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ORIGINAL ARTICLE

Population-based biobank participants' preferences for receiving genetic test results

Kayono Yamamoto[1,2], Tsuyoshi Hachiya[3], Akimune Fukushima[1,2], Naoki Nakaya[4], Akira Okayama[5], Kozo Tanno[6,7], Fumie Aizawa[8], Tomoharu Tokutomi[1,2], Atsushi Hozawa[4] and Atsushi Shimizu[3]

There are ongoing debates on issues relating to returning individual research results (IRRs) and incidental findings (IFs) generated by genetic research in population-based biobanks. To understand how to appropriately return genetic results from biobank studies, we surveyed preferences for returning IRRs and IFs among participants of the Tohoku Medical Megabank Project (TMM). We mailed a questionnaire to individuals enrolled in the TMM cohort study (Group 1; $n = 1031$) and a group of Tohoku region residents (Group 2; $n = 2314$). The respondents were required to be over 20 years of age. Nearly 90% of Group 1 participants and over 80% of Group 2 participants expressed a preference for receiving their genetic test results. Furthermore, over 60% of both groups preferred to receive their genetic results 'from a genetic specialist.' A logistic regression analysis revealed that engaging in 'health-conscious behaviors' (such as regular physical activity, having a healthy diet, intentionally reducing alcohol intake and/or smoking and so on) was significant, positively associated with preferring to receive their genetic test results (odds ratio = 2.397 (Group 1) and 1.897 (Group 2)). Our findings provided useful information and predictors regarding the return of IRRs and IFs in a population-based biobank.
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INTRODUCTION

There are ongoing debates on issues relating to the return of individual research results (IRRs) and incidental findings (IFs) generated by genetic research in population-based biobanks.[1] Such biobanks were originally established to 'contribute to future, yet unspecified, research hypotheses that will contribute to the advance of science'.[2] Almost all of these biobanks initially adopted the policy of not returning IRRs and IFs. However, with the progress of genome sciences, genetic results have gradually become useful information for understanding personal health. Some companies have started to offer genetic testing services directly to consumers, and laypeople have recognized the value of personal genetic information to their own health. Receiving individual genetic results has become a strong motivation to participate and continue participating in genetic cohort studies.[3,4] Reflecting these social demands, the policy of biobanks has gradually shifted to allow for the return of IRRs and IFs.[3–6] The debate surrounding the return of IRRs and IFs hinges on various issues, such as the analytical reliability and validity of the research results, clinical significance and actionability, the differences between biobank research and clinical research, researchers' obligations and responsibilities, constructing systems for returning results and participants' demands and attitudes regarding the return of results.[2,7–10] Although all of these issues are important to consider to ensure the secure and useful return of results, Murphy *et al.*[11] has suggested that obtaining informed consent from research participants is an essential presupposition. The Tohoku Medical Megabank Project (TMM) is similarly confronting this debate. This project, which comprises two organizations—Tohoku University's Tohoku Medical Megabank Organization (ToMMo) and Iwate Medical University's Iwate Tohoku Medical Megabank Organization (IMM)—was established in the disaster area of the Great East Japan Earthquake. This project aimed to reconstruct the medical system and implement personalized health care in the affected areas. General health and clinical information such as physiological data; questionnaires concerning health conditions, medical records and other follow-up data; and biospecimens (such as blood, serum, plasma and urine) were collected from project participants. All participants' biospecimens were subjected to biochemical testing, and >1000 participants' genomes and a few hundred omics (for example,

[1]Division of Innovation and Education, Iwate Tohoku Medical Megabank Organization, Disaster Reconstruction Center, Iwate Medical University, Iwate, Japan; [2]Department of Clinical Genetics, School of Medicine, Iwate Medical University, Iwate, Japan; [3]Division of Biomedical Information Analysis, Iwate Tohoku Medical Megabank Organization, Disaster Reconstruction Center, Iwate Medical University, Iwate, Japan; [4]Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan; [5]Research Institute of Strategy for Prevention, Tokyo, Japan; [6]Department of Hygiene and Preventive Medicine, School of Medicine, Iwate Medical University, Iwate, Japan; [7]Division of Clinical Research and Epidemiology, Iwate Tohoku Medical Megabank Organization, Disaster Reconstruction Center, Iwate Medical University, Iwate, Japan and [8]Center for Liberal Arts and Sciences, Iwate Medical University, Iwate, Japan
Correspondence: Dr K Yamamoto, Department of Clinical Genetics, School of Medicine, Iwate Medical University 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan.
E-mail: kyamamot@iwate-med.ac.jp
or Professor A Shimizu, Division of Biomedical Information Analysis, Iwate Tohoku Medical Megabank Organization, Disaster Reconstruction Center, Iwate Medical University 2-1-1 Nishitokuta, Yahaba, Shiwa, Iwate 028-3694, Japan.
E-mail: ashimizu@iwate-med.ac.jp
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transcriptome, methylome, proteome and metabolome) were analyzed. The analyzed and stored genome data could be used in early clinical interventions for genetic diseases caused by genetic mutations as well as to create a disease susceptibility prediction system in the near future. As of 1 February 2016, the TMM biobank has stored 63 300 DNA samples and 51 431 Japanese-cohort standard questionnaires.[12] The TMM has adopted 'a continuing consent' approach, whereby project organizers and staff have continuous contact with participants, and, as the study progresses, seek participants' re-consent when necessary.[13] This approach was chosen because it is generally believed that sufficient informed consent at the time of study enrollment is practically impossible.[13] At the point of enrollment in the TMM study, informed consent regarding the return of results generated by this genetic research was obtained. However, detailed information—such as the name of diseases in the returned genetic results, the natural history of those diseases and the possible influence of the receipt of the genetic test results on participants' life and health—had not yet been clearly explained to biobank participants. Therefore, it was necessary for TMM to re-inform the participants about the return of their genetic results based on greater empirical evidence on this topic. Knowing their own genetic risk status is generally considered to influence a number of areas of participants' and families' lives. In the traditional process of returning genetic results, clients who desire to know their own genetic status receive pre- and post-genetic counseling before undergoing genetic testing. These counseling sessions aim to help clients notice, understand and adapt to the medical, psychological and familial implications of the genetic contributions to disease.[14] However, in biobank research, there are generally insufficient genetic specialists to offer such counseling to all research participants.[15] In previous studies, such genetic specialists were referred to as genetic physicians or genetic counselors,[16,17] and there is a limited number of such specialists overall. Thus, a major concern has been that participants might not interpret their genetic results correctly, or that they might not use this information to benefit their own or their families' health. Of course, there is still little evidence for how the return of genetic results from biobank studies can influence participants' health, or even if participants would prefer to have their results returned. As such, in the present study, we surveyed the preferences for returning IRRs and IFs among participants of the TMM, and determined the relationship of these preferences with participants' genetic literacy, health-conscious behaviors and other demographic characteristics. In addition, we discuss the optimal methods for communicating genetic results from a population-based biobank.

MATERIALS AND METHODS

Study population

We performed a cross-sectional study of two groups. Group 1 (G-1) included participants enrolled in the TMM cohort study, whereas Group 2 (G-2) comprised residents of the Tohoku region (including the cities of Rikuzentakata and Ofunato in Iwate Prefecture, and Natori and Higashimatsushima in Miyagi Prefecture). We recruited G-2 as potential TMM participants because the TMM plans to recruit eight thousand people in the Tohoku region as participants.[13]

Study protocol

We mailed our questionnaire survey to all participants in G-1, who were selected via stratified random sampling according to their age and sex as listed on the cohort study entry lists from TMM. For G-2, we mailed the questionnaire to residents selected via simple random sampling from the telephone lists of Iwate and Miyagi prefectures. The respondents were required to be over 20 years of age, and family members were permitted to answer on behalf of selected respondents. We sent reminders to all participants who did not answer. All respondents received a 300-yen exchange check for their time. The data collection period was from October 2014 to March 2015.

Questionnaire development and administration

In this study, we analyzed participants' responses regarding 'preferences for receiving their genetic test results'. We also assessed the potential relationship of four sets of factors that might relate to such preferences: 'health-conscious behaviors,' 'communication with health professionals,' 'genetic knowledge,' and 'demographic data.' The questions for 'health-conscious behaviors' and 'communication with health professionals' were developed according to a literature review[18,19] and expert consultation. These experts included four senior genome medical research coordinators (senior GMRCs), who are genome research coordinators that are employed full-time and manage the communication and relations between the temporarily employed GMRC. They accurately understood the actual conditions of these participants. Then, the questionnaire was revised through a pilot study involving 20 GMRCs and members of the Division of Biomedical Information Analysis of the IMM to ensure that participants could comprehend it easily. The final versions of the 'health-conscious behaviors' questions dealt with regular physical activity, having a healthy diet, intentionally reducing alcohol intake and/or smoking, etc. (Appendix 1). The questions concerning 'communication with health professionals' assessed whether participants had a family physician or health care provider to consult about their health checkup results. We also developed drafts of the 'preferences for receiving their genetic test results' questions, again using a literature review and expert consultations. The experts included two geneticists, a molecular geneticist and a genetic counselor. The questionnaire was then revised in a focus group so that participants could comprehend it easily. The focus group, which took around two hours to complete, was held in June 2014 and comprised four senior GMRCs. The participants' preferences regarding the receipt of their own genetic information were chosen from among the following types of diseases: lifestyle diseases, pharmacogenetics, adult-onset clinically actionable diseases, adult-onset non-clinically actionable diseases and others (multiple answers possible). For 'genetic knowledge,' we employed the genetic knowledge questionnaire developed by Jallinoja.[20] Because the original questionnaire was published in English, it was translated into Japanese by a genetic counselor and then revised by a clinical geneticist and a molecular geneticist. This Japanese version was then back-translated by two native English-speaking professional translators. We sent the back-translated version and our explanation of the whole translation process to Dr Jallinoja, who gave us approval to use the questionnaire. Participants' preferred approaches to receiving their own genetic information were chosen from among the following: from a genetic specialist, from a family doctor, from a regional public health nurse, from a regional pharmacist, on television/telephone, by mail and on a web page (multiple answers possible).

Ethical statement

Ethical approval was obtained from the institutional review board of the Iwate Medical University School of Medicine (Approval ID: H26-57) and TMM Organization (Approval ID: 2014-12). Our study was conducted in accordance with the Declaration of Helsinki, Japanese Act on the Protection of Personal Information, and Japan Ethical Guidelines for Medical and Health Research Involving Human Subjects. The questionnaire was accompanied by a participant information sheet wherein the participants were asked to write their names and addresses and to complete and return the questionnaire. Informed consent was implied by returning the questionnaire.

Statistical analysis

Statistical analyses of the survey data were performed using IBM SPSS Statistics 22.0. For the hypothesis testing, P-values <0.05 were considered statistically significant. Descriptive statistics were used to summarize the demographic data of the participants. The Mann–Whitney U-test was used to analyze the ranked responses of participants' preferences for receiving their genetic test results between G-1 and G-2. We used the Mantel–Haenszel test to determine differences between G-1 and G-2 in participants' preferred approach to receiving their own genetic information, as well as participants' preferences for their own genetic information according to disease. For all further statistical

analyses—including group differences, correlations, and regression analysis—we grouped participants' Likert-scale answers for 'have preferences for receiving their genetic test results' into 'yes' and 'no' categories; participants who answered '1. I want to know' and '2. If I must answer, then I want to know' were considered the 'yes' group, '3. If I must answer, then I don't want to know' and '4. I do not want to know' were categorized as the 'no' group. We used the total scores of 'genetic knowledge.' For 'communication with health professionals,' participants who had at least one medical adviser were categorized as 'yes' and others were categorized as 'no.' Participants who had at least one health-conscious behavior were categorized as 'yes' and those who had none were categorized as 'no.' Participants were allowed to skip questions, and we excluded all missing and inconsistent responses from the analysis. To determine the univariate associations, we analyzed the differences between the yes and no groups for 'have preferences for receiving their genetic test results' in participants answers for 'health-conscious behaviors,' 'communication with health professionals,' 'genetic knowledge,' 'sex' and 'age' using Welch's *t*-tests and Pearson's χ^2-tests. The variables with a significant ($P<0.05$) association with either group for 'have preferences for receiving their genetic test results' were included in a logistic regression analysis.

RESULTS

Participant characteristics

Overall, 11 600 individuals were enrolled in the study, and 3709 returned the questionnaire. The response rates of G-1 and G-2 were 70.2% ($n=1123/1600$) and 26.6% ($n=2656/10\,000$), respectively. The age distributions of enrolled individuals in G-1 was shown in Appendix 2. The number of valid responses was 1031 in G-1 and 2314 in G-2. For both groups, male participants were of a higher median age than were female participants. Most of the female and male respondents in both groups were in the 40–64 and 65–74 age groups, respectively (Table 1, Appendix 3, Appendix 4).

Participants' knowledge of genetics

No significant differences were observed in genetic knowledge scores of respondents between the G-1 and G-2 groups (Table 2). The overall average percentage of correct answers was 73.3% in G-1 and 70.6% in G-2.

Participants' preferences to receive their own genetic information

The majority of respondents in both groups preferred to receive their own genetic information (that is, answered with '1. I want to know' or '2. If I must answer, then I want to know'), at 88.2% ($n=910/1031$) and 82.3% ($n=1903/2314$) for G-1 and G-2, respectively. A Mann–Whitney *U*-test was run to determine whether there were differences in participants' answers to 'preferences for receiving their own genetic information' between G-1 and G-2. Visual inspection of the distributions of these answers indicated that G-1 and G-2 were not similar. Nevertheless, 'preferences for receiving their own genetic information' scores for G-1 (mean rank = 1.54) were statistically significantly higher than were those for G-2 (mean rank = 1.73), $P<0.001$ (Figure 1).

Regarding the univariate analyses, we conducted Welch's *t*-tests and Pearson's χ^2-tests to compare the main variables between the yes and no groups for 'have preferences for receiving their own genetic information.' The results revealed significant differences in health-conscious behaviors, genetic knowledge and age within both G-1 and G-2. Sex significantly differed only in G-2 (Appendix 5). All variables showing a significant difference were included in the logistic regression analysis.

According to the logistic regression analysis, the regression models of G-1 and G-2 were significantly different, $\chi^2(4)$ G-1 = 33.578 and G-2 = 50.615, $P<0.01$, respectively. Of the four independent variables (health-conscious behaviors, genetic knowledge, sex and age), only two (health-conscious behaviors and age) were significantly related to preferring to receive their own genetic information in both groups. Furthermore, genetic knowledge and sex were significantly associated with preferring to receive their own genetic information only in G-2. More specifically, participants who reported at least one health-conscious behavior had greater odds of preferring to receive their own genetic test results (odds ratio (OR) = 2.397, 95% confidence

Table 1 Age distribution of participants ($n=3345$)

		Group 1			*Group 2*		
		Participants enrolled in the cohort study (n = *1031*)			*Residents of the Iwate and Miyagi prefectures* (n = *2314*)		
Age		*Male*	*Female*	*Subtotal*	*Male*	*Female*	*Subtotal*
20–29 years old	*n*	4	7	11	0	5	5
	(%)	(0.8)	(1.3)	(1.1)	(0)	(0.8)	(0.2)
30–39 years old	*n*	28	80	108	12	18	30
	(%)	(5.8)	(14.7)	(10.5)	(0.7)	(3.0)	(1.3)
40–49 years old	*n*	58	113	171	55	47	102
	(%)	(12.0)	(20.7)	(16.6)	(3.2)	(7.9)	(4.4)
50–59 years old	*n*	98	113	211	232	154	386
	(%)	(20.2)	(20.7)	(20.5)	(12.8)	(25.9)	(16.7)
60–69 years old	*n*	138	120	258	605	173	778
	(%)	(28.5)	(22.0)	(25.0)	(35.2)	(29.1)	(33.6)
70–79 years old	*n*	158	111	269	554	148	702
	(%)	(32.6)	(20.3)	(26.1)	(32.2)	(24.9)	(30.3)
Over 80 years old	*n*	1	2	3	262	49	311
	(%)	(0.2)	(0.4)	(0.3)	(15.2)	(8.2)	(13.4)
Total	*n*	485	546	1031	1720	594	2314
	(%)	(47.0)	(53.0)	(100.0)	(74.3)	(25.7)	(100)
Median age of subtotal (third quartile-first quartile)		64.00 (71.50–54.00)	56.00 (67.00–44.00)	60.00 (70.00–47.00)	69.00 (76.00–62.00)	64.00 (72.00–55.00)	67.00 (75.00–60.00)

Table 2 Genetic knowledge between our study groups and those of previous studies

		G-1 (n = *1031*)	*G-2* (n = *2314*)	*Jallinoja and Aro*[20] (n = *1216*)[a]	*Haga et al.*[33] (n = *300*)[b]
1.	One can see a gene with the naked eye.	92	90	87	99
2.	A gene is a disease.	89	84	87	98
3.	A gene is a molecule that controls hereditary characteristics.	61	65	63	84
4.	Genes are inside cells.	86	86	55	91
5.	A gene is a piece of DNA.	90	87	57	93
6.	A gene is a cell.	34	31	51	74
7.	A gene is a part of a chromosome.	80	78	45	91
8.	Different body parts include different genes.	56	50	36	67
9.	Genes are bigger than chromosomes.	78	70	41	83
10.	The genotype is not susceptible to human intervention.	48	48	77	25
11.	It has been estimated that a person has 22 000 genes[c]	53	57	18	60
12.	Healthy parents can have a child with a hereditary disease.	81	75	85	97
13.	The onset of certain diseases is due to genes, environment and lifestyle.	80	78	88	98
14.	The carrier of a disease gene may be completely healthy.	84	82	83	95
15.	All serious diseases are hereditary.	89	84	83	98
16	The child of a disease gene carrier is always also a carrier of the same disease gene.	70	64	60	85
Overall average score		73.3	70.6	63.5	83.6

Numbers refer to % of participants who answered the question correctly. G-1: Group 1 (that is, participants enrolled in cohort study); G-2: Group 2 (that is, residents of the Tohoku area).
[a]Study population for Jallinoja and Aro[20] comprised 1216 participants randomly selected from the general population in Finland. The age composition of the participants: 16–24 years, 11%; 25–44 years, 48%; 45–64 years, 41%.
[b]Study population for Haga *et al.*[33] comprised 300 participants enrolled in a genetic testing study of type 2 diabetes mellitus for the general public in Durham, North Carolina. The age composition of the participants: 18–29 years, 44%; 30–39 years, 19%; 40–49 years, 16%; 50–59 years, 11%; 60–69 years, 9%; and over 70 years, 1%.
[c]The number of genes was changed for each study to reflect current knowledge. Jallinoja and Aro[20] listed 7000 genes and Haga *et al.*[33] listed 22 000.

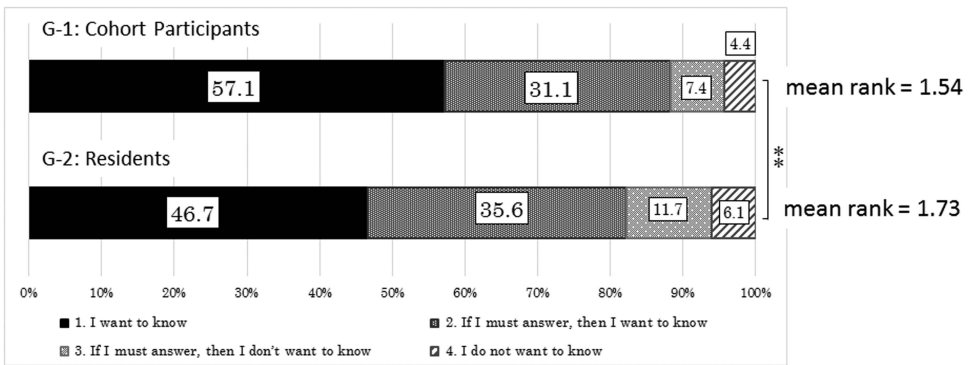

Figure 1 Percentage of participants' preferences for receiving their own genetic information. Group 1 (G-1) included the participants enrolled in the Tohoku Medical Megabank Project cohort study ($n=1031$). Group 2 (G-2) comprised residents of the Tohoku region (including the cities of Rikuzentakata and Ofunato in Iwate, and Natori and Higashimatsushima in Miyagi; $n=2314$). The Mann–Whitney *U*-test was used to analyze the ranked responses for participants' preferences for receiving their genetic test results between G-1 and G-2. $^{**}P<0.01$.

interval (CI) 1.403–4.094 (G-1) and OR = 1.897, 95% CI 1.323–2.670 (G-2)). Furthermore, as age increased, participants exhibited lower odds of preferring to receive their own genetic test results (OR = 0.960, 95% CI 0.943–0.978 (G-1) and OR = 0.989, 95% CI 0.979–1.000 (G-2)). In addition, in G-2, female participants had 1.601 times the odds of preferring to receive their results than did males (95% CI 1.214–2.112), whereas having greater genetic knowledge was associated with higher odds of preferring to receive their results compared to having lower genetic knowledge (OR = 1.090, 95% CI 1.047–1.136; Table 3).

Regarding participants' choices of how to receive their results, the majority preferred 'from a genetic specialist' in both groups (G-1: 62% and G-2: 60%). The second choices were 'by mail' in G-1 (52%) and 'from a family doctor' in G-2 (51%), whereas the third choices were 'from family doctor' in G-1 (31%) and 'by mail' in G-2 (37%; Figure 2). There were significant differences between G-1 and G-2 in these choices. Specifically, G-2 participants showed a greater preference to receive their results from 'from a family doctor' than did G-1 participants ($\chi^2(1)=23.341$, $P<0.0001$, OR = 1.573, CI 1.311–1.887) but had a lower preference to receive their results 'by mail' ($\chi^2(1)=26.393$, $P<0.0001$, OR = 0.634, CI 0.533–0.754).

The differences between participants' preferences to receive their own genetic information by disease characteristics are shown in Figure 3. Regarding preferences to receive their own genetic information by disease characteristics, the majority preferred to know the results for 'lifestyle diseases' in both groups (G-1: 85% and G-2: 84%). There were significant differences between the groups for these answers, with G-2 participants showing less of a preference to receive their results for 'pharmacogenetics' ($\chi^2(1)=6.471$, $P=0.011$, OR =

Table 3 Logistic regression analysis predicting the odds of participants' preferences for receiving their own genetic information by their characteristics

		Group 1						*Group 2*					
		Participants enrolled in the cohort study (n = *1031; Nagelkerke* R^2 = *0.062)*						*Residents of the Tohoku area* (n = *2314; Nagelkerke* R^2 = *0.036)*					
Characteristics		β	*s.e.*	P-*value*[a]	*Odds ratio*	*95% CI*		β	*s.e.*	P-*value*[a]	*Odds patio*	*95% CI*	
Health-conscious behaviors	Yes/no	0.874	0.273	0.001	2.397	1.403–4.094	**	0.631	0.179	<0.001	1.897	1.323–2.670	**
Genetic knowledge		0.057	0.041	0.165	1.059	0.977–1.148		0.086	0.021	<0.001	1.090	1.047–1.136	**
Sex	Male/female	0.229	0.202	0.256	1.257	0.847–1.868		0.471	0.141	0.001	1.601	1.214–2.112	*
Age		−0.040	0.009	<0.001	0.960	0.943–0.978	**	-0.011	0.005	0.047	0.989	0.979–1.000	*

[a]Pearson's χ^2-test.
$^{**}P<0.01$, $^{*}P<0.05$.

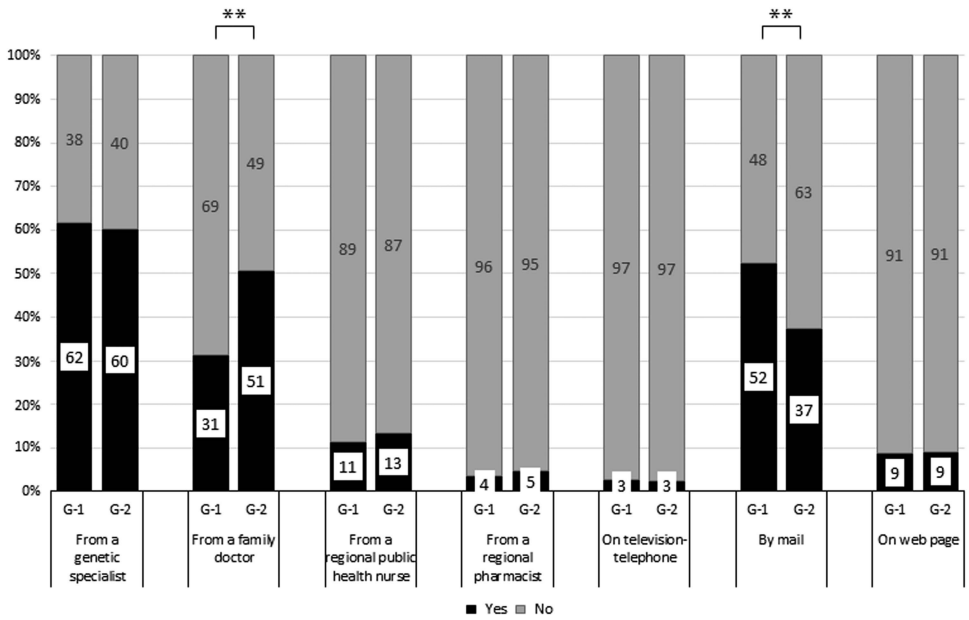

Figure 2 Participants' preferred method of receiving their own genetic information with Mantel–Haenszel testing in Group 1 (G-1) and Group 2 (G-2). $^{**}P<0.01$.

0.789, CI 0.659–0.944) and 'adult-onset clinically actionable diseases' ($\chi^2(1)=5.551$, $P=0.018$, OR = 0.807, CI 0.677–0.961) than did G-1 participants.

DISCUSSION

In the present study, we surveyed the preferences for returning individual genetic results among participants from the TMM cohort study (Group 1) and Tohoku residents (Group 2), and determined the relationships of these preferences with participants' demographic characteristics, genetic knowledge and health-conscious behaviors. Both of our participant groups were relatively older compared with participants in the Iwate and Miyagi prefecture data. The majority of participants preferred to receive individual genetic results. Furthermore, over 80% of participants wanted to receive genetic results for lifestyle diseases; by contrast, the percentage who wanted to receive results for adult-onset non-clinically-actionable diseases was 41% in Group 1 and 32% in Group 2. The most preferred approaches for returning genetic results were from a genetic specialist and by mail. Finally, several factors—including health-conscious behaviors, genetic knowledge and demographic data—influenced their preferences.

Participant characteristics

In G-1, the percentage of participants (male and female) in their 20 s and the percentages of male participants in their 30 s and 40 s were lower than were those in the general age distribution of the Tohoku area. This tendency was reflected in the age distribution of the enrolled individuals in G-1 (Appendix 2); furthermore, the percentage of male participants in their 60 s and 70 s was higher than that of the population of this area. The participants from the TMM cohort study were also relatively older, and our participants' age distribution was similar to that of the TMM cohort study. This tendency might be because the TMM cohort study recruited members of the National Health Insurance service in Japan. In G-2, a large percentage of participants were male and in their 60 s and 70 s. This tendency might be because we sent our questionnaire by mail, which might have been considered inconvenient by younger and early-middle-age people and thus created a potential disincentive for them to participate in our study. For future research, offering a web-based questionnaire could improve the response rate of those people. In the logistic regression analysis, age was also a predictor of participants' preferences to receive their own genetic information: that is, the older the participants, the

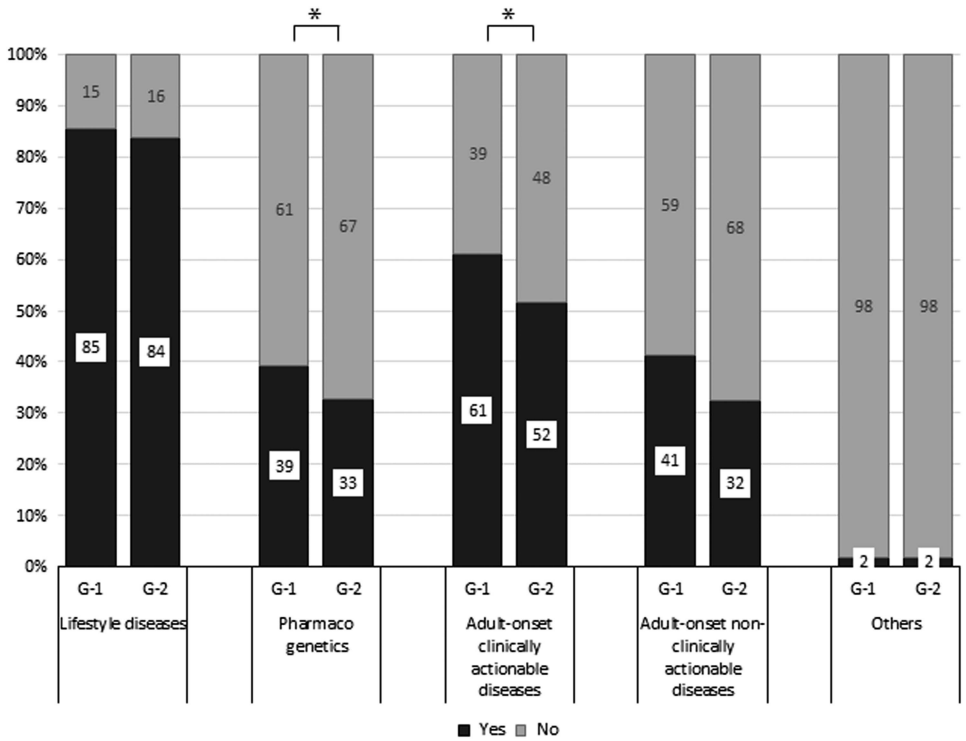

Figure 3 Differences in participants' preferences for receiving their own genetic information by disease with Mantel–Haenszel testing in Group 1 (G-1) and Group 2 (G-2). $*P<0.05$.

less likely they were to prefer receiving their genetic test results (Table 3). It is possible that the younger participants might have valued their genetic results to prevent future diseases and give indications about their future health, whereas older participants might not have. Future research is needed to clarify the reason for this finding.

Participants' preferences to receive their own genetic information

As noted above, there is some debate on how to best manage participants' preferences regarding the return of individual genetic results.[21] In clinical exome and genome sequencing, the American College of Medical Genetics and Genomics (ACMG) has published a list of genes that should be reported as incidental or secondary findings. Those genes were determined according to the clinical actionability of the identified genetic diseases, regardless of participants' preferences.[10] However, this recommendation has been criticized by some genetic specialists.[22] Through intensive discussion, participants' preferences have become more respected and the ACMG's recommendations were ultimately modified to permit participants to 'opt-out' of being returned their results.[23] The current list of genes to be reported is not a final, absolute decision on the part of the ACMG and it continues to change. Further research on the impact of returning secondary genetic findings is necessary.[24] Following the ACMG's recommendations, the Clinical Sequencing Exploratory Research Consortium and the Electronic Medical Records and Genomics Network have proposed similar recommendations for research sequencing studies, which state that participants must be adequately informed regarding the return of results and their right to refuse those results. These research sequencing recommendations also mentioned that participants' preferences might have a role in the choice of which research results should be returned; how to deal with these preferences, however, remains under discussion.[15] In our study, over 90% (G-1) and 80% (G-2) of participants preferred receiving their individual genetic results from the TMM's genome research study (Figure 1). This rate was similar to those reported in previous studies on laypeople,[16,25] but relatively higher than those among non-genetics health professionals[26] and clinical genetics professionals.[27] In our study, over 80% of them wanted to receive the genetic results regarding lifestyle diseases and over 50% of them preferred to receive the results regarding adult-onset-clinically actionable diseases. On the other hand, 41% of G-1 and 32% of G-2 wanted to receive their results even for diseases that were not clinically actionable (Figure 3). The previous studies also reported that participants preferred receiving their genetic results regardless of the medical actionability: among clinical genetics professionals[27] and primary care providers (that is, non-genetics health professionals),[26] 40% and over 50%, respectively, agreed that they would like to receive genetic results for non-clinically actionable diseases. In addition, some studies on biobank participants' and laypeople showed that over 70% of these individuals preferred receiving genetic results for non-clinically actionable diseases.[16,25] Our participants' percentage of non-clinically actionable diseases were notably lower rates than were those in previous studies among laypeople, which might mean that our participants had deliberate opinions regarding the return of genetic results for those non-actionable diseases. In addition, despite being actionable information, pharmacogenetic information was about as much in demand as was results for non-clinically actionable diseases. Furthermore, 11.8 and 17.8% of respondents in G-1 and G-2, respectively, did not want to receive any type of genetic result (Figure 1). Thus, the meaning and value

of genetic information might vary from person to person; as Murphy *et al.*[6] noted, whereas some people may want all of the available results, others may believe that such information would be a burden. In Japan, hereditary diseases have traditionally been stigmatized and discussion of such inherited conditions is often avoided.[28] It has been pointed out that the Japanese have feared both genetic diseases and the use of genetic information since their discovery. This may be related to the status of an individual in Japan as an integral part of a family which is less the case in the West. People have been afraid of any genetic disease in their family becoming publicly known because such information has also been used in the past and can still be used as an impediment to marriage.[29] Even now, though such fears regarding genetic discrimination have decreased, they still remain in the backround.[30] This cultural background may discourage individuals from participating in biobanks, as they might fear genetic discrimination in the context of their marriage, employment or insurance.[31] As such, it has typically been thought that relatively few Japanese laypeople prefer to receive their genetic results. Although there is no empirical data regarding the changes in preferences for returning genetic results over time in Japan, our results suggest that biobank participants in Japan prefer to receive their individual genetic results to the same degree as individuals in Western countries. This may represent a favorable change in the attitude of Japanese people towards genetic information. In addition, our results have suggested that the genetic information preferred by Japanese people is relatively unique. Consequently, obtaining more detailed informed consent from participants is crucial before beginning to return the genetic results from the TMM.

Participants' preferred approaches to receiving their own genetic information

In general, individual genetic results have been returned by doctors or genetic specialists in a clinical setting. In this setting, patients or clients can obtain sufficient knowledge about their genetic conditions and the influences of these conditions on their lives. In a previous study on returning genetic test results from biobank studies, genetic professionals also recommended to this 'face-to-face' approach,[17] as did biobank participants.[16,31] Over 60% of our participants similarly wanted to receive their results via this method (Figure 2). However, as the volume of individual results from biobank genome research is often quite large, the feasibility of returning results via this conventional approach is a concern to both information providers (for example, doctors, genetic specialists) and participants.[16,31,32] In previous research, almost 30% of prospective biobank participants wanted to receive their genetic results directly.[31] In our study, 52% of G-1 and 37% of G-2 participants similarly wanted to receive their results by conventional mail (Figure 2). However, genetic professionals have reported that individual genetic results from comprehensive genetic studies cannot be communicated effectively by conventional mail or e-mail.[17] Thus, despite both genetic specialists and participants actively seeking the most effective approach for the return of results from comprehensive genetic studies, a satisfactory approach for all parties has yet to be found. Participants of our study also wanted to obtain their genetic results from their family doctors. Thus, constructing a system of cooperation between family doctors and genetic specialists may be the key to achieving the appropriate return of genetic results for participants in population-based biobank studies. The genetic specialists at the TMM all hold posts in the clinical genetics departments of hospitals and, as such, already have some connections with family doctors in the area. In addition, organizing lectures on clinical genetics and the TMM genetic cohort studies for those family doctors might help to facilitate their cooperation. For the effective return of the TMM study results, it would also be important to construct a system of cooperation between GMRCs and genetic specialists. Approximately 150 GMRCs who have been trained in basic human genetics have been involved in obtaining the informed consent of participants in the TMM's study. In the planed system of cooperation, genetic specialists will manage the project and make decisions regarding what results should be returned and offer lectures on the return of genetic results to study participants. They will also offer genetic counseling to participants who have received positive results or have expressed a desire to receive genetic counseling. In the future, GMRCs who receive more training regarding clinical genetics might be able to explain the details regarding the return of genetic results to all of the participants in the TMM study individually, return negative results to participants, and report participants' responses to the genetic specialists. This system of cooperation between GMRCs and genetic specialists could well contribute to the resolution of the current issues of the time constraints of genetic specialists[29] and the general staff's lack of expertize in comprehensive genetic research.

Participants' knowledge of genetics

To make informed decisions, participants require sufficient knowledge of basic genetic science and heredity, especially regarding hereditary diseases and their implications. Several previous studies have researched laypeople's knowledge of genetic science and hereditary diseases using identical questions to those that we used.[20,33,34] Both of our groups were older (median age across the groups was 66.0 years) than were the participants of previous studies; nevertheless, our participants exhibited nearly equal levels of knowledge (Table 2). Genetic knowledge was, however, a weak predictor of G-2 participants' preferring to receive individual genetic results (OR = 1.09), and it was not a predictor in G-1 (Table 3).

In Japan, there has been no research using identical questions to ours. There was one Japanese study that used relatively similar questions regarding genetic knowledge, and found that higher genetic knowledge has positive effects on preferences to receive genetic testing results related to medical issues (for example, lifestyle diseases, cancer, congenital diseases, pharmacogenetics, aging, depression and obesity).[35] On the other hand, previous studies conducted abroad that used identical questions to ours reported that better knowledge does not necessarily lead to wider acceptance of genetic information.[34] Indeed, people with higher genetic knowledge typically express not only more enthusiasm but also more skepticism, fear[36] and uncertainty regarding the impact of receiving genetic information than do those with the lowest level of knowledge.[33] In summary, although genetic knowledge may to some degree influence peoples' preferences to receive individual genetic results, its effect seems to be limited.

Relationship between health-conscious behaviors and participants' preferences for receiving genetic information

According to the logistic regression analysis, engaging in health-conscious behaviors was a significant predictor of participants' preferences to receive their own genetic information. More specifically, participants who reported at least one health-conscious behavior, compared to those who reported none, had greater odds of preferring to receive their genetic test results in both groups (OR = 2.397 (G-1) and 1.897 (G-2), $P < 0.001$) (Table 3). As such, participants with health-conscious behaviors might have regarded genetic results as

useful information to protect their health, and they might be able to make good use of their genetic results to develop an effective and personally suitable diet and physical activity regimen, and choice of personally optimized medical checks. On the other hand, in previous research, providing individual genetic results for common complex diseases did not seem to promote risk-reducing behavior in the participants.[32] Therefore, based on our research results, we propose a study regarding the effects of returning the genetic results of common complex diseases to people who have notably high preferences for their genetic results returned and having health-conscious behaviors. For people who did not report had health-conscious behaviors, it would also be important to examine the reasons for their low preferences to receive their genetic test results. Offering combined genetic information and health care promotion strategies could help improve peoples' self-perceived health and health conditions.

In conclusion, we reported on biobank participants' preferences for receiving their own genetic information and investigated the influences of several factors—health-conscious behaviors, genetic knowledge and demographic data—on these preferences.

Nearly 90% of G-1 respondents (who participated to the TMM cohort study) and over 80% of G-2 respondents (who were residents of the Tohoku region) expressed a preference for receiving their genetic test results. However, our participants seemed to have a more deliberate perspective regarding the return of individual genetic results for non-clinically actionable diseases. Health-conscious behaviors and age were significant predictors of all participants' preference for receiving individual genetic results.

Study limitations

This study has several limitations. First, the response rate of Group 2, which was a residents' group in the Tohoku region, was relatively low (26.6%). Second, the residents who did not register their telephone numbers on the telephone lists of Iwate and Miyagi Prefectures were not included in our study because the participants of Group 2 were selected from telephone lists. In addition, we sent our questionnaires by postal service, which might have been considered inconvenient by young adults and those in the early years of middle age. They might be more familiar with internet devices than with snail mail, and the choice of the postal service might have created a potential disincentive for participation in our study. It is possible that these limitations affected this sample's distribution, which was biased toward older male participants. Third, our findings may have been influenced by response bias because the average age of our participants was greater than the average age of the total population of Japan. Fourth, all of the participants lived in the Tohoku region, and we did not research other areas in Japan. As such, our results may not be generalizable to other populations in Japan. This is notable because we found that the older the participants, the more their 'preference to receive their genetic test results' decreased. Consequently, the general population may show a greater preference for receiving their genetic test results. In addition, younger participants' preferences for the return of their results might have been affected by their desire for information for family planning; however, this likely did not influence the overall results, as relatively few participants were from the age groups associated with family planning. Finally, although our questionnaire was rigorously pilot-tested, it was not officially validated. Future research studies should assess both the social aspects of returning genetic tests results—such as participants' perceptions of genetic discrimination[37] or attitudes toward gene testing—and the medical aspects, such as participants' medical history or that of their families.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Wolf, S. M., Crock, B. N., Van Ness, B., Lawrenz, F., Kahn, J. P., Beskow, L. M. *et al.* Managingincidental findings and research results in genomic research involving biobanks & archived datasets. *Genet. Med.* **14**, 361–384 (2012).
2 Knoppers, B. M., Deschenes, M., Zawati, M. H. & Tasse, A. M. Population studies: return of research results and incidental findings Policy Statement. *Eur. J. Hum. Genet.* **21**, 245–247 (2013).
3 Kaufman, D., Murphy, J., Scott, J. & Hudson, K. Subjects matter: a survey of public opinions about a large genetic cohort study. *Genet. Med.* **10**, 831–839 (2008).
4 Bollinger, J., Bridges, J. F. P., Mohamed, A. & Kaufman, D. Public preferences for the return of research results in genetic research: a conjoint analysis. *Genet. Med.* **16**, 932–939 (2014).
5 Regier, D. A., Peacock, S. J., Pataky, R., van der Hoek, K., Jarvik, G. P., Hoch, J. *et al.* Societal preferences for the return of incidental findings from clinical genomic sequencing: a discrete-choice experiment. *CMAJ* **187**, 6 (2015).
6 Murphy, J., Scott, J., Kaufman, D., Geller, G., LeRoy, L. & Hudson, K. Public expectations for return of results from large-cohort genetic research. *Am. J. Bioeth.* **8**, 36–43 (2008).
7 National Research Council. *Issues in returning individual results from genome research using population-based banked specimens, with a focus on the National Health and Nutrition Examination Survey: A workshop summary* (National Academies Press, Washington, DC, USA, 2014).
8 Johns, A. L., Miller, D. K., Simpson, S. H., Gill, A. J., Kassahn, K. S., Humphris, J. L. *et al.* Returning individual research results for genome sequences of pancreatic cancer. *Genome Med.* **6**, 42 (2014).
9 Wallace, S. E. & Kent, A. Population biobanks and returning individual research results: mission impossible or new directions? *Hum. Genet.* **130**, 393–401 (2011).
10 Green, R. C., Berg, J. S., Grody, W. W., Kalia, S. S., Korf, B. R., Martin, C. L. *et al.* ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* **15**, 565–574 (2013).
11 Murphy, J., Scott, J., Kaufman, D., Geller, G., LeRoy, L. & Hudson, K. Public perspectives on informed consent for biobanking. *Am. J. Public Health.* **99**, 2128–2134 (2009).
12 Tohoku Medical Megabank Organization. Specimen & Data Collection. http://www.megabank.tohoku.ac.jp/english/sample/. Accessed on 27 February 2016.
13 Kuriyama, S., Nagami, F., Kawaguchi, Y., Arai, T., Kawaguchi, Y., Osumi, N. *et al.* The Tohoku Medical Megabank Project: design and mission. *J. Epidemiol.* **26**, 493–511 (2016).
14 Walker, A. P. *A guide to genetic counseling* 2nd edn (eds Uhlmann, W. R., Schuette J. L. & Yashar, B. M.) 7–11 (John Wiley & Sons, Hoboken, NJ, USA, 2009).
15 Jarvik, G. P., Amendola, L. M., Berg, J. S., Brothers, K., Clayton, E. W., Chung, W. *et al.* Return of genomic results to research participants: the floor, the ceiling, and the choices in between. *Am. J. Hum. Genet.* **94**, 818–826 (2014).
16 Allen, N. L., Karlson, E. W., Malspeis, S., Lu, B., Seidman, C. E. & Lehmann, L. S. Biobank participants' preferences for disclosure of genetic research results: perspectives from the OurGenes, OurHealth, OurCommunity Project. *Mayo Clin. Proc.* **89**, 738–746 (2014).

17 Yu, J. H., Harrell, T., Jamal, S., Tabor, H. K. & Bamshad, M. J. Attitudes of genetics professionals toward the return of incidental results from exome and whole-genome sequencing. *Am. J. Hum. Genet.* **95**, 77–84 (2014).
18 Japan Health Promotion & Fitness Foundation. Healthy-Japan 21, An attitude survey regarding public health promotion. http://www.kenkounippon21.gr.jp/kenkounippon21/database/data_1/5_kenkouzukuri/index.html. Accessed on 3 June 2014.
19 Takahashi, K., Kudo, K., Yamada, Y., Shao, L., Ishikawa, H. & Fukao, A. Relationship between health and social support for the prevention of lifestyle-related diseases. *J. Public Health.* **55**, 491–502 (2008).
20 Jallinoja, P. & Aro, A. R. Knowledge about genes and heredity among Finns. *Genet. Soc* **18**, 101–110 (1999).
21 Parker, L. S. Returning individual research results: what role should people's preferences play? *Minn. J. Law Sci. Technol.* **13**, 449–484 (2012).
22 Ross, L. F., Rothstein, M. A. & Clayton, E. W. Premature guidance about whole-genome sequencing. *Per. Med.* **10,** doi:10.2217/pme.13.51 (2013).
23 American College of Medical Genetics and Genomics. ACMG Updates Recommendations on "Opt Out" for Genome Sequencing Return of Results. https://www.acmg.net/docs/Release_ACMGUpdatesRecommendations_final.pdf. Accessed on 3 January 2016.
24 Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C. & Evans, J. P. 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.* **19**, 249–255.
25 Middleton, A., Morley, K. I., Bragin, E., Firth, H. V., Hurles, M. E., Wright, C. F. *et al.* Attitudes of nearly 7000 health professionals, genomic researchers and publics toward the return of incidental results from sequencing research. *Eur. J. Hum. Genet.* **24**, 21–29 (2016).
26 Strong, K. A., Zusevics, K. L., Bick, D. & Veith, R. Views of primary care providers regarding the return of genome sequencing incidental findings. *Clin. Genet.* **86**, 461–468 (2014).
27 Lemke, A. A., Bick, D., Dimmock, D., Simpson, P. & Veith, R. Perspectives of clinical genetics professionals toward genome sequencing and incidental findings: a survey study. *Clin. Genet.* **84**, 230–236 (2013).
28 Porter, G. in *Human Genetic Biobanks in Asia: Politics of trust and scientific advancement (Routledge Contemporary Asia Series)* (ed. Sleeboom-Faulkner, M.) 40–65 (Routledge, Oxon, 2009).
29 Macer, D. R.J. in *Encyclopedia of the Human Genome, 5 Volume Set: Genetic information and the family in Japan* (ed. Cooper D. a. v. i. d. N.) 855–859 (Nature MacMillan, 2003). http://www.eubios.info/Papers/nate587.htm Accessed 18 April 2017.
30 Murashige, N., Tanimoto, T. & Kusumi, E. Fear of genetic discrimination in Japan. *Lancet* **380**, 730 (2012).
31 Beskow, L. M. & Smolek, S. J. Prospective biorepository participants' perspectives on access to research results. *J. Empir. Res. Hum. Res. Ethics* **4**, 99–111 (2009).
32 Hollands, G. J., French, D. P., Griffin, S. J., Prevost, A. T., Sutton, S., King, S. *et al.* The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. *BMJ* **352,** doi:10.1136/bmj.i1102 (2016).
33 Haga, S. B., Barry, W. T., Mills, R., Ginsburg, G. S., Svetkey, L., Sullivan, J. *et al.* Public knowledge of and attitudes toward genetics and genetic testing. *Genet. Test Mol. Biomarkers* **17**, 327–335 (2013).
34 Calsbeek, H., Morren, M., Bensing, J. & Rijken, M. Knowledge and attitudes towards genetic testing: a two year follow-up study in patients with asthma, diabetes mellitus and cardiovascular disease. *J. Genet. Couns.* **16**, 493–504 (2007).
35 Tuchiya, A., Ohata, N., Watanabe, M., Sumida, T. & Takada, F. The determinant factor of social attitudes toward genetic technology: examining 'deficit model' in PUS. *Sociologos* **32**, 164–181 (2008).
36 Jallinoja, P. & Aro, A. R. Does knowledge make a difference? The association between knowledge about genes and attitudes toward gene tests. *J. Health Commun.* **5**, 29–39 (2000).
37 National Human Genome Research Institute. Genetic Discrimination. https://www.genome.gov/10002077/genetic-discrimination/. Accessed on 5 February 2016.

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APPENDIX 1

Questions regarding 'health-conscious behaviors':

What do you purposely do for your health?

Select all:

- □ Nothing
- □ Reduce alcohol consumption
- □ Reduce amount of smoking
- □ Exercise at least 30 minutes once per week
- □ Purposely move body during daily life
- □ Avoid eating between meals
- □ Purposely eat less
- □ Refrain from oily foods
- □ Reduce salt
- □ Try to eat fish
- □ Other ( )

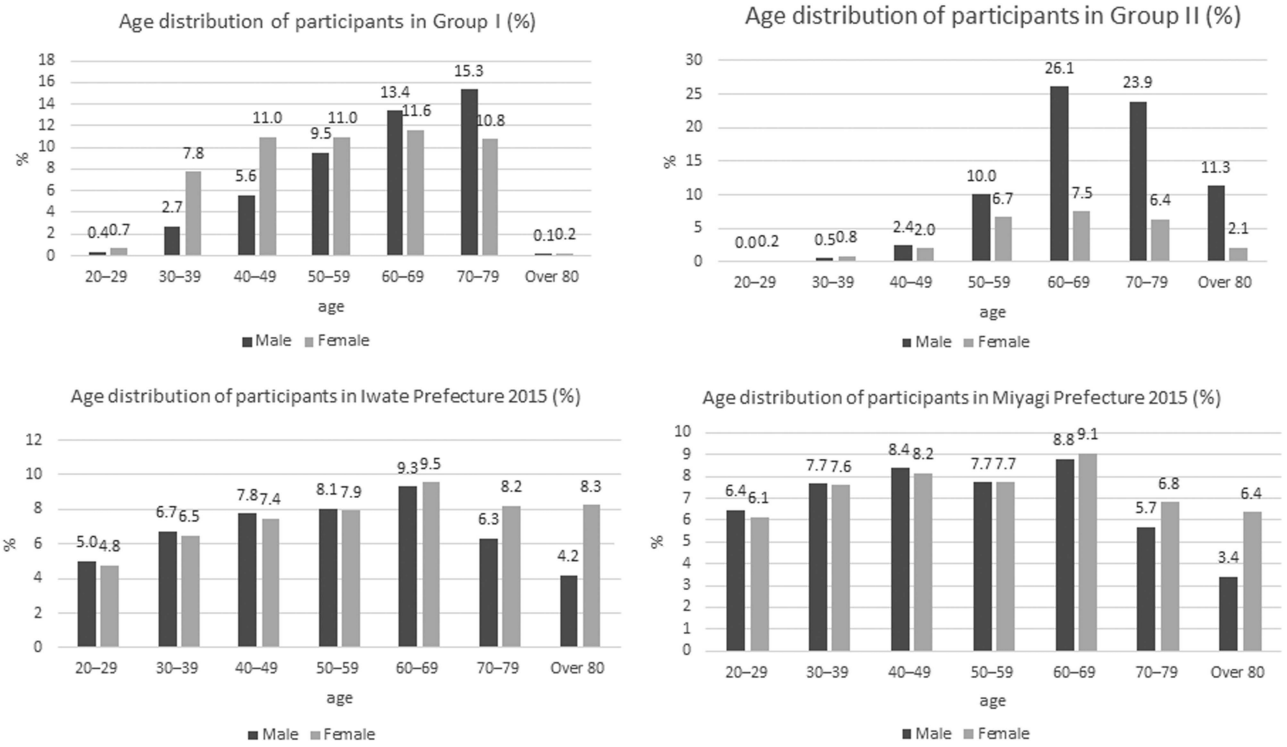
APPENDIX 2

The age distributions of enrolled individuals in G-1

Age	*Male (Iwate)*	*Male (Miyagi)*	*Male (Total)*	*Female (Iwate)*	*Female (Miyagi)*	*Female (Total)*
20–39 years old	38	47	85	80	80	160
40–49 years old	80	34	114	80	80	160
50–59 years old	95	85	180	80	80	160
60–69 years old	94	117	211	80	80	160
Over 70 years old	94	117	211	80	80	160

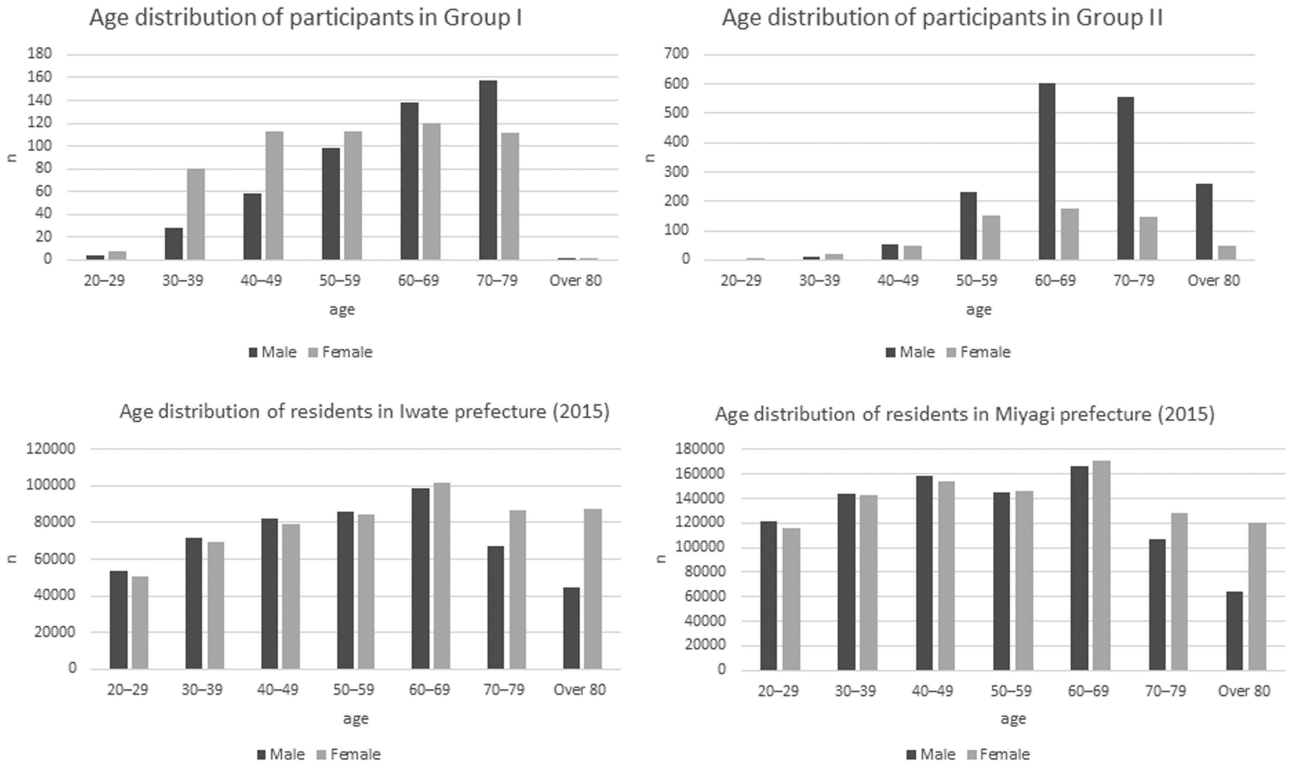
APPENDIX 3

The age distributions of G-1, G-2, and individuals living in Iwate and Miyagi prefectures (%)



APPENDIX 4

The age distributions of G-1, G-2, and individuals living in Iwate and Miyagi prefectures (*n*)



APPENDIX 5

Comparison of characteristics between the participants who answered 'yes' and those who answered 'no' to the 'have preferences for receiving genetic test results' item

		Group 1 (n = *1031*)				*Group 2* (n = *2314*)			
		Have preferences for receiving their genetic test results				*Have preferences for receiving their genetic test results*			
		Yes	*No*	*95% CI*	P-*value*	*Yes*	*No*	*95% CI*	P-*value*
Health conscious behaviors[a]	Yes	794	98	0.980–2.633	0.058	1757	361	1.186–2.343	0.003**
	No	116	23			146	50		
Communication with health professionals[1]	Yes	742	96	0.718–1.842	0.560	1691	358	0.856–1629	0.311
	No	168	25			212	53		
Genetic knowledge (average score ± standard deviation)[2]		11.8 ± 2.2	11.3 ± 2.6	(–1.007)– (–0.029)	0.038*	11.4 ± 2.4	10.7 ± 2.9	(–0.977) – (–0.367)	< 0.001**
Sex[a]	Male	418	67	0.997–2.139	0.051	1384	336	1.283-2.200	< 0.001**
	Female	492	54			519	75		
Age (average score ± standard deviation)[b]		57.5 ± 12.9	63.0 ± 11.3	3.258–7.645	< 0.001**	66.8 ± 11.3	68.8 ± 10.3	0.846-3.085	0.001**

[a]Pearson's chi-square test.
[b]Welch's t-test.
**P< 0.01, *P< 0.05.