A proposal on the first Japanese practical guidance for the return of individual genomic results in research settings

doi: 10.1038/s10038-019-0697-y

Journal of Human Genetics
https://doi.org/10.1038/s10038-019-0697-y

ARTICLE

A proposal on the first Japanese practical guidance for the return of individual genomic results in research settings

Yayoi Aizawa[1] · Fuji Nagami[1] · Noriko Ohashi[2] · Kazuto Kato[2]

Received: 25 June 2019 / Revised: 19 November 2019 / Accepted: 19 November 2019

Abstract

Large-scale, low-cost genome analysis has become possible with next-generation sequencing technology, which is currently used in research and clinical practice. Many attempts of returning individual genomic results have commenced not only in clinical practice, but also in research settings of several countries. In Japan, the government guidelines include a section on the disclosure of genetic information regarding genome analysis in research. However, no practical guidance for the return of individual genomic results in research settings (ROGRR) currently exists. We propose practical guidance regarding ROGRR in Japan based on extensive research, including a literature review of related previous studies, an examination of the relevant legislation in Japan, and interviews with stakeholders. The guidance we developed consists of "Points to consider" and "Issues for further discussion and consideration." The "Points to consider" were divided into five parts, from preliminary review before discussion of policy, to the actual return and follow-up process, in the order of the assumed ROGRR process. It is anticipated that a situation will arise where numerous research projects will consider ROGRR carefully and realistically in the future, and in the process of drafting such practical guidance, various issues requiring continuous discussion will emerge. The necessities of continuous discussion concerning ROGRR in Japan's context is increasing, particularly in terms of the ethical, legal, and social implications. We believe such discussions and considerations may contribute to creating a new system that will increase availability of personalized medicine and prevention using genetic information, allowing them to become useful to the broader population.

Introduction

Large-scale, low-cost genome analysis has become possible with next-generation sequencing technology, which is currently used in research and clinical practice. In 2013, the American College of Medical Genetics and Genomics published policy statements on the return of incidental findings (subsequently revised as "secondary findings") in clinical exome and genome sequencing [1, 2], which prompted widespread and diverse discussion [3–5]. There is also growing debate about returning genomic research results to participants [6–8]. Numerous attempts to return individual genomic results have been initiated not only in clinical but also in research settings in several countries [9–12].

In Japan, the government's *Ethical Guidelines for Human Genome/Gene Analysis Research* (JEGHG) includes a section on the Disclosure of Genetic Information regarding genome analysis in research, which states, "With regard to human genome/gene analysis research through which the genetic information of individual donors is obtained, when a donor has requested disclosure of that, the researchers shall, in principle, disclose the requested information." [13] This description reflects the importance of participants' right to know their own information, which may have great impact on the participants' health. Yet, there is little mention of specific points to consider [13]. Although Japanese academic society guidelines on clinical genetic testing have been presented [14], no practical guidance on the return of individual genomic results in research settings

These authors contributed equally: Yayoi Aizawa, Fuji Nagami

Supplementary information The online version of this article (https://doi.org/10.1038/s10038-019-0697-y) contains supplementary material, which is available to authorized users.

✉ Fuji Nagami
f-nagami@med.tohoku.ac.jp

[1] Department of Public Relations and Planning, Tohoku Medical Organization, Tohoku University, Sendai, Japan

[2] Department of Biomedical Ethics and Public Policy, Graduate School of Medicine, Osaka University, Osaka, Japan

(ROGRR) exists. Nevertheless, with the increase of data and knowledge on disease-causing variants, it is likely that researchers will need guidance to effectively deal with them. We posit that practical guidance tailored to the current state of affairs in Japan is needed for researchers handling ROGRR. Therefore, this study aims to propose the first Japanese practical guidance for ROGRR based on extensive research.

Methods

To understand the current circumstances affiliated with ROGRR, several investigations were conducted, including a literature review of previous studies on ROGRR, an examination of the relevant legislation in Japan, and interviews with stakeholders. Fifteen researchers and genomics experts were interviewed. In some interviews, interviewees' collaborators participated, increasing the total number of interviewees to 20. The researchers interviewed were the principal investigators of the ten themes of the Japan Agency for Medical Research and the Development funded Platform Program for Promotion of Genome Medicine Advanced Genome R&D, which was selected as the main target for large-scale projects on human genome analysis. The five experts other than the researchers were selected purposively for their wide range of knowledge of the issues around ROGRR, including medical geneticists, an expert of clinical laboratory, and an individual with a genetic condition. All interviews were recorded and with the permission of the interviewees, summaries were subsequently created and classified as points of interest. Based on these results, we prepared drafts of the practical guidance for ROGRR for stakeholders in Japan that consist of "Points to consider" and "Issues for further discussion and consideration," respectively. The drafts of the guidance were also reviewed by the five supervisors of the Japan Agency for Medical Research and the Development's research project mentioned above. Feedback was requested from 20 groups including the interviewees. The final version of the guidance and the summery of the investigations described above were published on the Japan Agency for Medical Research and the Development website in Japanese [15].

In this paper, we present "Points to consider" as suggestions that provide practical guidance in the "Results" section, while the "Discussion" section was composed based on "Issues for future discussion and consideration," as well as other content deemed relevant. Before each interview, we asked interviewees about recording and summarizing an interview for making drafts of the practical guidance, and verbal consent was obtained. Following the completion of this guidance, written informed consent (IC) regarding publishing was obtained from all interviewees. This study was approved by the Institutional Review Boards of Tohoku Medical Megabank Organization at Tohoku University (2019-4-004) and Osaka University (19041).

Results

Preliminary investigations

Literature review of previous studies on ROGRR

A total of 27 published research articles met the criteria and 22 projects were mentioned in those articles (Supplementary Table 1). There were 13 projects in the US, one each in the UK, Canada, Sweden, Estonia, Singapore, Germany, Australia, Switzerland, and Japan. Three projects returned results in medical research including the use of samples and information in biobanks. Five projects included research participants who were ostensibly healthy people. Eleven projects returned secondary findings in studies regarding rare diseases or cancer, and three projects were considering ROGRR in the future.

Examination of the relevant legislation in Japan

We investigated Japanese legislations related to the ROGRR. Major legislation governing the return (disclosure) of genomic results include the Act on the Protection of Personal Information and the related laws, JEGHG, Ethical Guidelines for Medical and Health Research Involving Human Subjects, among others (see Table 1). Under the Act on the Protection of Personal Information, personal information (including genomic information) should be disclosed if the concerned person requested, but this principle is exempted for research use. The use is regulated by research guidelines, such as JEGHG.

Research that analyzes germline variants requires adherence to the JEGHG, and it is based on the principle of disclosure if the concerned person requested, but nondisclosure is permitted in certain cases.

Interviews with stakeholders

All contacted persons participated in an interview. Interviews were conducted either at their office or in a public meeting room, and lasted 30–90 min. All researchers were engaged with human genome analysis research, and had various backgrounds, including physicians, molecular or informatics biologists, or researchers belonging to institutes not affiliated with medical institutions. Some researchers responded that their project planned to or did ROGRR, and the rest commented that their project could not ROGRR for some reasons. Some experts had experiences of ROGRR as

Table 1 Scope of applications and targets of major laws and guidelines

Name	Established year	Latest revision	Major scope of applications and targets
Act on the Protection of Personal Information	2003	2019	Private business operator handling personal information
Act on the Protection of Personal Information Held by Administrative Organs	2003	2019	State administrative organs
Act on the Protection of Personal Information Held by Incorporated Administrative Agencies	2003	2019	Incorporated administrative agencies
Ordinances for the Protection of Personal Information Held by Local Governments	–	–	Local governments
Fundamental Principles of Research on the Human Genome (Council for Science and Technology, Bioethics Committee)	2000	–	Research on human genome
Ethical Guidelines for Human Genome/Gene Analysis Research (MEXT, MHLW, METI)	2001	2017	Human genome/gene analysis research
Ethical Guidelines for Medical and Health Research Involving Human Subjects (MEXT, MHLW)	2014	2017	Medical and health research involving human subjects which is carried out by a Japanese research institution or carried out in Japan
Guidelines for clinical research of gene therapy (MHLW)	2002	2019	Clinical research of gene therapy[a]

MEXT Ministry of Education, Culture, Sports, Science and Technology, *MHLW* Ministry of Health, Labour and Welfare, *METI* Ministry of Economy, Trade and Industry

[a]These guidelines were newly established after substantial revision of the previous guidelines which were first enforced by MEXT and MHLW in 2002

researchers. Interview summaries classified as points of interest are shown in Table 2, and the detailed results were published as a report on the website [15].

Points to consider: return of individual genomic results in research settings

Introduction of "points to consider"

Several "Points to consider" were proposed for the practical guidance for ROGRR. Researchers determine the overall policy on ROGRR and proceed with the return process after a thorough investigation, which accounts for the characteristics of the genetic information. It is necessary to proceed according to the specific characteristics for each research project.

In a determination of the ROGRR policy of each project, it is required to observe the JEGHG and other relevant legislation and guidelines. Moreover, when implementing a return plan, the institutional review board of the relevant facility should be consulted and provide approval for said plan prior to its implementation.

This guidance does not recommend actively implementing ROGRR in every research project. However, as there may be possibly important findings related to the health and reproduction of research participants in the information obtained in research based on genomic analysis, we hoped that attempts of ROGRR in various situations will increase. Hopefully, this guidance will serve as a useful reference for the numerous situations that projects may need to consider ROGRR.

Scope of guidance

The return of germline genetic information is the primary target within ROGRR based on the description in the JEGEG. In addition to the return of primary findings (e.g., results concerning rare genetic diseases for patients), which has been carried out for a few decades, this section is concerned with the following possible situations in which ROGRR would occur: the return of relevant variant information in cases where intervention research (e.g., clinical trials) is conducted using the results of genome analysis, the return of genetic information aimed at evaluating the return process and psychosocial facts, and the return of secondary findings and incidental findings. New situations could emerge in the future, including the return of risk information on multifactorial diseases and returnable secondary findings from transcriptome/epigenome analysis. Moreover, given that the context of performing whole genome/exome analysis in research differs from clinical genetic testing, it was assumed that there would be situations where it would be difficult to clearly classify returnable genetic information into primary, secondary, and incidental findings. Therefore, comprehensive references will be provided in this guidance without classifying genetic information to return. Furthermore, although it is described as the "disclosure" of genetic information in JEGHG, we will use the term "return" in this

Table 2 Classified points of interest based on interviews summary

Main theme	Sub theme
1. Overview of research projects and current status of ROGRR	
2. Experiences and opinions about ROGRR	
(1) Determination of policy on ROGRR	(1) Research purpose and content (2) Systems and background on determination of policy (3) Research participants, numbers, situation eligible for ROGRR (4) Types of genetic information planned to return (5) IC and confirmation of preference for ROGRR (6) Actual methods and systems on ROGRR (7) Cost and human resources (8) Response for requests to disclosures
(2) Analysis related to information with possibility of return	(1) Quality control (2) interpretation (3) reidentification (4) confirmation testing
(3) ROGRR to research participants	(1) Results report (2) retaining records related to ROGRR (3) information to explain (4) follow-up
(4) Issues to be addressed by all stakeholders	(1) Establishing guidelines (2) coordinating among stakeholders (3) progress of medical research and healthcare (4) data sharing

guidance, as it is assumed that the variants related to the target genetic information have been detected and research participants will be informed of the results based on expert interpretation, genetic counseling, and adequate follow-up, including referrals to medical professionals.

Characteristics of germline genetic information

Depending on the type of information returned, ROGRR could lead to the genetic testing and diagnosis of research participants and their respective biological relatives. Therefore, it is necessary to consider the characteristics of genetic information just as carefully as genetic testing and diagnosis in clinical practice.

Points to consider on ROGRR

We assume that ROGRR consists of the following process: preliminary review before discussion of policy on ROGRR, discussion and determination of policy on ROGRR (a nonreturn policy is a possible option at this stage), IC and confirmation of preference for ROGRR, analysis related to information with possibility of return, and return of results to research participants who prefer the genetic information. Several pertinent points are listed below. Researchers ought to give due consideration to the circumstantial variation of each project (e.g., difficulty designing a plan in detail before the onset of research and limited participant contact during and after the study), while considering when and how to examine the following points.

Preliminary review before discussion of policy on ROGRR

When planning research, because the situations around ROGRR related to genetic information differ depending on the research purpose and content, it is advisable to review points (1) through (6) before designing the plan in detail regarding policy on ROGRR. A summary of this section is shown in Fig. 1.

(1) In interventional and observational research based on genetic information, it may be necessary to return the relevant genetic information to research participants. Confirm whether the return of the results is included in the main research purpose and content as in, for example, interventional research using the results of genome analysis to determine the administration of medication, or the return of genetic information to evaluate psychosocial factors or verify the return process. In applicable cases, proceed to (6), and consider the specific return details and methods in accordance with the purpose and content of the research, as well as points required by associated laws and guidelines.
(2) For research other than what was covered in (1), confirm whether the samples and information used for analysis are newly acquired in the research or based on the use of preexisting samples and information through the transfer of samples and information or cooperative research. Plans in place to acquire new samples and information should proceed to (4).
(3) Research on preexisting samples and information ought to carefully consider whether ROGRR is possible by checking the original terms of use and contractual content (with the supplier) in the transfer of samples and information or any cooperative research and the accompanying consent with respect to the possibility of ROGRR. It should also consider whether it is possible to reconnect genomic analysis results with individual information (e.g., contact

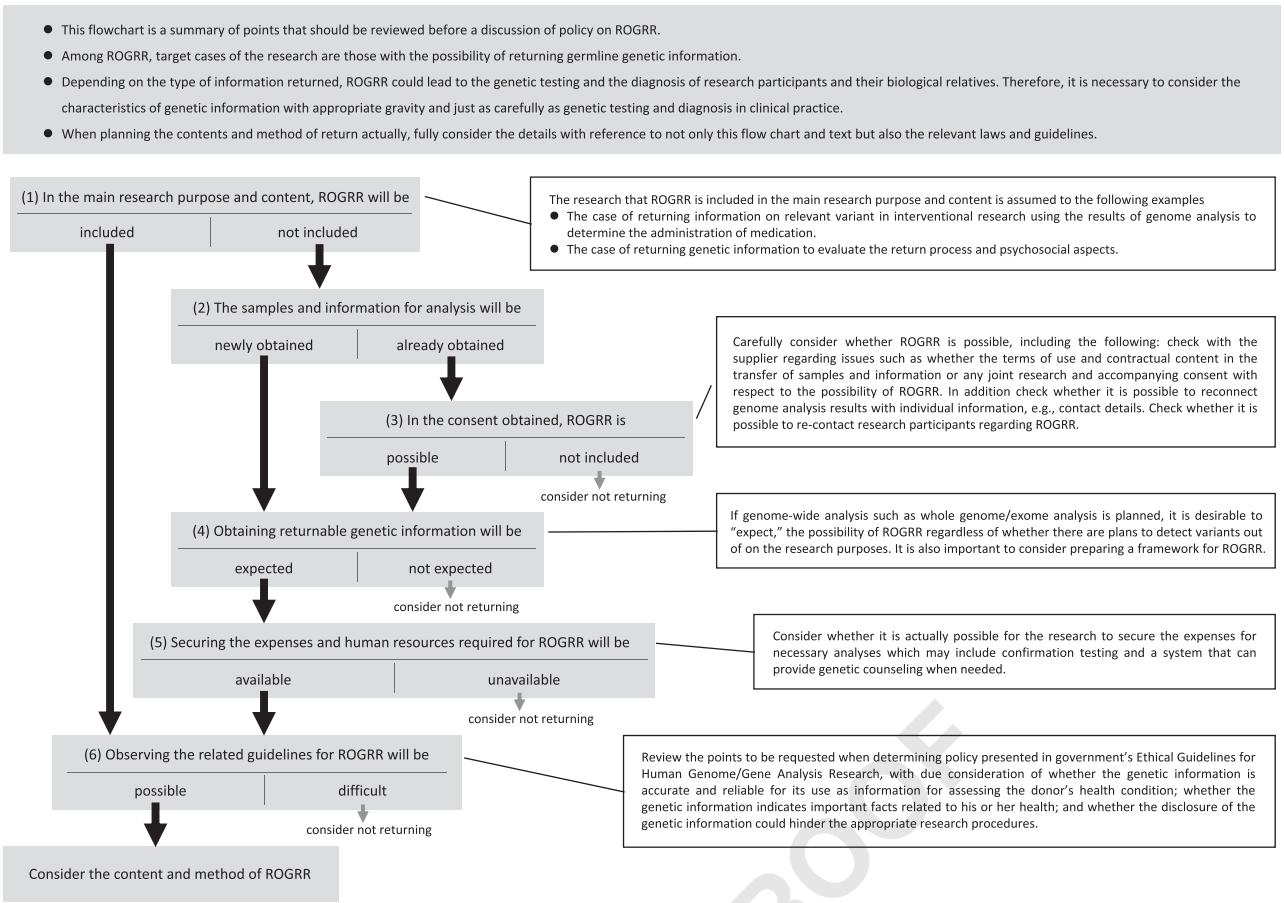

Fig. 1 Return of Individual Genomic Information in Research Settings (ROGRR): Flowchart for preliminary review before discussion on policy

details), and whether it is possible to recontact research participants regarding ROGRR.

(4) New research based on the acquisition of original samples and information or the use of preexisting data where ROGRR may be possible should consider whether returnable genetic information can be obtained. At this point, if genome-wide analysis (e.g., whole genome/exome analysis) is planned, researchers should expect possible ROGRR and examine the feasibility of actual return, regardless of whether the research planned to detect variants out of the research purpose.

(5) If returnable genetic information is expected to be obtained in (3), it is important to consider whether such research can feasibly secure the necessary financial and human resources for ROGRR, including analysis expenses, which may include confirmation testing, and a system that can provide genetic counseling.

(6) After considering points (1) through (5), review the points presented in JEGHG policy concerned with determining whether genetic information is accurate and reliable enough to assess donor's health condition, which indicate important facts related to his or her health, and whether such disclosure could disrupt the appropriate research procedures.

Discussion and decision of policy on ROGRR

(1) Framework for the consideration and decision of policy on ROGRR:

- Discuss the policy on ROGRR among researchers on the project, including researchers from cooperative research institutions, and in the case of using preexisting samples and information, the supplier of them.
- It is desirable to reference the opinions of diverse stakeholders, including potential eligible research participants and the researchers involved, when discussing policy. For large-scale projects and the expected return of various genetic information, consider, when necessary, requesting the assistance of external experts during the policy discussion stage.
- When deciding policy that does not plan to ROGRR, as a result of the aforementioned considerations, ensure

that the policy is in line with the JEGHG. This will include providing a clear explanation of why the results will not be returned on the IC form.
- The ROGRR policy should be approved by an Institutional Review Board.

(2) Points to consider for detailed discussion on ROGRR:

- Persons eligible for ROGRR:
  - It is important to keep in mind that some features of ROGRR differ from clinical situations that provide healthcare with genetic testing included. These features include the fact that research participants may not develop the specific disease being as research target (ROGRR may include unexpected findings for research participants), considerable time may elapse between providing IC and ROGRR, opportunities to make contact with researchers are limited, and it may be difficult to collect information, such as medical history and family history, in advance.
  - When research participants are obviously biologically related in Trio analysis and etcetera, give due consideration of the return process and heed particular attention to participants' "right not to know" among those that do not wish for ROGRR. This may entail providing an appropriate explanation of the nature of genetic information sharing among relatives while IC intentions are confirmed for ROGRR.
  - If research participants pass away by the time the ROGRR is ready, please carefully consider whether to return the results to the family of the deceased (biological relatives), while taking account of the characteristics of the genetic information being returned. If a policy allows ROGRR to family of the deceased (biological relatives), it is important to carefully consider aspects of the return process, including whether the deceased participant wishes the information to be returned to his/her family of the deceased (biological relatives) after death, and which family of the deceased (biological relatives) will receive the information.
  - If proxy consent is needed for research participants who, for example, has dementia or who is a minor, carefully consider policy following the JEGHG.
- Types of genetic information planned to return:
  - Examine what kind of genetic information can be returned. Candidates for ROGRR include primary findings (discovered in the research process) and secondary findings (entailing the targeted detection of variants). Carefully consider the accuracy and reliability of the candidate genetic information. When planning to return the information with uncertainty about accuracy or reliability necessarily, researchers should be mindful of the possible misunderstanding or psychological stress that may emerge in research participants.
  - Carefully consider whether the candidate genetic information returned may lead to carrier status or presymptomatic testing in participants and whether such information should be included for return. In the case that it is included, cautiously consider planning a return process that accommodates the potential medical and psychological impact on participants.
  - Carefully assess the potential impact that returning candidate genetic information could have on research participants post return and responses that could be anticipated based on the information at hand. In particular, when anticipating the return of pathogenic variants related to monogenic diseases (including multifactorial diseases with a clear involvement of specific genes), collect and evaluate any information related to the analytical validity, clinical validity, and clinical utility of the diseases. It is also highly recommended that physicians with extensive medical experience with the disease and experienced genetic counselors are involved in any deliberation and a system that allows the procurement of advice in advance is established. Specific points are illustrated in the subsequent paragraphs.
  - Consider whether the analytical validity of the candidate genetic information can be confirmed. It is important to verify whether there are available laboratories for confirmation testing as a clinical testing laboratory, because this process is also relevant to situations where genetic testing of biological relatives is conducted after ROGRR.
  - It is important to consider the method of variant interpretation and kind of variants to be returned when assessing the clinical validity of the candidate genetic information. It also particularly important to consider the variant interpretation process when information regarding the phenotype of research participants is limited; for example, in population-based research or when there are potential non/presymptomatic participants present.
  - When evaluating the clinical utility of the candidate genetic information, carefully consider, in addition to medical care following the return (e.g., treatment and prevention), whether medical care for the

disease is provided in the healthcare system (including descriptions of medical practice guidelines) and the accessibility of medical institutions to participants. It is particularly important to carefully consider whether follow-up is available with/without public insurance post return, in which there is a possibility of returning the candidate genetic information to presymptomatic participants.

- Ensuring systems to facilitate ROGRR as a research project:
  - The systems required for ROGRR vary depending on the scale of the research, the genetic information to be returned, and its disease frequency. Consider whether it is possible to ensure that there will be systems in place that respond appropriately to inquiries from research participants during the ROGRR process, including whether the researchers themselves will respond and/or the provision of opportunities for genetic counseling. When necessary, ensure a system that provides access to professional support for genetic counseling, including clinical geneticists and certified genetic counselors.
  - As research participants may need medical care after ROGRR, especially in the case of research conducted at institutes not affiliated with medical institutions and research that targets healthy people and the general population, it is desirable to consider in advance which medical institutions participants could be referred to.
  - Consider in advance who will pay for the expenses related to medical care after ROGRR, such as genetic counseling, confirmation testing, and responses to biological relatives, while bearing in mind that expenses may be high.
  - Please consider beforehand the response for requests to disclosures related to genetic information that the project was not expected to return.

IC and confirmation of preference for ROGRR

- For the IC process of the research, consider what kind of information will be communicated concerning ROGRR, including the content detailed in the IC documents. Take full account of the fact that confirming the preference for the return of specific genetic information may later lead to the delivery of unexpected information to research participants. Reflect on a return process that is conscious of the potential psychological impact, especially when detailed information is not provided on the genetic information expected in the ROGRR during IC. Moreover, give full consideration to the fact that time may pass from the point of IC to ROGRR, as stated previously.
- Consider the content of the IC documents including the differences from clinical testing, the expected period until the return, and the fact that there are various limitations on ROGRR. In particular, when the patients participate in research at a medical institution, pay close attention to the possibility that the participants may perceive ROGRR as clinical testing.
- The opportunities to confirm the intentions of research participants for ROGRR vary depending on the project. Fully reflect on the fact that it will be possible to confirm intentions for ROGRR in more detail.
- It is important to adopt more careful methods of identification when obtaining IC and confirming of the intentions for ROGRR. Consider what method will be used to confirm identity beforehand depending on the method of communication with research participants (e.g., face-to-face, telephone, or written communication).
- When confirming intentions for ROGRR, it is important to ensure research participants of their "right not to know." However, carefully consider the content and methods used to allow research participants to make an informed choice based on their full understanding, particularly when genetic information being potentially returned has extremely high clinical utility and failure to inform such information would be life-threatening.

Analysis related to information with possibility of return

(1) Quality control and confirmation testing:

- Depending on the research, the intended findings vary, including specific variants of individuals and statistical trends in groups, and so the quality of analysis required varies accordingly. Consider the methods of quality control during analysis in conjunction with the confirmation testing described below (based on the research purpose and content).
- Carefully consider the method and timing of confirmation testing beforehand, particularly when it is expected that results being returned may or will be used in clinical settings, including the recollection of samples and reanalysis of them at a clinical laboratory using a quality assurance system designed for clinical genetic testing; full consideration should be given to the risks, such as limits on the accuracy of the analytic methods, sample mix-ups due to de-identification, and human error. It is desirable to consider such things in advance, in conjunction with the system used for providing

genetic testing when biological relatives request testing following ROGRR.

2) Process for variant interpretation

- Implement the process of identifying candidate variants and interpreting their significance after carefully considering the specific procedure and system selected beforehand, including the use of reference databases and convening expert panels for interpretation.
- When returning results in situations characterized by limited opportunities to collect information on the phenotypes of the research participants beforehand, for example, in research that targets the general population and the return of secondary findings, careful consideration may be needed regarding the collection of information on clinical symptoms and family history and the use of reassessment by experts.
- Even when outsourcing analysis, including variant interpretation, to an external institution, such as a registered clinical laboratory, results should be returned only after fully considering and reinterpreting the results by research project.
- Consider the possibility of reanalysis and reinterpretation after ROGRR based on the information to be returned and the research purpose and content. In addition, when results are returned to participants, please ensure an opportunity to provide an explanation alongside a discussion of the limitations of such testing.

Return of results to research participants who prefer to receive the genetic information

(1) Process of ROGRR:

- When the preparations for returning genetic information are ready, reconfirm the intent of the research participants. In situations that did not provide detailed candidate genetic information beforehand, fully consider the procedure that may be involved in recontacting research participants to ensure their "right not to know." At this point, it is also desirable to consider the response policy given to research participants that do not request return or request postponing ROGRR beforehand.

- Confirm the understanding and memory of research participants and explain essential concepts again, as necessary, before ROGRR because the research participants will not recall details on ROGRR due to factors like the passage of time since their enrollment in research.
- When ROGRR, fully consider the fact that it may be difficult to collect information that causes ROGRR related psychological stress, such as social situations, including life events and the health condition of research participants; this is particularly pertinent for research in nonmedical institutions. For research that conducts genome-wide analysis, fully consider the possibility that unexpected results may be returned to research participants. Furthermore, please ensure that the research participants are informed in advance by including a description in IC documents that details the possibility of social disadvantage, such as genetic discrimination for ROGRR because of the lack of legal prohibition of genetic discrimination in Japan.
- Reflect on the return procedure that will be used (e.g., face-to-face, telephone, or written communication) as well as the explanatory content that will be included, depending on the type of genetic information and the particular circumstances of research participants. Substantively consider their privacy and the possibility of inducing psychological stress. In particular, it is desirable that the genetic information that indicates the risk of developing disease (e.g., monogenic diseases) is returned face-to-face in a place where privacy is ensured. When returning information related to health, please ensure the involvement of professionals, such as clinical geneticists, certified genetic counselors, and experts on the particular disease for the point of ROGRR, and implement the process of making genetic counseling available when necessary.
- Explain the characteristics of returning of research analysis results, that is not equivalent to clinical testing, as well as their limitations in comprehensible terms for research participants. Depending on the circumstances, also inform research participants that ROGRR and genetic testing related to such information is an advanced or innovative approach at present. In particular, when returning a negative genetic result of a disease, carefully explain the need to continue with healthy behavior, such as going for a health checkup and medical treatment, rather than ignoring or dismissing the possibility of a high risk of developing a disease.
- Even when ROGRR is employed face-to-face and by phone, it is desirable that documents that include the results and explanatory matters written in an understandable form are delivered to the research participants. Consider the possibility that other family members will also receive the results from the same project and prepare the report with his or her name on it, so the relevant participants will know that which report is their own.

(2) Records related to ROGRR:

It is desirable to retain records related to ROGRR including subsequent referrals to medical institutions for a certain period while anticipating being contacted by research participants. In addition, consider the method of record keeping within the research project in advance and have taken measures to prevent any leakage of information.

(3) Follow-up:

- When referring research participants to medical institutions, carefully provide an explanation of the specific details related to visiting a medical institution, including the expected procedures and approximate expenses for the research participant involved, after sharing sufficient information with the medical institution in the referral beforehand.
- Keep in mind that not all research participants that receive results will be continuously engaged with a medical institution, particularly when negative genetic results (such as no detection of significant genetic variants) are also included in the scope of the return. For most of the projects, though the research duration is limited, and it is desirable to provide a helpline to respond to contacts from research participants for a certain period after ROGRR. Also, reflect on the response following the end of the project period in advance.

Discussion

We proposed the first Japanese practical guidance for ROGRR. In Japan, there are few reports that have implemented ROGRR, particularly in large-scale genome research [16, 17], and it is anticipated in the future that many research projects will consider ROGRR carefully and realistically. To our knowledge, there are few cases such as our collaborative work with various experts regarding genomic research and healthcare and researchers specialized in ethical, legal, and social implications. In addition, in the process of drafting the practical guidance above described, we found various issues that require continuous discussion and engagement. Those that are particularly important are listed below.

First, it is fundamentally important to pursue continuous efforts related to enhancing genomic medicine delivery systems. Japan's healthcare system is characterized by access to advanced medical care at a low cost to patients owing to the universal insurance system that provides all citizens with public health insurance [18]. However, insurance often does not cover treatment options such as genetic testing, genetic counseling, and medical care; especially in surveillance and preventive treatments of presymptomatic individuals. For example, only 79 diseases are currently covered by insurance in Japan, while preventive management of hereditary breast and ovarian cancer syndrome, such as risk-reducing salpingo-oophorectomy and risk-reducing mastectomy, are only available at limited medical institutions and are not covered by insurance. The results of interviews with stakeholders suggested that this situation could represent an obstacle that may hamper the current positive perceptions of ROGRR carried out by researchers. It is important that personalized treatment and prevention based on genetic information be evaluated from multiple perspectives (e.g., medical economics or patient advocacy). Continued discussion on the medical care delivery system, including public insurance coverage, should be encouraged. It is necessary to direct existing efforts to develop systems that cater for large number of people who require genomic medicine and can provide access to appropriate treatment and prevention, beyond the issues related to ROGRR.

The second issue is the need to provide ROGRR support systems for researchers. In the research that ROGRR is not included in the original protocol, researchers have to make extra efforts when putting ROGRR into practice. Especially if the research is conducted by nonmedical professional researchers or institutes without any related hospital, there may be more difficulties on ROGRR. In particular, when genetic information outside of the researchers' expertise is selected as the target for the return, the process of interpreting pathogenic variants that require accuracy and reliability as well as referral to a clinical specialist, is a burden for researchers. If there will be actionable genetic information that is frequently returned, it is necessary to consider what efforts can be carried out to reduce the burden on researchers, including outsourcing processes related to the detection and determination of pathogenic variants, the creation of tailored results reports for entities external to the research project [19], and the use of medical institutional networks involved in genomic medicine.

The third pertinent issue is the expense associated with ROGRR. When implementing ROGRR, it is necessary to secure the expense budget required to conduct confirmation testing, recontact research participants, and return their results, especially in the case of secondary use of stored samples and information. However, in our interviews of researchers, some of them stated that it is difficult to figure out whether it is possible to include expenses related to ROGRR into their budget, particularly in the research where ROGRR is not included in the original protocol. Much research that accompanies large-scale genome analysis in Japan is conducted using grants predominantly funded by government agencies. We consider the guidance provided

by said funding agencies regarding ROGRR and distinct policy on its implementation in the budget would help researchers that think ROGRR is possible within their framework and technology.

In preparing this practical guidance, we conducted interviews with Japanese stakeholders, collected comprehensive information in Japan and overseas by conducing literature reviews, and attempted to propose a practical guidance that aligns with the current state of affairs in Japan. However, there are some limitations. We could not collect enough previous cases with ROGRR because we searched only published articles. The interviews had a small sample size with election method bias. Moreover, we compiled the guidance with a focus on the points to consider from the perspectives concerned with the ethical, legal, and social implications of ROGRR, and we could not treat some specific details, such as proxy consent and nonreturn policy. In the future, it is hoped that consideration regarding the practical guidelines on such matters like quality control will be advanced through expert-centered discussions. Under the current government's JEGHG, in principle, researchers requested to keep genetic information as de-identified data, and there is no description on how to manage such information for ROGRR. Given the possibility that genetic information returned is used in clinical practice and shared with biological relatives, we think that research projects have to respond to the inquiries from research participants at least for a while. On the other hand, it may raise another concern about protecting such personal information. We think that stored genetic information in a relinked state with personal information should be kept to a limited. We should discuss how we should store such information for ROGRR especially when it is conducted on a large scale.

It is necessary to continuously discuss the problems related to ROGRR in the context of Japan's genomic research and medicine practices, particularly regarding ethical, legal, and social implications. Moreover, we believe these discussions and considerations by various stakeholders, including research participants, researchers, and national government agencies, can contribute to creating a new system that will allow personalized medicine and prevention using genetic information to become more familiar and useful to the general population.

Acknowledgements The authors thank all the interviewees who led the Japanese genome studies and were involved in genomic medicine. The work is supported by the Japan Agency for Medical Research and Development (grant number 18km0405301). FN and YA are supported by the Tohoku Medical Megabank Project through the Ministry of Education, Culture, Sports, Science and Technology, Japan; by the Reconstruction Agency, Japan; by Japan Agency for Medical Research and the Development; grant numbers JP18km0105001 and JP18km0105002. Authors also thanked all members of the Tohoku Medical Megabank Organization, Tohoku University, and the Department of Biomedical Ethics and Public Policy, at Osaka University.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013;15:565–74.
2. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19:249–55.
3. Burke W, Antommaria AH, Bennett R, Botkin J, Clayton EW, Henderson GE, et al. Recommendations for returning genomic incidental findings? We need to talk! Genet Med. 2013;15:854–9.
4. Scheuner MT, Peredo J, Benkendorf J, Bowdish B, Feldman G, Fleisher L, et al. Reporting genomic secondary findings: ACMG members weigh in. Genet Med. 2015;17:27–35.
5. McGuire AL, Joffe S, Koenig BA, Biesecker BB, McCullough LB, Blumenthal-Barby JS, et al. Point-counterpoint. Ethics and genomic incidental findings. Science. 2013;340:1047–8.
6. National Academies of Sciences, Engineering, and Medicine. Returning individual research results to participants: guidance for a new research paradigm. National Academies Press; 2018. Q6
7. Wolf SM, Crock BN, Van Ness B, Lawrenz F, Kahn JP, Beskow LM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med. 2012;14:361–84.
8. Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, et al. Return of genomic results to research participants: the floor, the ceiling, and the choices in between. Am J Hum Genet. 2014;94:818–26.
9. Schwartz MLB, McCormick CZ, Lazzeri AL, Lindbuchler DM, Hallquist MLG, Manickam K, et al. A model for genome-first care: returning secondary genomic findings to participants and their healthcare providers in a large research cohort. Am J Hum Genet. 2018;103:328–37.
10. Smith LA, Douglas J, Braxton AA, Kramer K. Reporting incidental findings in clinical whole exome sequencing: incorporation of the 2013 ACMG recommendations into current practices of genetic counseling. J Genet Couns. 2015;24:654–62.
11. Alver M, Palover M, Saar A, Lall K, Zekavat SM, Tonisson N, et al. Recall by genotype and cascade screening for familial hypercholesterolemia in a population-based biobank from Estonia. Genet Med. 2019;21:1173–80.
12. Ormondroyd E, Mackley MP, Blair E, Craft J, Knight JC, Taylor JC, et al. "Not pathogenic until proven otherwise": perspectives of UK clinical genomics professionals toward secondary findings in context of a Genomic Medicine Multidisciplinary Team and the 100,000 Genomes Project. Genet Med. 2018;20:320–8.
13. Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry. Ethical guidelines for human genome/gene analysis research 2001 (Latest revision: 2017). https://www.mhlw. Q7

go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153405.pdf.
14. The Japanese Association of Medical Sciences. Guidelines for genetic tests and diagnoses in medical practice 2011. http://jams.med.or.jp/guideline/genetics-diagnosis_e.pdf.
15. Leading the way to Genomic Medicine by ELSI Research Program. Return of individual genomic results in research settings; a proposal on the points to consider and the discussion agenda for the future. https://www.amed.go.jp/content/000048196.pdf
16. Tohoku University Tohoku Medical Megabank Organization. Return of genomic results to cohort study participants. https://www.megabank.tohoku.ac.jp/english/research/cohortbiobank/ror/.
17. Kiyozumi Y, Horiuchi Y, Nishimura S, Kado N, Mizuguchi M, Shimoda Y, et al. Examination of the returning genomic results of secondary findings and genetic counseling systems in clinical genome study—Practice in Shizuoka Cancer Center Project HOPE. Jpn J Genet Couns. 2018;39:129–38.
18. Ministry of Health, Labour and Welfare. Overview of Medical Service Regime in Japan. https://www.mhlw.go.jp/bunya/iryouhoken/iryouhoken01/dl/01_eng.pdf.
19. Sapp JC, Johnston JJ, Driscoll K, Heidlebaugh AR, Miren Sagardia A, Dogbe DN, et al. Evaluation of recipients of positive and negative secondary findings evaluations in a hybrid CLIA-research sequencing pilot. Am J Hum Genet. 2018;103:358–66.

Journal : **10038**
Article : **697**

SPRINGER NATURE

Author Query Form

Please ensure you fill out your response to the queries raised below and return this form along with your corrections

Dear Author

During the process of typesetting your article, the following queries have arisen. Please check your typeset proof carefully against the queries listed below and mark the necessary changes either directly on the proof/online grid or in the 'Author's response' area provided below

Queries	Details Required	Author's Response
AQ1	Please confirm or correct the city and country name inserted in affiliations 1 and 2.	
AQ2	Please check your article carefully, coordinate with any co-authors and enter all final edits clearly in the eproof, remembering to save frequently. Once corrections are submitted, we cannot routinely make further changes to the article.	
AQ3	Note that the eproof should be amended in only one browser window at any one time; otherwise changes will be overwritten.	
AQ4	Author surnames have been highlighted. Please check these carefully and adjust if the first name or surname is marked up incorrectly. Note that changes here will affect indexing of your article in public repositories such as PubMed. Also, carefully check the spelling and numbering of all author names and affiliations, and the corresponding email address(es).	
AQ5	You cannot alter accepted Supplementary Information files except for critical changes to scientific content. If you do resupply any files, please also provide a brief (but complete) list of changes. If these are not considered scientific changes, any altered Supplementary files will not be used, only the originally accepted version will be published.	
AQ6	Please provide the place of publication for reference 6.	
AQ7	Please complete and update references 13, 14, 15, 16 and 18.	