Attitudes toward and current status of disclosure of secondary findings from next-generation sequencing: a nation-wide survey of clinical genetics professionals in Japan

AUTHOR(S):

Tsuchiya, Mio; Yamada, Takahiro; Akaishi, Rina; Hamanoue, Haruka; Hirasawa, Akira; Hyodo, Maki; Imoto, Issei; ... Yoshihashi, Hiroshi; Yotsumoto, Junko; Kosugi, Shinji

Attitudes toward and current status of disclosure of secondary findings from next-generation sequencing: A nation-wide survey of clinical genetics professionals in Japan

Mio Tsuchiya[1], Takahiro Yamada[1,17]*, Rina Akaishi[2,17], Haruka Hamanoue[3,17], Akira Hirasawa[4,17], Maki Hyodo[5,17], Issei Imoto[6,17], Tomoki Kosho[7,17], Kenji Kurosawa[8,17], Hiromi Murakami[1,17], Kaname Nakatani[9,17], Fumio Nomura[10,17], Aiko Sasaki[2,17], Kenji Shimizu[11,17], Mariko Tamai[7,17], Hiroshi Umemura[12,17], Atsushi Watanabe[13,17], Akiko Yoshida[14,17], Hiroshi Yoshihashi[15,17], Junko Yotsumoto[16,17], Shinji Kosugi[1,17]

[1] Department of Medical Ethics and Medical Genetics, Kyoto University School of Public Health, Kyoto, Japan
[2] Center of Maternal-Fetal, Neonatal and Reproductive Medicine, National Center for Child Health and Development, Tokyo, Japan
[3] Department of Clinical Genetics, Yokohama City University Hospital, Yokohama, Japan
[4] Department of Clinical Genomic Medicine, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan
[5] Department of Obstetrics and Gynecology, Hiroshima University Graduate School of Medicine, Hiroshima, Japan
[6] Department of Molecular Genetics, Aichi Cancer Center Research Institute, Nagoya, Japan
[7] Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan
[8] Division of Medical Genetics, Kanagawa Children's Medical Center, Yokohama, Japan
[9] Central Laboratory, Mie University Hospital, Tsu, Japan
[10] Divisions of Clinical Mass Spectrometry and Clinical Genetics, Chiba University Hospital, Chiba, Japan
[11] Division of Medical Genetics, Shizuoka Children's Hospital, Shizuoka, Japan
[12] Division of Laboratory Medicine, Department of Pathology and Microbiology, Nihon

University School of Medicine, Tokyo, Japan

[13] Division of Clinical Genetics, Kanazawa University Hospital, Kanazawa, Japan

[14] Laboratory for Retinal Regeneration, RIKEN, Center for Biosystems Dynamics Research, Kobe, Japan

[15] Department of Medical Genetics, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

[16] International University of Health and Welfare Graduate School, Tokyo, Japan

[17] The Social, Ethical and Legal Issues Committee, Japanese Society for Genetic Counseling

*Corresponding author:

Takahiro Yamada,
Department of Medical Ethics and Medical Genetics, Kyoto University School of Public Health
Yoshidakonoe-cho, Sakyo-ku, Kyoto 606-8501, Japan.
Tel: +81-75-753-9464
FAX: +81-75-753-4649
E-mail: taka0197@kuhp.kyoto-u.ac.jp

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Abstract

The management of secondary findings (SFs), which are beyond the intended purpose of the analysis, from clinical comprehensive genomic analysis using next generation sequencing (NGS) presents challenges. Policy statements regarding their clinical management have been announced in Japan and other countries. In Japan, however, the current status of and attitudes of clinical genetics professionals toward reporting them are unclear. We conducted a questionnaire survey of clinical genetics professionals at two time points (2013 and 2019) to determine the enforcement of the SF management policy in cases of comprehensive genetic analysis of intractable diseases and clinical cancer genome profiling testing. According to the survey findings, 40% and 70% of the respondents stated in the 2013 and 2019 surveys, respectively, that they had a SF policy in the field of intractable diseases, indicating that SF policy awareness in Japan has changed significantly in recent years. Furthermore, a total of 80% of respondents stated that their facility had established a policy for clinical cancer genome profiling testing in the 2019 survey. In both surveys, the policies included the selection criteria for genes to be disclosed and the procedure to return SFs, followed by recommendations and proposals regarding SFs in Japan and other countries. To create a better list of the genes to be disclosed, further examination is needed considering the characteristics of each analysis.

Introduction

In clinical exome and genome sequencing using next-generation sequencing (NGS), it is possible to identify and report secondary findings (SFs), which are findings beyond the intended purpose of the analysis, generated due to the nature of this technique. The discovery of SFs is an issue of concern as they may reveal that the patient is likely to develop a disease unrelated to the indication for ordering the sequencing but of medical value for the patient's future health.

Management of SFs before the introduction of the American College of Medical Genetics (ACMG SF v2.0) recommendations

In March 2013, the ACMG published the recommendations for the reporting of SFs identified from comprehensive genomic analysis using NGS [1]. Under the assumption that NGS is clinically used, the ACMG recommends that laboratories performing comprehensive genetic analysis using NGS and interpreting analytical results should report clinically actionable SFs, regardless of the intention or age of the patients, and lists 24 diseases and 56 genes to be reported as SFs. In 2014, the ACMG updated the recommendation to include the option to "Opt-Out" of receiving SFs [2]. In response to the announcement of these recommendations, discussions and studies on the reporting of SFs from analyses using NGS were initiated mainly among experts in the field of medical genetics. Some experts insist that the right of the patient to remain in ignorance should be respected [3], whereas others assert that the disclosure of SFs of clinical utility should be prioritized over the patient's autonomy [4].

In Japan, the following description was added to the guidelines known as the Ethical Guidelines for Human Genome/Gene Analysis Research [5], revised and enforced in 2013: "The research director has to decide the policy on the disclosure of SFs and explain them to the donor or parent/guardian to make them understand when informed consent is obtained." However, the policy for the reporting of SFs was not actively discussed in Japan at that time, and the status of and attitudes toward reporting SFs were also unclear. Findings beyond the intended purpose of the comprehensive genetic analysis are termed SFs in this manuscript. However, when the first

ACMG recommendation was published, these findings were termed incidental findings (IFs). Subsequently, ACMG updated the recommendation and changed the terminology from IFs to SFs because the genes in these tests are routinely analyzed intentionally, in contrast to genetic variants which are found incidentally [6].

Management of SFs after the introduction of the ACMG SF v2.0 recommendations

As described above, the ACMG updated the recommendations as ACMG SF v2.0 and revised the list of actionable genes to include 27 diseases and 59 genes in 2016 [6]. Subsequently, the Japan Society of Human Genetics (JSHG) announced the statement regarding genomic analysis using NGS in 2017 [7] and the Japan Agency for Medical Research and Development (AMED) released the proposal concerning the information transmission process in genomic medicine in 2018, which was updated in 2019 [8]. The scope of this proposal includes the field of rare diseases and clinical cancer genome profiling testing [9]. Regarding clinical cancer genome profiling testing in Japan, two commercial tests for cancer genome profiling have been approved as clinical tests, which are reimbursed by the national health insurance [10]. Therefore, as comprehensive genetic testing in clinical use, including cancer genome profiling, will be common in the near future it requires practical consideration of the management of SFs. However, the implementation of these recommendations and proposals in the clinical setting remains unclear.

The objectives of this study were to clarify the present status of reporting SFs from comprehensive genetic analysis of intractable diseases and clinical cancer genome profiling testing and to determine the attitudes of clinical genetics professionals toward reporting SFs in Japan. Additionally, regarding the comprehensive genetic analysis of intractable diseases, we examined chronological changes in the reporting of SFs before and after the introduction of the ACMG SF v2.0 recommendations in Japan.

Materials and Methods

Study design and methodology

We conducted a cross-sectional postal questionnaire survey. The participants of this survey were Japanese board-certified instructors of Clinical Geneticists and Certified Genetic Counselors, both of which are certified by the Japan Society of Human Genetics and Japanese Society for Genetic Counseling. Collaborators and persons with unknown addresses were excluded. This study was approved by the ELSI (ethical, legal and social issues) Committee of the Japanese Society for Genetic Counseling (JSGC). Considering that this study was a self-administered questionnaire survey distributed to genetics professionals, institutional review board approval was not required.

This study was conducted at two time points. Survey 1 was conducted from October 2013 to December 2013 prior to the publication of the ACMG SF v2.0 recommendations. Survey 2 was conducted from May 2019 to July 2019 following the publication of the ACMG SF v2.0 recommendations.

The execution of these surveys was approved by the Board Certification Committee for Clinical Geneticists and Japanese Association of Certified Genetic Counselors. A survey request statement, questionnaire, and self-addressed envelope were sent to the subjects, and the responses were collected by postal mail. The statement outlined background information on SFs in the United States and Japan to provide the participants with specific knowledge regarding SFs before answering the questionnaire. A reminder post card or mail was sent after the deadline for providing responses in order to increase the response rate.

The questionnaire was prepared based on previous studies [11-14] and the outcomes of the discussion with the members of the Social, Ethical, and Legal Issues Committee of JSGC.

Detailed survey information

Survey 1(2013)

Scope: SFs from genomic sequencing analysis for rare diseases. Definition of SFs: secondary findings detected beyond the initially intended purpose of the analysis. Question items (n=15):

153 respondents' characteristics (n=3) and experience with the clinical management of SFs (n=12).

154 *Survey 2 (2019)*

155 Scope: SFs from genomic sequencing analysis for rare diseases and cancer genome profiling.

156 Definition of SFs in rare diseases: detection of variants confirmed to be pathogenic that cause

157 symptoms other than those targeted to be diagnosed. Definition of SFs in clinical cancer

158 genome profiling: detection of germline variants confirmed to be pathogenic. Question items

159 (n=29): respondents' characteristics (n=3), experience with the clinical management of SFs in

160 rare diseases (n=11) and cancer genome profiling (n=15).

161 **Statistical analysis**

162 Statistical analysis was performed using SPSS Statistics for Windows, Version 20.0 (Armonk,

163 NY, IBM Corp). Participants with any missing values were excluded from the analysis. The

164 frequency distribution and response rate were investigated in each question.

165

166 **Results**

167 **Response rate**

168 In Survey 1, a total of 207 of the 389 subjects (53.2%) responded, which included 145 of the

169 264 certified instructors of clinical genetics (54.9%), and 62 of the 125 certified genetic

170 counselors (49.6%). In Survey 2, a total of 245 of the 533 subjects (46.0%) responded, which

171 included 141 of the 294 certified instructors of clinical genetics (48.0%), and 104 of the 239

172 certified genetic counselors (43.5%).

173 **Respondents' characteristics**

174 Of the 207 respondents, 75 (36.2%) were affiliated with the Department of Medical Genetics,

175 and 84 (40.6%) were in their 50s, accounting for the largest response rate in Survey 1 (Table 1).

176 The same trend was observed in Survey 2, in which 129 of the 245 respondents (52.7%) were

177 affiliated with the Department of Medical Genetics, and 88 (35.9%) were in their 50s,

178 accounting for the largest response rate in Survey 2 (Table 1).

Work experience related to the reporting of SFs from NGS analyses

In Survey 1, conducted before the introduction of the ACMG SF v2.0 recommendations, 29.0% (60/207) of the respondents were involved in genetic analyses using NGS. The majority of the respondents, 65.5% (38/58; two invalid responses were excluded), were mainly involved through “the clinical use of the results of genetic analyses,” while 64.4% of the respondents (38/59; one invalid answer was excluded), were involved in “whole exome analyses for diagnosis and treatment of intractable disease,” the most frequent genetic analysis (Figure 1-A, Figure 2-A).

In Survey 2, conducted after the introduction of the ACMG SF v2.0 recommendations, 66.1% (162/245) of the respondents were involved in genetic analyses using NGS. The majority of the respondents, 63.3% (103/162), were mainly involved through “conducting the pre-test informed consent/disclosing the result to the patient,” whereas 19.1% of the respondents (31/162) were involved in “cancer genome profiling,” the most frequently used genetic analysis. Furthermore, 42.0% (68/162) of the respondents were involved in “whole exome/genome analyses and panel testing for diagnosis and treatment of intractable diseases,” while 38.9% (63/162) were involved in “not only exome/genome analyses and/or panel testing for the diagnosis and treatment of intractable disease but also cancer genome profiling testing” (Figure 1-B, Figure 2-B). Therefore, 131 respondents had experience of being involved in comprehensive genetic analysis for the diagnosis and treatment of intractable diseases and 94 respondents had experience of being involved in cancer genome profiling testing.

Comprehensive genetic analysis for the diagnosis and treatment of intractable diseases

Experience with the clinical management of SFs before and after the introduction of the ACMG SF v2.0 recommendations

Notably, of the 60 respondents who had experience of being involved in genomic analyses using NGS before the introduction of the ACMG SF v2.0 recommendations, only 3 (5.1%, [3/59]; one invalid answer was excluded) had experience in the clinical management of SFs.

This confirmed that only a small number of respondents had experience in the clinical management of SFs, even though they had experience in genetic analyses. Moreover, one of the 3 respondents disclosed the SFs, which were known variants associated with skeletal dysplasia, to the patients.

On the other hand, of the 131 respondents who had experience in genetic analyses using NGS after the introduction of the ACMG SF v2.0 recommendations, 26.7% (35/131) had experience in the clinical management of SFs. Furthermore, 80.0% (28/35) of the respondents with experience in the clinical management of SFs disclosed SFs to the patient. The disclosed SFs were mainly variants related to hereditary cancer syndromes, such as hereditary breast and ovarian cancer syndrome, and hereditary cardiovascular diseases.

Policy for the clinical management on SFs

Of the 60 respondents who had the experience of being involved in genetic analyses using NGS before the introduction of the ACMG SF v2.0 recommendations, 37.3% (22/59; one invalid answer was excluded) answered that “there is no institutional policy, but a policy is set in each analysis,” while 5.1% (3/59) answered that “there is an institutional policy,” (Table 2-A) which clarified that some policy was established for managing SFs in 42.4% (25/59). Of the 25 respondents who answered that there were some policies on SF management, 80.0% (20/25) mainly involved in whole exome or whole genome analyses, and 20.0% (5/25) mainly involved in panel analyses. Regarding the detailed contents of the policy, 41.7% of the respondents (10/24; one invalid answer was excluded) answered that “a clinically useful SF is disclosed,” accounting for the highest response rate, whereas 29.2% (7/24) answered that “all SFs are not disclosed regardless of the clinical usefulness,” and 65.0% (6/24) selected “other,” (Figure 3) which clarified that the policy on the clinical management of SFs differed among genetic analyses and institutions. Of the respondents who selected “other,” the most frequently described content was “disclosure policy of SFs is decided by the Ethics Committee.”

Of the 131 respondents who had the experience of being involved in comprehensive analyses

using NGS after the introduction of the ACMG SF v2.0 recommendations, 48.1% (62/129; two invalid answers were excluded) answered that “there is no institutional policy, but a policy is set in each analysis,” while 17.8% (23/129) answered that “there is an institutional policy,” (Table 2-A) which clarified that some policy was established for handing SFs, based on the responses of 65.9% (85/129) of the respondents. Regarding the detailed contents of the policy, 69.4% (59/85) of the respondents answered that “a clinically useful SF is disclosed,” accounting for the highest rate (Figure 3).

Correspondence to patients

Of the 25 respondents who answered that there were some policies on SF management before the introduction of the ACMG SF v2.0 recommendations, 84.0% (21/25) answered that the policy was explained to patients when informed consent was obtained, while 16.0% (4/25) answered that the policy was not explained. Of the 21 respondents who explained the policy when informed consent was obtained, 70.0% (14/20; one invalid answer was excluded) confirmed the patient’s intention to disclose SFs, whereas 30.0% (6/20) did not confirm it. These results clarified that an explanation of the policy to the patients followed by confirming their intention was the main way of correspondence to patients.

Of the 85 respondents who answered that there were some policies on SF management after the introduction of the ACMG SF v2.0 recommendations, 92.9% (79/85) answered that the policy was explained to the patients when informed consent was obtained, while 7.1% (6/85) answered that it was not explained. Of the 79 respondents who explained the policy when informed consent was obtained, 68 (86.1%) confirmed the patient’s intention to disclose SFs, while 11 (13.9%) did not confirm it. Furthermore, of the 68 respondents who confirmed the patient’s intention to disclose SFs, 89.6% (60/67; one invalid answer was excluded) provided the opportunity to opt-out. These results clarified that an explanation of the policy to the patients followed by confirming their intention and providing the opportunity of opt-out was the main way of correspondence to patients.

Cancer genome profiling testing (After ACMG SF v2.0 recommendations)

Experience in the clinical management of SFs

Of the 94 respondents who had experience of being involved in cancer genome profiling testing, 43.0% (40/93; one invalid answer was excluded) had experience with SF clinical management, while 57.0% (53/93) did not have, which revealed that around 40% of the respondents had experience in SFs clinical management. Thirty-one (77.5%) of the 40 respondents with experience of SF clinical management disclosed it to the patient, and the disclosed SFs included known variants associated with hereditary cancer syndromes, such as hereditary breast and ovarian cancer syndrome and Li-Fraumeni syndrome.

Policy for the clinical management of SFs

Of the 94 respondents who had experience of being involved in cancer genome profiling testing, 32 (34.0%) answered that “there is no institutional policy, but a policy is set in each analysis,” whereas 40 (42.6%) answered that “there is an institutional policy,”(Table 2-B) which clarified that some policy was established for handing SFs in 72 (76.6%) of the responses. Regarding the detailed contents of the policy, 44.9% (31/69; three invalid answers were excluded) of the respondents answered that “a clinically useful SF is disclosed (including other than cancer-susceptibility gene),” accounting for the highest rate, and 36.2% (25/69) answered that “a clinically useful SF is disclosed (including cancer-susceptibility gene only),” accounting for the second highest rate (Figure 4), which clarified that clinically useful SFs are disclosed in general, however, there was controversy over whether to disclose only cancer-susceptibility genes.

Correspondence to patients

Of the 72 respondents who answered that there were some policies on the clinical management of SFs, 22.2% (16/72) answered that they were not involved in obtaining informed consent from patients as that was the responsibility of the physician in charge, while 77.8% (56/72) answered

that they were sometimes/always involved in obtaining informed consent from patients, which revealed that around 80% of the respondents were involved in obtaining informed consent from patients. Of the 56 respondents who answered that they were involved in obtaining informed consent from patients, 96.4% (53/55, one invalid answer was excluded) answered that the policy was explained to patients when informed consent was obtained. Of the 53 respondents who explained the policy when informed consent was obtained, 98.1% (51/52; one invalid answer was excluded) confirmed the patient's intention to disclose SFs. Furthermore, of the 51 respondents who confirmed the patient's intention to disclose SFs, 96.1% (49/51) provided the opportunity to opt-out. These results clarified that an explanation of the policy to patients followed by confirming their intention and providing the opportunity to opt-out was the main way of correspondence to patients.

Discussion

This JSGC study was a nationwide survey on SFs identified in comprehensive genomic analyses using NGS. The results provide insights and fundamental knowledge regarding the status and attitudes of genetics professionals toward returning SFs in Japan.

Comprehensive genetic analysis for diagnosis and treatment of intractable diseases

The survey for comprehensive genetic analysis of intractable diseases was conducted at two time points, before and after the introduction of the ACMG SF v2.0 recommendations, in 2013 (Survey 1) and 2019 (Survey 2), respectively.

Approximately 40% and 70% of the respondents answered that their facility had established a policy regarding the clinical management of SFs in Survey 1 and Survey 2, respectively, demonstrating an increasing focus on the management of SFs in Japan. In most of the policies, the SFs to be disclosed were limited to those with clinical utility. The stipulated procedure of returning SFs included: 1. informing the SF management policy, 2. confirmation of the patient's intention regarding disclosure, 3. guarantee of opt out opportunities. This procedure follows the

ACMG recommendations and proposal concerning the information transmission process in genomic medicine in Japan.

The percentage of respondents who had experience with dealing with SFs increased from 5% in Survey 1, to 30% in Survey 2. As mentioned above, the establishment of institutional policies for the clinical management on SFs may have contributed to this trend. The returned SFs included SFs related to cardiovascular diseases and hereditary cancers. The genes to be disclosed were decided following the recommendations and proposals made in Japan and other countries [6, 15].

Comprehensive analyses of intractable diseases using NGS are not performed in the clinical setting in Japan, with minor exceptions. The Medical Care Act of Japan stipulates that clinical tests should be performed in registered clinical laboratories to secure their accuracy [16]. The proposal concerning the information transmission process in genomic medicine also states that, "when returning the results of a research (primary and secondary findings) for clinical purpose, in principle, a confirmation test using recollected blood in registered clinical laboratory is necessary." [8] Therefore, it is necessary to re-evaluate the selection of genes to be disclosed from the viewpoint of accessibility to the confirmatory clinical testing. From the viewpoint of clinical utility, based on the recent clinical application of various treatments for hereditary diseases, such as enzyme replacement therapy and chaperone therapy for inborn errors of metabolism [17, 18] and gene therapy, antisense therapy and siRNA therapy for neuromuscular diseases [19-21], it may be necessary to form a consensus in Japan on what type of genes are considered actionable.

Cancer genome profiling testing

Cancer genome profiling testing had not been introduced into actual clinical practice in Japan as of 2013, and interest among genetic medicine specialists was low at that time. Therefore, this survey was conducted only in 2019, after the introduction of the ACMG SF v2.0 recommendations (Survey 2). Although approximately 80% of the respondents answered that

their facility had established some kind of policy regarding the experience in cancer genome profiling testing, they responded that there was no policy for returning SFs. The reasons for this might be that Survey 2 was conducted in May-July 2019, shortly after the publication of the proposal concerning the information transmission process in genomic medicine in Japan, and before the start of insurance coverage for cancer genome profiling testing. Therefore, it is possible that some facilities had not yet taken action to ensure the implementation of the guidelines for the clinical management of SFs. According to the responses, the most common selection criterion for the return of SFs was clinical utility. However, there was controversy over whether to only disclose cancer-susceptibility genes. Approximately 40% of the respondents had experience with the clinical management of SFs. Most of their experiences were related to the disclosure of SFs in hereditary cancer genes. The reasons for the institutional differences regarding whether to disclose non-cancer-susceptibility genes were the specification of the profiling test (i.e., whether the panel included non-cancer-susceptibility genes or not) and the policy of the expert panel.

The procedure of returning SFs in clinical cancer genome profiling testing also follows the ACMG recommendations and proposal concerning the information transmission process in genomic medicine in Japan.

Cancer genome medicine in Japan is provided at core hospitals for cancer genome medicine, which play a central role in the cancer genome medicine provision system (12 institutions), hub hospitals, which can complete the medical interpretation of cancer genome profiling at their own facilities (33 institutions), and liaison hospitals, which provide cancer genome medical care in cooperation with core hospitals and/or hub hospitals (161 institutions) [22, 23]. Two types of cancer genome profiling tests are covered by the national health insurance system since June 2019, and the demand for clinical cancer genome profiling testing is expected to increase further in the future. Therefore, one of the problems in the proper clinical management of SFs is the lack of resources for clinical genetics specialists. Hence, the proper management of SFs requires

standardization of the information transmission process. This study revealed that the policies of the facilities regarding the clinical management on SFs were generally standardized. However, there were differences in the selection criteria for the genes to be disclosed, related to whether or not to only include cancer-susceptibility genes. With regard to clinical cancer genome profiling testing, clinical genetics specialists and clinical oncologists should discuss the list of the genes to be disclosed while referring to previously published lists, such as the Potentially Actionable SFs Gene List [24] among proposals concerning the information transmission process in genomic medicine.

Summary of the survey findings

・There was a large increase in the number of respondents who reported that an institutional policy was implemented for the disclosure of SFs from the comprehensive analysis of intractable diseases, following the introduction of the ACMG SF v2.0 recommendations.

・The majority of respondents stated that their facility had established some sort of policy for clinical cancer genome profiling testing at the time of Survey 2 (May 2019).

・The policies, including the selection criteria of the genes to be disclosed, and the procedure for returning SF followed the recommendations and proposals regarding SFs in Japan and other countries.

This survey demonstrated that the policies for the clinical management of SFs from the comprehensive analysis of intractable diseases and clinical cancer genome profiling testing, followed Japanese and international SF recommendations and proposals. Considering that only 40% of the respondents stated that they had a policy on SFs in the field of intractable diseases at the time of the 2013 survey, the awareness of SFs in Japan has changed significantly in recent years. To create a better disclosure gene list, it is necessary to consider the respective characteristics of the comprehensive intractable disease test and the clinical cancer genome profiling test. We hope that this survey provides a basis for further practical discussions on the

clinical management of SFs in Japan.

Limitations

The response rate of Survey 1 and 2 was approximately 50%. Due to non-respondent bias, the result of this survey may not correctly reflect the overall conditions in Japan. Additionally, in this survey, we received responses from individual genetics professionals in Japan, not facilities. Therefore, there is a possibility that multiple people from the same facility may have responded, resulting in a duplicate count of the institutional policies. Hence, the results should be interpreted with caution considering this limitation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Titles and legends to figures

Figure 1. Main ways of involvement in genetic analyses using next-generation sequencing.

Black bars represent the question response rate. A) Survey 1 responses (n=58). B) Survey 2 responses (n=162).

Figure 2. Types of genetic analyses in which subjects are involved at a high rate.

Black bars represent the question response rate. A) Survey 1 responses (n=59). B) Survey 2 responses (n=162).

Figure 3. Detailed contents of the comprehensive genetic analysis for the diagnosis and treatment of intractable diseases policy.

Black bars indicate the question response rate in Survey 1 (n=24). Gray bars indicate the question response rate in Survey 2 (n=85).

Figure 4. Detailed contents of the clinical cancer genome profiling testing policy (n=69).

Black bars represent the question response rate.

Figure 1

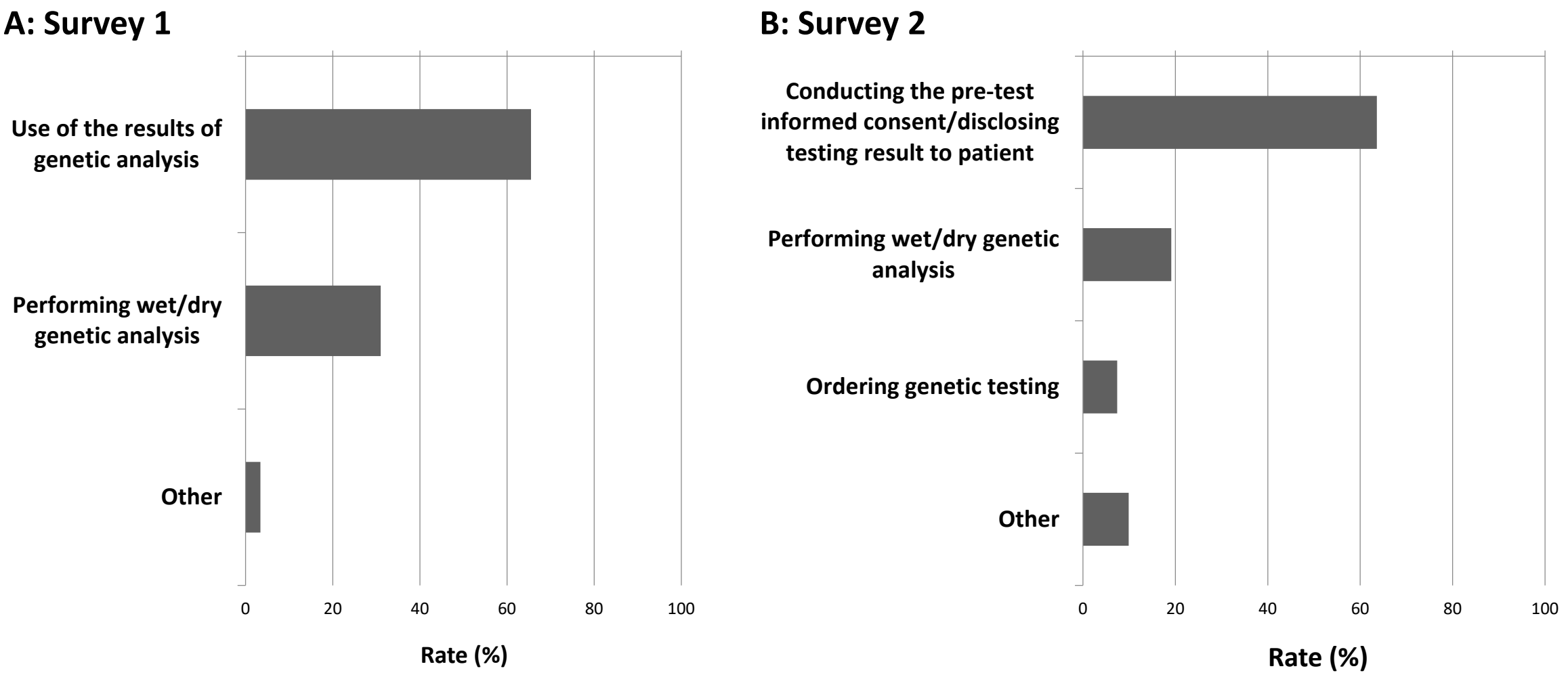

Figure 2

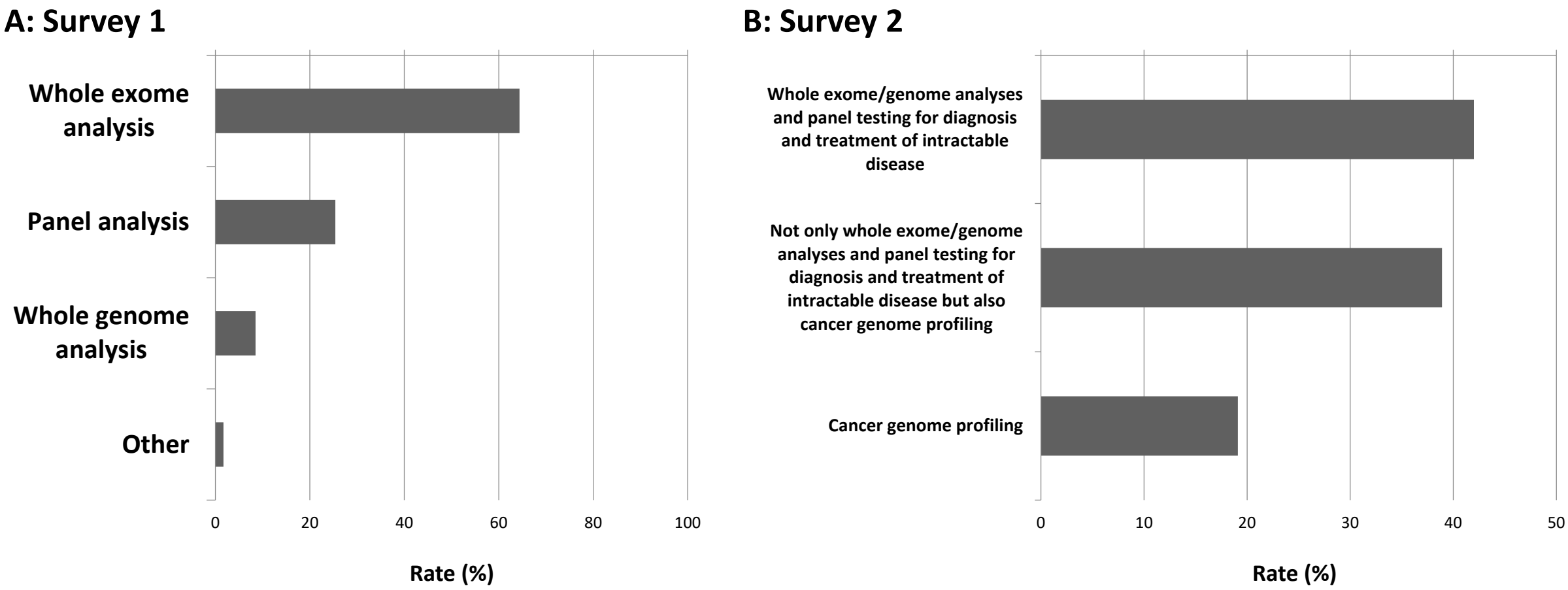

Figure 3

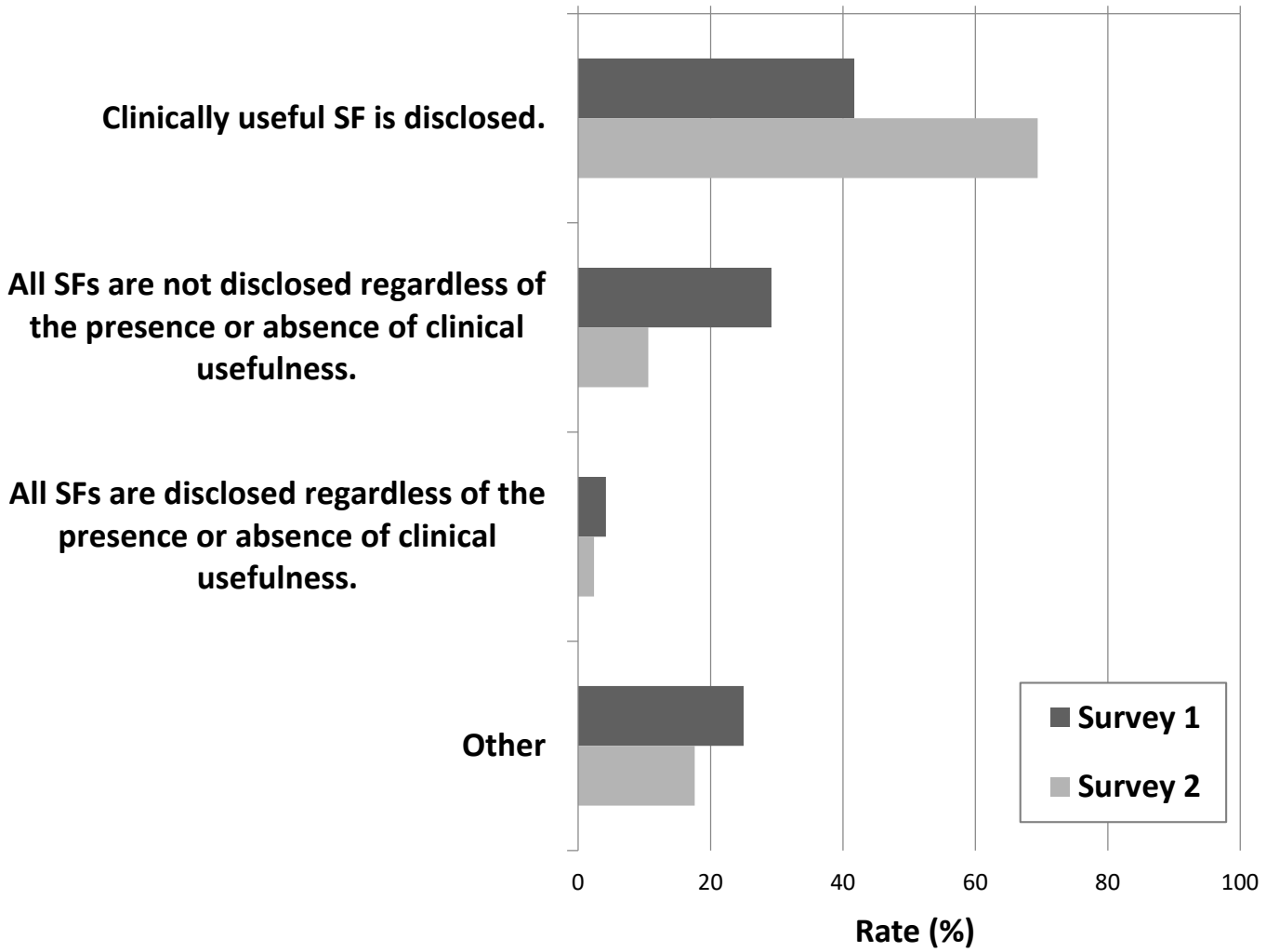

Figure 4

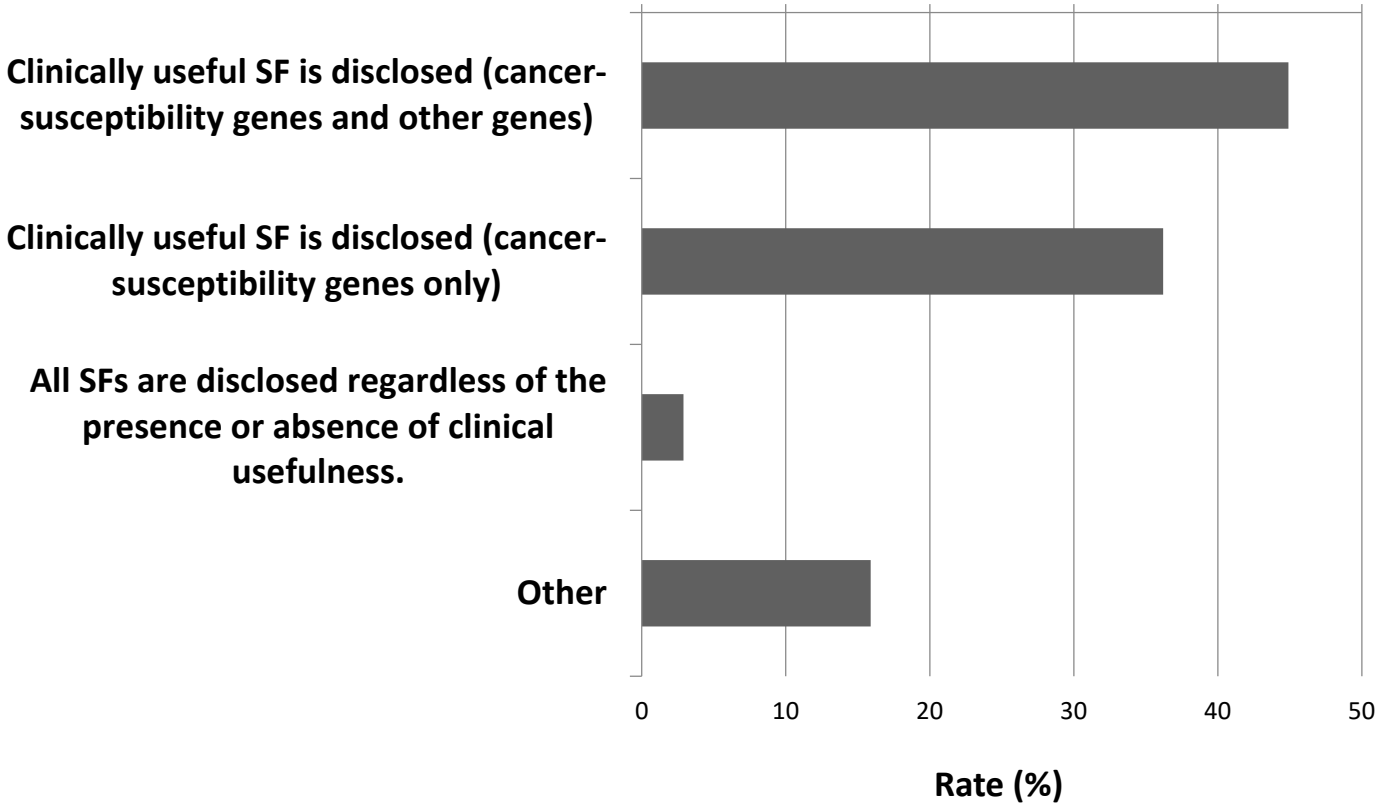

Table 1. Respondents' characteristics

Survey 1	N	Rate (%)
Affiliated department (N=207, multiple answers allowed)		
Department of Medical Genetics	75	36.2
Pediatrics	64	30.9
Gynecology	44	21.3
Neurology	8	3.9
Laboratory test	4	1.9
Others	54	26.1
Age (N=207)		
20s	7	3.4
30s	26	12.6
40s	59	28.5
50s	84	40.6
60s or older	31	15.0
Survey 2	**N**	**Rate (%)**
Affiliated department (N=245)		
Department of Medical Genetics	129	52.7
Pediatrics	31	12.7
Gynecology	26	10.6
Internal medicine	23	9.4
Surgery	2	0.8
Laboratory test	3	1.2
Others	31	12.7
Age (N=245)		
20s	20	8.2
30s	40	16.3
40s	45	18.4
50s	88	35.9
60s or older	52	21.2

Table 2. Policy on the clinical management of secondary findings

A. Comprehensive genetic analysis for the diagnosis and treatment of intractable diseases

	Survey 1 (N=59)		Survey 2 (N=129)	
	N	Rate (%)	N	Rate (%)
I do not know about the policy	7	11.9	9	7.0
There is no institutional policy, and no policy is set for each analysis	18	30.5	18	14.0
No policy is present now, but is planned for the future	9	15.3	17	13.2
There is no institutional policy, but a policy is set in each analysis	22	37.3	62	48.1
There is an institutional policy	3	5.1	23	17.8

B: Cancer genome profiling testing (N=94)

	N	Rate (%)
I do not know about the policy	0	0
There is no institutional policy, and no policy is set for each analysis	7	7.4
No policy is present now, but is planned for the future	15	16.0
There is no institutional policy, but a policy is set in each analysis	32	34.0
There is an institutional policy	40	42.6