected over several decades. In 2025, RERF plans to complete and publish analyses of radiation-related risk comparing subgroups of cancers of the breast (1958–2005), uterine corpus (1958–2011), and hematological malignancies (1950–2009). Analyses of soft tissue and bone tumors (1958–2003) and skin cancer (1958–2011) will continue, with expected publication of results in 2026.
- *Pathogenesis of myelodysplastic syndrome (MDS) (RP 1-17)*: A-bomb survivors have a high risk of hematological malignancies, but little is known about the mechanisms of radiation-induced myeloid malignancies. In 2025, we will complete and submit a manuscript on the phylogenetic analysis of whole exome sequencing (WES) using blood samples obtained before the diagnosis of MDS. We will further assess differences in the dynamics of structural variation between the low and high dose groups using WGS data to reveal the effects of A-bomb radiation on their mutational process.
- *Leukemia among A-bomb survivors (RP-P1-23)*: We will complete and submit a scientific paper regarding the applicability of targeted sequencing in old formalin-fixed paraffin embedded (FFPE) samples. If pilot study results indicate that samples can be sequenced successfully, we plan to initiate a related full-scale study "Identification of clinicopathological findings associated with radiation dose in hematological malignancies among atomic bomb survivors."
- *Radiation and Liver Cancer, (RP 9-92):* The established association between radiation and chronic hepatitis B virus (HBV) infection, together with the known roles of both radiation and HBV in risk of hepatocellular carcinoma imply that HBV is a mediator, but the extent of mediation has not been established. We will address potential mediation and moderation of radiation risk for hepatocellular carcinoma by hepatitis C virus (HCV) infection with concomitant adjustment for possible interaction between HCV and obesity, and prepare a manuscript describing the results.
- *Hiroshima and Nagasaki tumor/tissue registries (RPs 18-61, 29-60)*: Regular activities in National Cancer Registry and Nagasaki tissue registry continue under contract with each authority. The Dept. of Epidemiology will continue to crosscheck the subjects of RERF major cohorts against newly registered data with approval from each authority.
- *Pathology studies (RPs 5-89, 1-12)*: The indexing of FFPE tissue specimens within a new database will continue in collaboration with RERF's Biosample Research Center. Efforts to preserve and utilize pathological materials from A-bomb survivors will be continued in collaboration with local hospitals in Hiroshima and Nagasaki.

# **1.2 Radiation and Non-Cancer Effects**

• Updated Adult Health Study (AHS) report on non-cancer disease (RP2-75): We will complete analyses for the 9th report of AHS and summarize results of associations between radiation exposure and incidence of various non-cancer diseases, using revised organ doses based on the new J45 phantoms and updated longitudinal data with 22 years of additional follow-up since the last published report for all AHS cohort groups except those exposed *in utero*. Compared to Report 8, the new report will extend follow up to 2020 (vs.1958-1998) and examine twelve additional disease outcomes including valvular heart disease, hyperparathyroidism, and benign tumors of the colon and rectum. Health

examinations of AHS cohort members and collection of clinical and epidemiological data and related biosamples will continue throughout this time.

- *Radiation and Cataracts, (RP 5-15):* Although radiation effects on posterior subcapsular cataracts (PSC) have been documented among A-bomb survivors and other exposed populations, past reports of radiation effects on cortical (COR) and nuclear (NUC) cataracts have been inconsistent. A revised analysis of cataract risk using appropriate devices and diagnostic criteria to obtain more precise diagnosis will be completed and published, and analysis of *in utero* participants will begin.
- *Radiation and Atherosclerosis (RP2-11, RP 1-23-2)*: To understand the potential mechanisms by which radiation may promote atherosclerosis, we will complete statistical analyses of associations between cytokines, atherosclerosis, and radiation dose, and begin preparation of a manuscript.
- *Radiation and Stroke incidence (RP 1-21)*: Statistical analysis to determine the association between radiation and incidence of stroke will be completed, and a manuscript will be submitted.
- *Radiation and Myocardial infarction incidence (RP 1-22)*: A manuscript examining the association between radiation and myocardial infarction incidence will be prepared and submitted to an international journal.
- *Radiation and Heart disease (RP 2-14)*: The association between radiation and diastolic dysfunction, heart failure, and valvular heart disease will be analyzed, and a manuscript will be prepared.
- *Radiation and Thyroid conditions (RP 4-23)*: A previous AHS study conducted in 2007–2011 (1st cycle) reported increased radiation-related risk of thyroid nodules, but not of thyroid dysfunction and autoimmunity. In 2025, we will complete diagnosis and data cleaning of the 2nd examination cycle diagnosis of thyroid disorders (2018–2022), and continue collection of pathological information on thyroid nodules from medical institutions for the 3rd examination cycle. For the study of progression of thyroid nodules, we will examine the two-point data from baseline and the second cycle descriptively in preparation for a full-scale analysis (planned for 2027).
- *Radiation and Chronic kidney disease (CKD) (RP-A1-14)*: We will complete statistical analysis of the association between radiation and CKD, and prepare a manuscript.
- *Radiation and Diabetes (RP 1-15)*: We will investigate how radiation exposure affects conditions related to insulin resistance, such as steatotic liver disease.

# **1.3 Underlying Biological Mechanisms of Radiation Health Effects**

• *Preparation for AHS Genome Wide Association Study (RP P2-22):* A final evaluation will be made regarding whether whole genome amplification of DNA from Adult Health Study (AHS) blood smears stored over the long term (up to 50 years) can be used for high throughput genotyping platforms, such as those used for genome-wide association studies (GWAS). Results will be published. If genotyping is successful, a full-scale research plan will be developed.

- Evaluation of radiation-associated Clonal Hematopoiesis (CH) Human Studies, (RP 1-23-1): Clonal hematopoiesis, in addition to a potential link with hematological pathologies, may also be associated with cardiovascular risk. We will complete whole exome sequencing (WES) and T-Cell Receptor (TCR) deep-sequencing analysis of blood cell DNA obtained from about 150 A-bomb survivors in the AHS to characterize clonal expansion of hematopoietic stem cells in high-dose exposed survivors.
- *Radiation and Clonal Hematopoiesis (CH) Animal Studies (RP 1-23-3)*: To investigate the molecular mechanisms of inflammatory diseases due to radiation-associated CH, we will continue to characterize and track CH mutants in wild-type and atherosclerotic LDLR-KO mice after radiation exposure. We will complete a manuscript describing that CH involves expansions of both single nucleotide variants present before irradiation and deletions generated by or after irradiation, and that the trajectory of CH with multiple mutations is associated with increased inflammatory phenotypes. Further, we will construct phylogenetic trees of somatic mutations detected by WGS of single cell-derived hematopoietic colonies from mice that develop CH following irradiation. Based on the phylogenetic trees, we will reconstruct timelines of CH evolution in irradiated mice and prepare a manuscript describing the results. This approach could provide a method to analyze the effects of radiation and aging on human hematopoietic cell differentiation and expansion with a reconstructed timeline.
- Preliminary study of chromosome aberration frequency in hematopoietic stem cells (HSCs) following fetal irradiation of mice (RP P4-17): To further investigate mechanisms involved in the process of the disappearance of chromosomal aberrations that occurred in fetal LT-HSCs, we plan to update the current RP to include whole genome sequencing (WGS) analysis, which would make it possible to detect not only large structural variations such as translocations by chromosomal analysis, but also small mutations at the DNA sequence level. We believe that such a study will help us to better understand the effects of *in utero* exposure.
- Preliminary study on possible roles of oxidative stress response in protection against radiation-induced mutagenesis and oncogenesis in mice (RP P3-19): Somatic mutation analysis of mutant mice with NRF2 loss or activation by WGS will be completed to compare somatic mutations in LT-HSCs between the wild-type and mutant mice and to determine the role of NRF2 in protecting against spontaneous and radiation-induced somatic mutagenesis, and the results will be submitted for publication. Further, the analysis of somatic mutations in wild-type mice exposed to 3.8-Gy X-rays at 2 weeks of age will be conducted to compare somatic mutations in LT-HSCs between wild-type mice exposed at 2 weeks and 8 weeks, aiming to determine the effects of age at exposure on radiation-induced somatic mutagenesis. Additionally, we will investigate the effects of lower doses of X-irradiation, which are tolerable for one-week-old mice, to study somatic mutations.

# 2. Research Projects on the Health of A-bomb Survivors Children (F1)

• *Mortality surveillance for In Utero and F1 cohorts (RPs 1-75, 2-61, 4-75)*: Mortality follow-up for both cohorts will continue and the data will be completed through 2020. Archiving of early-period materials will continue in collaboration with the Research Resource Center of RERF.

- *F1 Offspring Clinical Study (FOCS), (RP 4-10)*: In 2025, we will summarize results of the analysis regarding the effects of parental radiation exposure on incidence of hypertension, diabetes, and dyslipidemia (hyper-LDL cholesterolemia and hypertriglyceridemia) using longitudinal follow-up data from the offspring of A-bomb survivors (2002-2020). These data will be the first incidence data for non-cancer effects in the F1 cohort (2002-2006 prevalence estimates published in 2013). Ongoing health examinations of FOCS cohort members and collection of clinical and epidemiological data and related biosamples will continue.
- *Transgenerational Effects, Trio Genome Study (RP 3-23)*: Understanding the hereditary genetic effects of A-bomb radiation has been a long-standing concern for atomic bomb survivors, their children, and the scientific community. Following determination of the gene list for return of secondary findings to study participants, and formation of an ethics advisory group, we plan to publicly announce the commencement of the Trio Genome Study. We will then proceed with genomic analysis of samples for which consent forms have been obtained. First, we will identify *de novo* mutations (including structural variants) that have occurred in children and determine parental origin of the mutations. After completion of genetic analyses and quality control, epidemiological analyses will be conducted to examine the association between the number of *de novo* mutations and parental exposure, as well as other factors such as parental age at the time of conception of the child. We will continue obtaining informed consent for remaining participants through this period. RERF will continue to promote communication between RERF and the public, research collaborators, and other key stakeholders.
- *Transgenerational Effects, Animal Studies (RP 2-13, RP S3-11)*: Analyses of spontaneous *de novo* structural variants in the mouse germline will be completed and published. We have successfully developed a methodology to capture genomic structural changes at a larger scale than common structural variants, which we plan to verify using techniques such as ultra-long-read sequencing. Mutations in minisatellite regions have long been a focus of radiation research. If this analysis system can be established, it will enable the study of minisatellite mutations throughout the genome. Once we can construct a method to capture such genomic changes, we will test it on mouse models of radiation exposure. If successful, we plan to use this method in the Trio Genome Study and studies of somatic mutations in A-bomb survivors. A paper will also be prepared on the results of collaborative research with outside institutes and universities regarding dose and dose rate effects on transgenerational genetic effects.

#### **3.** Research to Elucidate Individual Doses and Effects from the A-bombs

- *Shielding Survey and Dosimetry (RP 18-59)*: The Department of Statistics will complete work on an updated organ dosimetry system using modern, sophisticated J-45 computational phantoms.
- *Dosimetry Error*: The Department of Statistics will complete formal re-evaluation of the currently utilized methods used to correct random dosimetry error in RERF analyses. We will investigate the importance of distinguishing between subjects with complete vs. average shielding parameters, different shielding scenarios (e.g., inside shielding or outside), and whether the assumed amount of random dosimetry error should be retained.

# 4. Project to Communicate Research Results and to Collaborate with Other Scientific Organizations

- *Communicating Research Results*: In addition to publication of RERF research in peerreviewed academic journals, RERF will contribute to high-visibility reports by international dosimetry and radiation risk assessment groups such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the International Commission of Radiation Protection (ICRP).
- *Continuing collaboration*: RERF's long-term collaboration with numerous Japanese and international institutions is expected to continue in 2025, including:
  - a. Partnerships with the Universities of Hiroshima, Nagasaki, Kurume
  - b. Collaboration with the U.S. National Cancer Institute
  - c. Collaboration with the University of Washington
  - d. Collaboration with Outside Investigators:
    - 51 Japanese Institutions
    - 6 North American Institutions
    - 9 European Institutions
    - 1 Asian Institution

#### **5.** Training programs for domestic and overseas specialists

RERF will hold a training course for non-epidemiologist radiation researchers to learn the basics of epidemiological research and increase understanding of radiation health risks. In addition, RERF will train persons capable of working in the fields of radiation protection, radiation emergency medical care, and radiobiological research.

- i) RERF intends to hold an epidemiological training course for radiation biologists in Japan to enhance understanding of results from epidemiology research on A-bomb survivors.
- ii) RERF will accept overseas research trainees to support the activities of such organizations like the Hiroshima International Council for Health Care of the Radiationexposed (HICARE), the Nagasaki Association for Hibakusha's Medical Care (NASHIM), and the Japan International Cooperation Agency (JICA).
- iii) RERF plans to accept physicians and researchers from overseas to provide them with training through the Ministry of Health, Labor and Welfare (MHLW)-sponsored FY2025 International Exchange and Research Program.
- iv) The Department of Statistics will apply to the International Fellowships for Research in Japan program, sponsored by the Japan Society for the Promotion of Science (JSPS), upon application from candidate trainees, and provide research opportunities to post-doctoral researchers from various countries.

# 6. Public Information Programs

The mission of RERF is 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 A-bomb survivors and to enhancement of the health of all humankind. These programs aim to communicate and promote the further understanding of RERF research results to the A-bomb survivors and their children, who have long appreciated and cooperated in RERF research, as well as to the local communities. In addition, RERF is considering the continued use of expert consulting services to scrutinize

and revamp existing public information programs and also will promote PR activities for the foundation's 50th anniversary program, relocation to the Kasumi campus of Hiroshima University, and genome sequencing study of genetic effects. In FY2025, RERF will engage in the following public information programs.

#### i) Communication of Research Results

RERF will engage in PR activities to broadly communicate to society its research results and the importance of its future research, contribution to the maintenance of the health and welfare of the A-bomb survivors, and enhancement of the health of all humankind. Focusing on PR activities related to its genome sequencing study of genetic effects in particular, RERF will continue to hold public lectures and study sessions and release information on its official website and through various media. Specifically, RERF will open an official portal for the genome sequencing study, release videos of interviews and explanations by research scientists online, and publish a special issue of brochure to be distributed among the study participants. RERF will consider planning effective methods of conveying information while enhancing its relationships with media outlets. It also plans to consult external PR experts to enhance its information releases related to research.

#### ii) RERF's 50th Anniversary Program

RERF sees its 50th Anniversary as a chance to relay its research achievements up to now, its contribution to the maintenance of the health and welfare of the A-bomb survivors and to the enhancement of the health of all humankind, and the significance of its upcoming research activities to the A-bomb survivors, their children, and the local communities. RERF will plan activities, including commemorative ceremonies and a publication so that even more individuals in Japan and around the world come to recognize the significance of its work.

#### iii) Open House

The upcoming Open Houses will be RERF's second time holding the events in person since the classification of COVID-19 was changed to Category 5 under the Act on the Prevention of Infectious Diseases. RERF will continue aiming to increase opportunities for direct dialogues with the local communities as much as possible. The event working committees consist of 29 employees from Hiroshima and Nagasaki joined by three members of the Public Relations & Publications Office. Together, they will enrich the popular content from past events and also use videos and photographs related to RERF's research and facilities to communicate its research achievements to date, how RERF has contributed to the maintenance of the health and welfare of the A-bomb survivors and enhanced the health of all humankind, and the significance of its upcoming research to the A-bomb survivors, their children, and the local communities to improve their understanding of RERF research programs.

#### iv) International Peace Activities Based on Research Results

As requested by the City of Hiroshima, RERF has annually received the ambassadors to Japan on August 6 since 2022. In FY2024, a total of 37 diplomatic representatives from 23 countries and organizations visited RERF, and they were given an overview of ABCC–RERF's history and research findings, and a facility tour. The City of Hiroshima has already contacted RERF regarding this matter in FY2025, and the foundation will start preparations when there is a formal request. Since FY2025 marks the 80th anniversary of atomic bombing, more people from more countries than last year are expected to visit RERF. In FY2024, the Indian ambassador to Japan and scientists from the University of Pennsylvania also visited

RERF, and RERF will accordingly address such requests in FY2025 also.

v) Official Website

Through the "What's New" section of its official website, RERF will continue to provide comprehensive information on its activities and add more understandable content about its research. Seeing Hiroshima Laboratory's relocation as a chance to improve its official website drastically, RERF will prepare to analyze its current website and devise a plan for its redesign by consulting external experts.

#### vi) Facility Tours and School Visits

RERF will continue to present information on its research achievements to date, its contributions to the maintenance of the health and welfare of the A-bomb survivors and to the enhancement of the health of all humankind, and the significance of its upcoming research by receiving visitors and visiting schools. This will include more than distributing information—RERF will continue its efforts to ensure the significance of its research is understood by people from all walks of life: A-bomb survivors, their children, researchers, government personnel, peace volunteers, students, members of the communities, overseas visitors, and others. In addition, RERF will make effort to enhance relationships with administrative agencies and other relevant bodies to reach a wide group of people.

(Other public relations activities)

- Releasing accessible information about research results through press releases and conferences.
- Regularly tracking coverage in the media and planning the maintenance and enhancement of relationships with the media through close communication.
- Preparing a synopsis for each paper and communicating research results in an accessible manner.
- Regularly responding to everyday inquiries from outside parties.
- Preparing to revise its current PR materials in anticipation of Hiroshima Laboratory's relocation to the Kasumi campus of Hiroshima University (handbooks, leaflets, booklets, etc.).
- Creating a digital archive of videos and still images of the historically significant structures of the current Hiroshima Laboratory.

# **II. Operation and Management of RERF**

# 1. Research Resource Center

We will further enhance the visualization content of the biosample inventory information, which was launched in FY2024 on the Research Resource Center (RRC) portal site, an internal website. At the same time, we will create a new category of controlled access visualization content that links biosample inventory information with clinical and epidemiological data. Additionally, while we have been exploring the development of an integrated environment for the biosample database and the research database, we will determine whether to build a new database environment or expand the existing research database to ensure practical usability for research. Based on this decision, we will implement the most appropriate solution. Furthermore, to enhance in-house research computing resources, we will introduce a high-performance server capable of GPU computing and

promote its utilization among RERF researchers. To enable unified access to all these research resources *via* the RRC portal site, we will continue to improve and expand the portal.

## 2. Relocation of the Hiroshima Laboratory

We will proceed with the plan to relocate the laboratory to Hiroshima University's Kasumi Campus.

#### 3. Discretionary working system

It is time for RERF to start new studies with a long-term vision, based on its accumulation of previous research. Improving RERF's working system is essential to enable these studies to progress. A discretionary working system is a suitable work arrangement for jobs that demand advanced expertise, such as those associated with research scientists. The ability to adjust work hours flexibly and efficiently according to the progress of a study or its individual characteristics is expected to lead to higher research quality and productivity. The system will also make it easier to coordinate the timing of key meetings and discussions in interactions with researchers in Japan and overseas, leading to further opportunities for collaboration. As a result, RERF's international research network is expected to be strengthened, and its research activities will become more diversified and in-depth. Introducing a discretionary working time system is also expected to improve the work-life balance and assist research scientists in maintaining high motivation levels in the long term.

#### 4. Cross-appointments

RERF has reached the milestone of its 50th anniversary since its establishment and has formulated a strategic plan that anticipates future research studies. In addition to traditional epidemiological studies, newly formulated research protocols include mechanistic research on the effects of radiation by analyzing biological samples from atomic bomb survivors and their children using the latest technology. Experts in various fields are essential to advancing A-bomb survivor research using the latest technologies. However, RERF will certainly remain understaffed if it attempts to cover all these specialties with its in-house experts alone. To overcome these constraints, RERF will need to expand areas of expertise lacking internally by intensifying collaborative research and also introducing a cross-appointment system, as is common in universities and research institutions, to create an environment that facilitates the availability of experts from outside the organization. It is expected that introducing this system will facilitate the exchange of personnel with universities and research institutions and ensure the availability of personnel with the latest expertise in areas that RERF does not cover.

# 5. Revision of the rules and regulations

RERF revises the current regulations and establishes new regulations based on revisions to laws and regulations and regular reevaluation by the sections in charge. In FY2025, revisions to regulations necessitated by the Hiroshima Laboratory's relocation and other required revisions will be made to keep the foundation's management operations appropriate. Doing so will provide RERF with regulations befitting of a public interest incorporated foundation funded by the U.S. and Japanese government subsidies.