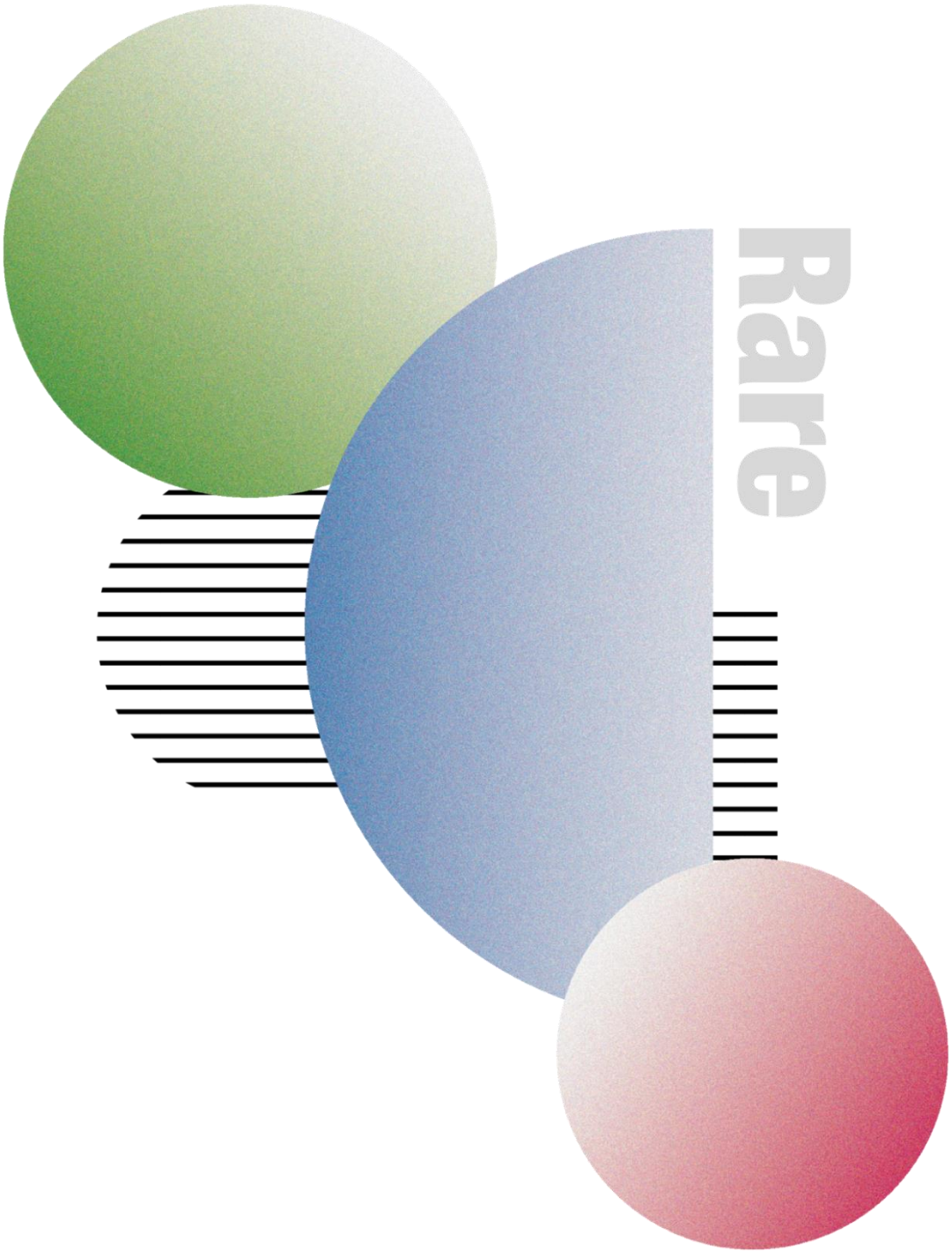


Survey on challenges faced by healthcare professionals in rare diseases [Main part]

Initiative on Rare and Undiagnosed Diseases (IRUD)
Rare Disease Consortium Japan (RDCJ)
Japan Pharmaceutical Manufacturers Association (JPMA)

IRUD

Rare Disease Consortium Japan

JPMA

Greetings

Due to their rarity and low social awareness, research and development (R&D) of treatments for rare diseases tends to be delayed, and even in Japan, many patients and their families still face difficulties in diagnosis and treatment. Initiative on Rare and Undiagnosed Diseases (IRUD), Rare Disease Consortium Japan (RDCJ), and Japan Pharmaceutical Manufacturers Association (JPMA) have each been working hard to overcome these difficulties in their own way.

IRUD is an initiative aimed at supporting diagnosis and facilitating access to treatment for patients with undiagnosed and rare diseases. Using advanced genetic analysis technology, experts from across Japan have come together to identify causative genes and pursue new diagnostic possibilities through the sharing of clinical information.

RDCJ was established with the aim of solving problems related to rare diseases, advancing research, and developing patient-centered medical services and treatments through collaboration between the private sector, academia and industry. Researchers from universities and research institutes, experts from pharmaceutical companies and members of patient advocacy groups have been actively working together to overcome intractable and rare diseases.

JPMA has been committed to the realization of patient-participatory healthcare, contributing to global medical advancements through the development of innovative pharmaceuticals since its inception. In 2021, JPMA launched the 'Rare and Intractable Disease Task Force.' In 2023, we conducted and published a 'Survey on the challenges faced by patients with rare diseases', compiled recommendations on rare diseases and orphan drugs, and have been working in collaboration with stakeholders to address those challenges.

IRUD, RDCJ, and JPMA executed this survey together with the goal of 'contributing to improving the quality of medical care and research on intractable and rare diseases by identifying challenges faced by healthcare professionals involved in rare diseases and proposing and implementing solutions, thereby contributing to patients and their families.'

This survey investigated the challenges faced by healthcare professionals, who are important stakeholders supporting rare disease healthcare, and identified the direction of problem-solving in rare disease healthcare and the actions required for each stakeholder. This survey also targeted healthcare professionals who have been leading the way in rare disease medicine in specific medical departments and disease areas in Japan. By expanding and delving deeper into the survey population in the future, we aim to further concretize the challenges and expectations identified in this survey and advance towards realizing the envisioned ideal state.

We hope that through this publication, various stakeholders, including healthcare professionals, academic societies, patient advocacy groups, government, pharmaceutical and other industries will come together and contribute to the realization of a society in which more patients can live with peace of mind as soon as possible.

November 2024

Initiative on Rare and Undiagnosed Diseases

Rare Disease Consortium Japan

Japan Pharmaceutical Manufacturers Association

Table of Contents

Summary

A rare disease is a disease with extremely few patients, and it is estimated that there are over 7,000 rare diseases worldwide. There are many patients in Japan who suffer from symptoms that have not been diagnosed at many medical institutions and whose causes and treatments are unknown.

Following the enactment of the Act on Medical Care for Patients with Intractable Diseases in 2014, stakeholders have been diligently working to resolve challenges related to rare diseases through research and clinical projects via IRUD and public-private partnership projects such as RDCJ.

However, the 'Survey on challenges faced by patients with rare diseases (February 2023, JPMA)' [a] reported that patients still face many challenges, indicating that the path to resolving challenges in rare disease medicine is long and arduous for many stakeholders. To overcome these difficulties, it was vital to accurately understand the realities and challenges faced by healthcare professionals, who are key stakeholders supporting rare disease medical care and to identify the specific desired state and actions required for each stakeholder.

Therefore, a quantitative web survey with 327 participants and qualitative interviews with 15 participants were executed among healthcare professionals (specialists, non-specialists, genetic counselors, and nurses involved in actual clinical practice, clinical researchers (basic and applied) involved in R&D, and clinical researchers (development) to shed light on the current state of rare disease medical care from a variety of perspectives, the difficulties (sense of challenges) and their background and the expectations of stakeholders (pharmaceutical industry, academic societies, patient advocacy groups and the government).

From the perspective of each healthcare professional, we identified challenges in five areas - basic and applied research, development and clinical trials, diagnosis, treatment and prognosis management, and disease awareness. Secondary information on international cases was separately researched to compare and analyze the current state of rare disease medicine in Japan, including why these challenges are currently important in Japan. Furthermore, based on the expectations of stakeholders – the pharmaceutical industry, academic societies, patient advocacy groups and the government, we have identified the desired state, pragmatic actions, and roles required for the improvement of rare disease medicine.

As a result, five directions for resolving the challenges and actions required for each stakeholder were identified (below are the main ones). At the same time, these points also highlight areas where Japan is lagging internationally, emphasizing the need for stakeholders to fulfill their roles and collaborate to bridge the gap (details in the main document).

1. **Accelerate research and development for new modalities[1] for drug discovery and diagnostics, and building an ecosystem for this purpose**
   - [Pharmaceutical Industry & Academic Societies] Accelerating R&D through domestic and international seed[2] acquisition, cross-industry collaboration, and the creation of similar opportunities
   - [Government] Support for R&D and promoting measures for early diagnosis
   - [Patient Advocacy Group] Enhancement of organizational function, enhancement of PPI[3] through inter-organizational collaboration and dissemination of needs
   - [Government] Cutting-edge technology in drug discovery such as GMP[4]-compliant facilities and CPC[5], infrastructure support
   - [Government] Drug pricing that contributes to increasing the attractiveness of Japan's rare disease market, introduction of a pharmaceutical system and bold deregulation that contributes to the benefit of patients

[1] Novel treatments and diagnostic technologies, such as cell and gene therapy, that offer new opportunities for treatment of diseases that were previously inaccessible to treat.
[2] Fundamental research results and technologies that can be applied to the development of new drugs and research into treatment methods
[3] Patient and Public Involvement: Efforts to actively involve patients and citizens and have their opinions and needs reflected
[4] Good Manufacturing Practice
[5] Cell Processing Center: A special facility for handling, processing and culturing patients' cells, mainly in regenerative medicine and cell therapy.

2. **Improved access to medical institutions and professionals that can provide testing, diagnosis and treatment as well as information on pharmaceuticals and products in development**
   - [Academic Societies / Government] Consolidation and networking of functions between medical institutions and healthcare professionals to speed up testing
   - [Pharmaceutical industry / Academic Societies / Patient Advocacy Groups / Government] Ensuring the quality and strengthening standardization and dissemination of information related to testing, treatment, medicines and clinical trials
   - [Government] Establishment of a data infrastructure and system to promote cooperation between medical institutions and improve the efficiency of information transmission
   - [Government / Patient Advocacy Groups] Improving the functionality of the entire medical system related to rare diseases through legislation, establishment of registries[6] and promotion

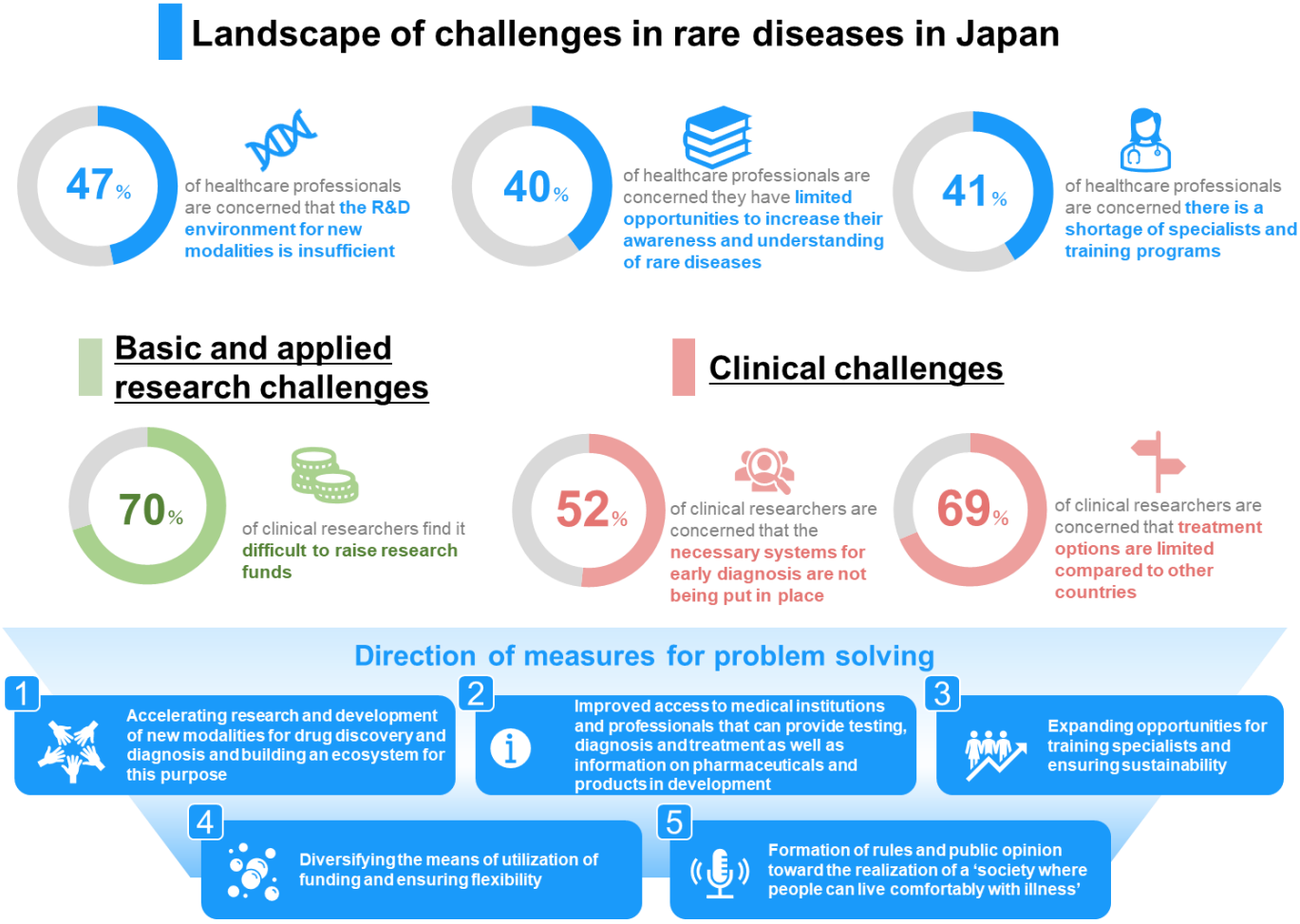
3. **Expanding opportunities for training specialists and ensuring sustainability**
   - [Government] Eligibility for medical fees related to rare disease medical care and expanding incentives
   - [Academic Societies / Government] Creating an attractive career development environment, sharing role models, success stories and minimizing barriers to participation
   - [Academic Societies / Government] Establishment of programs in specialized education courses and accelerating the mobility of human resources
   - [Government] Strengthening literacy among government personnel involved in drug development, medical welfare and reducing disparities

4. **Diversifying the means of utilization of funds and ensuring flexibility**
   - [Government] Hiring personnel, increasing the budget required for infrastructure development, ensuring flexibility in certification requirements for research funds, expanding the scope of targets and accelerating the attraction of private funds
   - [Patient Advocacy Groups] Diversifying activities and expanding fundraising methods through dissemination and strengthening organizational functions

5. **Formation of rules and public opinion toward the realization of a 'society where people can live comfortably with illness'**
   - [Government] Policy discussions aimed at reducing the burden on patients and families (introduction of intractable and rare diseases in the primary education course, introduction of special measures in research and development and clinical practice, etc.)
   - [Pharmaceutical industry / Academic Societies / Patient Advocacy Groups] Communicating the necessity and value of rare disease medical care and drug discovery in Japan

[6] A database that collects and manages medical data on patients with a disease.

Figure S-1: Landscape of challenges for healthcare professionals and the direction of measures



1. Background and purpose of the survey

The ‘Survey on challenges faced by patients with rare diseases (February 2023, JPMA)’ [a] once again highlighted the fact that many challenges remain unresolved for patients and their families affected by rare diseases, making it necessary to hear the voices of healthcare professionals supporting rare disease medical care in Japan and implement concrete initiatives.

IRUD, RDCJ and JPMA planned this survey with the aim of ‘contributing to improve the quality of medical care and research related to intractable and rare diseases by identifying challenges faced by healthcare professionals involved in rare diseases and proposing and implementing solutions, thereby contributing to patients and their families.’

In planning and promoting this survey, we utilized the IRUD and RDCJ healthcare professional networks, requested a quantitative survey (online questionnaire) from approximately 1,000 people (healthcare professionals belonging to the IRUD Diagnostic Committee, healthcare professionals introduced by the committee and healthcare professionals participating in the RDCJ) and received responses from 327 people. Additionally, we received cooperation from a total of 15 healthcare professionals who participated in the qualitative survey (interviews).

To ensure neutrality and objectivity, this survey was executed with the planning and operational support of a third-party organization (EY Strategy & Consulting Co., Ltd.).

2. Definition of rare diseases

A rare disease refers to a disease with an extremely small number of patients, and it is said that there are more than 7,000 rare diseases in the world [b]. Because of the small number of patients, it is difficult for patients' voices and needs to be heard, which leads to delays in R&D and insufficient care in actual clinical practice. The United States, Europe and Japan each have different definitions for designating a rare or intractable disease, and they are defined mainly in terms of patient population, severity of the disease, business viability, unmet needs, efficacy and safety (Figure 2-1).

Figure 2-1:

Definitions of rare and designated intractable diseases in each country (underlying laws and regulations) [c], [d], [e], [f]

Classification	US (Orphan Drug Act)	Europe (EC No. 141)	Japan	
			Rare diseases (Pharmaceutical and Medical Device Act)	Designated intractable disease (Intractable Diseases Act)
Patient population	▸ The number of patients is less than 200,000 (equivalent to approximately 0.06% of the total population)	▸ The number of patients is less than 0.05% of the total population (equivalent to approximately 220,000 people)	▸ The number of patients in Japan is less than 50,000 (equivalent to approximately 0.04% of the total population)	▸ The number of patients in Japan is less than 0.01% of the total population (equivalent to approximately 120,000 people)
Severity of disease	N/A	▸ Even if the morbidity condition is not met, a drug may be designated if it is indicated for treating a life-threatening, severely debilitating or severe chronic disease	▸ A drug or medical device indicated for treatment of severe diseases, including diseases that are difficult to treat	▸ Diseases that require long term treatment
Business potential	▸ Even if the incidence rate condition is not met, a product may be subject to designation if it is expected that R&D costs will not be recovered through sales in the United States	▸ A drug may be designated if it is a rare disease treatment drug with no prospect of recovery from investment	N/A	N/A
Unmet needs	N/A	▸ There are no satisfactory EMA-approved alternatives or there is a significant benefit to patients with the disease	▸ It is a drug or medical device that is highly necessary for medical purposes ▸ No suitable medicine, medical device or treatment	▸ The mechanism of disease onset is unclear ▸ There is no established treatment
Efficacy/safety	N/A		▸ Expected to be more effective or safer than existing products ▸ It is a drug or medical device that has a theoretical basis for use in the target disease and has an appropriate development	N/A

3. Approach

To identify the challenges faced by healthcare professionals from a more multifaceted perspective, this survey requested responses from healthcare professionals involved in rare disease care in multiple occupations (including concurrent positions) in R&D and clinical practice (Figure 3-1).

The quantitative survey targeted healthcare professionals belonging to the IRUD Diagnostic Committee, healthcare professionals referred by the committee and healthcare professionals participating in the RDCJ.

In the qualitative survey (Figure 3-2), the survey was executed on those who offered to cooperate and could arrange the schedule among the participants of the quantitative survey, with priority given to having as many healthcare professionals participate as possible. Therefore, there is some bias in the attributes of the survey subjects (age, gender, position, medical department, type of facility, amount of experience, etc.), and healthcare professionals with relatively little involvement in rare diseases are not included. In the [Main Section], the results and opinions related to the main points of discussion are described and all survey results including other detailed data are published in the attached [Reference Section].

Figure 3-1: Approach overview

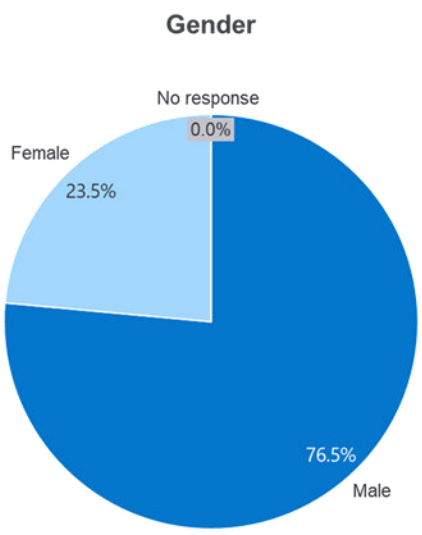
Classification	Quantitative (web survey) research	Qualitative (interview) research
Purpose	▸Quantitatively identify the current status, challenges, and future expectations of rare disease medical care	▸Identify context and reality of quantitative survey responses
Region	▸Nationwide	
Duration	▸25th July 2024 to 23rd August 2024	▸2nd September 2024 to 13th September 2024
Target person (job type)	▸Clinical physicians: specialists and non-specialists ▸R&D: clinical researchers (basic and applied), clinical researchers (development)* ▸Other HCPs** (genetic counselors, nurses) *Doctors involved in clinical trials **Healthcare Professionals	
Recruitment method	▸Approximately 1,000 medical professionals, including those who belong to the IRUD Diagnostic Committee, those who have been introduced by the committee, and those who participate in the RDCJ	▸Those who agreed to participate out of the 327 people who participated in the quantitative survey
Number of valid responses	▸327	▸15
Analysis assumptions and constraints	▸In accordance with the recruitment method, some attributes (age, gender, position, medical department, etc., explained in detail in the main text) are biased ▸Responses by job type include multiple responses (concurrent positions)	
Inspection Agency	▸EY Strategy & Consulting Co., Ltd. ▸Social Survey Research Information Co., Ltd.	

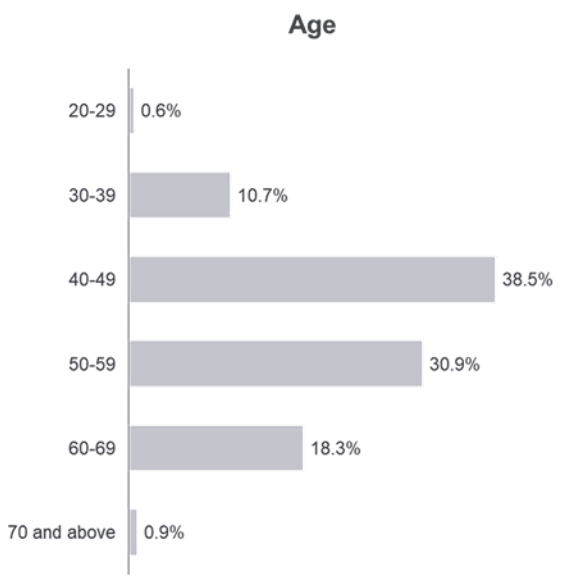
Figure 3-2: Details of qualitative interviewees

	#	Occupation/activity ratio (total 10)						Facility Attributes				Experience		
		Clinician (specialist)	Clinician (non-specialist)	Clinical researcher (basic and applied)	Clinical researcher (Development)	Other HCPs	Clinical researcher – Details*	Facility type	Region	Department/Disease area	Professional staff Yes/No	Years involved	Consulted by [Person]	Consulted [Person]
Specialist	1-1	3	2	2	2	2	n/a	University Hospital	Kansai	Paediatrics	Full-time	10~	20	10
	1-2	3	4	1	0	2	n/a	National and public hospitals (other than university hospitals)	Chubu/Hokuriku	Paediatrics	Full-time	~3	5	30
	1-3	4	0	6	0	0	n/a	University Hospital	Tokyo Metropolitan Area/South Kanto	Collagen Disease	No	10~	30	5
Non-specialist	2-1	1	8	0	0	1	n/a	Hospitals and Clinics	Tokyo Metropolitan Area/South Kanto	Neurology	Full-time	10~	15	5
	2-2	3	4	2	1	0	Basic, Applied (Non-clinical), Clinical/Clinical Trials, TR	University Hospital	Northern Kanto/Koshinetsu	Paediatrics	Full-time	10~	10	0
	2-3	1	8	1	0	0	n/a	University Hospital	Tokyo Metropolitan Area/South Kanto	Paediatrics	Full-time	3~10	10	20
Clinical researcher (basic and applied)	3-1	0.5	0.5	5	4	0	Basic, Applied (Non-clinical), Clinical/Clinical Trials, TR	National and public hospitals (other than university hospitals)	Tokyo Metropolitan Area/South Kanto	Neuromuscular disease	Full-time	10~	0	0
	3-2	2	0	5	2	1	Basics, Applications (Non-clinical), TR	University Hospital	Chubu/Hokuriku	Other general hereditary disease	No	10~	0	0
	3-3	4	0	6	0	0	Basic, applied (non-clinical), clinical/trial	University Hospital	Tokyo Metropolitan Area/South Kanto	Paediatric diseases	Full-time	10~	10	10
Clinical researcher (development)	4-1	5	0	1	4	0	Basic, clinical trials, TR	University Hospital	Chugoku and Shikoku	Neuromuscular disease	Full-time	10~	30	20
	4-2	8	0	1	1	0	Clinical trials	National and public hospitals (other than university hospitals)	Kansai	Endocrinology and Metabolic Disease	Full-time	10~	100	10
	4-3	5	1	3	1	0	Basic, clinical and experimental	University Hospital	Chugoku and Shikoku	Immunodeficiency disease	Full-time	10~	10	5
	4-4	0	0	0	5 IRUD Clinical Researcher	5 Genetic Counsellor	Clinical trials	University Hospital	Kansai	All other hereditary disease	Full-time	3~10	0	0
Other HCPs	5-1	Genetic counselors: 8, Nurses/midwives: 2					n/a	University Hospital	Chugoku and Shikoku	Department of Clinical Genetics and Gene Therapy	Full-time	10~	0	0
	5-2	Genetic counselor: 10					n/a	University Hospital	Kyushu	Department of Clinical Genetics and Gene Therapy	Full-time	10~	0	0

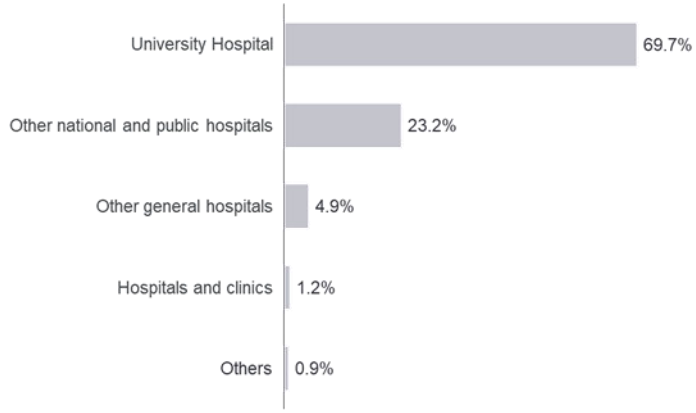
*TR (Translational research): A field of medical research that considers the process from non-clinical research to clinical development as a continuum, aiming for a smooth transition from basic research to clinical application.

Respondent attributes

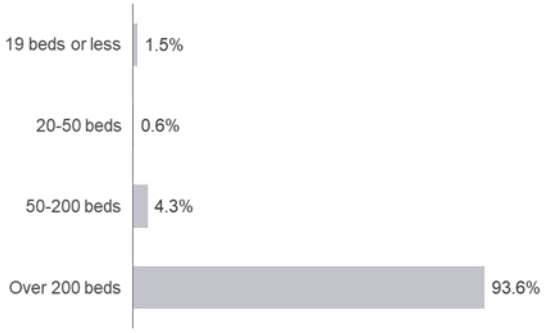




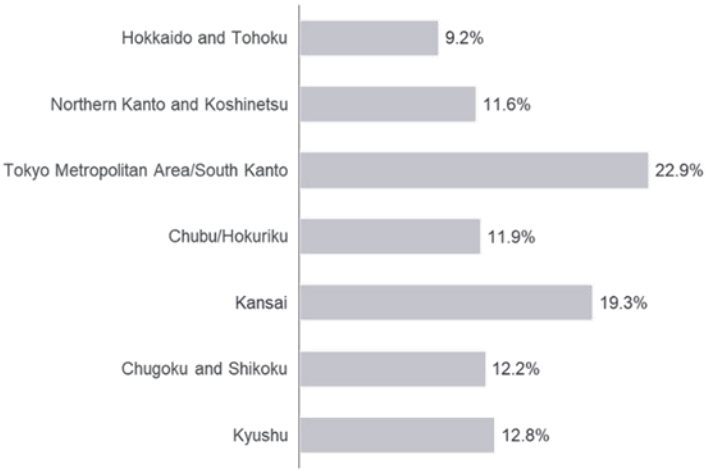
Type of facility



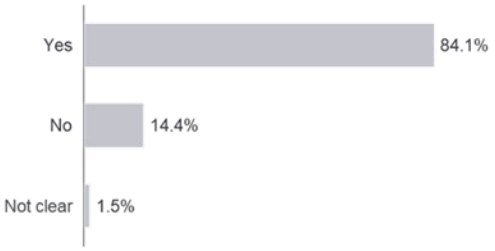
Number of hospital beds at affiliated facilities



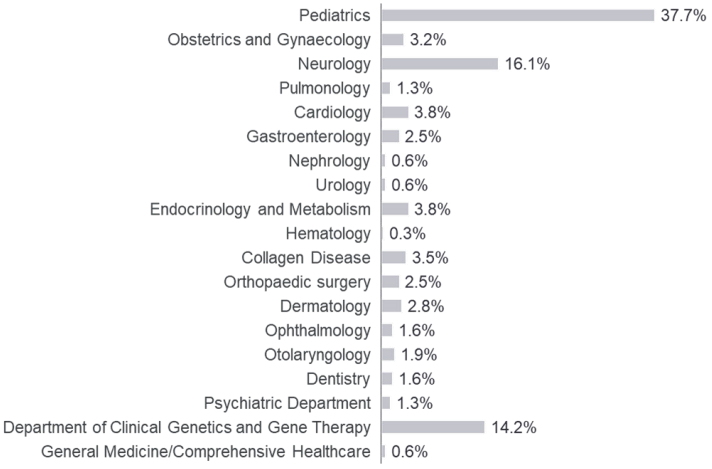
Region/area of affiliated facility



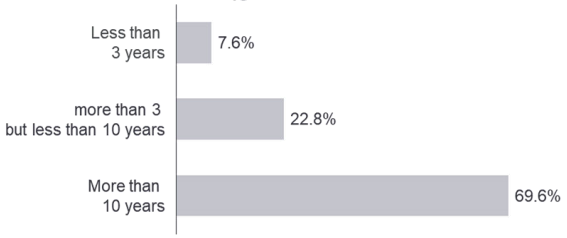
Availability of specialized staff at affiliated facilities



Departments Specialists, non-specialists, other HCPs (genetic counselors, nurses)



Years of experience in rare disease treatment for support specialists, non-specialists, and other HCPs (genetic counselors and nurses)



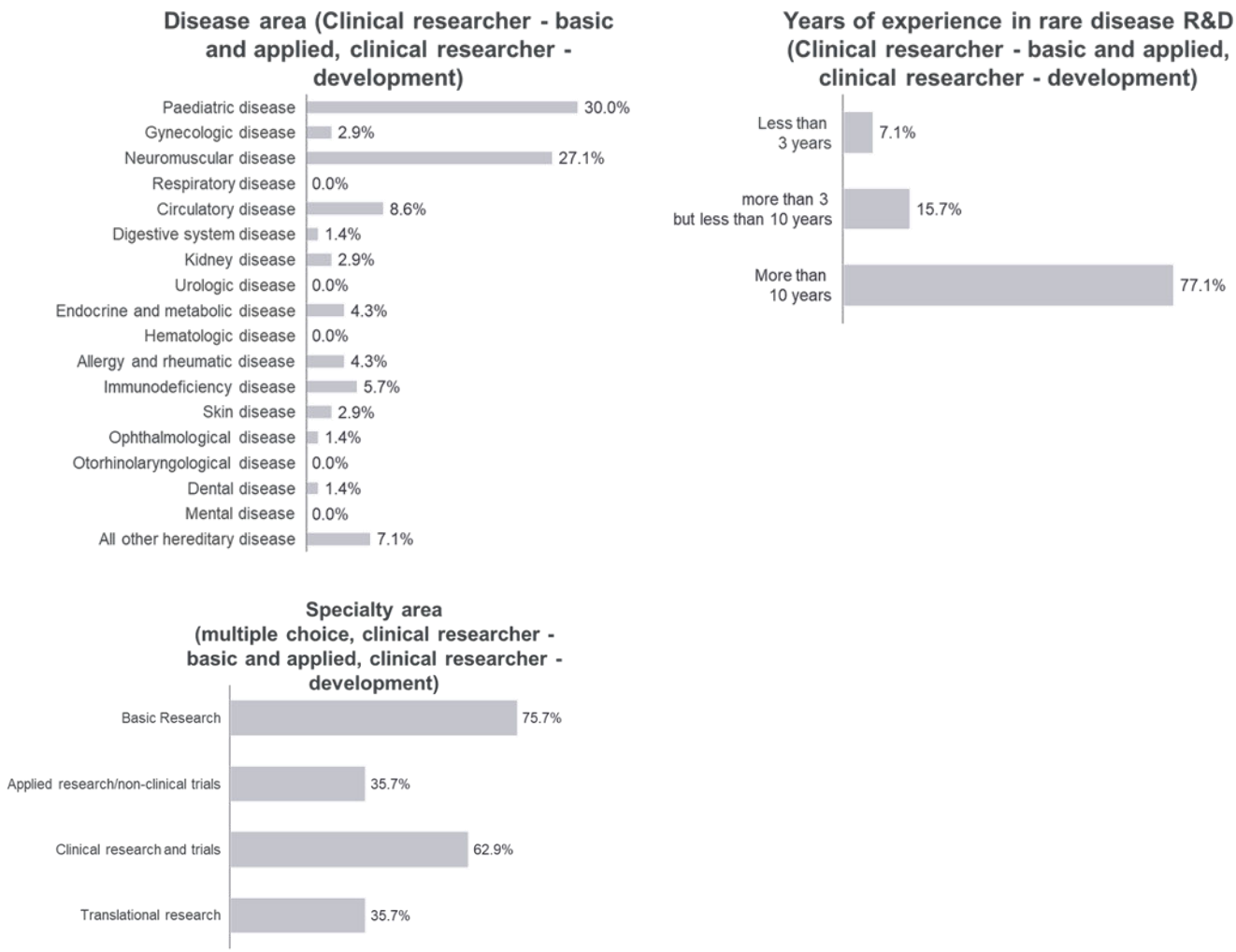
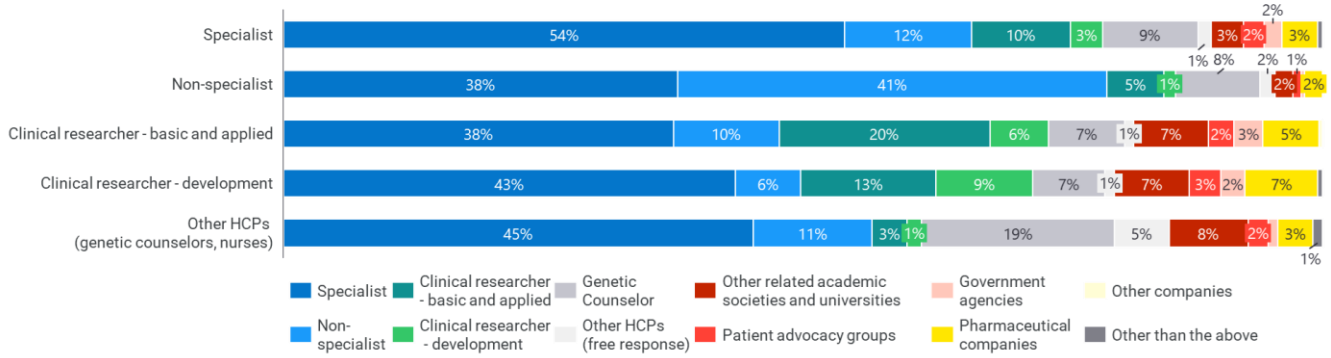


Figure 3-3: Percentage of people with experience of collaboration with other healthcare professionals and stakeholders



■Survey: Web survey
■Question: Regarding your activities related to rare diseases in the past year, have you collaborated with others? Please answer with an integer between 0 and 10 so that the total for the people you collaborated with is 100%.
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Attitude and motivation to participate in activities related to rare diseases

This survey confirmed the attitude and motivation for involvement in activities related to rare diseases (Figure 3-4). Many healthcare professionals place top priority on contributing to patients despite their busy schedules, but at the same time, there are many situations where they have no choice but to participate in activities on a semi-volunteer basis in addition to their daily work, and they are involved in situations without clear rules or incentives.

To improve rare disease medical care, it is necessary to create an environment in which healthcare professionals can continuously focus on activities related to rare diseases and contribute to patients and their families.

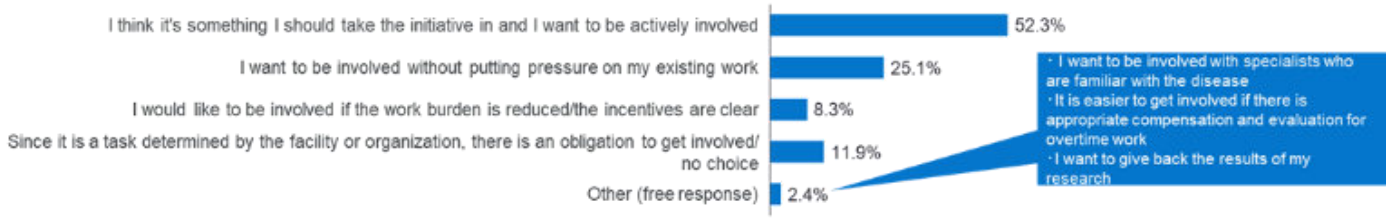
"Research into rare diseases is very labor intensive, and the work is diverse and burdensome. I want to get involved, but the total workload is too much, and I am struggling. If I could get support from my department, I would be able to concentrate more on rare disease activities.
(Specialist / Collagen Disease Department)

"Naturally, I would like to be actively involved, and my motivation is not the pursuit of profit, but the search for a future understanding and solution for rare diseases.
(Clinical researcher (Basic and applied) / Other hereditary diseases)

"In Japanese society, we tend to expect people to do things with good intentions, and there is a trend to expect researchers to donate their time and abilities for free. This will not increase the number of people who join us. Isn't it better to be able to pursue fulfillment based on the premise that people receive compensation for their work?
(Clinical researcher (Basic and applied) / neuromuscular disease)

"Although we feel the need to be proactive in solving patients' problems, we are troubled by the discrepancy between our own motivation and what we are able to do as this puts a strain on our daily work.
(Genetic Counselor / Clinical Genetics)

Figure 3-4: Attitude and motivation towards activities related to rare diseases – Top selection result



■Survey: Web survey
■Question: Please choose the top three that apply to you regarding your attitude and motivation for participating in activities related to rare diseases (ranking format)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

4. Survey results

4.1 The landscape of challenges in rare diseases in Japan

4.1.1 Overall landscape of challenges in rare diseases in Japan

- Across professions, there was a strong sense of challenge in creating an environment for R&D of new modalities, and it was shown that related bottlenecks included budgets / fundraising, human resource development / recruitment and infrastructure development such as manufacturing facilities.
- Lack of awareness and understanding of rare diseases among healthcare professionals, the long time it takes to test and obtain a definitive diagnosis, and the low diagnosis rate remain top challenges unresolved for many healthcare professionals.

The challenges faced by healthcare professionals dealing with rare diseases exist in a variety of areas, from R&D to clinical practice, but the biggest challenge felt across professions is one related to resources (lack of funds, human resources and infrastructure) (Figure 4.1.1-1).

In particular, the top three challenges ranked as, No.1 '1-1 Insufficient R&D environment for new modalities for rare diseases,' No.2 '3-1 Lack of human resources involved in rare diseases / Lack of programs necessary for training,' and No.4 '1-3 Lack of incentives to promote R&D' are all perceived as challenges caused by a lack of budget or human resources. The underlying reasons cited were a lack of budget to hire specialized human resources and difficulties in career development (lack of evaluation and compensation as per workload, high barrier to obtaining specialized qualifications, lack of specialized education and no option to even get on the starting line of a career).

No.3 '2-2 Healthcare professionals have little awareness or understanding of rare diseases,' and No.5 '2-4 It takes time to perform tests and get a definitive diagnosis / diagnosis rate is low,' [a] are challenges that have been pointed out before, but they show the difficulty of solving the problem. Genetic testing in the pediatric field requires faster definitive diagnosis, early medical intervention and securing time for patients' families to face the rare disease leading to greater possibilities for support from Patient Advocacy Groups, so there are high expectations.

Many healthcare professionals chose the challenge as 'because it is directly related to my work and I feel it every day' (Figure 4.1.1-2), which shows that these challenges are evident in practice requiring urgent action.

> *The lack of R&D environment for new modalities is largely due to budget challenges. The government requires high quality control standards (GMP) to be met, but budget required for capital investment is not allocated and policy and reality are at odds. Compared to other countries, major universities in Japan do not have sufficient facilities to meet high quality control standards.*
> (Clinical researcher (development) / Immunodeficiency Disease)

> *Public funding is limited, making it difficult to hire and develop human resources. Compared to other countries where young researchers can move between multiple laboratories and build diverse careers, Japan has a strong hierarchical mindset, resulting in little mobility of human resources.*
> (Specialist / Pediatrics)

> *It takes about 1.5 years to make a definitive diagnosis, and the accuracy is only about 50%. Because the disease has a large and irreversible impact on pediatric patients, a diagnosis not only enables early treatment, but also allows parents to spend time dealing with the child's environment and to receive peer support[7], which contributes greatly to the child's subsequent personality development and growth. There is a need to improve the speed and accuracy of testing and diagnosis.*
> (Specialist / Pediatrics)

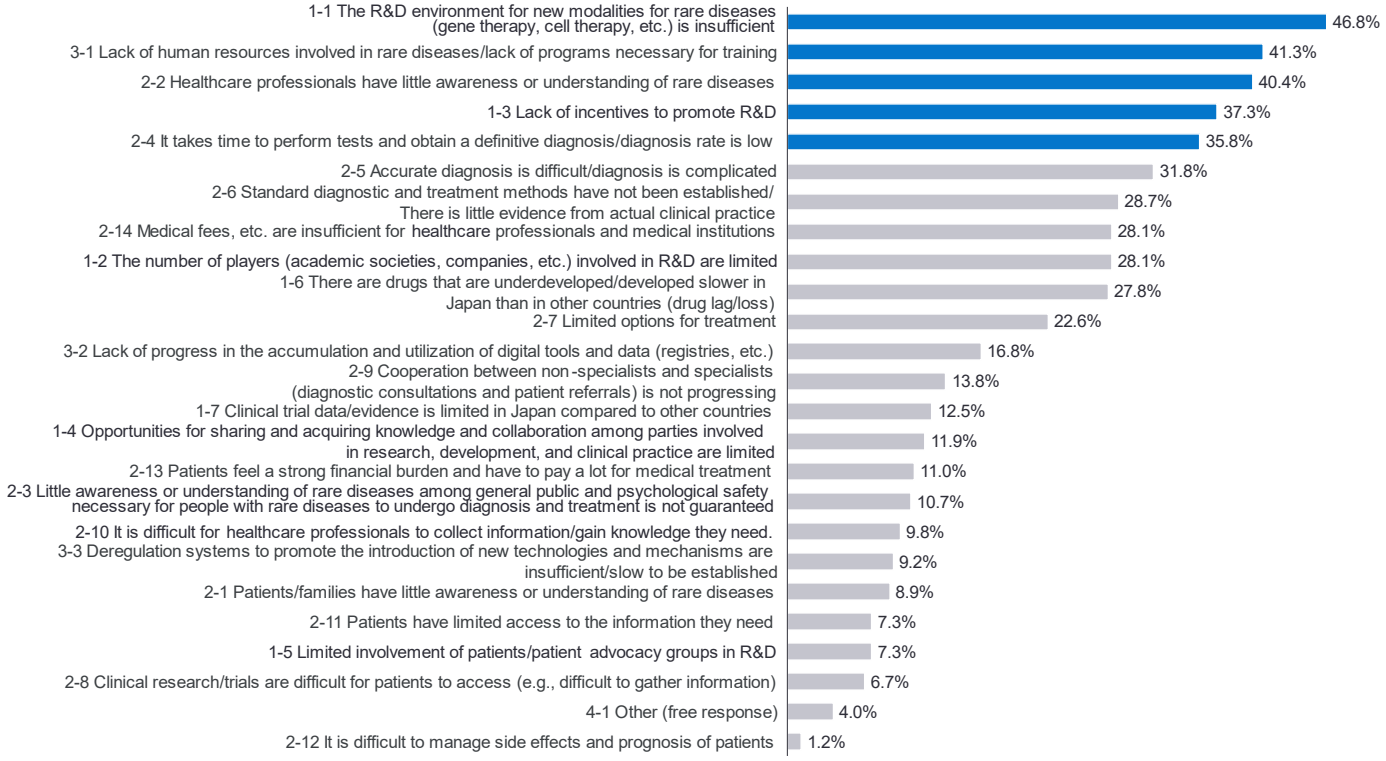
> *Many genetic analysis and counseling services are not covered by insurance, making it difficult for medical institutions to make a profit. There is a shortage of people to carry out these tasks because there is no appropriate compensation (evaluation or remuneration) for the time spent. There are few opportunities for young people to*

[7] Peers with similar experiences of illness or disability provide practical support to each other

learn the practical aspects and rewards of working with patients over a long span of time (10 to 20 years).

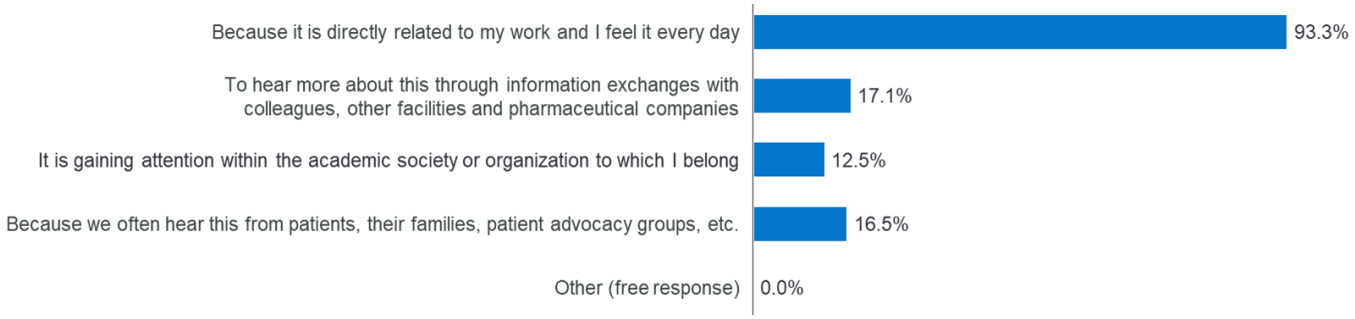
(Clinical researcher (development) / Endocrinology and Metabolic Disease)

Figure 4.1.1: Overview of the challenges facing rare diseases in Japan



■Survey: Web survey
■Question: What are the most pressing challenges regarding rare diseases in Japan? (Select 5)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.1-2: Overview of the challenges facing rare diseases in Japan – reasons for selection



■Survey: Web survey
■Question: Please answer the reason (multiple choices possible)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Overall picture of perceived challenges: by occupation

In terms of perceived challenges by occupation (Figure 4.1.1-3), '1-1 Insufficient R&D environment for new modalities for rare diseases' was chosen as the number one challenge not only by clinical researchers (basic and

applied) and clinical researchers (development) directly involved in R&D, but also by specialists, indicating that acceleration of drug discovery is required in actual clinical practice.

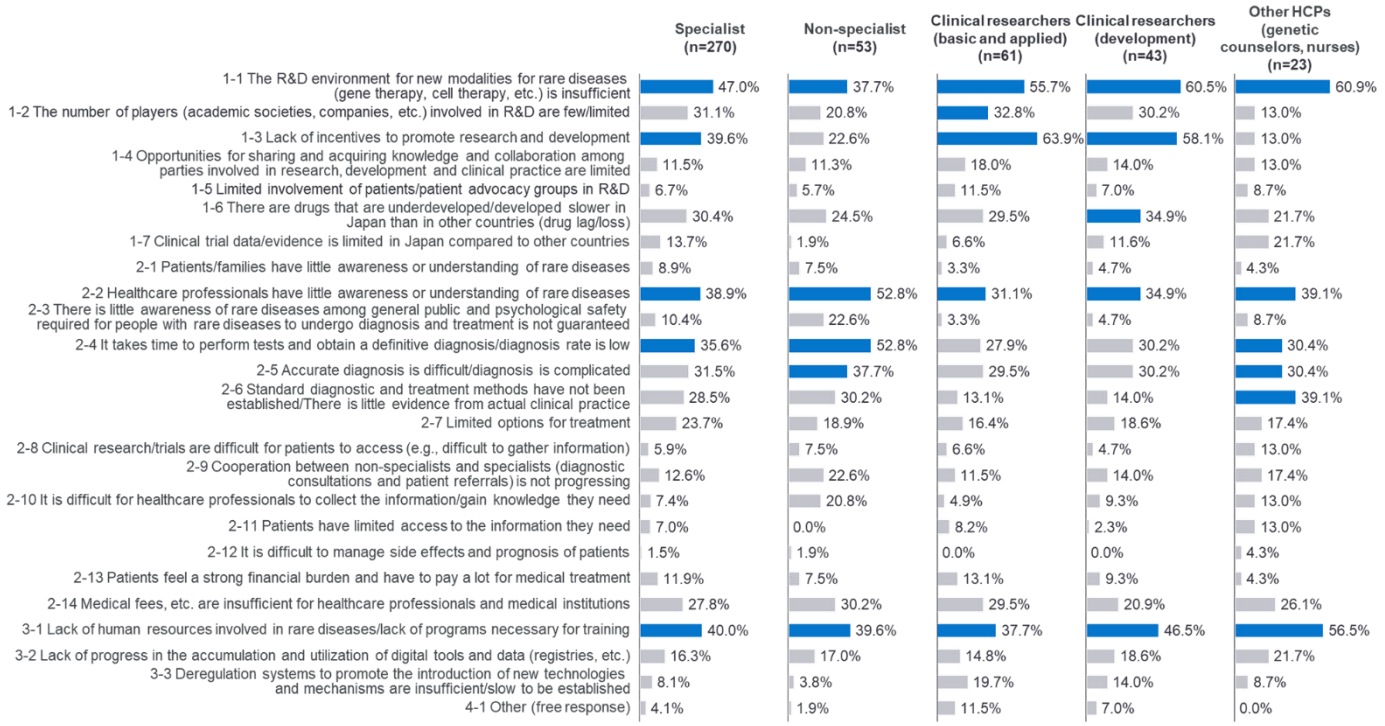
Among non-specialists, '2-2 Healthcare professionals have little awareness or understanding of rare diseases' ranked higher than other professions, indicating a lack of knowledge and experience.

The top challenges that clinical researchers (basic and applied) felt were '1-3 Lack of incentives to promote R&D' and '1-2 The number of players (academic societies, companies, etc.) involved in R&D are few/limited.'

Among clinical researchers (development), '1-6 There are drugs that have not been developed / are slow to be developed in Japan compared to overseas (drug lag / loss, etc.)' ranked high compared to other professions, indicating that drug lag / loss is recognized by physicians involved in clinical trials of rare diseases.

Other HCPs (genetic counselors and nurses) were aware of challenges from patient's perspective, such as '2-4 It takes time to perform tests and get a definitive diagnosis / diagnosis rate is low,' '2-5 Accurate diagnosis is difficult / diagnosis is complicated,' and '2-6 Standard diagnostic and treatment methods have not been established / there is little evidence in actual clinical practice.' In addition, just like specialists, '3-1 Lack of human resources involved in rare diseases / Lack of programs necessary for training' ranked second, strongly suggesting a shortage of specialized personnel in actual clinical practice.

Figure 4.1.1-3: Overview of the challenges facing rare diseases in Japan – by occupation



■Survey: Web survey
■Question: Please answer the most important challenge you feel is related to rare diseases in Japan (choose 5, multiple choice)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Overall picture of challenges: by medical department and by disease research area

Comparing the answers by medical department, which had particularly high numbers of responses in actual clinical practice (Figure 4.1.1-4), the top answers commonly included '1-1 Insufficient R&D environment for new modalities for rare diseases (gene therapy, cell therapy, etc.),' '1-3 Lack of incentives to promote R&D,' and '3-1 Lack of human resources involved in rare diseases / Lack of programs necessary for training,' which matched the trends in the answers across all occupations. Since the proportion of healthcare professionals in pediatrics, neurology, and department of clinical genetics and gene therapy was high in this quantitative survey, it

is assumed that many opinions are related to challenges in these medical departments.

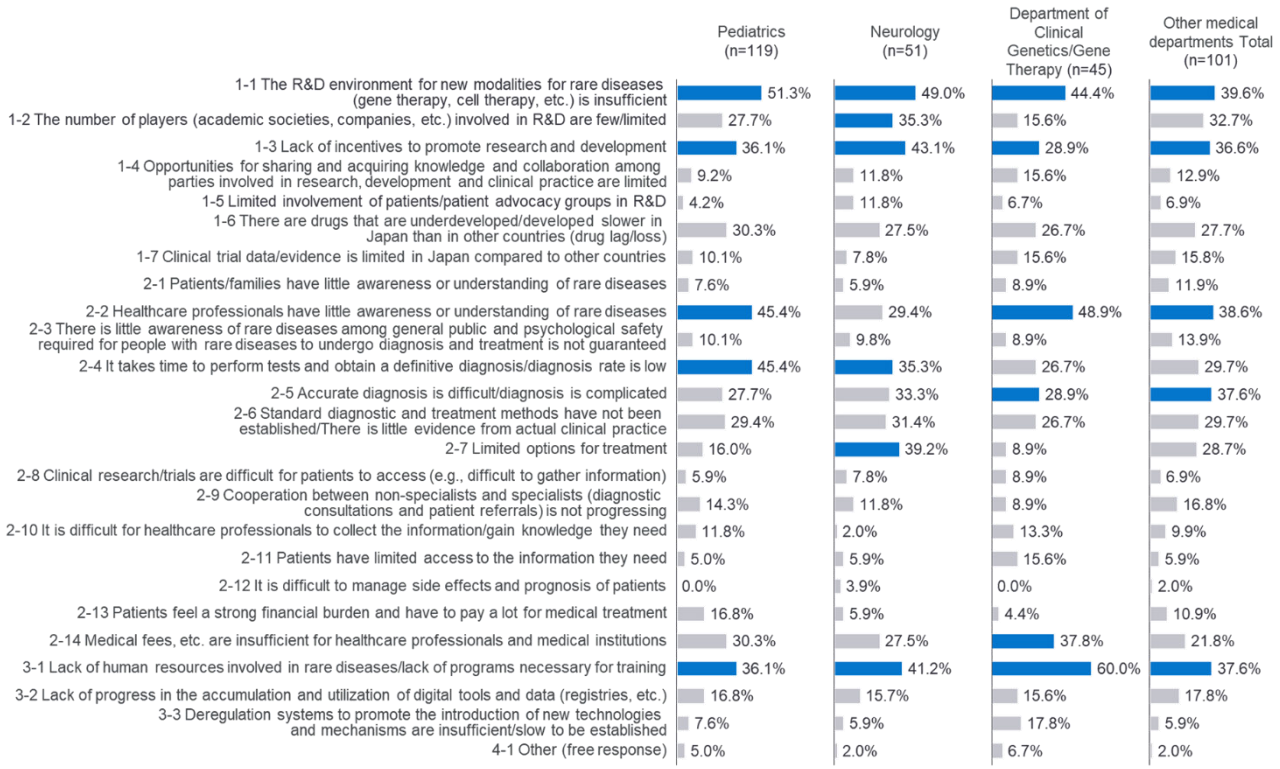
In pediatrics, ‘2-4 It takes time to perform tests and get a definitive diagnosis / diagnosis rate is low’ was ranked second highest compared to other medical departments, which is a major challenge. This is presumably because, as mentioned above, early intervention can lead to improved prognosis in children, and time is particularly important for parents to face their child's illness.

On the other hand, even in areas such as neuromuscular disease where there is a certain level of awareness (accounting for approximately 25% of the 341 designated intractable diseases) [g], ‘1-2 The number of players (academic societies, companies, etc.) involved in R&D are few/limited’ is ranked among the top challenges, which may indicate that the challenges will become more apparent as efforts are made.

Additionally, in department of clinical genetics and gene therapy, the answers chosen were ‘2-14 Medical fees are insufficient for healthcare professionals and medical institutions’ and ‘3-1 Lack of human resources involved in rare diseases / Lack of programs necessary for training.’ In medical institutions with clinical genetics, functions are divided such that when the main department is not decided, another department will treat the patient alone, which is likely to result in shortage of personnel with entire burden on few people. This shows that many healthcare professionals feel that they are not being compensated appropriately.

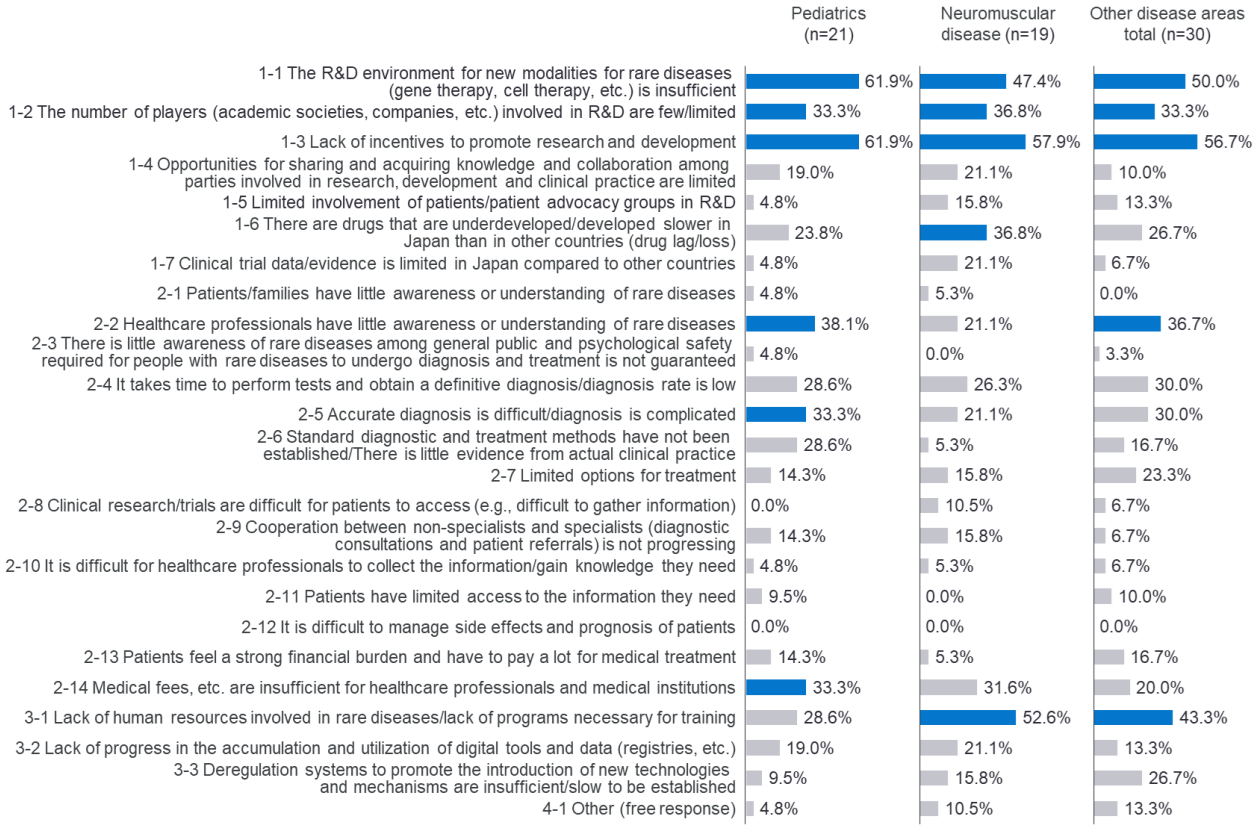
The results by disease research area (Figure 4.1.1-5) also show a similar trend in the top-ranked challenges. In neuromuscular disease, where practical application has progressed relatively well in Japan, the challenge of ‘3-1 Lack of human resources involved in rare diseases / Lack of programs necessary for training’ was ranked high. However, it is necessary to dig deeper into the unique challenges of each disease area.

Figure 4.1.1-4: Overview of the challenges facing rare diseases in Japan – by medical department



■Survey: Web survey
■Question: Please answer the question about the most pressing challenges surrounding rare diseases in Japan (choose 5, multiple choice)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)
*Medical departments with 15 or more respondents selected

Figure 4.1.1 5: Overview of the challenges facing rare diseases in Japan – by disease research area



■Survey: Web survey
■Question: Please answer the question about the most pressing challenges surrounding rare diseases in Japan (choose 5, multiple choice)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)
*Research areas with 15 or more respondents were selected

Overall picture of challenges: by region

Comparing challenges felt by healthcare professionals in Tokyo metropolitan area and outside (Figure 4.1.1-6), in Tokyo, "2-14 Medical fees are insufficient for healthcare professionals and medical institutions," ranked high, while in areas outside Tokyo it was, "2-2 Healthcare professionals have little awareness or understanding of rare diseases." Since Tokyo has a high concentration of medical institutions, including those in other specialties, it may be because healthcare professionals are not receiving appropriate compensation for activities related to rare diseases. It may also be because outside Tokyo, there is even less awareness and understanding of rare diseases, or a shortage of human resources.

Another challenge that was pointed out in comparison to urban and rural areas was the uneven distribution of human resources. The reasons cited for the lack of genetic counselors and specialist staff resources in rural areas compared to urban areas were the lack of role models and fewer educational opportunities. There is also room for improvement in awareness of activities related to rare diseases, such as a lack of awareness of the existence of nationwide initiatives.

In addition, even in urban areas, the information necessary for building networks between medical institutions and making referrals may not be made public, which could lead to delays in patient referrals. This gives us a glimpse into the status in which medical institutions and doctors have differing opinions about the information necessary for patient referrals and the standards for their use.

On the other hand, some have pointed out that a system should be promoted that allows for centralized medical care to be provided in response to geographical disparities. There are opinions stating that not only in urban areas but also in rural areas, functions are not centralized, shared, or networked within medical domain, which ultimately increases the burden on patients until definitive diagnosis. There is also opinion that the dispersion of cases reduces the efficiency of human resource development and accuracy of diagnoses, resulting in a vicious cycle of declining diagnosis rates.

The treatment of rare diseases requires specialized expertise, and there are few human resources involved.

The networks between medical institutions are not systematized but personalized, which may ultimately strain the medical systems and prolong the time it takes for patients to receive a definitive diagnosis.

> *In the process of acquiring a subspecialty, there is no option to consider a career in genetic medicine. Even if people are interested and try to do so, there are limited opportunities to experience training in rural areas. Even if the need for specialist staff is understood, there are no actual role models, so even young people are excluded from career goals. There are also regions where nationwide initiatives such as IRUD have not taken root.*
> (Specialist / Pediatrics)

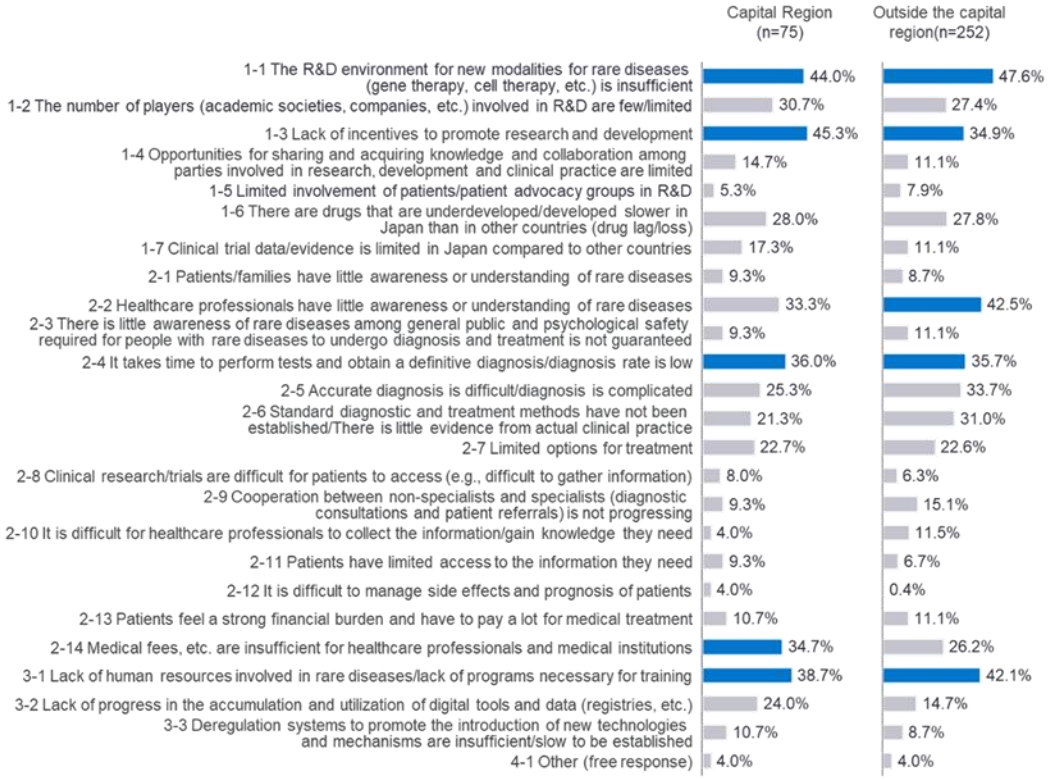
> *In urban areas, there are too many options and it is difficult to decide which hospital to refer patients to. In most cases, the test results of other medical institutions are not made public, so it is difficult to trust them with patients. Even large hospitals may not have genetic specialists, so doctors are hesitant to refer patients to a specialist unless they know the doctor.*
> (Non-specialist / Neurology)

> *As telemedicine advances in the future, geographical constraints will likely disappear and consolidation between medical institutions will likely progress.*
> (Clinical researcher (basic and applied) / Pediatrics)

> *University hospitals are concentrated in urban areas, but functions are not consolidated, and doctors do not necessarily know each other, so patients are unable to consult appropriately even when they suspect they have an illness, which can result in them being passed around from one hospital to another.*
> (Clinical researcher (basic and applied) / Pediatrics)

> *In rural areas, the number of cases is limited because there is no system for centralized examinations, which results in a vicious cycle of difficulty in training personnel or a lower diagnosis rate because inexperienced doctors examine patients. Japan has many small hospitals, so centralization is not possible. Access may be good for patients, but from the perspective of rare disease treatment, having physically scattered bases is not necessarily suitable.*
> (Clinical researcher (development) / Immunodeficiency Disease)

Figure 4.1.1-6: Overview of rare disease challenges in Japan – by region



■Survey: Web survey
■Question: Please answer the most important challenge you feel is related to rare diseases in Japan (choose 5, multiple choice)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

4.1.2 Challenges in research and development

- Given the limited treatment options for rare diseases, there are high expectations for the acceleration of drug discovery using new modalities. However, delays in the development and utilization of resources (budget, human resources, data, samples) necessary for promoting R&D, as well as the difficulty of conducting integrated, cross-disciplinary R&D with an eye toward an exit strategy, have been highlighted.
- Identifying therapeutic targets and improving drug delivery technologies are essential in basic and applied research, but there is a strong demand for the utilization of clinical specimen and registry data, which are necessary to accelerate research, and for the development of an attractive research environment for the specialized personnel who can utilize these data.
- In terms of development and clinical trials, the current pharmaceutical affairs and drug pricing system is not attractive to pharmaceutical companies, leading to drug lag and loss in Japan and access to development and clinical trial information has been pointed out as challenges. There is growing need to ensure the sustainability of development, clinical trials and to organize and utilize information.

Current state of research and development: Expectations for progress in research and development

When asked about their expectations for progress in research and development regarding rare diseases in their area of expertise, nearly 40% of healthcare professionals responded that it is difficult to expect any progress at the moment, and the same proportion responded that they do have any expectations (Figure 4.1.2-1).

The reasons given for disease areas where there is hope are that information on new drugs under development provides a prospect for treatment, that drugs that act on causative genes have been developed, and that causes and countermeasures can be explained to patients. On the other hand, the reasons given for disease areas where there is no hope are that the causative genes have not been clarified and that there is room for technical improvement in terms of the introduction efficiency and side effects of gene therapy. Another challenge specific to rare diseases was the difficulty of collecting clinical trial data.

In terms of responses by occupation (Figure 4.1.2-2A), specialists, non-specialists, and other HCPs (genetic counselors and nurses) involved in clinical practice answered that it was "difficult to expect anything at this time" or "don't know," while clinical researchers (basic and applied), clinical researchers (development) involved in R&D answered that they "can expect something after four years." There were also comments that there is a lack of information about the progress of R&D in clinical practice, and it is possible that the difference in expectations is reflected in the difference in information exposed in R&D and clinical practice. Overall, 20% of healthcare professionals answered as "don't know," suggesting that information about pharmaceuticals under development may not be reaching them sufficiently, leading to a lack of recognition and understanding.

On the other hand, in the responses by medical department (Figure 4.1.2-2B), healthcare professionals in neurology (specialists, non-specialists, and other HCPs) most frequently chose "expected after 4 years" (45.7%), showing a different trend from the overall trend. Expectations may be higher in the field of neurology, where practical application has progressed relatively well in Japan.

It was shown that these responses stem from what healthcare professionals experience in their daily work (Figure 4.1.2-3).

“Identifying the target gene and improving the efficiency of gene transfer are key, and this requires the evolution of basic research. It is necessary to reduce side effects and improve the technology to a level that can be used in clinical practice.
(Specialist / Collagen Disease Department)

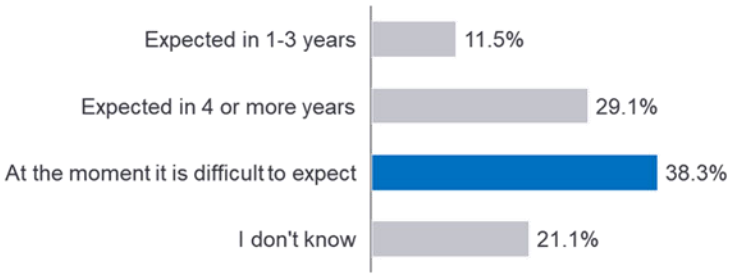
“If the number of patients is small, it is difficult to collect data for large-scale clinical trials, etc. If the number of patients is small, it is difficult to put a study into clinical practice.
(Non-specialist / Neurology)

“Regarding genetic diseases, the development of nucleic acid medicine and other technologies is promising. Identifying the causes of the disease and countermeasures and creating a story of diagnosis and treatment is also important in bringing hope to patients.
(Clinical researcher (development) / neuromuscular disease)

“Knowing the progress of research and development gives patients hope for their lives. There is often a lack of information about what research is being executed and where, so I would like to see research progress made visible and information made available to patients in a timely manner and in an easy-to-understand manner via websites, etc.
(Genetic Counselor / Clinical Genetics)

“It is necessary to create a community to develop human resources involved in rare diseases and the academic societies in charge should take the lead in creating the community. In addition, I have participated in a study group organized by a pharmaceutical company in the past, which led to a collaborative research project, and I feel that pharmaceutical companies have a large role to play.
(Specialist / Collagen Disease Department)

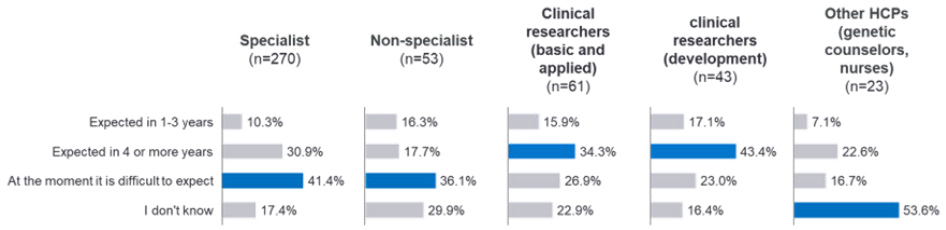
Figure 4.1.2-1: Expectations for progress in R&D leading to fundamental treatments for rare diseases



■Survey: Web survey
■Question: Please answer the question about the rare disease you answered in Q13 (Please answer the main rare disease names among your activities related to rare diseases in the past year (up to 5 names allowed)). Do you expect progress in research and development that will lead to a fundamental treatment for the rare disease?
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

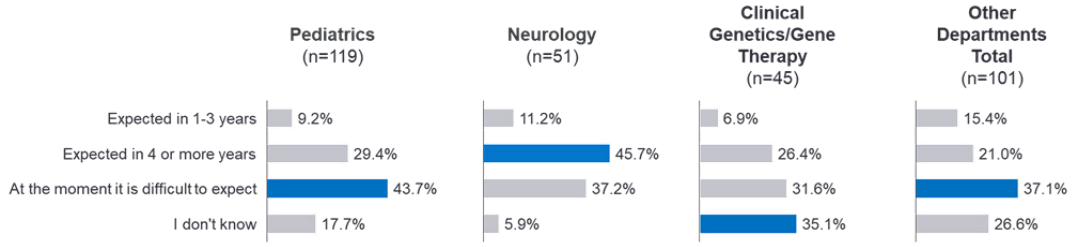
Figure 4.1.2-2: Expectations for progress in R&D leading to fundamental treatment of rare diseases
- A by occupation type / B by medical department

A



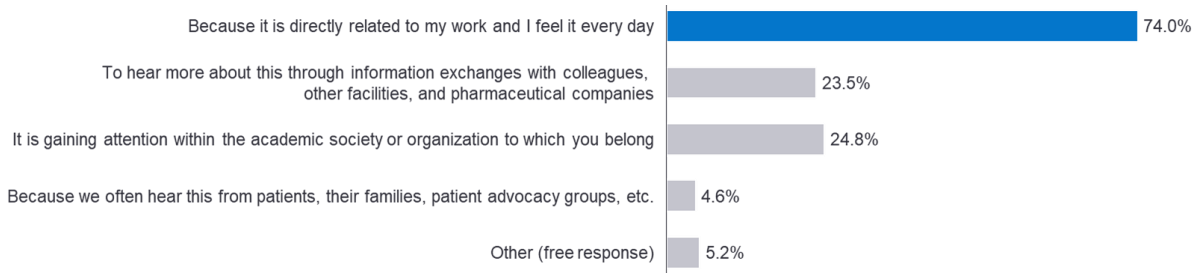
■Survey: Web survey
■Question: Please answer the question about the rare disease you answered in Q13. Do you expect progress in R&D leading to a fundamental treatment for the rare disease? (Q13: Please answer the name of the main rare disease among your activities related to rare diseases in the past year (up to 5 answers possible)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

B



■Survey: Web survey
■Question: Please answer the question about the rare disease you answered in Q13. Do you expect progress in R&D leading to a fundamental treatment for the rare disease? (Q13: Please answer the name of the main rare disease among your activities related to rare diseases in the past year (up to 5 answers possible)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.2-3: Expectations for progress in R&D leading to fundamental treatments for rare diseases – reasons



■Survey: Web survey
■Question: Please answer the reason (multiple choices possible)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Challenges in basic and applied research

In the quantitative survey results (Figure 4.1.2-4~7), challenges related to a lack of funds, players, human resources and bases were ranked high across all occupations, specialties and disease areas, including '3-6 Limited means of raising research funds / Low allocation / Lack of flexibility in use (difficulty in recruiting students and researchers, etc.).' The background to these challenges includes the difficulty of hiring young people and building their careers, lack of collaboration between organizations as well as the importance of disseminating success stories related to rare disease research and increasing the number of researchers by spreading awareness of the appeal of research.

In basic and applied research, there is a need to identify target genes and accelerate gene transfer technology. However, it was pointed out that differences in research progress arise due to the difficulty of identifying research areas with an eye toward exit strategies, a lack of collaboration with companies, difficulties in obtaining clinical samples due to rare diseases and challenges with collaboration between organizations and securing human resources.

In addition, limited collaboration between research organizations resulted in a lack of sharing of knowledge and slower research progress. Furthermore, it was pointed out that society's intolerance of risks and challenges may be hindering bold research and its implementation in society.

In this section, by summarizing the relationship between the sense of challenges raised in the qualitative and quantitative surveys (Figure 4.1.2-8), we can see that the status in which progress in basic research necessary for the development of new treatments and medicines is delayed is due to multiple challenges. The absence of an exit strategy and the complexity of regulations and rules regarding R&D suggest that the unique characteristics of rare diseases are not taken into consideration, and that a necessary collaborative system and the development of specialized human resources to promote this are necessary.

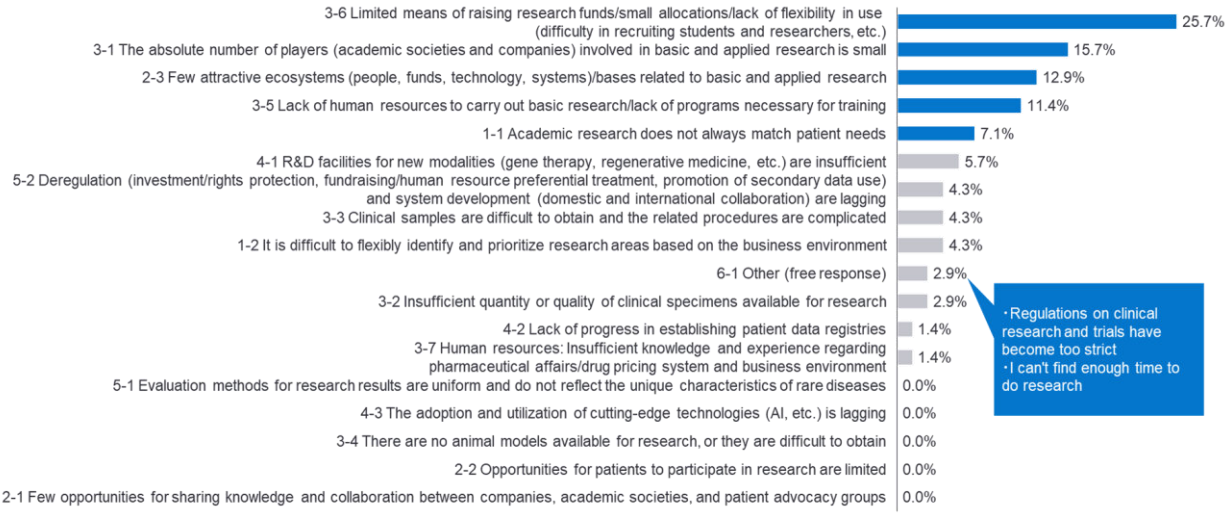
> *In Europe and the United States, funding sources for research are broad and diverse, and beneficiaries of research results, such as Patient Advocacy Groups, actively provide funds. Goals are clear to advance research that meets patients' needs.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

> *Young researchers need an opportunity to become aware of and understand rare diseases, and at the same time, the government needs a budget to secure employment for young researchers. By creating success stories and spreading awareness of the appeal of rare disease activities, a virtuous cycle of training and employment may be created.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

> *Similar efforts are underway in various places, but knowledge is not being shared or coordinated. To accelerate research, it is necessary to create a network that goes beyond peer groups.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

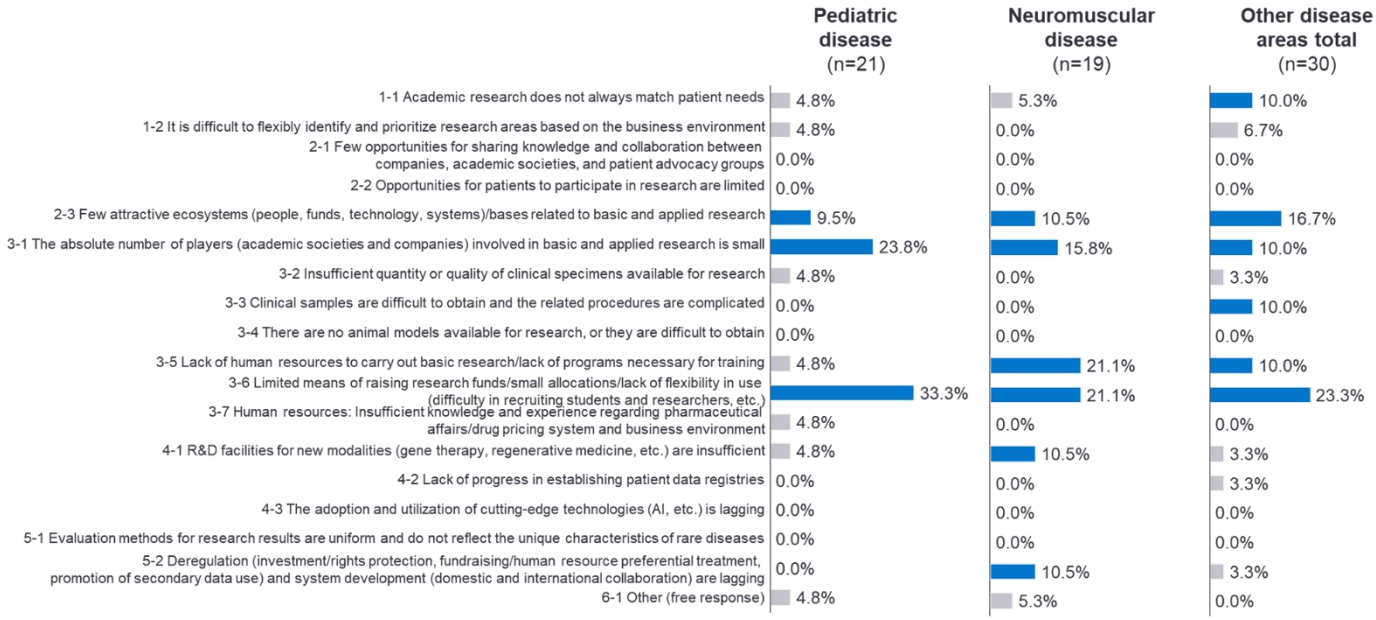
> *In Japan, social consensus takes priority when it comes to the social implementation of research and development, and there is insufficient discussion of "what should be prioritized for the patient in front of us." There is a strong tendency to be intolerant of risks and challenges, and a system should be established that allows patients and their families to receive exceptional technology and assistance if they can tolerate the risks.*
> (Clinical researcher (basic and applied) / General hereditary disease)

Figure 4.1.2-4: Challenges in basic and applied research – Top selection results



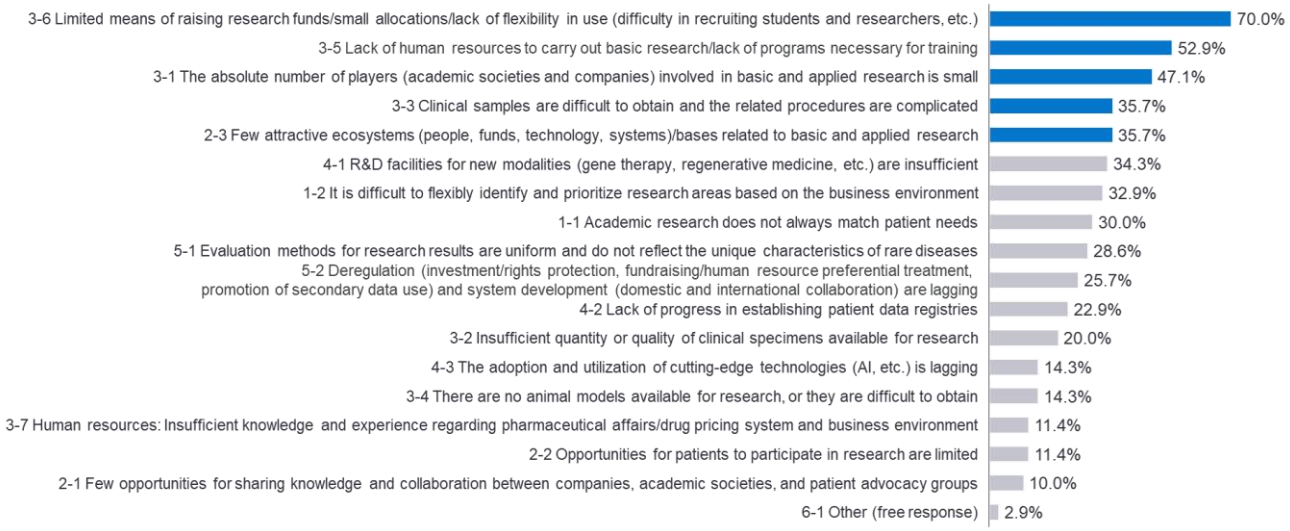
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-5: Challenges in basic and applied research – Top selection results by disease area



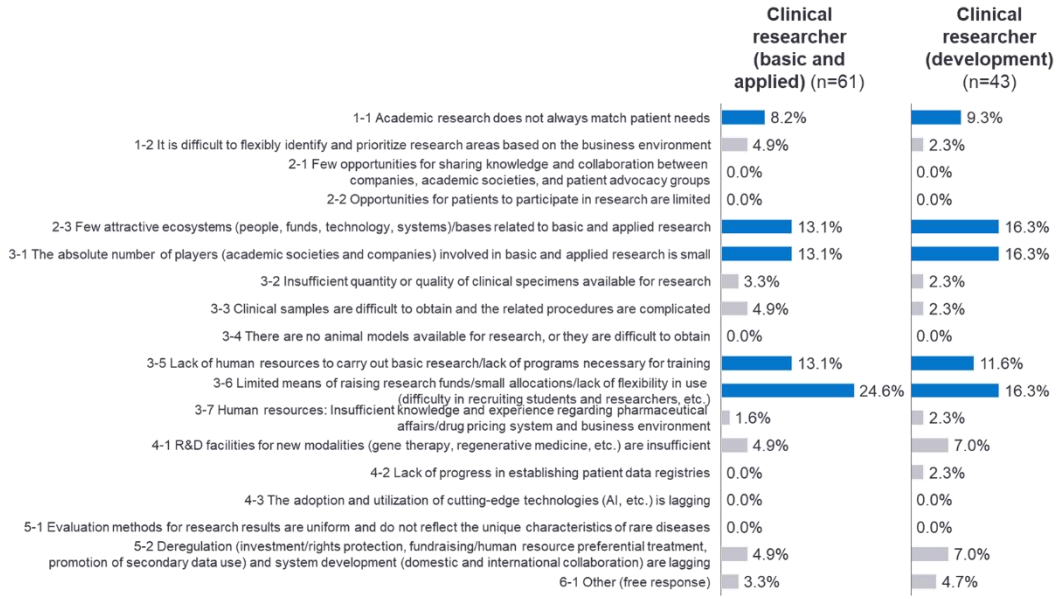
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-6: Challenges in basic and applied research – Top 5 selection results



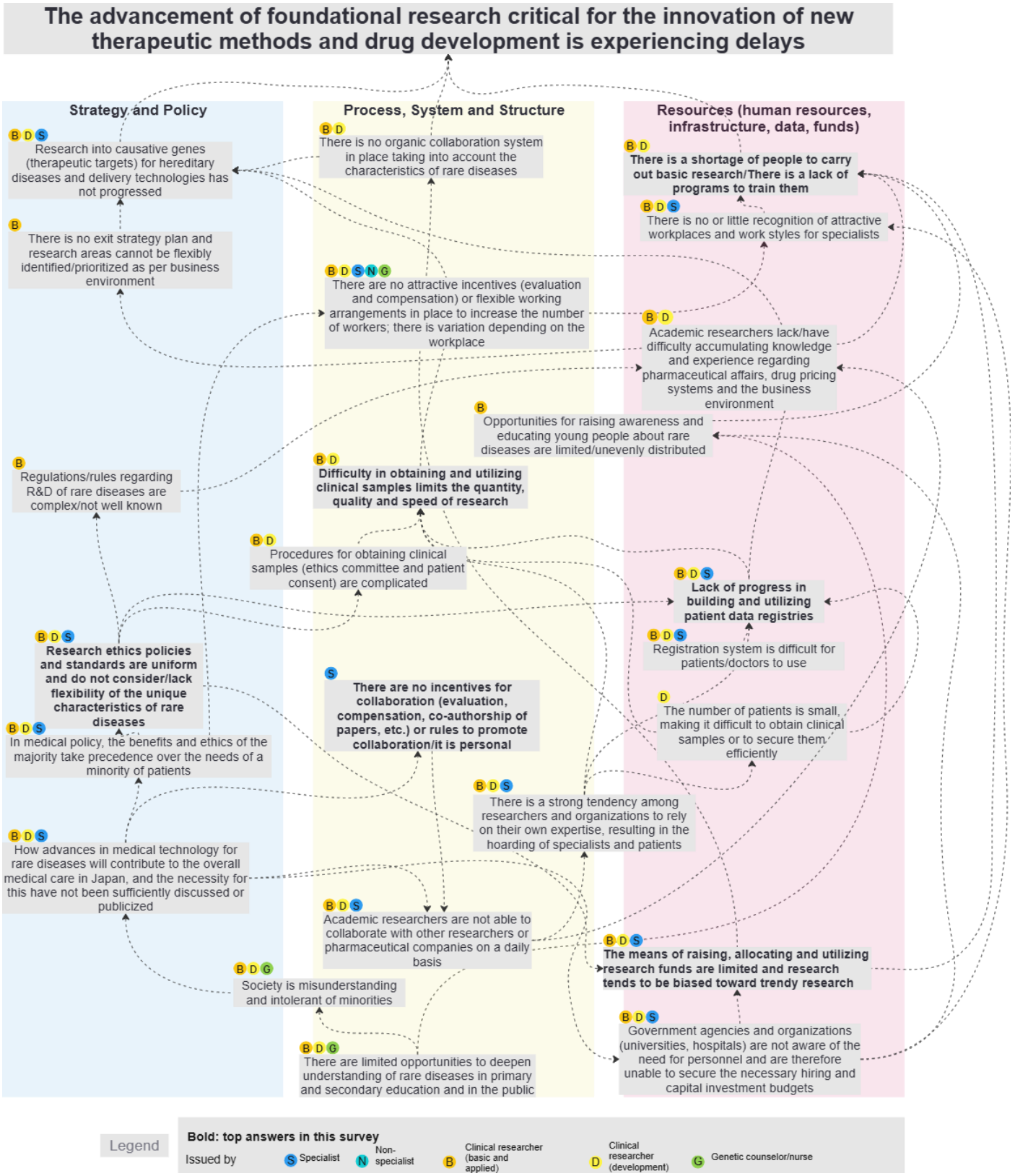
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-7: Challenges in basic and applied research – Top 5 selection results by occupation



■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-8: Overall landscape of challenges in basic and applied research



Challenges in development and clinical trials

In terms of perceived challenges in development and clinical trials, in addition to fundraising and human resource development, the top three challenges cited were delays in establishing a development environment for new modalities and drug lag / loss compared to overseas (Figure 4.1.2-9).

As pointed out in the section on basic and applied research, when choosing a career in rare diseases, it is essential to have a career image and training / employment environment that will serve as an attractive role model for researchers, in addition to a sense of fulfillment and fair compensation (evaluation and remuneration). This is supported by the fact that clinical researchers (development) ranked the lack of attractive ecosystems (people, funds, technology, systems) and bases involved in development among the top answers in the response category (Figure 4.1.2-10).

The reasons cited for drug lag loss include the difficulty for pharmaceutical companies in recouping their investments in R&D in the Japanese market, the small number of bases for overseas companies, and the fact that information about the development environment in Japan is not / cannot be communicated. It was also found that healthcare professionals involved in development and clinical trials place great importance on how to create a sustainable development environment for companies.

Another challenge that was cited as a top challenge was the difficulty of recruiting subjects for clinical trials due to the small number of subjects for rare diseases (Figure 4.1.2-11). The background to this was pointed out to be that stakeholders who should be aware of the opportunities and necessities involved in development and clinical trials are unable to access the necessary information accurately, easily and quickly.

In addition, one of the points to be considered in the future was that there has been insufficient discussion on the balance between efficacy and safety in the development of diagnostic drugs / pharmaceuticals for rare diseases, and the urgency of rare diseases has not been considered. Considering the situation where the minority opinions of rare disease patients are not necessarily reflected and are left behind, and healthcare professionals involved in research and development are caught in the middle, the need for discussion on how to establish a system that considers the characteristics of rare diseases was pointed out (4.1.2-12).

> *We are struggling with the fact that relying solely on universities for development funding is insufficient. We hope for funding from the private sector, but we also need to create a system that will allow us to build up our own track record.*
> (Clinical researcher (development) / Endocrinology and Metabolic Disease)

> *Pharmaceutical companies see the Japanese market as lacking a system that allows them to recoup their investments. It is only natural that companies will not be able to develop new drugs unless they create a system that allows them to commercialize their products. In addition, the number of overseas pharmaceutical companies and ventures with bases and networks in Japan is decreasing, and it is unclear where in Japan they can provide information on new drug approvals from overseas and who they can connect with to have concrete discussions about development in Japan.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

> *Because rare diseases affect only a small number of patients, there is little economic incentive for pharmaceutical companies, and the low motivation of industry is a clear barrier.*
> (Clinical researcher (basic and applied) / Endocrinology and Metabolic Disease)

> *Overseas companies and bio ventures consider the attractiveness of the Japanese market and the development environment when deciding whether to conduct clinical trials, but they are hesitant to enter the Japanese market because the status in Japan is not properly communicated.*
> (Specialist / Pediatrics)

> *Compared to other countries, the uptake of diagnostic drugs and medicines is lagging, and we hope to see further acceleration of swift and flexible procedures that consider the characteristics of rare diseases, which require high urgency. We need to work on schemes and ease procedures that allow for the smooth uptake of new*

technologies and treatments once certain procedures have been completed, based on the premise that rare diseases are more urgent than other diseases. The government should take the lead, but we also hope to see active lobbying of pharmaceutical companies.
(Clinical researcher (development) / Immunodeficiency disease)

"The development of new modalities for drugs for rare diseases has not progressed, and even if a diagnosis is made, there is no solution that can be proposed to patients. We have no choice but to limit ourselves to symptomatic treatment, which is very frustrating.
(Clinical researcher (development) / General hereditary disease)

"There are limited incentives for development researchers. A virtuous cycle has not been created in which researchers can gain a sense of fulfillment and income, which in turn leads to active research and ultimately produces people who are motivated to succeed. It is necessary to create high-quality educational programs, but it is also important to consider whether young researchers can embody the ideal they truly aspire to by pursuing such a career.
(Clinical researcher (development) / Immunodeficiency disease)

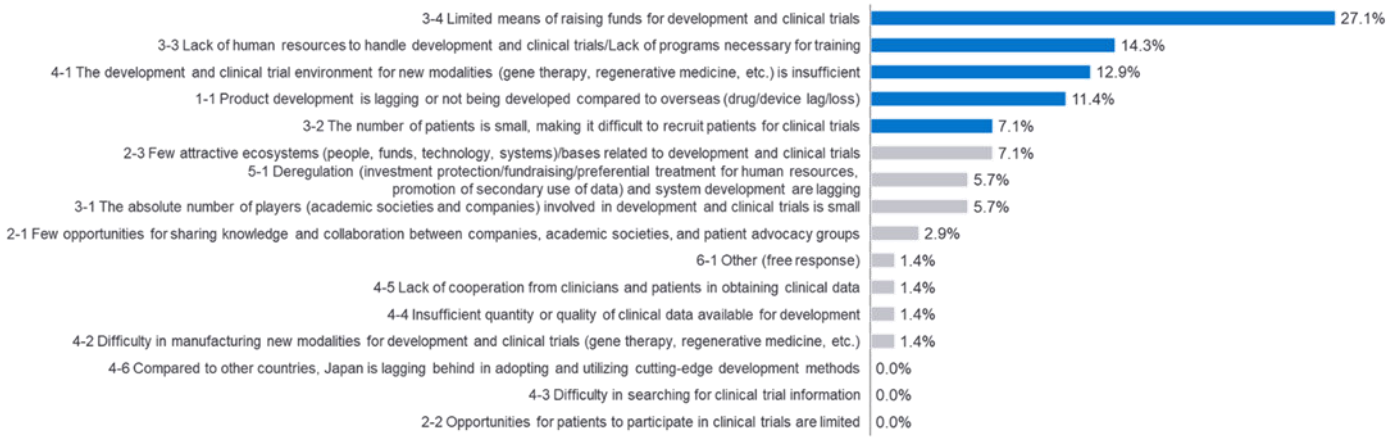
"Working efficiently within a pre-determined framework has become the goal, and fewer young doctors feel motivated to work closely with patients for a long time, such as in the treatment of rare diseases. On the other hand, the burden on those who take on this role is heavy, so the way in which doctors are trained should also be reviewed.
(Clinical researcher (development) / neuromuscular disease)

"It is extremely difficult to recruit subjects who meet the conditions. One of the reasons is insufficient awareness among subjects, hence if clinical trial information were managed centrally and it were easy to identify clinical trial information that meets the conditions, it may be convenient for both healthcare professionals and subjects. In addition, it is desirable to accelerate participation in international joint clinical trials as it is often difficult to recruit subjects even if a drug that has already been approved in the US or EU and is later approved in Japan.
(Specialist / Pediatrics)

"The effectiveness of pharmaceuticals is not properly evaluated. Due to the conservative national character compared to other countries, there are cases where there is insufficient discussion on the balance between efficacy and safety, considering the urgency of rare diseases, resulting in complicated development procedures that slow down the process.
(Clinical researcher (development) / Immunodeficiency disease)

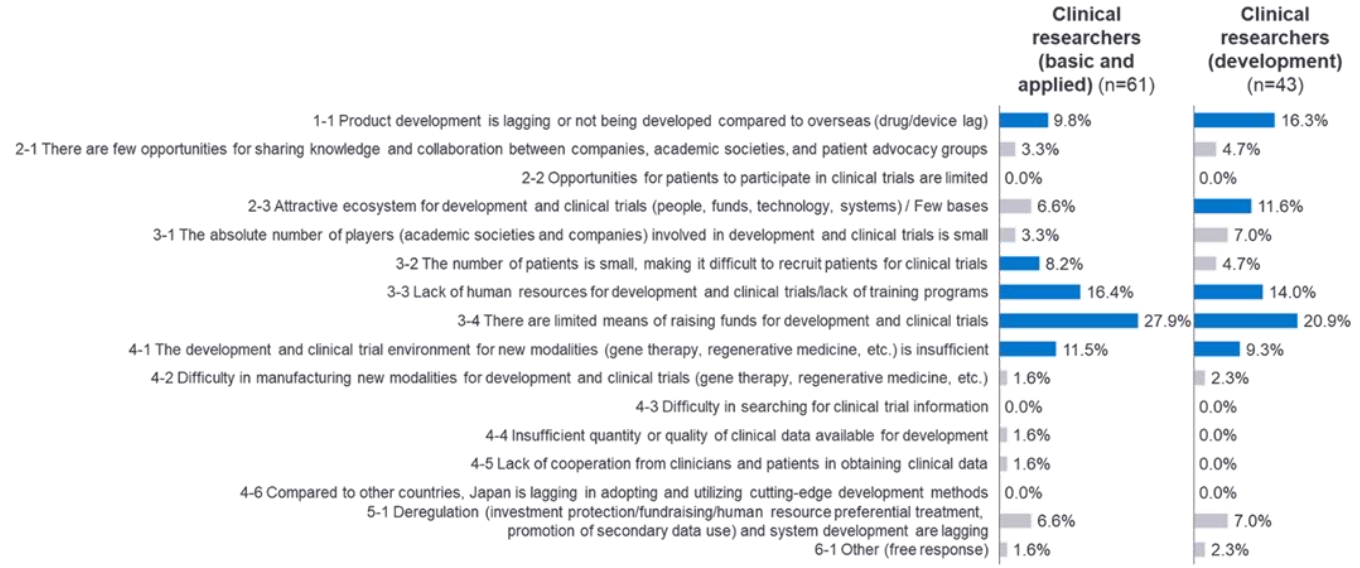
"Development involves risks, and when social responsibility arises, standards should be set by the government rather than being left to researchers.
(Clinical researcher (basic and applied) / Pediatrics)

Figure 4.1.2-9: Challenges in development and clinical trials – Top selection results



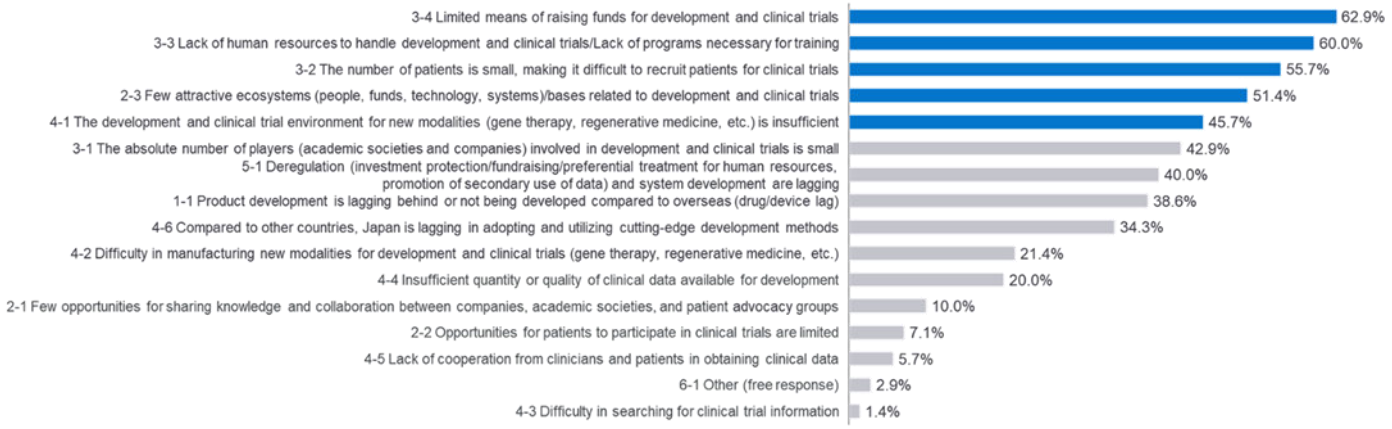
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most challenging regarding development and clinical trials (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-10: Challenges in development and clinical trials – Top selection results by occupation



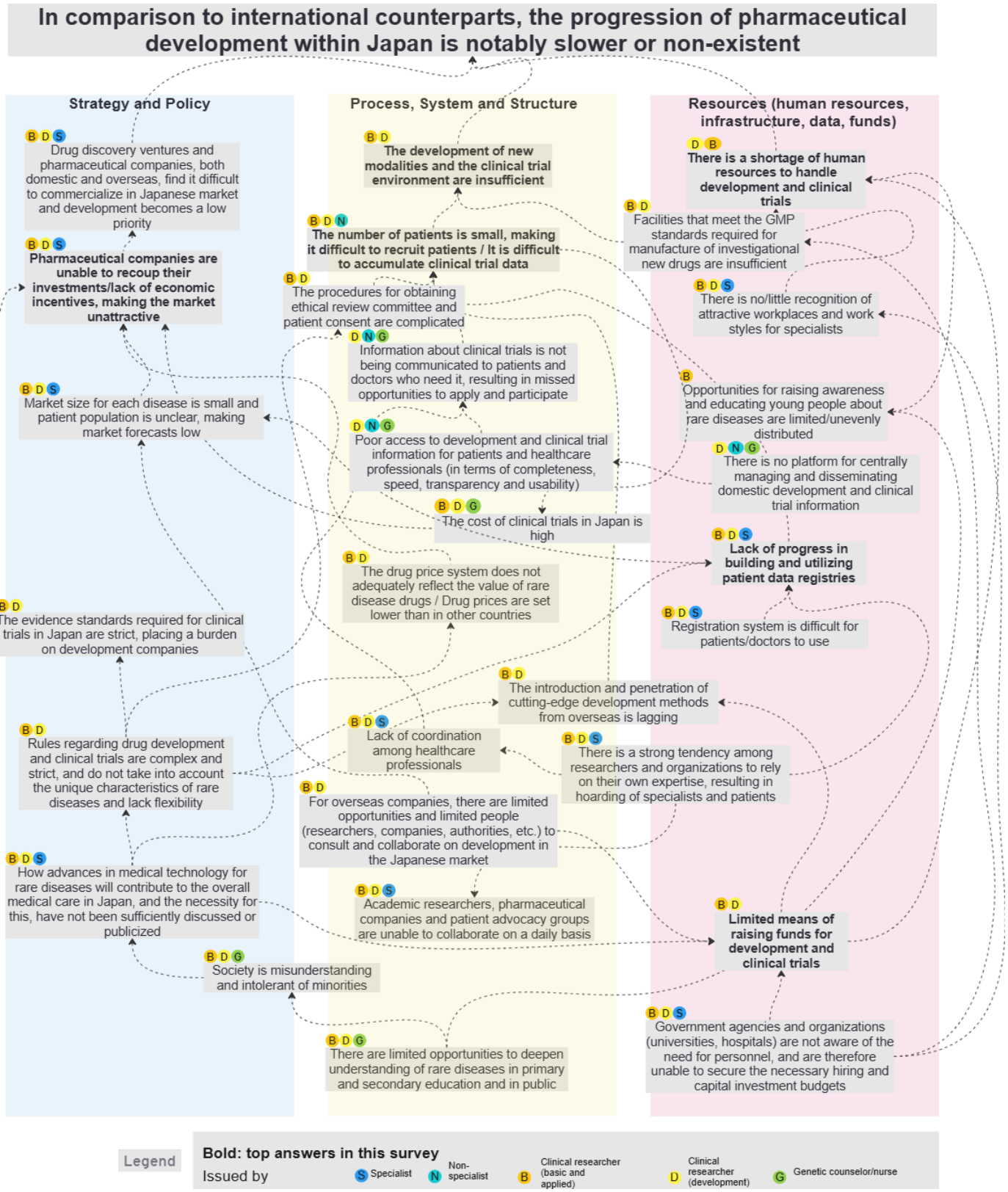
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most challenging regarding development and clinical trials (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-11: Challenges in development and clinical trials - Top 5 selection results



■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most challenging regarding development and clinical trials (ranked)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

Figure 4.1.2-12: Overall landscape of challenges in development and clinical trials



4.1.3 Column: Challenges and outlook in drug discovery research for rare diseases

Yoshitsugu Aoki, MD, PhD
Director, Department of Molecular Therapy, National Institute of Neuroscience,
National Center of Neurology and Psychiatry (NCNP)
Representative, Rare Disease Consortium Japan

Drug discovery research for rare diseases is a globally recognized field. In particular, the development of new modalities is a critical element that offers hope to patients and provides new treatment options. The keys to success include genetic diagnostics and elucidation of pathophysiology, understanding patient needs, securing funding and talent, establishing patient registries, strengthening corporate incentives including drug pricing systems, and developing the drug discovery ecosystem. Furthermore, it is essential to build a consistent platform from development to practical application through close collaboration between research and medical practice.

The interim report of the Cabinet Secretariat Planning Council in June 2024 pointed out drug lag and loss, declining international competitiveness and insufficient industry-academia-government collaboration as challenges facing Japan. In addition, strict safety evaluations are a factor that delays the early provision of treatment, and the small number of patients makes it difficult to obtain statistically significant results in clinical trials.

Duchenne muscular dystrophy (DMD), on which we are currently conducting research and development, is an extremely severe monogenic disease, but there are approximately 4,000 patients in Japan, a relatively large number of patients for a rare disease. DMD is considered a prototype disease for the development of new treatment modalities, as the relationship between genotype and phenotype has been elucidated in detail. In the development of Viltolarsen, an antisense oligonucleotide-based drug for DMD, the following efforts were made through collaboration between industry, academia, the government and the private sector: joint research and development by researchers, healthcare professionals, and pharmaceutical companies, Patient and Public Involvement (PPI) in research, securing a high-purity, large-scale manufacturing system for antisense oligonucleotide-based drugs, support for nonclinical research and investigator-initiated trials using public funds, construction of a patient registry, establishment of a hospital network for conducting clinical trials, and introduction of a conditional early approval system. The establishment of such a platform for drug discovery has established a system that seamlessly connects the process from drug development to treatment provision.

We urge physicians to understand and actively engage in drug discovery research. Feedback from clinical practice is essential for the development and improvement of new treatments, and collaboration between healthcare professionals and researchers will become increasingly important. On the other hand, the rare disease market is a high-risk area for companies, with low profitability and difficult investment recovery. However, with the advancement of basket trials and stratified medicine, the commercial appeal of rare disease drug discovery is gradually increasing. To accelerate research and development of new modalities and realize a sustainable drug discovery environment, a rapid approval process and a drug pricing system that allows companies to easily recover investments are essential. Additionally, rare disease treatments require complex technologies and expertise, so it is urgent to develop advanced manufacturing facilities and train personnel with specialized knowledge. Moreover, as many rare diseases are classified as unmet medical needs, flexible responses and accelerated approval procedures by regulatory authorities are strongly demanded.

To address these challenges, we have launched Rare Disease Consortium Japan. We aim to strengthen collaboration between industry, patients, academia, government, and the private sector, and to pioneer future medical services based on medical research and drug discovery for rare diseases. Personally, I would like to promote in silico drug discovery that combines medical big data and next generation AI with biomimetic systems (MPS), as well as promote the introduction of decentralized clinical trials, thereby contributing to the efficiency and speed of non-clinical and clinical trials.

4.1.4 Challenges in diagnosis

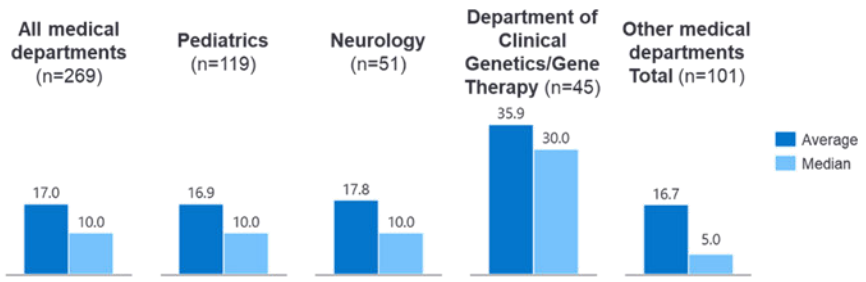
- The perceived challenges in diagnosis remain the accuracy and speed of diagnosis, and the reasons cited for this include a shortage of specialists who can make correct diagnoses and engage with patients, as well as a lack of platforms or mechanisms that facilitate collaboration between medical institutions and facilitate access to systematic information related to medical institutions and doctors, which is essential for patients to decide whether to seek medical help or not
- In addition, considering that many rare diseases are genetic [h], there is room for improvement in the methods of early intervention, particularly in children, in reducing the economic and physical burden on patients involved in testing and in the support system for testing

Actual state of diagnosis: Number of patient referrals and collaboration between doctors

Specialists are referred an average of 17 patients suspected of having a rare disease per year (Figure 4.1.4-1), of which the number of patients referred to the department of clinical genetics and gene therapy is significantly higher, at an average of 36 per year. This is because the department of clinical genetics and gene therapy serves as a base for treating patients with rare diseases within medical institutions. Regarding collaboration and consultation between healthcare professionals, specialists are consulted by other healthcare professionals 12.1 times per year, while non-specialists consult other healthcare professionals only 3.8 times per year, which is significantly lower (Figure 4.1.4-2).

However, the fact that the physicians working as specialists in this survey were physicians involved with IRUD or RDCJ may have influenced the result.

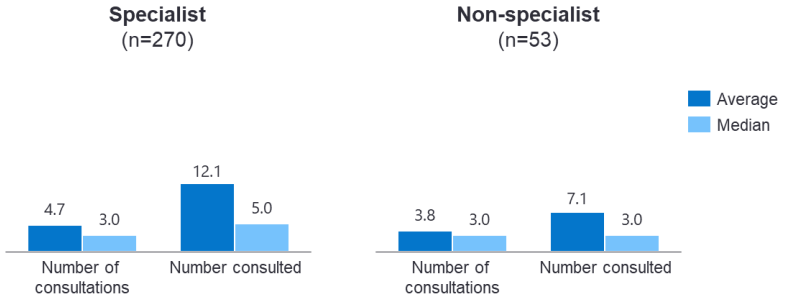
Figure 4.1.4-1: Number of patients with suspected rare diseases referred to specialists per year



*Analysis results excluding responses of 200 or more as outliers

■Survey: Web survey
■Question: Q6 If you answered "1. Responsible for making diagnostic and treatment decisions as a clinical doctor (specialist / quasi-specialist)" to the question about your occupation, please tell us how many patients with suspected rare diseases you are referred to each year (numeric answer)
■Subjects: 269 specialists

Figure 4.1.4-2: Number of consultations related to diagnosis / year



■Survey: Web survey
■Question: Regarding consultations related to rare disease diagnoses, how many times per year do you consult with others? (Answer with a number)
■Subjects: 302 specialists and non-specialists *Responses of 100 or more were excluded from the analysis as outliers

Status of diagnosis: Duration and Number of Facilities Involved in Reaching a Definitive Diagnosis

In this survey, healthcare professionals working as specialists were asked about the time and number of facilities required for their patients from their first consultation to a definitive diagnosis (Figure 4.1.4-3).

Across medical specialties, 53.3% of specialists responded that they reached a definitive diagnosis within one year and two facilities, but on the other hand, 39.2% responded that it took more than a year regardless of the number of facilities, and 25.2% responded that it took three or more facilities regardless of the period, indicating that the burden of diagnosis on patients remains large.

Considering that the physicians working as specialists who were the subjects of this survey were physicians working at core hospitals related to IRUD or RDCJ, the actual situation nationwide may be that this leads to a longer period until a definitive diagnosis is made and an increase in the number of referral facilities, so further verification is needed.

Figure 4.1.4-3 Duration and Number of Facilities Involved in Reaching a Definitive Diagnosis

	Less than 6 months	Less than 1 year	More than 1 year	More than 3 years	Total
1 facility	19.6%	4.5%	5.5%	1.5%	31.2%
2 facilities	13.6%	15.6%	11.1%	3.5%	43.7%
3 facilities	0.5%	3.5%	6.5%	4.0%	14.6%
4 facilities	2.0%	1.5%	2.0%	5.0%	10.6%
Total	35.7%	25.1%	25.1%	14.1%	100.0%

Less than 1 year with 2 facilities or less: 53.3%

More than one year regardless of number of facilities: 39.2%

3 or more facilities regardless of duration: 25.2%

■Survey: Web survey
■Question: Please tell us how long it took for the most recent rare disease patient to be diagnosed after their first visit, and to which medical institution they were referred after their first visit (select one)
■Subjects: 270 specialists

Challenges in diagnosis

The top challenges felt in terms of challenges in diagnosis (Figure 4.1.4-4) were a lack of specialists and volunteers necessary for early diagnosis (59.5%), delays in establishing a system (51.6%), the burden of testing on patients (45.9%), a lack of information necessary for diagnosis (45.6%), and difficulty in recalling a diagnosis (44.9%).

As in R&D, the challenge in terms of human resource development in clinical practice is large in all professions (Figure 4.1.4-5), and even specialists feel that it is difficult to develop and secure human resources. The background to this was pointed out to be a lack of incentives and a high workload.

Additionally, non-specialists were unable to easily identify the information necessary for disease recall or diagnosis at the point of care, indicating that providing the information necessary for diagnosis and collaboration with specialists remains key.

In relation to this, it has been pointed out that when it comes to collaboration between specialists and non-specialists, there is limited information on medical institutions and doctors with knowledge and experience in specific rare diseases, as well as limited means of sharing information for collaboration. It can be said that there is room for improvement in the accuracy, recency, and ease of access of the information used by healthcare professionals involved in diagnosis.

In addition to these challenges, when viewed by medical department (Figure 4.1.4-6), the top challenges were the incorporation and utilization of data and advanced technology (diagnostic support AI) (pediatrics), motivating patients to undergo testing (neurology), and the lack of incentives for consultation and referrals between healthcare professionals (clinical genetics). In addition, since incentives to accelerate patient referrals are not necessarily clear, the report suggests the need for a system in which doctors who suspect a disease can actively and efficiently refer patients to specialists, as well as the need for processes, structures and platforms necessary for collaboration between healthcare professionals (Figure 4.1.4-7).

> *For doctors who have just started working with rare diseases, in addition to ideals and motivation, incentives related to remuneration, time and workload are also important. What young doctors today want is to work efficiently and fairly as specialists and degrees and titles themselves are not very motivating.*
> (Clinical researcher (development) / neuromuscular disease)

> *The rapidity of diagnostic processes is critical, particularly in neonatology, where prompt identification of conditions can substantially improve clinical prognoses. Hence, there is an urgent need to augment the framework for expedited and streamlined diagnostic testing and result analysis.*
> (Specialist / Pediatrics)

> *To reduce the number of facilities and time it takes to reach a definitive diagnosis, it is necessary to make it easy for cases to accumulate and easy for patients to*

access the facility. Even if it is difficult to make a definitive diagnosis at the first visit, it is important to avoid repeated transfers to hospitals over a wide area to reduce the burden on patients, and the aim should be to complete the diagnosis within a specialized facility. In addition, to lower the psychological hurdle for referring physicians, it is essential to clearly indicate where facilities and specialists specializing in rare diseases are located, as well as the referral criteria.
(Specialist / Collagen Disease Department)

“As a specialist, I would like to speak up if I think something is wrong, but there are many cases where the possibility of a rare disease is not considered, or there is hesitation among colleagues, and as a result, the matter is left unattended. It is important to properly evaluate the degree of contribution, such as by co-authoring a paper with the referring physician.
(Specialist / Collagen Disease Department)

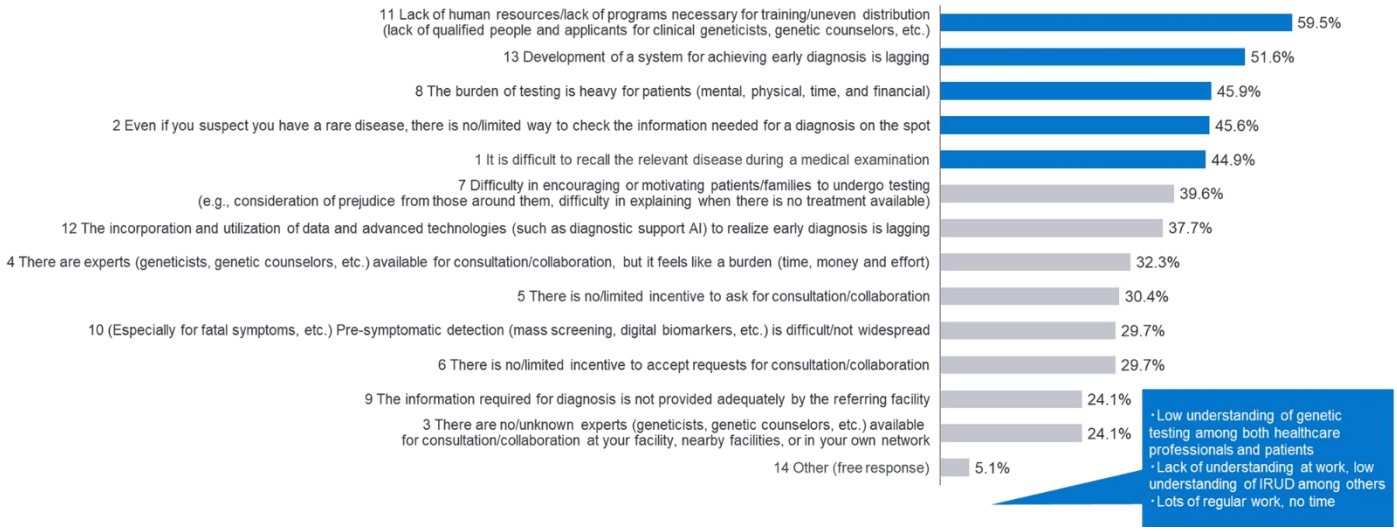
“The key to early diagnosis is how to promote newborn mass screening and expand the scope of its targets. This will eliminate the need to repeat unnecessary tests and treatments. The government should allocate more of its budget to this.
(Specialist / Pediatrics)

“There are not necessarily doctors with sufficient knowledge and experience in genetic testing, so patients cannot be referred easily and irresponsibly.
There is a need to make doctors and medical institutions more visible, and to have a platform for sharing test results between specialists and non-specialists.
(Non-specialist / Neurology)

“Genetic testing is important, but it can be difficult to decide whether to test when no treatment is yet available.
(Non-specialist / Pediatrics)

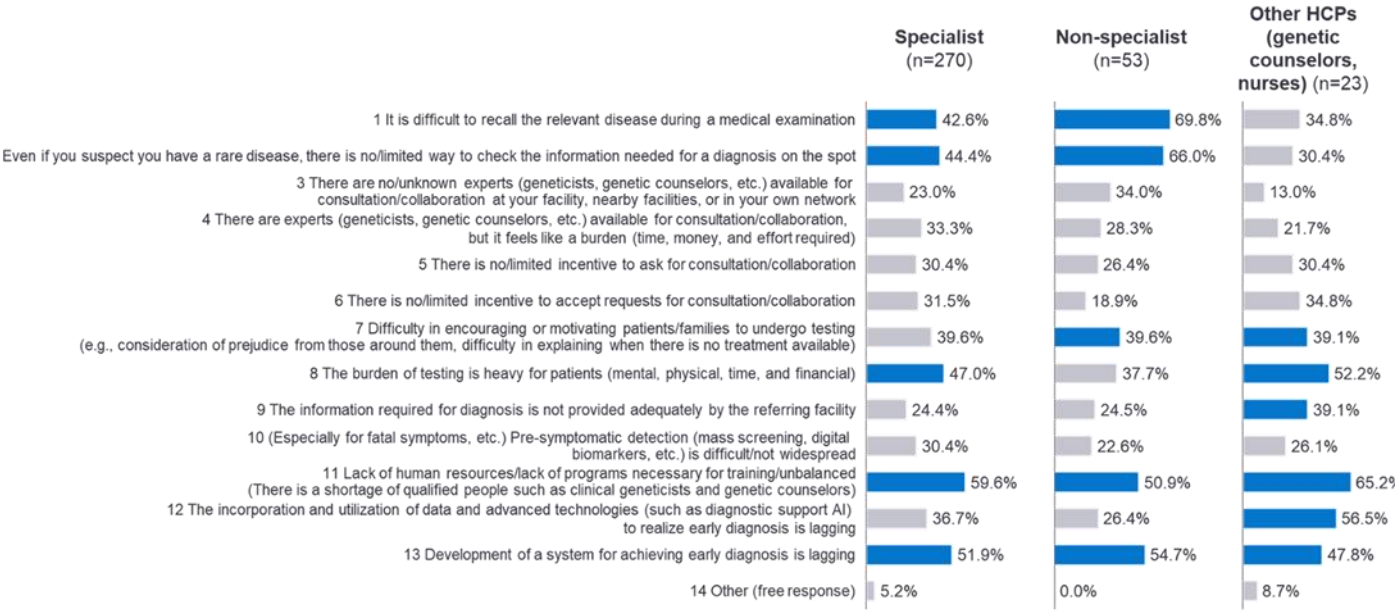
“When collaborating with other medical institutions, only information that can be included in the patient's referral letter can be provided or obtained, so if data could be shared more quickly, referrals may also increase.
(Clinical researcher (development) / Immunodeficiency Disease)

Figure 4.1.4-4: Diagnostic Challenges – Top 5 Selection Results



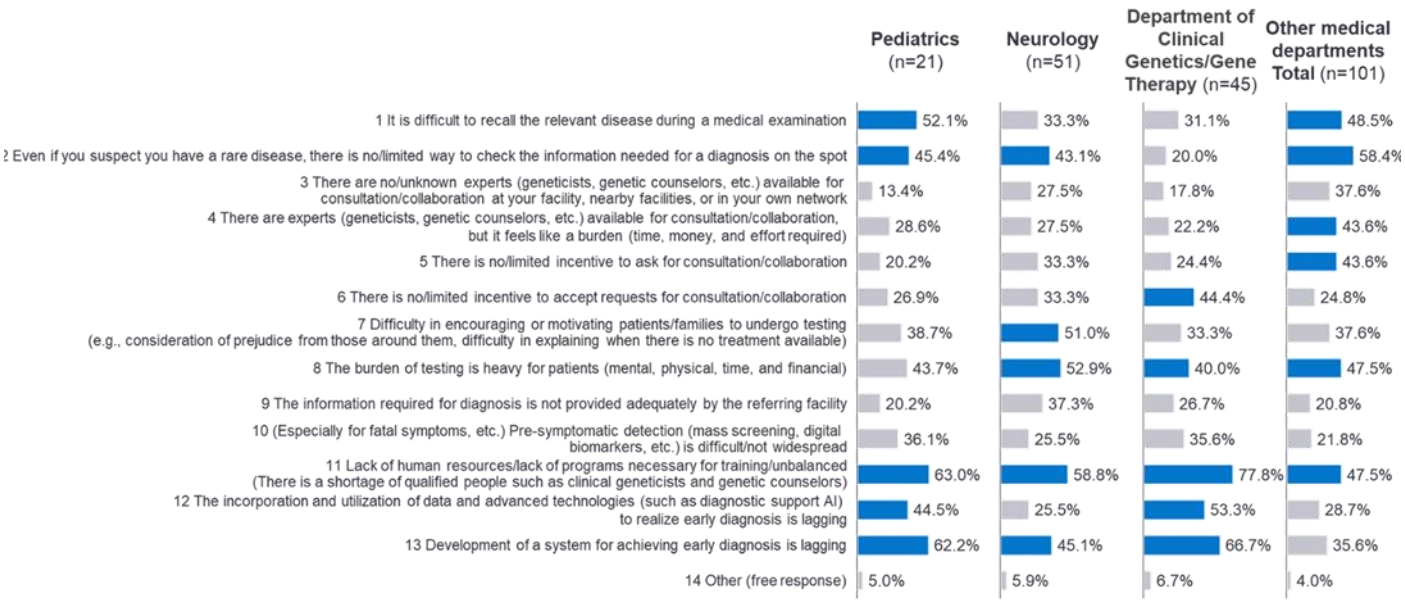
■Survey: Web survey
■Question: Please select the top 5 most pressing challenges you feel are related to diagnosis (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.4-5: Diagnostic Challenges – Top 5 Selection Results Selection Results (by occupation)



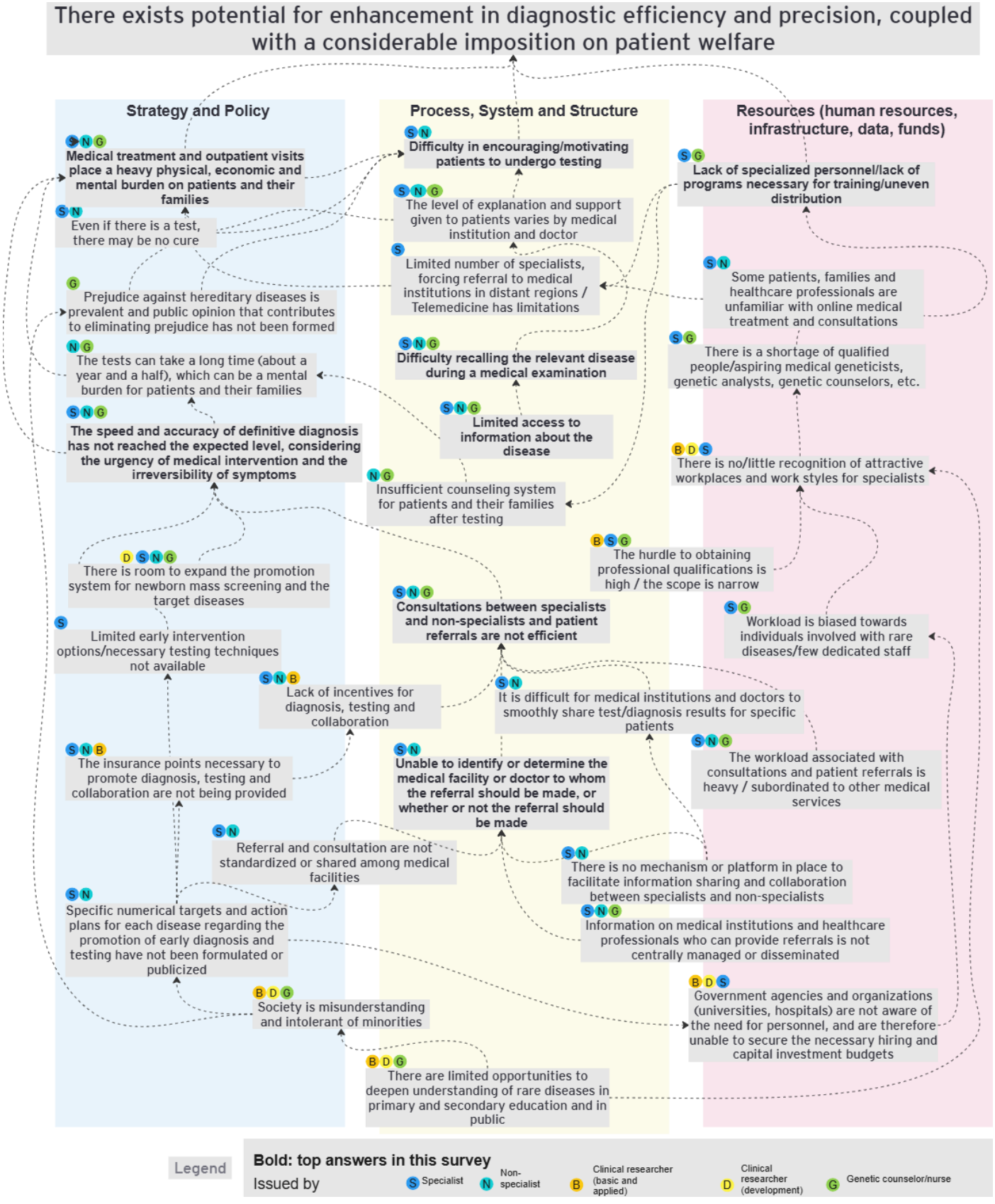
■Survey: Web survey
■Question: Please select the top 5 most pressing challenges you feel are related to diagnosis (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.4-6: Diagnostic Challenges – Top 5 Selection Results (by medical department)



■Survey: Web survey
■Question: Please select the top 5 most pressing challenges you feel are related to diagnosis (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.4-7: Overall landscape of challenges in diagnosis



4.1.5 Challenges in treatment and prognosis management

- In Japan, treatment options are limited compared to other countries (drug lag / loss), and the urgent need to promote drug discovery is a common challenge in R&D and diagnosis.
- The progress of drug development varies greatly by disease, and the number of patients and cases is limited, so evidence building in actual clinical practice and the establishment of guidelines are often not progressing, making the equalization[8] of medical care for rare diseases a challenge.
- In a situation where treatment plan must be decided by trial and error, importance is placed on research papers, academic societies, and pharmaceutical companies as the main sources of information.
- Both specialists and non-specialists believe that regional collaboration should be strengthened, and the reasons cited for this include the lack of available patient data, the hurdles to using it and the lack of networks between medical institutions and doctors.

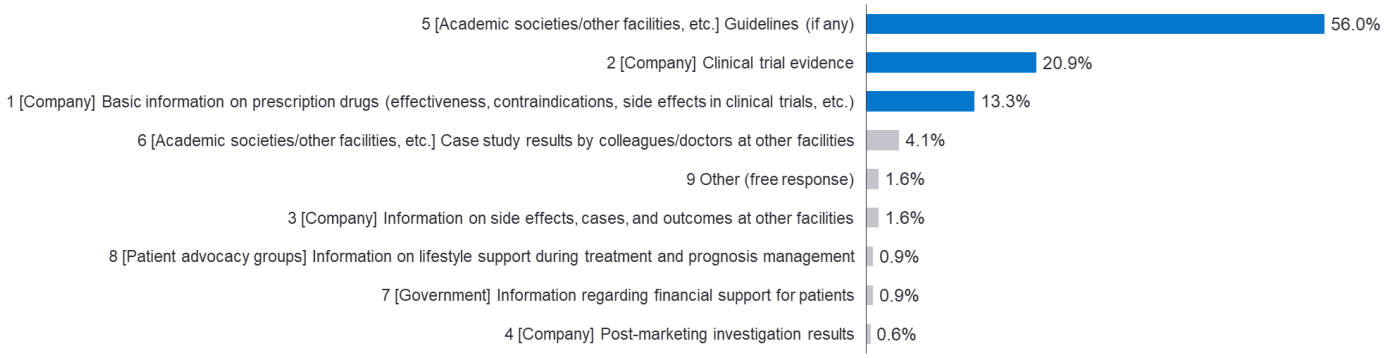
The current state of information collection and utilization in treatment and prognosis management

As mentioned above, collecting and utilizing information is essential for activities related to rare diseases, so we checked the status of information collection and utilization in treatment and prognosis management.

Guidelines from academic societies, evidence from clinical trials and product information provided by companies were given importance as information to be used in treatment and prognosis management (Figure 4.1.5-1).

In terms of sources of information (Figure 4.1.5-2), in addition to information from academic journals, academic conference presentations and websites, importance was placed on collecting information through pharmaceutical companies. By occupation (Figure 4.1.5-3), non-specialists and other HCPs (genetic counselors and nurses) were found to place more importance on contact with pharmaceutical companies than specialists.

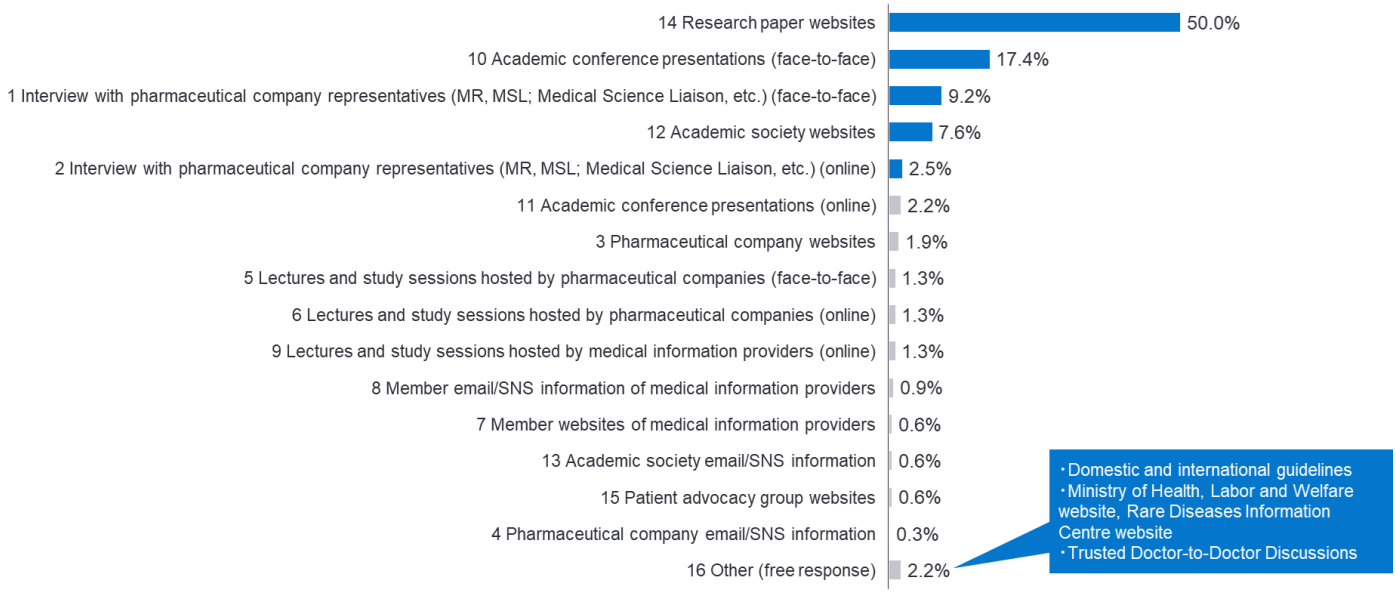
Figure 4.1.5 1: Types of information collected and used in treatment and prognosis management – Top selection results



■Survey: Web survey
■Question: Please select the top three most important types of information to be collected and utilized in treatment and prognosis management (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

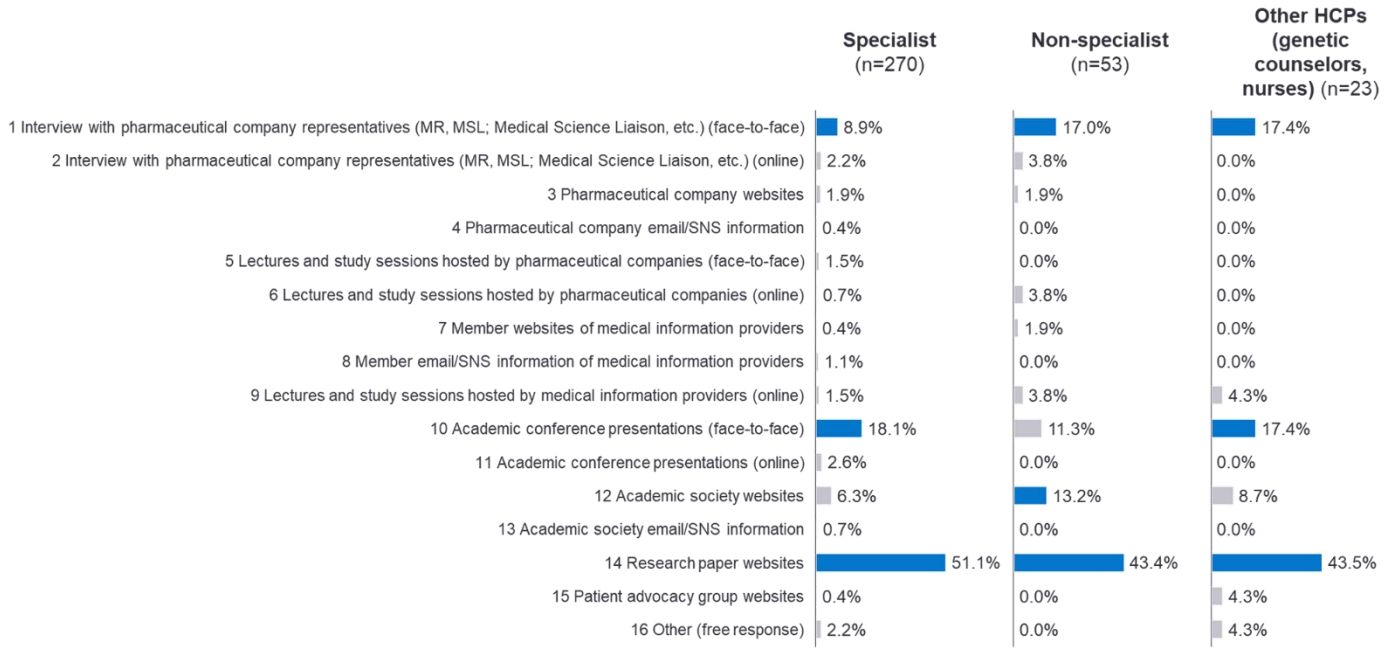
[8] To spread the quality and delivery of medical care equally across the country

Figure 4.1.5-1: Source of information to be collected and utilized in treatment and prognosis management – Top selection result



■Survey: Web survey
■Question: Please select your top 5 preferred sources (media / channels) of information to be collected and utilized in treatment and prognosis management (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.5-2: Source of information collected and used in treatment and prognosis management – Top selection results, by occupation



■Survey: Web survey
■Question: Please select your top 5 preferred sources (media / channels) of information to be collected and utilized in treatment and prognosis management (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Challenges in treatment and prognosis management

In terms of perceived challenges across professions, in addition to 'limited treatment options compared to overseas' (= drug lag / loss), 'lack of evidence' and 'limited means / opportunities for healthcare professionals to gather the information they need' were ranked highly (Figure 4.1.5-4).

Comparing the responses by occupation (Figure 4.1.5-5), the challenge for '1 Limited treatment options' was greater among specialists (32.6%) and other HCPs (43.5%) than among non-specialists (24.5%). In addition, the challenge for '3 Lack of evidence' was greater among specialists (14.4%) and other HCPs (17.4%) than among non-specialists (5.7%). It can be said that the challenge is more pronounced among healthcare professionals directly involved in treatment.

Furthermore, non-specialists felt that 'limited means / opportunities to gather information' was a bigger challenge (22.6%) than other healthcare professionals, and it would be desirable for academic societies and pharmaceutical companies to provide more information. Human resource challenges were ranked highly among non-specialists and other HCPs (genetic counselors in third place, non-specialists in fourth place), indicating the difficulty of securing human resources for rare disease medical care.

In addition to the above, the overall response (Figure 4.1.5-6) was challenges with reverse referrals from specialists to non-specialists (43.0%). As with research and development and diagnosis, collaboration between medical institutions and doctors is essential. There were also challenges with building a platform for obtaining information on medical institutions and doctors that can be referred and for easily sharing patient and clinical data at the time of referral and the need to review the design of these systems was also made clear (Figure 4.1.5-7).

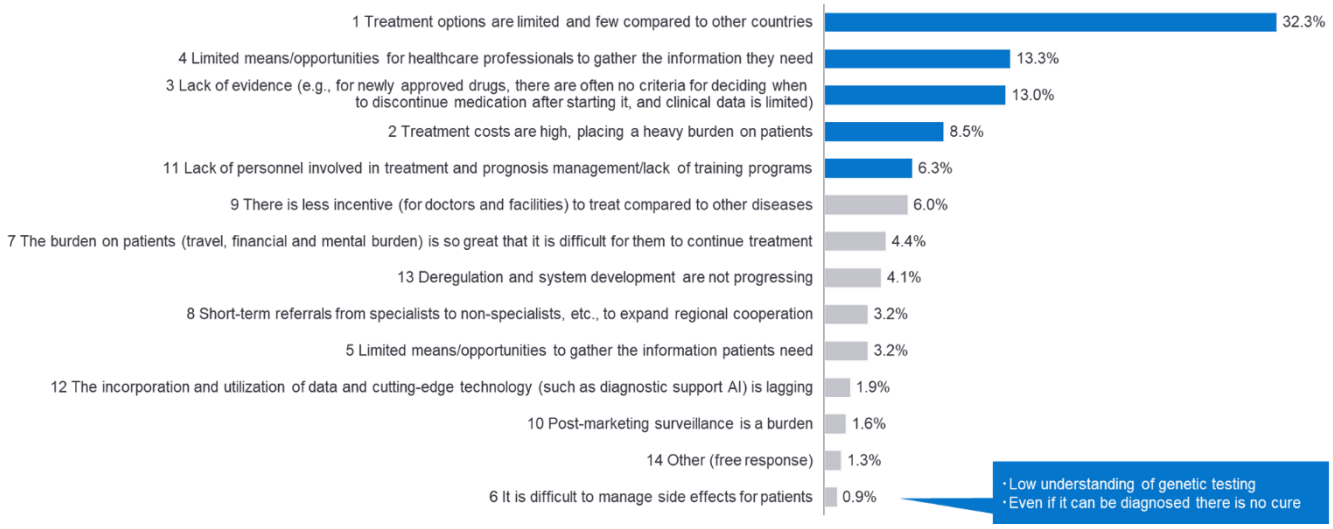
> *Among the next generation of doctors, there are very few who are interested in or want to work with rare diseases. Japan's medical policy prioritizes learning from a variety of experiences at clinics, etc., and there is little exposure to rare diseases.*
> (Specialist / Pediatrics)

> *There are also situations where there are few cases and evidence, and treatment plans must be decided by trial and error. Furthermore, training personnel is extremely difficult. It is important to efficiently separate and advance personnel training.*
> (Non-specialist / Pediatrics)

> *Because patient test data is personal information, it is not shared between medical institutions, and accessible actual clinical data is limited. A process and infrastructure are needed to determine diagnostic and treatment plans for specific patients based on shared evidence.*
> (Clinical researcher (development) / Endocrinology and Metabolic Disease)

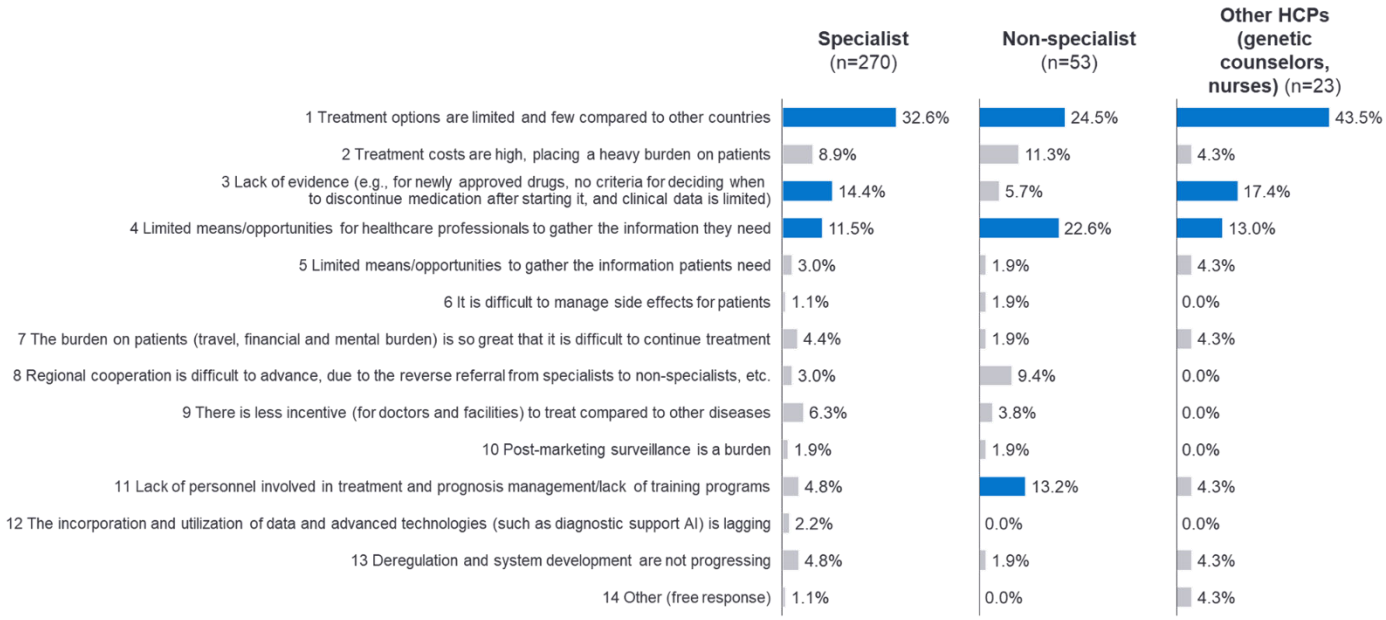
> *In cases where a patient has a highly specialized condition, they may not be able to receive a referral. Many people find it difficult to deal with pediatric diseases in particular.*
> (Non-specialist / Pediatrics)

Figure 4.1.5-3: Challenges in treatment and prognosis management – Top selection result



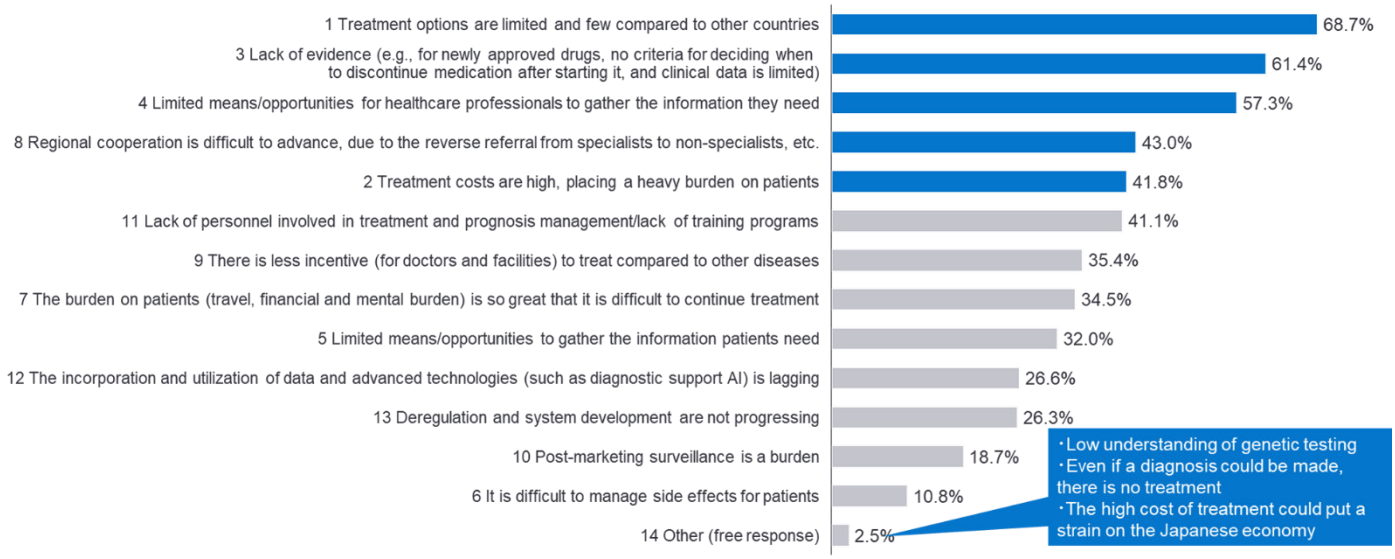
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most important in terms of treatment and prognosis management (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.5-4: Challenges in treatment and prognosis management – Top selection results by occupation



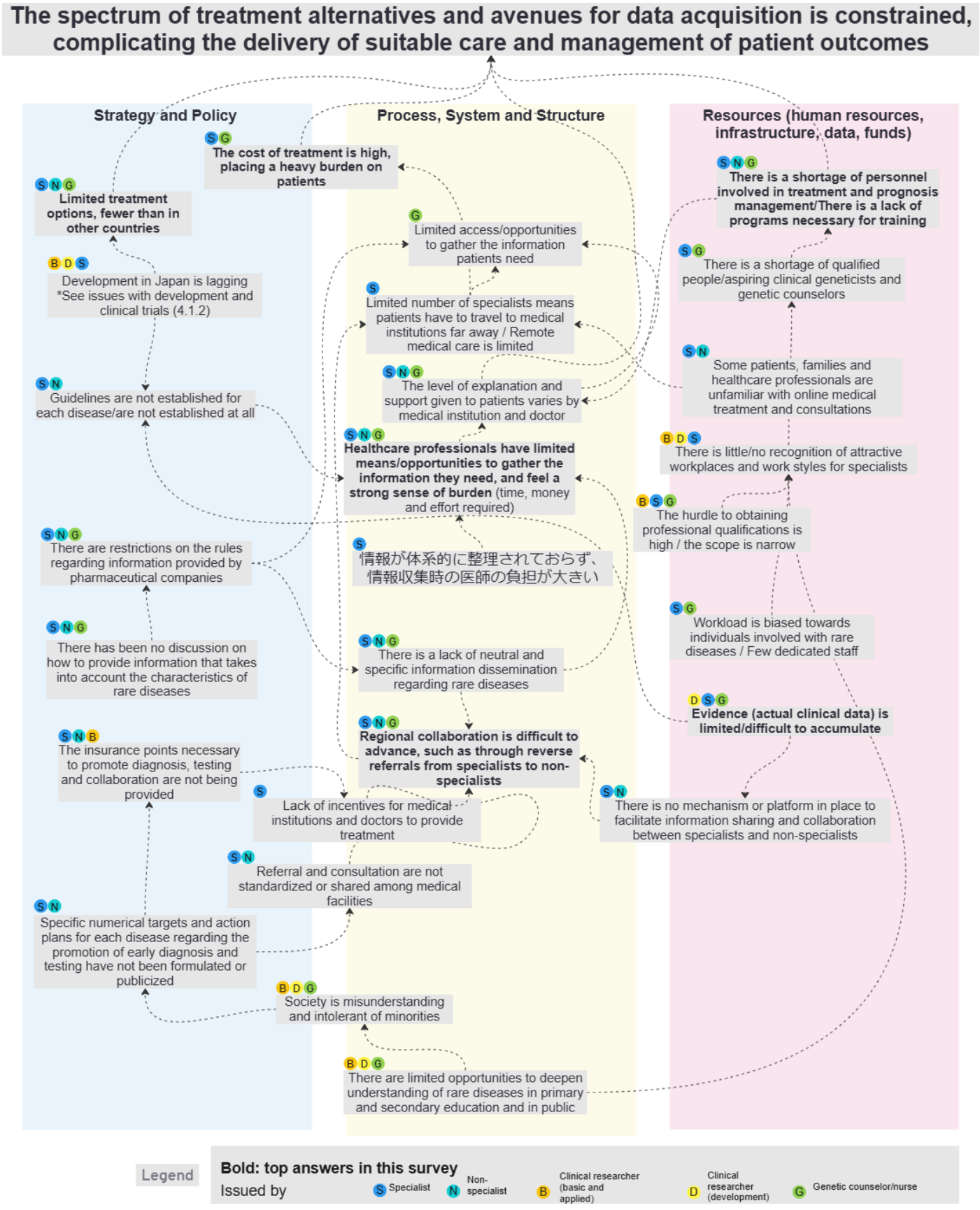
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most important in terms of treatment and prognosis management (ranking format)
■ Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.5-6: Challenges in treatment and prognosis management – Top 3 selection results



■Survey: Web survey
■Question: 5 Limited means / opportunities to gather the information patients need
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.1.5-7: Overall picture of challenges in treatment and prognosis management



4.1.6 Challenges in disease awareness activities

- Rare diseases are diverse, and healthcare professionals themselves have difficulty deepening their awareness and understanding of each rare disease, leading to a situation in which work is easily personalized and unevenly distributed depending on the department and position within the medical institution.
- Accuracy, timeliness and accessibility are important when raising awareness of rare diseases for patients and their families. The challenge is to ensure that the opinions of rare disease patients and their families are not overlooked, and to create a society in which they can live comfortably with their illnesses while ensuring psychological safety.

Current status regarding disease awareness

The main players effective in raising disease awareness for patients and their families were academic societies, Patient Advocacy Groups, and medical institutions (Figure 4.1.6-1) using websites as an effective media / channel (Figure 4.1.6-2).

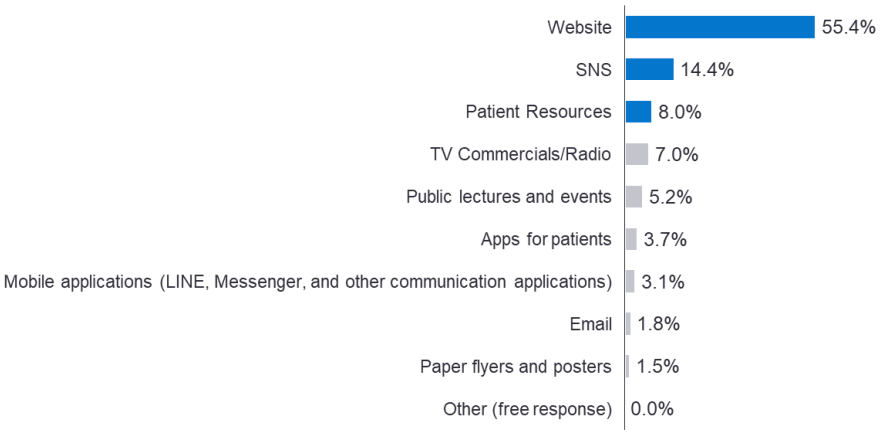
The main players effective in raising disease awareness for healthcare professionals were academic societies, medical institutions and pharmaceutical companies (Figure 4.1.6-3) using websites, face-to-face and online communication, lectures and study sessions held by pharmaceutical companies and academic societies as effective media / channels (Figure 4.1.6-4).

The main players effective in raising disease awareness for the public were Patient Advocacy Groups, academic societies and the government (Figure 4.1.6-5) using websites, TV, radio and SNS as effective media / channels (Figure 4.1.6-6).

Figure 4.1.6-1: Effective players for disease awareness activities (for patients and their families)

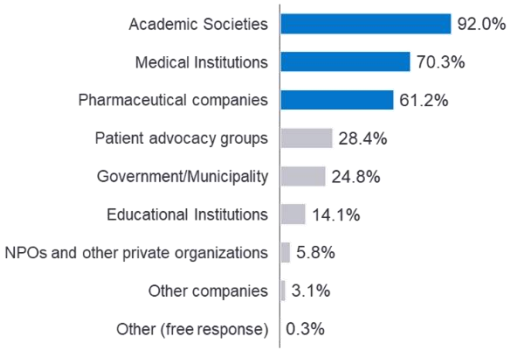
■Survey: Web survey
■Question: Please answer the three questions about what you think would be most effective in raising awareness about rare diseases? (for patients and their families) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development), and other HCPs (genetic counselors and nurses)

Figure 4.1.6-2: Effective media / channels for disease awareness activities (for patients and their families)



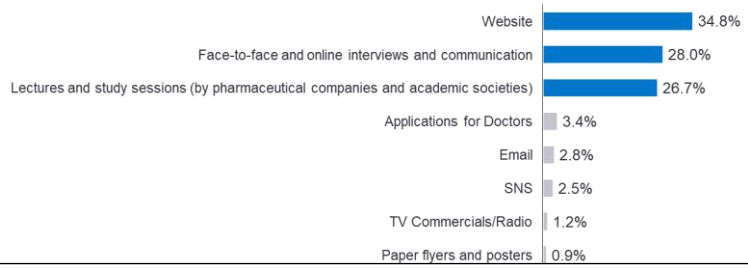
■Survey: Web survey
■Question: Please choose the three most effective media / channels for raising awareness about rare diseases (for patients and their families) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-3: Effective players in disease awareness activities (for healthcare professionals)



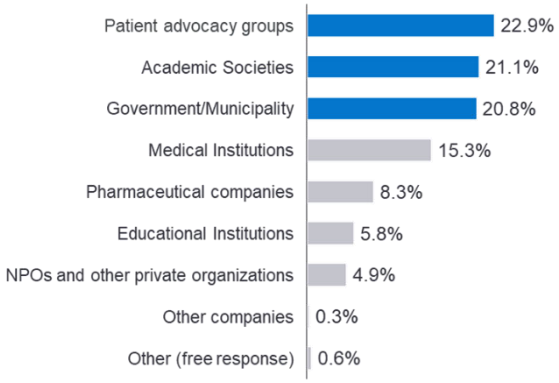
■Survey: Web survey
■Question: Please select three answers that you feel are effective in raising awareness of rare diseases (for healthcare professionals) (ranking format)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-4: Effective media / channels for disease awareness activities (for healthcare professionals)



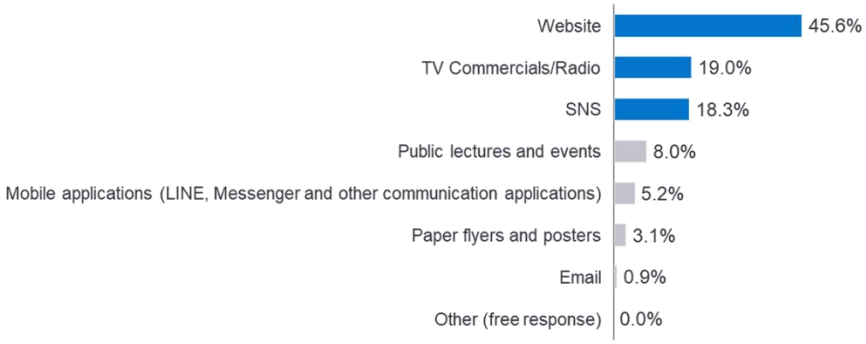
■Survey: Web survey
■Question: Please choose the three most effective media / channels for raising awareness of rare diseases (for healthcare professionals) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-5: Effective players in disease awareness activities (for the public)



■Survey: Web survey
■Question: Please select the three most effective organizations that conduct awareness-raising activities (for the public) related to rare diseases (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-6: Effective media / channels for disease awareness activities (for the public)



■Survey: Web survey
■Question: Please select the three most effective media / channels for raising awareness of rare diseases (for the public) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Challenges in disease awareness activities

In disease awareness activities, the major challenges were recognized as limited opportunities / means to deepen awareness and understanding of rare diseases for both healthcare professionals themselves and patients / families and the heavy burden they felt (Figure 4.1.6-7). The common background to these challenges was that information on rare diseases (diseases, medicines, treatments, medical institutions, etc.) was not systematically organized, and the amount and quality of information varied by disease.

Additionally, the hurdles to gathering information are even higher for patients and families who are unfamiliar with specialized information gathering tools such as research paper sites or the most appropriate search methods and it was also pointed out that there are restrictions on pharmaceutical companies providing information to patients.

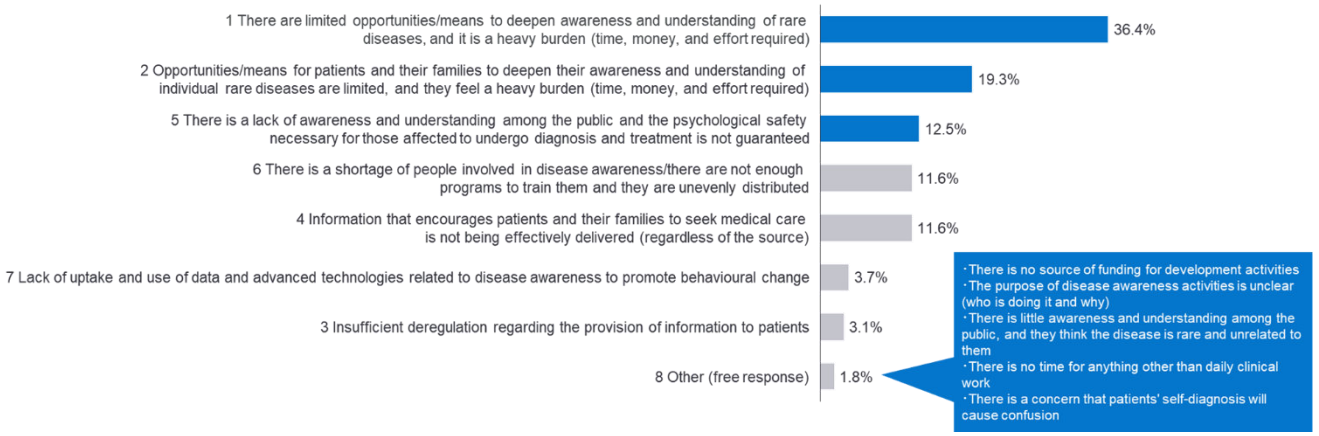
In the results by occupation (Figure 4.1.6-8, 9), non-specialists, clinical researchers (development), and other HCPs (genetic counselors and nurses) answered '4 Information that encourages patients and families to actively seek medical attention is not being effectively delivered (regardless of source).' Genetic counselors pointed out the existence of prejudice and discrimination

among patients and families, which may be an obstacle to them seeking medical attention.

In relation to the above, it was found that a foundation is needed for society to recognize and support the realities of patients and families with rare diseases, as awareness-raising activities for the public have not yet been incorporated into the school curriculum and understanding has not yet spread. In addition, among clinical researchers (basic and applied), '6 There is a shortage of personnel involved in disease awareness / the programs necessary for training are lacking / unevenly distributed' was ranked high, which is consistent with the challenges in training personnel pointed out in '4.1.2 Challenges in R&D' above.

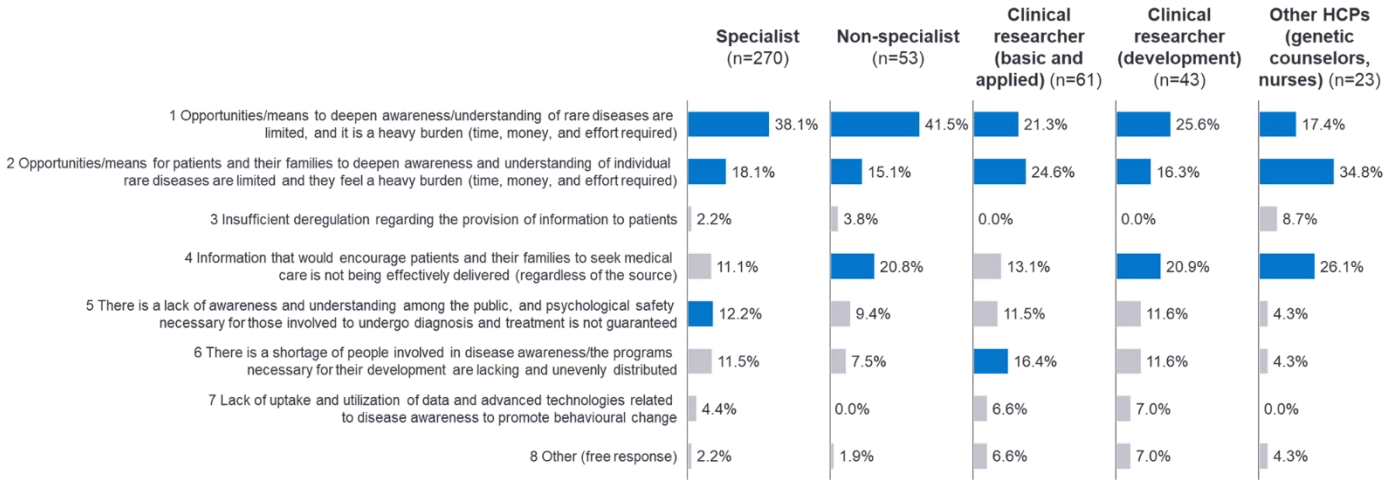
Sorting out these causal relationships reveals that there is intolerance and lack of awareness and understanding of rare diseases in the public, as well as flexible system design that considers the characteristics of rare diseases and further investment in research and development is needed (Figure 4.1.6-10).

Figure 4.1.6-7: Challenges in disease awareness activities – Top selection results



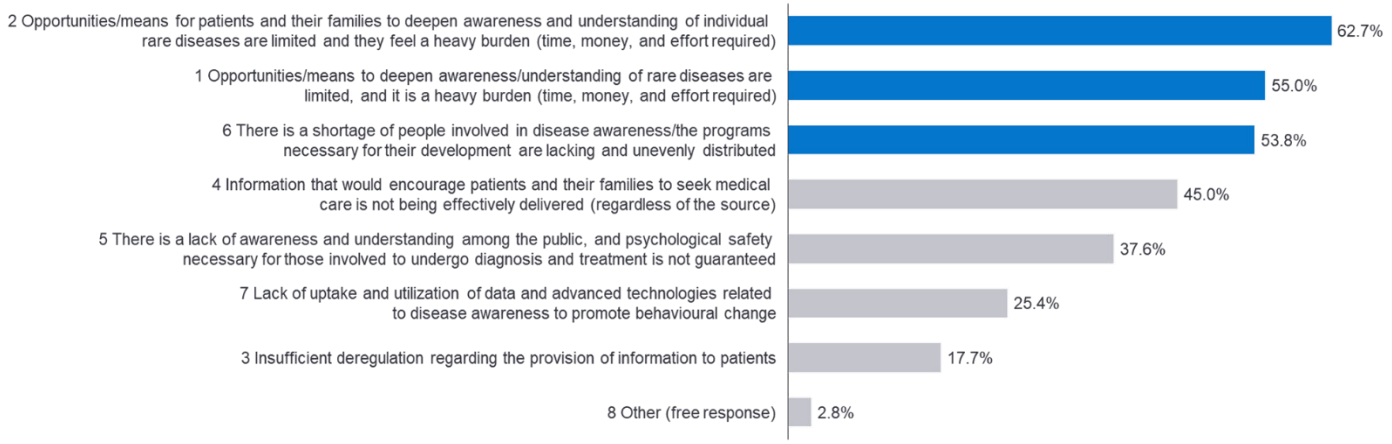
■Survey: Web survey
■Question: Please answer the top three challenges you feel are most challenging regarding disease awareness activities (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-8: Challenges in disease awareness activities – Top choice results by occupation



■Survey: Web survey
■Question: Please answer the top three challenges you feel are most challenging regarding disease awareness activities (ranking format)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Figure 4.1.6-9: Challenges in awareness-raising activities – Top 3 selection results



■Survey: Web survey
■Question: Please answer the top three challenges you feel are most challenging regarding disease awareness activities (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

There is a need to include mechanisms within the undergraduate education and training system to deepen understanding of rare diseases, such as having students volunteer for Patient Advocacy Groups from their student days.
(Specialist / Pediatrics)

Just because it is a hereditary disease, clinicians have a strong sense of complexity and avoid it. In addition, scientific verification is needed to raise awareness of the disease among patients and to determine what would lead to a recommendation to see a doctor.
(Specialist / Collagen Disease)

Raising awareness about a disease for which there is no cure only increases anxiety in patients. It is necessary to use information with high sensitivity and specificity to raise awareness.
(Non-specialist / Neurology)

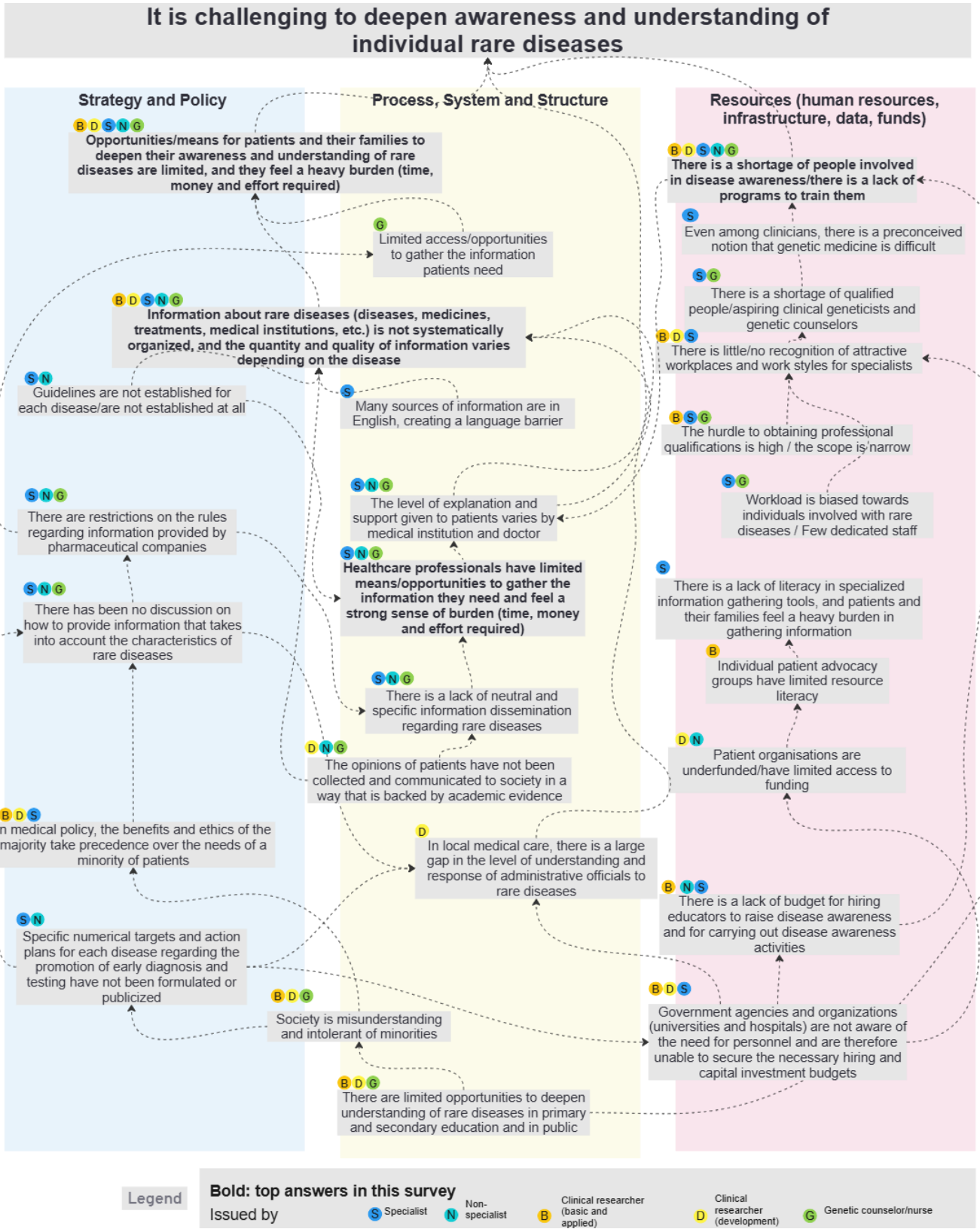
There is a lack of awareness and understanding among the public and the psychological safety necessary for those affected to undertake diagnosis and treatment is not guaranteed. In some cases, diagnosis and treatment are delayed because parents are not aware of their child's developmental delay or that there are treatments available. There is also insufficient deregulation regarding the provision of information to patients, and it would be appreciated if pharmaceutical companies also provided information.
(Non-specialist / Pediatrics)

In Japan, there is a strong tendency for peer pressure and conservatism to prevail, and when new medical policies or technologies are introduced, it is society rather than patients who tend to resist them. Even if an agreement has been reached with medical institutions and with patients / families in crisis situations, opinions that come from a position that does not fully understand the parties involved are highlighted. The needs of people with rare diseases are often overlooked in the name of public interest. A regulatory system that returns to basics should be considered.
(Clinical researcher (basic and applied) / Other hereditary disease)

In Japan, patients with the disease suffer from friction and prejudice even within society and their own families, even though it is not publicly known. In some cases, discriminatory attitudes are at the root of it all, so it is necessary to create a system that makes it easier for anyone to enter society by educating children about genetics from an early age.
(Genetic counselor / Genetics department)

Information on the progress of development should be systematically organized and made more accessible to patients and healthcare professionals. This could encourage patients to seek medical treatment, motivate them to go to hospitals, and ultimately lead to improved diagnosis rates.
(Genetic counselor / Genetics department)

Figure 4.1.6-10: Overall picture of challenges in awareness-raising activities



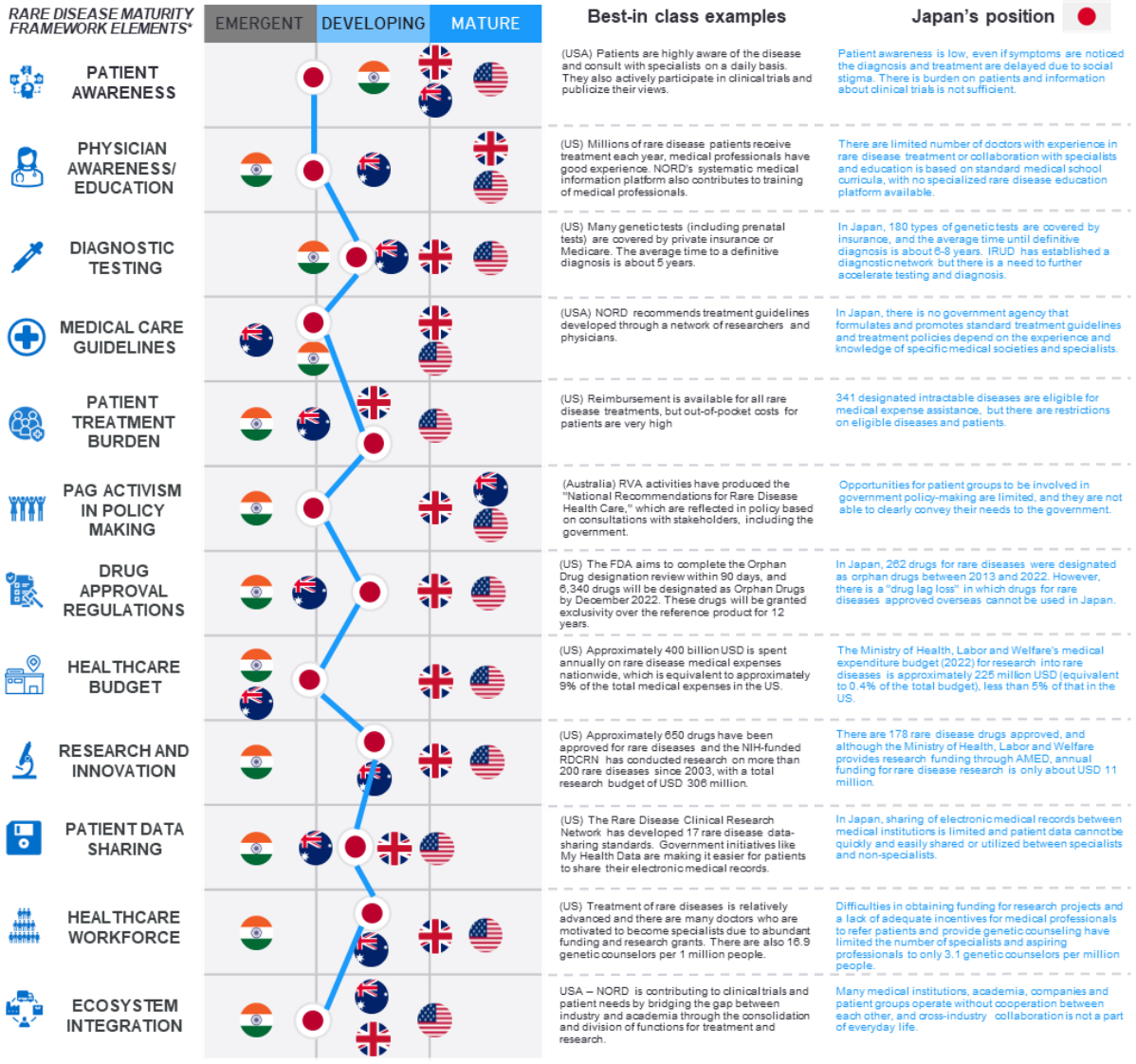
4.1.7 Column: Position of Japan's medical system for rare disease in globe

Based on the status and challenges of rare disease medical care in Japan that have been identified thus far, we investigated secondary information on cases overseas [a] (USA, UK, Australia, India) and compared it with the status in Japan to analyze the areas where there is a large discrepancy with cutting-edge cases (Figure 4.1.7).

Compared to countries with advanced initiatives such as the United States and the United Kingdom, Japan has particularly large gaps in terms of disease awareness, diagnosis and testing processes, the establishment of treatment guidelines, the involvement of Patient Advocacy Groups in policymaking, the allocation of medical costs and the consolidation and division of functions of the ecosystem and significant improvements are expected in the future.

Both results are consistent with the challenges felt by healthcare professionals and the next section will provide a detailed explanation of what the ideal status in Japan should be and specific actions to eliminate these gaps.

Figure 4.1.7 Comparison of healthcare infrastructure for rare diseases in Japan and overseas



*Countries have been ranked on each element based on the healthcare infrastructure available for supporting RD patients
IRUD: Initiative on Rare and Undiagnosed Disease RDCRN: Rare Diseases Clinical Research Network

4. Survey results

4.2 Direction of measures

4.2.1 Ideal state in research, development and clinical practice

- In terms of research and development, there were hopes for the development of a research environment for new modalities, the training and promotion of human resources, and the development of treatment methods through collaborative research with companies.
- In clinical practice, it was expected that the speed and accuracy of testing and diagnosis would improve, and that treatment options would be expanded for patients.

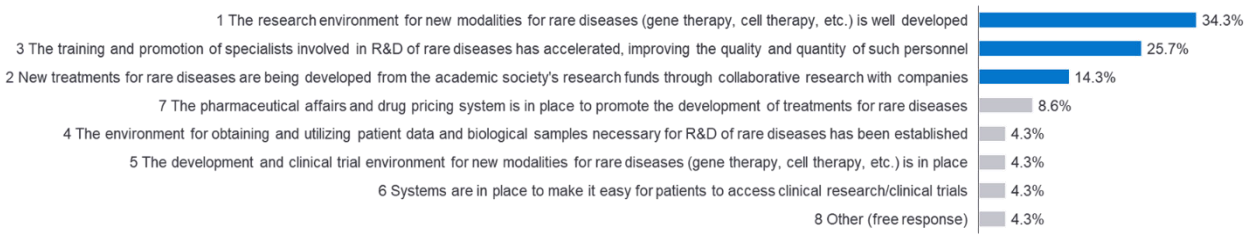
The development of a research environment for new modalities was the most anticipated outcome for both clinical researchers (basic and applied) and clinical researchers (development), followed by the development and promotion of human resources and collaborative research with companies (Figure 4.2.1-1).

Both reaffirm that there are high expectations for accelerating drug discovery and for developing and securing the necessary human resources which were mentioned as challenges in the previous chapter.

Similarly, in actual clinical practice, the challenges raised in the previous chapter include improving diagnostic accuracy and speed, expanding treatment options for patients and reducing the burden on patients associated with diagnosis and treatment, as well as improving access for clinical trials (Figures 4.2.1-2, 4.2.1-3).

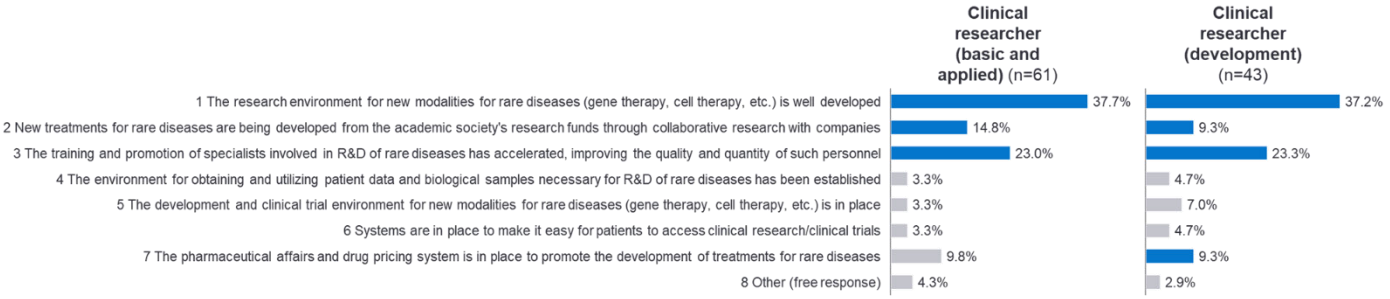
All these results are consistent with the challenges we have discussed so far and in the next section we will take up in detail the actions expected of each stakeholder.

Figure 4.2.1-1: What research and development should be like – Top selection result



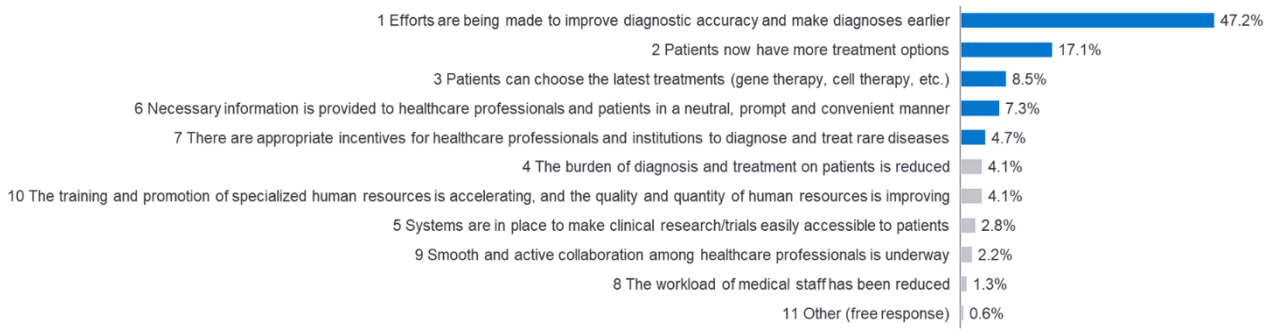
■Survey: Web survey
■Question: Based on the R&D challenges you have answered so far, please select top three answers that you agree are the way things should be (ranked)
■ Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.1-2: The Ideal State of Research and Development – Top Selection Results by Job Type



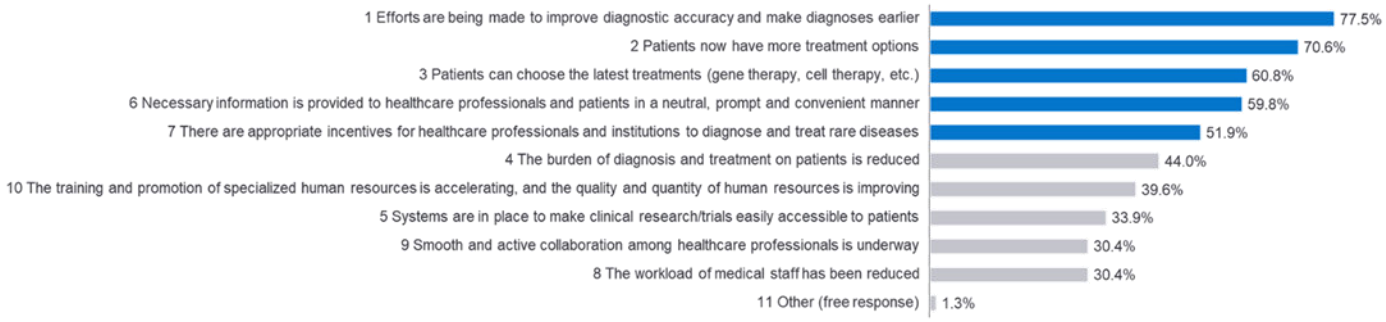
■Survey: Web survey
■Question: Based on the research and development challenges you have answered so far, please select top three answers that you agree are the way things should be (ranked)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.1-3: What should be done in clinical practice – Top selection result



■Survey: Web survey
■Question: Based on the challenges you have answered so far in your clinical practice, please select the top 5 that you agree are the way things should be (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.1-4: What should happen in clinical practice – Top 5 selection results



■Survey: Web survey
■Question: Based on the challenges you have answered so far in your clinical practice, please select the top 5 that you agree are the way things should be (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

4.2.2 Expectations for the pharmaceutical industry

- The pharmaceutical industry was expected to accelerate the discovery and development of new modalities and build an ecosystem for this purpose, improve access to information on medical institutions, healthcare professionals and pharmaceuticals / development products involved in testing and treatment and contribute to the formation of rules and public opinion toward the realization of a 'society in which people can live comfortably with illness.'
- Specifically, there is a need to accelerate R&D by incorporating funds from both within Japan and overseas, by collaborating across industries, by creating opportunities for such collaboration to ensure the quality of information related to testing, treatment, pharmaceuticals and clinical trials, to strengthen the standardization and dissemination of such information and to disseminate information on the necessity and value of rare disease medical care and drug discovery in Japan.

To realize the ideal state, expectations regarding R&D for pharmaceutical companies (Figures 4.2.2-1, 4.2.2-2) included support for both research and manufacturing of new modalities such as gene therapy and cell therapy.

In relation to this, it is hoped that collaboration with academia with an eye toward exit strategies, consultation services on R&D related systems such as pharmaceutical affairs, sharing of know-how, provision of research funds and sharing of clinical trial information will all be necessary to accelerate drug discovery.

In terms of human resource development and exchange, in addition to creating opportunities / space for the dispatch of personnel and joint research to enable closer collaboration between the private sector and academia, there was also hope for companies to clearly disclose information on focus areas to facilitate smoother negotiations on licensing and other matters aimed at the social implementation of drug discovery funds.

In actual clinical practice (figures 4.2.2-3, 4.2.2-4), there are high expectations for the development of new treatments, elimination of drug lag and development of diagnostic methods. In addition, an attitude that contributes to eliminating the perception gap between stakeholders and accelerating collaboration by increasing awareness and understanding of rare diseases among healthcare professionals, patients, and their families through efforts to disseminate information about pharmaceuticals and products under development in a more neutral and centralized manner, is needed.

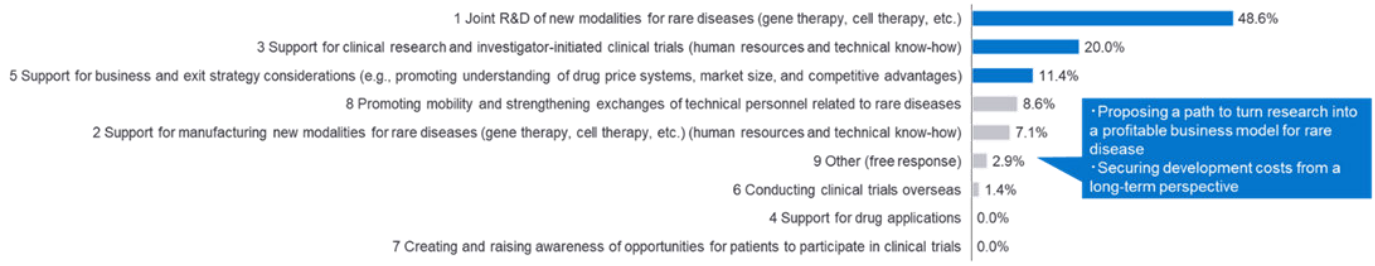
It was expected that the project would accelerate R&D through the incorporation of funds from both within Japan and overseas, collaboration across industries and the creation of similar opportunities, ensure the quality and standardization of information related to testing, treatment, pharmaceuticals and clinical trials and strengthen rare disease medical care and drug discovery in Japan (Figure 4.2.2-5).

> *I would like to see more efforts put into drug discovery for rare diseases and efforts to improve the accuracy of testing and diagnosis. Specifically, I would like to see continued visualization and update of progress of rare disease research, improved accessibility, creation of a system for accumulating genetic analysis data in Japan and the development of domestic drugs.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

> *I hope to create collaborative opportunities with academia and build closer ties. I believe that an environment in which academia, pharmaceutical companies, and Patient Advocacy Groups can naturally interact daily, such as by sending researchers from pharmaceutical companies to academia or creating joint research spaces, will become an important ecosystem for the development of new drugs.*
> (Clinical researcher (basic and applied) / neuromuscular disease)

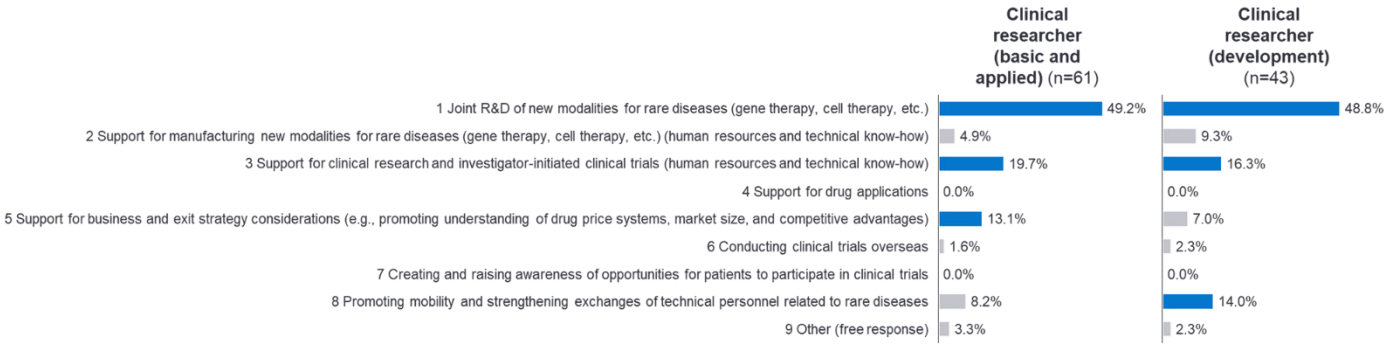
> *We hope to be able to communicate clinical trial information to patients and healthcare professionals in an easy-to-understand manner, and to lead to the development of new drugs.*
> (Specialist / Pediatrics)

Figure 4.2.2-1: Expectations for the pharmaceutical industry in research and development – Top selection results



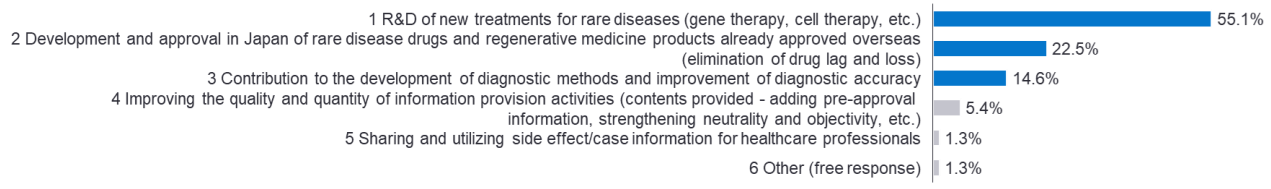
■Survey: Web survey
■Question: Please list your top three expectations for the pharmaceutical industry to achieve the ideal state (ranked)
■ Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.2-2: Expectations for the pharmaceutical industry in R&D – Top selection results by job type



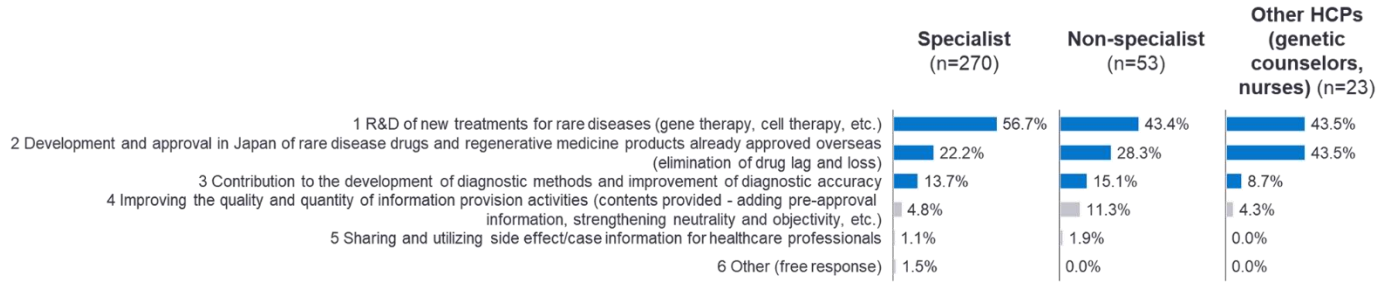
■Survey: Web survey
■Question: Please list your top three expectations for the pharmaceutical industry to achieve the ideal state (ranked)
■ Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.2-3: Expectations for the pharmaceutical industry in clinical practice – Top selection results



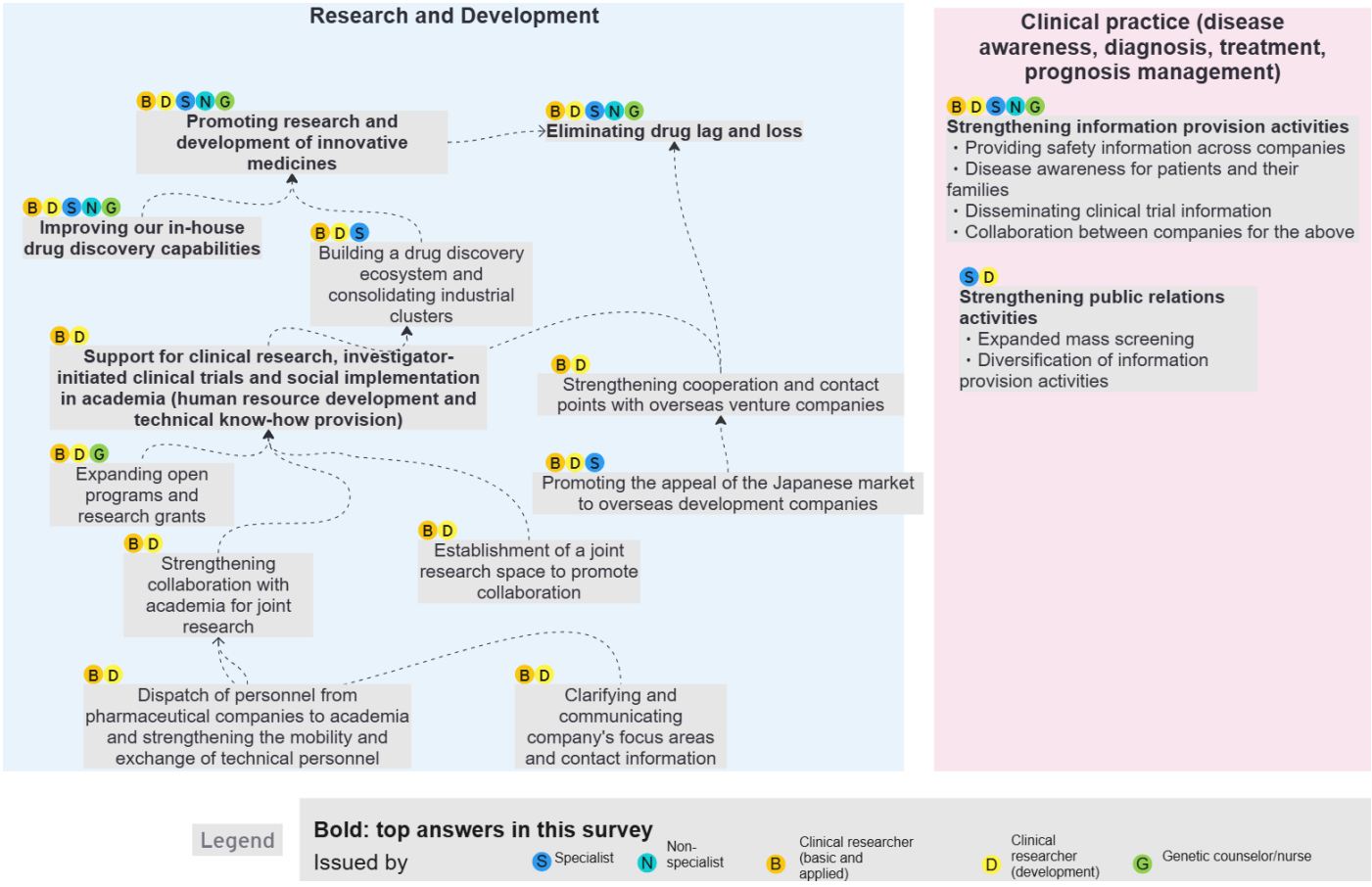
■Survey: Web survey
■Question: Please list your top three expectations for the pharmaceutical industry to achieve the ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.2-4: Expectations for the pharmaceutical industry in clinical practice – Top choice results by occupation



■Survey: Web survey
■Question: Please list your top three expectations for the pharmaceutical industry to achieve the ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.2-5: Overall expectations for the pharmaceutical industry



4.2.3 Expectations for academic societies

- The academic societies were expected to contribute to improving access to information on medical institutions, healthcare professionals, and pharmaceuticals / products under development involved in testing and treatment, expanding opportunities for training specialists and ensuring sustainability, and contributing to the formation of rules and public opinion toward the realization of a 'society in which people can live comfortably with their illnesses.'
- Specifically, there is a need to consolidate and network functions between medical institutions and healthcare professionals, speed up testing, create an attractive career development environment, disseminate role models and success stories, minimize barriers to participation, improve programs in specialized education courses and accelerate the mobility of human resources, and disseminate information about the necessity and value of rare disease medical care and drug development in Japan.

To realize the ideal status, clinical researchers (basic and applied) suggested that academic societies should provide incentives to secure human resources, while clinical researchers (development) suggested industry-government-academia collaboration (e.g., establishment of a consortium to develop treatments for rare diseases) (Figures 4.2.3-1, 4.2.3-2).

In actual clinical practice, the top priorities were the development of guidelines, the creation of educational opportunities, and the sharing of information overseas (Figures 4.2.3-3, 4.2.3-4). Specifically, to provide and expand educational opportunities related to rare diseases, it was necessary to increase the number of specialists and candidates involved in rare diseases by clarifying role models and career paths. To achieve this, it is necessary to build a system that contributes to more sustainable human resource development within the academic community, such as an appropriate evaluation and compensation system and improvements to the working environment, as well as to secure a budget to expand employment opportunities.

In addition, it was hoped that academic societies would take advantage of their neutrality and personal network to engage in proactive activities, such as eliminating vertical organizational silos and promoting collaboration among medical researchers, expanding reach to overseas companies by serving as a liaison office connecting with overseas bio ventures, and establishing and supporting a clinical trial framework that covers the entire country (Figure 4.2.3-5).

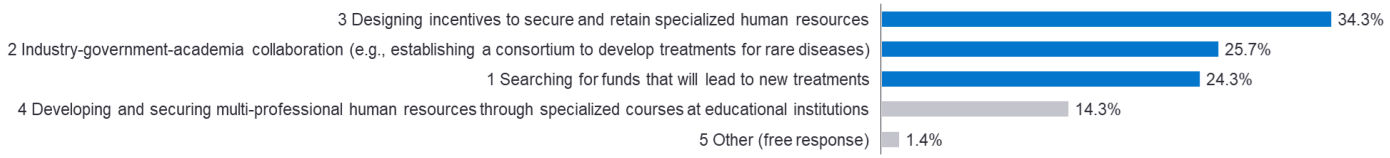
> *I would like them to compile and disseminate accurate information regarding treatment and diagnostic needs, etc.*
> (Non-specialist / Pediatrics)

> *Many of the patients who come to our hospital are referred from other hospitals, but some doctors are unsure of which patients they can refer to the hospital, so we feel it is necessary to strengthen awareness of referral criteria for each medical institution. We need to clarify which medical institutions have what expertise and the referral criteria for specialized facilities for each disease to accelerate cooperation between medical institutions.*
> (Specialist / Pediatrics)

> *We hope to see coordination of referrals from non-specialists to specialists to create an environment where referral sources can feel confident in referring patients in a timely manner.*
> (Non-specialist / Neurology)

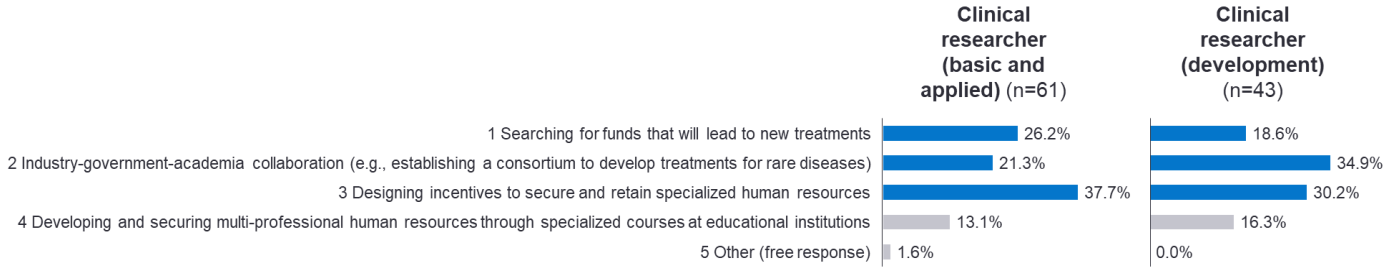
> *I want the unified voices of patients to be backed by academic evidence, that individual patients are not able to convey to the government. I believe that academic societies could complement the validity and importance of individual patients' claims. Internet has improved access to information, but erroneous understandings and different interpretations have increased as well. I want the academic society to clearly communicate what information is correct and what is incorrect.*
> (Clinical researcher (development) / All other hereditary disease)

Figure 4.2.3-1: Expectations for academic societies in research and development – Top selection results



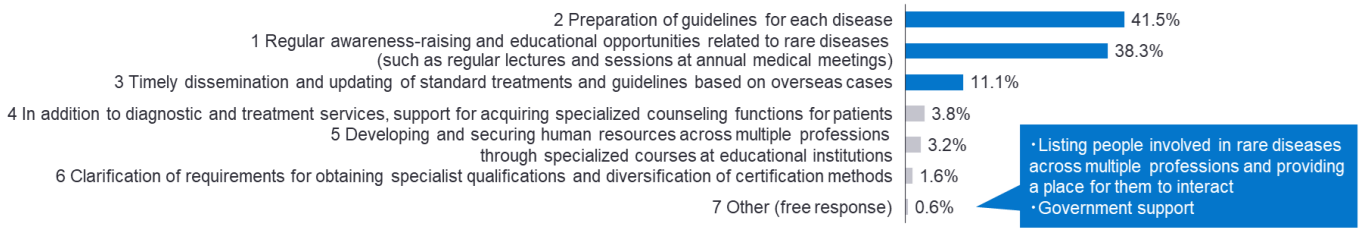
■Survey: Web survey
■Question: Please list your top three expectations from academic societies to realize your ideal state (ranked)
■ Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.3-2: Expectations for academic societies in research and development – Top selection results, by occupation



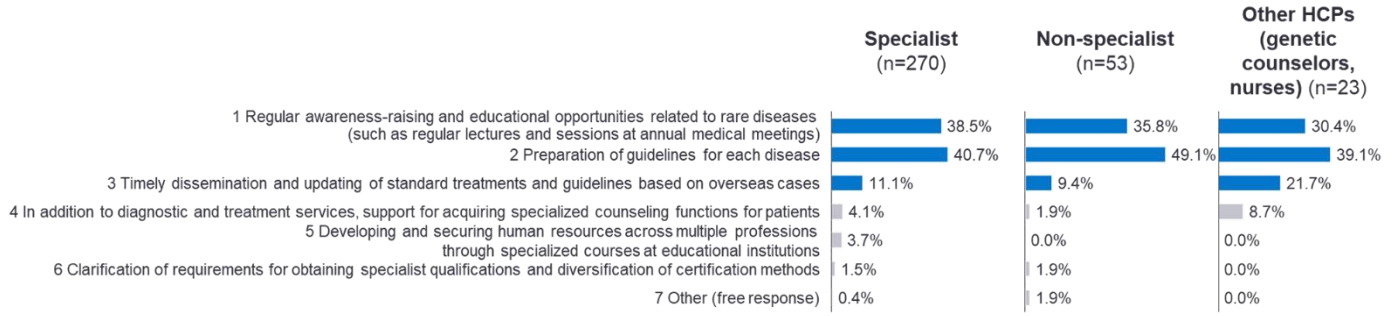
■Survey: Web survey
■Question: Please list your top three expectations from academic society to realize your ideal state (ranked)
■ Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.3-3: Expectations for academic societies in clinical practice – Top selection results



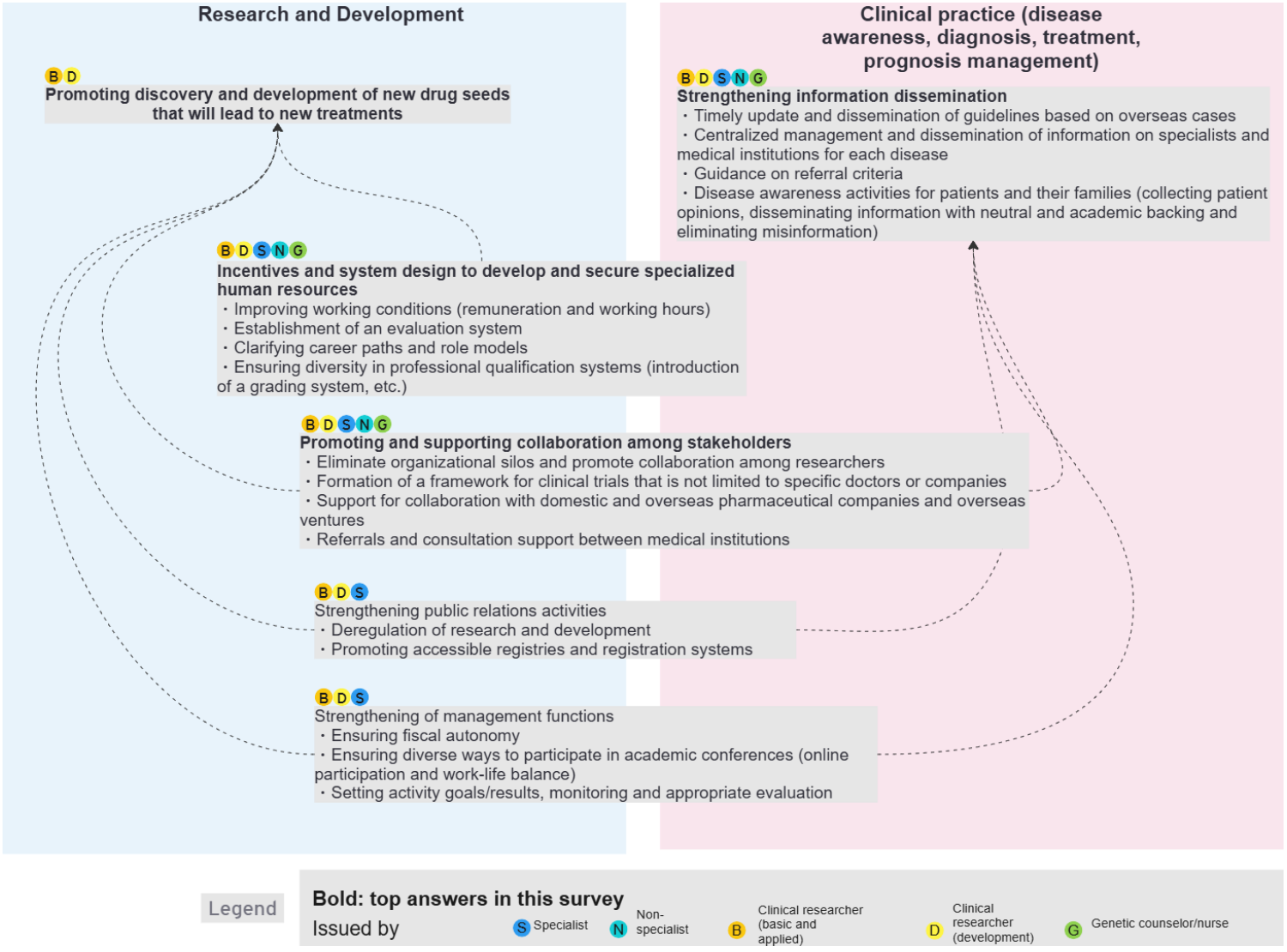
■Survey: Web survey
■Question: Please list your top three expectations from academic society to realize your ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.3-4: Expectations for academic societies in clinical practice – Top selection results by occupation



■Survey: Web survey
■Question: Please list your top three expectations from academic society to realize your ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.3-5: Expectations for academic society



4.2.4 Expectations for patient advocacy groups

- Patient advocacy groups were expected to accelerate the discovery and development of new modalities through collaboration with others and build ecosystems and systems for this purpose, improve access to information on medical institutions, healthcare professionals, and pharmaceuticals / products in development involved in testing and treatment, ensure diversification and flexibility in fund-raising and utilization methods, and participate in forming rules and public opinion to realize a 'society in which people can live comfortably with their illnesses.'
- Specifically, there is a need to strengthen organizational functions, advance PPI through inter-organizational collaboration, communicate needs, cooperate in registry construction, diversify activities and disseminate information to expand fundraising methods and strengthen organizational functions, and disseminate information about the necessity and value of rare disease medical care and drug discovery in Japan.

To realize this ideal state, there are high expectations that patient advocacy groups will increase their involvement in R&D, such as identifying needs in R&D, collaborating with academic societies and companies, and cooperating in building registries (Figures 4.2.4-1, 4.2.4-2).

To achieve this, there is a need to acquire the knowledge and skills to collaborate with each stakeholder, to become more involved in R&D that meets the needs of patients themselves, and to promote collaboration between patient advocacy groups as well as individual activities to raise resources (budgets and personnel) and societal interest.

In actual clinical practice, there was hope for strengthening information dissemination (Figures 4.2.4-3, 4.2.4-4). Specifically, in addition to the management activities of patient advocacy groups, there were hopes for fostering opportunities to involve more stakeholders and strengthening fundraising through external information dissemination activities such as charity and crowdfunding. These efforts would lead to awareness of organization and increase in activities in relevant disease field with expanded support by strengthening the organization and functions, patients' needs will be disseminated to the government and society and rare disease medical care will be considered proactively (Figure 4.2.4-5).

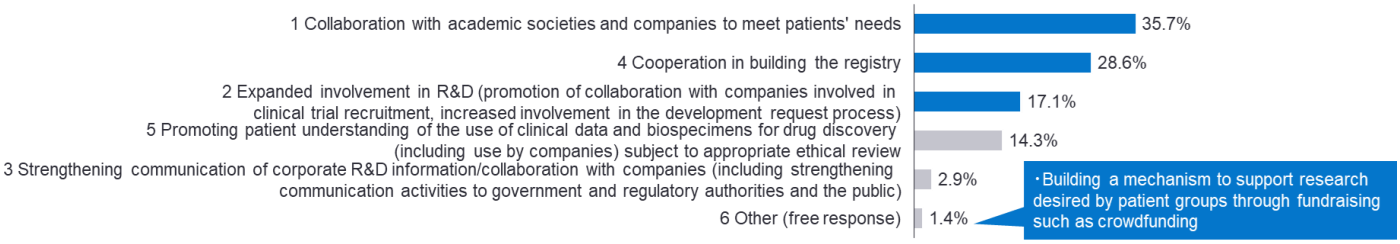
“*As a patient advocacy group, I would like to see the FDA actively involved in R&D and clinical activities. For example, while it is not easy for patients to register in the registry, without a foundation of patient data, further development is not possible, so I would like to see* Patient Advocacy Groups *actively cooperate with the FDA.*
(Clinical researcher (development) / All other hereditary disease)

“*Currently, the activities of each patient advocacy group vary, but regardless of the disease, patient advocacy groups are asked to improve peer support for patients and their families who cannot be supported by healthcare professionals.*
(Specialist / Pediatrics)

“*I believe that the existence and activities of patient advocacy groups have a major impact after a definitive diagnosis, and I hope that they will provide support to patients in terms of how to deal with the disease and in their daily lives mainly in terms of prognosis management.*
(Non-specialist / Neurology)

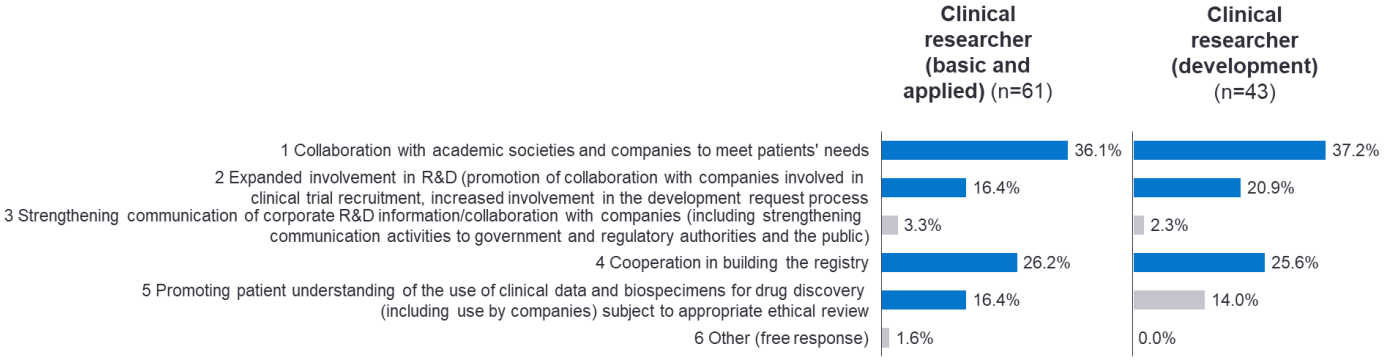
“*I would like them to strengthen their activities to raise awareness of themselves through media exposure, activities in the field of education, crowdfunding, etc. I think that by involving more stakeholders, creating contact points, and deepening mutual understanding, activities will accelerate.*
(Clinical researchers (basic and applied) / Other general hereditary disease)

Figure 4.2.4-1: Expectations for patient advocacy groups in research and development – Top selection results



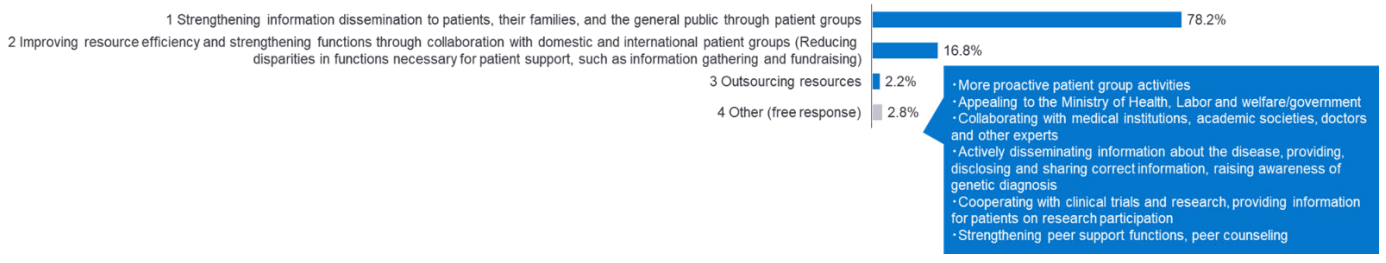
■Survey: Web survey
■Question: Please list your top three expectations of patient advocacy groups to achieve your vision (ranked)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.4-2: Expectations for patient advocacy groups in R&D – Top choice results by occupation



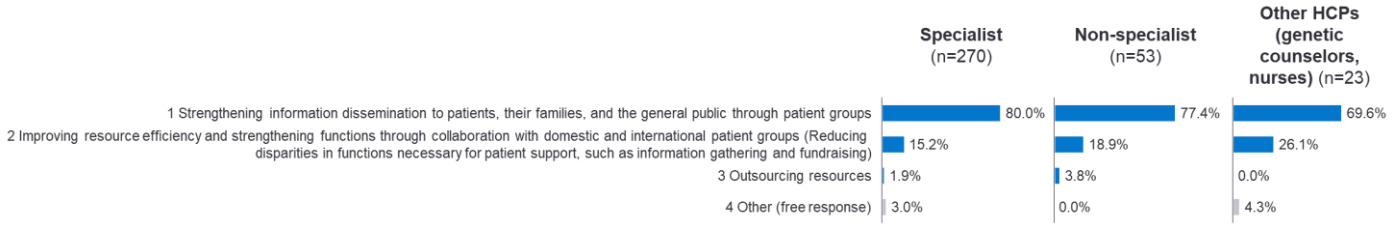
■Survey: Web survey
■Question: Please list your top three expectations of patient advocacy groups to achieve your vision (ranked)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.4-3: Expectations for patient advocacy groups in clinical practice – Top choice results



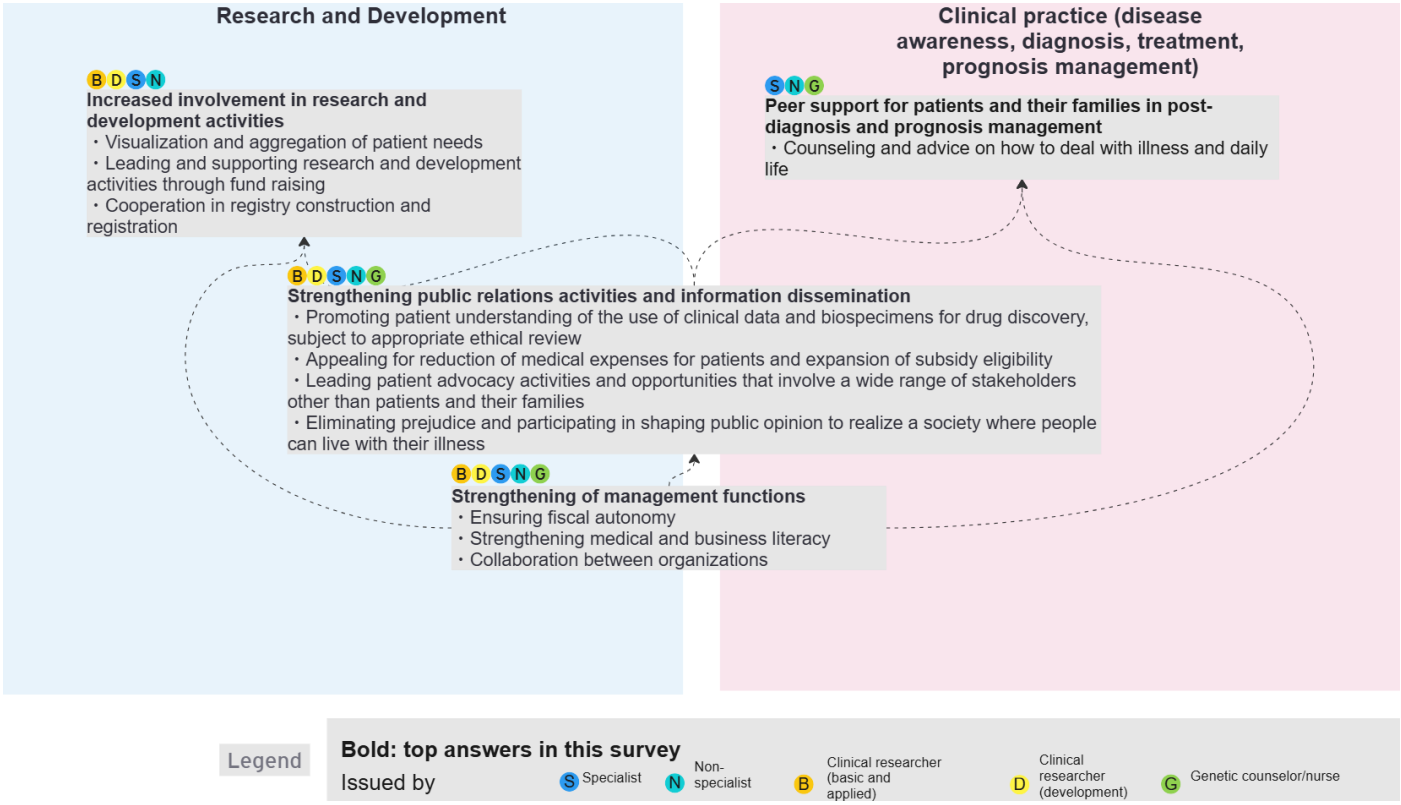
■Survey: Web survey
■Question: Please list your top three expectations of patient advocacy groups to achieve your vision (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.4-4: Expectations for patient advocacy groups in clinical practice – Top choice results by occupation



■Survey: Web survey
■Question: Please list your top three expectations of patient advocacy groups to achieve your vision (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.4-5: Overall Expectations of patient advocacy groups



4.2.5 Expectations for government and regulatory authorities

- Government and regulatory authorities were expected to support the promotion of R&D and policies related to the diagnosis of rare diseases; build ecosystems to accelerate drug discovery and development of new modalities; improve access to medical institutions and healthcare professionals who can perform testing and treatment and information on pharmaceuticals and products under development; expand opportunities to train specialized human resources and ensure sustainability; ensure diversification and flexibility in fund-raising and utilization methods; and contribute to the formation of rules and public opinion toward the realization of a 'society in which people can live comfortably with their illnesses.'
- Specifically, there is a demand to support the introduction of cutting-edge technology and infrastructure in drug discovery, such as GMP-compliant facilities and CPCs, promotion of drug pricing and pharmaceutical systems that will contribute to increasing the attractiveness of Japan's rare disease market, bold deregulation that will benefit patients, promotion of cooperation between medical institutions and the development of data infrastructure and systems to improve the efficiency of information transmission, improvement of the overall functionality of the medical system related to rare diseases through legislation, the development of registries, expansion of recipients and incentives for medical remuneration related to rare disease medical care, and policy discussions aimed at reducing the burden on patients and their families (such as the introduction of curricula on intractable and rare diseases in primary and secondary education, and special measures in research, development, and clinical practice).

To realize the ideal status, there are high expectations for government and regulatory authorities to support R&D related to the diagnosis of rare diseases. There are also high expectations for diversifying the means of fundraising for research, supporting R&D of new modalities, supporting the acceleration of animal model research and non-clinical trials, and establishing a drug price system that can properly evaluate the value of drugs for rare diseases (Figures 4.2.5-1, 4.2.5-2). Specifically, there were requests to lower the hurdles for R&D, simplify and ease the complex pharmaceutical system to eliminate drug lag and loss, establish a drug price system that can properly evaluate the value of drugs so that companies can recover their investments and promote drug discovery, and increase the budget necessary for training programs and employment of human resources who will be responsible for rare disease treatment in the future.

In addition, in actual clinical practice, there were expectations for support related to accelerating early diagnosis, disseminating the latest treatment methods, promoting collaboration between medical institutions and doctors, and strengthening expertise (Figures 4.2.5-3, 4.2.5-4). Specifically, in addition to involving various stakeholders, such as expanding mass screening, patient registries, promoting the use of medical data, consolidating and sharing functions in rare disease medical care (Center of Excellence, CoE [9]), and establishing rare disease-related programs in primary and secondary education and specialized education, administrative leadership through legal development was required. In relation to this, about human resource development, there were expectations for improving literacy and understanding not only in central government ministries and agencies but also in local government settings. These points were also mentioned in 4.1 Challenges, and concrete discussions are required to be promoted in the future.

> *"There are significantly fewer GMP-compliant facilities and CPC equipment related to new modalities compared to Europe and the United States, making securing materials a challenge.*
> (Clinical researcher (basic and applied) / Collagen Disease Department)

[9] To systematically create facilities and organizations that provide excellent treatment and research in specific medical fields

It is becoming more difficult to obtain funding from pharmaceutical companies, and the problem is that the government is not providing any budgetary support or alternatives to these situations. The current research grant system should be made more flexible, including reviewing the amount of funding and the selection criteria.
(Clinical researcher (basic and applied) / Pediatrics)

Clinical trial information is not being communicated to subjects sufficiently, making it extremely difficult to recruit appropriate subjects. If clinical trial information were centrally collected and there was a system that allowed users to narrow down clinical trial and subject information, it would be convenient for both healthcare professionals and subjects.
(Specialist / Pediatrics)

We hope that the government will aim to create a society in which 'patients can access the information and medicines they need' and 'patients and their families can live the same lives as healthy people' through a significant increase in budgets and personnel, relaxation of restrictions on the provision of information by the pharmaceutical industry and a review of genetics and diversity primary education.
(Clinical researcher (development) / All other hereditary disease)

I hope to see deregulation that will make it easier for industry-government-academia collaboration to proceed, genetic education for younger generations to help create a society free of prejudice and friction, and the development of mechanisms and systems that will allow people in rural areas to seamlessly receive medical care, such as testing and examinations, for rare diseases. I look forward to government leadership in the discussion of how to create a society that tolerates risk and failure.
(Clinical researcher (basic and applied) / All other hereditary disease)

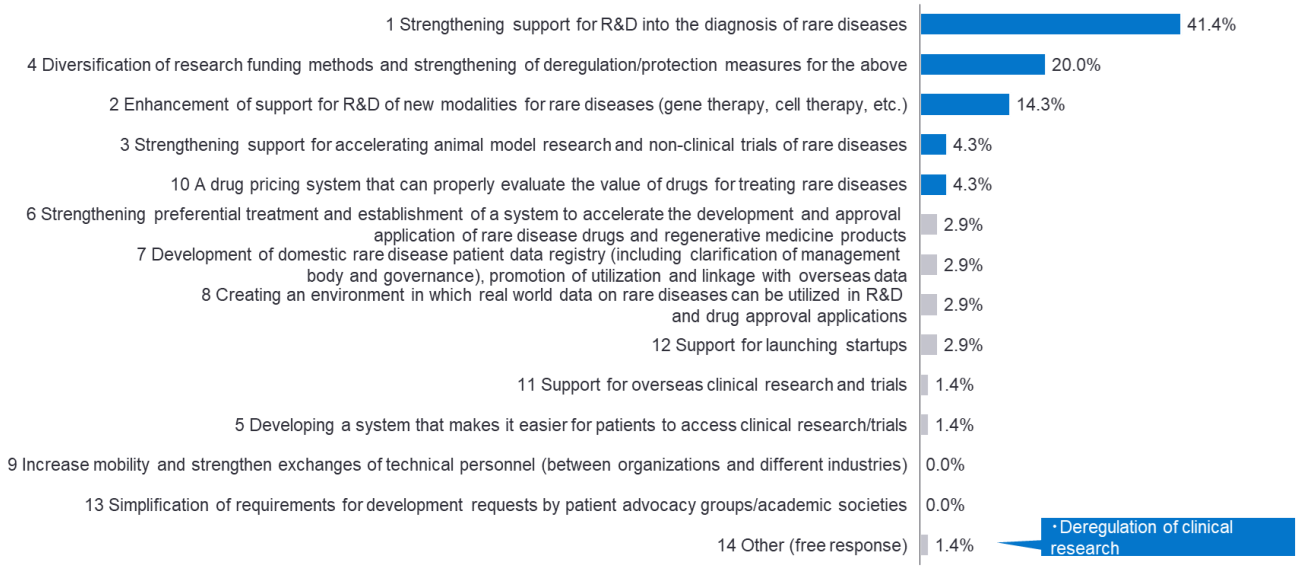
To resolve the shortage of human resources at medical institutions, we need to secure the necessary budgets for hiring and training full-time staff, make it easier to startup ventures on campus, and design incentives within academia through a review of personnel evaluation and rules on part-time work.
(Specialist / Collagen Disease Department)

Currently, registries are left to the discretion of individual organizations and individuals, but it would be ideal to have a registry system established as infrastructure by the government, like that for cancer, so that it can be used for research leading to the resolution of rare disease challenges. It would also be necessary to link this to the designated intractable disease system, and to relax regulations to promote the use of data.
(Specialist / Pediatrics)

The information provided by the government is often needed later, and the information itself is complicated and difficult to understand, which may result in delayed adoption of the system. I would like to see the system itself, such as medical fees, made easier to understand, and effectively communicated to healthcare professionals and facilities at the time they need it. I would also like to see the government strengthen its consultation function, which allows for frequent consultations, rather than simply communicating information one-way.
(Non-specialist / Neurology)

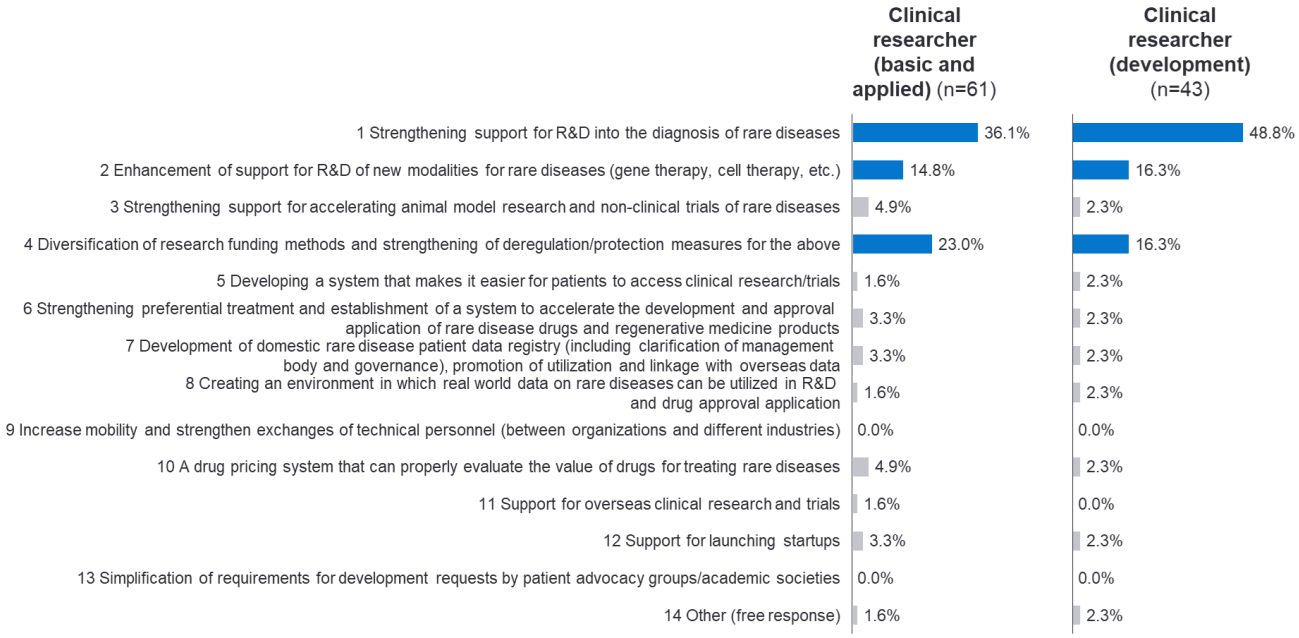
There is a large gap in understanding and response to rare disease medical care among local government officials, and policies are not unified. It is necessary to secure opportunities to deepen awareness and understanding.
(Clinical researcher (development) / Endocrinology and Metabolic Disease)

Figure 4.2.5-1: Expectations for government and regulatory authorities in R&D – Top selection results



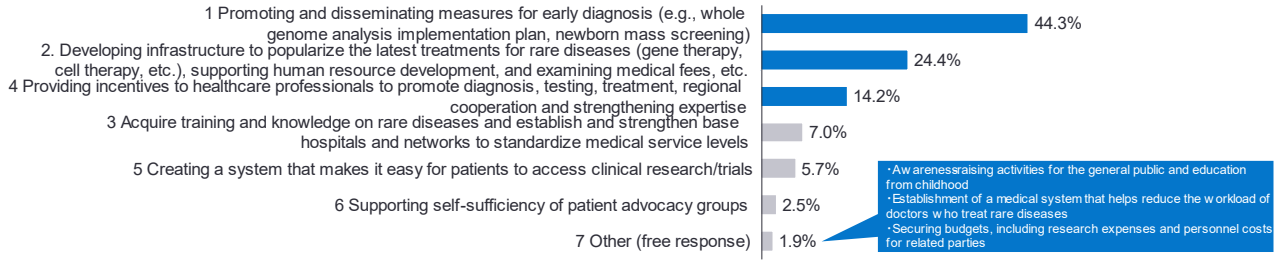
■Survey: Web survey
■Question: Please select the top five options that you expect from government and regulatory authorities to achieve the ideal state (ranked)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.5-2: Expectations for government and regulatory authorities in R&D – Top selection results by occupation



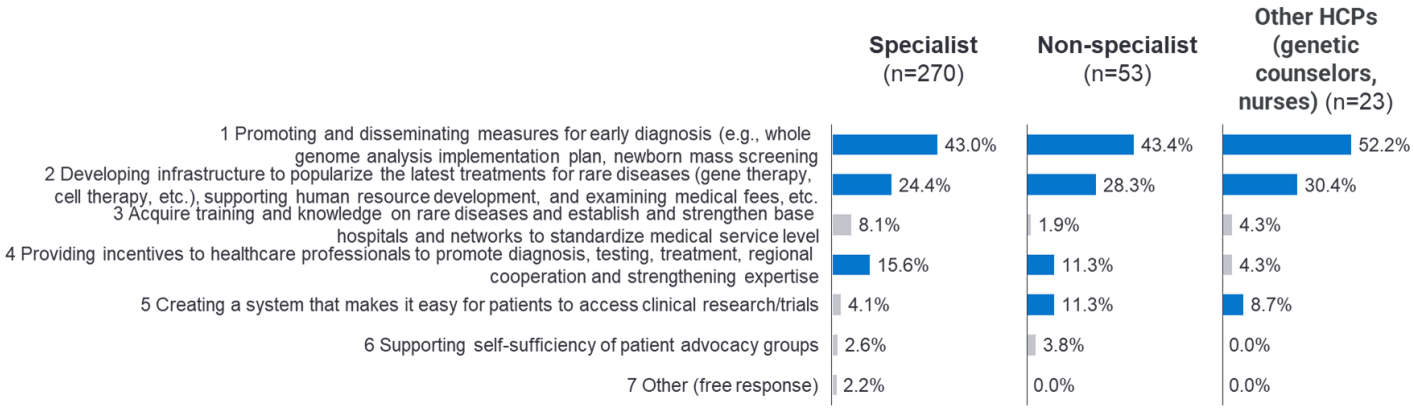
■Survey: Web survey
■Question: Please select your top five expectations of government and regulatory authorities to achieve the ideal state (ranking format)
■Subjects: 70 clinical researchers (basic and applied), clinical researchers (development)

Figure 4.2.5-3: Expectations for government and regulatory authorities in clinical practice – Top choice results



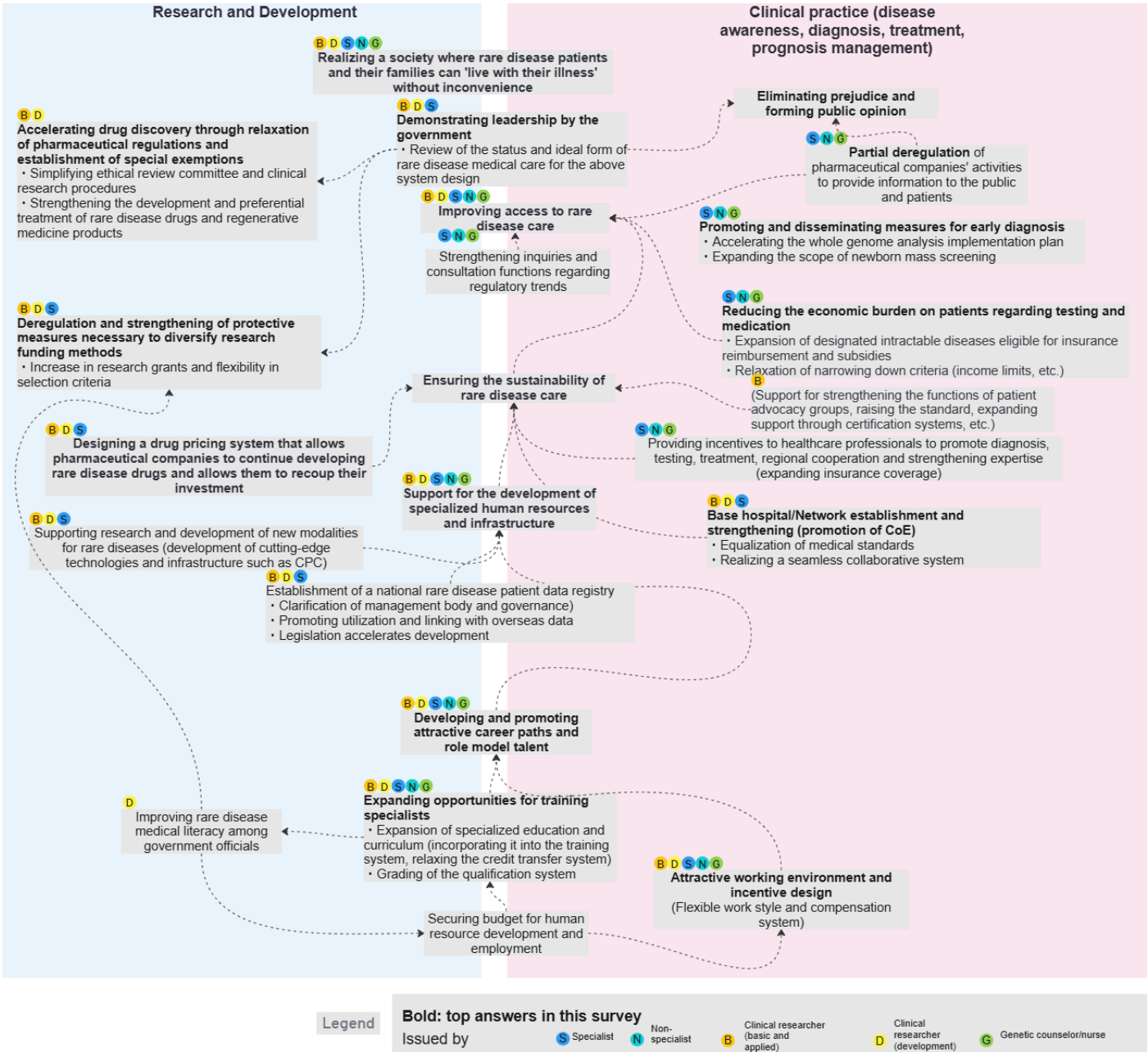
■Survey: Web survey
■Question: Please list your top three expectations of government and regulatory authorities to achieve the ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.5-4: Expectations for government and regulatory authorities in clinical practice – Top results by occupation



■Survey: Web survey
■Question: Please list your top three expectations of government and regulatory authorities to achieve the ideal state (ranked)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

Figure 4.2.5-5: Overall expectations of government and regulatory authorities



4.2.6 Column: Future expectations for rare disease medicine

Hidehiro Mizusawa, MD, PhD
Principal Investigator, Initiative on Rare and Undiagnosed Diseases (IRUD)
President Emeritus, President Special Advisor, National Center of Neurology and Psychiatry (NCNP)

On this occasion, Initiative on Rare and Undiagnosed Diseases (IRUD), Rare Disease Consortium Japan, and Japan Pharmaceutical Manufacturers Association have joined forces to carry out this comprehensive survey. We are delighted to share the findings and, simultaneously, outline strategic directions for addressing the identified challenges. IRUD has garnered support from a multitude of researchers, physicians, and healthcare professionals, marking this survey as unprecedented in its scope, and effectively bringing to light the myriad challenges faced by stakeholders daily. The challenges have been systematically cataloged and scrutinized from multiple angles, offering a holistic overview as well as detailed insights into diagnosis, treatment, and research and development. Moreover, we have synthesized and evaluated potential solutions, segmenting them by domain for ease of reference for those in search of domain-specific information.

Rare and intractable diseases are often mired in diagnostic uncertainty due to their scarcity and complexity, which in turn hampers the progress of therapeutic advancements, resulting in a substantial quandary. Since its establishment as a flagship initiative by Japan Agency for Medical Research and Development (AMED) in 2015, IRUD celebrates its tenth anniversary, having registered 9,046 families, completed analyses for 7,316, and identified causative factors in 3,521 cases, accounting for 48% of the total. Notably, this includes instances where novel genetic variants have been discovered, leading to the recognition of new disease entities and the initiation of therapeutic development, as well as cases where a diagnosis was finally secured after a prolonged diagnostic odyssey, with some patients fortuitously having access to existing treatments that led to recovery. The feedback from patients has been overwhelmingly positive, yet there have also been instances of bewilderment, underscoring the realities of genomic medicine in our nation.

In a serendipitous alignment, the "Act on the comprehensive and planned promotion of measures to ensure that the public can receive high-quality and appropriate genomic medicine with peace of mind," also known as the Genome Medicine Promotion Act, came into effect in May 2023, with the foundational plan currently under development. The insights derived from this survey are anticipated to enhance the substance and practicality of this foundational plan. As the survey has unveiled, the landscape of rare and intractable diseases is fraught with formidable challenges. Nevertheless, the success of IRUD in pinpointing genetic variants in nearly half of the undiagnosed cases, coupled with the development of gene therapies that have enabled previously immobile infants to stand and walk, heralds an optimistic future for the realm of rare and intractable diseases. It is our sincere hope that this report will make a meaningful contribution to the realization of that promising future.

5. Conclusion

In this survey, we identified challenges from the perspective of healthcare professionals in five areas (1. Basic and applied research, 2. Development and clinical trials, 3. Diagnosis, 4. Treatment and prognosis management, 5. Disease awareness) and analyzed their underlying causes. Furthermore, we clarified expectations of each stakeholder (pharmaceutical industry, academic societies, patient advocacy groups, and the government) and organized the ideal form for improving medical care for rare diseases, specific response measures and their roles.

As detailed in this report, there are numerous challenges in the diagnosis and treatment of rare diseases. Notably, delayed diagnoses, limited treatment options, and difficulties for patients in accessing information are among the key challenges. Overcoming these challenges necessitates the cooperation and collaboration of all stakeholders, not only in enhancing diagnostic techniques and developing new treatments but also in strengthening patient support. Additionally, it is crucial to deepen public understanding of the challenges associated with rare diseases through awareness campaigns.

This survey also targeted healthcare professionals who have been leading the way in rare disease medicine in specific medical departments and disease areas in Japan. By expanding and delving deeper into the survey population in the future, we aim to further concretize the challenges and expectations identified in this survey and advance towards realizing the envisioned ideal state.

We, IRUD, RDCJ and JPMA, express our respect for the energetic activities and significant contributions of all those involved to date. We are committed to working in collaboration with stakeholders to address the diverse challenges surrounding healthcare professionals identified in this survey, with the goal of creating a more livable society for patients with rare diseases and their families.

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Rare diseases clinical research network
https://www.rarediseasesnetwork.org/
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Rare Diseases NSW
https://rarediseasesnsw.org.au/
Government of Western Australia Department of Health
https://www.health.wa.gov.au/
Australian children living with rare diseases: health service use and barriers to accessing care
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https://www.rarediseases.in/
RARE-X
https://rare-x.org/
Department of Health and Family Welfare - Institutions Treating Rare Diseases
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https://pubmed.ncbi.nlm.nih.gov/37795705/

7. Authors and acknowledgments

IRUD

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Rare Disease Consortium Japan

Rare Disease Consortium Japan was established on February 29, 2024, as an organization that promotes medical research and drug discovery for rare diseases, with collaboration amongst industry, academia, the public, and private sectors at its core with the aim of realizing patient-centered medical services. The fact that we were able to conduct the 'Survey on the challenges faced by healthcare professionals in rare diseases' in collaboration with the JPMA and IRUD was a valuable opportunity to give momentum to our organization's activities. We would like to express our sincere gratitude to all those involved who provided their support and cooperation in carrying out this project.

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JPMA

Rare and Intractable Disease Task Force

Japan Pharmaceutical Manufacturers Association (JPMA) organized Rare and Intractable Disease Task Force in 2021 to pay tribute to the dedicated activities and significant contributions of those involved in intractable and rare diseases and to play a part in this effort. In 2023, we executed and published a ‘Survey on the challenges faced by healthcare professionals in rare diseases’, compiled a recommendation on rare and intractable diseases and are working with relevant parties to resolve these challenges. We would like to express our sincere gratitude to all those involved for their support and cooperation in conducting the survey on the challenges facing healthcare professionals in rare diseases and in compiling this report.

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EY Parthenon

Building a better working world

(Planning and management support)

EY Parthenon Health & Life Sciences team has developed feasible strategies that go beyond the traditional framework of consulting to ensure sustainable development of healthcare system for the next 100 years and provides optimal services to all stakeholders across industries. Leveraging our global network and scale, members with diverse expertise we have organically collaborated with a wide range of stakeholders to conceive and implement problem-solving solutions that transcend the boundaries of private, public and academic sectors. In this survey, we supported the planning and management of the survey together with IRUD, RDCJ and JPMA. We would like to express our sincere gratitude to all involved parties, and we will continue to aim to build a better working world for all those involved in rare diseases.

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- To maintain neutrality, this report uses survey data executed by IRUD, RDCJ, and the Japan Pharmaceutical Manufacturers Association (JPMA) on behalf of a third-party organization (EY Strategy & Consulting Co., Ltd.)
- Although we strive to ensure the accuracy, validity, and timeliness of the information provided in this survey, we do not guarantee it
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