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)

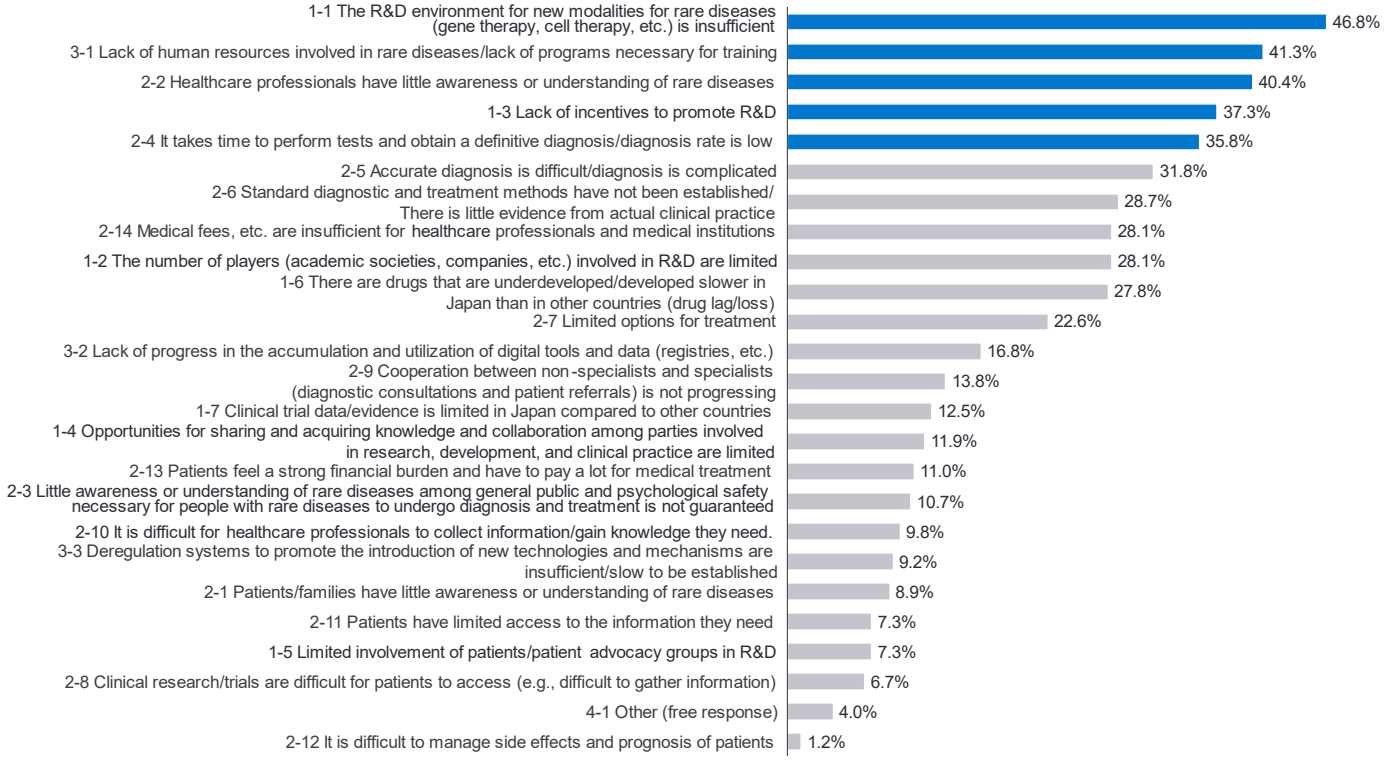
> *Many genetic analysis and counseling services are not covered by insurance, making it difficult for medical institutions to make a profit. There is a shortage of people to carry out these tasks because there is no appropriate compensation (evaluation or remuneration) for the time spent. There are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

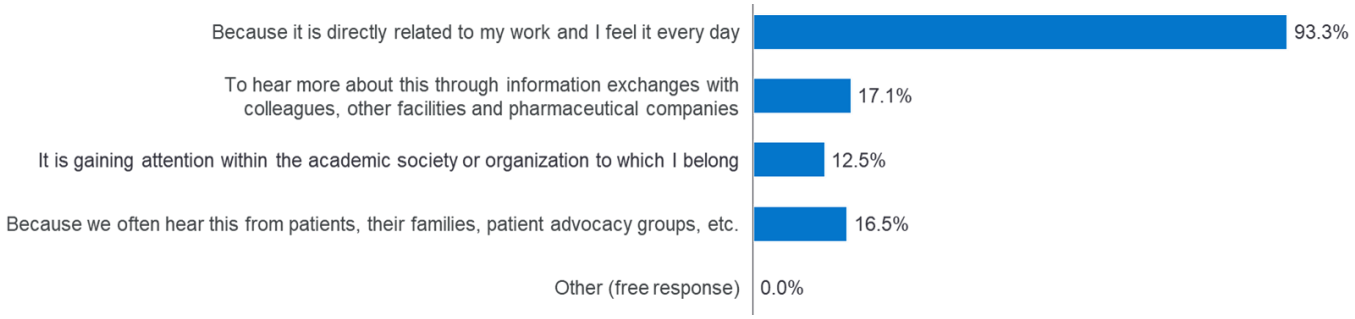
(Clinical researcher (development) / Endocrinology and Metabolic Disease)

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.

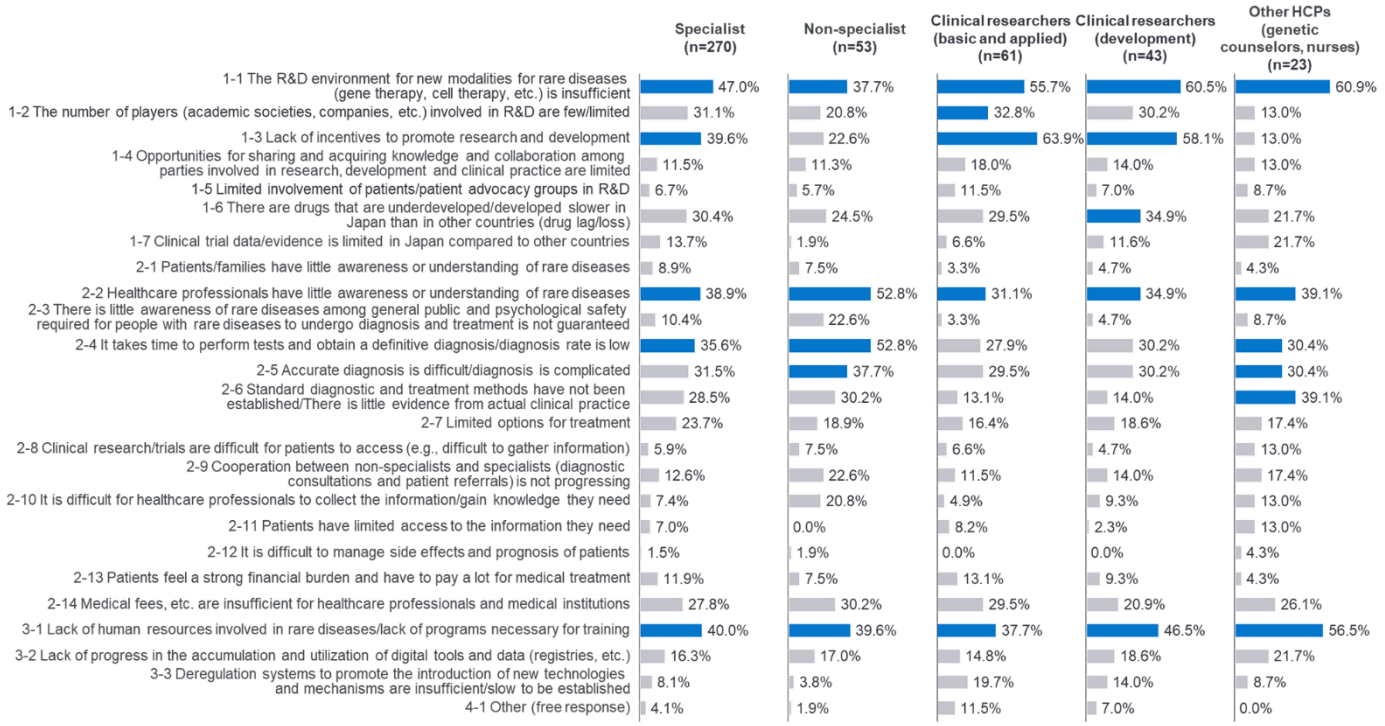
Among non-specialists, '2-2 Healthcare professionals have little awareness or understanding of rare diseases' ranked higher than other professions, indicating a lack of knowledge and experience.

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.

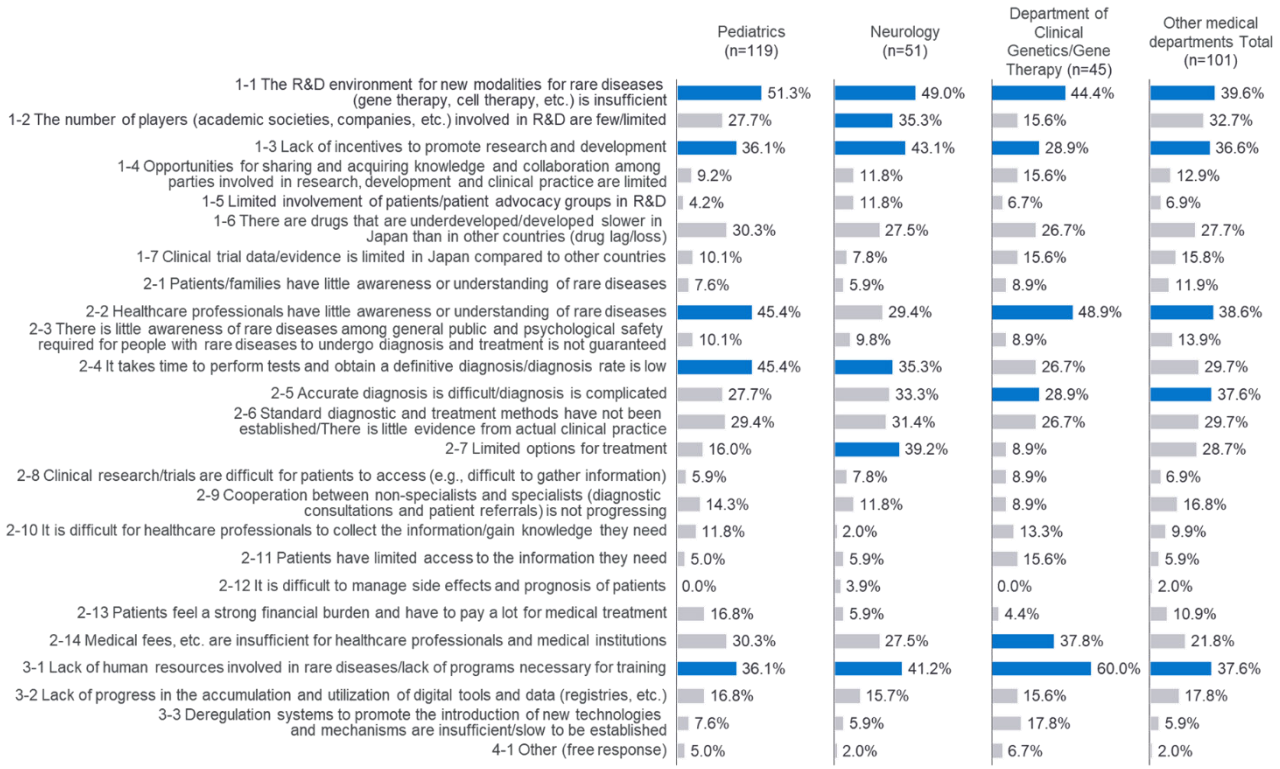
In pediatrics, ‘2-4 It takes time to perform tests and get a definitive diagnosis / diagnosis rate is low’ was ranked second highest compared to other medical departments, which is a major challenge. This is presumably because, as mentioned above, early intervention can lead to improved prognosis in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

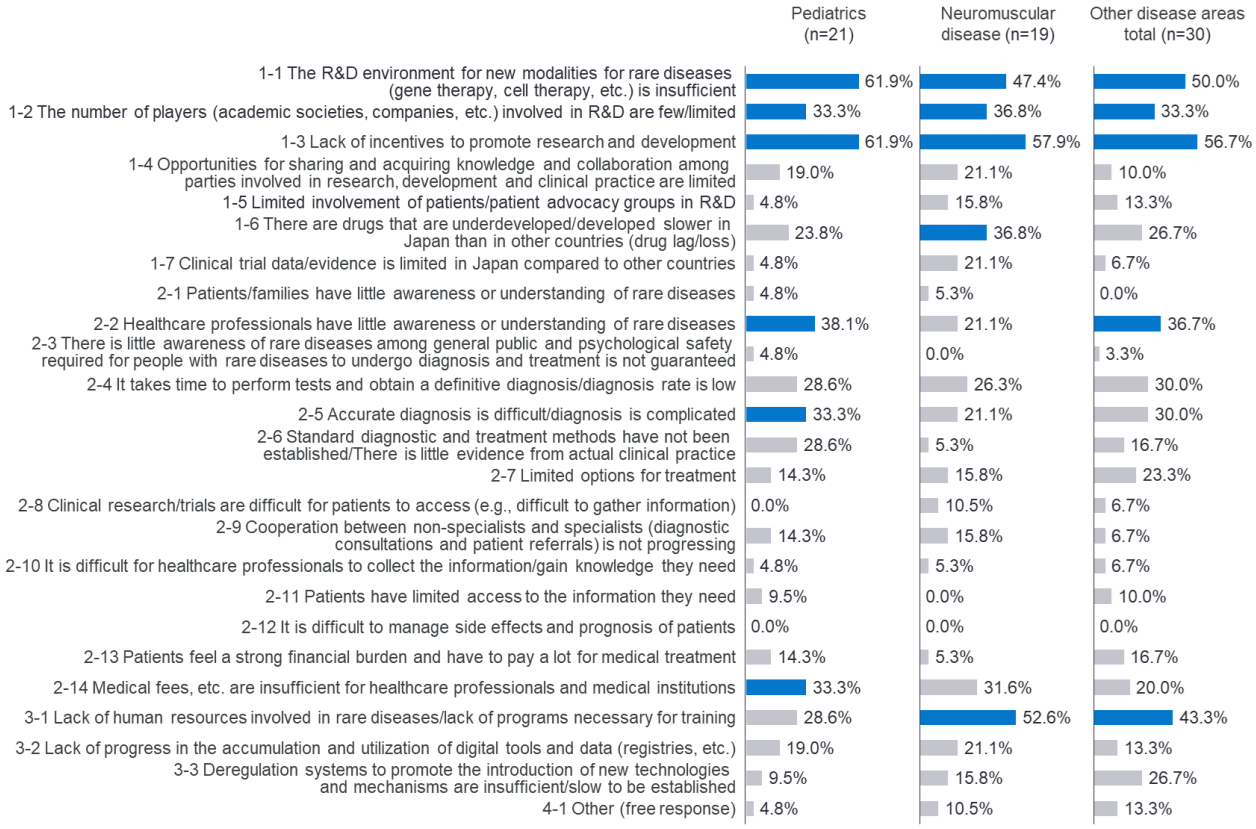
The results by disease research area (Figure 4.1.1-5) also show a similar trend in the top-ranked challenges. In neuromuscular disease, where practical application has progressed relatively well in Japan, the challenge of ‘3-1 Lack of human resources involved in rare diseases / Lack of programs necessary 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)

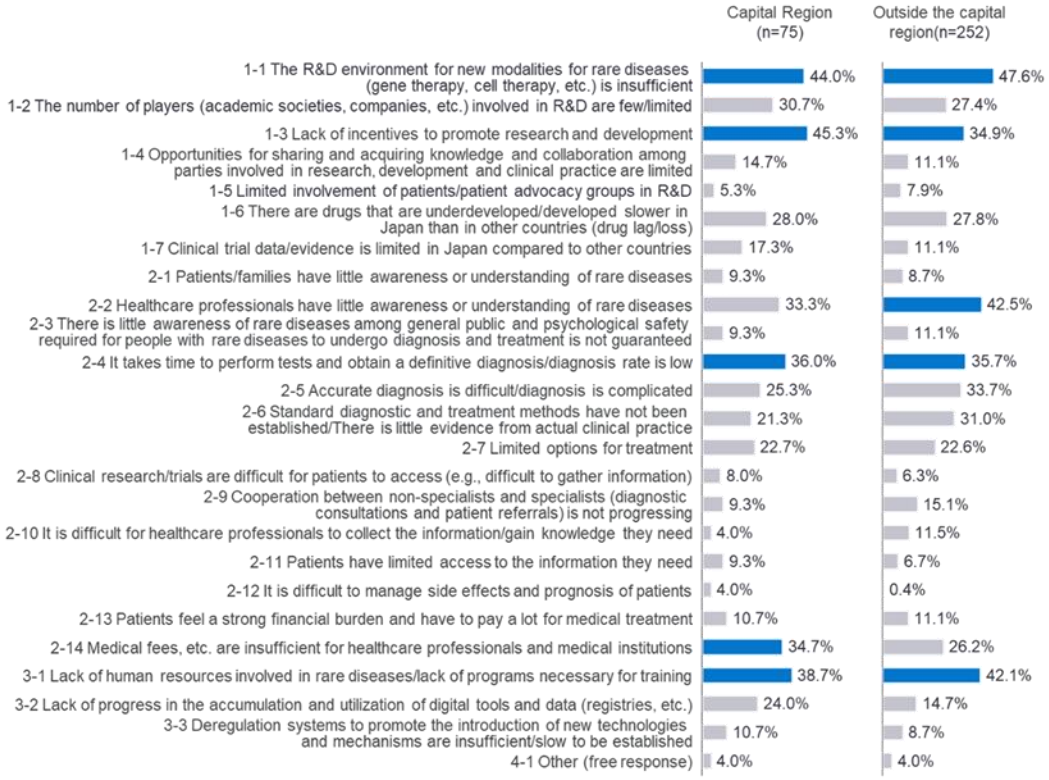
> *In urban areas, there are too many options and it is difficult to decide which hospital to refer patients to. In most cases, the test results of other medical institutions are not made public, so it is difficult to trust them with patients. Even large hospitals may not have genetic specialists, so 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)

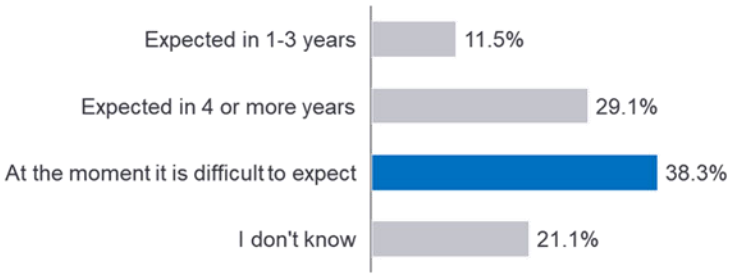
“If the number of patients is small, it is difficult to collect data for large-scale clinical trials, etc. If the number of patients is small, it is difficult to put a study into clinical practice.
(Non-specialist / Neurology)

“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)

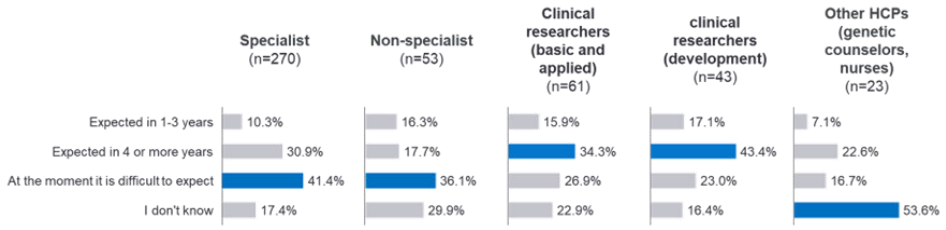
Figure 4.1.2-1: Expectations for progress in R&D leading to fundamental treatments for rare diseases



■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)

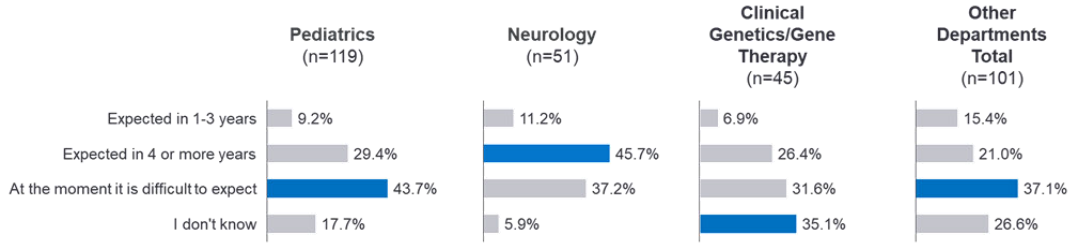
Figure 4.1.2-2: Expectations for progress in R&D leading to fundamental treatment of rare diseases
- A by occupation type / B by medical department

A



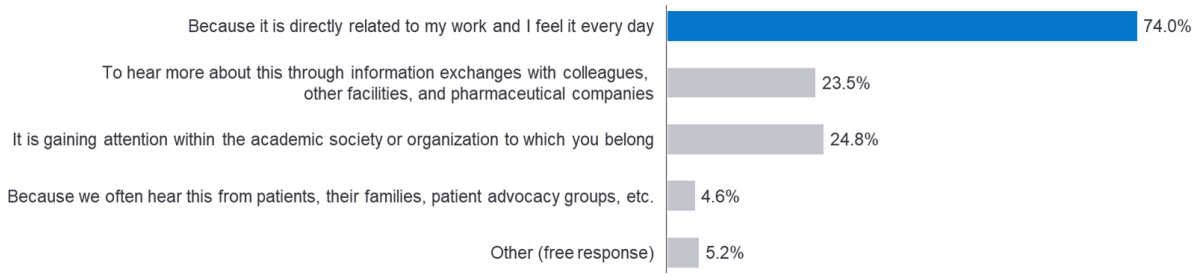
■Survey: Web survey
■Question: Please answer the question about the rare disease you answered in Q13. Do you expect progress in R&D leading to a fundamental treatment for the rare disease? (Q13: Please answer the name of the main rare disease among your activities related to rare diseases in the past 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.

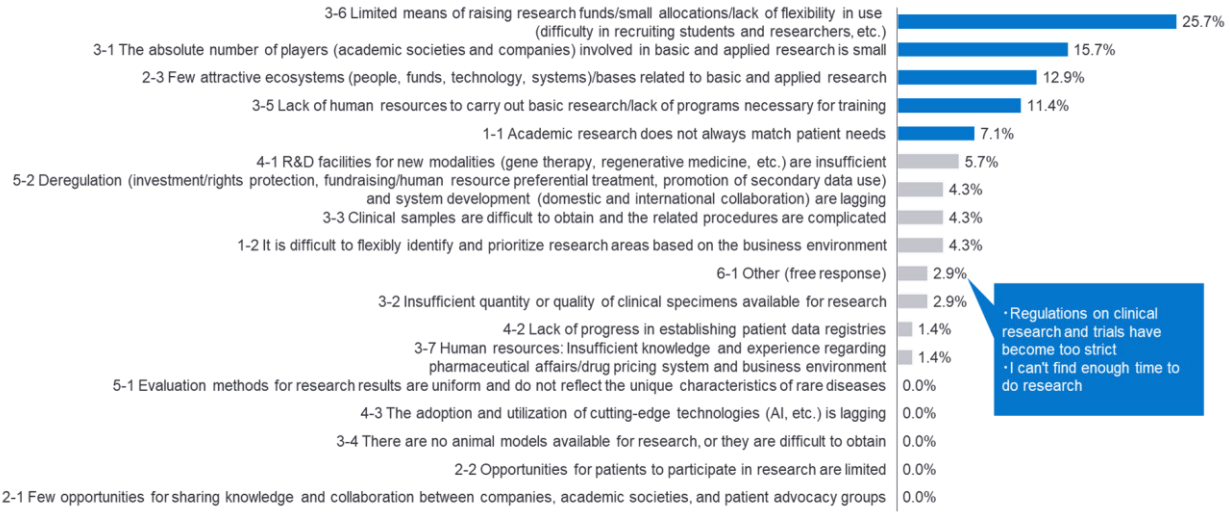
> *In Europe and the United States, funding sources for research are broad and diverse, and beneficiaries of research results, such as Patient Advocacy Groups, actively provide funds. Goals are clear to advance research that meets patients' needs.*
> (Clinical researcher (basic and applied) / neuromuscular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

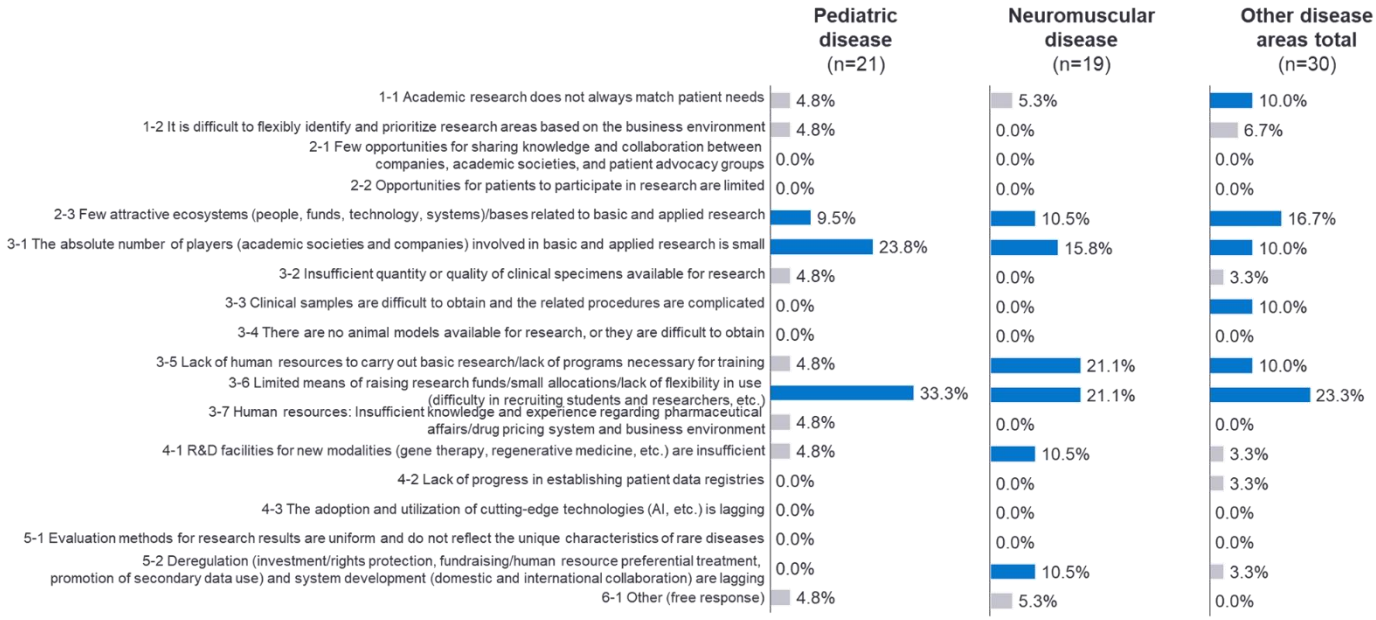
> *In Japan, social consensus takes priority when it comes to the social implementation of research and development, and there is insufficient discussion of "what should be prioritized for the patient in front of us." There is a strong tendency to be intolerant of risks and challenges, and a system should 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



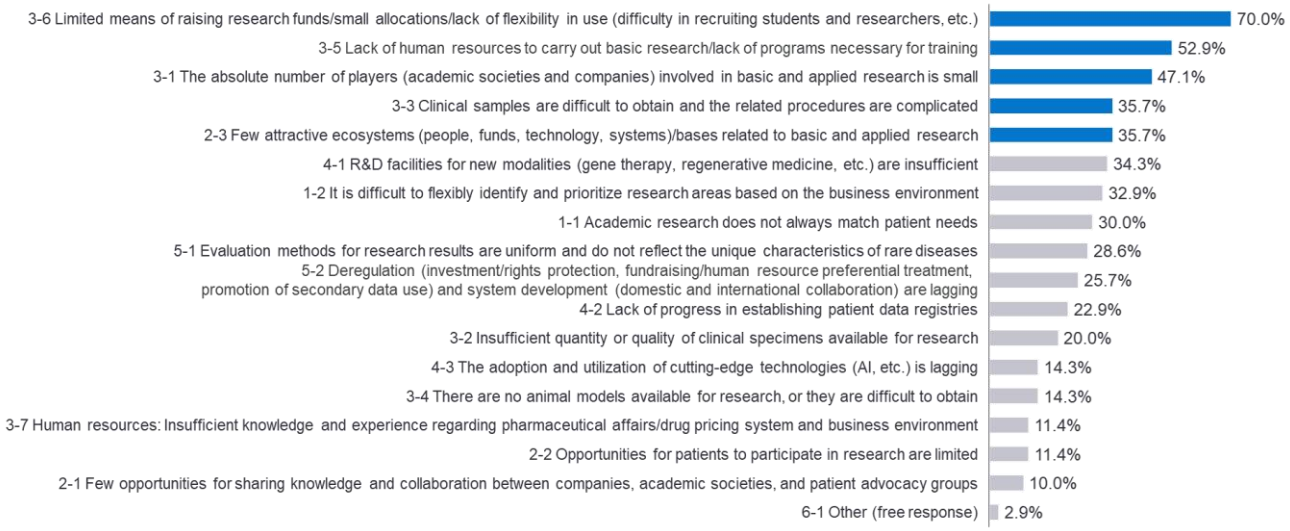
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

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



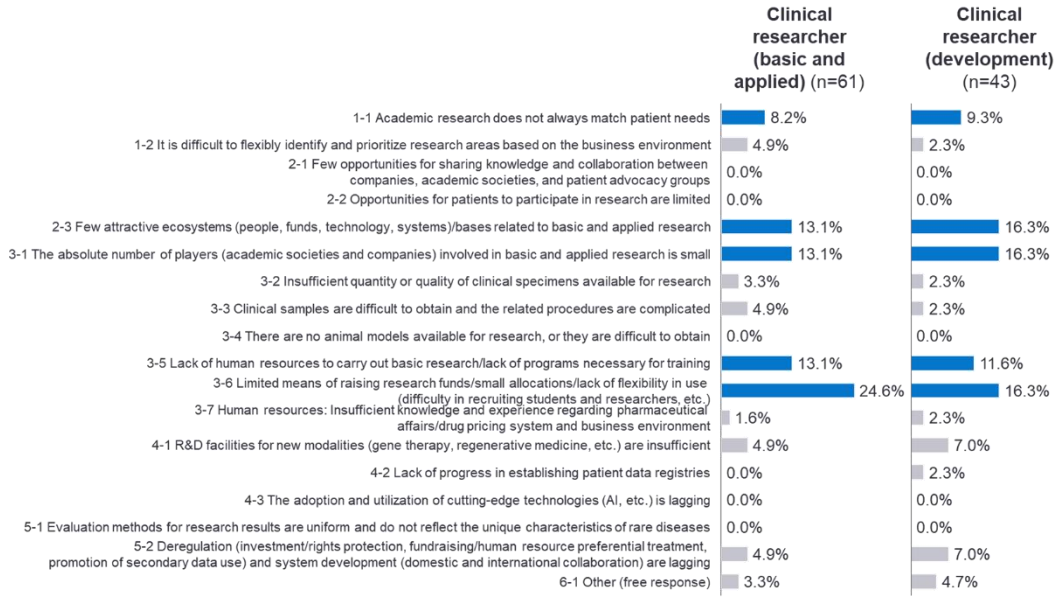
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

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



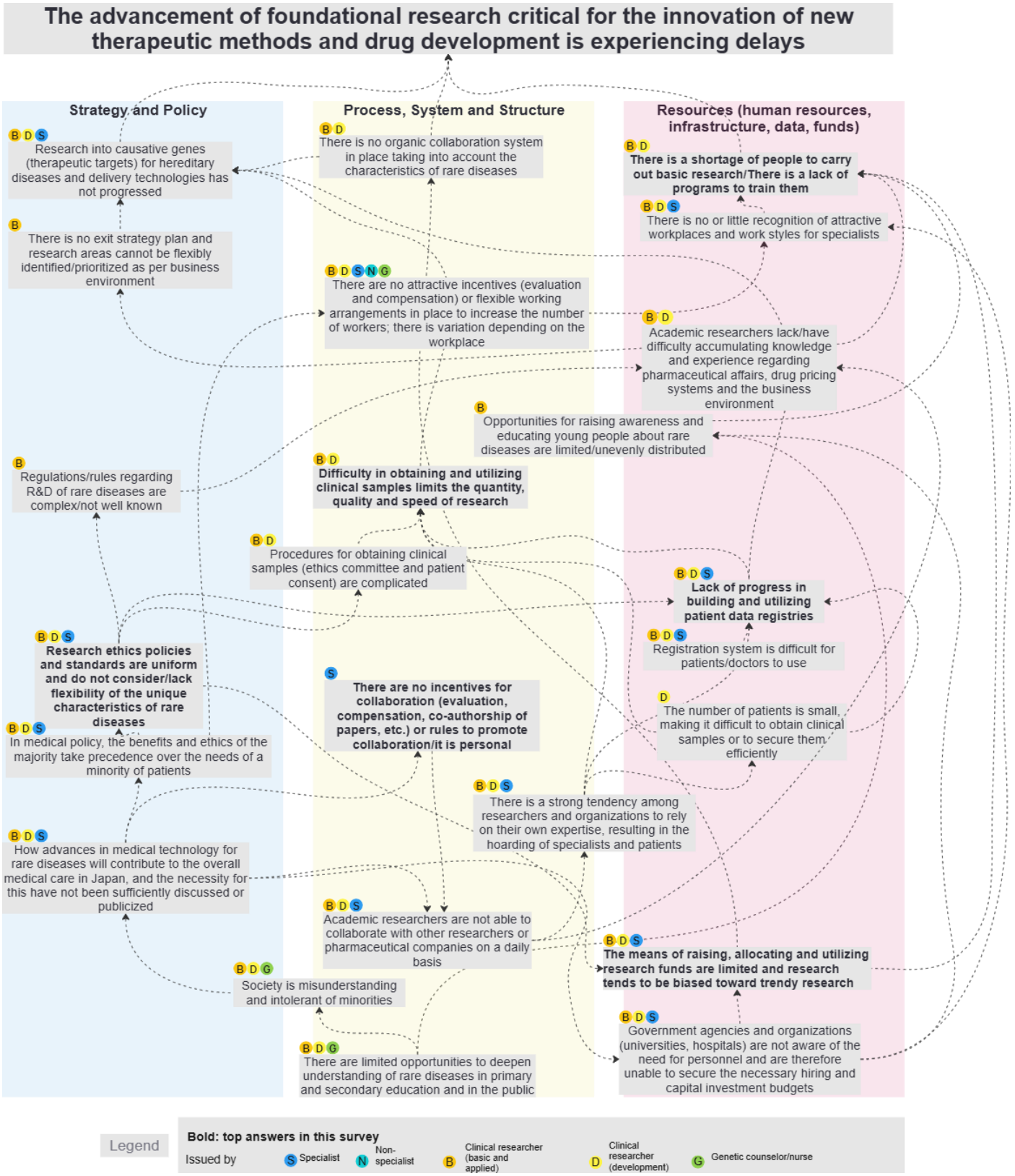
■Survey: Web survey
■Question: Please select the top 5 challenges that you feel are most important in basic and applied research (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

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)

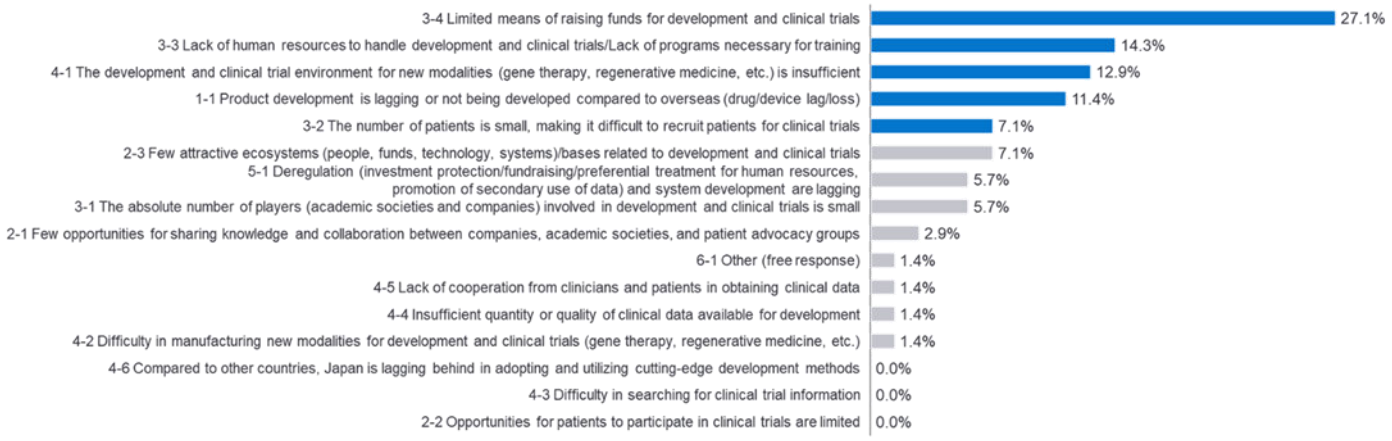
"Working efficiently within a pre-determined framework has become the goal, and fewer young doctors feel motivated to work closely with patients for a long time, such as in the treatment of rare diseases. On the other hand, the burden on those who take on this role is heavy, so the way in which doctors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

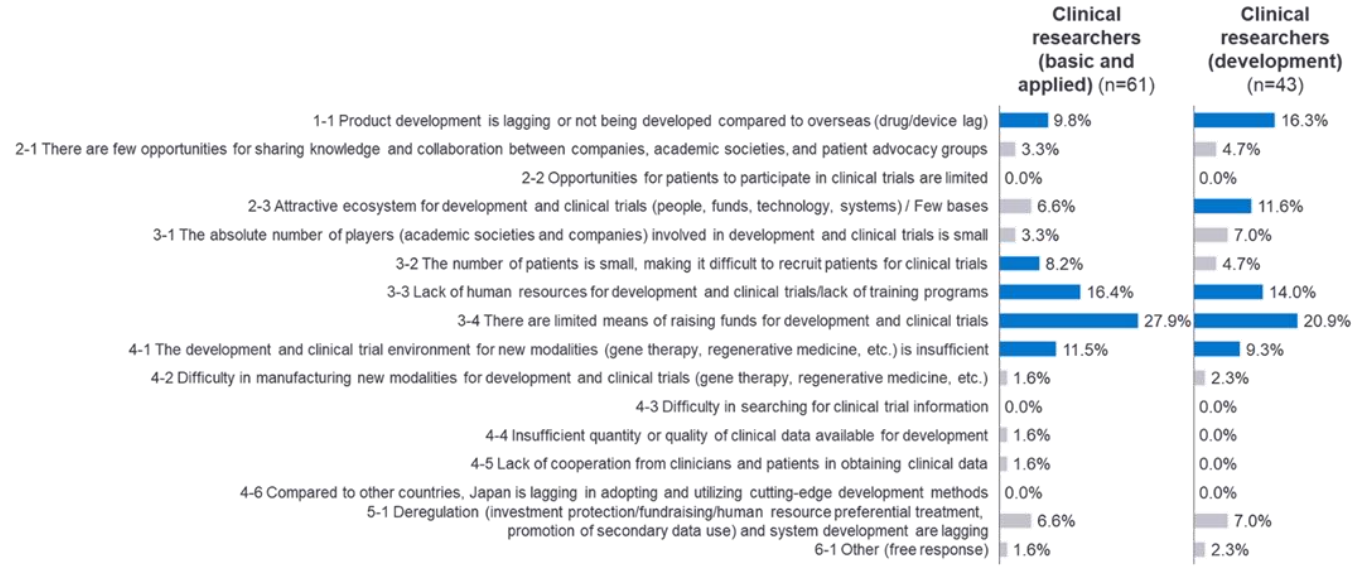
"Development involves risks, and when social responsibility arises, standards should be set by the government rather than being left to researchers.
(Clinical researcher (basic and applied) / Pediatrics)

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



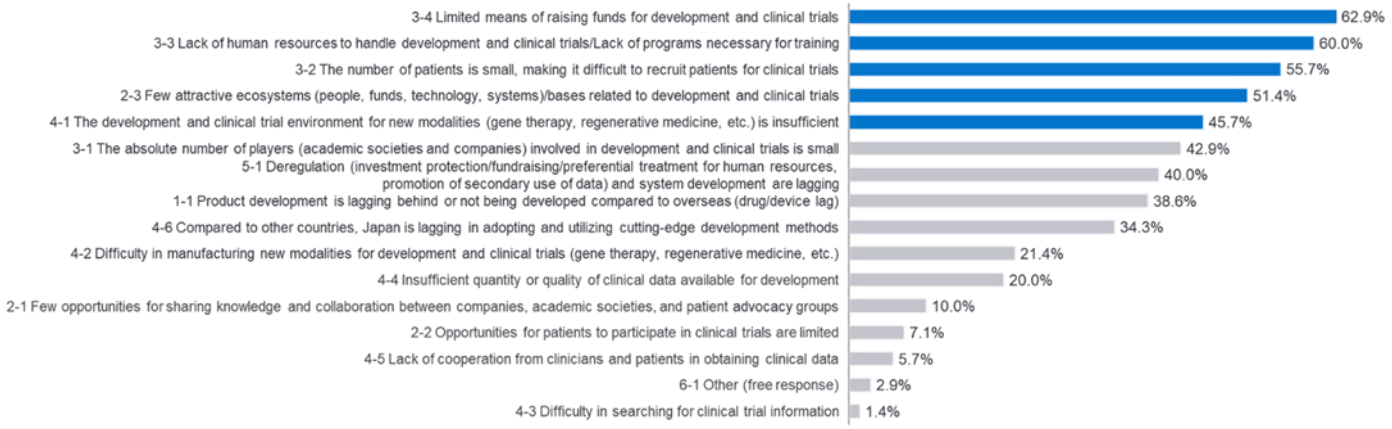
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most challenging regarding development and clinical trials (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

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



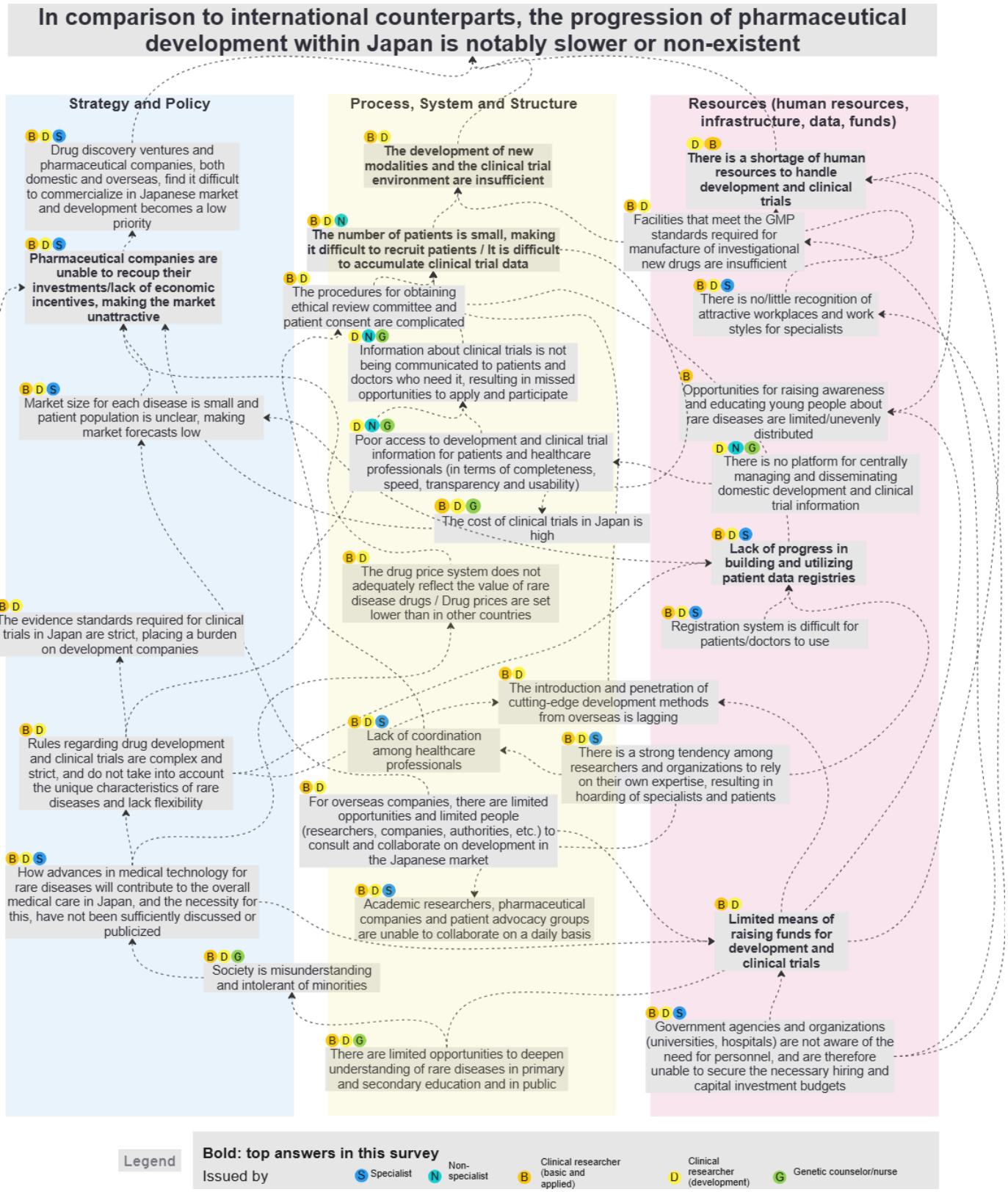
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most challenging regarding development and clinical trials (ranking format)
■Subjects: 70 clinical researchers (basic and applied) and clinical researchers (development)

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

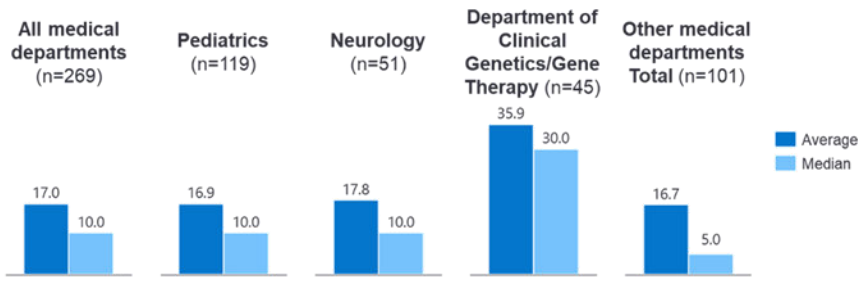
- The perceived challenges in diagnosis remain the accuracy and speed of diagnosis, and the reasons cited for this include a shortage of specialists who can make correct diagnoses and engage with patients, as well as a lack of platforms or mechanisms that facilitate collaboration between medical institutions 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.

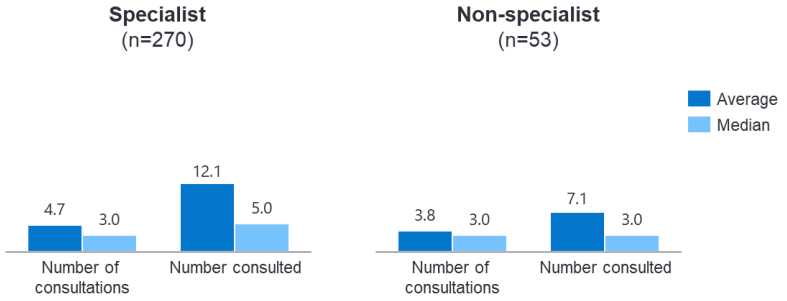
Figure 4.1.4-1: Number of patients with suspected rare diseases referred to specialists per year



*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)

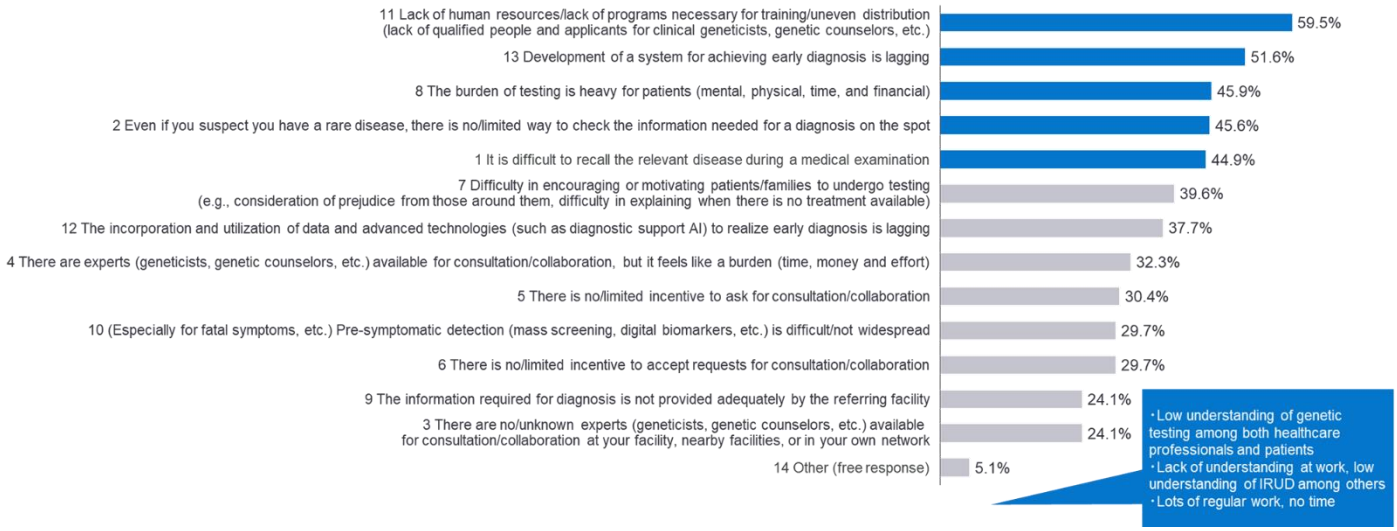
“The key to early diagnosis is how to promote newborn mass screening and expand the scope of its targets. This will eliminate the need to repeat unnecessary tests and treatments. The government should allocate more of its budget to this.
(Specialist / Pediatrics)

“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)

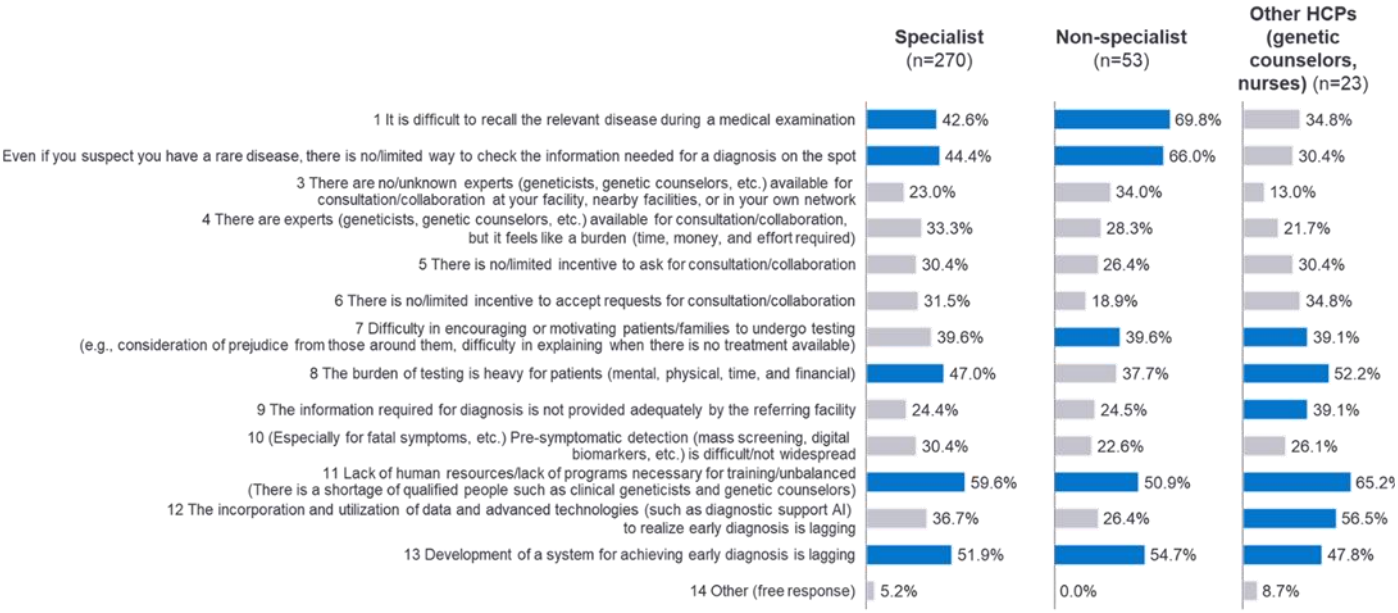
“When collaborating with other medical institutions, only information that can be included in the patient's referral letter can be provided or obtained, so if data could be shared more quickly, referrals may also increase.
(Clinical researcher (development) / Immunodeficiency Disease)

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



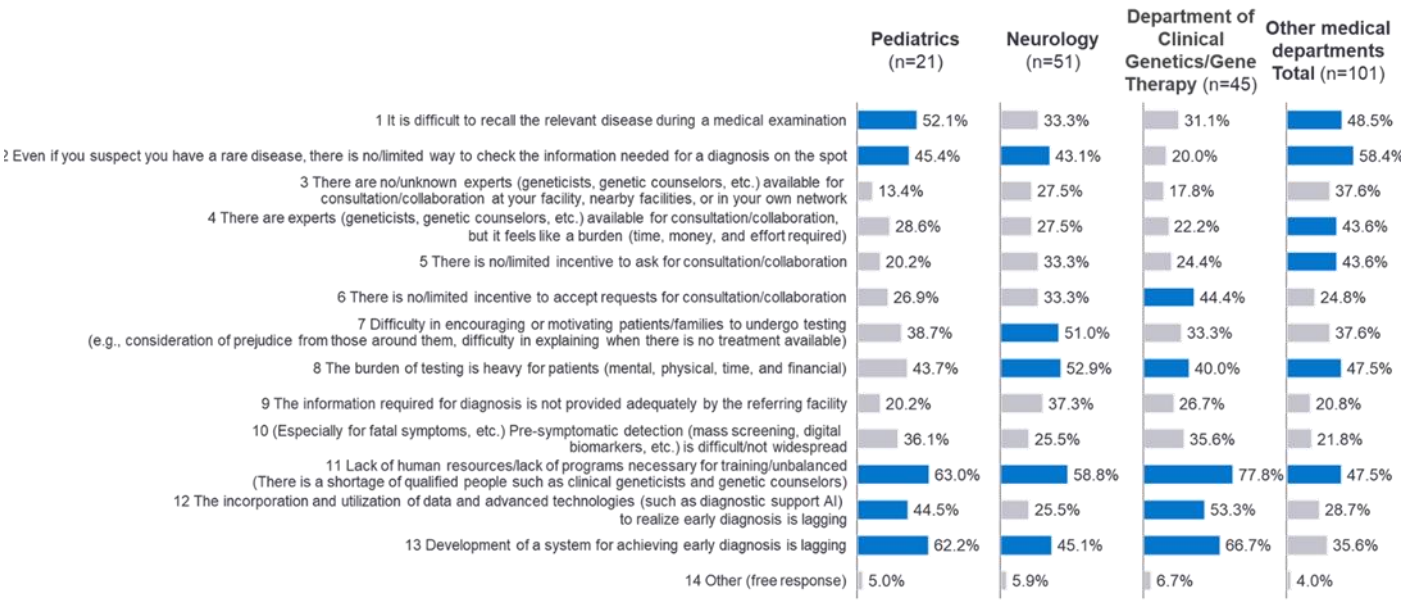
■Survey: Web survey
■Question: Please select the top 5 most pressing challenges you feel are related to diagnosis (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

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



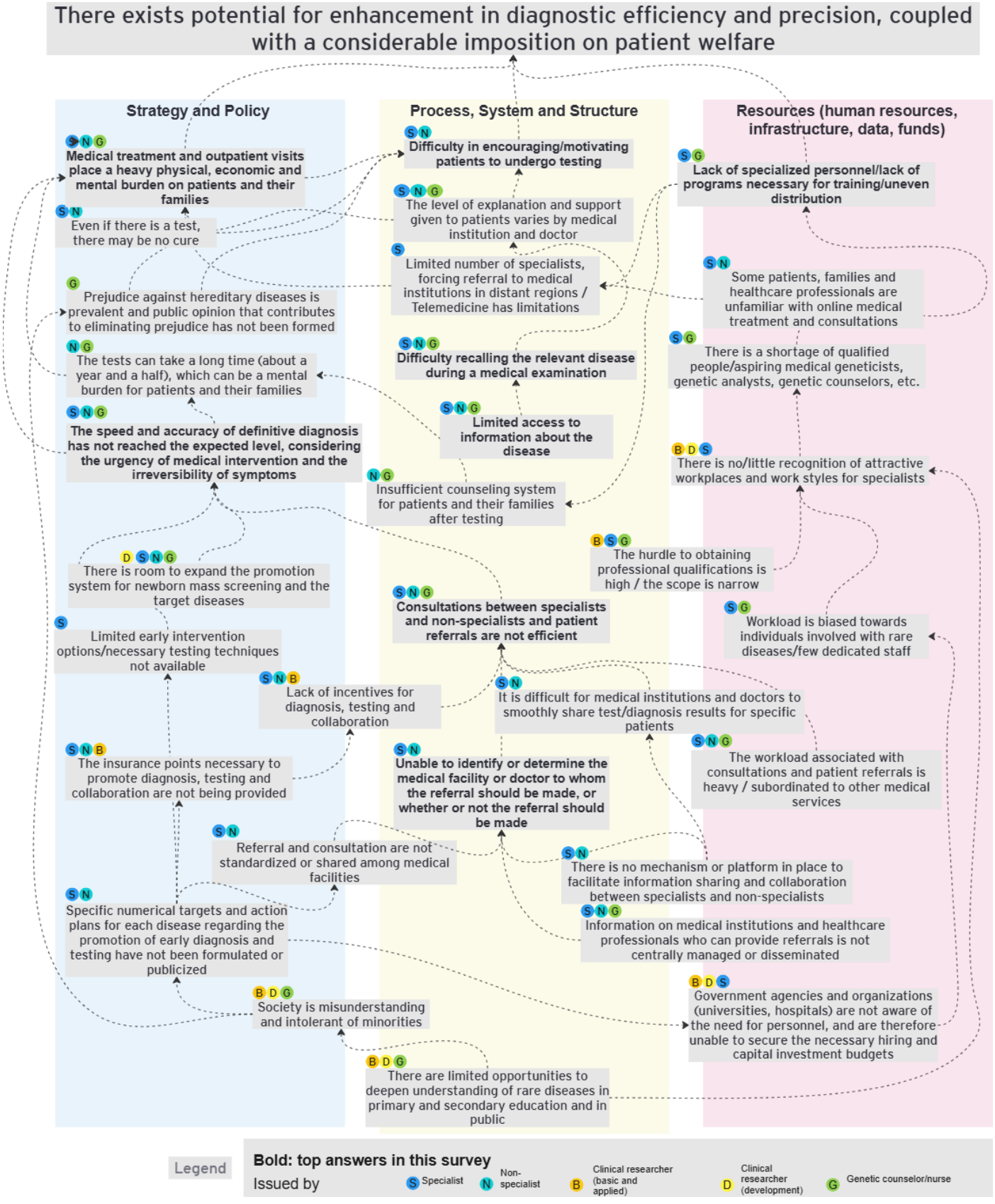
■Survey: Web survey
■Question: Please select the top 5 most pressing challenges you feel are related to diagnosis (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

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.

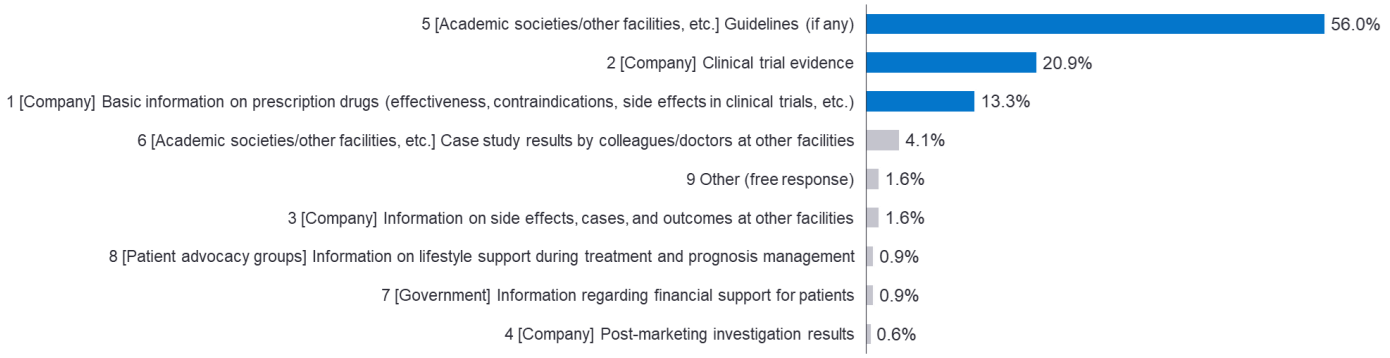
The current state of information collection and utilization in treatment and prognosis management

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.

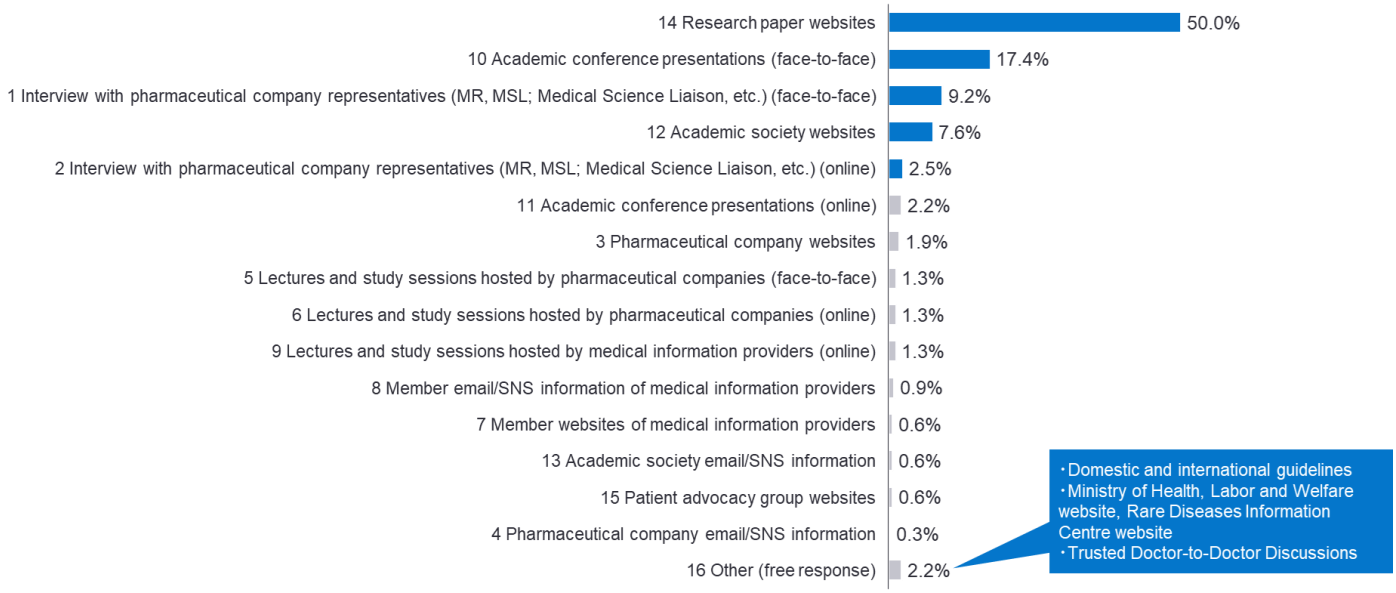
Figure 4.1.5 1: Types of information collected and used in treatment and prognosis management – Top selection results



■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)

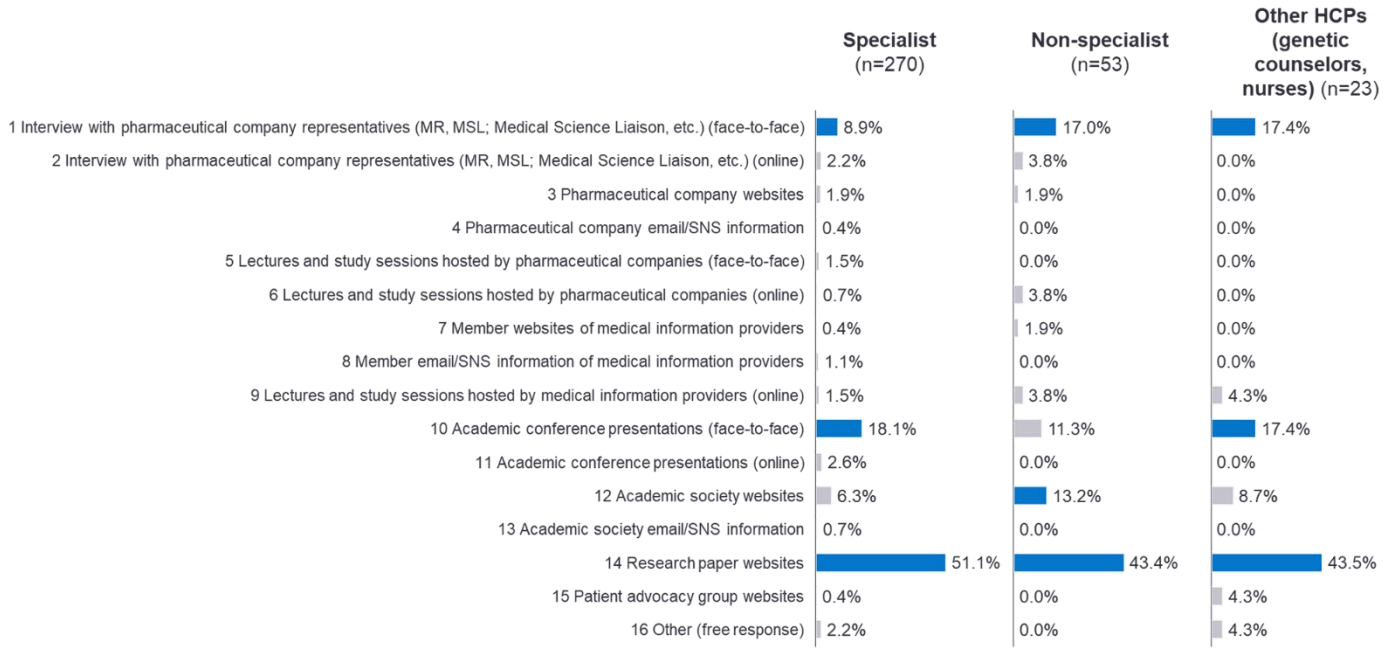
[8] To spread the quality and delivery of medical care equally across the country

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).

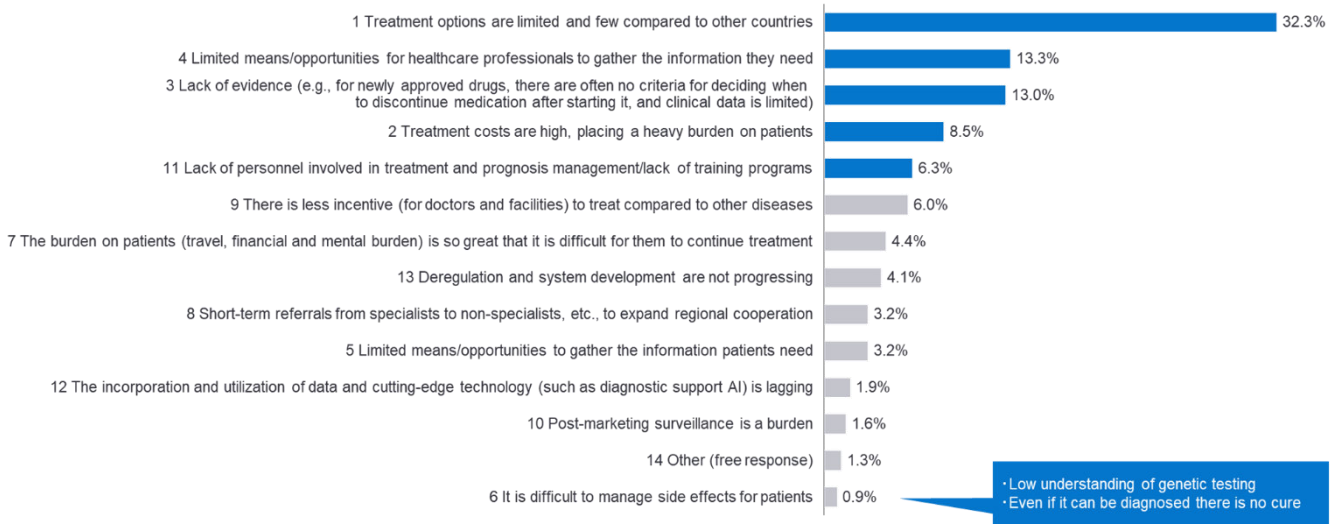
> *Among the next generation of doctors, there are very few who are interested in or want to work with rare diseases. Japan's medical policy prioritizes learning from a variety of experiences at clinics, etc., and there is little exposure to rare diseases.*
> (Specialist / Pediatrics)

> *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)

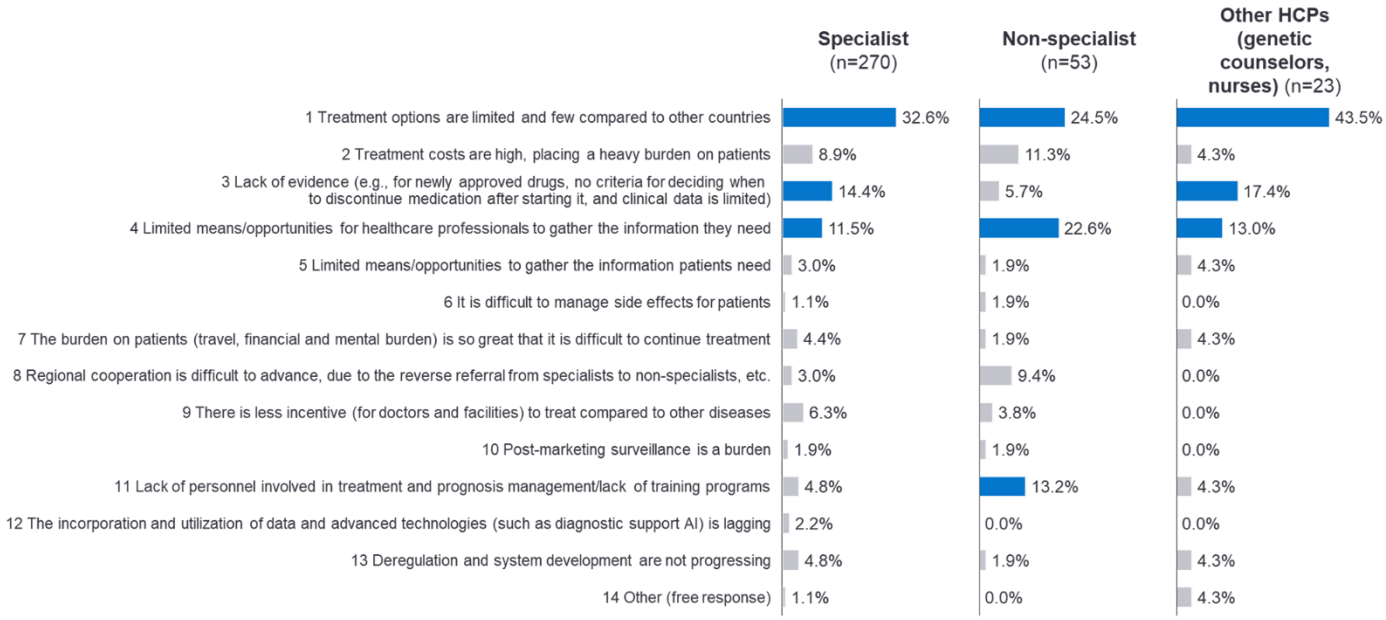
> *In cases where a patient has a highly specialized condition, they may not be able to receive a referral. Many people find it difficult to deal with pediatric diseases in particular.*
> (Non-specialist / Pediatrics)

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



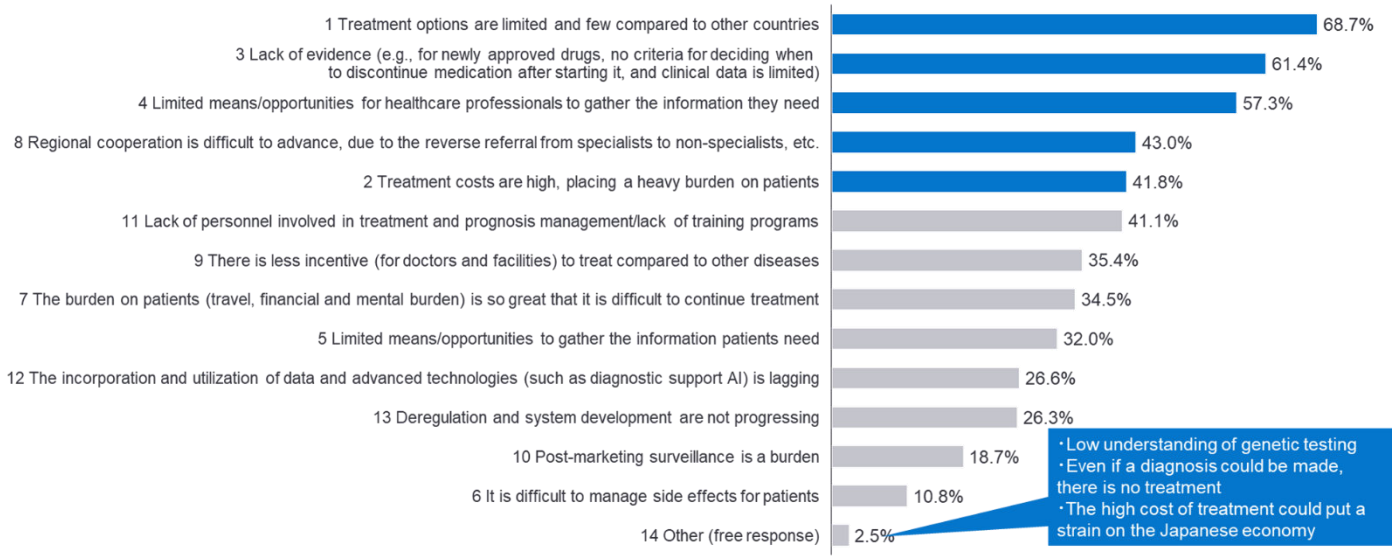
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most important in terms of treatment and prognosis management (ranking format)
■Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

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



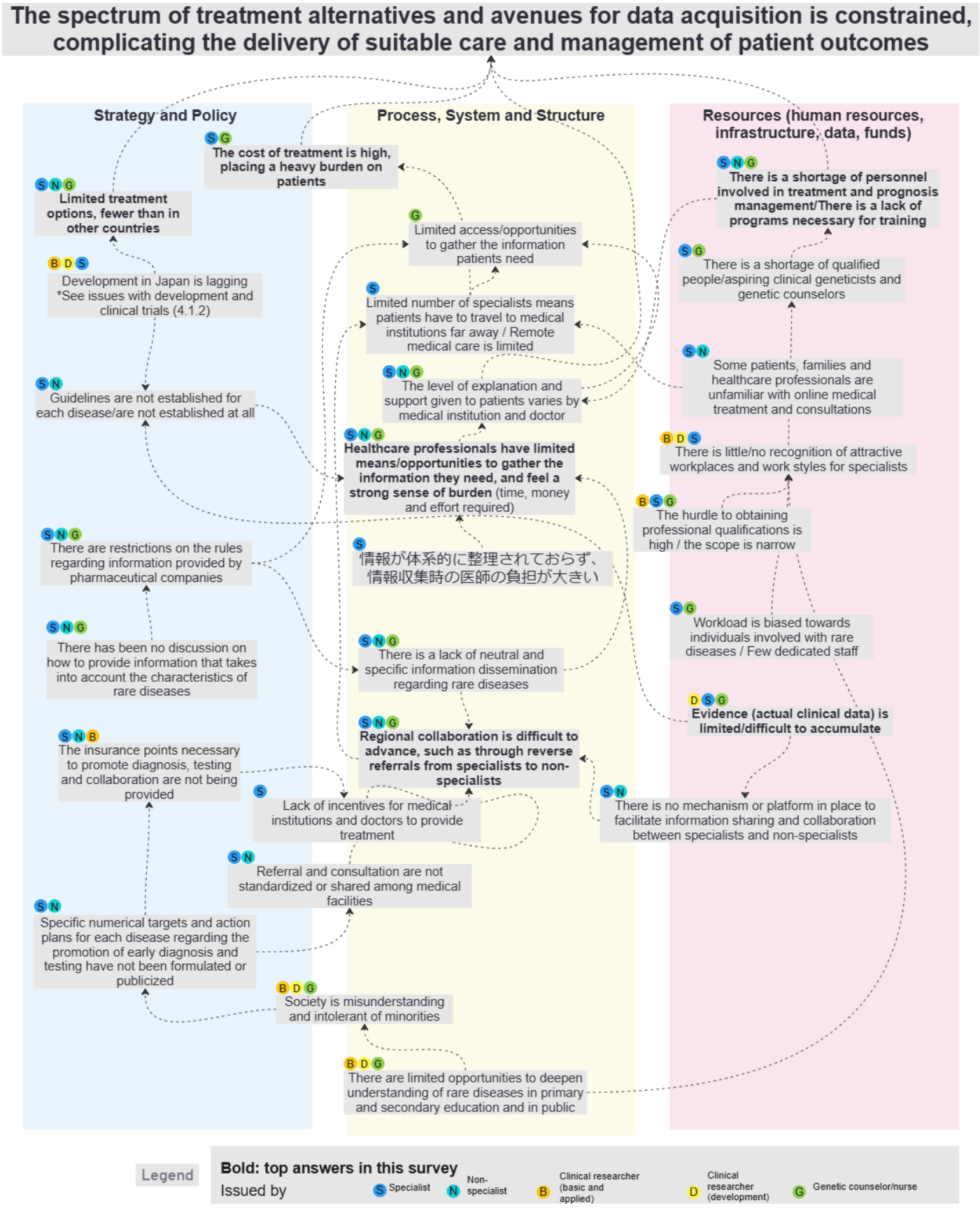
■Survey: Web survey
■Question: Please select the top 5 challenges you feel are most important in terms of treatment and prognosis management (ranking format)
■ Subjects: 316 specialists, non-specialists, and other HCPs (genetic counselors and nurses)

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).

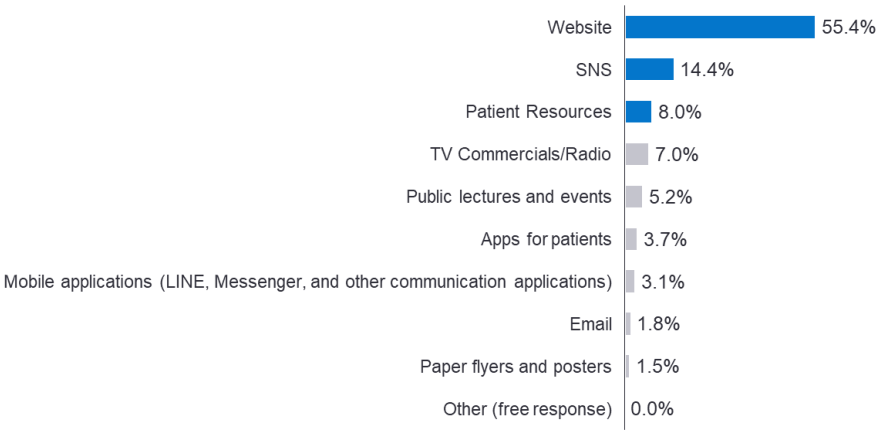
The main players effective in raising disease awareness for healthcare professionals were academic societies, medical institutions and pharmaceutical companies (Figure 4.1.6-3) using websites, face-to-face and online communication, lectures and study sessions held by pharmaceutical companies and academic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

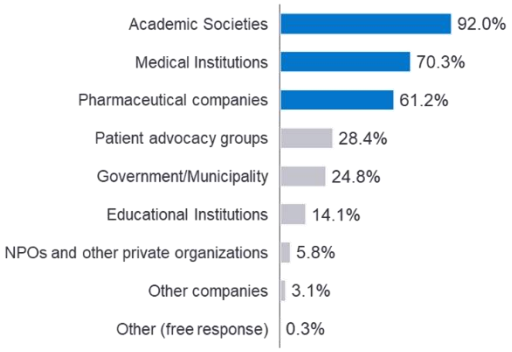
■Survey: Web survey
■Question: Please answer the three questions about what you think would be most effective in raising awareness about rare diseases? (for patients and their families) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers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



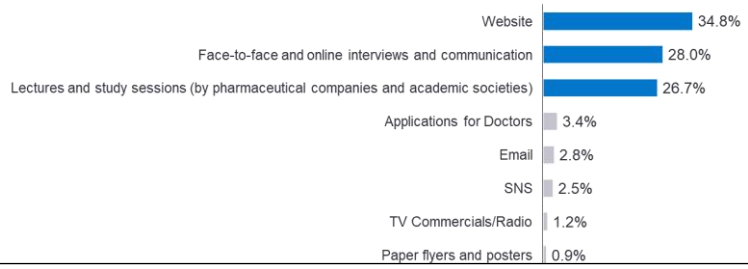
■Survey: Web survey
■Question: Please choose the three most effective media / channels for raising awareness about rare diseases (for patients and their families) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other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

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



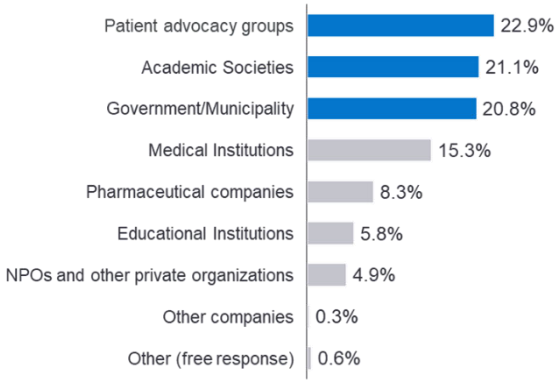
■Survey: Web survey
■Question: Please select three answers that you feel are effective in raising awareness of rare diseases (for healthcare professionals) (ranking format)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other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

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



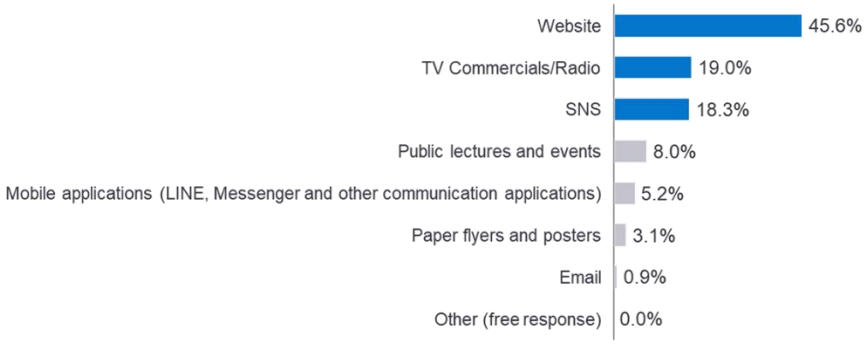
■Survey: Web survey
■Question: Please choose the three most effective media / channels for raising awareness of rare diseases (for healthcare professionals) (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs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

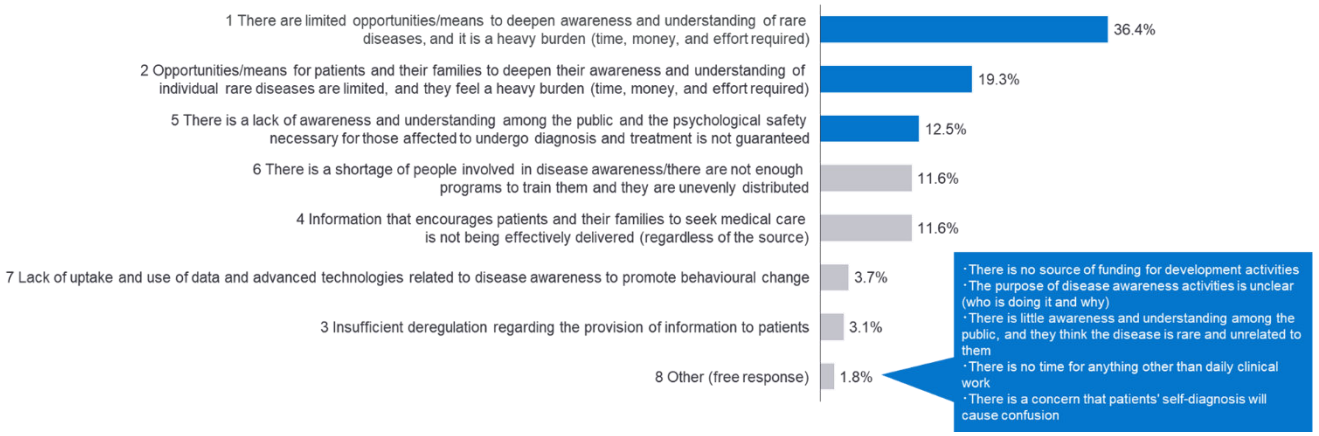
In the results by occupation (Figure 4.1.6-8, 9), non-specialists, clinical researchers (development), and other HCPs (genetic counselors and nurses) answered '4 Information that encourages patients and families to actively seek medical attention is not being effectively delivered (regardless of source).'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

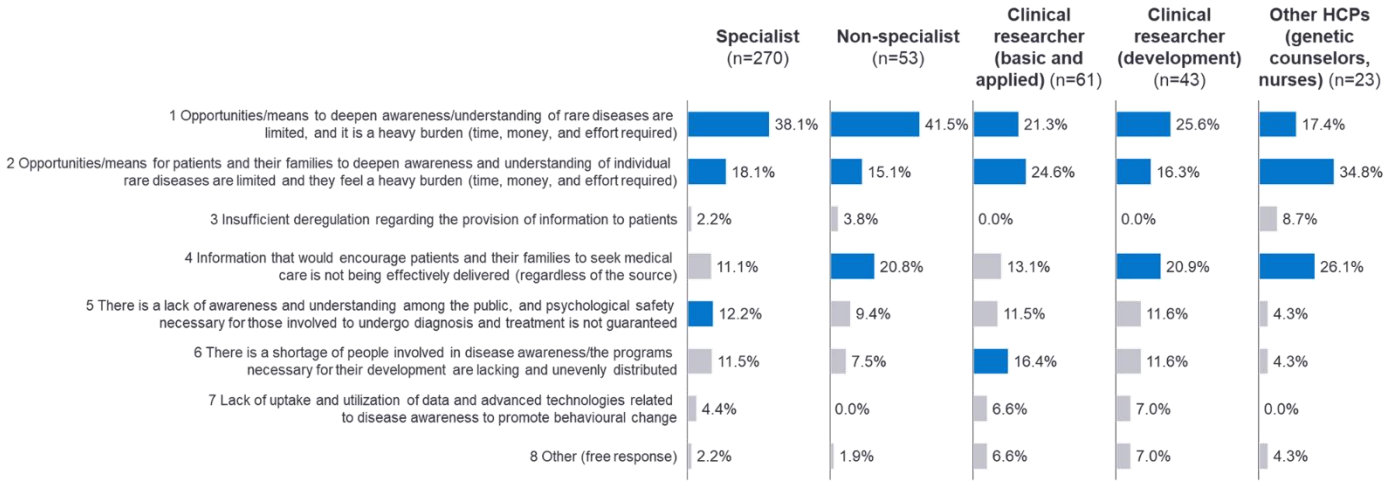
Sorting out these causal relationships reveals that there is intolerance and lack of awareness and understanding of rare diseases in the public, as well as flexible system design that considers the characteristics of rare diseases and further investment in research and development is needed (Figure 4.1.6-10).

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



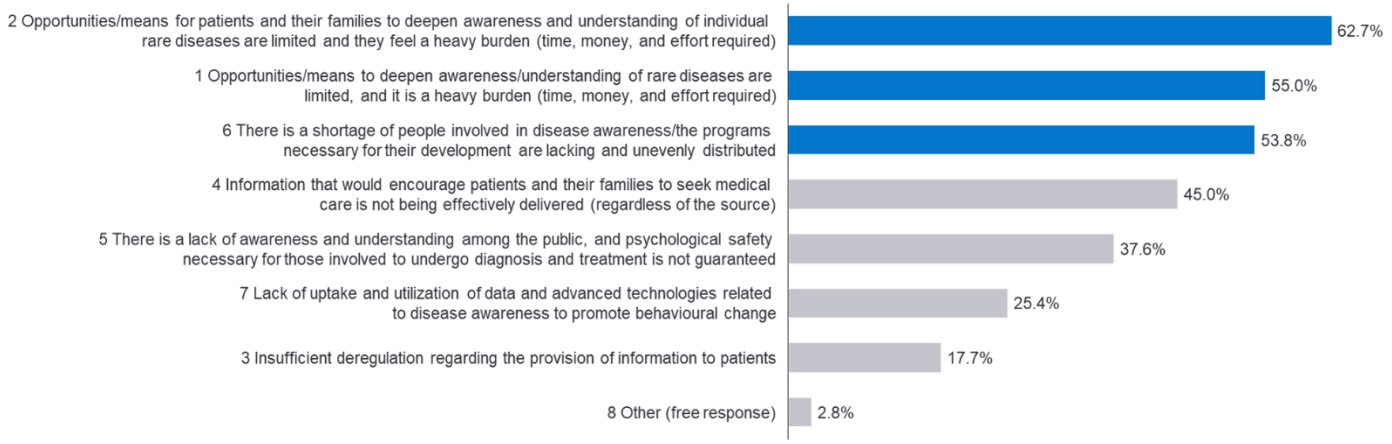
■Survey: Web survey
■Question: Please answer the top three challenges you feel are most challenging regarding disease awareness activities (ranked)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors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

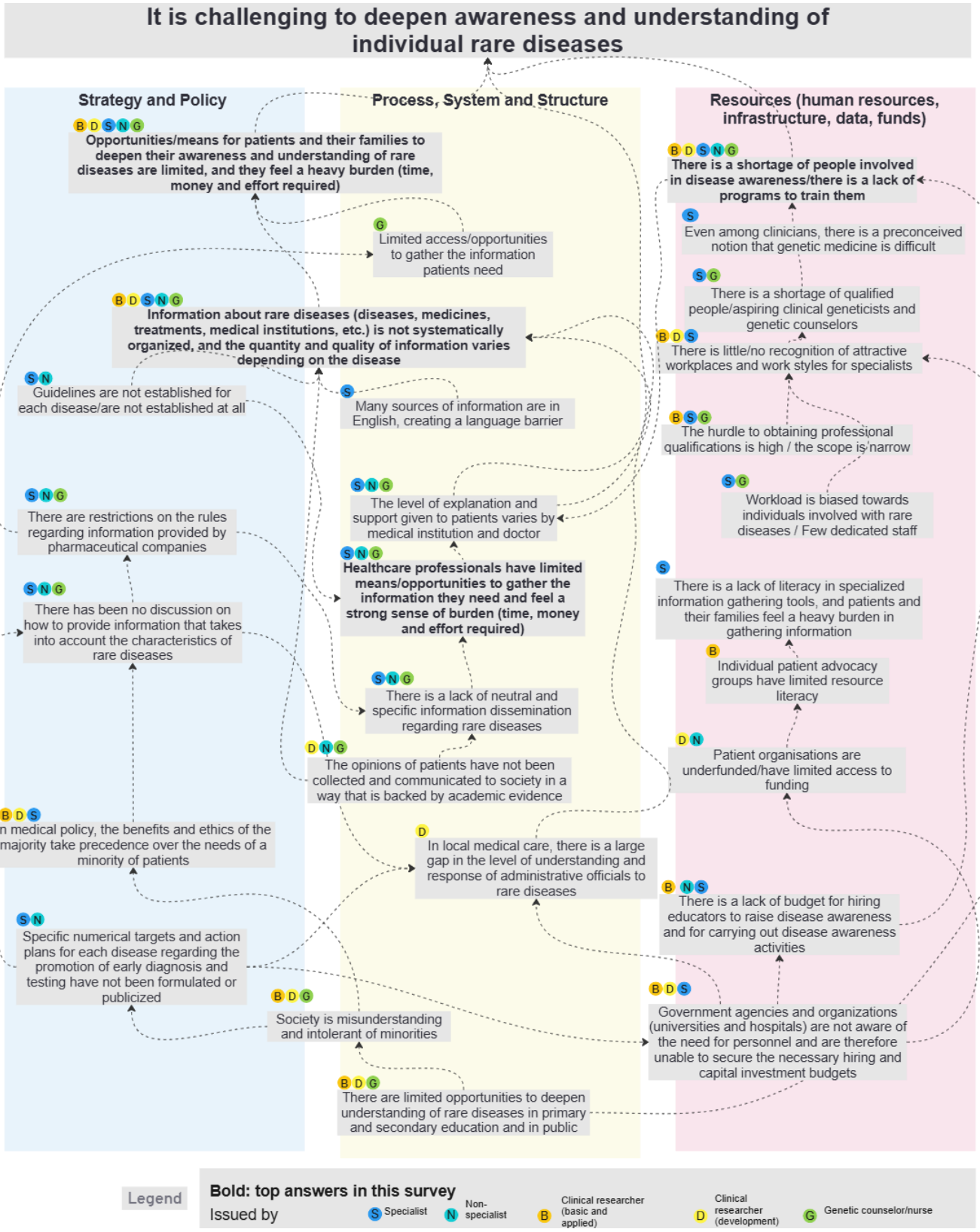
There is a lack of awareness and understanding among the public and the psychological safety necessary for those affected to undertake diagnosis and treatment is not guaranteed. In some cases, diagnosis and treatment are delayed because parents are not aware of their child's developmental delay or that 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



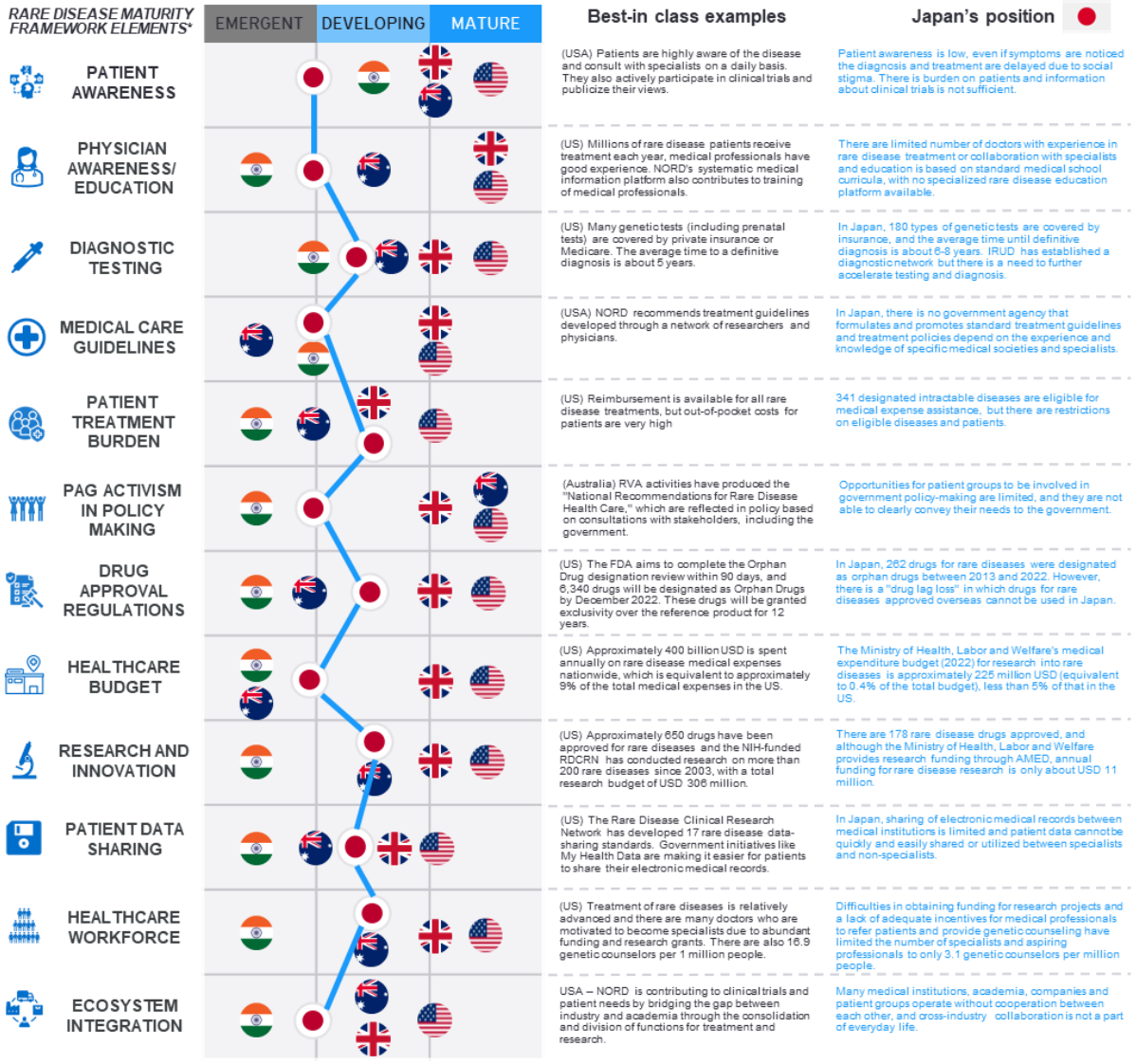
4.1.7 Column: Position of Japan's medical system for rare disease in globe

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