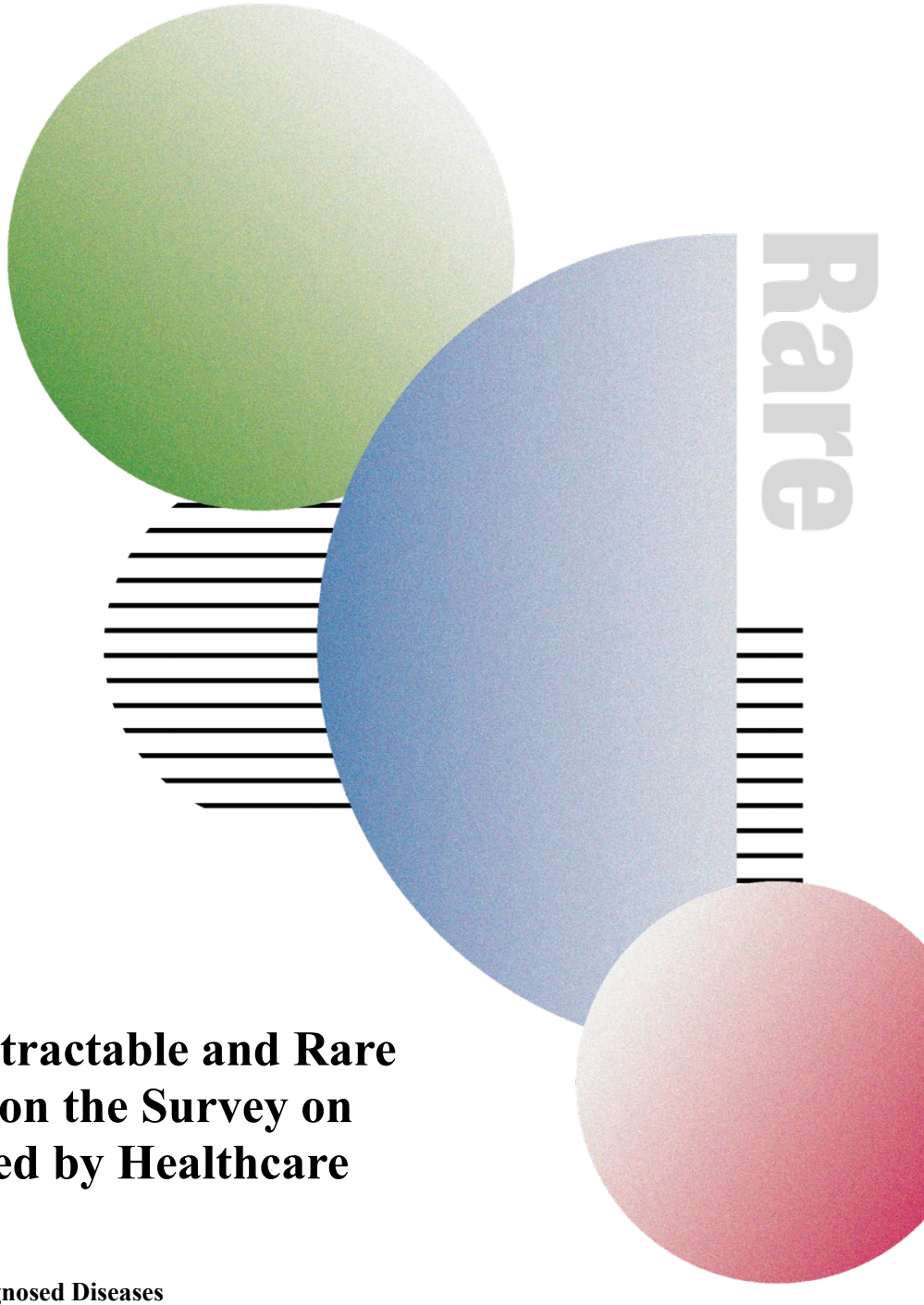


Proposals on Intractable and Rare Diseases Based on the Survey on Difficulties Faced by Healthcare Professionals

Initiative on Rare and Undiagnosed Diseases

Rare Disease Consortium Japan

Japan Pharmaceutical Manufacturers Association

IRUD

日本希少疾患コンソーシアム
Rare Disease Consortium Japan

製薬協

Greeting

Research and development of treatments for rare diseases often lag behind due to their rarity and low public awareness. In Japan, many patients and their families still face difficulties in diagnosis and treatment. The Initiative on Rare and Undiagnosed Diseases (IRUD), Rare Disease Consortium Japan (RDCJ), and Japan Pharmaceutical Manufacturers Association (JPMA) have each been working to overcome these difficulties from their respective positions.

The IRUD is an initiative aimed at supporting diagnosis and promoting access to treatment for patients with undiagnosed and rare diseases. By utilizing advanced genetic analysis technologies, experts across the country have been working together to identify the causative gene and explore new diagnostic possibilities through the sharing of clinical information.

The RDCJ was established with the aim of solving rare disease challenges, advancing research, and developing patient-centered medical services and therapeutic drugs through collaboration among industry, patients, academia, government, and the public. Researchers at universities and research institutions, experts at pharmaceutical companies, and members of patient groups have been working together actively to overcome intractable and rare diseases.

Since its establishment, the JPMA has contributed to global medical care through the development of innovative new ethical drugs, with the aim of "realizing patient-participating medical care." The association launched the Intractable and Rare Disease Task Force in 2021, released the "Survey on Difficulties Faced by Patients with Rare Diseases" and the "Proposals on Intractable and Rare Diseases" in 2023, and has been working to resolve issues in cooperation with relevant stakeholders.

In 2024, the IRUD, RDCJ, and JPMA conducted and published the "Survey on Difficulties Faced by Healthcare Professions in Rare Diseases" in collaboration. Based on the survey results, we have summarized the direction for resolving the issues in these proposals. Through this document, we hope that various stakeholders, including healthcare professionals, academic societies, patient groups, the government, and the pharmaceutical and other industries, will work together through co-creation to contribute to the realization of a society where more patients with intractable and rare diseases can live with peace of mind as soon as possible.

January 2026
Initiative on Rare and Undiagnosed Diseases
Rare Disease Consortium Japan
Japan Pharmaceutical Manufacturers Association

TABLE OF CONTENTS

1. Definition of rare diseases, intractable diseases, and designated intractable diseases

Rare diseases refer to diseases with a very small number of patients. Although the number of patients per disease is small, over 6,000 rare diseases have been identified worldwide, with the total number of patients estimated to be 300 million[1]. While the definition of rare diseases varies by country, according to the "designation system for orphan drugs, orphan medical devices, and orphan regenerative medicine products, etc." under the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" (hereinafter, the PMD Act), the Minister of Health, Labour and Welfare can designate products that meet all three of the following criteria as orphan drugs, orphan medical devices, or orphan regenerative medical products: 1) the number of target patients (shall be less than 50,000 in Japan. However, for designated intractable diseases, the population shall be up to about 0.1% of the total population); 2) high medical need; and 3) high feasibility of development. The threshold for the patient numbers is less than 200,000 in the U.S., and less than 5 per 10,000 population in Europe. This equates to a population ratio of approximately < 0.04% in Japan, < 0.06% in the U.S., and < 0.05% in Europe. In addition, it has been reported that 80% of rare diseases are genetic diseases and 95% have no treatment options[2].

In relation to rare diseases, there are "intractable diseases" and "designated intractable diseases." Under the "Act on Medical Care, etc. for Patients with Intractable Diseases (hereinafter, the Intractable Diseases Act)" enacted in 2015, intractable diseases are defined as those that meet the following four criteria: 1) the mechanism of onset is unclear; 2) no treatment method has been established; 3) the disease is rare; and 4) long-term medical care is required. Designated intractable diseases are those that meet the above four criteria, plus two additional criteria: 5) the number of patients in Japan does not reach a certain threshold (about 0.1% of the population); and 6) objective diagnostic criteria (or equivalents) have been established. Based on the opinions of the Health Sciences Council, the Minister of Health, Labour and Welfare designates these diseases, which then become eligible for medical expense subsidies. As of April 1, 2025, 348 diseases have been designated (Figure 1).

1) Orphanet, EURORDIS-Rare Diseases Europe, The National Rare Diseases Office of Ireland 'Rare is not rare' New scientific paper confirms 300 million people living with a rare disease worldwide: https://download2.eurordis.org/pressreleases/PrevalencePaper_JointStatement_170919_Final.pdf
2) IFPMA, "Rare diseases_create a future that leaves no one behind": https://www.jpma.or.jp/globalhealth/status_effort/2018/lofurc0000002tc7-att/2018_03.pdf

Figure 1 Definition of rare diseases, intractable diseases, and designated intractable diseases in Japan

	Rare diseases	Intractable diseases and designated intractable diseases
Overview	<Criteria for designation of orphan drugs, orphan medical devices, and orphan regenerative medicine products, etc.> ○ Number of targets • The number of patients in Japan is less than 50,000. • In the case of designated intractable diseases, up to about 0.1% of the population ○ High medical need ○ High feasibility of development	<Intractable diseases> ○ The mechanism of onset is unclear; ○ No treatment methods have been established; ○ The disease is rare; and ○ Long-term medical care is required. <Designated intractable diseases (subject to medical care subsidies)> Intractable diseases designated by the Minister of Health, Labour and Welfare which meet all of the following criteria based on the opinions of the Health Science Council: ○ The number of patients does not reach a certain threshold (approximately 0.1% of the population); and ○ Objective diagnostic criteria (or equivalents) have not been established.
Rationale	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act)	Act on Medical Care, etc. for Patients with Intractable Diseases (Intractable Diseases Act)
Number of diseases	Approximately 6,000 (worldwide)	348 designated intractable diseases

2. JPMA's approach to intractable and rare diseases

The number of patients with intractable and rare diseases is small, and patients and their families face various challenges, such as the time required to confirm diagnosis, limited treatment options, and a lack of social understanding and support. A wide range of efforts is underway to address the challenges faced by patients with intractable and rare diseases and their families, including formulation and promotion of various programs and measures by the government, daily clinical practice at medical institutions, implementation of basic research and clinical research by academia, and support activities by patient groups. In order to honor the dedicated activities and significant contributions of stakeholders to date, and to play a part in efforts to address the challenges, the JPMA launched the Intractable and Rare Disease Task Force in October 2021. The Intractable and Rare Disease Task Force consists of members from multiple pharmaceutical companies, and is committed to addressing various challenges surrounding patients with intractable and rare diseases and their families in a cross-sectional manner, aiming to create a society where they can live with greater peace of mind. Major efforts to date are summarized below (Table 1), and most recently, the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases" was released in November 2024.

As a result of sorting out the difficulties faced by healthcare professionals as revealed by the survey, three main challenges that pharmaceutical companies should address were identified and proposals for each challenge were summarized in Chapters 2 through 4. These chapters include proposals from the RDCJ, representing the viewpoints of academia and patients and their families, in addition to the perspective of pharmaceutical companies. Because it is necessary for stakeholders to work together, proposals from the RDCJ were added to Chapter 5 regarding challenges related to the expansion of development opportunities for specialized human resources and the viewpoint of patients and their families.

■ Major challenges to be addressed by the pharmaceutical industry

[1] Enhancing of information provision activities

[2] Expansion of newborn mass screening

[3] Acceleration of R&D

Table 1 Major efforts made by the Intractable and Rare Disease Task Force

Timing	Efforts
February 2023	To sort out challenges that the pharmaceutical industry should address in intractable and rare diseases for solutions, a comprehensive survey was conducted to understand the difficulties faced by patients and families and challenges at each stage of the patient journey (from onset and diagnosis to treatment and follow-up). In February 2023, the "Survey on Difficulties Faced by Patients with Rare Diseases" was published.
July 2023	Based on the various challenges faced by patients and their families as revealed by the survey, three important challenges that pharmaceutical companies should address were identified: [1] limited information and difficulty in accessing necessary information; [2] a lack of social understanding and knowledge of rare diseases; and [3] limited treatment options and a lack of radical treatment. In July 2023, these were compiled and released as proposals.
November 2024	Based on the voices of healthcare professionals supporting medical care for rare diseases in Japan, the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases" was released in collaboration with the IRUD and RDCJ to accelerate more specific efforts.

3. RDCJ's approach to intractable and rare diseases

The RDCJ is a collaborative platform founded on the philosophy of "promoting drug discovery for rare diseases" and "leaving no one behind." The RDCJ aims to build and operate a patient-centered drug discovery ecosystem tailored to the social and institutional environment of Japan. Their major role is to bring together five key stakeholders, industry, patients and patient groups, academia, government, and citizens, to seamlessly link basic research to social implementation, and to develop solutions to complex challenges that are difficult to address from any single perspective. They promote cross-divisional discussions and consensus-building, and act as a "co-creation platform" that reconnects the often fragmented drug discovery process according to the patient's timeline.

Their operations are based on a cyclical model where challenges are shared at the Executive Committee, the working group takes charge of drafting and implementing proposals, and the results are presented at the annual meetings. Furthermore, they are actively engaged in awareness-raising activities, such as study meetings, information provision, lectures and contribution activities, and "lay-summary lectures" designed for junior high school students. The working group is responsible for N-of-1 studies, including genome editing therapies, and for formulating proposals and promoting social understanding. It has established an environment where diverse stakeholders from industry,

patients, academia, government, and private sector can gather and discuss. In addition, they have been enhancing the sustainability of their activities by standardizing secretariat functions, such as membership management, accounting, legal affairs, public relations, annual meetings, and international relations, and securing a variety of financial resources, such as membership fees, sponsorships, donations, and grants, while considering future corporate incorporation.

Through such activities (Table 2), the RDCJ will prepare standardized protocols that can be used in medical practice for intractable and rare diseases. In addition, their mission is to link drug discovery in the rare disease area originating in Japan to the world and deliver new drugs to patients as soon as possible. To this end, the RDCJ exists to gather the knowledge, experience, and resources of industry, patients, academia, government, and private sector to draw a 'blueprint' using a common language.

Table 2 Major efforts of the RDCJ

Timing	Efforts
2019	Started dialogue and collaboration, starting with the Rare Disease Conference.
July 2023	Held a symposium to commemorate the inauguration. Shared a roadmap that integrates the patient journey, decentralized clinical trials, regulatory affairs and policies, and investment and financial circulation.
February 2024	Formally launched as a voluntary organization.
October 2024	Launched membership recruitment. Opened the door to patients, patient groups, companies, academia, and individuals.
February 2025	An annual meeting was held at Shonan Health Innovation Park. The theme was "Confronting the essence of drug loss among industry, patients, academia, government, and the public—to deliver new drugs to patients with rare diseases." In addition, in collaboration with the JPMA, IRUD, and EY Strategy and Consulting Co., Ltd., they conducted surveys of healthcare professionals (327 quantitative and 15 qualitative surveys). The identified challenges and their proposed solutions were reported at the annual meeting.

4. IRUD's approach to intractable and rare diseases

The IRUD is an R&D program sponsored by the Japan Agency for Medical Research and Development (AMED) that aims to confirm diagnosis and develop treatment for patients with rare and undiagnosed diseases that are difficult to diagnose in usual medical care. Since its launch in 2015, a nationwide diagnostic system has been established.

The objectives of this program are to confirm diagnosis using innovative technologies such as whole-exome analysis, provide diagnostic support through the sharing of clinical information, elucidate pathological conditions, create treatment seeds, and promote data sharing through international collaboration. A comprehensive diagnostic system combining clinical information and genetic analysis has been established, and the IRUD Exchange database to enable international collaboration via the Matchmaker Exchange is also currently being developed.

In addition, the IRUD has introduced the concept of "micro attribution" that emphasizes the contribution of all research participants and established a system that considers research ethics. As of March 2025, 536 experts from 21 specialized fields across 535 institutions in Japan have participated in the diagnostic collaboration, and a system has been established to allow patients with any symptoms anywhere in the country to participate.

Furthermore, DNA and cell linearized lymphocytes at the Resource Center are being consistently utilized, while functional analysis of candidate genes is progressing efficiently at the Disease Model Center. The major achievements to date are as follows (Table 3):

Table 3　Major achievements of the IRUD

Major achievements	
Diagnostic support for known diseases	• As of the end of March 2025, 28,207 individuals from 9,908 families have been enrolled, and analysis of 8,090 families has been completed. Diagnoses have been confirmed for 3,894 families (a diagnosis rate of 48.1%). • In some cases, effective treatments were available, and confirming a diagnosis led to successful treatment.
Discovery of new diseases	• Previously unknown novel genes, diseases, and phenotypes (covering 50 diseases as of March 2025) have been discovered through the analysis of the IRUD. • These diseases have gained international recognition through academic conferences and published papers, and studies on the elucidation of disease mechanisms and the development of treatment methods have been conducted. Concurrently, patients have become eligible for various benefits, such as medical subsidies for pediatric chronic diseases.
Human resource development	In the fields of intractable diseases and genomic medicine, between 4,000 and 10,000 professionals are trained annually across 32 categories, including certifications for clinical genetics specialists and genetic counselors.

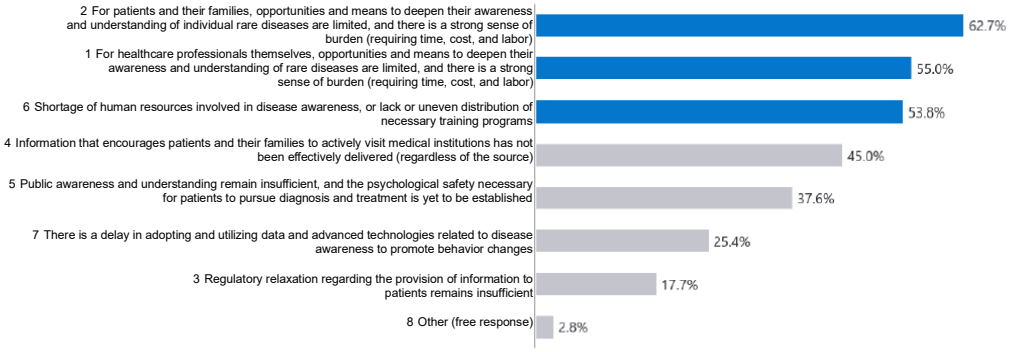
CHAPTER 2 Challenges and proposals related to disease awareness and patient information in intractable and rare diseases

1. Disease awareness for intractable and rare diseases

[Background]

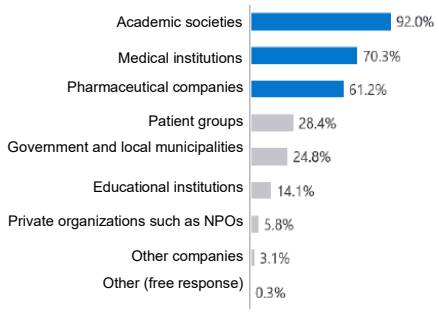
Due to the diversity of intractable and rare diseases, it is inferred that not only patients and their families but also healthcare professionals themselves find it challenging to deepen the recognition and understanding of individual rare diseases. In the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases"[1], more than half of the respondents reported "having limited opportunities or means for themselves or patients and their families to deepen the awareness and understanding of rare diseases" as a challenge regarding disease awareness activities, suggesting that healthcare professionals themselves have a strong sense of burden in information gathering (Figure 2). Furthermore, 61.2% of the healthcare professionals answered that "pharmaceutical companies" would be an effective channel for rare disease awareness activities targeting healthcare professionals (Figure 3).

Figure 2 Challenges in disease awareness activities: Top 3 choices



■ Survey: Online survey
■ Question: Please select and rank the top three challenges related to disease awareness activities.
■ Targets: 327 healthcare professionals (HCPs), including specialists, non-specialists, basic and applied research physicians, R&D physicians, and others (genetic counselors and nurses)

Figure 3 Entities effectively implementing disease awareness activities (for healthcare professionals)



■ Survey: Online survey
■ Question: Please select and rank the top three entities that you think are effectively implementing activities to raise awareness of rare diseases (for healthcare professionals).
■ Targets: 327 healthcare professionals (HCPs), including specialists, non-specialists, basic and applied research physicians, R&D physicians, and others (genetic counselors and nurses)

On the other hand, while expectations for “pharmaceutical companies” are not high as the main entities implementing activities to raise awareness for patients and their families, some suggest that they should provide accurate and fair information directly to patients, families, and the general public as a way to help create an environment where healthcare professionals can better focus on diagnosis and treatment. There is a need for an attitude of contributing to the elimination of awareness gaps among stakeholders and the acceleration of collaboration. This can be achieved by raising the awareness and understanding of rare diseases among healthcare professionals, patients, families, and the general public.

“Public awareness and understanding remain insufficient, and the psychological safety necessary for patients to pursue diagnosis and treatment is yet to be established. In some cases, diagnosis and treatment are delayed because parents may not recognize their child’s developmental delays or are unaware that effective treatment options exist.

Regulatory relaxation regarding the provision of information to patients remains insufficient, and it would be helpful if information was provided by pharmaceutical companies as well.” (Non-specialist/Pediatrics) “Raising awareness for diseases for which treatments are not available may only fuel patient anxiety. It is necessary to implement awareness-raising activities using information with high sensitivity and specificity.” (Non-specialist/Neurology)

[Challenge]

Based on the “Proposals on Intractable and Rare Diseases” and “Challenges of Rare Diseases in Japan,” the challenges regarding disease awareness for patients by pharmaceutical companies can be summarized as follows:

Challenges	Contents
Difficulty in transmitting information	If there is only one treatment option, there is a high risk that disease awareness activities may be misunderstood as promotion. Example) When a company manufacturing Drug A, which is the only approved drug for a rare disease, launched a disease awareness site, just mentioning “early treatment is important for this disease” may be regarded as a promotion to Drug A.
Low social recognition	Disease awareness is low, and the impact of awareness-raising activities remains limited. Example) Since the number of patients with rare diseases is small, the level of awareness and interest is low, and there are few opportunities for media coverage in news, newspapers, and television programs, making it difficult for disease awareness campaigns to achieve widespread recognition.

Divergence from the actual patient voice	It is difficult to match the actual patient needs with the company's information transmission. Example) Due to low awareness of rare diseases, companies have limited opportunities to collect patient feedback; consequently, it is difficult to sufficiently reflect the "patient's viewpoint" necessary for disease education.

[Past efforts]

To address the above challenges, the JPMA's Intractable and Rare Disease Task Force has promoted the following efforts:

- Coordination and dissemination of member companies' efforts for intractable and rare diseases
  A summary of member companies' activities regarding intractable and rare diseases was published on the JPMA website in 2022 and subsequently revised in 2024.
- Co-hosting the Rare Disease Day symposia
  The JPMA co-hosted the Rare Disease Day symposia in 2024 and 2025 jointly with the RDD Japan Secretariat. These symposia provided a platform for dialogue among various stakeholders, including patients and patient groups, government officials, healthcare professionals, and pharmaceutical companies, and were also covered in the media as part of the Rare Disease Day, which is held around the world.

Based on the needs of healthcare professionals and patients as well as the situations of pharmaceutical companies, we present the following proposals:

[Proposal]

Pharmaceutical companies, which act as information providers and play a role in complementing the information provided by healthcare professionals, will contribute to bridging the awareness gap among stakeholders and accelerating collaboration as much as possible by enhancing the recognition and understanding of rare diseases among healthcare professionals, patients, and their families.

The following are examples of efforts made by the JPMA:

1. Although various efforts by the JPMA member companies on intractable and rare diseases are made public on the JPMA website, review the industry-wide approach to information disclosure to minimize the burden on those seeking information.
2. Hold the Rare Disease Day Symposium jointly with the RDD Japan in February every year. Establish a forum for discussion among various stakeholders such as patients, healthcare professionals, government officials, and pharmaceutical companies, to facilitate dialogue and resolve challenges in collaboration.

3. By clarifying the boundary between disease awareness and advertising and supporting pharmaceutical companies to properly understand related regulations, foster an environment that promotes smooth disease awareness activities while ensuring strict compliance.

The following are examples of efforts made by the RDCJ:

1. As a neutral platform to which stakeholders across the industry, patients, academia, government, and the public gather, the RDCJ will facilitate regular surveys and dissemination of information regarding patient needs and difficulties, providing information that will contribute to the improvement of recognition and literacy according to the target audiences, while creating opportunities for cross-functional collaboration.

1) Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases: https://www.jpma.or.jp/information/industrial_policy/rare_diseases/iryousya/index.html

2. Transmission of clinical trial information

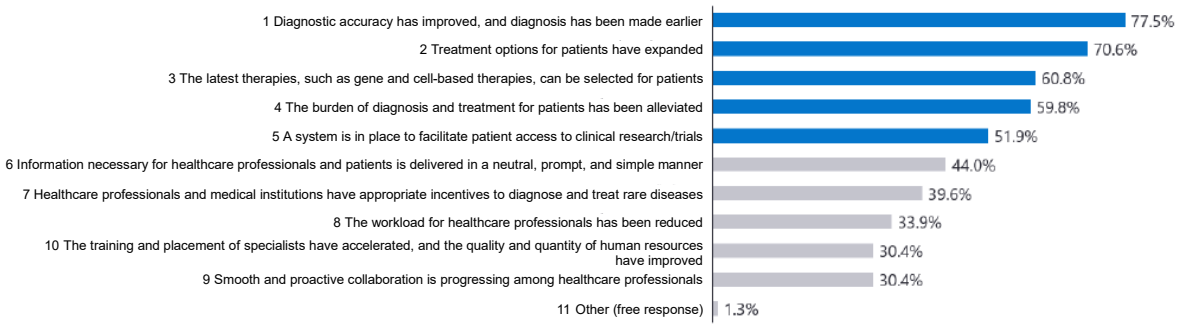
[Background]

In Japan, clinical trial information for drugs is accessible to both healthcare professionals and patients, through the Japan Registry of Clinical Trials (jRCT) and other websites. On the other hand, to prevent false or misleading advertising and to ensure patient protection, the advertising of unapproved drugs, etc. is prohibited under the PMD Act (Article 68 of the PMD Act). Therefore, it is not permitted in principle to disclose the names of investigational products or their indications to the general public.

[Challenge]

Particularly in the field of rare and intractable diseases, access to clinical trial information is often directly linked to treatment opportunities, and therefore it has been pointed out that the above-mentioned restrictions on information provision can lead to disadvantages for patients.
In the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases," 55.7% of healthcare professionals identified "the small patient population and the resulting difficulty in clinical trial/study recruitment" as a challenge in development and clinical trials, and some respondents commented that information dissemination to potential participants remains insufficient. In addition, 51.9% of the respondents identified that "A system is in place to facilitate patient access to clinical studies/trials" as an ideal state in actual clinical practice, and pharmaceutical companies are expected to communicate clinical trial information to both patients and healthcare professionals in an easy-to-understand manner (Figure 4).

Figure 4 Ideal visions for actual clinical practice: Top 5 choices



- Survey: Online survey
- Question: Based on the challenges in actual clinical setting that you have selected so far, please select and rank the top five goals or visions that you endorse as the ideal state to be pursued.
- Targets: 316 healthcare professionals (HCPs), including specialists, non-specialists, and others (genetic counselors and nurses)

<Voices of healthcare professionals (expectations for pharmaceutical companies)>

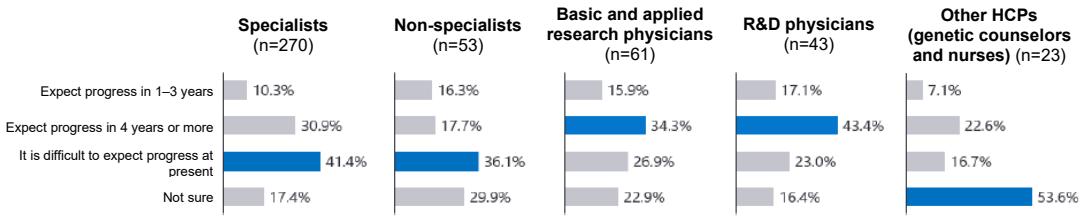
"I expect that clinical trial information will be provided to patients and healthcare professionals in an easy-to-understand manner and that new drugs will be developed." (Specialist/Pediatrics)

"It is extremely difficult to recruit subjects who meet the criteria. One of the reasons is the insufficient dissemination of information to potential subjects. It would be beneficial for both healthcare professionals and subjects if clinical trial information was managed centrally, making it easier to identify trials that meet specific criteria.
In addition, since it is often difficult to recruit subjects in Japan for drugs that have already been approved in the U.S. or EU, it is desirable to accelerate Japan's participation in global multi-center clinical trials." (Specialist/Pediatrics)

The major problems related to clinical trial information include the restricted scope of information that pharmaceutical companies can provide, difficulty patients face in accessing detailed information of a clinical trial due to the lack of investigational product names when they search information online based on information such as disease or company names from clinical trial advertisements, and difficulty in judging whether or not the clinical trial information obtained is the same information.

The current "**Survey on Difficulties Faced by Healthcare Professions in Rare Diseases**" suggested that healthcare professionals may not have sufficient access to information regarding drugs currently under development. In the question about expectations for R&D progress toward radical treatments for rare diseases in the survey, expectations tended to be high among doctors involved in research, and there were comments indicating that information on R&D progress is insufficient in actual clinical practice. Furthermore, 20% of the respondents as a whole answered that they were "not sure (regarding their expectations for R&D progress)." This suggests the existence of healthcare professionals who lack access to information on R&D progress, and that the resulting information gap among different professions is directly connected to the variation in their expectations for R&D advancement (Figure 5).

Figure 5: Expectations for R&D progress toward radical treatments for rare diseases (by profession)



[Past efforts]

To solve these problems, the JPMA has been working to improve access to information on drugs and clinical trials and promote a correct understanding of such information by expanding the provision of accurate, easy-to-understand, and easily accessible information to the public. Specifically, the JPMA has been advocating for improved access to clinical trial information through several key efforts: managing the secretariat for the "Association for Creating a Society with Universal Access to Clinical Trials"—founded by patients, families, healthcare professionals, and

researchers; establishing guidelines for providing information on clinical trials to patients and the general public; publishing the "JPMA Policy Proposals 2025" and proposals for intractable and rare diseases; and presenting at the Regulatory Reform Promotion Council of the Cabinet Office. As a result, the following outcomes have been achieved to date:

- The JPMA has served as the secretariat for the "Association for Creating a Society with Universal Access to Clinical Trials" founded by patients, families, healthcare professionals, and researchers in 2023. To improve the accessibility of jRCT and the clinical study environment for patients—while also enhancing the drug discovery environment for researchers—the JPMA has facilitated ongoing multi-stakeholder dialogues, including with authorities. Furthermore, it has supported the submission of formal petitions for jRCT modifications and engaged in activities to raise awareness and disseminate information.
- Regarding the handling of provision of clinical trial information, the Ministry of Health, Labour and Welfare (MHLW) clarified that provision of information under certain conditions does not constitute advertising, and it has become possible to display the generic names and symbols of investigational products[1)].
- In association with the proposal to review clinical trial advertising regulations at the Regulatory Reform Promotion Council, discussions were held on providing information in a way that protects public interests[2)]. It was subsequently stated that the Regulatory Reform Implementation Plan approved by the Cabinet in June 2025 will undergo further review in FY2025[3)].
- "Regulations for clinical trial advertising" were discussed at the Pharmaceuticals and Medical Devices System Subcommittee of the Health Science Council of the Ministry of Health, Labour and Welfare held in July 2025. A policy was presented to clarify the applicability of advertising under the PMD Act to enable the proactive dissemination of information, including investigational product names and developmental codes. This applies specifically to participant recruitment, provided that certain conditions are met, such as "limiting the information to what is necessary for participant recruitment and restricting it to the duration of the clinical trial[4)]."
- In July 2025, the "Intractable Disease Clinical Trial Web" was launched in collaboration with the National Institutes of Biomedical Innovation, Health and Nutrition and the Research Group for "Strategic Comprehensive Research for Promoting Research and Improving Medical Care to Overcome Intractable Diseases" as a research project of intractable diseases of the MHLW, with the aim of providing patients with intractable and rare diseases and their families with an accessible and easy-to-search platform for clinical trial information[5)].

In addition, the MHLW plans to implement large-scale improvements to jRCT to enhance user-friendliness, focusing on better searchability and visibility. The immediate priorities include upgrading the search function and promoting the secondary use of data.

In addition, efforts to provide clinical trial information are currently underway, including plans to review mechanisms for matching patient disease information with clinical trial/study information

from medical institutions[6]. While the JPMA has been actively participating in these reviews, many challenges remain, such as further expanding information and determining how best to deliver it to patients. Therefore, based on such background and efforts, we make the following proposals:

[Proposal]

Since the "**Survey on Difficulties Faced by Patients with Rare Diseases"**[7] indicates major challenges related to access to information and content, we will continue to listen to and interact with patients and the public to provide accurate and easy-to-understand information for easier access, fostering an environment where patients can properly comprehend their disease, treatment options, and clinical trials.

The following are examples of efforts made by the JPMA:

1. Revision and dissemination of guidelines for providing clinical trial information
   As advertising regulations for clinical trial information will be relaxed only for the purpose of recruiting participants in clinical trials, revise the "Guidelines for Providing Information on Clinical Trials to Patients and the General Public" to broaden the dissemination of accessible information to patients.
2. Expansion of information provided on jRCT and the Intractable Disease Clinical Trial Web
   Promote the disclosure of summaries of information, including clinical trial results, on jRCT, and the registration of clinical trial site addresses, while advancing efforts toward push-type information delivery. Unlike jRCT, which is a system for submitting clinical research protocols and other notification procedures, the Intractable Disease Clinical Trial Web aims to provide clinical trial information specifically for patients with rare diseases and will continue to explore further updates to make the website more user-friendly and easier for patients to understand.
3. Strengthening of awareness-raising activities through collaboration with diverse stakeholders
   In collaboration with academia and patient groups, raise awareness of jRCT and the Intractable Clinical Trial Web among patients, the public, and healthcare professionals. In addition, work to standardize the quantity and quality of clinical trial information disclosed by pharmaceutical companies at a high level and conduct activities that contribute to the development of industry-wide rules and improved efficiency of information disclosure, ensuring that content is presented in a clear and easy-to-understand manner for patients and the public.
4. Enhancing public understanding of clinical trials
   Since in Japan, there are concerns that low public awareness of clinical trials hinders participant recruitment, leading to delays in conducting trials and a decline in drug discovery capabilities, conduct awareness-raising activities to broadly communicate the social significance of clinical trials.

1) "Handling of Provision of Clinical Trial Information," Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
January 24, 2023: https://www.mhlw.go.jp/content/001048483.pdf

2) The 1st Health, Medical, and Nursing Care Working Group, Regulatory Reform Promotion Council, Cabinet Office, March 6, 2025: https://www8.cao.go.jp/kisei-kaikaku/kisei/meeting/wg/2501_02medical/250306/medical01_agenda.html
3) The Regulatory Reform Implementation Plan, Health, Medical, and Nursing Care Working Group, Regulatory Reform Promotion Council, Cabinet Office, June 13, 2025: https://www8.cao.go.jp/kisei-kaikaku/kisei/publication/program/250613/01_program.pdf
4) Issues for the Implementation of the Act Partially Amending the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Pharmaceuticals and Medical Devices System Subcommittee, Health Science Council, July 23, 2025: https://www.mhlw.go.jp/content/11121000/001521143.pdf
5) Intractable Disease Clinical Trial Web: https://nanbyo-chiken.nibn.go.jp/
6) The 2025 Summary Report on Future Directions for the Promotion of Clinical Trials/Studies, Clinical Research Committee, Health Science Council, June 30, 2025: https://www.mhlw.go.jp/content/10808000/001510857.pdf
7) Survey on Difficulties Faced by Patients with Rare Diseases: https://www.jpma.or.jp/information/industrial_policy/rare_diseases/report/index.html

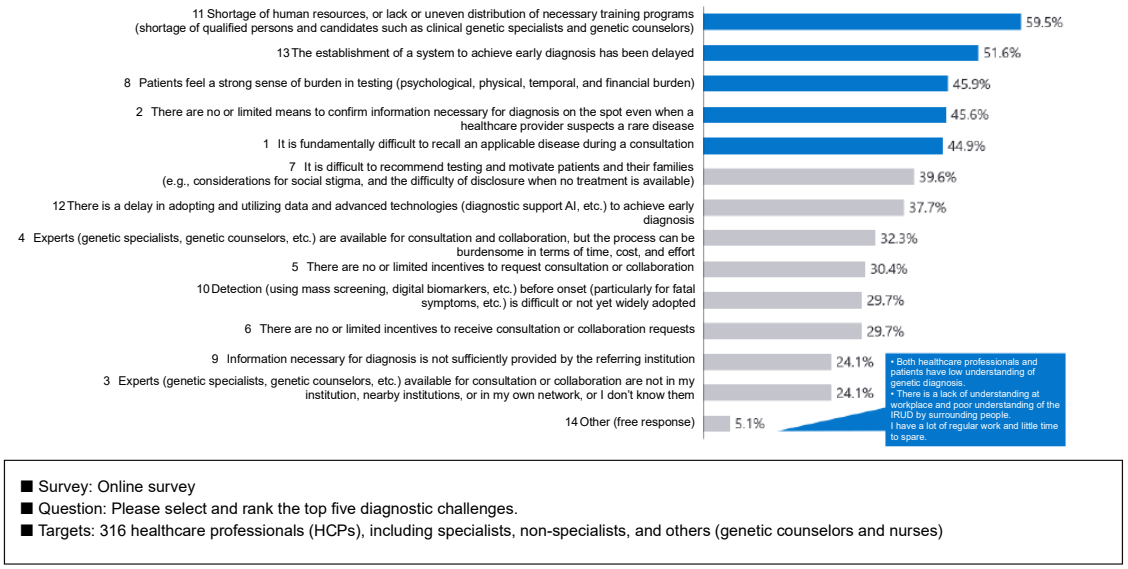
CHAPTER 3 Challenges and proposals for strengthening the early diagnosis system for intractable and rare diseases

1. Expansion of newborn mass screening for early diagnosis of intractable and rare diseases

[Background]

In the diagnosis of rare diseases, the biggest challenge faced by healthcare professionals is "delay in establishing early diagnosis systems." This is attributable to the following structural issues: the very low prevalence of the disease; insufficient knowledge of the disease among healthcare professionals; the "inability to suspect" the disease prior to diagnosis; regional disparities in the distribution of specialists; the underdeveloped diagnostic techniques and testing systems; and insufficient information coordination between departments and medical institutions. In fact, according to the "Survey on Difficulties Faced by Healthcare Professions in Rare Diseases," 51.6% of respondents answered that "The system to achieve early diagnosis is being delayed," which highlights the real voices from the field (Figure 6).

Figure 6 Diagnostic challenges: Top 5 choices



■ Survey: Online survey
■ Question: Please select and rank the top five diagnostic challenges.
■ Targets: 316 healthcare professionals (HCPs), including specialists, non-specialists, and others (genetic counselors and nurses)

The survey also highlighted that strengthening collaboration and information sharing between non-specialists and specialists is essential to improve the situation. Furthermore, enhancing newborn mass screening systems was identified as a key solution for achieving early diagnosis.

<Feedback from healthcare professionals>

"The speed of diagnosis is critical. Particularly in newborns, early diagnosis can significantly improve prognosis. Therefore, it is essential to strengthen systems that allow for more rapid and simple testing and interpretation of results." (Specialist/Pediatrics)

"The key to early diagnosis lies in promoting and expanding the scope of newborn mass screening. This would eliminate the need for repetitive, unnecessary tests and treatments. The government should allocate a larger budget to this area." (Specialist/Pediatrics)

[Challenge]

Newborn mass screening is an important public health strategy to prevent the onset of intellectual disabilities and serious complications by early detection of congenital metabolic abnormalities and endocrine diseases in the early stage after birth, leading to appropriate treatment. In Japan, it was launched as a government-subsidized program in 1977. Currently, screening is conducted for 20 diseases by local governments nationwide, maintaining a consistently high screening rate[1)]. However, the following challenges remain:

- There is no legal basis for the implementation or quality control. Furthermore, both the explanation of results to parents and the follow-up systems remain inadequate, and a system for testing quality control and information sharing has yet to be established.
- Since the program is implemented as a budget project of local governments, there are regional disparities in the availability of additional screening items across different municipalities.
- In some cases, the system for coordinating with specialized medical institutions and the transition to detailed examinations have not kept pace with the expansion of target diseases for testing.

As for the number of diseases subject to newborn mass screening, there is a need to establish a systematic selection process based on scientific evidence and further expand the target diseases. In the United States, 37 diseases are recommended as target diseases based on the "Recommended Uniform Screening Panel (RUSP)" established by an advisory committee of the Department of Health and Human Services, and many states implement their newborn screening programs according to the RUSP[2)]. While differences in disease classification and medical care systems need to be taken into account, it is important to implement a flexible and prompt review of the target diseases in light of advancements in treatment methods and testing technologies.

[Past efforts]

In Japan, the addition of target diseases has been individually reviewed based on findings from research groups and academic societies. Recently, CPT2 deficiency, a type of fatty acid metabolism disorder, was added, reflecting the ongoing expansion of the program based on scientific evidence[3)]. The national and local governments have initiated pilot projects for conditions, such as severe combined immunodeficiency (SCID) and spinal muscular atrophy (SMA), for which early detection is crucial due to advancements in treatment methods[1)]. With the advancement of testing technology, the tandem mass spectrometry has been introduced, and the range of target diseases has expanded. The research project of AMED is also promoting the development of selection criteria for diseases[4)].

However, while the number of candidate diseases has increased due to the practical application of new testing and treatment methods, there are still no clear criteria for expanding the list of new target diseases. As mentioned above, the United States facilitates the selection of target diseases based on scientific evidence and ensures nationwide implementation according to the RUSP[5)].

Establishing a treatment method is a prerequisite for expanding the target diseases for newborn mass screening, and the contributions of pharmaceutical companies are essential in this process. As stated previously, with the emergence of effective therapeutic drugs for SMA and SCID, there is a growing movement to expand the screening panel to include diseases for which treatment options are available and early therapeutic intervention is critical. Furthermore, by collaborating with universities and medical institutions to support the research and implementation of novel testing methods, they are actively involved in developing testing kits and diagnostic technologies, thereby improving testing precision and addressing new target diseases.

[Proposal]

The following are examples of efforts made by the JPMA:

1. Position the expansion of newborn mass screening as a priority issue of Policy Proposals 2025 towards the strengthening of the system for early diagnosis of rare diseases.
    - Support the design of a system that prioritizes adding diseases with established treatment methods, based on evidence-based selection criteria, and at the same time, communicate the efficacy and social significance of these treatment methods to advocate for the necessity of introducing screening.
    - Promote R&D to advance testing technologies, improve response capabilities to new diseases, strengthen collaboration with the government, medical institutions, and research organizations to address municipal disparities in testing, establish a cooperation system with specialized medical institutions, and enhance communication to parents/guardians and support for follow-up.

1) "Newborn Mass Screening," Document 1-4, 2nd Meeting of the Subcommittee on Maternal and Child Health Care, Children and Families Council, November 22, 2023: https://www.cfa.go.jp/assets/contents/node/basic_page/field_ref_resources/ce28e632-7504-4f83-86e7-7e0706090e3f/49ba4893/20231122_councils_shingikai_seiiku_iryou_tWs1V94m_06.pdf
2) Recommended Uniform Screening Panel, The Newborn Screening Information Center (NBSIC), December 2024: https: //newbornscreening.hrsa.gov/about-newborn-screening/recommended-uniform-screening-panel
3) Equal Employment, Children and Families Bureau, MHLW, Notification No. 0707-2 "Addition of CPT2 Deficiency," July 7, 2017: https://www.jsms.gr.jp/download/MHLW_MCH_20170707.pdf
4) Post-hoc Assessment Report, Comprehensive Research Project for Overcoming Emerging Conditions in Child Health and Development, Japan Agency for Medical Research and Development, June 21, 2023: https://www.amed.go.jp/content/000120172.pdf

5) “Comprehensive Research Report: Identification of Challenges in Newborn Screening Based on International Comparisons,” Health and Labour Sciences Research Grant, 2022: https://mhlw-grants.niph.go.jp/system/files/report_pdf/202310062A-buntan13.pdf

CHAPTER 4 Challenges and proposals accelerating R&D of therapeutic drugs for intractable and rare diseases

1. Stakeholders' efforts to develop therapies for intractable and rare diseases and promote drug discovery

Various stakeholders, including the government, patient groups, and pharmaceutical companies, have pointed out the importance of developing treatments for intractable and rare diseases and promoting drug discovery.

In December 2023, the 1st Conference on the Strategy to Promptly Deliver the Latest Pharmaceuticals to the Public Through Enhanced Drug Discovery Capabilities (hereinafter, the "Council for Enhancing Drug Discovery") was held. In the interim report, reflecting the recognition of challenges such as "drug lag and drug loss, the decline in the international competitiveness of Japan's pharmaceutical industry, and the lack of comprehensive and overall strategies involving industry, academia, and government," the following strategic goals were set: "deliver the latest drugs promptly to patients," "make Japan a global hub for drug discovery," and "build a sustainable system for investment and innovation[1)]." In the report, as a strategic direction for delivering the latest drugs to the public promptly, it states: "The strengthening of drug discovery capabilities should ultimately aim at the swift delivery of the latest drugs to the public. Resolving the current drug lag and drug loss is an urgent priority. (Omitted)...Drugs for pediatric use and intractable and rare diseases are often passed over for development by companies due to small patient populations. Therefore, strong government involvement is required. For this reason, after evaluating the effectiveness of conventional incentive measures, it is necessary to take steps to strengthen the operation of the system and enhance approaches to companies."

Based on this interim report, the Gate Opening Summit for Innovative Drug Discovery was held in July 2024[2)]. Government officials, domestic and overseas pharmaceutical companies, VCs, startups, university personnel, etc. attended the meeting to discuss future measures, including initiatives for the drug discovery ecosystem and the framework for the Public-Private Council. In FY2025, a Public-Private Council was established to discuss and examine the policies and progress of measures for fostering the drug discovery ecosystem, taking into account the needs of companies. In addition, the Strategic Goals and Action Plan Following the Interim Report were published. To ensure the prompt delivery of the latest drugs to the public, KPIs were established for resolving drug loss and the number of orphan drug approvals, with a commitment to following up on their progress[3)].

The 3rd Healthcare and Medical Strategy, approved by the Cabinet in February 2025, outlines specific measures for the five-year period from FY2025 to FY2029 to realize a health and longevity society where citizens can enjoy healthy, long lives. As part of promoting R&D that contributes to solving social challenges, the acceleration of development for pediatric, rare disease, and AMR-related drugs was prioritized[4)].

The Basic Policy on Economic and Fiscal Management and Reform 2025 (Honebuto Policy 2025), approved by the Cabinet in June 2025, states in Chapter 3 "Realizing a Mid-to-Long Term Sustainable Economy and Society": "To strengthen drug discovery capabilities and promote

innovation, the government will strive to enhance the overall command function while advancing structural reforms in the pharmaceutical industry, and implement integrated policies to develop the drug discovery ecosystem, expand the healthcare market, and reinforce the foundation of drug discovery, in accordance with the Healthcare and Medical Strategy[5].”

In the same month, the Public-Private Council for Enhancing Drug Discovery Capabilities was held. Under this council, a working group was convened to discuss specific details regarding the policies, challenges, and improvement measures for fostering the drug discovery ecosystem[6].

The JPMA has conducted the “Survey on Consumer Awareness of Drugs and the Pharmaceutical Industry” annually since 2014. According to the 18th report released in February 2025, 89.9% of respondents agreed (answering “I agree” or “I somewhat agree”) that “developing therapeutic drugs for diseases for which no adequate drugs exist is significant for society.” This demonstrates high public understanding regarding the necessity of developing therapeutic drugs for conditions with unmet medical needs, such as intractable and rare diseases[7].

Furthermore, the “Survey on Difficulties Faced by Patients with Rare Diseases” published by the JPMA’s Intractable and Rare Disease Task Force in February 2023, reported feedback from patients and their families who anticipate the development of therapeutic drugs for intractable and rare diseases. In this survey, when asked about their views on treatment, assuming a therapeutic drug for their rare disease was available overseas but not in Japan, 81.3% of patients expressed a desire to “wait until the treatment becomes available in Japan.” This is primarily due to the physical challenges of traveling abroad and the high financial burden.

Given the strong expectations and desire of patients to receive treatment in Japan, it is necessary to consider drug and loss as a social issue and work together with related stakeholders to solve it.

While other countries are advancing the development of genomic data infrastructures, Japan established its “Action Plan for Whole Genome Sequencing (Version 1)” in 2019. The plan aims to improve treatment precision for each and every patient and provide new treatments for patients with cancer and rare diseases who currently lack treatment options[8]. Following the “Action Plan for Whole Genome Sequencing Roadmap 2021,” the “Action Plan for Whole Genome Sequencing 2022” was established. Under this plan, discussions are ongoing to develop a business implementation structure through collaboration among industry, government, academia, patients, and the public. In the Policy Proposals 2025[9], the JPMA has been appealing to accelerate its efforts to realize genomic medicine, and has been discussing and making proposals with stakeholders.

In addition, many patient groups, led by the Japan Patients Association (JPA), a federation of patient groups for intractable and rare diseases, have issued petitions and proposals addressing the various challenges surrounding intractable and ultra-rare diseases.

[Petitions and reports from patient groups for intractable and rare diseases]

- In April 2025, the Japan Patients Association (JPA) submitted a petition to the Minister of Health, Labour and Welfare regarding the development of new treatment methods, etc.[10]
- Mr. Takeyuki Akiyama, Board Member of the Japanese Lysosome Disease Patients and Family Association and Honorary President of LysoBridge JAPAN (Japan MPS Patient and Family

Group), proposed institutional challenges and reforms for ultra-rare diseases at the Public-Private Council held in June 2025[6].

As described above, alongside the legislation and policies promoting therapeutic drug development for rare and intractable diseases, there are high expectations from patients and their families for the development. To address these challenges, the JPMA's Intractable and Rare Disease Task Force identified solutions for priority challenges across three key areas: R&D, the regulatory system, and the drug pricing system. These solutions are summarized in this chapter as the following four proposals:

- Promotion of effective use of state-of-the-art technologies, research facilities, and equipment that contribute to drug discovery research through industry-academia collaboration
- Environment for clinical research and clinical trials for intractable and rare diseases
- Domestic regulatory measures for rare diseases and international harmonization of regulations
- Drug pricing system for therapeutic drugs for intractable and rare diseases

1) Summary of the Interim Report: Conference on the Strategy to Promptly Deliver the Latest Pharmaceuticals to the Public through Enhanced Drug Discovery Capabilities, Office of Healthcare Policy, Cabinet Secretariat: https://www.cas.go.jp/jp/seisaku/souyakuryoku/pdf/chuukantorimatome_gaiyou.pdf
2) Gate Opening Summit for Innovative Drug Discovery, Office of Healthcare Policy, Cabinet Secretariat (held on July 30, 2024): https://www.cas.go.jp/jp/seisaku/souyakuryoku/shiryou/ecosummit_purpose.pdf
3) "Conference on the Strategy to Promptly Deliver the Latest Pharmaceuticals to the Public Through Enhanced Drug Discovery Capabilities," Strategic Goals and Action Plan Following the Interim Report, Office of Healthcare Policy, Cabinet Secretariat (July 2024): https://www.cas.go.jp/jp/seisaku/souyakuryoku/pdf/chuukantorimatome_mokuhyou.pdf
4) The 3rd Healthcare Policy and the Promotion Plan for Medical Research and Development, National Healthcare Policy Secretariat, Cabinet Office (June 2025): https://www.meti.go.jp/shingikai/mono_info_service/medical_equipment_healthcare/pdf/007_01_00.pdf
5) Basic Policy on Economic and Fiscal Management and Reform 2025 (Honebuto Policy 2025): https://www5.cao.go.jp/keizai-shimon/kaigi/cabinet/honebuto/2025/2025_basicpolicies_ja.pdf
6) Public-Private Council for Enhancing Drug Discovery Capabilities (held on June 26, 2025): https://www8.cao.go.jp/iryou/kanmin_kyogikai.html
7) "The 18th Survey on Consumer Awareness of Drugs and the Pharmaceutical Industry" (February 25, 2025): https://www.jpma.or.jp/news_room/release/2025/250225_2.html
8) Action Plan for Whole Genome Sequencing (Version 1) (December 20, 2019): https://www.mhlw.go.jp/content/10601000/000579016.pdf
9) JPMA Policy Proposals 2025 (February 2025) https://www.jpma.or.jp/vision/backnumber/policy_recommendations2025/eo4se30000005lnf-att/2025.pdf

10) Petition by the Japan Patients Association (April 4, 2025): https://nanbyo.jp/appeal/250404yobo1.pdf

2. Effective use of state-of-the-art technologies, research facilities, and equipment that contribute to drug discovery research through industry-academia collaboration

[Background]

The JPMA has set a goal of "building a 'drug discovery platform' that leads the world from the area of excellence in research in academia" and promotes initiatives to build Japan's strengths in drug discovery in fields that are difficult for individual pharmaceutical companies to address, by having the pharmaceutical industry proactively collaborate with academia and the government. In the pharmaceutical industry, industry-academia-government collaboration policies contributing to drug discovery research have been continuously implemented since Policy Proposals 2019, and results are steadily emerging. [1)]

On the other hand, the R&D environment for intractable and rare diseases still faces numerous challenges. In the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases," the most common response, at 46.8%, was that "the R&D environment for new modalities (such as gene and cell therapies) for rare diseases is insufficient." This indicates that many healthcare professionals still perceive challenges in the infrastructure for research into new modalities.

[Challenge]

In drug discovery for intractable and rare diseases, expectations for innovative modalities are increasing. However, advanced and specialized facilities and data are essential for this R&D, requiring considerable cost and expertise.

Although advanced facilities and joint utilization systems are being developed at some universities and companies, the effective sharing and utilization of these facilities have not progressed sufficiently. This is due to the inadequate functioning of shared networks, delays in establishing shared systems, and specific issues unique to each field[2)]. Furthermore, intractable and rare diseases are characterized by "a small number of patients," "a high diversity of conditions," and "varying data structures for each disease." Consequently, it is difficult to secure "a sufficient volume of data" for statistical analysis.

[Past efforts]

The Research and Development Infrastructure Subdivision of the Ministry of Education, Culture, Sports, Science and Technology (MEXT) has reported the "Summary of Issues Concerning the Promotion of Shared Use of Advanced Research Facilities and Equipment," and the government is currently organizing policies to promote the shared use of research facilities. As examples in academia, research support centers such as the "Research Core Center" at the Institute of Science Tokyo have been established. Similarly, the private sector is developing facilities to promote collaborative research, such as Mitsui Fudosan's "Mitsui Link-Lab." The AMED also promotes the maintenance of shared facilities supporting drug discovery research and the promotion of external shared and technical support through the "Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)," thereby contributing to the advancement of life science research,

particularly within academia. These efforts will enhance the quality of the R&D environment for intractable and rare diseases.

Regarding data challenges, the 2025 amendment to the Medical Care Act has enabled the MHLW to conduct linked analysis between the “Intractable Disease Patient Database,” the “Database of Specific Pediatric Chronic Diseases,” and other public databases (such as the NDB), facilitating the development of a new data infrastructure for the R&D of treatments for rare and intractable diseases.

[Proposal]

The following are examples of efforts made by the JPMA:

1. Engage in discussions with academia, the government, and industries in different fields to promote the utilization of exploratory technologies and large-scale research facilities that contribute to drug discovery research for new modalities.
   *Although this point is also included in the Policy Proposals 2025, it is mentioned again in this proposal due to its critical importance from the perspective of intractable and rare disease areas.

The following are examples of efforts made by the RDCJ:

1. The RDCJ will promote N-of-1 + drug discovery for ultra-rare diseases with extremely small patient populations. (This includes creating cases in Japan, drafting guidelines, collaborating with relevant academic societies, and establishing rules.)

1) Policy Proposals 2025 (JPMA): https://www.jpma.or.jp/news_room/release/2025/eo4se30000005mgq-att/2025.pdf
2) Summary of Issues Concerning the Promotion of Shared Use of Advanced Research Facilities and Equipment (MEXT): https://www.mext.go.jp/content/20240724-mxt_kibanken01-000037229_1.pdf

3. Environment for clinical research and clinical trials for intractable and rare diseases

[Background]

Because the number of patients with rare diseases is very small, it is difficult to evaluate investigational products solely in Japan. In the “Survey on Difficulties Faced by Healthcare Professions in Rare Diseases” conducted in 2025, healthcare professionals identified several challenges in development and clinical trials. High-ranking challenges included: “The means of financing development and clinical trial funds are limited;” “The human resources are lacking/the training programs necessary for are insufficient;” “It is difficult to recruit subjects for clinical trials;” and “The clinical trial system compatible with new modalities has not been established.” In this survey on the overall challenges faced by healthcare professionals, difficulties in clinical trials, in particular, were common regardless of the size of medical institutions or disease areas, reflecting systemic and structural challenges.

[Challenge]

Clinical trials/studies in rare diseases have the following challenges:

- It is difficult to secure a sufficient number of subjects because the patient population is small and scattered nationwide, necessitating a long registration period. Consequently, there is a limited number of medical institutions and human resources familiar with the diseases where clinical trial/study feasibility is low, and who are capable of handling new modalities (such as gene therapy and regenerative medicine).
- It is difficult for companies to conduct clinical trials due to business profitability, which also creates a barrier for overseas pharmaceutical companies and startups to enter the Japanese market. For this reason, development may need to be conducted through investigator-initiated clinical trials; however, in such cases, securing funding remains a major challenge.
- Information on a limited number of clinical trials/studies is not integrated and dispersed, making it difficult for healthcare professionals and patients to access necessary information.

[Past efforts]

To address these challenges, the government and relevant organizations have been promoting the establishment of clinical trial networks, disease networks, and registries not only for rare diseases but also for other diseases. Furthermore, they have focused on relaxing regulations, introducing expedited review systems, developing human resources, and fostering public and patient understanding and participation in clinical trials/studies[1) 2)].

In the field of rare diseases, efforts are also being made to establish infrastructures to address challenges such as small patient populations and geographic dispersion. These include organizing nationwide disease registries, promoting participation in global clinical trials, and considering the introduction of decentralized clinical trials (DCTs).

[Proposal]

While various efforts have already been made to improve the environment for clinical trials/studies, the following examples highlight the JPMA's efforts to improve the effectiveness of clinical trials/studies, especially in the areas of intractable diseases and rare diseases, and to resolve drug lag and drug loss:

1. Further enhancing the maintenance and utilization of registries for intractable and rare diseases
    - To facilitate the planning and implementation of clinical trials/studies and patient recruitment by companies, establish a centralized rare disease registry by integrating existing disease-specific registries, currently maintained under varying standards, and by enhancing information disclosure.
2. Promoting improved access to clinical trials/studies for patients
    - To reduce the burden on local and home-based patients participating in clinical trials/studies and to expand their opportunities, promote the adoption of DCTs by implementing telemedicine systems, collaborating with partner and satellite medical institutions, and the utilization of digital tools, and the establishment of delivery systems for investigational products that require specialized handling, such as gene and regenerative therapies.
    - In the area of pediatric rare and intractable diseases, we aim to improve access to clinical trials/studies by utilizing existing support systems for patients and medical institutions. This includes specialized diagnostic institution search engines and initiatives such as the "Healthy Parents and Children" campaign.
3. Clinical trial/study implementation system corresponding to new modalities and global clinical trials
    - To certify and foster specialists and medical institutions capable of responding to the unique study designs of new modalities and their handling, develop and promote education and training programs. These programs aim to encourage young physicians, researchers, and clinical trial staff, such as CRCs, to participate in rare disease trials.
    - For global clinical trials, establish systems and align with regulations to minimize Japan-specific requirements and ensure global consistency.

It is also important to create an environment where various businesses including overseas startups can easily conduct clinical trials/studies in Japan.

For this reason, it is necessary to proactively disseminate information in English regarding the development of rare disease registries, as well as recent improvements in the clinical trial environment and updated application requirements.

Furthermore, to secure funding for investigator-initiated clinical trials, it is desirable to establish financial support mechanisms by expanding public subsidy systems and fostering collaboration between companies and academic societies.

These efforts should enhance the feasibility of clinical trials/studies in the field of rare diseases and realize the early provision of new treatment options for patients.

1) Public-Private Council for Enhancing Drug Discovery Capabilities (Cabinet Office)
https://www8.cao.go.jp/iryou/kanmin_kyogikai.html
2) The 2025 Summary Report on Future Directions for the Promotion of Clinical Trials/Studies
https://www.mhlw.go.jp/stf/newpage_59245.html

4. Domestic regulatory measures for intractable and rare diseases and international harmonization of regulations

[Background and challenges]

Japan's regulatory system is undergoing significant evolution to enhance drug discovery capabilities and align with international regulatory standards. In particular, a system to eliminate the drug lag and drug loss is being developed, encompassing measures such as the establishment of overseas bases of the Pharmaceuticals and Medical Devices Agency (hereinafter, the PMDA), the promotion of global clinical trials, and a review of the conditional approval system. These measures enable prompt and flexible actions, facilitating the delivery of drugs to patients as soon as possible, even in fields where development has traditionally been challenging, such as rare and intractable diseases and pediatric drugs (including the addition of pediatric indications). However, these measures have just started, and how to operate them in the future is very important.

In the "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases," the expectations for regulatory authorities in R&D (Figure 4.2.5-1) include: strengthening institutional frameworks and incentives to accelerate the development and approval application of orphan drugs and regenerative medical products; enhancing the maintenance and utilization of domestic rare disease patient registries; and establishing an environment where overseas data collaboration and real-world data (RWD) for rare diseases can be utilized for R&D and approval applications.

----------<*Feedback from healthcare professionals*>

"Currently, registries are managed by individual organizations and individuals. It is desirable for the government to establish a standardized registration system as infrastructure and provide a legal framework—similar to the cancer registry—so that it will be used in research that leads to solving the challenges of rare diseases. It is also necessary to relax the regulations to link them to the designated intractable disease system and promote the utilization of data." (Specialist/Pediatrics)

"The introduction of diagnostics and drugs is lagging behind other countries. Given the nature of rare diseases with high urgency, I look forward to further accelerating swift and flexible procedures. Based on the high urgency of the diseases compared to others, it is necessary to establish schemes that allow for the smooth adoption of new technologies and treatment methods once certain procedures are completed, as well as efforts to relax the procedures. While the government should play a central role, I also expect proactive engagement from pharmaceutical companies." (R&D physicians/Immunodeficiency Diseases)

[Past efforts]

Recent regulatory trends and past efforts are as follows:

1. Council on the Future of Pharmaceutical Regulations for Strengthening Drug Discovery Capabilities and Ensuring Stable Supply[1)]

The Council, which was held from July 2023 to March 2024, mainly discussed three issues related to regulatory affairs: criteria for orphan drug designation, regulatory approaches contributing to the promotion of pediatric drug development, and the necessity of Japanese clinical data in confirmatory studies and the optimization of rapid approval systems. The notification that was issued after that

(see below) stated that, for orphan drugs, the applicability of sub-stratification, medical necessity, and re-examination period should be clarified, and for development of pediatric drugs, pediatric product development plans should ideally be formulated during the development phase of the adult version, outlining the scope and basic principles. In addition, the PMDA outlined the criteria under which an application for approval may be filed without clinical study data from Japanese patients, provided that confirmatory clinical studies have been conducted only overseas for drugs used for rare diseases, etc.:

- Criteria for orphan drug designation
  - Partial Amendment to the "Handling of Designation of Orphan Drugs" (PSB/PED Notification No. 0116-1 and PSB/MDED Notification No. 0116-1, joint notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau and the Director of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated January 16, 2024)
  - Questions and Answers (Q&A) on the Handling of Designation of Orphan Drugs (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated January 16, 2024)
  - Partial Amendment to the "Handling of Priority Reviews" (PSB/PED Notification No. 0116-2 and PSB/MDED Notification No. 0116-2, joint notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau and the Director of the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated January 16, 2024)
  - Partial Amendment to the "Handling of the Reexamination Period" (PSB/PED Notification No. 0116-3, notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated January 16, 2024)
- Regulatory approaches contributing to the promotion of pediatric drug development
  - "Development of Pediatric Drug Plans during Adult Drug Development" (PSB/PED Notification No. 0112-3, notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated January 12, 2024)
  - Partial Amendment to the "Development of Pediatric Drug Plans during Adult Drug Development" (PSB/PED Notification No. 0329-1, notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated March 29, 2024)
  - Questions and Answers (Q&A) on the Development of Pediatric Drug Plans during Adult Drug Development (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated March 29, 2024)
  - Establishment of the Regulatory Consultation Center for Pediatric and Orphan Drugs within the PMDA
- Reviewing the necessity of Japanese clinical data in confirmatory studies and the optimization of rapid approval systems
  - Reviewing the necessity of Japanese clinical data in regulatory reviews in Japan (necessity of Japanese phase I study when participating in global clinical trials)

- "Basic Principles for Conducting Phase I Studies in Japanese Subjects Prior to Joining Global Clinical Trials for Drugs with Preceding Clinical Development Abroad" (PSB/PED Notification No. 1225-2, notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated December 25, 2023)
- Questions and Answers (Q&A) on the "Basic Principles for Conducting Phase I Studies in Japanese Subjects Prior to Joining Global Clinical Trials for Drugs with Preceding Clinical Development Abroad" (Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated December 25, 2023)
- "Basic Principles for Japanese Subject Data in Cases where Confirmatory Clinical Trials for Orphan Drugs are Conducted Only Overseas" (PSB/PED Notification No. 1023-3, notification from the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, MHLW, dated October 23, 2024)

2. The amended PMD Act

The amended PMD Act, which was promulgated in May 2025, included the following points as measures related to pharmaceutical regulations:

- The conditional approval system will be reviewed, and approval shall be possible in cases such as where clinical efficacy can be reasonably expected.
- It is obligatory for marketing authorization holders of drugs to formulate plans for the development of pediatric drugs, and if the re-examination period has already reached its maximum (10 years), it can be further extended by up to two years.
- A fund to support the practical application of innovative new drugs will be established.

3. Establishment of the PMDA overseas offices

- The PMDA Asia Office was established in Thailand on July 1, 2024. The PMDA Washington D.C. Office was established in the United States on November 1, 2024.
- In the Basic Policy on Economic and Fiscal Management and Reform 2024, approved by the Cabinet on June 21, 2024, it is stated that the government will "promote international regulatory harmonization by leveraging the PMDA's overseas offices" in "3. Basic policies and important challenges by major sector (promoting healthcare, including strengthening drug discovery capabilities)."

4. Conference on the Strategy to Promptly Deliver the Latest Pharmaceuticals to the Public Through Enhanced Drug Discovery Capabilities

- The interim report advocates for revising drug regulations based on global clinical trials and promoting Japanese initiatives internationally and the development of low-profitable orphan drugs for intractable and rare diseases.

- Strategic Goals and Action Plan Following the Interim Report: The number of approvals of orphan drugs (150) (accumulated from FY2024 to FY2028) was set as an outcome target.

[Proposal]

As shown above, actions to promote domestic pharmaceutical affairs-related measures and international regulatory harmonization are being legislated and implemented through official notifications. However, these efforts are still in progress. The following are examples of efforts made by the JPMA:

1. The JPMA will provide recommendations to the MHLW and PMDA through various Working Groups (WGs) and Task Forces (TFs) to streamline regulatory reviews and surveys.
   <Example 1: The conditional approval system should be further revised to ensure that drugs for intractable and rare diseases are approved more promptly. >
   <Example 2: Under the revised system, a growing number of products are being designated as orphan drugs. However, many of these products are currently excluded from priority review and priority face-to-face consultation, resulting in delays in reaching patients. It is essential that all products designated as orphan drugs be eligible for both priority review and priority face-to-face consultation. >
   <Example 3: It is necessary to review the current utilization of the Consultation Center for Pediatric and Orphan Drugs and consider measures to improve it. >
2. The JPMA will support the PMDA U.S. Office, established in 2025, from the perspective of the pharmaceutical industry.
   <Example: It is essential to proactively communicate the attractiveness and flexibility of Japan's regulatory system to overseas companies to promote entry into the Japanese market for drugs targeting intractable and rare diseases. Potential methods for communication include strengthening English-language dissemination of information regarding system guidelines, review information, and development support systems, as well as active transmission at international conferences and forums. >
3. The JPMA will request that Japanese authorities enhance incentive measures for companies developing orphan and pediatric drugs, as well as promote the utilization of Real-World Data (RWD).
   <Example 1: Although the revised PMD Act has clarified the use of RWD in post-marketing surveillance, its application in approval reviews and clinical trials for intractable and rare diseases remains limited. There should be institutional support to facilitate this. >
   <Example 2: We believe it is necessary to introduce a system that allows for exceptional measures when patients and their families are willing to accept the associated risks. Furthermore, a regulatory system that incorporates patient voices (e.g., involving patient groups in the approval review process) should be established. To achieve this, it is essential to foster public education and open discussion to increase societal acceptance. >

The following are examples of efforts made by the RDCJ:

1. The RDCJ will strive to disseminate information on Japan's current status, unique challenges (including regulatory trends), and international cases through cross-sectoral collaboration among industry, patients, academia, government, and the public, involving both domestic and overseas stakeholders.

1) Report by the Council on the Future of Pharmaceutical Regulations for Strengthening Drug Discovery Capabilities and Ensuring Stable Supply
https://www.mhlw.go.jp/content/11121000/001248959.pdf

5. Drug pricing system for therapeutic drugs for intractable and rare diseases

[Background]

Therapeutic drugs for intractable and rare diseases represent irreplaceable hope for every single patient and stand as symbols of medical advancement, regardless of the small patient population. In recent years, the emergence of innovative drugs—such as gene and cell therapies that differ from conventional modalities—has made it possible to effectively address diseases once considered difficult to treat.

However, among drugs approved and launched in Western countries since 2014, a certain number of products, both in new and existing modalities, remain undeveloped in Japan despite the presence of target diseases. A breakdown of new modalities by disease reveals that more than half of the new modalities target rare diseases, making it apparent that treatment options are failing to reach patients in Japan compared to those in Western countries[1)].

The "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases" pointed out as an R&D challenge that the current regulatory and drug pricing systems are unattractive to pharmaceutical companies seeking to conduct development and clinical trials, leading to "drug lag" and "drug loss" in Japan. To accelerate R&D for new modalities and achieve a sustainable drug discovery ecosystem, it is essential to design systems that include not only expedited approval processes but also pricing structures that allow companies to recoup their investments.

<Feedback from healthcare professionals>

"Due to the small patient populations, there are few economic incentives for rare diseases for pharmaceutical companies. The low motivation within the industry clearly stands as a significant barrier." (Basic and applied research physician/Endocrine and Metabolic Diseases)

"The Japanese market is perceived as lacking a framework that allows companies to recoup their investments. It is only natural that we cannot expect companies to pursue drug development unless we create a framework for business viability. Furthermore, as overseas pharmaceutical companies and startups with bases or networks in Japan decrease, it has become unclear where or to whom information on overseas new drug approvals should be provided to initiate concrete discussions on development in Japan." (Basic and applied research physician/Neurological and Muscular Diseases)

"I hope to see deregulation of funding for all R&D stakeholders and the establishment of a drug pricing system that enables companies to easily recoup their investments. We need a mindset shift from adhering to existing systems to how to achieve our goals and how the government will be involved in achieving the goals." (Basic and applied research physician/Neurological and Muscular Diseases)

[Challenge]

As the aging population, declining birthrate, and advancing medical technologies strain healthcare budgets each year, reforming the social security system including reviewing benefits and burdens is an unavoidable challenge.

On the other hand, to continuously create innovative new drugs, it is essential to establish a virtuous cycle where the new drugs created are appropriately evaluated, and the resulting revenues are reinvested into early-stage R&D to drive the next wave of innovation. Particularly in the field of intractable and rare diseases, small patient populations often prevent pharmaceutical companies from recouping long-term investments.

Under the current system, the Cost-Calculation Method is applied to many innovative drugs because they lack suitable comparator drugs for pricing purposes. However, because the Cost-Calculation Method determines prices through a summation of total manufacturing costs and operating margins, it fails to fully reflect the diverse value of a drug. As a result, companies may find it difficult to launch innovative drugs in Japan until overseas evaluations are established, hindering early access to these drugs within the country. Furthermore, frequent system changes aimed at securing financial resources undermine market predictability, dampening corporate incentive for development.

[Past efforts]

In order to appropriately evaluate highly novel and innovative new drugs without delay relative to advanced countries and introduce them in Japan, the JPMA has requested the evaluation of the drug pricing system for the early introduction to Japan during discussions for the FY2024 Drug Pricing System Reform. As a result, measures for the elimination of drug lag and drug loss were implemented in the FY2024 Drug Pricing System Reform. These include introducing a rapid introduction premium, reviewing foreign average price adjustment rules, reviewing the premium for promoting new drug discovery and resolving off-label use, and flexibly judging premium rates such as marketability and pediatric premiums, under the policy of "taking drug pricing measures to promote the appropriate evaluation of innovation of innovative new drugs in order to realize the elimination of drug lag and drug loss in addition to strengthening the drug discovery capabilities in Japan[2)]."

However, there are still challenges with the more essential value evaluation of new drugs, especially the base price calculation method instead of the Cost-Calculation Method. Under these circumstances, it is necessary to establish a new system that allows companies to provide evidence for innovative drugs under certain rules, ensuring that calculated prices reflect the individuality of each drug. Appropriately evaluating the value of innovative drugs and maintaining it throughout their patent periods will enhance the attractiveness of the Japanese market, thereby helping to accelerate early access in Japan.

[Proposal]

The following are examples of efforts made by the JPMA:

In order to continuously create therapeutic drugs for intractable and rare diseases with limited patient populations, it is essential to establish a virtuous cycle where the new drugs created through substantial, long-term R&D investment are appropriately evaluated, and the resulting revenues are reinvested into early-stage R&D to drive the next wave of innovation. In addition, the rules have become complicated due to repeated changes in the system, and it is necessary to build an "attractive market" that can draw foreign investment by reviewing the system to make it simpler and more

predictable. Therefore, the JPMA proposes a drug pricing system that appropriately evaluates the value of innovation.

1. Introduction of a new framework for appropriate evaluation of innovative new drugs
    - A new framework to better evaluate the value of innovative new drugs, such as new modalities
2. Drug price maintenance throughout the patent period for innovative new drugs
    - Revision of drug prices by category to keep the prices of innovative new drugs simple
    - Review of re-pricing for market expansion: Establishing a framework that avoids disincentivizing development for rare, pediatric, and intractable diseases with high medical needs
    - A new framework to re-evaluate the value of therapeutic drugs when additional evidence is obtained after insurance coverage

1) The 2nd Conference on the Strategy to Promptly Deliver the Latest Pharmaceuticals to the Public Through Enhanced Drug Discovery Capabilities
Challenges and Measures for Enhancing Japan's Drug Discovery Capabilities (February 8, 2024):
https://www.cas.go.jp/jp/seisaku/souyakuryoku/dai2/siryou3.pdf
2) FY2024 Drug Pricing System Reform, MHLW (March 5, 2024)
https://www.mhlw.go.jp/content/12400000/001238906.pdf

6. Column: Aiming to overcome intractable and rare diseases

Hidehiro Mizusawa, Representative of the IRUD, Special Advisor to the President, National Center of Neurology and Psychiatry

Due to their rarity, intractable and rare diseases are difficult to diagnose, and the number of researchers is limited, and there is little industrial incentive to address them. Consequently, the elucidation of disease mechanisms and the development of treatment methods remain significantly delayed. In recent years, following the success of the Human Genome Project, comprehensive genome analysis technologies have advanced remarkably. It is now possible to perform whole exome and whole genome sequencing with high precision, speed, and cost-effectiveness, significantly facilitating the diagnosis of rare genetic diseases. In the IRUD, a diagnosis has been confirmed for nearly half of the cases. However, these world-class results imply that more than half of the cases remain undiagnosed. Therefore, it is necessary to address and resolve these remaining undiagnosed cases.

In the IRUD, clinical information is standardized using HPO (Human Phenotype Ontology), and the registration rate is as high as approximately 80%. By sharing this data globally, it is expected that more than 300 N-of-1 cases will be successfully identified as the underlying cause. In addition, starting in FY2024, the Disease Model Center was internalized to initiate efficient functional analysis of candidate genes. Furthermore, in cooperation with the relevant research group, the implementation of whole genome sequencing has increased the diagnosis rate by nearly 10%.

As of November 14, 2025, according to OMIM (Online Mendelian Inheritance in Man), the number of genetic neurological conditions is estimated at 10,300. Of these, the causative genes have been identified for 7,072 diseases, while the remaining 3,228 remain unidentified. While various projects are currently being carried forward overseas alongside the IRUD, comprehensive genome analysis is usually performed only after patients visit the hospital. Instead of this, a more proactive approach would be to launch an international collaborative project provisionally titled “Comprehensive Genetic Elucidation Project for Intractable Diseases (provisional name),” aimed at proactively identifying all genes responsible for unidentified single-gene diseases. As one can easily imagine, the causative gene of a single-gene disease is highly likely to serve as an important target molecule in a variety of pathological molecular circuits (networks) in humans. Even a modest increase in the current elucidation rate from 70% to 80% could significantly accelerate the in silico identification of candidate genes long before 100% is reached.

While our genome consists of approximately 3 billion base pairs, only about 1.5% of it actually codes for proteins. Recently, an increasing number of diseases caused by abnormalities in non-coding regions are being documented. Now that whole genome sequencing has become possible, there are high expectations that the functions and roles of these regions, which make up the majority

of the genome, will be elucidated. Undoubtedly, unknown principles of life lie hidden within them, and their elucidation is considered essential for the advancement of humanity.

Furthermore, while both diseases and normal traits are determined by the interaction between the genome and the environment, common diseases affecting large populations involve multiple or many genes. These are referred to as multifactorial or sporadic diseases. The elucidation of the mechanisms of these multifactorial diseases is just beginning, and whole genome sequencing is expected to play a crucial role. Furthermore, as all factors except the genome are the environment, and given that environmental impacts are mediated via gene expression, it is essential to conduct comprehensive genomic research in a broad sense that includes RNA.

This is exactly why countries around the world are now competing fiercely to advance genomic medicine and genome science.

As outlined above, while a breakthrough in research is vital to overcoming intractable diseases, it is equally essential to enhance the practical aspects of medical and nursing care for patients in front of us. Currently, under the guidance of the intractable disease medical liaison council and intractable disease consultation and support center at the prefecture level, and the regional intractable disease countermeasures council at the public health center level, various institutions, including core hospitals for intractable disease care, specialty-specific core hospitals, cooperative hospitals, and general hospitals and clinics, work together to support patients with intractable diseases. It is clear that many stakeholders are involved. It is extremely important to ensure collaboration among all parties, especially those directly engaged in nursing care. For example, the establishment and utilization of a meeting body such as the “Intractable Disease Medical and Welfare Liaison Council (provisional name)” is expected to help stakeholders gain a comprehensive understanding of the entire medical and nursing care landscape for rare diseases. Since similar approaches have already been conducted and yielded positive results in fields such as dementia, having specific personnel or facilities manage multiple disease areas is expected to lead to the more effective use of limited regional resources. Additionally, many patients with intractable diseases would benefit if municipal-level facilities and systems, such as regional comprehensive support centers, were made more widely accessible.

CHAPTER 5 Challenges and proposals on the perspectives of specialized human resources and patients' families in intractable and rare diseases

1. Expanding development opportunities and ensuring sustainability for specialized human resources in intractable and rare diseases

[Background]

In the field of rare diseases, the establishment of diagnostic methods and the development of therapeutic drugs are often delayed, and shortages of human resources such as researchers and healthcare professionals, as well as insufficient recognition and knowledge, are major challenges. In rare and ultra-rare diseases for which diagnostic methods have not been established, it is also difficult to organize patient groups to conduct activities. The "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases" also emphasized the "lack of human resources" and "lack of training programs" among healthcare professionals. Thus, it is necessary to proactively improve the specialized education for researchers supporting the R&D of new modalities applicable to rare diseases, the education of healthcare professionals who have learned diagnostic techniques including genomic analysis, and the education of patients and their families to facilitate Patient and Public Involvement (PPI) in research. We propose that the RDCJ, committed to addressing challenges in rare disease drug discovery, function as a platform to lead education and awareness-raising activities, and by engaging relevant clinical and basic research societies, universities, medical institutions, and patient groups, provide comprehensive opportunities for education and awareness.

[Challenge]

Regarding the development of experts in rare diseases, the primary challenges are a fundamental shortage of human resources and a lack of established training programs. For example, in university education such as medical and pharmaceutical schools, education specialized in rare diseases is fragmentary, and opportunities to systematically acquire expertise are limited. The diagnosis, treatment, and drug discovery for rare diseases are significantly more challenging compared to common disease areas with large patient populations.; therefore, there is an urgent need to foster experts capable of addressing each of these conditions.

Even when experts in rare diseases are trained, limited mobility of human resources makes it difficult to achieve efficient drug discovery and medical care. Human resources are often confined within their respective organizations—basic research, clinical practice, companies, and government—resulting in a limited exchange of knowledge and experience. In the R&D of new modalities, there is a shortage of personnel with the necessary cross-disciplinary skills.

In addition, human resources capable of proactively engaging in R&D and medical care for rare diseases have not been developed due to PPI, fund-raising, etc., and it is also necessary to develop systematic education programs, develop role models, and provide successful examples.

[Past efforts]

- Creation of drug discovery seeds and improvement of environment by the AMED (e.g., Practical Research Project for Rare and Intractable Diseases and promotion of PPI)

- MEXT's Project for Establishing Centers for Developing Advanced Medical Professionals (balancing clinical education and research activities for medical students)
- MHLW-sponsored e-learning programs (ICRweb, eAPRIN, etc.)
- Government policy to strengthen drug discovery capabilities
- Designated intractable disease physician or designated medical institution system
- Educational programs for patients and their families, such as PPI by civic groups
- Launch of the RDCJ

[Proposal]

The following are examples of efforts made by the RDCJ:

1) Development of systematic education programs focused on rare disease drug discovery and medical care
   [1] In cooperation with the RDCJ and related academic societies, the RDCJ will consider the development and introduction of a systematic curriculum specialized in medical examination and treatment of rare diseases at medical institutions.
   [2] Provide lectures and seminars specialized in the development of treatment methods for rare diseases by the RDCJ members, and related healthcare professionals and researchers at universities, research institutes, and academic societies and seminars. Recognizing that many rare diseases are congenital conditions caused by genetic mutations, provide guest lectures and online content for secondary education to deepen understanding of genetics, genomics, phenotypes, diseases, and PPI to foster a truly diversity, equity, and inclusion (DE&I) society.

2) Establishing a mechanism to improve human resource mobility and support career progression
   [1] Introduce training programs that allow students, young researchers, and healthcare professionals to learn about rare diseases.
   [2] The RDCJ members and other stakeholders will advocate for the expanded use of the cross-appointment system, and by increasing dual-appointment positions within companies and government agencies for university faculty, clinicians, and patients and their families, facilitate the sharing of know-how.
   [3] Expand the options for career paths involved in policy planning and practical research so that rare disease researchers including the RDCJ can also be involved in government and corporate activities according to their interests and aptitudes.
   [4] Aim to expand employment opportunities for young researchers in addition to R&D by encouraging the AMED, etc. enhance research funding and grants specialized in rare diseases.
   [5] The RDCJ will participate in designing mechanisms that provide additional incentives for rare disease learning, PPI, and career path selection, beyond those available for common diseases, and advocate for their adoption by the government, companies, and academia.
   [6] Present role models and best practices from the RDCJ and its stakeholders as attractive career paths.

3) Strengthening of human resources and information exchange through international collaboration

[1] Promote exchange programs that foster collaboration between rare disease networks in Western countries and those related to rare diseases in Japan, while supporting the development of human resources with global networks and perspectives.

[2] The RDCJ and affiliated organizations will advocate for mutual exchange through initiatives such as international collaboration sessions at academic conferences, aiming to foster information exchange and collaboration with rare disease networks in Western countries.

4) Toward the realization of N-of-1 drug development in Japan

[1] The RDCJ will proactively participate in and drive discussions on the design of clinical evaluation methods, including outcome measures evaluable in single cases, comparison methods with natural history data, estimation techniques, and safety monitoring methods.

[2] The RDCJ will encourage regulatory authorities and the government to ensure regulatory and legal development and flexible operation of the review and approval system.

[3] The RDCJ will support discussion of frameworks to provide additional incentives other than sales profit for pharmaceutical and manufacturing companies engaged in orphan drug discovery.

[4] In order to ensure the sustainability of N-of-1 drug discovery, the RDCJ will provide a forum for discussion with stakeholders on the funding and reimbursement schemes and cost-sharing such as exploring public funds, the flexible application national and private insurance, and other sustainable financing options, to facilitate the design of these systems.

2. Perspective of patients' families

[Background]

In this chapter, intractable and rare diseases are defined as "intractable rare diseases," common challenges from the perspective of patients and their families are organized, and necessary measures are summarized and proposed.

Based on statistics showing that approximately 6 million people—about 5% of the Japanese population—suffer from intractable rare diseases, each patient requires nursing care from at least two people (primarily family members), and even a conservative estimate suggests that over 18 million people are directly affected daily[1]. Compared with the population of about 14 million people in Tokyo, the impact is significant.

Even under the single term "intractable rare diseases," the nature and degree of "intractability and rarity" vary greatly. Since the associated challenges are also diverse, generalizing these issues is not always easy.

The JPMA has conducted surveys on difficulties to identify and organize challenges that the pharmaceutical industry should address regarding intractable rare diseases. In this survey, three major challenges were identified: (1) limited information and difficulty in accessing necessary information; (2) a lack of social understanding and knowledge of these diseases; and (3) limited treatment options and a lack of radical treatment. In July 2023, these were released as proposals. However, most of these issues remain unresolved as of 2025.

Instead of focusing only on the "disease" itself, we focus on the multifaceted and unique needs of patients with intractable rare diseases, as well as the impact on them and their families, and present comprehensive proposals for addressing these challenges.

[Challenge]

[1] "Limited information and difficulty in accessing necessary information"

While the lack of "information" related to intractable rare diseases and their treatments is often highlighted, the needs of patients and their families extend far beyond the availability of therapeutic drugs alone. In order to live a social life with intractable rare diseases, "information" is necessary from administrative, social welfare, economic, and mental aspects.

In the absence of a fundamental therapeutic drug, there is a need for multifaceted treatment drugs and methods to address diverse and changing symptoms, and access to "information" based on the multidisciplinary specialized expertise across various fields is also necessary.

International academic papers, etc. are usually published in English. Even when R&D are progressing overseas, it is often difficult for patients and their families in Japan to access this information due to language and technical barriers.

[2] "A lack of social understanding and knowledge of these diseases"

Unlike common diseases, the number of patients for each intractable rare disease is very small. Therefore, there is little shared awareness in society, making it difficult to gain public understanding and empathy. While active awareness-raising activities are sometimes carried out by patient groups, etc., there are many cases where not only the pathology and the reality of patients' lives, but also the names of the diseases themselves remain unknown to the public. A lack of understanding means

there is no way to grasp the harsh reality faced by patients and the families supporting them. Consequently, this fails to lead to appropriate societal responses or support. In other words, the lack of opportunities to know intractable rare diseases in the first place underlies the challenge.

[3] "Limited treatment options and a lack of radical treatment"

Among intractable rare diseases, there is no therapeutic drug for 90% or more of them, and about 80% of them are hereditary, 70% are severe, and 60% are infantile-onset pediatric diseases. Among them, one in three patients does not survive to reach their fifth birthday[2]. In reality, patients and their families cannot even have opportunities to appeal the necessity of therapeutic drugs. The information gap from overseas is as described above. Similarly, a gap exists in access to therapeutic drugs, and "drug loss" remains a critical and ongoing challenge[3].

[Past efforts]

Major efforts made by the JPMA's Intractable and Rare Disease Task Force

- "Survey on Difficulties Faced by Patients with Rare Diseases" released in February 2023
- Proposals on the three key challenges to be addressed by pharmaceutical companies, released in July 2023
- "Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases" (IRUD, RDCJ, and JPMA), released in November 2024

[Proposal]

The following are examples of efforts made by the RDCJ:

1. Facilitating information provision and collection

[1] Building a one-stop core information network

It is inherently difficult for patients and their families to even identify what meaningful information or support systems are available to them, as well as where to find the appropriate consultation desks.

To ensure that stakeholders from all backgrounds can smoothly gather information, it would be effective for the RDCJ to serve as a coordinating hub in establishing a core information network. This platform, developed in collaboration with domestic and international patient groups, medical institutions, government, academia, and companies, would serve as a one-stop information hub for people related to intractable rare diseases. By consolidating the existing bases, comprehensive content can be developed, and accurate and high-quality information can be enhanced through expert supervision, while at the same time, efficient and timely provision of information can be enabled.

[2] Launch of peer support and information exchange communities

In order to reduce anxiety and prevent isolation of patients and their families, the RDCJ and patient groups will collaborate to launch interactive, cross-disease peer support communities.

[3] Explanations via AI translation and lay summaries

The RDCJ will support the provision of information through AI translation and lay summaries so that patients and their families can access overseas information efficiently while ensuring the accuracy and quality of information.

2. Enhancing public awareness, understanding, and realistic support

[1] Improving science, medical, and social welfare literacy and advocacy

In many cases of intractable and rare diseases, patients and their families face many limitations that make self-help and mutual support difficult. Therefore, the fundamental prerequisite for a solution is for the general public to take ownership of these issues and engage with them proactively. Advocacy by the general public is essential. To build this foundation, the RDCJ will help promote a pivotal role in long-term, continuous outreach to educational institutions and the general public.

[2] Psychological support

Patients and their families are forced to live under tremendous physical and mental strain every day, and witnessing the progression of a loved one's illness—combined with anxiety about the future and a lack of prospects, social isolation, chronic sleep deprivation, and the relentless nature of irreplaceable care—often leads to a breakdown in their physical and mental well-being. The RDCJ will work with professional organizations, patient groups, and existing support services to improve access to expert counseling and strengthening grief care services.

[3] Addressing regional disparities in medical care

Patients with intractable and rare diseases and their families must rely on medical and social welfare support provided under frameworks such as the "Act on Medical Care for Patients with Intractable Diseases" (Act No. 50 of 2014), also known as the "Intractable Disease Act," and the "Act on Support for Children in Need of Medical Care and Their Families" (Act No. 81 of June 18, 2021), also known as the "Medical Care Children Support Act." Recently, regional disparities have continued to widen regarding the scope and extent of public support from local governments, as well as access to highly specialized care at medical institutions. The RDCJ will advocate for fair and equitable solutions, including the urgent reallocation of resources.

[4] Enhancement of economic support and improvement of QOL

For intractable rare diseases, in addition to the high medical expenses, patients and their families also face hidden burdens that often go unrecognized. This includes, for example, nursing supplies, medical devices, nutritional supplements, expenses for caregivers and nursing care, transportation and accommodation costs. In addition, , because it is often difficult for patients and their families to maintain full-time employment, their household finances are frequently under significant pressure. Financial hardship is closely associated with caregiver burden and reduced quality of life[4)], the RDCJ will advocate for a central role in further enhancing the medical expense subsidy system and burden reduction measures.

[5] Provision of medical and nursing care support/respite care (temporary hospitalization or short-term stays)

The physical and psychological fatigue caused by the constant care of the patient by the family is substantial. In particular, in cases of severe and progressive infantile-onset diseases, family members who provide most of the child's daily care are forced to respond to changing symptoms and associated needs. The RDCJ will promote, in collaboration with relevant stakeholders, the expansion of places and opportunities where these families can rest with peace of mind and recover.

3. Promotion of R&D for therapeutic drugs

In drug discovery R&D for intractable rare diseases, clinical data are often provided by patients who do not benefit from established therapeutic drugs or may die before such treatments become available. In other words, patients and their families provide information and cooperate with research for little to no reward, or for only a very slim chance of benefit. Furthermore, in the case of pediatric patients, families often have no choice but to provide information or cooperate with research as representatives on behalf of the child, and the child's assent should be respected whenever appropriate.

While adding financial and regulatory incentives to academia, companies, etc. can drive R&D, the incentive truly sought by patients and their families, which is the "establishment of therapeutic drugs," is never realized in most cases. What added value can be provided to patients and their families? With respect and gratitude, and by treating intractable rare diseases as a shared social challenge, the RDCJ will help foster an environment where all stakeholders contribute from their respective positions toward a resolution.

1) Challenges of Rare Diseases in Japan (January 2020)
https://genetics.qlife.jp/wp-content/uploads/RD_WhitePaper.pdf
2) Knowledge on rare diseases and orphan drugs:
http://www.orpha.net/
3) Summary Results by the Research Group of the MHLW Special Research Project FY2024: "Investigation of the Actual Status of Drug Loss and Construction of Solutions" (March 31, 2025):
https://www.mhlw.go.jp/content/10808000/001462594.pdf
4) Rare disease, common struggles: quality of life, caregiver burden and financial wellbeing of family caregivers in Poland:
https://www.nature.com/articles/s41598-025-08866-7

3. Aiming for a rare disease ecosystem that leaves no one behind

Yoshitsugu Aoki, Representative of the RDCJ, Director of Department of Molecular Therapy, National Institute of Neuroscience, National Center of Neurology and Psychiatry

For nearly a quarter of a century, I have engaged in the research and clinical care of rare neuromuscular diseases, such as muscular dystrophy. Although I was involved in the commercialization of viltolarsen, the first domestically produced antisense oligonucleotide drug in Japan, I have always been struck by the towering wall that lies between “developing a drug” and “delivering it to the patient.” The phenomenon of “drug loss,” where drugs regularly used overseas remain undeveloped or unapproved in Japan, symbolizes this structural distortion. Realizing that the future of rare disease medical care cannot be secured without facing this reality, like-minded partners from industry, patient groups, academia, and other stakeholders gathered to form the RDCJ. Launched on February 29, 2024, as a “co-creation platform,” the RDCJ views “advancing drug discovery” and “leaving no one behind” on the same horizon. We promote patient-centered challenge sharing, information organization, and consensus building. While stakeholders across industry, patients, academia, government, and the public each play important roles in shaping the system, the RDCJ serves as a hub for discussion and collaboration.

This proposal originates from the “Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases.” Using the voices from the field as a guide, such as the reality of long and difficult diagnostic journey, the difficulty of accessing clinical trials/studies, the complexity of regulatory and pricing systems, and the shortage of human resources, time, and information, it outlines “who, where, and what must be addressed to change society,” forming a framework that can be implemented in both policy and practice. During the editing process, at a reception following the National Forum on Intractable and Chronic Diseases 2025, I had a brief conversation with a representative of a patient group. After reviewing materials and explanations from government officials, the person remarked that some discussions can at times feel exclusionary and that doctors may appear to belong to the established side of the system. The person also noted that the RDCJ should not be seen as a burden borne by any one individual. These words captured an anxiety that patients' lived experiences could be erased by words spoken with good intentions, yet they also held hope for changing the future together in the same space. As a researcher and physician, I too may unconsciously stand on the side of eugenic thinking or power structures. Unless I confront this fact, the phrase “patient-centered” can easily become hollow. Her quiet words struck me deeply.

The vision presented in these proposals is straightforward. It is to establish a system that connects patients to specialized medical care and support from when rare diseases are suspected and shorten the “diagnostic odyssey” by leveraging the IRUD and newborn mass screening. We must develop global clinical trials, decentralized clinical trials (DCTs), registries, and real-world data to ensure that treatments established overseas are available in Japan without significant delay, making “drug loss” a rare exception. At the same time, specific procedures and indicators, such as single-arm

studies, N-of-1 studies, CMC for new modalities, and evaluation systems that include home-based care, must be incorporated. We must build a foundation for transparent, fair, and patient-inclusive discussions on access to treatment, the conditions under which it is provided, and the acceptable level of risk. This includes opening paths for the education and careers of professionals supporting rare disease medical care and creating mechanisms for early participation by patient groups and families.

I still carry in my heart those brief words heard in the corner of that reception. Rare disease drug discovery and access are matters of “technology” and “systems,” but they are also a fundamental question of “how to create a society where every person finds dignity and joy in their being.” It is my hope that these proposals serve as a small step toward sharing this question with society and expanding a rare disease ecosystem, where no one is left behind, from Japan to the world.

CHAPTER 6 Closing

1. Concluding words

Based on the results of the “Survey on Difficulties Faced by Healthcare Professionals in Rare Diseases” published in November 2024, we have identified three key challenges to be addressed by pharmaceutical companies and summarized proposals for each in Chapters 2 through 4. Furthermore, Chapter 5 outlines proposals to address challenges regarding the expansion of opportunities for specialized human resource development and the perspective of patients and their families.

To resolve the diverse challenges surrounding intractable and rare diseases, it is essential for various stakeholders, including the government, healthcare professionals, academia, patient groups, pharmaceutical companies, and other industries, to work together. To realize a society where patients with intractable and rare diseases and their families can live more comfortably, the JPMA, IRUD, and RDCJ will continue to collaborate and cooperate from our respective positions.

2. List of stakeholders

Initiative on Rare and Undiagnosed Diseases (IRUD)
Hidehiro Mizusawa, Representative of the IRUD, Special Advisor to the President, National Center of Neurology and Psychiatry
Shinji Kosugi, Specially Appointed Professor, Kyoto University
Naomichi Matsumoto, Professor, Yokohama City University
Kenjiro Kosaki, Professor, Keio University
Tadashi Kaname, Director, National Center for Child Health and Development
Atsushi Sugie, Professor, Kyoto Institute of Technology

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

Hideo Miki, Secretary General, C4U Corporation, Center for Gene Therapy Research, Jichi Medical University
Naoto Inukai, Lead Representative, Takeda Pharmaceutical Company Limited
Akitsu Hotta, Director, Center for iPS Cell Research and Application (CiRA), Kyoto University
Hiroyuki Shibasaki, Director, Japan Muscular Dystrophy Association
Yukari Blumenthal, Director, Astellas Pharma Inc.
Shunsuke Arami, EY Strategy & Consulting Co., Ltd.

Japan Pharmaceutical Manufacturers Association (JPMA)
Intractable and Rare Disease Task Force
Ichiro Tamatomi, Task Force Leader, Astellas Pharma Inc.
Shinji Takeuchi, Sub-leader, Kissei Pharmaceutical Co., Ltd.
Yuki Kato, Sub-leader, Takeda Pharmaceutical Company Limited
Yoko Yano, Astellas Pharma Inc.
Kenichi Fuchibe, Kyowa Kirin Co., Ltd.
Kazunobu Idota, Sanofi K.K.
Masatsugu Kobayashi, Sumitomo Pharma Co., Ltd.
Shota Watanabe, Daiichi Sankyo Company, Limited
Kaori Akimoto, Pfizer Japan Inc.
Toshiyuki Karumori, Pfizer Japan Inc.