# RARE DISEASES IN TURKEY

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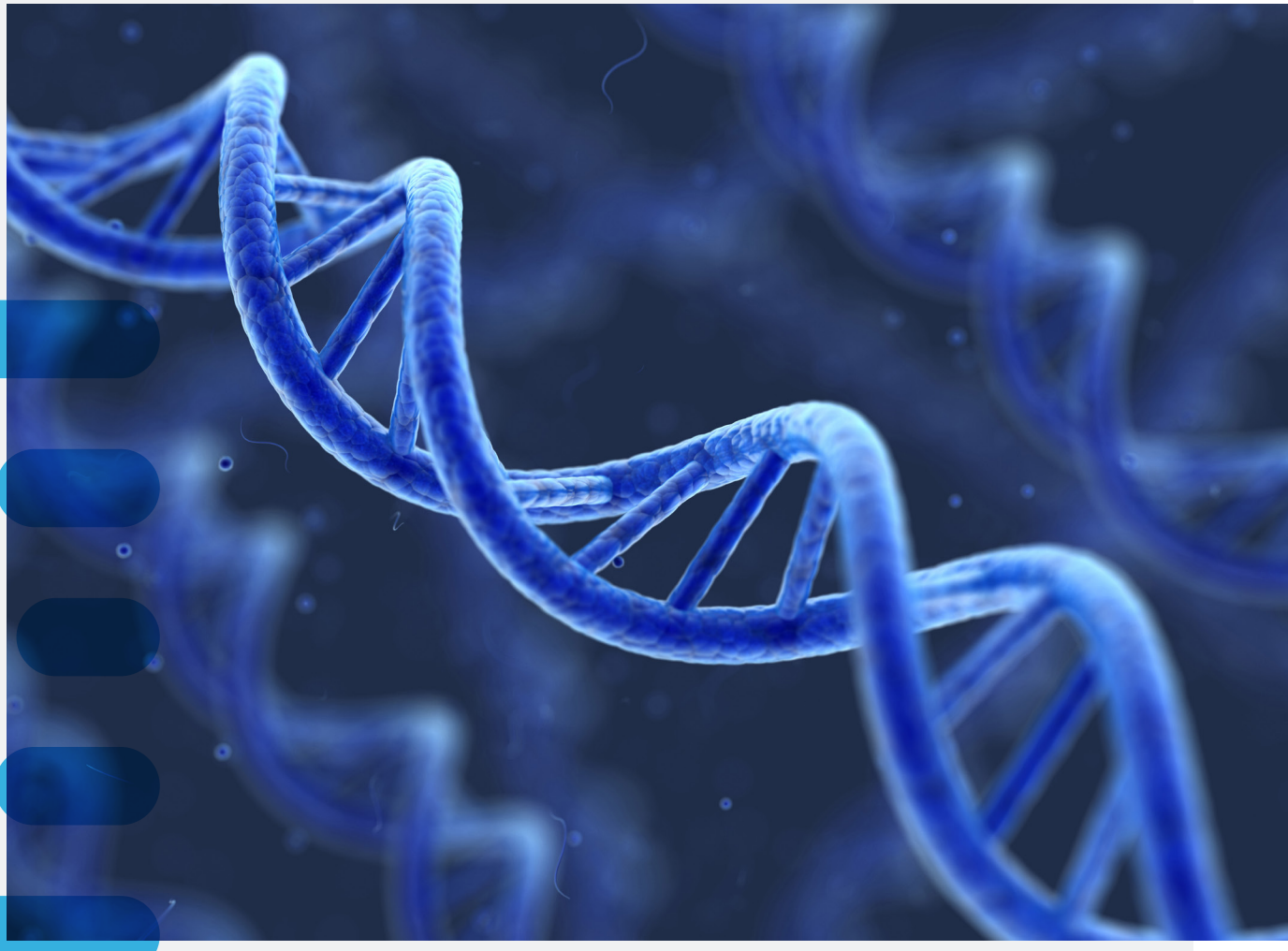

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# ABBREVIATIONS

| | |
|---|---|
| **AGÖK** | Alternative Reimbursement Commission |
| **CAH** | Congenital adrenal hyperplasia |
| **CF** | Cystic fibrosis |
| **COPD** | Chronic obstructive pulmonary disease |
| **DMD** | Duchenne muscular dystrophy |
| **EMA** | European Medicines Agency |
| **ERN** | European Reference Network |
| **EU** | European Union |
| **EUCERD** | European Union Committee of Experts on Rare Diseases |
| **FDA** | U.S. Food and Drug Administration |
| **GMS** | Genomic Medicine Sweden |
| **HSGM** | General Directorate of Public Health |
| **ICD-10** | 10th Revision of International Classification of Diseases |
| **İGÖK** | Medicinal Product Reimbursement Commission |
| **ILD** | Interstitial lung disease |
| **IPF** | Idiopathic pulmonary fibrosis |
| **IVF** | In vitro fertilization |
| **KHGM** | General Directorate of Turkish Public Hospitals |
| **MoH** | Ministry of Health |
| **MPS** | Mucopolysaccharidosis |
| **NGS** | Next-generation sequencing |
| **NIH** | National Institutes of Health |
| **NORD** | National Organization for Rare Disorders |
| **NPD** | Niemann-Pick disease |
| **OECD** | Organisation for Economic Co-operation and Development |
| **PAH** | Pulmonary arterial hypertension |
| **PGD** | Preimplantation genetic diagnosis |
| **R&D** | Research and development |
| **SHGM** | General Directorate of Health Services |
| **SMA** | Spinal muscular atrophy |
| **SSI** | Social Security Institution |
| **SUT** | Healthcare Implementation Communiqué |
| **TBMM** | Grand National Assembly of Turkey |
| **TİTCK** | Turkish Medicines and Medical Devices Agency |
| **TÜBİTAK** | The Scientific and Technological Research Council of Turkey |
| **TÜSEB** | Health Institutes of Turkey |
| **USA** | United States of America |

# EXECUTIVE SUMMARY

"Rare diseases" is the common name given to many diseases each of which is rarely seen in the community, for an important part of which there is no standard diagnosis and treatment method yet and even some of which have not been medically identified yet.

Even though clear definition of rare diseases differs in various parts of the world, the general tendency is to make this definition on the basis of prevalence. According to the definition accepted in the European Union (EU), for a disease to be considered "rare", its prevalence must be 1/2000 and below. In our country, EU definition is taken as basis in the Rare Diseases Health Strategy Document and Action Plan published by the Ministry of Health in November 2022. [1] [2] [124]

No comprehensive research has been made on the prevalence of rare diseases in Turkey; however, according to a statistical study conducted considering the rare disease prevalence assumed by the European Commission, it is estimated that there are more than 5 million individuals in Turkey who have any rare disease. On the other hand, very high consanguineous marriage rates in Turkey compared to Europe (23.2% vs below 5%, respectively) suggests that prevalence of rare diseases in our country might be higher than that in Europe.[1] [3] [4] [5] [124]

Across the world, nearly 8000 rare diseases have been identified so far, with new ones being added every year. More than 70% of the identified diseases are genetic disorders and around 70% emerge during the childhood. These diseases impact on various areas of the body and usually progress and contribute to disability or premature death. They cause a significant burden on both the health system and the national economy because they are usually chronic and result in the need for inpatient or regular outpatient treatment. In a study conducted in the United States of America (USA), the direct and indirect annual total financial burden of 379 diseases representing around 50% to 60% of the population with rare diseases was estimated to be around 1 trillion Dollars. [1] [2] [6] [7] [8] [124]

Treatments to be developed for rare diseases will make positive effect on the clinical course of patients, on the quality of life of patients and their relatives and on the health systems of countries, as they will enable more effective control of diseases. However, treatments have been developed only for 5% of the identified rare diseases until today. The main reasons for this include the challenge in and high cost of developing medicinal products for these diseases which spread over a wide range and each of which is seen in a very limited patient population, yet unresolved mechanism or underlying reasons of some very rare diseases and therefore the impossibility of conducting any research and development (R&D) study aimed at treatments for them.[1]

*Across the world, approximately 8000 rare diseases have been identified so far, with new ones being added every year. Around 70% of the identified diseases emerge during the childhood.*

For effective management of rare diseases, carrying out R&D studies for these diseases, prevention and early diagnosis of diseases, patients' access to all treatments they need including supportive therapies, keeping patient records in the long term and regularly and raising awareness of both the healthcare professionals and the general public are of critical importance. For the purpose of performing the foregoing all together and consistently, legal regulations, national policy documents and action plans have been created over the years. Major

examples include legal regulations and national policy documents put into effect in the USA, EU and various Asian countries since 1983. Among the European countries, France, in particular, has come to the fore with its sustainable national policies in this field.

Considering that the effects of rare diseases on the population and health system may be different for each country, the policies developed by the states in the management of these diseases are very important. A national policy for rare diseases had not been established in the past in Turkey; however, significant progress has been made in this area thanks to the previous efforts and the Ministry of Health published the 2023-2027 Rare Diseases Health Strategy Document and Action Plan in November 2022. Ministry of Health General Directorate of Health Services (SHGM) and Health Institutes of Turkey (TÜSEB) are among the public institutions that are actively operating in the area of rare diseases in our country. As of 2020, Department of Autism, Mental Special Needs and Rare Diseases established under SHGM became the public unit responsible for drafting the plan, policy and legislation on rare diseases and building infrastructure for screening, early diagnosis and management of rare diseases.[9] [10]

The priority way of lessening the burden of rare diseases on the community and state is, if possible, prevention of formation of these diseases. When it comes to genetic diseases, pre-marital screening programs enable this. Various hereditary blood diseases and spinal muscular atrophy (SMA) are screened in this context in our country and couples under risk are provided with consultancy in relation to this.[11] [12]

In addition, thanks to preimplantation genetic diagnosis (PGD) applied in in vitro fertilization (IVF) treatment, ill or carrier couples are enabled to have

healthy babies. Accordingly, infrastructure works by the Ministry of Health were completed in our country and PGD applications were included in the scope of reimbursement by Social Security Institution (SSI) as of August 2021. Within this framework, for couples at risk, the costs of the application for more than 50 different genetic diseases are covered by the government.[13]

*Thanks to all newborn screening efforts made in Turkey, annually roughly 4500 children are protected from the consequences of their existing diseases, and emergence of disability is prevented.*

Furthermore, a number of diseases which, if diagnosed early, can be controlled using the available treatments or progress of which can be delayed have been included in newborn screening. In our country, as of the end of 2021, 6 rare diseases were included in this screening program. Thanks to all newborn screening efforts made in Turkey, annually roughly 4500 children are protected from the consequences of their existing diseases, and emergence of disability is prevented. Moreover, it is stated that works are under way to expand the scope of disease in newborn screenings. Considering that newborn infants are screened for more than 50 rare diseases in Italy and various states of the USA and for more than 26 in Taiwan, the opportunity of expanding the scope of this program in Turkey is apparently available.[14] [15] [16]

Almost all of the genetic tests for diagnosis of rare diseases can be performed in certain public and private healthcare institutions. When considered in the general sense, the infrastructure for genetic diagnosis centers is available in our country and the tests required for the diagnosis of rare genetic diseases are accessible. However, some experts mention a confusion regarding genetic tests in Turkey. The Regulation on Genetic Diseases Assessment Centres published in January 2020 set out the criteria for the centers established with the aim of diagnosis of genetic diseases and providing consultancy on genetics, which, in this way, targeted the improvement and standardization of the quality of service provided at the relevant centers.[17]

Even if the symptoms of each rare disease, the course of disease, diagnosis methods and patient needs differ, one of the most important issues addressed for many rare diseases is the prolonged and challenging diagnosis process. The main reasons for this include the fact that making a differential diagnosis by eliminating other diseases takes long time for the rare diseases in question; when only symptomatic treatment is applied against the initial symptoms, time is lost until the other symptoms appear; where diseases affect different systems of the body, time is lost because physicians with any specialty other than those specialized in the subject matter are consulted when initial symptoms appear; and that because only around 500 rare diseases have their specific codes in ICD-10 coding system, in some cases, the diagnosis for a patient cannot be seen clearly by other physicians who were consulted with different symptoms because, even if an initial diagnosis was made for a patient, the initial diagnosis could not be entered in e-Nabız system clearly.[10] [18]

In an attempt to resolve problems attributable to coding, TÜSEB translated into Turkish the nomenclature of Orphanet, the widest rare diseases information network on the global scale, which codes all identified rare diseases in detail, and initiated a study for integrating it into e-Nabız system. On the other hand, it is of great importance that all physicians have a high level of knowledge and awareness of rare diseases and the process is managed with a multidisciplinary approach, in order to minimize the time spent during diagnosis. The network of centers of excellence in France spread across the country sets a good example for the steps that might be taken in Turkey. In addition to these, studies have been started in France and Switzerland for integration of full genome sequencing method into the health system which will, in particular, enable earlier and accurate diagnosis of genetic diseases.[10] [15] [19] [20]

In managing rare diseases, easy access to the right treatment following timely and accurate diagnosis

is also very important. On the other hand, when compared to the wide range of rare diseases, the number of treatments developed for them is quite limited. The most important reason for this is the difficulty in conducting and high cost of R&D studies for those diseases as each of them affects only a very limited number of people. For the purpose of resolving this problem, treatments addressed to a limited number of patients in many countries in the world have been defined as "orphan drugs", and R&D activities and market access timelines and processes for these drugs have been supported with a number of legal regulations. Even though various efforts were made in our country for a legal regulation on orphan drugs since 2009, no law or regulation has been put into effect.

On the other hand, patients in Turkey have access in various ways to 151 of 416 drugs in total that were given the status of an orphan drug, which is still valid, by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA); however, only 76 of these drugs are authorized in Turkey and 75 of them are brought into our country via Foreign Drug List.[7] [21] [22]

The Ministry of Health and Social Security Institution in Turkey endeavor to ensure that treatments developed for unmet needs of patients, so long as they meet the necessary conditions, are authorized in Turkey and the patients are provided with free access to them. However, disruptions occur with regard to market access processes for innovative drugs, in particular in terms of time.

In a study which reviewed 57 orphan drugs approved by EMA between 2017-2020, it was seen that only 8 of them could be accessed in Turkey with reimbursement, falling far behind the average in Europe which was 21. Moreover, it was found that only 2 of those 8 drugs were authorized and the others could be accessed via Foreign Drug List. Again, in the same study, it was observed that since the approval of the EMA, the reimbursed access of these drugs to Turkey through the Foreign Drug List was provided in an average of 461 days, compared to 102 days in Germany. [15] [23]

In Turkey, during authorization processes, priority assessment application can be filed for innovative products that meet the unmet needs; however, the process still takes longer than predicted. In order to resolve this problem, the Regulation on the Authorization of Medicinal Products for Human Use was updated on 11 December 2021; with the arrangements introduced, it was aimed to align the relevant content included in the regulation with the conditional and exceptional authorization procedures included in the EU Directive.[10] [24]

Medicinal products authorized in Turkey are priced by the Ministry of Health on the basis of reference price system and the exchange rates that are fixed yearly.

Reimbursement applications for medicinal products filed with SSI after obtaining marketing authorization are reviewed by Medicinal Product Reimbursement Commission (İGÖK) or Alternative Reimbursement Commission (AGÖK). As in the case of authorization, products that have the status of an orphan drug abroad do not undergo a different process in Turkey during pricing and reimbursement processes either; however, just like the prioritization criteria in the authorization process, it is also important in the

reimbursement review that the product responds to an unmet need.

Pricing and reimbursement of orphan drugs that take an important place in the treatment of rare diseases with innovative approaches is a globally considered matter; because the general perception caused by the high cost per patient of some orphan drugs suggests that the total economic burden caused by those drugs is high as well. In contrast to this general judgement, orphan drugs make up only a little portion of the whole drug market. An analysis by IQVIA showed that the share of orphan drugs in the US drug market was 11% in 2019 while the share of the same in the European market was 3.5% in 2016.[25]

Various attempts have been made in the EU member states in order to provide the patients with faster and more affordable access to orphan drugs and similar innovative treatments. Among the outstanding examples are the increased bargaining power of multiple countries by acting together in the pricing and reimbursement processes and utilization of alternative reimbursement models in the reimbursement processes.[26] [27] [28]

Since rare diseases usually affect more than one part of the body, treatment of these diseases requires a multidisciplinary approach just like the diagnosis thereof does. Therefore, it is of great importance that the healthcare infrastructure for managing these diseases is sufficient in terms of quality, quantity and extent and structured to be available for a multidisciplinary approach.

One of the most important elements of a strong healthcare infrastructure is the human resource. Availability of qualified human resource in the management of rare diseases is very important for ensuring that patients are diagnosed timely and high-quality healthcare services are provided. Opening relevant centers and laboratories and providing technical infrastructure is necessary for sure; however, it is an absolute priority that there are sufficient number of specialists who are capable of performing diagnosis, treatment and follow-up those patients.

The number of specialist physicians in various branches in Turkey have increased over time but the number of specialist physicians per patient in our country is yet far behind OECD average and an inequality is observed in the distribution of specialist physicians across the country. The same is true for both the nurses who play an important role in the diagnosis and treatment of rare diseases and the employees such as auxiliary staff, technicians, social workers, psychologists who take part in various stages of treatment and follow-up processes. There is need for increasing the number of all these expert human resources, making them widespread and carrying out activities for standardization of their services across the country.[10] [29] [30]

Another important element of healthcare infrastructure is the healthcare institutions. In our country, rare diseases are mostly managed at the research and education hospitals, university hospitals and city hospitals which are tertiary healthcare institutions. There are polyclinics or centers specialized in certain rare diseases or disease groups, under the relevant department, in some of these institutions. The only group among them for which standards have been set with a particular regulation is the neuromuscular disease centers. In addition to them, centers called "Center for Rare Diseases" have been

started to be established in various institutions, recently. These centers in limited number that are yet quite new and under development currently focus rather on research activities in this field.

Multidisciplinary management of rare diseases abroad is carried out via centers of excellence. The primary objective of these centers called "Center of Excellence" in the USA and "Centre of Expertise" in the EU countries is to enhance access by individuals affected by rare diseases to diagnosis, treatment and follow-up processes and thereby improve those processes; to promote cooperation; to raise awareness and to form a basis for research activities in this field by facilitating accumulation and sharing of knowledge. The centers in question in the EU have an important place in the management of rare diseases and are the most important matters addressed by member states in their national plans and strategies for rare diseases. These centers established in many countries for different rare diseases are specialized places where comprehensive research is conducted in relation to a specific rare disease and studies are performed for the diagnosis and treatment of those diseases. For a center to be qualified as a "centre of expertise" in the EU, it must comply with the accreditation criteria set by EU Committee of Experts on Rare Diseases (EUCERD). These centers may be provided with facilities by the EU such as funding support and delivery of training to the healthcare personnel employed at the centers.[31] [32]

There is no center of excellence for rare diseases in Turkey with documented compliance with EUCERD criteria or accredited by the relevant agencies in our country. The Ministry of Health, in its various declarations, highlighted the importance of centers of excellence for rare diseases and stated that the efforts thereof were being made, however, the current situation demonstrates that this has not been reflected in practice yet.

When it comes to rare diseases, it is highly important that patients are followed up and recorded in the long run. This, on one hand, facilitates patient recruitment for clinical trials for new treatments and contributes to obtaining epidemiology and real-world data, setting treatment standards for diseases, increasing life expectancy with the available treatments, improving patient care, and planning of healthcare system in an effective manner, on the other.[33] [34]

*When it comes to rare diseases, it is highly important that patients are followed up and recorded in the long run.*

As of September 2020, a review of 793 patient record systems reported by Orphanet from 36 EU and neighboring countries showed that there were only 5 patient record studies from Turkey and this number was 158 for Germany, 150 for France and 89 for Italy.[34]

Considering the total population of Turkey, estimated total number of individuals affected by rare diseases and the level of risk for genetic diseases due to the high rates of consanguineous marriage especially in certain regions; it is expected to derive benefit from generalization of patient record studies in our country with regard to management of rare diseases.

Patient record studies also contribute to R&D activities carried out in the field of rare diseases. The importance of the said activities is great for the patients; because figuring out the underlying mechanisms of these diseases will enable their timely and accurate diagnosis, and the development and administration of the right treatments for them. Thanks to better understanding of rare diseases and development of treatment options for more rare diseases, more effective treatments will be administered instead of treatments with low effects against their high costs, and a decrease in public health expenditures will be attained on the global scale.[35]

For this reason, research in the field of rare diseases is encouraged through various ways in many countries all over the world. Incentives offered by the regulations on orphan drugs are the most important ones. Since the release of the first orphan drug regulation in 1983 in the USA, studies on developing drugs for rare diseases have gained momentum.[1]

Besides orphan drug regulations, states have incorporated promotion of scientific research in this field into their national plans for rare diseases. EU gave place to research on rare diseases in two different research and innovation programs covering the years 2007-2020 and transferred funds in excess of 620 million Euros to more than 120 rare disease research projects between 2007-2013.[15] [19]

*With the acceleration in R&D activities especially in relation to orphan drugs in the recent years, a global increase has been observed in the number of clinical trials for rare diseases.*

In Turkey, on the other hand, there are scarcely any research by national resources in the field of rare diseases. In 2021, TÜSEB and the Scientific and Technological Research Council of Turkey (TÜBİTAK) created a call for scientific studies on the early diagnosis and follow-up of rare diseases; however, there are opportunities in our country to create further studies in this field.[36] [37]

Goals and responsible organizations for R&D activities have been identified in the Rare Diseases Health Strategy Document and Action Plan. These goals include supporting preclinical and clinical studies, development of diagnostic and screening tests, supporting scientists and production facilities to develop advanced technology products locally, providing the infrastructure required to develop pharmaceuticals.[124]

Clinical trials constitute the stage of R&D activities for drugs which holds the largest share. With the acceleration in R&D activities especially in relation to orphan drugs in the recent years, a global increase has been observed in the number of clinical trials for rare diseases. When looked at the industry-sponsored clinical trials that were active as of December 2021 in Turkey; it was seen that 137 (20%) of the 684 trials in question pertained to rare diseases other than rare cancers, and this number rose to 431 (63%) when trials for rare cancers were included as well.[7] [38]

Our country represents a significant patient potential for rare disease clinical trials with its large population posing relatively high risk of having rare genetic diseases; however, it falls behind this potential with respect to the number of clinical trials per person. There are a variety of areas of opportunity in Turkey for more patients to take advantage of such research. In particular, it is supposed that actions to be taken for raising awareness of patients and for patient recruitment and easy patient access will contribute to increasing the number and extending the scope of clinical trials for rare diseases in our country.[39]

Despite the ever-increasing R&D activities all over the world, the unmet treatment need for most rare diseases continues to stand as a big problem. In addition to this, these diseases have significant physical, psychological, social and economic impacts on patients. Moreover, patients' relatives as well as the patients are substantially affected by the wearisome process caused by rare diseases. In a study, it was found that individuals affected by rare diseases, and their families used 30% of their annual income for out-of-pocket expenses incurred in relation to the disease.[40] [41]

From the viewpoint of patients and patients' relatives, the main problems in diagnosis-treatment-follow-up processes of rare diseases in Turkey are described as the insufficient healthcare infrastructure, poor multidisciplinary approach, disruptions and restrictions in access to certain diagnosis methods and treatments, lack of knowledge and awareness among the community and the healthcare professionals, limited communication and collaboration between the stakeholders, inadequate social and psychological support, and absence of national database and patient record systems.[42]

It is essential that access by individuals affected by rare diseases to healthcare services and social and economic facilities is not restricted because their diseases affect limited number of people, and that those individuals have the right and quality of life equal to that of other individuals within the community. To that end, it is highly important to generate national-level solutions to the problems encountered around rare diseases and to put those solutions into practice in cooperation with the relevant stakeholders.

In line with the issues addressed in the report, 10 areas of improvement have been determined by IQVIA which have been grouped under the headings of national policies, infrastructure and R&D. There are various opportunities for improvement in Turkey in the aforesaid areas of improvement. A total of 19 solution suggestions have been developed by IQVIA for those opportunities.

**Table 1: Improvement Suggestions by Area of Improvement**

| | | |
|---|---|---|
| **National policies** | National plan, strategy and legislation | **N1.** Determination and follow-up of implementation of national plans, policies and strategies specific to rare diseases under the leadership of a joint commission |
| | | **N2.** Determining the definition of orphan drug in compliance with the international standards and forming the relevant legislation |
| | Access to diagnosis and treatment | **N3.** Acceleration of authorization process in treatment of rare diseases |
| | | **N4.** Improvement of pricing and reimbursement processes for treatment of rare diseases |
| | | **N5.** Facilitating access to tests and medical devices used in the diagnosis and treatment of rare diseases |
| | National and international cooperations | **N6.** Active involvement of Turkey in the prominent organizations in the world on rare diseases |
| | | **N7.** Forming the basis for putting into practice and extending the scope of public-private partnerships in the field of rare diseases |
| | Awareness of rare diseases within the community | **N8.** Taking actions aimed at raising public awareness and knowledge of rare diseases |
| | | **N9.** Strengthening patient associations and improving communication with international organizations |
| **Infrastructure** | Expert human resource | **I1.** Increasing access to specialist physicians taking part in the diagnosis and treatment of rare diseases |
| | | **I2.** Increasing access to specialist physicians taking part in the diagnosis and treatment of rare diseases |
| | | **I3.** Raising awareness of rare diseases of physicians and other healthcare personnel working at the primary health care institutions |
| | | **I4.** Establishing and strengthening national and international reference and communication networks in the field of rare diseases |
| | Protective and preventive healthcare infrastructure | **I5.** Expansion of diseases covered by screening program and improvement of consultancy services provided to patients who are identified to be in the risk group as a result of screening |
| | Multidisciplinary approach | **I6.** Creating centers of expertise where a multidisciplinary approach specific to rare diseases is adopted and setting accreditation criteria for these centers and ensuring control thereof |
| | Data network | **I7.** Keeping regular records of and following up patients who are diagnosed with a rare disease and individuals who are at risk |
| | | **I8.** Providing flexibility for conducting real-world data studies for treatments used in the area of rare diseases, which can be accessed in our country but have not yet been authorized |
| **R&D** | R&D facilities | **R1.** Supporting R&D activities for development in Turkey of products for the diagnosis and treatment of rare diseases, forming the suitable basis for these activities and providing incentives |
| | Clinical trials | **R2.** Increasing the number of clinical trials performed in Turkey in the field of rare diseases |

# 1. OVERVIEW OF RARE DISEASES

The concept "rare diseases" first emerged in 1980s and represents numerous diseases that are rare in the society, a considerable proportion of which has no standard diagnosis or treatment methods yet and some of these are not even medically defined.

### 1.1 Definition of "Rare Diseases"

Rare diseases are chronic and generally progressive diseases that are seen rarely across the society. Prevalence of a disease is required to be 1/2,000 or lower to be qualified as "rare" in the European Union. This upper limit used in the definition of rare disease was specified as a maximum of 200,000 people with the disease among country population in the United States of America and a maximum of 50,000 people in Japan. While the accurate definition differs across geographical regions in the world, the general trend is to base the definition "rare disease" on prevalence ground.[1] [2]

Development of the concept of "rare disease" that essentially lacks a medical definition allowed small groups of patients with a very limited chance for diagnosis and treatment to unite and express themselves and in particular to draw attention to the needs in treatment domain. First proposed in USA, this concept has been adopted not only by the patients and patient families but also by policymakers, healthcare professionals and the pharmaceutical industry through nearly 40 years since then.[43]

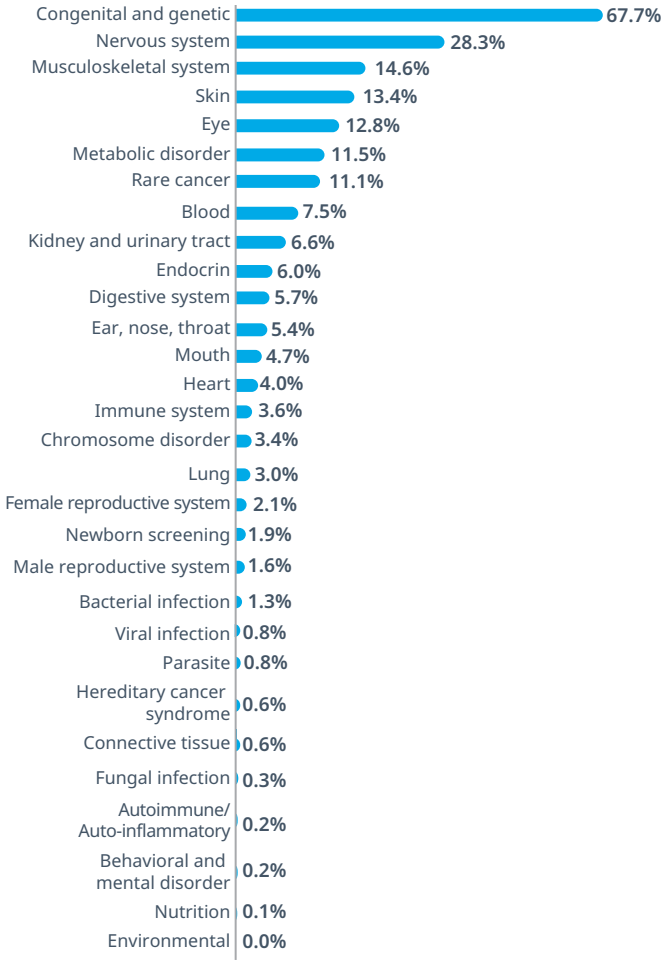
Many steps have been taken also in our country both by the government and the other stakeholders. These steps will be addressed in detail later in the report. All these initiatives including the Rare Diseases Health Strategy Document and Action Plan published by the Ministry of Health, are based on the "rare disease" definition by the European Union.

### 1.2 The Extent of Rare Diseases

There are nearly 8,000 rare diseases globally described so far with 3 to 4 new diseases added each year. 71.9% of these are genetic diseases and 69.9% appear at childhood.[1] [2]

Some rare diseases only affect a certain system in the body while many have effects on more than one site. Based on the body site they affect, the US Department of Health and Human Services categorized 4,408 of the diseases registered in the Orphanet international knowledge network, the reference source for rare diseases. When this study, in which diseases can be assigned to one or more categories according to their impacts, is analyzed; it is seen that 67.7% of the evaluated diseases are in the categories of congenital and genetic diseases, 28.3% are in the nervous system diseases, 14.6% are in the musculoskeletal diseases category, and more than 60% are in more than one category.[7] [44]

**Figure 1. Categories of Rare Diseases Based on the Body Site Affected**




Source: 1. https://rarediseases.info.nih.gov/diseases/categories. Access: November 8, 2021; 2. IQVIA analysis.

## 1.3 Epidemiology and the Population Affected by Rare Diseases

The Council of the European Union reported in their action recommendations on rare diseases issued in 2009 that 6% to 8% of the European population is affected by these diseases.[45]

While this value was regarded for the prevalence of rare diseases across Europe and in Turkey since then, various scientific studies try to estimate the overall prevalence more accurately. A study published in 2019 estimated the overall prevalence of rare diseases included in the Orphanet knowledge network. In this study which excludes cancer types, infections and intoxications for which the frequency is reported in terms of incidence, the prevalence of all other rare diseases combined in Europe was estimated to be 3.5% to 5.9%. Based on this value that is considered to be conservative and also adopted by the EURORDIS, the largest network of patient associations on rare diseases in the world, it is estimated that approximately 30 million people in Europe and nearly 300 million people worldwide are affected by rare diseases.[2]

No comprehensive research has been made on the prevalence of rare diseases in Turkey; however, according to a statistical study conducted considering the rare disease prevalence assumed by the European Commission, it is estimated that there are around 5 million individuals in Turkey with any rare disease. On the other hand, it is considered that the prevalence of rare diseases in our country may be even higher than the European level. This is primarily caused by the fact that consanguineous marriage rate that elevates the occurrence risk of genetic diseases is 23.2% in Turkey while it is less than 5% in Europe.[1] [3] [4] [5]

In addition to areas they affect, rare diseases also vary by prevalence. Some diseases are seen in approximately 50/100,000 individuals while some have only been identified in a number of persons so far worldwide. A review of the 5,304 diseases in the Orphanet with available estimated prevalences showed that 84.5% of these have a prevalence of less than 1/1,000,000. However, 4.2% of rare diseases with the most frequently seen prevalence rate (10 to 50/100,000) constitutes 77.3% to 80.7% of the total patient burden.[2]

On the other hand, some rare diseases that are very rare in the entire world may be more frequently seen in certain regions. The reasons for this may include the fact that diseases more prevalent in certain races are seen more frequently in geographical areas densely populated by that race and that marriage between relatives is more common in certain countries, increasing the risk of genetic diseases. For instance, Behçet's disease, beta thalassemia and familial Mediterranean fever, described as a rare disease in international sources, are not considered as rare diseases in Turkey.[1] [3]

Epidemiology studies with rare diseases are limited since very limited numbers of individuals have these

in the society, and it is very difficult to estimate the number of individuals affected. This information was represented as a broad range rather than a precise ratio also for a considerable proportion of diseases with prevalence data on the Orphanet. Although individuals affected by certain rare diseases are followed-up through patient registry studies or similar initiatives in some countries with patient numbers gradually becoming clearer, analyzes and patient number estimates based on available sources on rare diseases are open for improvement.

### 1.4 Financial Burden due to Rare Diseases

Considered separately, thousands of rare diseases are found with limited number of patients; however, some of these were not accurately defined in the 10th Revision of International Classification of Diseases (ICD-10). This makes calculation of the total financial burden caused by rare diseases difficult. However, due to the large share of individuals affected by rare diseases in the total population and since these diseases are typically chronic, progressive and lead to disability or death, the overall financial burden caused by rare diseases is expected to be high.[46] [47] [48]

To estimate this financial burden, various studies have been performed recently. In the US where a total of 25 to 30 million patients are affected by rare diseases, a survey was organized in 2019 with the participation of 1,399 individuals representing 379 rare diseases. According to the results, the overall financial burden caused by these 379 rare diseases affecting approximately 15.5 million patients was estimated to be 966 billion dollars. Medical expenditures (outpatient and inpatient care in healthcare institutions, doctor visits, prescribed medicines and administration of these, medical devices, etc.), indirect financial burden (early retirement, lost workforce, not participating in social services, etc.) and other cost items (transportation, education, experimental therapies, mandatory modifications of home and tools, etc.) constituted 43%, 45% and 12% of this sum, respectively.[8]

Another study in the US investigated a sample that included 35.6 million inpatient registries throughout the country in 2016. Registries associated with rare diseases based on ICD-10 codes constituted 32% of the entire sample and the total cost of these hospitalizations was calculated to be 768 billion dollars. Costs associated with other hospitalizations that formed 68% of the registries, on the other hand, was 880 billion dollars. Accordingly, it was concluded that the burden per capita on healthcare institutions brought by individuals affected by rare diseases is much higher compared to individuals affected by other conditions.[49]

Complete recovery of these diseases or controlling progression is expected through development of effective treatments in the field of rare diseases resulting in favorable outcomes in terms of both patients' and patient relatives' lives and healthcare system and economics.  However, developing treatments in this field is complicated by the considerably wide spectrum that impact areas of these diseases are distributed and the fact that each disease affects a very limited number of patients.

The limited number of patients hampers both scientific studies to understand the respective disease and sufficient number and variety of patient enrollment to clinical investigations required in the development processes of medicines. Therefore, while developing treatments to target these diseases means a long and costly research & development (R&D) process, utilization of these treatments only by small patient groups restricts the return of this cost in terms of income to pharmaceutical companies.

*Complete recovery of these diseases or controlling progression is expected through development of effective treatments in the field of rare diseases resulting in favorable outcomes in terms of both patients' and patient relatives' lives and healthcare system and economics.*

Orphan Drug Act came into force in the US in 1983 to overcome the obstacles and to allow the development of treatments for rare diseases. This was followed by some Asian countries and then by the European Union (EU). Thereby, providing incentives to pharmaceutical companies to develop and market these products was allowed by giving the status "orphan drug" to products pharmaceutical companies normally would avoid developing and marketing because they target very small patient groups.[43] [50]

# 2. RARE DISEASE POLICIES IN THE WORLD AND IN TURKEY

First described officially in the 1980s, the concepts "rare disease" and "orphan drug" have been accepted by all relevant stakeholders including policymakers in many leading countries in the world through nearly 40 years since then. Many studies have been performed on this subject in our country as well both by the government and other stakeholders, and these concepts took place in the Rare Diseases Health Strategy Document and Action Plan recently published by the Ministry of Health.

### 2.1 Rare disease Policies in the World

The US was the first country to establish a legislative regulation on rare diseases and orphan drugs by the "Orphan Drug Act" approved in 1983. This regulation allowed governmental incentives to encourage pharmaceutical companies to invest in developing and marketing of treatments to be used in rare diseases. Subsequently, countries like Singapore (1991), Japan (1993) and Australia (1998) developed similar regulations. The Rare Diseases Act of 2002 approved in the US was another important progress in the field. Through this regulation, the Office of Rare Diseases Research that was founded under the National Institutes of Health (NIH) takes various responsibilities to provide support to clinical studies especially for rare diseases and to enable coordination among the investigators studying on this field.[51] [52]

The first regulation recognized in Europe was the "Regulation on Orphan Medicinal Products" approved in 1999 by The European Parliament. Through this regulation, the criteria for the definition of orphan drug were established in the EU, the definition of rare disease was determined and the incentives were defined to develop medicines for these diseases. This regulation formed the basis for developing a general strategy to support member countries in the management of rare diseases in the EU.[53]

The “Rare Diseases Task Force” was recognized in January 2004 by the European Commission decision. The targets included in the “Communication on Rare Diseases: Europe’s Challenge” report issued by the European Council in 2008 were to increase awareness on rare diseases, to support rare disease policies in member countries, and to form collaboration, coordination and regulation for the rare diseases in Europe.[54]

*First described officially in the 1980s, the concepts "rare disease" and "orphan drug" have been accepted by all relevant stakeholders including policymakers in many leading countries in the world through nearly 40 years since then.*

Following this report, the European Council called for the member countries to create their own national plan and strategy for rare diseases via the “Council Recommendation on Action in the Field of Rare Diseases” in 2009. The major topics in this document included creating definitions, coding and registries in rare diseases, establishing reference centers, providing specialty and knowledge across the EU, strengthening patient organizations, and sustainability.[45]

EUROPLAN project was formed (April 2008-March 2011) funded by the European Commission to accelerate the development of national plans and strategies in the field of rare diseases in member countries. EUCERD was founded in 2009 to support the execution of identified goals accordingly. Replacing these committees in late 2013, the “Expert Group on Rare Diseases” (EGRD) continues to help the European Commission to shape rare disease policies.[55]

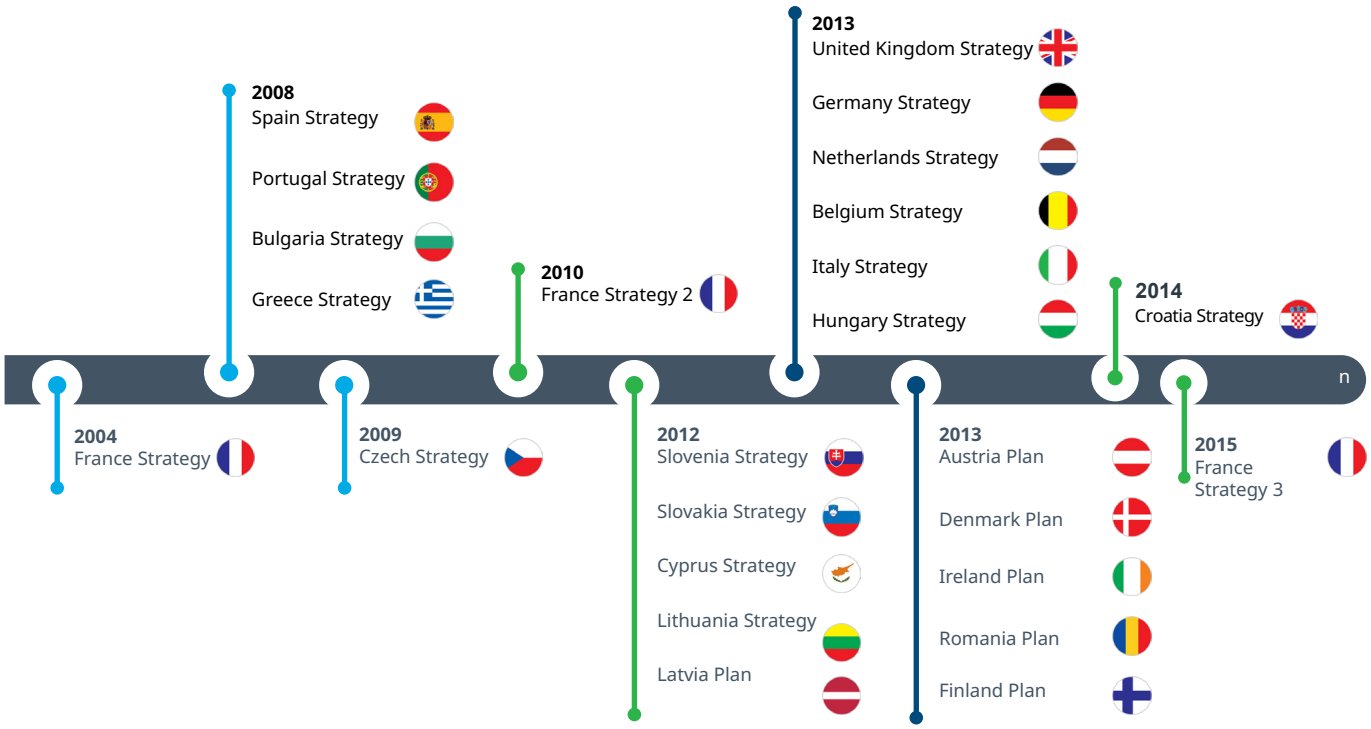
Between March 2012 and August 2015, the “EUCERD Joint Action” provided support for member countries to develop strategies in the field of rare diseases, provide customized social services and integrate rare diseases into fundamental social policies, codify and classify rare diseases, etc. As a consequence of all these efforts by the EU, the member countries formed national

rare disease plans based on their own timing plans, budgets and needs.

France, Bulgaria, Spain and Portugal had national rare disease plans before the call by the European Council in 2009. France, in particular, is the leading country with the national plan on rare diseases formed in 2004. Other European countries that formed their own national plans or strategies on rare diseases within this period are presented in Figure 2. The differences between countries in terms of the extent and financing of their plans also affect the magnitude of the effect they produce. A list of the main subjects in common addressed in the relevant policies may include providing specialist care for rare diseases within the existing healthcare system, coding rare diseases in health data systems with relevant details, forming national registry systems, and providing information on rare diseases via Orphanet.

Studies to elaborate rare disease policies and to improve the coding system for rare diseases was continued as part of "RD-Action". These studies were jointly funded by the 3rd EU Health Program between years 2015-2018.[15]

**Figure 2: National Plans and Strategies of Countries for Rare Diseases**




Sources: 1. European Commission: implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02) September 2014. 2. Rodwell C, Aymé S. Rare disease policies to improve care for patients in Europe. Biochim Biophys Acta. 2015 Oct;1852(10 Pt B):2329-35. doi: 10.1016/j.bbadis.2015.02.008. Epub 2015 Feb 25. PMID: 25725454. 3. Vol 82. Supl. 1 - Galicia Clínica (galiciaclinica.info). 4. Belgium – RD-ACTION : DATA AND POLICIES for rare diseases. 5. Rare Diseases Strategy of the Spanish (eurordis.org) .p.26. 6. EURORDIS - The Voice of Rare Disease Patients in Europe. 7. Cyprus – RD-ACTION : DATA AND POLICIES for rare diseases. 8. UK Plan for rare diseases consultation launched - GOV.UK (www.gov.uk)

France as the pioneer of national plans in the field of rare diseases has implemented three complementary plans so far. Announced in late 2004 to cover years 2005-2008, the initial plan was granted a special fund to be executed and took shape within the framework of certain goals that included increasing the level of knowledge and consciousness on rare diseases both among patients as well as healthcare professionals and across the society, improving access to diagnostic and treatment opportunities, maintaining research activities in the field of rare diseases, in particular rare disease treatments, and developing international collaboration for rare diseases. For the action plan, formed in accordance with these primary goals, the steps included quality assessment of the existing reference centers and communication network, improving access to genetic diagnosis, developing a newborn screening for rare diseases, easy access and correct use of orphan drugs and other drugs as well as all other medical devices demanded by patients, training and informing healthcare professionals, informing the patients and strengthening the investigations.[56]

*France as the pioneer of national plans in the field of rare diseases has implemented three complementary plans so far.*

Prepared for the period 2011-2014 by evaluating the results from the first plan, the second plan with a budget of 180 million Euros targeted to carry forward the steps taken in the previous one. Some important steps targeted in the second plan are as follows:

- Establishing the Scientific Collaboration on Rare Diseases Foundation to allow investigations on rare diseases and coordinate these;
- Generating a National Rare Diseases Database to facilitate mapping patient needs and the treatments they receive and inclusion of these into epidemiologic studies and clinical trials. This national registry system was expectedly based on a common minimum data set for reference and regional centers as well as all the patients and rare diseases;
- Improving the follow-up of activities for patients including adoption of Orphanet nomenclature for patient follow-up;
- Enabling access to next-generation sequencing (NGS) technology for genetic diagnosis. The goal was to ensure most laboratories in France have NGS potential for the genetic diagnosis of a wide range of rare diseases within planning period and to maximize the extent of diagnosis;
- Converting reference and regional centers into a limited number of (around twenty) harmonized rare diseases networks that bring all stakeholders together and focus on homogeneous disease groups. The purpose was to facilitate the access by patients to appropriate diagnosis, treatment, social service and follow-up opportunities through these networks. Connecting these networks to European Reference Networks (ERN) for rare diseases was also considered;
- Forming a task force to monitor reference centers and the national rare disease networks that will be established;
- Taking necessary steps to ensure access to novel medicines or to authorized drugs prescribed off-label depending on patients' needs, and reimbursement of these treatments;
- Making progress in developing clinical guidelines for rare diseases;
- Training of the physicians and paramedical staff;
- Coordinating healthcare services and social services in a better way;
- Creating a single common hotline throughout Europe for better informing the patients by supporting Orphanet and Rare Diseases Information Services and for rare disease service lines.

An administrative committee was formed that will meet at least once a year to effectively implement the plan in accordance with the calendar and manage its follow-up, and five work groups were formed under

this committee to help implementing the plan.[56]

These two plans implemented by France had considerable success and enabled a significant progress in the treatment of rare diseases and investigations in this field. Centers of excellence, reference centers and rare disease networks constituted the ground for an organizational structure that enables patients access healthcare services and cumulative knowledge in this field. This structure also allowed collection of the clinical data essential for treatment, prevention and investigation activities. In addition to all these, the first plan also encouraged a closer collaboration between patient organizations and stakeholders providing healthcare services.[57]

*The national plans of France that address all aspects of effective management of rare diseases contains realistic steps to be taken with the participation of relevant stakeholders within a certain timing plan and budget.*

Despite all these favorable advances, the delays patients experience during the course of diagnosis necessitated maintaining studies on structuring and coordination. Besides, a need arose to establish national databases that are connected to Europe-wide databases to overcome problems due to the rarity of these diseases, thus to accelerate the development of novel treatments. These challenges and the developments in genetics that has an important role in many rare disease investigations played an important role in determining the targets of the third plan.[57]

Prepared for the period 2018-2022, the primary aim of this plan was to enable access to diagnosis, treatment and relevant care services within a year from obtaining the first specialist opinion on patients affected by rare diseases. The only exception is when scientific and technical knowledge are not sufficient for an accurate diagnosis. This plan also targets to include all patients currently not received a diagnosis into global diagnostic and investigation studies. In line with these goals, the plan took shape around 11 points of focus:

- Reducing the delays in diagnosis and the number of undiagnosed patients
- Neonatal screening for early diagnosis and improving prenatal and preimplantation diagnostic capabilities
- Data sharing to help diagnose and develop new treatments
- Encouraging access to treatment in rare diseases
- Accelerating investigations in the field of rare diseases
- Encouraging innovation and access to innovation
- Improving treatment pathways
- Facilitating the integration of patients and patient relatives affected by rare diseases
- Training healthcare professionals and social service workers to better identify and manage rare diseases
- Fortification of the role of rare disease networks on treatment and investigation issues
- Identifying the roles and tasks of national stakeholders in the field of rare diseases[57]

The national plans of France that address all aspects of effective management of rare diseases contains realistic steps to be taken with the participation of relevant stakeholders within a certain timing plan and budget. Making France the leading country across the European Union in the field of rare diseases, these plans represent a good example for countries without a national plan for rare diseases.

## 2.2 Policy Studies Conducted in Turkey

Given the fact that the effects of rare diseases on the population and health systems they affect may vary by country, the policies developed by the states for management of these diseases are quite important. Public institutions that actively carry out activities on rare diseases in our country include Ministry of Health General Directorate of Health Services (SHGM) and TÜSEB. As of 2020, the Department of Autism, Mental Special Needs and Rare Diseases, established under the SHGM, has become the public department responsible for preparation of plans, policies and regulations regarding rare diseases and forming the infrastructure for screening, early diagnosis and management in rare diseases.[9]

No national policy or action plan in force is currently implemented in Turkey; however, significant advances have been made through previous investigations on this subject and, in November 2022, SHGM Department of Autism, Mental Special Needs and Rare Diseases published the 2023-2027 Rare Diseases Health Strategy Document and Action Plan.[10]

Some prominent studies conducted in previous years by the Ministry of Health and other public institutions are presented below:

- Present problems and solution recommendations for rare diseases and orphan drugs were discussed at the TAIEX workshop held in May 2009 with the regulatory board involving the Ministry of Health.[58]
- Recommendations from representatives of the sector were obtained through the "National Orphan Drug Draft Guidelines" prepared by the Turkish Medicines and Medical Devices Agency (TİTCK) in 2011.[59]
- Information regarding rare diseases in pediatric metabolism, endocrinology and neurology fields were provided in the "Rare Diseases" report prepared by the Ministry of Health Department of Patient Rights and Medical Social Services in 2014.[58] [60]
- In September 2014, the "Rare Diseases and Orphan Drug Symposium and Orphan Drug Legislation Workshop" was held by the Association for Developing Drug Consciousness and Rational Drug Use and the orphan drug draft guidelines prepared by the Ministry of Health were presented for the opinion of stakeholders.[61]
- The statement, "Capacity will be formed in our country in the field of rare diseases," was included in the Structural Transformation Program in Health Industries Action Plan as part of the Tenth Development Plan (2014-2018), and the following goals were identified:
  - » Creating neonatal and prenatal screening programs to define rare diseases and determine their prevalence and to form a registry system and the statistics;
  - » Establishing and supporting authorized diagnosis and treatment centers for the research and application in this field;
  - » Establishing the physical infrastructure and legislation background to manufacture orphan drugs in our country;

» Enabling flexible pricing and discount rates for orphan drugs and inclusion of these in reimbursement system;

» For rare diseases that can be treated with Advanced Medical Treatment Products, defining diagnostic/screening tests outside the package as part of reimbursement by tertiary care institutions.[62]

- "Performing a detailed analysis on the present situation and needs on rare diseases in our country and generating a policy for orphan drugs in line with the results" was included as a goal in the Turkish Pharmaceutical Industry Strategy Document and Action Plan 2015-2018 prepared by the Ministry of Science, Industry and Technology in 2015. According to a statement in this plan, the purpose was "to create an inventory registry system first on rare diseases in our country and centers where these rare diseases can be diagnosed, to enable the communication between the available reference network systems in the world on rare diseases and the reference system that is established, and to develop special policies to bring and manufacture drugs used in rare diseases."[63] [64]
- During the Turkish Medical World Congress II held in October 2015 by the collaborative work of TÜSEB and the Ministry of Health, General Directorate of EU and Foreign Affairs, "Rare Diseases Work Group" was formed, and rare diseases were discussed.[58] [60]
- In February 2016, "World Rare Diseases Day Symposium" and "National Action Plan for Rare Diseases in Turkey Workshop" were held with the collaboration of SHGM and Turkish Armed Forces Medical Command. Within different working groups, the problems and solution recommendations for the identified topics in the field of rare diseases were discussed.[60]
- At the Rare Diseases Awareness Day Meeting held by TÜSEB Maternity, Child and Adolescent Health Institute in 2016, Ministry of Health Strategic Targets for Rare Diseases were summarized under 7 topics:

» Target 1. Studies on developing knowledge and awareness [Responsible: General Directorate for Health Research (SAGEM) and the stakeholders]

» Target 2. Enabling access to diagnosis and treatment and developing existing diagnosis and treatment [Responsible: Healthcare facilities, SHGM, General Directorate of Turkish Public Hospitals (KHGM)]

» Target 3. Research and development studies [Responsible: TÜSEB and universities]

» Target 4. Development of screening programs [Responsible: General Directorate of Public Health (HSGM)]

» Target 5. Epidemiologic studies on rare diseases [Responsible: TÜSEB, universities and HSGM]

» Target 6. Support for access to orphan drugs and research [Responsible: TİTCK, SSI]

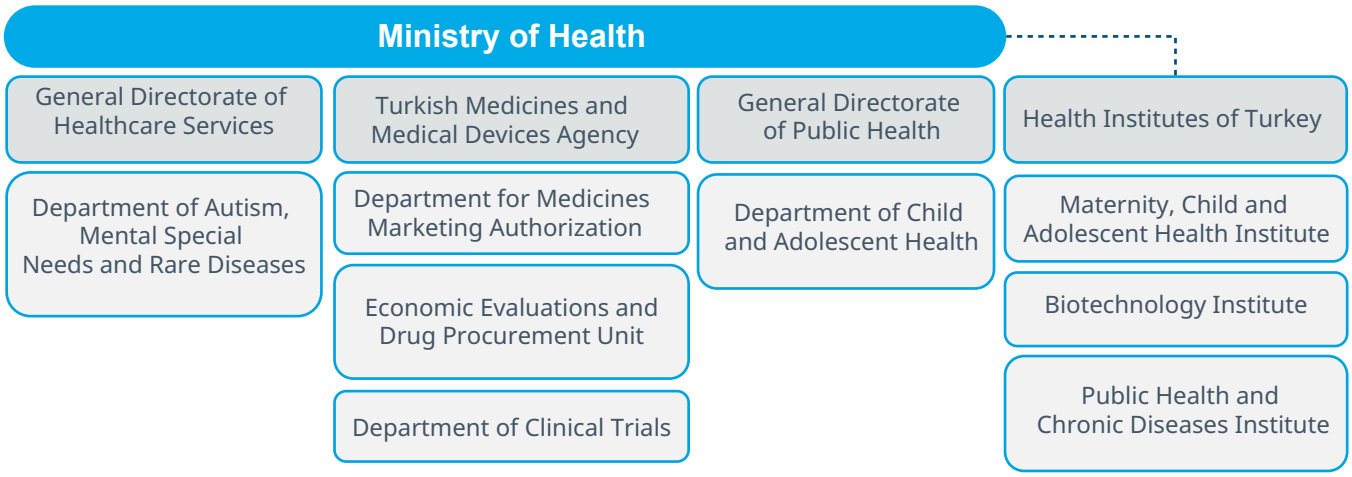
» Target 7. Providing care services and social support [Responsible: Healthcare institutions, regional governments, SHGM, KHGM, Ministry of Family and Social Policies][60]

- Featured topics at the "International Panel and Workshop for Rare Diseases" held in January 2017 in Ankara by the collaboration of SHGM and TÜSEB were challenges in rare diseases, laboratory practices, R&D studies and orphan drugs. Studies were made in this workshop to generate a "National Rare Diseases Action Plan" with the contribution of leading specialists. [60]
- At the "February 28th Rare Disease Day Meeting" held by TÜSEB in 2018, senior management from the Ministry of Health noted that a new strategic plan was created with the stakeholders in the field of rare diseases. [60]
- In September 2019, the rare diseases report was issued by TÜSEB.
- In 2020, the TBMM published the Rare Diseases Commission report.
- In 2021, "Rare Diseases Awareness Day Symposium"

was held by TÜSEB Institute for Turkish Public Health and Chronic Diseases and SHGM Department of Autism, Mental Special Needs and Rare Diseases. Successful studies in Turkey on rare diseases and the problems and opportunities seen in the management of rare diseases were discussed in the panels held as part of the meeting. In addition, the case of Ireland was cited as a good practice regarding National Action Plan.[65]

Although all these studies clearly demonstrate that rare diseases are in the agenda of the Ministry of Health, the absence of an official national rare disease plan before 2022 was considered to be a significant flaw in this field. Therefore, the Department of Autism, Mental Special Needs and Rare Diseases published the 2023-2027 Rare Diseases Health Strategy Document and Action Plan to lay out Turkey's roadmap and action plan in rare diseases together with related stakeholders. Carrying out studies to implement identified targets is as important as to form the plans and strategies. Thus, certain main indicators were identified in EU member countries to monitor to what extent rare disease plans are implemented.[10] [66] [67] [124]

**Figure 3: Departments within the Ministry of Health That Conduct Activities on Rare Diseases in Turkey**



# MANAGEMENT OF RARE DISEASES

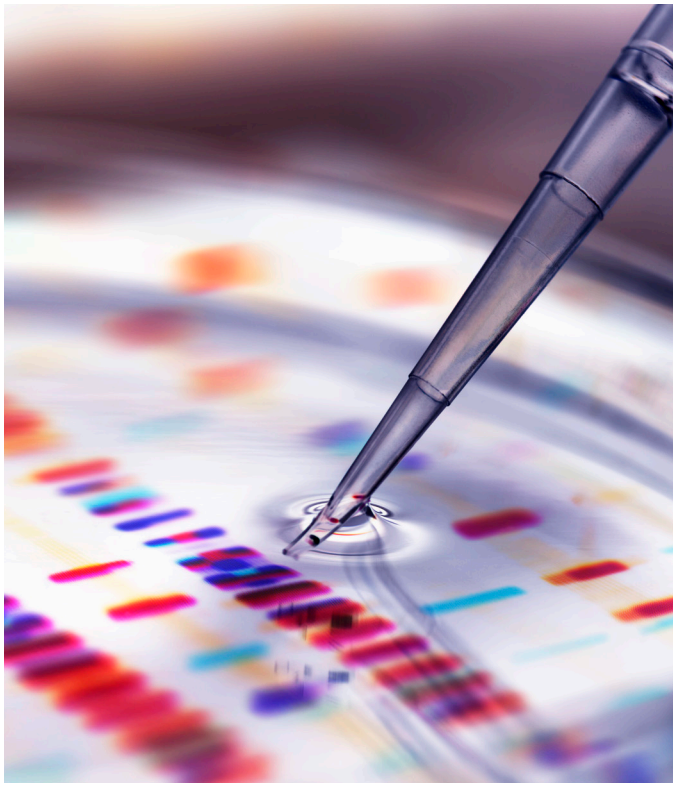
Like other diseases, rare diseases also go through diagnosis, treatment and follow-up processes. However, these processes are quite long and challenging unlike other common diseases. Establishing the correct diagnosis takes years for many rare diseases with limited treatment options, and the diagnosis-treatment-follow-up process generally necessitates a multidisciplinary approach. Most of the time, the life expectancy is short, and the quality of life is low in individuals affected by these diseases. Prevention or early diagnosis of these diseases by screening programs help alleviating the burden on both the patients and patient relatives and the government since these constitute a heavy burden on both parties both material and mental.

## 3.1 Protective Healthcare Services, Screening and Early Diagnosis

### Neonatal Screening Program

Because most rare diseases appear in the childhood and are genetically inherited, diagnosing these diseases at an early age is important. Neonatal Metabolic and Endocrine Disease Screening Program (NTP) is conducted by HSGM Department of Child and Adolescent Health in our country under the Ministry of Health. The diseases screened as part of this program include phenylketonuria, congenital hypothyroidism, biotinidase deficiency, cystic fibrosis and congenital adrenal hyperplasia (CAH). Screening for CAH was started in the identified pilot cities in 2017 and is continued in 41 cities as of 2021. Screening of other diseases in the panel are also continued across Turkey. Finally, spinal muscular atrophy (SMA) was included in the neonatal screening program in late 2021. Starting appropriate treatment early and preventing irreversible damage due to the disease by taking measures are targeted by early diagnosis in babies with all these diseases.[12] [68]

Owing to all neonatal screening studies conducted in Turkey, approximately 4,500 children are being protected from the consequences of existing diseases and disability is being prevented. Moreover, it is stated that works are under way to expand the scope of disease in newborn screenings.[12]



However, it is possible to extend neonatal screening to more diseases that can benefit from early diagnosis. The current neonatal screening program in Taiwan encompasses more than 26 diseases. In Canada, 22 diseases are covered by neonatal screening across the states, while it exceeds 30 in certain states. Similarly, more than 50 diseases are being tested by neonatal screening in the United States of America. In Europe, Italy has been the country to implement neonatal screening most extensively and successfully. Fulfilling all the criteria specified in this field by EURORDIS, Italy included more than 50 diseases into the neonatal screening program. On the other hand, the program pursued in England was extended to include 9 diseases in 2015. Despite this extent that may be considered quite limited compared to Italy, using all genome sequencing methods in all neonatal screenings thereafter and thus enabling more individuals with rare diseases have the chance to access early diagnosis and treatment by development of more affordable next generation technologies has been brought into discussion.[15] [69] [70] [71]

EURORDIS recommends adopting the Wilson and Jungner Principles and Practice of Screening for Disease criteria in broadening the extent of neonatal screening programs. These criteria, set forth in 1968 and functioning as a guide for screening tests in every country including Turkey are as follows:

- Elimination or minimization of any damages
- Paying regard to concerns on confidentiality and autonomy
- Assessment of moral, legal and social aspects
- Being aware that most of the screening is made for hereditary disorders and this may lead to consequences for the family members.[72]

**Premarital Screening Program**

Premarital Hemoglobinopathy Screening Program is being carried out across the country to avoid hereditary hematologic diseases such as sickle cell anemia and thalassemia which happen to be an important public health problem in our country in new births. Appropriate guidance is provided to couples to get genetic counseling if they both are carriers based on the tests made by drawing a blood sample from each spouse-to-be before the marriage. Furthermore, follow-up of individuals with the disease, prolonging life expectancy and improving the quality of life was intended by collecting clinical information from family doctors regarding premarital screenings and hemoglobinopathies through the data collection system.[68]

Another important progress was that screening for SMA was made obligatory for marrying couples based on the Premarital National SMA Carrier Screening Program announced in 2021. Thus, future parents will be able to know if they are carriers and choose alternative ways to have a healthy baby. As a consequence of this development that is so important for the society, a decrease is anticipated in healthcare costs spent for relevant treatments by preventing the disease beforehand.[12]

**Preimplantation Genetic Diagnosis and IVF Treatment**

With the help of PGD used in the IVF procedure, couples with the disease or carrier couples can have healthy babies. Expanding prenatal diagnosis and IVF applications are among the most important steps to be taken in avoiding hereditary rare diseases. In line with this, the infrastructure studies in our country carried out by the ministry have been completed and PGD applications were included into SSI coverage as of August 2021. Costs of the application carried out for more than 50 genetic diseases including mucopolysaccharidosis (MPS), cystic fibrosis (CF), Duchenne muscular dystrophy (DMD) and SMA are being covered by the government.[73] [74]

**Laboratories and Genetic Diagnostic Centers**

Almost all genetic tests for rare diseases are being performed in certain public and private healthcare institutions. In addition, some of these tests can be done within private genetic laboratories. The Rare Diseases in All Aspects report issued by TÜSEB Maternity, Child and Adolescent Health Institute in 2019 stated that a total of 27 hospitals are found in 17 cities that have a licensed genetic diagnosis center together with at least 5 pediatric subspecialists. Eight of these are hospitals under the Ministry of Health and 19 are university hospitals (Table 1). There is a total of 88 Genetic Diagnosis Centers licensed by the Ministry of Health across Turkey including private institutions as of February 2021 (Table 2).[17] [73]

**Table 2: Hospitals with a Licensed Genetic Diagnosis Center Where 5 or More Pediatric Subspecialists are Employed (12.04.2019)**

| | CITY | HOSPITAL | TYPE OF INSTITUTION | NUMBER OF SUBSPECIALISTS |
|---|---|---|---|---|
| 1 | İstanbul | Marmara University Pendik Training and Research Hospital | MoH | 31 |
| 2 | | İstanbul Faculty of Medicine | University | 30 |
| 3 | | Cerrahpaşa Faculty of Medicine | University | 24 |
| 4 | | SBÜ Ümraniye Training and Research Hospital | MoH | 18 |
| 5 | | SBÜ Kanuni Sultan Süleyman Training and Research Hospital | MoH | 13 |
| 6 | | SBÜ Dr. Sadi Konuk Training and Research Hospital | MoH | 8 |
| | | **İstanbul Total** | | **124** |
| 7 | Ankara | Hacettepe University İhsan Doğramacı Pediatric Hospital | University | 55 |
| 8 | | Gazi University | University | 35 |
| | | **Ankara Total** | | 90 |
| 9 | İzmir | Ege University | University | 45 |
| 10 | | 9 Eylül University | University | 35 |
| 11 | | SBÜ Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital | MoH | 23 |
| | | **İzmir Total** | | **103** |
| 12 | Kayseri | Erciyes University | University | 30 |
| 13 | | Kayseri City Hospital | MoH | 10 |
| | | **Kayseri Total** | | 40 |
| 14 | Bursa | Uludağ University | University | 22 |
| 15 | | High Specialization Training and Research Hospital | MoH | 10 |
| | | **Bursa Total** | | **32** |
| 16 | Antalya | Akdeniz University | University | 18 |
| 17 | Samsun | Ondokuz Mayıs University | University | 23 |
| 18 | Kocaeli | Kocaeli University | University | 14 |
| 19 | Eskişehir | Osmangazi University | University | 14 |
| 20 | Adana | Adana City Hospital | MoH | 13 |
| 21 | Manisa | Celal Bayar University | University | 13 |
| 22 | Elazığ | Fırat University | University | 11 |
| 23 | Aydın | Adnan Menderes University | University | 10 |
| 24 | Denizli | Pamukkale University | University | 10 |
| 25 | Malatya | İnönü University | University | 8 |
| 26 | Erzurum | Atatürk University | University | 8 |
| 27 | Kahramanmaraş | Necip Fazıl City Hospital | MoH | 5 |

Source: TÜSEB; Her Yönü ile Nadir Hastalıklar (2019)

In general, it is observed that the tests required for the diagnosis of rare diseases are made accessible and there is an infrastructure for genetic diagnosis centers. However, some of the experts involved in the production of the Rare Diseases in All Aspects report by TÜSEB expressed the inadequacy of genetic tests, and it was emphasized in the report that a chaos is going on in Turkey about genetic tests and excessive number of blood samples go abroad. As a solution, establishing a national genetic centers network was recommended with all licensed genetic diagnosis centers regularly sending monthly data to the ministry and standardizing their reporting systems in line with the international nomenclature. The Regulation on Genetic Diseases Assessment Centres published in January 2020 set out the criteria for the centers established with the aim of diagnosis of genetic diseases and providing consultancy on genetics, which, in this way, targeted the improvement and standardization of the quality of service provided at the relevant centers.[17]

*It was indicated that in Turkey, individuals with rare diseases spend approximately 7 years until the correct diagnosis and visit nearly 8 specialists.*

### 3.2 Diagnosing Rare Diseases

Even if the symptoms of each rare disease, the course of disease, diagnosis methods and patient needs differ, one of the most important issues addressed for many rare diseases is the challenging diagnosis process. The time and effort spent from the initial signs until definitive diagnosis is the leading one.

A study published in the USA in 2013 stated that the average time from the appearance of symptoms to establishing definitive diagnosis in rare diseases is 4.8 years and patients visit an average of 7.3 physicians during this period. It was indicated that in Turkey, individuals with rare diseases spend approximately 7 years until the correct diagnosis and visit nearly 8 specialists.[75] [76]

There are factors that prolong and complicate achieving the correct diagnosis in rare diseases. Primarily, each rare disease affects a very limited number of patients and most of them either have subcategories or the initial signs vary between patients and may appear in different systems of the body. Therefore, experts use differential diagnosis methods to establish the definitive diagnosis of certain diseases that are very rare or that show signs that are impossible to distinguish at first from other diseases, and this process may take a long time.

Similarly, initial signs of some rare diseases are confused with some chronic diseases even by physicians specialized in this field, and the patient is given treatments to suppress the symptoms only instead of what is needed until new signs emerge with the progression of the disease. For instance, the first signs of some rare diseases are confused with frequently seen chronic disorders such as asthma or chronic obstructive pulmonary disease (COPD) and the patients only enter differential diagnosis when other signs become significant.[10]

Another factor is that patients go to physicians who are specialized in branches other than the rare disease groups that lead to these initial signs. This makes it difficult to find the source of symptoms and associate these with a rare disease. For example, certain rare neuromuscular diseases may present with signs such as gait disturbances or autism during childhood, and the patients visit branches like orthopedics, pediatric mental health or family medicine instead of pediatric neurology. The inadequate level of consciousness and knowledge as well as medical experience on these diseases among physicians specialized in different fields result in treating these patients only for the signs they show with the underlying actual cause sometimes not diagnosed for years.[10]

Lastly, ICD-10 code system that is used in the world and in Turkey is utilized when entering patient diagnoses into the central patient follow-up system of the Ministry of Health, e-Nabız. The accurate diagnostic code of diseases sometimes may not be entered in this system where a diagnostic code is specified for only

500 of nearly 8000 known rare diseases and the next expert physician examining the patient may not clearly see the actual diagnosed disease. Similarly, sometimes an ICD-10 code is entered to the e-Nabız database solely based on the symptoms the patient presented with, leading to missing the actual diagnosis. To solve such problems, TÜSEB collaborated with Orphanet. Within this collaboration, the international and detailed nomenclature used in the Orphanet data network was translated into Turkish and made ready to integration to the e-Nabız system.[10] [77]

Besides, most of these rare diseases are chronic, progressive and even life threatening. The delays along the diagnostic course due to misdiagnosis or failure to identify the diseases may lead to rapid progression of diseases that may otherwise be treated or slowed down if diagnosed earlier, and to irreversible damages in the patients. Damages that may occur in individuals with rare diseases are not limited to physical or mental problems; additional psychological, social and economic problems are also commonly seen. Indeed, these problems become the problem of a much larger population by affecting patient relatives and families besides the patient. From the perspective of healthcare system, these erroneous or inadequate treatments administered due to delayed accurate diagnosis lead to excessive burden each year on the government's health budget.

High level of knowledge and consciousness on these diseases among physicians whom patients first visit and referral of patients to relevant specialties without delay in case these diseases are suspected are very important. Besides, competent centers are needed where specialists are available and appropriate diagnostic testing can be done since diagnosing many rare diseases is difficult and requires multidisciplinary approach.

To establish the correct diagnosis timely, screening programs and technical infrastructure are very important as well as the presence of a center of excellence network and the level of knowledge and experience healthcare professionals have. These centers play an important role in the training

of healthcare professionals, coordination of the investigations and facilitating diagnosis in France where more than 600 specialty and reference centers are available.[15]

The developing gene technology also allows early and accurate diagnosis. France Genomic Medicine Initiative and Genomic Medicine Sweden (GMS) conduct studies to develop tailor made diagnostics and treatment with the help of this technology. Within the framework of these studies, the goal is to establish an expedited and correct diagnosis in individuals with a suspected rare disease by the integration of the entire genomic sequencing into the healthcare system.[19] [78]

The accurate and timely diagnosis of patients is a prerequisite for countries to get success in the management of rare diseases. Timely access of patients to appropriate medical care and treatment may be enabled by the help of studies performed in this field and significant improvements may be obtained in the quality of life and life expectancy.

### 3.3 Access to Treatment

As stated in the first section of the report, developing treatments for rare diseases is challenging since they constitute a wide spectrum, and each has a very limited patient population. In addition to this, the mechanisms or underlying causes have not yet been understood in some very rare diseases and R&D studies to treat these have not been possible. Although nearly 8000 rare diseases have been identified so far, available treatments were developed only for 5% of these.[1][124]

Orphan drugs have an important place among treatments developed for rare diseases. At present, a total of 416 drugs have a valid orphan drug status given by FDA or EMA. In Turkey, patients can access 151 of these by various ways: 76 are authorized while 75 are brought to our country by Foreign Drugs List.[7] [21] [22]

**Access to Medicines Used in the Treatment of Rare Diseases in Turkey**

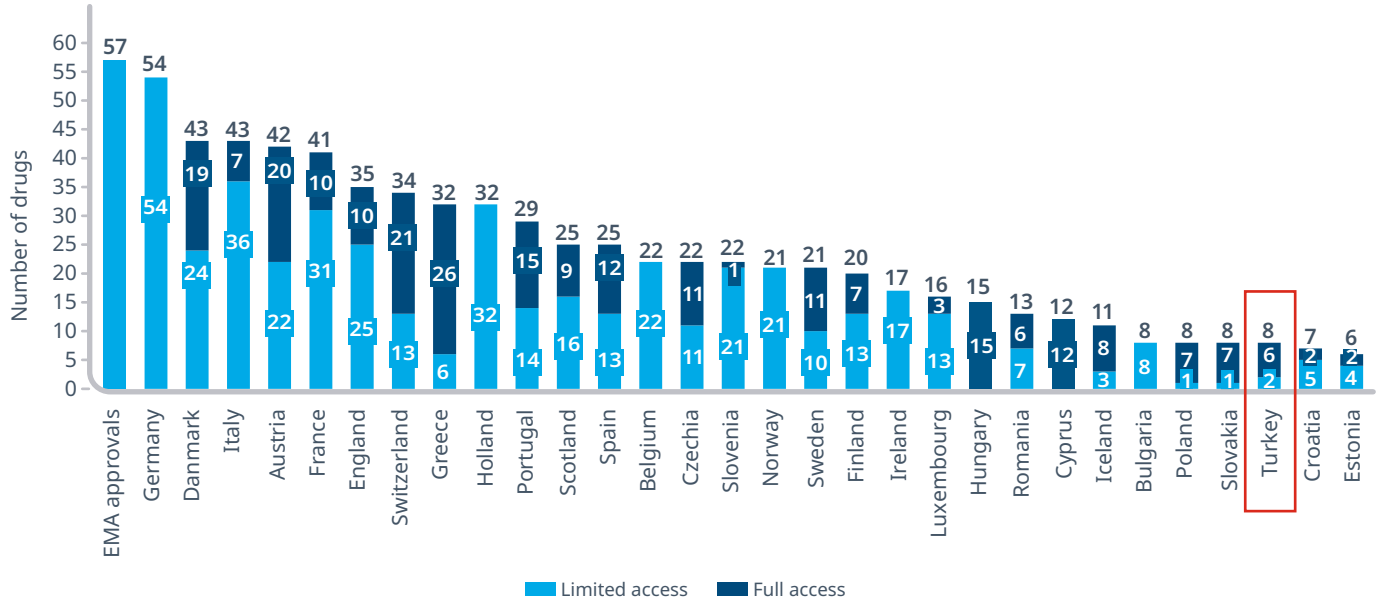
The Ministry of Health and Social Security Institution in Turkey endeavor to ensure that treatments developed for unmet needs of patients, so long as they meet the necessary conditions, are authorized in Turkey and the patients are provided with free access to them. However, disruptions occur regarding market access processes for innovative drugs, in particular in terms of time.

The patients in Turkey have access to 151 medicines that are categorized as orphan drug by the FDA or EMA, while only half of these are authorized in Turkey.[7] [21] [22]

In a study that analyzed the access to orphan drugs across Europe, it was found that only 8 out of 57 orphan drugs approved by the EMA were accessible in Turkey with reimbursement during the period 2017-2020, which is quite lower than the average 21 in Europe. Moreover, it was found that only 2 of these reimbursed 8 products were authorized with the remaining 6 being accessed through the Foreign Drugs List. In the same study, it was seen that orphan drugs authorized in Turkey were included into reimbursement coverage within an average of 461 days from the date of marketing authorization. Whereas in Germany, of the 57 orphan drugs with EMA approval, 54 were granted marketing authorization and reimbursement and this process took 102 days on average from approval by the EMA. Although no fund has been specified to facilitate access to orphan drugs in Germany, various attempts target to facilitate the access. One of these is the exemption of orphan drugs from health technologies assessment process with their total annual impact on the budget being anticipated to be lower than 50 million Euros. Through a similar practice, orphan drugs with a total annual budget impact lower than 30 million Euros are granted full reimbursement in France without health technologies assessment.[15] [23] [79]

*The patients in Turkey have access to 151 medicines that are categorized as orphan drug by the FDA or EMA, while only half of these are authorized in Turkey.*

**Figure 4: Access to Orphan Drugs Approved by the EMA between 2017-2020**




Source: IQVIA, EFPIA Patients W.A.I.T. Indicator 2021 Survey, 2022.

**Channels to Access Innovative Drugs in Turkey**

In Turkey, patients can access innovative drugs via one of three channels: drugs authorized in Turkey, Prescription-based Foreign Drug Supply Program, and Compassionate Early Access to Drug Program.

Authorized Drugs

The principal way to access a new drug in Turkey is through marketing authorization by the Ministry of Health. Once approved for marketing authorization, a drug undergoes assessment by SSI in case of reimbursement application. Assessment process of the products remain affirmative for marketing authorization and subsequently reimbursement applications, if they are scientifically proven to provide benefit to the patients, allowing patients access those innovative treatments. Seventy-six products positioned as orphan drugs in the EU or USA are currently available under license in Turkey.

Prescription-based Foreign Drug Supply Program

Drugs not authorized in Turkey but still needed for treatment of patients can be obtained from abroad by physicians through Turkish Pharmacists' Association (TEB), İbn-i Sina Health Social Security Center under SSI or the International Healthcare Services Corporation (USHAŞ) with the "Foreign Drug Use Application" to TİTCK. Applications that are found to be eligible by the scientific advisory board are approved on patient basis. [3]

After the application made to the SSI, drugs added to the Foreign Drugs List are granted reimbursement if the reply is positive. On the other hand, application for marketing authorization is required within 3 years of inclusion of these drugs into the Foreign Drugs List, and authorization to be issued within 2 years of application. Whether the drugs not meeting these will remain in the list is subject to Presidential decree. There is the risk that access to any drug this way may not be consistent as authorized drugs due to this restriction.

In addition, costs of these drugs lead to a considerable burden on the payer party since drugs added to the Foreign Drugs List are imported based on overseas prices and actual exchange rates. This cost is covered by the SSI in case the reimbursement application is approved and mostly will not be paid for by the patients; however, drugs that are not approved for reimbursement based on various reasons despite meeting unmet treatment needs may be submitted to jurisdiction, resulting in the interruption of patient treatment.[10]

### Compassionate Use Programs

This is a program aiming to allow free of charge supply of drugs unauthorized in Turkey by the company to patients with a life-threatening disease, for whom treatment with products authorized in our country failed and who cannot be enrolled into any clinical trial, based on humane reasons. With some exceptions, drugs that have completed Phase II studies and entered Phase III studies are included in this program in the world.[80]

## Orphan Drug Legislation

### Orphan Drug Legislation Studies in the World

Since each rare disease affects only a limited population, the income from these treatments is still low despite more challenging and costly R&D processes for treatments developed for these diseases. Therefore, it appears that the pharmaceutical industry did not make R&D investments in this field in previous years since drug development activities for rare diseases were commercially unattractive. Legal regulations and legislations have been introduced by various countries that provide financial incentives to enable development of treatments for rare diseases. "Orphan Drug Act" was introduced in 1983 in the USA as the pioneer in this field and governmental incentives were formed for the development of new treatments. Subsequently, many countries led by Singapore, Japan, Australia, the European Union, Taiwan, South Korea have brought regulations in this field. Some countries that have an orphan drug legislation are shown in Table 3.[81]

**Table 3: Major Countries with An Orphan Drug Legislation**

| COUNTRY | DEFINITION OF RARE DISEASE | LEGISLATION | YEAR |
|---|---|---|---|
| USA | <200,000 cases | Orphan Drug Act | 1983 |
| | | Rare Disease Act | 2002 |
| Singapore | <20,000 cases | Medicines Act (Chapter 176, Section 9) | 1991 |
| Japan | <50,000 cases | Pharmaceutical Affairs Law | 1993 |
| Australia | <2,000 cases | Orphan Drug Program | 1998 |
| EU (28 countries) | <5/10,000 | Orphan Medicinal Product Reg. (EC) No. 141/2000 | 1999 |
| | | Pediatric Regulation Reg. (EC) No. 1901/2006 | |
| | | Regulation on Advanced Therapy Medicinal Products Reg. (EC) 1394/2007 | |
| Taiwan | <1/10,000 | Rare Disease and Orphan Drug Act | 2000 |
| South Korea | <20,000 cases | Orphan Drugs Guideline | 2003 |
| Colombia | <1/5,000 | Law 1392 | 2010 |
| Argentina | EU definition | Law 26.689 | 2011 |
| Peru | No definition | Law 29698 | 2011 |
| Mexico | EU definition | Article 224 revision | 2012 |
| Brazil | <65/100,000 | National Policy for Rare Diseases | 2014 |
| Philippines | <1/20,000 | Rare Disease Act of the Philippines | 2016 |

Interestingly, developing countries also have made certain laws and regulations on orphan drugs besides developed and leading countries in pharmaceutical R&D. These laws and regulations both support the pharmaceutical R&D ecosystem in these countries and target to bring regulations for subjects such as the management of rare diseases, raising awareness among patients, patient registry systems, and clinical trials on rare diseases. The Orphan Drug Program introduced in Australia in 1998 brought financial and marketing incentives to companies that are developing drugs for patients affected by rare diseases. This step is parallel to the incentives provided by Australia to the clinical investigations in the country during the following years to support local R&D activities.[39] [81]

### Orphan Drug Legislation Studies in Turkey

Studies on orphan drug legislations in Turkey started in 2009, and the draft Guidance on Orphan Drugs that was prepared was presented to the sector for opinion in April 2011; however, our country is still lacking a definition of orphan drug and a legislation specific to orphan drugs despite years of studies on this issue.

Shifting of rapid developments in the fields of gene technology and biotechnology as well as innovation from big companies to smaller enterprises provide an opportunity for economies such as Turkey that are developing and willing to invest in R&D. Given the potential contribution it makes to the management of rare diseases, patient registry programs and clinical investigations; regulations made by relevant institutions will be highly beneficial to improve access to treatments by individuals with rare diseases in our country the same way as many other developed or developing countries. Examples of these regulations may include the facilitation of clinical investigation processes on rare diseases or delaying observational studies on drugs' side effects to post-approval period.[65]

## Access to Market

### Marketing Authorization Process

Since no definition of orphan drug or a legislation is currently available in our country, drugs used in the treatment of rare diseases are subject to the rules and regulations specified for other treatments for market access and reimbursement processes.

*Shifting of rapid developments in the fields of gene technology and biotechnology as well as innovation from big companies to smaller enterprises provide an opportunity for economies such as Turkey that are developing and willing to invest in R&D.*

Regulatory activities of medical products are governed by the Department of Medicines Marketing Authorization under TİTCK. Applications with full documentation are accepted after the submissions are reviewed within the 30-day preliminary assessment period following marketing authorization application. The marketing authorization process is to be finalized within 210 days after the application is accepted. The companies may request priority for products that meet certain conditions. The respective prioritization guidelines indicate that the marketing authorization process will be finalized within 180 days for prioritized applications and in 150 days for highly prioritized applications. In the case of existing practices, however, it is seen that the defined periods cannot be exercised and that delays occur during the market access of the products.[82]

Provision of treatments in the field of rare diseases to patient access in a more predictable and expedited way is of importance in Turkey as well as the entire world. Application for prioritization can be made in the context of "innovative product" during the authorization process of respective treatments in Turkey, while being positioned as an orphan drug internationally does not favorably contribute to the evaluation made by the institution. Subjects assessed in these applications include criteria such as the additional benefit from the product, innovation, efficacy on the society, safety advantage, public cost advantage and technology transfer to the country. It is already known that a more comprehensive evaluation is needed for the positive contribution of drugs used in

the treatment of rare diseases for which it is difficult or in some cases even impossible to estimate the number of affected patients compared to other diseases due to the relatively limited patient population each one individually has, and that cost advantage assessment is more difficult compared to other diseases. In line with this, various countries adjust the marketing authorization processes to expedite the market access of relevant treatments. Examples of these adjustments include where clinical study data for the product is submitted after the marketing approval through conditional authorization. In our country, with the adjustments made in the authorization regulations published on 11 December 2021, it was targeted to harmonize the relevant content in the regulations with the conditional and exceptional regulatory procedures found in the European directive. Accordingly, introduction of exceptional regulatory processes was planned to be conducted together with the benefit-risk evaluation of treatments in cases where these data cannot be obtained due to regulations that allow submission of clinical study data after the conditional approval of a product that is highly needed or due to the rarity of the diseases.[10] [24]

**Cost and Reimbursement**

**Medicinal products authorized in Turkey are priced by the Ministry of Health on the basis of reference price system and the exchange rates that are fixed yearly.** Applications for the drugs for which reimbursement application was made to the SSI after the approval of marketing authorization are evaluated by the Drug Reimbursement Commission or the Alternative Reimbursement Commission. Reimbursement Commissions meet under the directorship of the SSI with the contribution of representatives from the Ministry of Health, the Ministry of Treasury and Finance and the Presidency of Strategy and Budget. Drug Evaluation Commission may take advice from the Medical and Economic Evaluation Commission should the need arise. Additionally, it is possible to get support from experts and key opinion leaders outside the institution through establishing Scientific and Academic Advisory Commissions in the course of drug assessments. Drugs that are granted approval for reimbursement based on the decision of relevant commissions are covered by the SSI and conditions relevant to the payment are issued in the on Healthcare Implementation Communiqué (SUT).[3]

*Pricing and reimbursement of orphan drugs that take an important place in the treatment of rare diseases with innovative approaches is a globally considered matter.*

Pricing and reimbursement of orphan drugs that take an important place in the treatment of rare diseases with innovative approaches is a globally considered matter, because the general perception caused by the high cost per patient of some orphan drugs suggests that the total economic burden caused by those drugs is high as well. In contrast to this general judgement, orphan drugs make up only a small portion of the whole drug market. An analysis performed by IQVIA demonstrated that the share of orphan drugs was 11% in the US drug market in 2019, and 3.5% in the European market in 2016.[25]

Innovative approaches are being adopted in market access processes to solve these problems in Spain where market access of innovative drugs is delayed due to the disorderly structure of pricing and reimbursement processes in addition to budget pressure. Because assessments that consider short-term budget impact in Spain ignored the acquisitions that treatments for rare diseases provide in the long term, a high-priced medicine model was preferred in previous years for the reimbursement assessments of certain innovative drugs including orphan drugs. A treatment must meet three basic criteria to be assessed in this framework:

- Having a substantial economic impact
- Meeting an important need

- Addressing a small group of patients

Utilization of real world data was stipulated while making result-based contracts for innovative products for rare diseases that are evaluated within this framework. The duration of outputs that contracts are based on and contract models were given shape based on the expected time of positive outcomes in patients. Through the implementation of these contracts, market access processes for such products worked faster than normal and the patients accessed these treatments earlier.[26]

Among the members of the EU, some countries formed various unions in recent years by joint action in the pricing and reimbursement processes to determine the prices and reimbursement conditions in the most effective way through rationalist and innovative solutions. Some of these continued with member countries involved in this formation only, while initiatives such as the Beneluxa (Belgium, The Netherlands, Luxembourg, Austria and Ireland) and Visegrad (Croatia, Hungary, Lithuania, Poland and Slovakia) accept other countries that are or are not EU members through participant consent.[27] [28]

Given the place of orphan drugs in total drug expenditures and successful examples of global market access processes, effective use of similar innovative solutions in Turkey is expected to contribute to improved and expedited patient access to innovative treatments.

### 3.4 Diagnosis and Treatment Coordination

Qualification of the healthcare infrastructure in terms of quality, quantity and extensiveness and structuring

it in a way suitable for multidisciplinary approach are crucial in the management of rare diseases.

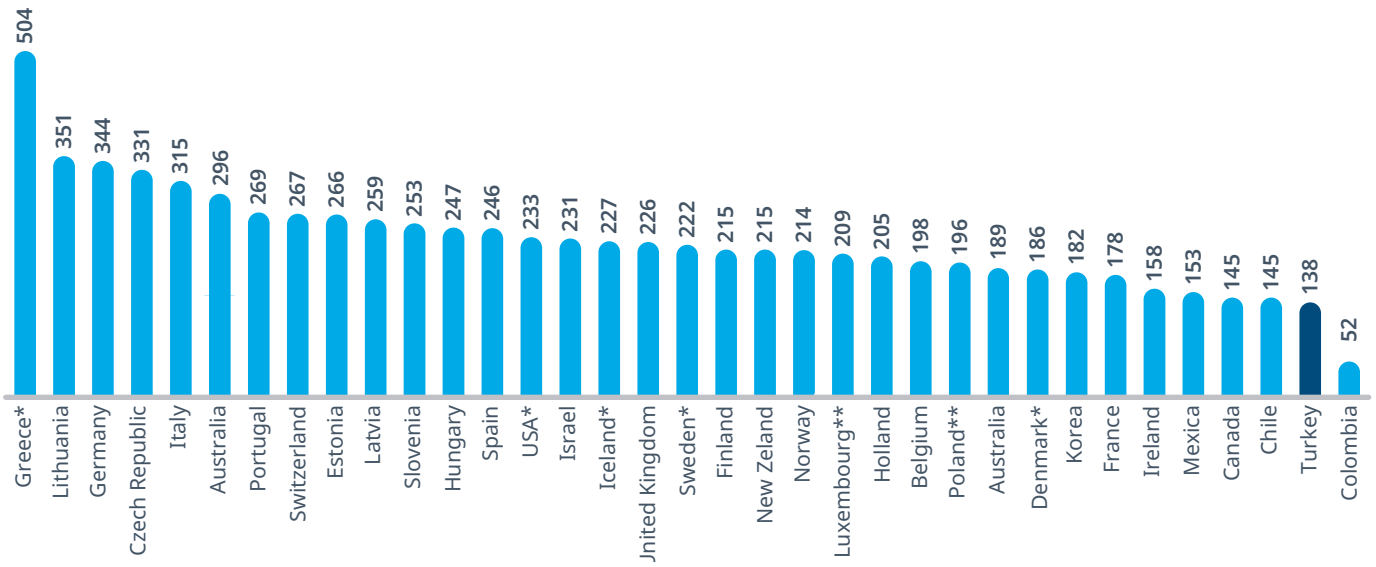
**Human Resource Expert in Rare Diseases**

Although different specialties deal with different diseases due to the diversity of body system they affect, certain specialties become prominent given that 70% to 80% of all rare diseases are inherited and typically occur during childhood. It is very important to increase the number of specialists involved in the management of rare diseases and to extend the healthcare service provided to people with rare diseases throughout the country. Health Minister pointed out the importance of expert force trained on rare diseases in his briefing and indicated that between the years 2017-2021, the number of pediatrics subspecialists increased from 1695 to 2140, child and adolescent mental health specialists from 400 to 1272, and genetic specialists from 242 to 422.[13]

Availability of qualified human resource in the management of rare diseases is very important for ensuring that patients are diagnosed timely and high-quality healthcare services are provided. Opening relevant centers and laboratories and providing technical infrastructure are necessary for sure; however, it is an absolute priority that there are enough specialists who are capable of performing diagnosis, treatment and follow-up of those patients. Specially, the number of physicians in pediatric subspecialties who have a critical role in the follow-up of rare diseases is still considered low. The distribution of pediatric subspecialists across the country shows that approximately 70% of these specialists are in 7 big cities while no pediatric subspecialist is available in 29 cities.[30]

Turkey is behind OECD countries in terms of the number of total specialists per person including resident doctors (Figure 5).[29]

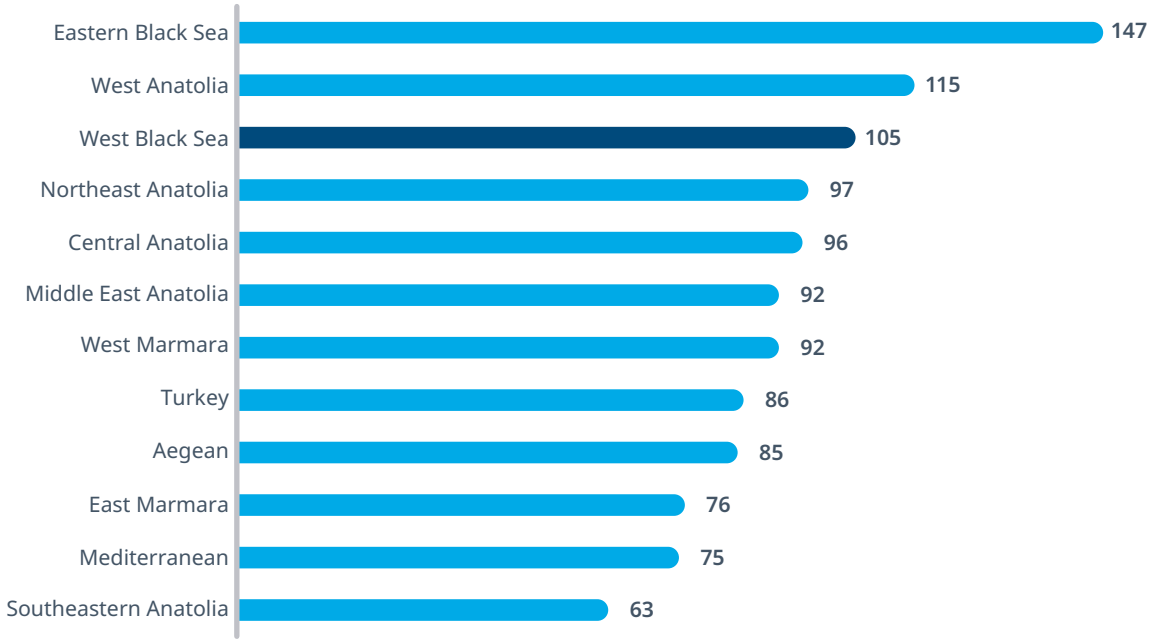
**Figure 5: Specialist Density by Country, 2020 (per 100,000 people)**




* 2019 data are used. ** 2017 data are used.
Source: OECD

However, distribution of specialists by region is not even: The overall number of employees in the health institutions in Turkey demonstrate that the number of specialists per person in eastern regions is lower than Turkey average (Figure 6).[30]

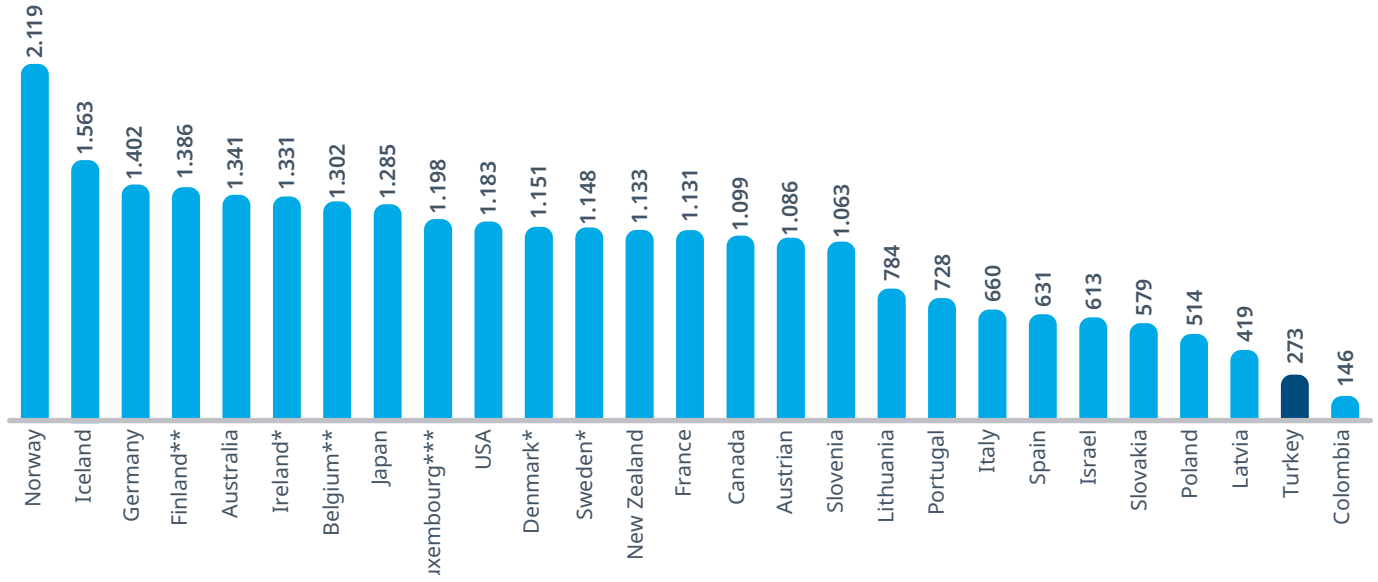
**Figure 6: Number of Specialists per 100,000 People, 2020**




Source: Republic of Turkey Ministry of Health, Annual of Health Statistics, 2020.

Nurses also play a supporting role in the treatment and follow-up of patients affected by rare diseases; however, Turkey falls behind the OECD countries in terms of the number of occupationally active nurses per person in various countries (Figure 7).[29]

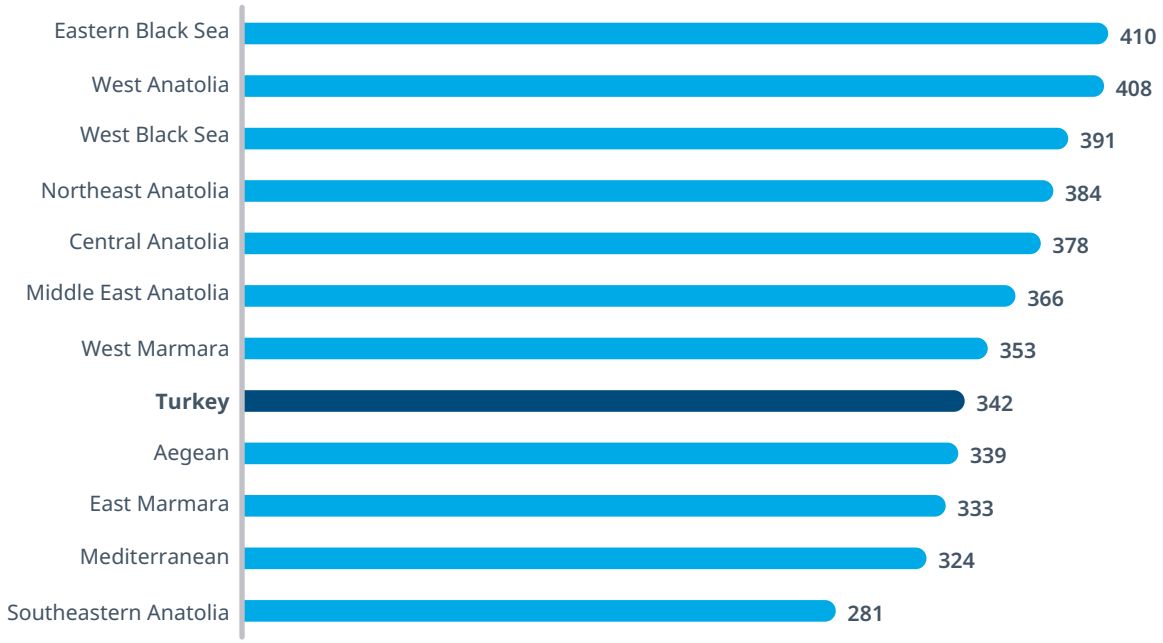
**Figure 7: Density of Occupationally Active Nurses by Country, 2020 (per 100,000 people)**




* 2019 data are used. ** 2018 data are used. *** 2017 data are used.
Source: OECD

In terms of the overall number of nurses and midwifes across Turkey, Southeastern Anatolia region falls behind all geographical regions (Figure 8).[30]

**Figure 8: Number of Nurses and Midwifes per 100,000 People, 2020**




Source: Republic of Turkey Ministry of Health, Annual of Health Statistics, 2020.

In addition to the medical services and medical treatments provided in rare diseases, it is also important to provide physical therapy and rehabilitation services as well as social and psychological support to patients in need. It is observed that while patients in our country are currently provided with these services, qualified personnel number is insufficient and regional differences may be seen in the number of healthcare practitioners per person, in access to service, and in service quality. Therefore, the number and quality of personnel trained on rare diseases such as the auxiliary staff, technicians, social services experts and psychologists needs to be improved and studies are needed on standardization of services to enable equal access of patients to healthcare services.[10]

**Rare Diseases Diagnosis and Treatment Centers**

Due to the multitude of rare diseases and the small number of patients affected by each of these and because most rare diseases affect more than one body system, these patients require follow-up in a special and multidisciplinary approach. In our country, rare diseases are mostly managed at the training and research hospitals, university hospitals and city hospitals which are tertiary healthcare institutions. Under the relevant department in some of these institutions, there are polyclinics or centers specialized in certain rare diseases or disease groups. Additionally, centers referred to as "Rare Diseases Center" are recently being established within some institutions. These centers in limited number that are yet quite new and under development currently focus rather on research activities in this field.

**Diagnosis and Treatment Centers and Outpatient Clinics Specific to Diseases**

Centers and polyclinics that are focused on various groups of rare diseases are currently active under relevant departments of tertiary care institutions across Turkey. The only group among them for which standards have been set with a particular regulation is the neuromuscular disease centers. These centers provide specialized healthcare service for the needs of patients with neuromuscular diseases. With the "Regulations on Neuromuscular Diseases Department" issued in June 2021, the guidelines were established for the opening of relevant units, their physical conditions, and personnel standards.[83]

Centers and polyclinics in Turkey that provide specialized healthcare on neuromuscular diseases are presented in Table 4.

**Table 4: Centers and Polyclinics Providing Specialized Service on Neuromuscular Diseases**

| CITY | NUMBER OF CENTERS | NAME OF INSTITUTION |
|---|---|---|
| İstanbul | 4 | Bakırköy Mazhar Osman Training and Research Hospital<br>Sadi Konuk Training and Research Hospital<br>Ümraniye Training and Research Hospital<br>Gaziosmanpaşa Training and Research Hospital |
| Ankara | 1 | Dışkapı Yıldırım Beyazıt Training and Research Hospital |
| İzmir | 1 | Tepecik Training and Research Hospital |
| Antalya | 1 | Antalya Training and Research Hospital |
| Eskişehir | 1 | Eskişehir City Hospital |

| CITY | NUMBER OF OUTPATIENT CLINICS | NAME OF INSTITUTION |
|---|---|---|
| İstanbul | 3 | Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital<br>Medeniyet University Göztepe Training and Research Hospital<br>Fatih Sultan Mehmet Training and Research Hospital |
| Bursa | 1 | Bursa High Specialization Training and Research Hospital |
| Balıkesir | 1 | Atatürk City Hospital |
| Çanakkale | 1 | Mehmet Akif Ersoy State Hospital |
| Sakarya | 1 | Sakarya Üniversitesi Training and Research Hospital |
| Burdur | 1 | Burdur State Hospital |
| Denizli | 1 | Denizli State Hospital |
| Adana | 1 | Adana State Hospital |
| Kahramanmaraş | 1 | Şehit Necip Fazıl State Hospital |
| Konya | 1 | Konya Training and Research Hospital |
| Kayseri | 1 | Kayseri City Hospital |
| Trabzon | 1 | Trabzon Kanuni Training and Research Hospital |
| Samsun | 1 | Samsun Training and Research Hospital |
| Malatya | 1 | Malatya Training and Research Hospital |
| Elazığ | 1 | Fethi Sekin City Hospital |
| Diyarbakır | 1 | Gazi Yaşargil Training and Research Hospital |
| Şanlıurfa | 1 | Mehmet Akif İnan Training and Research Hospital |
| Van | 1 | Van Training and Research Hospital |

Sources: 1. https://shgmnadirdb.saglik.gov.tr/TR-77495/noromuskuler-hastaliklar-merkezleri.html#. 2. https://umraniyeah.saglik.gov.tr/TR,538102/noromuskuler-hastaliklari.html. 3. https://vaneah.saglik.gov.tr/TR,525583/hastanemiz-bunyesinde-noromuskuler-poliklinigi-acildi-30042021.html

The patients are followed up in a multidisciplinary approach in these centers which allow collaborative work of healthcare professionals who are well informed and experienced on rare neuromuscular diseases. An important infrastructure to accelerate diagnostic course, to administer correct treatment under appropriate conditions and to improve patients' conditions of care is provided thanks to the coordinative work of various specialties such as neurology, physical therapy and rehabilitation, cardiology, thoracic diseases, and nutrition. However, the capacity of established neuromuscular disease centers across Turkey is still insufficient with some of these currently being passive. The Ministry of Health is accordingly continuing studies to disseminate neuromuscular disease units and to enhance the service quality of existing units. The studies made or designed so far for these centers make a good example for the units of service planned for other diseases.[10] [13] [17]

### Rare Diseases Centers

"Rare Disease Centers" have been established as a result of applications made to the Council of Higher Education (YÖK) by the universities in Turkey. The purposes of founding these centers are to make contribution into the cumulative knowledge formation on rare diseases, to increase clinical trials and to improve patients' chances of diagnosis and treatment. In our country, a total of 5 Centers for Rare Diseases have been founded in Ankara and İstanbul as of late 2021. These centers are presented in Table 5.[84]

**Table 5: Centers of Rare Diseases in Turkey**

| NAME OF THE CENTER | DATE OF ESTABLISHMENT | CITY |
|---|---|---|
| Hacettepe University Center for Genomics and Rare Diseases (HÜGEN) | July 2017 | Ankara |
| Acıbadem University Rare Diseases and Orphan Drugs Application and Research Center (ACURARE) | 2017 | İstanbul |
| Ankara University Rare Diseases Application and Research Center (NADİR) | June 2021 | Ankara |
| Lokman Hekim University Undiagnosed Rare Diseases and Orphan Drugs Application and Research Center | June 2021 | Ankara |
| İstanbul University Faculty of Medicine Rare Diseases Research Laboratory | October 2021 | İstanbul |

Sources: 1. http://www.hugen.hacettepe.edu.tr/geneltanitim.shtml; 2. https://www.ankara.edu.tr/universitemiz-bunyesinde-nadir-hastaliklar-uygulama-ve-arastirma-merkezi-kuruluyor/; 3. https://www.lokmanhekim.edu.tr/wp-content/uploads/2021/06/nadir-hastal%C4%B1klar-mevzuat.pdf; 4. https://kasder.org.tr/istanbul-tip-fakultesi-nadir-hastaliklar-arastirma-laboratuvari-acilisindaydik/.

### Centers of Excellence

Centers of excellence in various countries are known as “Center of Excellence” in the US and “Centre of Expertise” in the EU countries. The main purpose of these centers is to improve processes by increasing patients’ access to diagnosis, treatment and follow-up processes, develop collaboration, increase awareness, and form the basis for research activities in this field by facilitating cumulative knowledge and sharing.

National Organization for Rare Disorders (NORD) announced in the US that 31 centers of excellence will be established across the country in November 2021. The targets of these centers include creating new treatment guidelines, developing medical education and training for families, generating safe and effective reference pathways, and bringing new treatments and innovation to research areas.[85]

In the EU, these centers referred to as “centre of expertise” were first officially introduced within the framework of Recommendations on Quality Criteria for Centres of Expertise on Rare Diseases in Member Countries by the EUCERD at the end of a long effort

in 2011. These centers have an important place in the management of rare diseases and are the primary subject that EU countries included in their national rare disease plans and strategies. These centers established in many countries for different rare diseases are specialized places where comprehensive research is conducted in relation to a specific rare disease and studies are performed for the diagnosis and treatment of those diseases. For a center to be qualified as a "center of expertise" in the EU, it must comply with the accreditation criteria set by the EUCERD. These centers may be provided with facilities by the EU such as funding support and delivery of training to the healthcare personnel employed at the centers.[31] [32]

EUCERD has suggested 10 basic criteria to consider while establishing centers of expertise on rare diseases in EU member countries:

1. Having adequate capacity to manage individuals with rare diseases and to provide them with specialist opinion, adherence to good practice guidelines for diagnosis and treatment
2. Availability of access by patients to a multidisciplinary team of experts (integration of medical services and other healthcare services with psychological and social support)
3. Ensuring treatment quality, compliance with internal and external quality regulations, recommending indicators of treatment quality
4. The level of expertise documented by annual referral, expert opinion, papers, donations and volume of education
5. Research activities, participation in collecting data and clinical investigations
6. Establishing collaborations that allow continuous treatment during transition from childhood to adolescence and adulthood
7. Establishing collaborations that allow continuous treatment across all disease phases
8. Collaborations with laboratories and patient associations and with other specialty centers nationally, across Europe and at international level
9. Making adjustments for patient referral within the country and between EU countries
10. Considering e-health solutions

Regular evaluation of the centers of expertise has been recommended as defined in the authorization processes in that country. Thus, a decision maker authorizing a center may withdraw authorization in case of the center's failure to fulfill one or more specifications or when national service is no longer needed.[86]

One of the best centers of expertise examples across Europe is the Birmingham Children's Hospital in England. Harboring the first center for rare diseases in the country, the hospital offers treatment through 11 centers of expertise for more than 500 rare diseases to approximately 9,000 children coming from far and wide. Some of these centers are the single center in the country authorized for the related rare diseases or one among a few. These centers offer service with physicians from all specialty fields that have a role in the management of relevant diseases together with nurses, genetic experts, dieticians, physiotherapists, psychologists and family communications specialists

that are specialized in this field. The patients are viewed by all relevant branch doctors and by other healthcare practitioners during regular follow-ups. The hospital's new center for rare diseases that is going to open is planned to provide a total of 57 different clinical services for various diseases.[87]

The communication between the centers of expertise founded for different rare diseases or disease groups with other similar national or international centers is important for facilitating referral of patients to relevant centers or healthcare institutions, allowing sharing of knowledge and experience, leading the way for comprehensive data accumulation, and contributing to the investigations in this field. Therefore, centers of expertise in the EU countries are encouraged to connect to both national center of expertise networks and to ERN. As of 2018, a total of 24 ERNs were formed that involve more than 300 hospitals in 26 countries and more than 900 expert units. Thus, the patients do not travel unless they need to, the "specialty" they need is delivered by the help of reference networks, and patients are able to access the best possible diagnosis, treatment and care where they live.[31]

There is no center of excellence for rare diseases in Turkey with documented compliance with EUCERD criteria or accredited by the relevant agencies in our country. Previous studies on this subject report that in the context of the circular issued by the Ministry of Health in April 2019 for establishing centers of excellence in our country, those service units within health institutions in Turkey with appropriate human resource capacity, health technologies profile and physical infrastructure are going to be defined as "center of excellence".[88]

Following the publication of the circular, it has been reported by different sources that the Ministry and its relevant departments have proceeded with their work on this subject. In July 2020, Department of Autism, Mental Special Needs and Rare Diseases and TÜSEB Healthcare Services Quality and Accreditation Institute met to discuss studies that are conducted for centers of excellence. Finally, it was remarked in the declaration by the Health Minister in February 2021 that emphasis was given to establishing specialized service units and centers of excellence in providing healthcare service for rare diseases and that centers of excellence for rare diseases were also included in the centers of excellence that were planned to be founded with standard identification studies started by forming commissions on this field. Announcements by the Ministry emphasize the importance of centers of excellence in the field of rare diseases and that studies on this subject are going on, while this is not reflected in practice given the current situation.[13] [89]

*There is no center of excellence for rare diseases in Turkey with documented compliance with EUCERD criteria or accredited by the relevant agencies in our country.*

**Patient Registry Studies**

The limited population affected by each rare disease makes it difficult both to collect long term and consistent data on rare diseases and to access correct patients for R&D studies in this field. Therefore, regular follow-up and recording of patients affected by rare diseases both facilitate patient enrollment to clinical investigations for new treatments and contribute to obtaining epidemiology and real life data, forming treatment standards for diseases, increasing life expectancy with available treatments, improving patient care, and effective planning of the healthcare system.[33] [34]

With this purpose, local or international patient registry systems have been created in many countries worldwide in various therapy areas. NORD that brings patient associations together in the US, a leading country in the field of rare diseases, has launched a patient registry program known as IAMRARE®. Within the framework of this program, patient registry studies have been initiated for more than 40 rare diseases, and over 13,600 patients have been included in the program. Within the framework of this program, an online patient registry program has been formed with the contribution

of FDA, NIH, patients, organizations, and experts in this field. The relevant stakeholders are able to initiate high quality patient registry studies in line with the needs on this cloud-based, dynamic and easy-to-access platform, and participants can easily access to the platform based on individual attributes.[90]

As of September 2020, a total of 793 registry systems for various diseases from 36 EU and nearby countries have been reported by Orphanet. 70% of these were described as national registry systems while the rest were defined as regional, Europe-wide or international systems. 83% of these studies are public while 17% are private patient registry systems. Among the countries reported, Germany has the highest number of registry systems with 158 studies, followed by France and Italy with 150 and 89 studies, respectively.[34]

In Turkey, 5 national and public patient registry studies have been reported for different rare diseases:

1. Behçet's disease
2. Duchenne and Becker muscular dystrophy and spinal muscular dystrophy
3. Cystic fibrosis
4. Pediatric atypical hemolytic uremic syndrome
5. Severe chronic neutropenia[34]

Considering the level of risk for genetic diseases due to the total population of Turkey, estimated total number of individuals affected by rare diseases and the high rates of consanguineous marriage especially in certain regions; it is expected to derive benefit from generalization of patient record studies in our country with regard to management of rare diseases.

EUCERD specified 10 basic principles to develop patient registry studies:

1. Patient registry studies should be considered a global priority for rare diseases
2. Patient registry studies for rare diseases should have the largest possible geographic extent.
3. Patient registry studies for rare diseases should be based on a disease or a disease group rather than a certain therapeutic intervention.
4. A consistent effort should be made for collaboration and harmonization of patient registry studies for rare diseases.
5. A minimum common body of data elements should be used consistently during all patient registry studies for rare diseases.
6. The information obtained from patient registry studies for rare diseases should be associated with relevant biobank data.
7. Patient registry studies for rare diseases should include data directly reported by patients in addition to the data reported by healthcare professionals.
8. Collaborations between the government and the private sector should be encouraged to make patient registry studies for rare diseases sustainable.
9. The patients should be involved equally as the other stakeholders in the management of patient registry studies for rare diseases.
10. Patient registry studies for rare diseases should be utilized as a basic tool to form and support patient communities.[33] [91]

### 3.5 R&D Activities in the Field of Rare Diseases

Drug development attempts targeting rare diseases have gathered speed since the first Orphan Drug Act of 1983 was issued in the US.[1]

Today, R&D studies for these diseases have reached such a point that nearly 5000 investigation projects on 2000 rare diseases are currently being conducted within EU borders. Additionally, a total of over 650 clinical investigations including orphan drug studies are being conducted on more than 300 rare diseases; however, there are thousands of rare diseases that have not been studied in any trial. In particular, studies conducted for diseases with a prevalence of less than 10/100,000 are quite limited.[35]

**Research Incentives and Projects**

R&D studies on the field of rare diseases are essential for the patients since unraveling the mechanisms underlying diseases allow timely and accurate diagnosis as well as developing proper treatments. Through better understanding of rare diseases and as treatment options are developed for more rare diseases, more efficient treatments will be used instead of costly treatments despite being less efficacious and a global drop will be achieved in public health expenditures.[35]

*Unraveling the mechanisms underlying diseases allow timely and accurate diagnosis as well as developing proper treatments.*

Therefore, investigations on rare diseases are by various means encouraged in many countries worldwide. Incentives provided by orphan drug regulations are the foremost. The act that came into force in 2000 in the EU has supported product development processes through research grants and protocol support in addition to raising economic return expectations for the products to enhance investments into the field of rare diseases. It was demonstrated in an economic modelling that in the absence of this regulation, only 45% would have been developed out of 142 orphan drugs developed between 2000-2017 and approved in the EU.[92]

In addition to the regulations for orphan drugs, states included incentives for scientific research on this field in their national plans for rare diseases. The EU included investigations for rare diseases in two different research and innovation programs involving the years 2007-2020 and transferred funds of more than 620 million Euros into over 120 rare disease research projects between 2007-2013. On a country basis:

- Germany provided resources for 12 rare disease research projects via Federal Ministry of Education and Research between 2012-2017 and transferred additional funds to this field through initiatives such as the National Genome Research Network.
- Founded in 2018 with financial support by Vinnova – the Swedish Agency of Innovation – and by the university hospitals countrywide and gathering physicians, scientists, and industrial and patient associations together, the Genomic Medicine Sweden (GMS) initiative targets to implement precision medicine practices in the country and to accomplish high technology R&D activities.
- The Chinese Alliance of Rare Diseases created the first national plan for research intended for the prevention and treatment of rare diseases.
- The Canadian government, through the Canadian Institutes of Health Research, is devoting resources to translational medicine and to maintaining rare disease models with newly formed teams of researchers and consortia.
- France, a pioneer country in the field of rare diseases, is funding more than 300 clinical investigations through collaboration with the national and international institutions.[15] [19]

In Turkey, nationally sourced research on rare diseases is too scarce. In the report of Rare Disease Day Symposium held in February 2021, TÜSEB emphasized the importance of enhancing research in this field and remarked that the funding organizations in the country called for this issue and supported the studies. Within the scope of two calls by TÜSEB for R&D and validation studies in the fight against SMA in 2021, the goals were to support projects that offer innovative solutions and technological products for developing and manufacturing domestic diagnostic kits to be used in the early diagnosis of the disease, to decrease the incidence in our country and to alleviate the economic and social burden of the disease.[65] [93]

In 2021, TÜBİTAK also made a call within the European Joint Programme on Rare Diseases framework. The purpose of the call, entitled “Improving Healthcare Service Practices and the Daily Lives of Individuals Living with Rare Diseases and Human Sciences Research” was to support social and human projects on this field.[94]

### Clinical Research

Clinical research has the biggest share in R&D investments: Phase I, II and III studies constitute 50.2% of the total pharmaceutical R&D investment and reaches up to 61.6% when Phase IV studies are included. Similarly, clinical research is also of great importance throughout pharmaceutical R&D processes for rare diseases, and studies on rare diseases have an increasing contribution among clinical studies.[38] [39]

Review of the clinical trials that are supported by the industry and are active as of December 2021 in Turkey showed that 137 out of 684 active trials (20.0%) investigated rare diseases other than rare cancers and the number ascends up to 431 (63.0%) when studies on rare cancers are included. Among these clinical trials, the rare disease with the biggest contribution is multiple sclerosis (MS) with 25 studies, followed by hemophilia with 11 studies.[7] [38]

With a population at relatively high risk for harboring rare genetic diseases, our country represents an important patient potential for clinical trials on rare diseases; however, it fails to reach the potential in terms of clinical trials conducted per capita. Opportunity areas and policy recommendations to allow more patients to benefit from clinical trials in Turkey were analyzed in detail in IQVIA's "Benefits of a Clinical Research Strategy for Turkey – A Roadmap for Innovation-driven Growth" report. Each of the opportunity areas included under patient recruitment, process, infrastructure, and cost and incentives categories also apply to the clinical trials on rare diseases. Actions that particularly target patient recruitment and ensuring easy access to patients with increased patient awareness have a great importance in rare disease trials.[39]

### 3.6 Challenges that Confront Patients and Patient Relatives

Although rare diseases are usually life-threatening, lifelong diseases that lead to serious symptoms, today still there is an unmet treatment need for many of them. Because they are rare and since each disease has its own characteristics, healthcare professionals have limited knowledge and experience regarding these conditions. Therefore, ambiguous processes may occur due to lack of information in the management of rare diseases, and the families' need to receive reliable information may not be met in some cases. With little medical and scientific data, these diseases have notable physical, social and economic effects on the patients. Moreover, the patient's immediate circle is also substantially affected by the wearisome course caused by the rare disease.[40]

People with rare diseases may experience physical effects due to the disease itself or side effects of the treatment that include pain, weight loss, lack of appetite, fatigue and sleeping problems. On the other hand, witnessing physical pain and other unfavorable conditions experienced by their children or close relatives lead to psychological breakdown in other family members.[40]

Because diagnostic process is usually prolonged and compelling and treatment options are either not available or access to them is limited, psychological conditions like depression or anxiety in addition to emotions such as high level of anxiety, fear, anger and disappointment may occur in people with rare diseases as well as their families. Compared to overall population, depression and unhappiness are reported to happen 3 times higher in individuals with rare diseases. Social isolation is also frequently observed due to exposure of the patients to discrimination or bullying in educational, business and social life. It is essential to provide the help and support that the individuals with rare diseases need and to reintegrate these individuals into the society.[95]

Besides the physical and psychosocial dimensions, rare diseases also bring a substantial economic burden to

families. They both lose time and are negatively affected financially due to numerous visits to various experts until the correct diagnosis is made. Furthermore, families with no access to diagnostic and treatment opportunities due to regional conditions are obliged to travel to distant places to receive the healthcare service they need and face with many direct and indirect costs such as workforce loss and expenditures for transportation and accommodation. This is not limited to the diagnostic process alone; it may continue during the treatment course of the patient. In addition, the equipment for patients requiring continuous home care support and the excessive costs they bring may contribute to additional expenses for the families. Typically, one of the parents quit work to undertake the care of their child with a rare disease, and this may lead to financial suppression of the family.[40]

According to the study conducted by EURORDIS in 2017 with the contribution of more than 3000 individuals, 7 of every 10 patients or individuals dealing with patient care either quit job or have to reduce the time they spend for work. A study conducted to determine the individuals with rare diseases in Turkey and the economic burden on their families brought by the disease showed that families spent 30% of their yearly

income on out-of-pocket expenditures due to the disease.[41] [95]

In the workshop organized by the "Joint Intelligence Platform for Needs Analysis of Rare Disease Patients and Patient Relatives" to demonstrate the current situation of the problems experienced in our country due to rare diseases and to develop recommendations, problems under 4 topics were identified: diagnostic process, treatment course, social life and communication-coordination problems. Problems such as the congestion in hospitals, problems in accessing certain materials, test kits and medicines used in diagnostic procedures, and poor multidisciplinary approach as well as lack of communication between departments may lead to delays in diagnostic processes and may eliminate the chance of early treatment of certain diseases. Additionally, poor communication between the physician and the patient, and not informing the patients or guiding them for psychological support make it even more difficult for the patients. For the treatment process, patients particularly living in remote geographies have been reported to have problems accessing healthcare services due to the limited number of specialist physicians and nurses working on the field of rare diseases. It has been noted that accessing medicines also is troublesome and that medicines left out of or excluded from reimbursement coverage despite being approved by the Ministry of Health put patients into trouble. In addition, it was observed that there were inadequacies in areas such as home care services, physical medicine and rehabilitation services and social services support, and reimbursement problems for certain materials and medical devices used by the patients. The importance of communication and coordination was emphasized in the study and issues were addressed such as collaboration problems among associations, lack of informative publications on rare diseases, and lack of a national database and patient registry system. In addition to all these problems, patients and families with rare diseases face with countless problems also at work and in educational and social lives.[42]

*The devastating effects of rare diseases on patients, their families and on the society need to be assessed from an integrative perspective.*

The devastating effects of rare diseases on patients, their families and on the society need to be assessed from an integrative perspective. It is important to include approaches to meet various degrees of relevant patient needs in national health policies. Rare diseases are those most prone to be excluded from access to healthcare services and the principle of comprehensiveness of care due to affecting a narrow patient group and low level of awareness. Each member of the society should be provided with equal rights to access the treatment, care and education services they need, and no patient group should be allowed to feel like ostracized. Collaboration of all stakeholders including physicians, investigators, the industry, patients and their families, patient associations, nongovernmental organizations and in particular the government itself is important to improve quality of life in individuals with rare diseases and to allow them equally access every domain of life.[42]

# 4. EXAMPLES OF RARE DISEASES

Diseases in a wide spectrum of rare diseases differ not only in terms of the systems they affect in the body and the therapy areas, but also in terms of their prevalence, root causes, age of onset or diagnosis, diagnosis and treatment options and unmet needs. To highlight these differences, 6 rare diseases with different characteristics are given as examples in this report.

**Table 6: Disease Examples Summary Table**

| | IDIOPATHIC PULMONARY FIBROSIS (IPF) | PULMONARY ARTERIAL HYPERTENSION (PAH) | SICKLE CELL ANEMIA | DUCHENNE MUSCULAR DYSTROPHY (DMD) | CYSTIC FIBROSIS (CF) | MUCOPO-LYSACCHA-RIDOSIS (MPS) | NIEMANN-PICK DISEASE (NPD) |
|---|---|---|---|---|---|---|---|
| Estimated Population Affected (in 100,000 individuals) | 14-43 | 1.5-5 | <10 | ~25 live male births | ~33 births | ~4 births | <5 |
| Therapy Area | Pulmonology | Cardiology | Hematology | Neurology | Pulmonology | Metabolism | Metabolism |
| Cause | Not known | Hereditary, unknown | Hereditary | Hereditary | Hereditary | Hereditary | Hereditary |
| Age of Onset | 50+ | Adult | 6 months | 3-5 | 0-2 | 1-2 | 0-Adult |
| Effect Caused by the Disease<br>1 – Mild disability<br>2 – Severe disability<br>3 – Death | 2-3 | 1-2-3 | 1-2-3 | 2-3 | 2-3 | 2-3 | 2-3 |
| Diagnostic Facilities<br>1 – Low<br>2 – Moderate<br>3 – High | 1-2 | 2 | 2-3 | 2 | 2-3 | 2 | 2 |
| Treatment Facilities<br>1 – Low<br>2 – Moderate<br>3 – High | 1 | 2-3 | 2-3 | 1-2 | 1 | 1-2 | 1 |
| Unmet Needs | Curative treatment, survival time, quality of life | Curative treatment | Curative treatment, quality of life | Curative treatment, survival time, quality of life | Curative treatment, survival time, quality of life | Curative treatment, survival time, quality of life | Curative treatment, survival time, quality of life |

Sources: 1. Orphanet; 2. Stakeholder interviews; 3. IQVIA analysis.

## 4.1 Idiopathic Pulmonary Fibrosis (IPF)

**Definition and Epidemiology of the Disease**

Idiopathic Pulmonary Fibrosis is a chronic and progressive interstitial lung disease (ILD) of unknown cause that manifest with symptoms including cough, shortness of breath, fatigue, and chest pain due to hardening of the air vesicle walls in the lung. It is more frequently observed in male individuals over 50

years of age. The disease course may vary between patients. Turkey is lacking a current national patient registry study or epidemiological study in IPF field; however, the number of patients may be identified based on the studies performed for interstitial lung diseases. According to a study conducted in the US, it is estimated to be observed in 14.0 to 42.7 in 100,000 individuals. It is thought to affect approximately 3 million people worldwide and 30,000 in Turkey.[96] [97]

### Management of the Disease: Diagnosis and Treatment

IPF is diagnosed by lung tomography and the exclusion of other diseases. Biopsy, i.e., surgical sampling of the lung tissue may be used as necessary for definitive diagnosis. IPF may be confused with various diseases like chronic obstructive pulmonary disease (COPD) or asthma due to similar symptoms, resulting in loss of time in the course of diagnostic process.

It is important in terms of disease course in patients with IPF to receive early diagnosis and start treatment in the early stage. Diagnostic rate for IPF is reported to increase through years due to factors including more widespread use of tomography in our country as well as worldwide, increase in the number of scientific studies and awareness regarding the disease.

Multidisciplinary approaches are needed in centers where diagnosis and treatment of diseases in the ILD class such as IPF are made. It is essential to form multidisciplinary councils that include experts like radiologists, rheumatologists, pathologists and in particular pulmonologists.

Pulmonologists who are experienced in IPF disease are few in number in our country; however, it is thought that the number of specialists taking part in diagnostic and treatment processes of IPF is increased compared to previous years due to increased recognition of the disease. In addition, the diagnostic process should be supported by tomography assessments by radiologists experienced in this area. Given that the radiologists and pulmonologists in our country specialized in this field specifically are inadequate in number, patients going to hospital with IPF signs are many times referred to other centers (Table 7). According to the results from a survey study among patients with IPF in our country, patients had a mean time loss of 1.5 years before diagnosis.[10]

**Table 7: Distribution of Chest Diseases Specialists, Radiologists, Rheumatologists and Pathologists in Tertiary Care Institutions**

| | PULMONOLOGY | RADIOLOGY | RHEUMATOLOGY | PATHOLOGY |
|---|---|---|---|---|
| İSTANBUL | 24% | 24% | 20% | 20% |
| ANKARA | 18% | 17% | 21% | 16% |
| İZMİR | 10% | 7% | 8% | 9% |
| KONYA | 3% | 3% | 3% | 3% |
| ANTALYA | 2% | 3% | 4% | 3% |
| BURSA | 2% | 2% | 4% | 2% |
| ADANA | 2% | 2% | 3% | 3% |
| KAYSERİ | 2% | 2% | 2% | 2% |
| SAMSUN | 1% | 2% | 2% | 2% |
| ESKİŞEHİR | 2% | 2% | 2% | 2% |
| OTHER | 33% | 37% | 31% | 38% |
| **TOTAL** | **2037** | **2258** | **458** | **1268** |

Source: IQVIA OneKey Database, September 2022.

With a severe course and high mortality, this disease causes irreversible damage to the lungs. No pharmaceutical treatment is currently available to cure or stop the progression of the disease; however, antifibrotic drugs added to treatment options in recent years help slowing down disease progression. All the treatments for IPF that are approved in foreign countries are also approved and reimbursed in our country. In addition to these treatments, support therapies such as pulmonary rehabilitation and oxygen therapy are also provided within reimbursement coverage; however, pulmonary rehabilitation is not available in all centers. Besides, symptoms due to the disease and concomitant diseases are also treated. Lung transplantation is an important treatment option that prolongs life; however, it is recommended only in a limited patient group since it is a high-risk procedure. [10] [98] [99] [100] [101]

### 4.2 Pulmonary Arterial Hypertension (PAH)

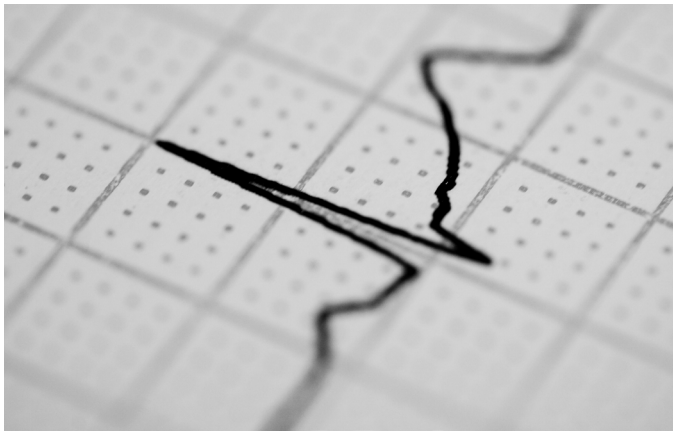
**Definition and Epidemiology of the Disease**

Pulmonary arterial hypertension is a chronic and progressive cardiopulmonary disease in which blood pressure is increased within the pulmonary arteries that carry the blood from the heart to the lungs. Some causes of PAH can be known (heritage, etc.) while the cause of some types is not understood (idiopathic). Pulmonary hypertension is a disease that may lead to cardiac failure and can be life threatening.

With a frequency of 15 to 50 individuals in a million, it is estimated to affect between 105,000 and 350,000 people worldwide. It is estimated that there are 3,500 to 4,000 patients with PAH in our country.

**Management of the Disease: Diagnosis and Treatment**

Symptoms of PAH may not manifest in the early stages and may appear in time as the disease progresses. Symptoms usually seen include shortness of breath, fatigue, and dizziness. The diagnostic process in patients with PAH may be prolonged since these symptoms are seen in other diseases as well and various tests and investigations are needed for definitive diagnosis. Tests such as chest X-ray, Echo, ECG, cardiac catheterization, pulmonary function tests, exercise tolerance testing, ventilation/perfusion scintigraphy, and pulmonary vasoreactivity are used in the diagnostic course. Since the disease has no differential signs, it may take approximately 2-3 years to establish the diagnosis. Like in many diseases, administration of available treatment options following early diagnosis may substantially limit disease progression in PAH. Thus, early diagnosis helps prolonged life expectancy and improved quality of life. Moreover, an excessive economic burden on public healthcare spending budget may be prevented by early diagnosis, given that annual treatment costs in these patients are lower compared to those generated during advanced stages of the disease.



Cardiologists are mostly involved in the diagnosis and follow-up of patients with PAH. Awareness for pulmonary hypertension diseases is usually high among specialists of this branch. Although prominent centers in the field of PAH exist in our country, these are limited in terms of number and distribution. It is apparent that infrastructure studies to improve services provided for patients living in peripheral areas, increased awareness and knowledge in the field of PAH for specialists available in these areas and developing a multidisciplinary approach in relevant centers are needed. Especially, it is essential to establish a communication network between centers known for PAH treatment and cardiologists treating patients with PAH in other regions, for patients who need to travel to another district to continue their treatment and follow-ups despite their inconvenient physical conditions.

There is no exact treatment for PAH; however, it is

known that the quality of life can be improved and survival can be prolonged by slowing down disease progression by using drugs that are being developed. Furthermore, pulmonary hypertension has 14 treatment options which position it as the disease with 3rd highest number of FDA-approved treatments among rare diseases. All the treatments approved in foreign countries are also available in our country. Some of these are already authorized. Drugs that are not yet approved can be obtained through Foreign Drugs List.

The course of the disease varies between individuals resulting in varying treatment needs. Different treatments are available that are administered by oral route, by inhalation or by infusion directly into vessels or under the skin. Patients to be administered these treatments may vary depending on disease severity.

Available medicines developed for PAH help recovery of the heart by loosening the constricted arteries in the lungs thereby facilitating blood flow. Available treatments are classified into 3 different groups based on the pathways they affect (endothelin, nitric oxide, prostacyclin). These treatments may be used alone or in combination with treatments that affect other pathways to control disease progression. Despite being approved by health authorities such as FDA and EMA, early sequential combination use of combination treatments is not reimbursed by SSI in our country. This may lead to problems in the treatment of some patients with advanced stage PAH.

Patients with no answer to available treatments but suitable for lung transplant are referred to relevant transplantation centers for treatment. In our country, three centers actively perform lung transplantation. These centers are presented in Table 8.

**Table 8: Centers Performing Lung Transplantation in Turkey**

| |
|---|
| **İstanbul Kartal Koşuyolu High Specialization Training and Research Hospital** |
| **Ankara City Hospital** |
| **Ege University Hospital** |

Patients may also use different treatments such as diuretics, oral anticoagulants, or digoxin in addition to treatments for PAH to control their symptoms. Apart from pharmaceutical treatments, oxygen therapy is administered for patients with PAH with low oxygen levels and pulmonary rehabilitation programs are implemented to help patients breathe more comfortably. Centers offering these programs that are quite beneficial for patients with PAH are needed to be developed and made widespread.

In addition to all these, providing nursing support for the education and follow-up of patients with PAH during the course of the treatment is also important and required. Currently nursing support is available for certain medicines; however, supports that can be provided to the patients and physicians by the private sector are considerably restricted by the regulatory agency. At this point, public-private collaborations should be considered to improve the treatment experience of patients and support improving healthcare service quality delivered to patients.[10] [102] [103]

### 4.3 Sickle Cell Anemia

**Definition and Epidemiology of the Disease**

Diseases occurring due to mutation of hemoglobin in the blood in hereditary genes leading to impaired function are called hemoglobinopathies in general. The prevalence of these diseases is considerably high in Mediterranean countries including Turkey. Besides, the high proportion of consanguineous marriage in Turkey is also an important factor that elevates the frequency of these hereditary diseases. Sickle cell anemia is one of the hemoglobinopathy diseases seen in our country.

According to a study on harboring thalassemia gene in Turkey, the prevalence of carrier individuals is found to be 2.1%. The frequency of sickle cell trait is reported to be 0.3-0.6% across Turkey with particularly higher prevalence in Adana, Mersin and Antakya compared to other cities. The number of homozygous patients with sickle cell anemia in Turkey is estimated to be nearly 2,500.

Sickle cell anemia is among diseases for which the Ministry of Health should be notified following birth. ICD-10 diagnostic codes are in general correctly entered into the system for highly recognized diseases such as sickle cell anemia; however, this data governed by the ministry is not easy to access for either statistical or scientific purposes.[10]

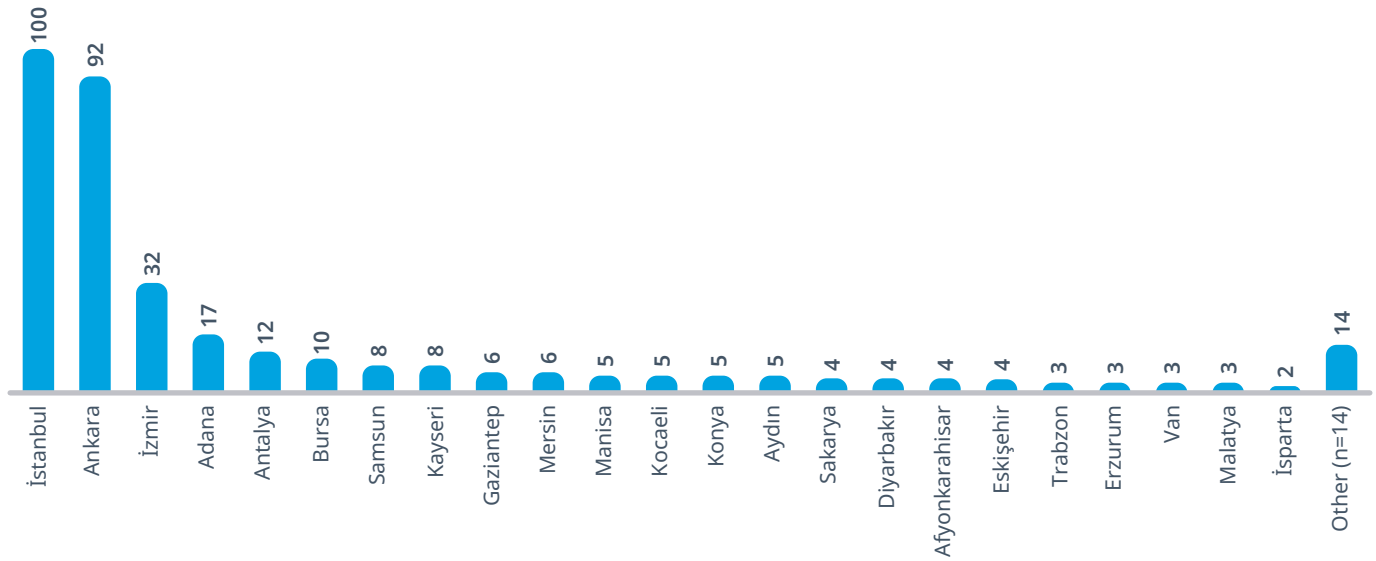
**Management of the Disease: Diagnosis and Treatment**

Similar to other hereditary hematologic diseases, sickle cell anemia is a preventable disease by appropriate measures. The strategies and practices in Turkey were established by the Regulation for Hereditary Blood Diseases recognized in 1984, and special centers were established for patient follow-up. In this regard, hereditary blood diseases are the only disease group to have dedicated regulations. It is seen that progress is achieved in preventing the spreading of diseases owing to successful past applications, while today regulations are not perfectly implemented due to some operational flaws.

In Turkey, testing is mandatory before marriage to reveal whether couples carry the identified diseases; however, follow-up deficits are seen after this in the identification and referral of carrier couples. Many follow-up centers for hematologic diseases that were established in the past either are closed or have lost functionality.

First signs of the disease begin to appear from 6th month in infants with sickle cell anemia. Before this, diagnosis of a baby in the absence of signs may only be established if parents are known to be carriers. Besides prevalence, awareness and knowledge of physicians also vary by region. Pediatricians or family practitioners trained or experienced in the Mediterranean or Southeastern Anatolia regions have a higher level of awareness compared to those in other regions. Therefore, they can refer patients to a pediatric hematologist without delay. A total of 355 pediatric hematology and oncology specialists are available in tertiary care institutions across 37 cities in Turkey (Figure 9).

**Figure 9: Number of Pediatric Hematology and Oncology Specialists in Tertiary Care Institutions by Cities**




Source: IQVIA OneKey Database, September 2022.

The pharmaceutical therapy in sickle cell anemia targets to control symptoms. In addition to these medicines, therapies such as the treatment of pain attacks, hydroxy urea treatment and blood transfusion are also administered. Stem cell transplantation as the curative treatment option can be performed only in limited number of centers to a small group of patients. SSI covers the costs of bone marrow transplantation solely for patients meeting the conditions specified in SUT; however, these strict conditions substantially narrow suitable patient pool and many patients are left out of reimbursement coverage.

Genetic hematologic diseases are known to lead to a significant burden on patients, families, the community and healthcare system. Currently, implementation of present regulations supported by policies and measures to prevent occurrence of respective diseases is required.[10] [68] [104] [105] [106]

Greece is a country where the prevalence of sickle cell anemia is higher than other countries. From 1970 onwards, studies to prevent sickle cell anemia have been carried out in Greece to reduce the burden of the disease on the community and healthcare system. In addition to large screening studies within this framework, increased awareness through mainstream media, schools and similar institutions as well as gynecology clinics played an important role in efforts to prevent the disease. Thus, annual number of new sickle cell anemia cases was reduced to approximately one tenth of predicted.[107]

## 4.4 Duchenne Muscular Dystrophy (DMD)

**Definition and Epidemiology of the Disease**

Duchenne muscular dystrophy is a progressive and fatal inherited neuromuscular disease caused by genetic mutations and develops with the degeneration of skeletal muscles, smooth muscles and cardiac muscle. Since the gene that causes the disease is inherited by recessive heredity on X chromosome, DMD mostly affects male individuals while the high consanguineous marriage rate does not directly affect the prevalence of DMD.[10] [108]

International studies indicate the prevalence of DMD in the US and UK as 15.9 and 19.5, respectively, in every 100,000 male births. No national patient registry study or epidemiological studies in this field are available in Turkey but the prevalence is thought to be parallel that in Europe. The incidence of DMD is reported to be 1/3000 to 1/5000 (mean 1/4000) live male births. Carrier women typically show no symptoms but a small percentage exhibit lighter forms of the disease. It is thought that there are approximately 15,000 patients with DMD, and 140-150 new cases are added each year.[1]

**Management of the Disease: Diagnosis and Treatment**

The disease typically appears between 3 to 5 years of age with motor developmental delay, proximal muscular weakness and difficulty in standing. Some patients can be detected before the symptoms appear, thanks to the creatine kinase elevation detected incidentally in the blood test. DMD is diagnosed by demonstration of the gene mutation using molecular genetic diagnostics. Genetic testing required for diagnosis is easily available in our country. In certain cases where genetic tests fail to confirm the diagnosis, the definitive diagnosis can be established by testing the presence of the protein dystrophin in muscle biopsy samples. Based on disease progression, children with DMD usually become dependent on wheelchair as of 9 to 11 years of age and begin to have difficulty in breathing. Patients with DMD are known to live until 20-30 years of age due to frequently seen cardiac problems and respiratory failure; however, as a result of improvements in standards of treatment and care in recent years in this field, survival rates are continuously increasing.[1]

The effectiveness of DMD treatments that are

developed may be enhanced by early diagnosis that allow starting treatment before the symptoms appear. In addition, identification and prevention of the disease before it manifests are as important as early diagnosis. Women at risk for being a carrier in the patient's family should be referred to genetic counselling to identify their carrier status before giving birth. PGD and IVF applications that help carrier individuals have healthy babies in more than 50 diseases including DMD have been included in reimbursement coverage by the SSI as of August 2021. This progress represented an important step in preventing the occurrence of genetically inherited rare diseases.

Among ICD-10 diagnostic codes, there is one diagnostic code that encompass all muscular dystrophy types; however, the absence of a diagnostic code dedicated to DMD may bring problems in the diagnostic process. Irrelevant ICD-10 diagnostic codes not reflecting the patient's current situation can be entered into the system particularly in certain conditions that require supportive treatment. At this point, availability of diagnostic codes specific to rare diseases and utilized correctly in practice is a factor that ensures collection of accurate data as well as facilitating the follow-up of diagnostic and treatment course in patients.[10]

The patients may lose time visiting other specialties such as general pediatricians, orthopedists, child psychiatrists and family practitioners; however, it can be concluded that physicians in our country have a high level of awareness in general. In the management of DMD, a comprehensive healthcare service needs to be offered from the time of diagnosis that includes functional assessment, rehabilitation and other supportive services in addition to follow-up by a pediatric neurologist. These services have an important role in improving the quality of life in patients with DMD. Within this context, the treatment and follow-up of patients with DMD are carried out in centers and outpatient clinics in our country specialized in neuromuscular disorders. In neuromuscular disease centers, patient access to comprehensive treatment and complementary care services they need on a regular basis is facilitated through a multidisciplinary approach that includes departments such as pediatric neurology, pulmonology, cardiology, orthopedics, and physical medicine and rehabilitation. However, active centers and the healthcare staff working in these centers are inadequate in number to meet the needs. The respective centers are analyzed in more detail in the sections of this report addressing healthcare infrastructure.[10] [83]

No definitive treatment is available for DMD. As a standard, the patients receive treatment with glucocorticoids which is supported with services such as cardiac care or physical therapy. Nonetheless, important progresses have been made in recent years regarding newly developed treatments for DMD. Approved by FDA and EMA, respectively, two drugs (eteplirsen, ataluren) developed using genetic approach and slowing down disease progression can be obtained in our country within the scope of Foreign Drugs List. These costly and mutation-specific drugs demonstrate efficacy only in a certain group of patients with DMD. No treatment is yet available for all patients with DMD to target all the organs and respiratory and cardiac muscles. On the other hand, some patients require regular use of respirators; the cost for these devices is partly covered by the SSI while the rest is defrayed by patients.[109]

It is essential to help contribution of the children with DMD into social life safely by providing health and education services with small adjustments that can meet the needs of children with the disease during different periods. At the same time, collaborative action of the family, physician, the instructor and social service authorities is also of great importance in the entire process. In addition to all of these, patients from different regions of the country are to be provided with all the services planned within a certain standard.[10]

Like in other rare diseases, patients under regular treatment and follow-up owing to identification of the disease in childhood leave pediatric subspecialist and switch to the supervision of a specialist in adults by the time they begin entering adulthood. In addition to the close ties established in years between the patient and the physician, the need to avoid interruption of multidisciplinary treatment and follow-ups makes this switch more delicate. A detailed model was materialized in Ireland for this situation that addresses switching from pediatric healthcare services to adulthood services in the framework of the National Clinical Programme for Rare Diseases.[110]

### 4.5 Cystic Fibrosis (CF)

**Definition and Epidemiology of the Disease**

Cystic fibrosis is a hereditary disease that affects mucous and salivary glands and has serious effects on many different systems and organs in the body, in particular respiratory and digestive systems. Since it is inherited by recessive genes, it may occur in the children of carrier couples.

The prevalence of cystic fibrosis in our country is found to be 1 in 3000 births in a limited number of studies. Clinical and demographic characteristics of patients that are registered in the system can be monitored through the "National Cystic Fibrosis Registry" in Turkey. There are 2002 actively followed-up patients with CF in various centers in Turkey. [111] [112] [113]

**Management of the Disease: Diagnosis and Treatment**

Cystic fibrosis has been part of the newborn screening program in our country since 2015. Presence of the disease can be diagnosed by a blood test from heel lance in the newborn; in some cases, however, diagnosis cannot be established until advanced stages of the disease. Cystic fibrosis is typically diagnosed before the age of two, based on sweat test and genetic testing.

Symptoms that occur due to cystic fibrosis may vary between individuals. In patients with cystic fibrosis, the mucous layer that becomes thick and sticky in the lungs not only prevents comfortable breathing but also increases the risk of developing pulmonary infections. Because it affects the pancreas, hampering the release of enzymes required for digestion, patients may exhibit nutritional disorders or other digestive problems. Additionally, problems such as fatigue, low blood pressure, cardiac disorders, diabetes and osteoporosis may occur.

Cystic fibrosis may arise due to various mutations in the respective chromosome. Since a high variety of mutations is seen in our country, in some cases the mutation cannot be detected using available screening tests, making genetic testing and diagnostic processes more difficult for the patient.

Currently no exact treatment of cystic fibrosis is available. Treatments that are developed target to improve lifespan and quality of life. In addition, patients with cystic fibrosis require supportive treatments including pulmonary rehabilitation, physical therapy and oxygen therapy. Besides the medicines and supportive treatments provided, special education, nutrition counseling, and psychological and social support play crucial roles. Lung transplantation may be required in advanced stages of the disease due to pulmonary complications in patients with cystic fibrosis.

Flaws have been observed in the diagnosis and follow-up processes in patients with cystic fibrosis, particularly for diseases identified during the neonatal

screening program. Because cystic fibrosis is a serious disease leading to irreversible harms to the body, it is essential to complete relevant diagnostic tests as rapidly as possible and refer the patient for appropriate preventive treatment.[10]

### 4.6 Mucopolysaccharidosis (MPS)

**Definition and Epidemiology of the Disease**

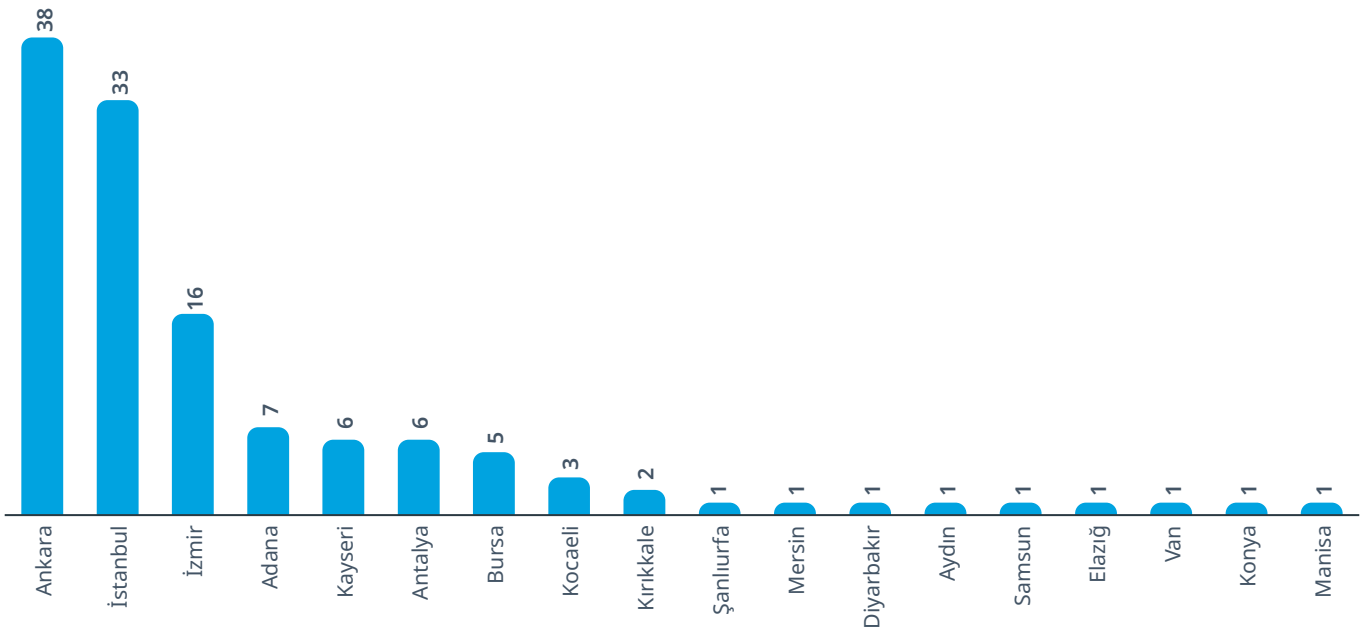
Mucopolysaccharidosis is a hereditary and rare disease in the class of lysosomal storage diseases that occur due to no or insufficient production of certain enzymes in the body. Excessive accumulation of complex carbohydrates in the body due to enzyme deficiency leads to permanent damage in various organs and systems and affects the physical and mental development of the patient. There are 7 known types of MPS. The symptoms and the course and severity observed in patients may vary by the type of MPS as well as between patients with the same type of MPS.

The prevalence of the disease also varies according to the type of MPS; however, the overall prevalence of MPS worldwide is reported to be 1 in 25,000 births. The exact number of patients with MPS in Turkey is unknown; however, it is thought to be higher than the global average due to high rates of consanguineous marriage in our country.[114]

**Management of the Disease: Diagnosis and Treatment**

Symptoms such as multiple organ involvement, physical abnormalities and joint problems are usually seen in patients with MPS. In general, the awareness of pediatricians in metabolic diseases is high in our country; pediatricians refer suspected patients to pediatric metabolism specialists. In most cases, symptoms begin to appear around 1-2 years of age. The deficient enzyme should be demonstrated by laboratory tests, or the respective gene disorder should be detected using genetic testing to diagnose the disease. Tests used to diagnose MPS are available in most regions, particularly in large cities while contract laboratories are available for the delivery of blood samples in smaller cities without such opportunities. Despite advanced laboratory possibilities, patients with MPS are having problems accessing health services in many regions due to the lack of pediatric metabolism experts. A total of 125 pediatric metabolism specialists are available in tertiary care institutions across 18 cities in Turkey (Figure 10).

**Figure 10: Number of Pediatric Metabolism Specialists in Tertiary Care Institutions by Cities**




Source: IQVIA OneKey Database, September 2022.

It is possible to prevent certain irreversible damages in patients through early diagnosis of the disease. MPS is not currently included in the neonatal screening program; however, pilot neonatal screening programs have been launched in selected centers in collaboration with the Ministry of Health. Moreover, in the context of studies to prevent the disease, preimplantation and in vitro fertilization services are reimbursed to help families that have children with MPS give birth to healthy babies.

Pediatric metabolism doctors are involved in the management of MPS while various experts can work together to control the symptoms due to the disease. No treatment is available so far to eliminate MPS; however, the goal of available treatments is to prolong life by preventing disease symptoms and organ damage. Various treatment options are available such as enzyme replacement therapy and symptomatic treatments for different subtypes of the disease. In addition, certain gene studies are continued around the world for some types of MPS.

A problem in the management of rare metabolic diseases in Turkey is the limited access by patients to certain treatments. In particular, it was recently noted that patients in our country could not access certain treatments approved by the health authorities in the EU and US. However, clinical studies underway around the world can as well be conducted in certain centers that have advanced options in this field, thereby providing innovative drugs and costless treatment opportunities.

Apart from pharmaceutical treatment, services such as physical therapy, special education and psychological support are provided in the scope of reimbursement; however, the level of knowledge and awareness regarding rare diseases is needed to be enhanced in professionals in this field.[10]

### 4.7 Niemann-Pick Disease (NPD)

**Definition and Epidemiology of the Disease**

Similar to MPS, NPD is also a hereditary and rare metabolic disease among approximately 50 lysosomal storage diseases identified so far. There are 4 types of NPD, namely Type A (NPD-A), B (NPD-B), C (NPD-C) and D (NPD-D). The disease is caused by the congenital deficiency of certain proteins and enzymes in the body. It results in the accumulation of lipids in various organs, and the age of onset, organs affected by the disease, and the life expectancy vary according to the subtypes.[115] [116] [117]

NPD Type A and B in total are observed in 1/167,000 to 1/250,000 individuals in Europe. NPD-A is more frequent among Ashkenazi Jews and the prevalence in this community is estimated to be 1/33,000. Being the most frequently seen NPD type that may occur at varying ages, the worldwide prevalence of NPD-C at birth is estimated to be 1/45,000 to 1/268,000.[116]

The prevalence of NPD is not known accurately in Turkey; however, it may be considered to be higher than the global average due to high rates of consanguineous marriage in our country.

**Management of the Disease: Diagnosis and Treatment**

The signs of NPD may differ based on the subtype. NPD-A signs appear within several months of birth and it is the most severe among all NPD types. It leads to severe brain damage in addition to enlarged liver and spleen. Patients with NPD-A typically live for a maximum of three years.[117] [118]

Like NPD-A, NPD-B is also due to the congenital deficiency of the enzyme sphingomyelinase; however, NPD-B generally appears before the age of ten and follows a more moderate course compared to Type A. This subtype not predominantly affecting the brain usually leads to interstitial lung disease and enlargement of the liver and the spleen. The patients can survive until late childhood to early adulthood;

however, they have a substantially low quality of life due to growing complications, in particular worsening pulmonary functions.[116] [117] [118]

Resulting from the congenital deficiency of NPC1 or NPC2 proteins, Type C typically appears during childhood but may occur at any time from infancy to adulthood. With varying initial signs depending on the age of onset, the disease which leads to severe brain damage in time, results in walking and swallowing difficulties and progressive loss of vision and hearing. Depending on the age of onset and the severity of symptoms, the life expectancy in patients ranges from several months to approximately 30 years. [116] [118] [119]

Despite the high level of awareness among pediatricians in Turkey regarding metabolic diseases, signs of NPD may be confused with those of many other diseases, particularly with other lysosomal storage diseases, notably Gaucher.[10]

Neither of the subtypes of NPD have a treatment with certain innovative treatments still being developed. The available treatments only suppress symptoms to improve the quality of life in patients or to slow down the progress of some symptoms. Timely and accurate diagnosis of the disease may help improving the quality of life and help delaying the neurological symptoms in some patients with NPD-C.[120]

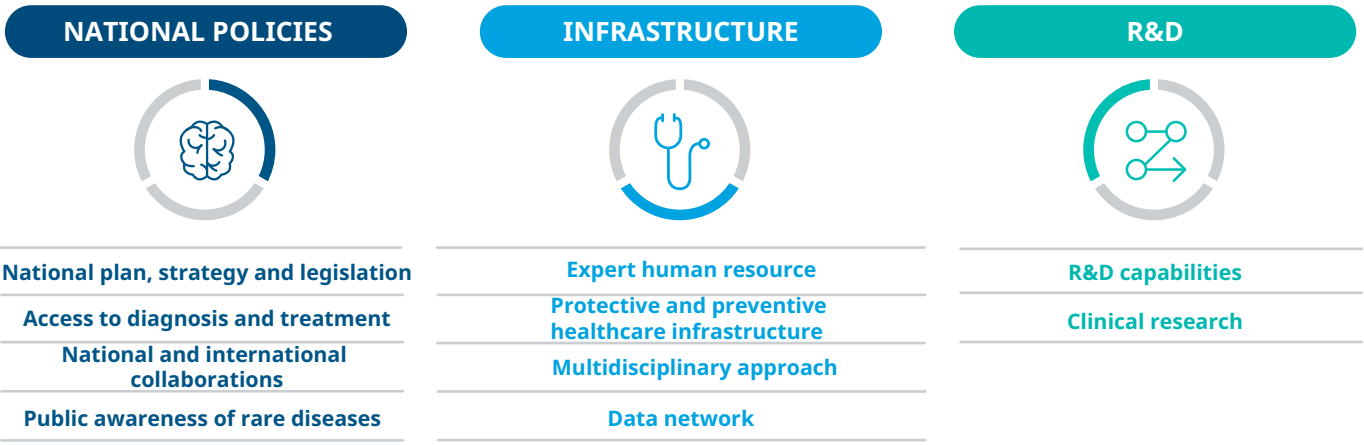
The International Niemann-Pick Disease Alliance (INPDA), an international solidarity network of patients and patient relatives, has prepared informative materials for healthcare professionals in collaboration with the private sector. In addition to the basic information regarding the disease, these materials also contain simple but detailed information on what various signs of the disease might be, how patients and their relatives can verbalize these signs, diagnostic methods, and how individuals with suspected disease should be referred to specialists.[120]

Implementation of a similar practice in Turkey at the level of specialties most visited by respective patients will play a supportive role in faster differential diagnosis.

# 5. RECOMMENDATIONS

In line with the topics addressed in the context of the report, 10 improvement areas were specified by IQVIA. These areas were grouped under national policies, infrastructure and R&D (Figure 11).

**Figure 11: Improvement Areas**




Four improvement areas were identified associated with rare diseases under the heading of National Policies: national plan, strategy and legislation, access to diagnosis and treatment, national and international collaborations, and public awareness of rare diseases.

Under the Infrastructure heading, 4 areas of improvement were identified as expert human resource, protective and preventive healthcare infrastructure, multidisciplinary approach, and data network.

Lastly, improvement areas were identified as R&D capabilities and clinical research under the R&D heading.

Various improvement opportunities are found in all these areas in our country. At the time this report was prepared, a detailed list of recommendations was formed for these opportunities by IQVIA. The recommendations in this detailed list later were gathered under 19 divergent topics.

## 5.1 National policies

Successful examples worldwide have demonstrated the importance of developing national policies in the field of rare diseases and sustainably executing and developing these in the long term in the effective management of rare diseases. In our country, although various studies have been conducted to date on rare diseases, these were not continued and remained individual or disorganized attempts. There is a need to develop and implement national policies in the field of rare diseases for effective nationwide management of this diseases.

### National plan, strategy and legislation

The initial and most basic step to be taken for effective nationwide management of rare diseases is to generate and actualize a long-term national plan and strategy that involves all stakeholders and carry out relevant legislative arrangements.

***Recommendation N1: Determination and follow-up of implementation of national plans, policies and strategies specific to rare diseases under the leadership of a joint commission***

Generating a national plan specific to rare diseases in Turkey is an important need to ensure a continuous access to high-quality health and care services, primarily the diagnosis and treatment of patients with rare diseases. A strategy document and action plan for rare diseases was prepared by the Ministry of Health

at the time this report was written, and published in November 2022. As for the examples in Europe, it is observed that encouraged by the European Commission, many countries and notably France have created a plan for rare diseases in line with their own healthcare system and needs.

Management of rare diseases requires duties and responsibilities by a range of stakeholders. Accordingly, generation of a Rare Diseases Commission under leadership of the Ministry of Health involving all significant stakeholders both public or nonpublic will help adoption of these plans and policies by all the stakeholders and establishing the coordination between various institutions. Generation of the plan and strategy needed on rare diseases and implementation of the planned actions will be possible under the leadership of the respective commission. As important as generating the national plan is the adoption and implementation of identified actions by the relevant institutions and formation of a control mechanism to ensure follow-up of this process. In line with this purpose, inclusion of rare diseases in the Development Plan and high level policy documents, primarily strategy documents of the relevant ministries will be a significant step in receiving support and contribution of all stakeholders.

***Recommendation N2: Determining the definition of orphan drug in compliance with the international standards and forming the relevant legislation***

The development process of medicines used in the treatment of rare disease can be more difficult, longer and more costly. Besides, many countries have formed orphan drug legislations that specify the definition of orphan drug and form a ground to provide various incentives for the respective medicines with little sales potential due to the small number of patients, to encourage their development and delivery. Thus, patients with rare diseases could acquire the right to access to treatments and medicines as easily as those with more common diseases.

There is a need for an orphan drug legislation in Turkey. The obstacles in the delivery of these treatments to patients may considerably be eliminated by certain incentives offered like in example countries; however, a definition of orphan drug should be made first to determine how to consider a medical product as an orphan drug.

*Many countries have formed orphan drug legislations that specify the definition of orphan drug and form a ground to provide various incentives.*

Beside legislations for rare diseases, it is important to adjust other relevant regulations accordingly. For instance, the regulations in force in our country regarding intellectual property may be reviewed in the context of orphan drugs and these drugs may be granted privileges involving additional time like in Europe.

**Access to diagnosis and treatment**

Various studies are being carried out in our country to facilitate the access to diagnosis and treatment for individuals with rare diseases; however, additional steps are needed across the nation to increase access.

***Recommendation N3: Acceleration of authorization process for rare disease treatments***

It is very important to initiate appropriate treatment as soon as possible in patients with rare diseases following the diagnosis. Delays in delivering medicines used in the treatment of these diseases to market make it more difficult for the patients to access respective treatments. Expediting the regulatory process for medicines used in the treatment of rare diseases may shorten the time medicines are delivered to the market thereby avoiding patient and physician victimizations. Adjustments to shorten authorization approval time specified for these products include exemption of certain treatments from some processes approved by international health authorities, high priority during regulatory process, and conditional approval for these treatments.

***Recommendation N4: Improvement of pricing and reimbursement processes for rare disease treatments***

Medication prices are lower in our country compared to many countries due to practices such as reference price system pertinent to import medicines, fixed exchange rate used in medicine pricing, and mandatory institutional discount. Allowing patients to access many treatments in the extent of reimbursement, these practices may lead to access problems for some treatments used in rare diseases with high average costs per patient. In some cases, pharmaceutical companies search for different access channels while some treatments are inaccessible. As a result, patients in Turkey have more delayed and limited access to orphan drugs approved by the EMA compared to patients in EU countries, as stated in Section 3 of the report. Developing a range of practices and incentives to offer solutions to accessing problems due to pricing processes will help enhanced access to relevant therapies. For instance, the exchange rate factor to be used in the pricing of orphan drugs may be set to 100% instead of 60%.

On the other hand, budget impact-oriented approach in reimbursement processes may not be completely appropriate for rare diseases for which there is unmet medical need. A reliable budget impact analysis may not be possible most of the time for these diseases with limited epidemiologic studies and very small number of patients. Hence, the need to assess these treatments through a perspective different than the traditional approach is obvious. For certain treatments difficult to access using standard methods, employing health outcomes (or value)-based alternative reimbursement models or health technology assessment methods like multi-criteria decision-making may be considered. Releasing guidelines that specify agreement frameworks may be considered to implement and reproduce such agreements.

***Recommendation N5: Facilitating access to tests and medical devices used in the diagnosis and treatment of rare diseases***

Ensuring easy and continuous access to genetic tests and medical devices used in the diagnosis and treatment of rare diseases is very important in the effective management of rare diseases. Patients can have expedited access to diagnosis by increasing the laboratory capacity offered by the public and improving service quality. In addition, increased access to novel diagnostic technologies that are developed and utilized in the world (e.g., NGS) also in our country will have considerable contributions both to the patients and physicians in early diagnosis. Moreover, in addition to the test and laboratory services provided by the public, collaborations with the private sector may be considered to ensure that more patients access these services faster, and making necessary adjustments to actualize these incentives and forming favorable political grounds may be promoted.

Additionally, many individuals with rare diseases use at least one medical device to survive. High contribution costs paid for such equipment brings a considerable financial burden on patients and their families. Lowering the contributions for these medical devices that patients have to use regularly will play an important role in alleviating this burden.

**National and international collaborations**

Regular sharing of cumulative knowledge and collaborations to produce innovative and sustainable solutions have great contributions in rare diseases. Turkey has various opportunities to take steps on these issues at national scale.

***Recommendation N6: Active involvement of Turkey in the prominent organizations in the world on rare diseases***

Accumulation of knowledge and ensuring accurate information sharing are quite important in the field of rare diseases. Representation and active contribution of Turkey in organizations working on the field of rare diseases in Europe and in the world will be an important acquisition. Participation of our country not only in organizations on rare diseases but also in international formations on important concepts for rare diseases such as value-based healthcare systems and healthcare technology assessment will provide considerable value.

***Recommendation N7: Forming the basis for putting into practice and extending the scope of public-private partnerships in the field of rare diseases***

In addition to public services in rare diseases, private support is also important to provide benefits in the effective management of rare diseases. By virtue of

public and private collaboration and through supporting start-up ecosystem, projects can be implemented to support the treatment course of patients by providing added value and making their lives easier.

**Public awareness of rare diseases**

The common thread for most rare disease patients and their relatives includes lack of easy access to reliable information regarding the disease and restricted contribution into daily life due to various causes. The awareness to be generated in the community is thought to contribute both to the patients and their relatives and to effective management of these diseases.

***Recommendation N8: Taking actions aimed at raising public awareness and knowledge of rare diseases***

Individuals with a rare disease may feel isolated and lonely due to their disease. Lack of sufficient awareness in the society makes it more difficult for the patients and their relatives. The society can be made conscious on rare diseases and informed correctly through activities arranged by physician and patient associations, public institutions and the private sector to increase public awareness on rare diseases.

In addition, because there are numerous rare diseases each of which is seen in a limited number of patients, accessing reliable information on rare diseases can be more difficult compared to other treatment areas. Forming an online platform that ensures rapid access to accurate information by people with rare diseases and their relatives may support patients during the course of treatment and follow-up.

Additionally, some of the inherited diseases in Turkey have been included in premarital and neonatal screening programs. Couples found to be at risk may benefit from genetic counseling provided free of charge by the government and in vitro fertilization services; however, the awareness on all these options is very low. efforts to raise awareness across the community will help to increase consciousness regarding these options and to eradicate prejudices in certain fractions of the society.

***Recommendation N9: Empowering patient associations and improving communication with international organizations***

Patient associations are the stakeholders with the highest direct interaction with the patients and their relatives. Furthermore, they are among the most effective formations to ensure representation of the patients and their communication with other stakeholders in the ecosystem, as part of the opportunities from this interaction. Therefore, patient associations should be supported and empowered, their contribution to international federations should be encouraged and they should be included in relevant decision-making processes in healthcare services as a stakeholder in the healthcare system.

*Lack of sufficient awareness in the society makes it more difficult for the patients and their relatives.*

## 5.2 Infrastructure

All the stakeholders involved in the diagnosis and treatment course of rare diseases do their best; however, a range of improvement areas are found in terms of healthcare infrastructure and the capacity of healthcare services for effective management of these diseases.

**Expert human resource**

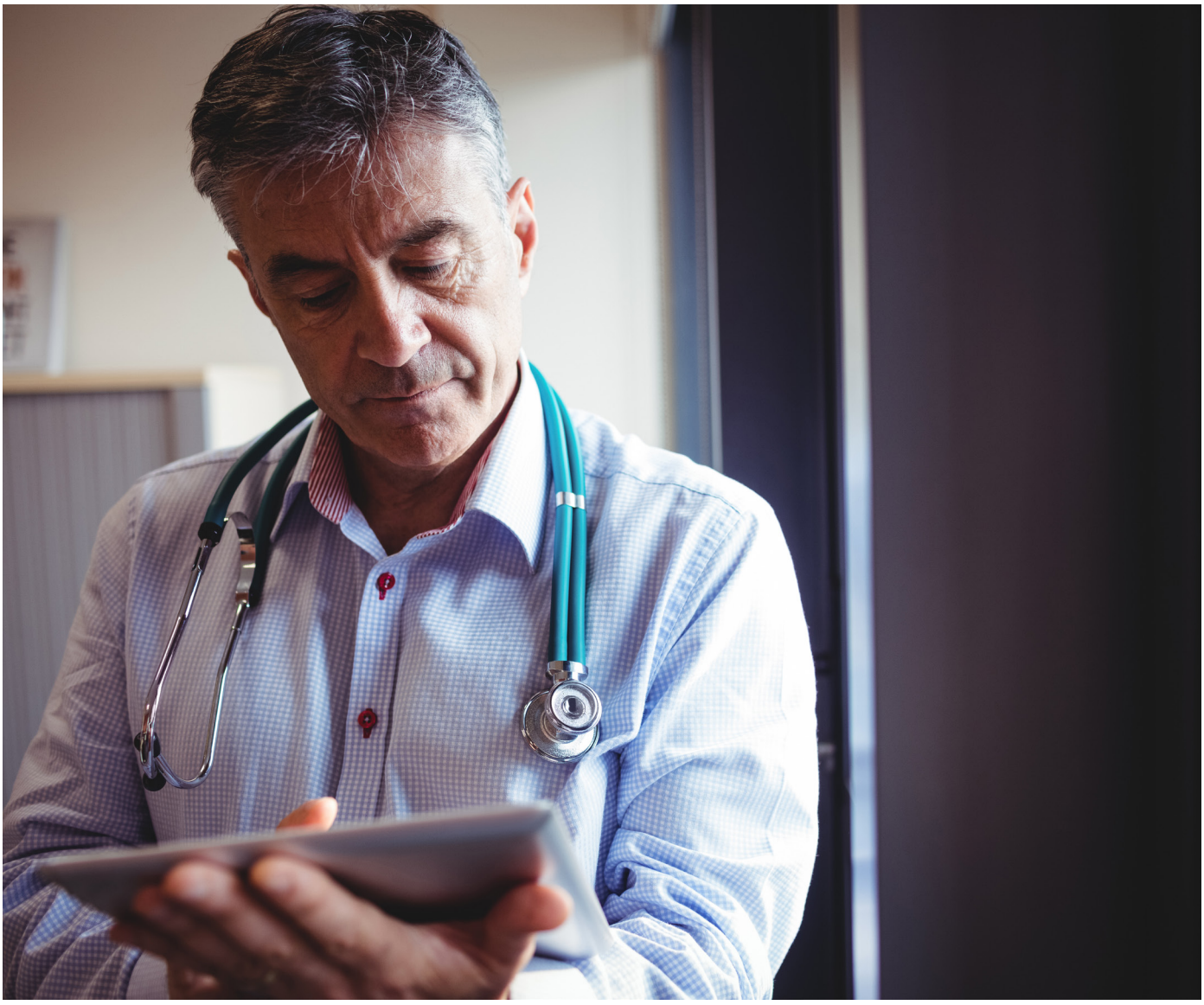
Expert human resource plays an important role in each step of correct diagnosis of the patients and the conduct of their treatment and care. There are improvement opportunities for increasing and most properly managing this capacity that is limited in our country.

***Recommendation I1: Increasing access to specialist physicians taking part in the diagnosis and treatment of rare diseases***

The diagnosis and treatment of rare diseases in Turkey is performed typically in tertiary healthcare institutions by physicians who are experts in their fields. The inadequate number of physicians in the relevant specialties and condensation of these in certain geographic regions are among the most important

problems that make it difficult for the patients to timely and continuously access the healthcare services. Efforts by the Ministry of Health to identify the number and distribution of specialist physicians in Turkey taking part in the management of rare diseases and to improve the current situation will be an important step in improving patient access. In line with this, quota plannings for missing specialties may be reviewed.

In addition, increasing the number of physicians may not always be a sufficient solution. Availability of respective specialists – who are already few in number – predominantly in big cities is a significant obstacle in patient access to healthcare services for those living far from central districts. Patients in some regions have to make a travel to receive diagnosis or to continue treatment and follow-up, yet most patients do not have this opportunity due to physical disability or financial restrictions. Therefore, it is important to increase the number of respective specialists as well as widening their geographic distribution. In cities without resident specialists, remote healthcare services may be provided by utilizing communication technologies such as telemedicine between the patients and specialists. In addition, a system may be developed to support participation of family practitioners working in these regions in the follow-up of individuals with rare diseases, forming a bridge between the patient and the specialist following up the patient. In cases where patients must physically see the specialist physician, support from the government for the travel expenses of patients and patient relatives in poor financial condition will contribute to solve the problem of accessing specialists.



***Recommendation I2: Improving access to medical support services staff and social services staff to take part in the management of rare diseases who have been trained on rare diseases***

In addition to pharmaceutical treatments in rare diseases, special support treatments are needed depending on disease characteristics and course. An integral treatment should be ensured for patient needs through supportive services such as home care, special nutrition, psychotherapy, and physical therapy and rehabilitation. These services are provided by various departments in our country including the Ministry of Health and the Ministry of Family and Social Services. A coordination center may be formed allowing collaboration of different departments to improve the service quality provided, to ensure standardization, and to help individuals with rare diseases easily benefit from services they need. At present, the number of personnel taking part in support services offered to people with rare diseases and the service capacity may be determined, programs designed, and a needs analysis performed to create human resource trained in the field of rare diseases. Accordingly, organizing training programs to increase the number of resources that primarily include nurses, physical therapists, social service experts, special training teachers, psychologists and child development specialists, and giving information to existing staff on rare diseases will help improvement in accessing support services.

***Recommendation I3: Raising awareness of rare diseases of physicians and other healthcare personnel working at the primary health care institutions***

Timely intervention to the patient by early diagnosis is very important in rare diseases. Both patients and their families have an important role in this. Since these diseases are very rare and the signs they present may be confused with other diseases, the diagnosis of rare diseases is a considerably long and challenging process even under the supervision of a specialist doctor.

Majority of rare diseases are typically observed after birth or during childhood due to genetic inheritance. It is important to refer the patients and their relatives to relevant branches by the family practitioner as soon as possible in case a deviation or a suspicious sign is

captured within routine development phases of children. Accordingly, high level of awareness on rare diseases by family doctors and other healthcare personnel providing primary care will help shortening the time spent in patient travel and early diagnosis. Besides family doctors, awareness of other primary care physicians on rare diseases and their capability to properly refer patients at the time of diagnosis is also important.

Primary care institutions can have a role not only in the diagnosis step but in the follow-up process of patients. In small cities lacking relevant specialists involved in the management of rare diseases, family practitioners can provide support to patients in maintaining current treatment, management of possible complications, regular controls and follow-up of their health status, and providing training and appropriate guidance.

To enhance awareness in this field, physicians and other personnel working in primary care institutions should be provided with regular up-to-date trainings on rare diseases. Apart from this, prospective doctors can be informed on rare diseases starting from the college years and can graduate with a certain level of awareness with the inclusion of up-to-date information on rare diseases in the medical education curriculum.

***Recommendation I4: Establishing and strengthening national and international reference and communication networks in the field of rare diseases***

Because for each disease there is limited number of patients, the exchange of cumulative knowledge gained so far on rare diseases with other physicians and centers is quite valuable. Communication networks to be established on the ground of specialty will enable closer contact between specialists taking part in the management of rare diseases in our country and facilitate this communication and collaboration. It is also necessary to make these networks widely used and enable their sustainability. Therefore, creating an incentive mechanism may be considered to enhance collaboration between specialists. Besides, introducing Orphanet which provides content on rare diseases both for specialists and the patients and making it widely used will promote enhancement and communication of cumulative knowledge on rare diseases. Benefits of active utilization of Orphanet may be explained to specialist physicians working in this field while informative trainings may be organized and mechanisms that encourage utilization may be developed.

At international level, formations in which Turkey can directly or indirectly participate may be identified and representation of our country in these platforms should be ensured. Although our country cannot directly participate in the European Reference Networks, for instance, conduction of joint projects may be considered through collaborative work with certain centers. Enabling transfer of experience and information through collaborations with leading reference centers in other countries will contribute to providing a higher quality healthcare service to the patients in our country.

**Protective and preventive healthcare infrastructure**

A developed healthcare infrastructure is required to effectively conduct prevention, diagnosis and treatment of rare diseases. Although healthcare services are accessible throughout the country, improvement opportunities are found in certain points.

***Recommendation I5: Expansion of diseases covered by screening program and improvement of consultancy services provided to patients identified to be in the risk group as a result of screening***

It is important to prevent births with rare diseases by utilization of premarital genetic tests and preimplantation genetic diagnosis methods. Particularly high frequency of consanguineous marriage in our country compared to others further increases the significance of these screenings. In the extent of preventive and protective healthcare services, premarital screening programs should be broadened with the inclusion of different diseases and should be generalized across the country. For this purpose, patients eligible for screening programs can be evaluated under leadership of a committee, and prioritization and significance studies may be performed based on certain criteria.

*Because for each disease there is limited number of patients, the exchange of cumulative knowledge gained so far on rare diseases with other physicians and centers is valuable.*

It is essential to systematically follow up on individuals shown to be in the risk group at screening and provide counselling based on their needs. Regular follow-up of at-risk families may be enabled through family practitioners, and a central system may be developed to allow accessing other at-risk individuals in the family tree by keeping record of all individuals in the risk group. Besides, studies should also be continued to expand the diseases having reimbursement support for treatments that help families have healthy babies.

Preventing the birth of babies with rare diseases is among the first measures to be taken; however, utilization of neonatal screening programs should be made widespread for conditions not recognized or avoided before birth. Multidimensional factors such as availability of treatment for that disease, diagnosis method and prevalence may be analyzed to extend the present disease panel in Turkey and the patients with priority can be identified accordingly.

**Multidisciplinary approach**

Multidisciplinary approach plays an important role in effective management of rare diseases. Application of this approach to all health institutions across the country is of great importance for early diagnosis and treatment success in these diseases.

Recommendation I6: Creating centers of expertise where a multidisciplinary approach specific to rare diseases is adopted and setting accreditation criteria for these centers and ensuring control thereof

Many rare diseases require coordinative work of different specialties in the course of diagnosis and treatment. For certain rare disease fields, establishment of specialty centers aiming to offer integral solutions for various needs of individuals will be beneficial. Our country already harbors centers established for certain diseases. The criteria that qualify the relevant center as a specialty center should be determined and a control mechanism should be formed to standardize the services provided in the available centers and to improve the quality of these services. In addition, promotions and incentives may be implemented to encourage units to become specialty centers and physicians to work in these centers.

**Data network**

Keeping the record of diseases each being very rare and regular monitoring of these records make a great contribution to effective management of these diseases throughout the country. There are numerous enterprises in this area in the world while accessing data regarding rare diseases is not always possible.

***Recommendation I7: Keeping regular records of and following up on patients who are diagnosed with a rare disease and individuals who are at risk***

Achieving robust data is considerably challenging in rare diseases; however, both public and the private sector need national data obtained in this field in terms of planning healthcare services and to deliver appropriate treatments to patients by demonstration of treatment needs, respectively. Therefore, studies should be performed to form patient registry systems for rare diseases and to keep these up to date. Moreover, decision support systems may be formed by using advanced methods including artificial intelligence in the analysis of comprehensive data and access to diagnosis may be accelerated.

*Keeping the record of diseases each being very rare and regular monitoring of these records make a great contribution to effective management of these diseases throughout the country.*

In addition, the data gathered in the present system of the Ministry of Health may be made accessible and usable for scientific studies in the field of rare diseases; however, ICD-10 diagnostic codes currently used in the system are not adequate for accurate coding of every rare disease. The quality and reliability of the data obtained may be improved by the utilization of a common classification and a code system suitable for rare diseases. Materialization of studies to effectively use the Orphanet nomenclature conducted by TÜSEB in the diagnostic coding of rare diseases will be highly beneficial.

***Recommendation I8: Enabling flexibility to conduct real life data studies for rare disease treatments that are accessible but not yet authorized in our country***

Certain products that are used in rare diseases but not yet authorized in our country can be accessed through Foreign Drugs List within the extent of reimbursement or through compassionate use programs. Permission from the Ministry of Health for treatment centers to collect and publish real life data regarding these products and to generate common data with other centers will contribute to the effective management of respective diseases.

### 5.3 R&D

Many studies are being conducted worldwide to develop innovative diagnostic and treatment methods targeting rare diseases; in our country, however, such studies are still very limited. Opportunities are found

in Turkey to enhance R&D studies in this field both in clinical and preclinical phases.

### R&D capabilities

Studies intended to develop innovative products to be used in the treatment of rare diseases in Turkey are rather limited to individual and small scaled initiatives, universities, and programs launched by TÜSEB and TÜBİTAK. Various steps must be taken to increase studies in this field.

***Recommendation R1: Supporting R&D activities for development of products in Turkey for the diagnosis and treatment of rare diseases, forming the suitable basis for these activities and providing incentives***

Developing incentive policies in this field is important to enhance R&D activities for innovative products in our country and to allow Turkey to become a center of attraction in this field. By promotion of the innovation ecosystem, scientists in our country and from all around the world working in this field may be allowed to conduct R&D activities in Turkey.

In addition to this, offering incentives like in foreign countries regarding the intellectual property rights of innovative products will support innovative pharmaceutical and medical device companies to conduct R&D studies in our country.

For this purpose, forming the infrastructure required for preclinical studies in the initial phase of product development will set the stage for global companies to conduct R&D activities in Turkey before the clinical phase.

### Clinical research

Efforts to develop clinical research in our country have accelerated in recent years but these efforts remain to reach the desired size. Various policies to be implemented in this field will allow Turkey to become one of the leading countries in the world in the field of clinical research.

***Recommendation R2: Increasing the number of clinical trials performed in Turkey in the field of rare diseases***

Within the report titled "Benefits of a Clinical Research Strategy for Turkey – A Roadmap for Innovation-based Growth" issued by IQVIA in 2020, factors of importance for clinical research were addressed under patient recruitment, process, infrastructure, and cost and incentives headings. 12 recommendations were presented targeting developmental areas on these subjects, and the recommendations were assessed based on their degree of potential impact and difficulty of implementation:

- Patient recruitment
  - » Establish a central patient database
  - » Design a patient referral system
  - » Raise public awareness
- Process
  - » Streamline and centralize documentation and ethics committee submission
  - » Reinforce implementation of ethical review standards
- Infrastructure
  - » Build an investigator network
  - » Increase capacity in a wider range of institutions
  - » Provide formal education, academic incentives,

career advancement opportunities

» Revise R&D regulation

» Establish clinical research centers with dedicated staff

- Cost and incentives

» Improve accounting systems in healthcare institutions

» Increase incentives for companies to run clinical research in Turkey

These recommendations that target the development of clinical research in our country were addressed in the mentioned report in full detail.

### 5.4 Execution of recommendations

Each of the 19 recommendations discussed in detail above has been built in light of the insight acquired from stakeholders who contributed to this report and of global best practices. Therefore, all these recommendations are anticipated to make important contributions to development opportunities in the field of rare diseases in Turkey. However, it is impossible to actualize them all at the same time. Prioritization of the recommendations will contribute to forming an effective action plan.

Thus, these 19 recommendations have been evaluated by the report's project task force in terms of the level of effect they will bring into the field of rare diseases and the level of difficulty to implement (Figure 12).

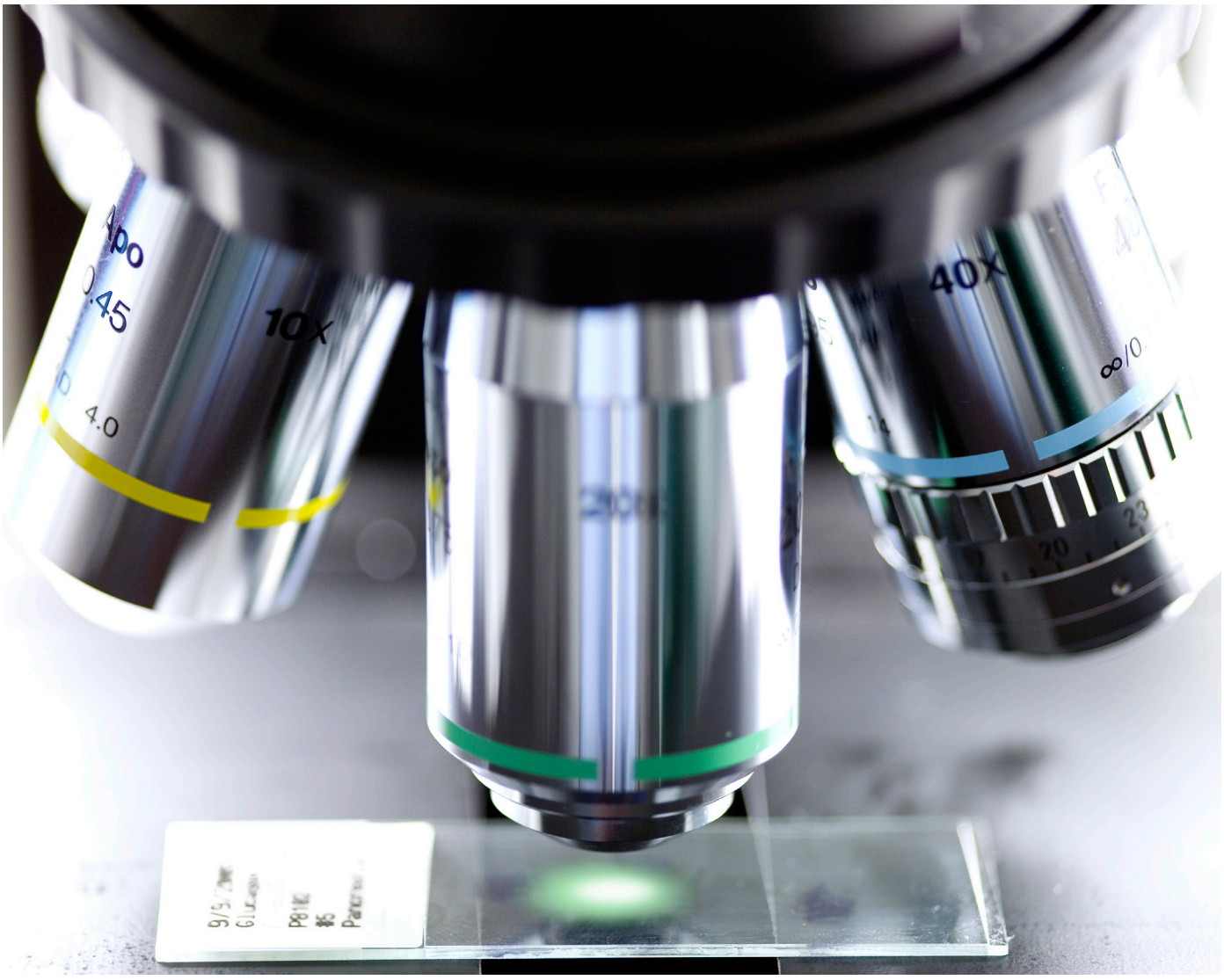


**Figure 12: Prioritization of Recommendations**


This evaluation reveals the importance of the action steps to be taken regarding national policies and infrastructure in the field of rare diseases. In the action plan that is generated with respect to these recommendations and prioritization, identification of stakeholders and their responsibilities for each recommendation, planning of the time and resource required for this in detail, and assigning an authority to monitor the actions will make a great contribution to materialization of effective solutions.

# REFERENCES


1. TÜSEB, «Nadir Hastalıklar Raporu,» İstanbul, 2019.
2. S. Nguengang Wakap, D. M. Lambert, A. Olry and et al, "Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database," Eur J Hum Genet, 28, p. 165–173, 2020.
3. TBMM, «Parliamentary Research Commission Report,» 2020.
4. H. Hamamy, S. Antonarakis, L. Cavalli-Sforza and et al, "Consanguineous marriages, pearls and perils:Geneva International Consanguinity Workshop Report," Genet Med 13, p. 841–847, 2011.
5. Turkstat, «Status of consanguineous marriage by sex, SR Level 1 and three major provinces,» 2016.
6. [Online]. Available: https://rarediseases.info.nih.gov/diseases/categories. [Accessed: November 8, 2021].
7. IQVIA analysis.
8. Lewin Group, "The National Economic Burden of Rare Disease Study," 2021.
9. [Online]. Available: https://shgmnadirdb.saglik.gov.tr/Eklenti/40255/0/2020orphonetyilliktoplantisiposterpdf.pdf. [Accessed: October 2021].
10. Stakeholder interviews. [Interview]. October-December 2021.
11. General Directorate of Public Health Department of Child and Adolescent Health, [Online]. Available: https://hsgm.saglik.gov.tr/tr/cocukergen-tp-liste/hemoglobinopati-kontrol-program%C4%B1.html. [Accessed: November 2021].
12. [Online]. Available: https://www.saglik.gov.tr/TR,86761/sma-bilim-kurulu-bakan-fahrettin-kocabaskanliginda-toplandi.html. [Accessed: October 2021].
13. [Online]. Available: https://www.aa.com.tr/tr/saglik/sgk-geri-odemesi-kapsaminda-nadir-hastaliklarayonelik-gebelik-oncesi-tani-uygulamasi-baslatilacak/2157844. [Accessed: October 2021].
14. [Online]. Available: https://www.saglik.gov.tr/TR,86761/sma-bilim-kurulu-bakan-fahrettin-kocabaskanliginda-toplandi.html. [Accessed: December 2021].
15. S. Dharssi, D. Wong-Rieger, M. Harold and S. Terry, "Review of 11 national policies for rare diseases in the context of key patient needs," Orphanet J Rare Dis., pp. 12(1):63. doi: 10.1186/s13023-017-0618-0, 31 Mar 2017.
16. EURORDIS, [Online]. Available: https://www.eurordis.org/news/harmonised-newborn-screeningeurope-window-opportunity-we-should-not-miss. [Accessed: January 2022].
17. TÜSEB, «Her Yönü ile Nadir Hastalıklar,» 2019.
18. Bearryman, E.; EURORDIS, "Does your rare disease have a code?," 2 March 2015. [Online]. Available: http://www.eurordis.org/news/does-your-rare-disease-have-code.
19. [Online]. Available: https://genomicmedicine.se/en/. [Accessed: December 2021].
20. [Online]. Available: https://www.icpermed.eu/en/2025-France-Genomic-Medicine-Initiative-Acomprehensive approach.php. [Accessed: December 2021].
21. [Online]. Available: www.fda.gov. [Accessed: September 29, 2021].
22. [Online]. Available: www.ema.europa.eu. [Accessed: September 29, 2021].
23. IQVIA, "EFPIA Patients W.A.I.T. Indicator 2021 Survey," 2022.

24. Republic of Turkey Ministry of Health, «Regulation on the Marketing Authorization of Medicinal Products for Human Use» Official Gazette, December 11, 2021.
25. IQVIA, "Orphan Medicines Launch Excellence – Sustaining launch success of Orphan Medicines come ofage," 2019.
26. RARE IMPACT, "Improving patient access to gene and cell therapies for rare diseases in Europe – A review of the challenges and proposals for improving patient access to advanced therapeutic medicinal products in Spain," 2020.
27. The Beneluxa Initiative on Pharmaceutical Policy, "Terms of Reference," 2018.
28. "Memorandum of Understanding on Cooperation in the Field of Fair and Affordable Pricing of Medicinal Products," 2017.
29. "OECD Statistics," 2019. [Online]. Available: https://stats.oecd.org/.
30. Republic of Turkey Ministry of Health, «Health Statistics Yearbook» 2019.
31. V. Hedley and et al, "2018 Report on the State of the Art of Rare Disease Activities in Europe," July 2018.
32. [Online]. Available: https://kasder.org.tr/nadir-hastaliklar-icin-yol-haritasi-olusturulacak/. [Accessed: December 2021].
33. EURORDIS, "Eurordis Policy Fact Sheet – Rare Disease Patient Registries," 2013.
34. «Rare Disease Registries in Europe,» September 2020. [Online]. Available: www.orpha.net.
35. EURORDIS, "Eurordis Policy Fact Sheet – Needs and Priorities for Rare Disease Research".
36. TÜSEB, [Online]. Available: https://www.tuseb.gov.tr/haberler/tuseb-den-sma-ile-mucadeleye-ozel-ikiyeni-cagri-15022021. [Accessed: December 2021].
37. TÜBİTAK, [Online]. Available: ejprd_jtc2021_tubitak_1071_programi_surec_dokumani.pdf. [Accessed: December 2021].
38. [Online]. Available: www.clinicaltrials.gov. [Accessed: December 2021].
39. IQVIA, «Benefits of a Clinical Research Strategy for Turkey – A Roadmap for Innovation Driven Growth,» 2020.
40. H. Aslantürk, M. Derin ve S. Arslan, «NADİR HASTALIKLARIN AİLELER ÜZERİNDEKİ PSİKO-SOSYAL, FİZİKSEL VE EKONOMİK ETKİLERİ,» Tıbbi Sosyal Hizmet Dergisi, pp. 80-94. 10.46218/tshd.798177, 2019.
41. SEPD, «Nadir Hastalıklarla Yaşayan Hanelerin Cepten Yaptıkları Sağlık Harcamaları,» Şubat 2021.
42. «Nadir Hastalıklar Hasta ve Hasta Yakınları İhtiyaç Analizi Ortak Akıl Platformu® Çalışma Raporu,» [Online]. Available: http://sepd.org.tr/wp-content/uploads/2020/01/Nadir-Hastal%C4%B1klar- %C4%B0htiya%C3%A7-Analizi-%C3%87al%C4%B1%C5%9Ftay-Raporu_01.pdf.
43. C. Huyard, "How did uncommon disorders become 'rare diseases'? History of a boundary object. Sociol Health Illn.," 2009 May; 31(4):463-77. doi: 10.1111/j.1467-9566.2008.01143.x. PMID: 19397760.
44. [Online]. Available: https://rarediseases.info.nih.gov/diseases/categories. [Accessed: November 8, 2021].
45. Council of the European Union, "Council recommendation on an action in the field of rare diseases,"2009.
46. S. Garrison, A. Kennedy, N. Manetto and A. N. Pariser, "The Economic Burden of Rare Diseases: Quantifying the Sizeable Collective Burden and Offering Solutions. Health Affairs Forefront.," February 1, 2022.
47. A. Tisdale, C. M. Cutillo, R. Nathan and et al, "The IDeaS initiative: pilot study to assess the impact of rare

diseases on patients and healthcare systems," Orphanet J Rare Dis 16, 429, 2021.

48. U.S. Government Accountability Office, "Rare Diseases: Although Limited, Available Evidence Suggests Medical and Other Costs Can Be Substantial," October 2021.
49. A. A. Navarrete-Opazo, M. Singh, A. Tisdale and et al, "Can you hear us now? The impact of health-care utilization by rare disease patients in the United States," Genet Med 23, 2194–2201, 2021.
50. [Online]. Available: www.eurordis.org. [Accessed: December 2021].
51. 51. [Online]. Available: https://ncats.nih.gov/about/center/org. [Accessed: October 2021].
52. [Online]. Available: https://www.rarediseasesnetwork.org/. [Accessed: October 2021].
53. "Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products".
54. "Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare diseases: Europe's challenges".
55. "Commission Expert Group on Rare Diseases," [Online]. Available: http://ec.europa.eu/health/rare_ diseases/expert_group/index_en.htm.
56. EUCERD Joint Action, "2014 Report on the State of the Art of Rare Disease Activities in Europe: Part I – Overview of Rare Disease Activities in Europe," 2014.
57. Ministry of Social Affairs and Health and Ministry of Higher Education, Research and Innovation, "French National Plan for Rare Diseases 2018-2022 – Sharing innovation, a diagnosis and a treatment for all".
58. [Online]. Available: https://www.acibadem.edu.tr/assets/pdf/kemal-memisoglu.pdf . [Accessed: October 2021].
59. D. Ürek and S. Karaman, "Önemli Bir Halk Sağlığı Sorunu Olarak Nadir Hastalıklar ve Yetim İlaçlar," Hacettepe Sağlık İdaresi Dergisi, 22(4): 863-878, 2019.
60. Ö. İnce ve M. Tarim, «Türkiye Cumhuriyeti Sağlık Bakanlığı Politika Ve Stratejilerinde Nadir Hastalıkların Yeri: 2002-2018 Dokümanlarının İçerik Analizi.,» 2018.
61. İlaç Bilincini Geliştirme ve Akılcı İlaç Derneği, «"Nadir Hastalıklar ve Yetim İlaç Sempozyumu ve Yetim İlaç Yönetmelik Çalıştayı" Toplantı Tutanağı,» 2014.
62. [Online]. Available: https://www.gmka.gov.tr/dokumanlar/yayinlar/2014-2018_Sa%C4%9Fl%C4%B1k%20End%C3%BCstrilerinde%20Yap%C4%B1sal%20D%C3%B6n%C3%BC%C5%9F%C3%BCm%20Program%C4%B1-Eylem%20Plan%C4%B1.pdf. [Accessed: October 2021].
63. Republic Of Turkey General Directorate of the Ministry of Science, Industry and Technology, «A Strategy and Action Plan for the Pharmaceutical Sector 2015-2018,» 2015.
64. [Online]. Available: https://www.titck.gov.tr/Dosyalar/Ilac/SaglikEndustrileriKoordinasyon/EK-1%20T%C3%BCrkiye%20%C4%B0la%C3%A7%20Sekt%C3%B6r%C3%BC.pdf. [Accessed: October 2021].
65. TÜSEB-TÜHKE, «Nadir Hastalıklar Farkındalık Günü Sempozyumu Raporu,» February 2021. [Online]. Available: https://www.tuseb.gov.tr/tuhke/uploads/genel/files/nadir_hastaliklar_raporu.pdf.
66. [Online]. Available: http://www.europlanproject.eu/Resources/docs/2008-2011_3. EUROPLANIndicators.pdf. [Accessed: October 2021].
67. [Online]. Available: https://www.radico.fr/images/documents-utiles/europe/EUCERDRecommendations-Indicators-adopted.pdf. [Accessed: October 2021].

68. General Directorate of Public Health Department of Child and Adolescent Health, [Online]. Available: https://hsgm.saglik.gov.tr/tr/cocukergen-tp-liste/yenidogan_tarama_programi.html. [Accessed: November 2021].

69. [Online]. Available: https://www.nhs.uk/conditions/baby/newborn-screening/blood-spot-test/. [Accessed: December 2021].

70. [Online]. Available: https://pharmaphorum.com/patients/public-approval-whole-genome-sequencingnewborn-screenings-uk-wide-rollout/. [Accessed: December 2021].

71. [Online]. Available: https://www.eurordis.org/news/harmonised-newborn-screening-europe-windowopportunity- we-should-not-miss . [Accessed: January 2022].

72. EURORDIS, "Policy Fact Sheet – Newborn Screening," 2013.

73. [Online]. Available: https://www.aa.com.tr/tr/saglik/sgk-geri-odemesi-kapsaminda-nadir-hastaliklarayonelik-gebelik-oncesi-tani-uygulamasi-baslatilacak/2157844. [Accessed: October 2021].

74. SSI, «Healthcare Implementation Communiqué, List of Hereditary Diseases for the use of Preimplantation Genetic Diagnosis and In Vitro Fertilization (Annex-2/K)».

75. P. A. Engel and et al, "Physician and patient perceptions regarding physician training in rare diseases: the need for stronger educational initiatives for physicians," Journal of Rare Disorders, vol. 1, no. 2, 2013.

76. [Online]. Available: https://www.medimagazin.com.tr/guncel/genel/tr-nadir-hastaliklar-gunundeturkiye-profili-yaklasik-7-milyon-kisi-11-681-80647.html. [Accessed: November 2021].

77. E. Bearryman, "EURORDIS; Does your rare disease have a code?," March 2, 2015.

78. [Online]. Available: https://www.icpermed.eu/en/2025-France-Genomic-Medicine-Initiative-Acomprehensive-approach.php. [Accessed: December 2021].

79. B. Zamora, F. Maignen, P. O'Neill and et al, "Comparing access to orphan medicinal products in Europe," Orphanet J Rare Dis 14, 95, 2019.

80. Republic of Turkey Ministry of Health, «Guideline for Humanitarian Program on Early Access to Drugs».

81. N. Khosla and R. Valdez, "A compilation of national plans, policies and government actions for rare diseases in 23 countries," Intractable Rare Dis Res., 2018 Nov; 7(4):213-222. doi: 10.5582/irdr.2018.01085.

82. Turkish Medicines and Medical Devices Agency, «Guideline for Working Principles and Procedures of Human Medicinal Products Priority Assessment

83. I. Institute, "Orphan Drugs in the United States - Rare Disease Innovation and Cost Trends through 2019," 2020.

84. Republic of Turkey Ministry of Health «Regulation on Neuromuscular Diseases Unit» Official Gazette, June 4, 2021.

85. [Online]. Available: https://www.acibadem.edu.tr/haberler/nadir-hastaliklar-ulkemizde-guncel-durumve-acurare. [Accessed: December 2021].

86. [Online]. Available: https://rarediseases.org/committing-to-care-access-equity-and-research-nordannounces-31-rare-disease-centers-of-excellence/. [Accessed: December 2021].

87. EURORDIS, "2013 EURORDIS Policy Fact Sheet – Centres of Expertise," 2013.

88. [Online]. Available: https://bwc.nhs.uk/rare-diseases. [Accessed: December 2021].

89. [Online]. Available: https://ohsad.org/wp-content/uploads/2019/04/30498mukemmeliyet-merkezlerihakkinda-genelge-2019-8pdf.pdf. [Accessed: November 2021].

90. [Online]. Available: https://www.tuseb.gov.tr/tuska/haberler/sghm-otizm-zihinsel-ozel-gereksinimlerve- nadir-hastaliklar-dairesi-baskanligi-ve-enstitumuz-arasinda-mukemmeliyet-merkezleri-hakkindaistisare- toplantisi-

gerceklestirildi. [Accessed: November 2021].

91. [Online]. Available: https://rarediseases.org/iamrare-registry-program/. [Accessed: December 2021].
92. EUCERD, "EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection to the European Commission, Member States and All Stakeholders," June 5, 2013.
93. Dolon, "Estimated impact of EU Orphan Regulation on incentives for innovation," 2020.
94. TÜSEB, [Online]. Available: https://www.tuseb.gov.tr/haberler/tuseb-den-sma-ile-mucadeleye-ozel-ikiyeni-cagri-15022021. [Accessed: December 2021].
95. TÜBİTAK, «EJP RD Call for 2021 National Application Rules,» 2021.
96. EURORDIS, "A Rare Barometer Survey", Juggling Care and Daily Life," 2017 .
97. [Online]. Available: https://www.nhs.uk/conditions/idiopathic-pulmonary-fibrosis/ . [Accessed: November 2021].
98. [Online]. Available: https://www.boehringer-ingelheim.com.tr/solunum/ipf/ipf-nedir. [Accessed: November 2021].
99. [Online]. Available: https://www.solunum.org.tr/menu/115/idiopatik-pulmoner-fibrozis-ipf-nedirbelirtileri-tani-ve-tedavi-yontemleri.html. [Accessed: December 2021].
100. [Online]. Available: https://www.solunum.org.tr/TusadData/userfiles/file/PATIENT%20 INFORMATION%20FOR%20IDIOPATHIC%20PULMONARY%20FIBROSIS%20(IPF)%20.pdf. [Accessed: December 2021].
101. [Online]. Available: https://www.solunum.org.tr/TusadData/userfiles/file/PATIENTS%20 DIAGNOSED%20 WITH%20PULMONARY%20FIBROSIS%20(PF)%20OR%20IDIOPATHIC%20 PULMONARY%20FIBROSIS%20 (IPF).pdf. [Accessed: December 2021].
102. [Online]. Available: https://www.solunum.org.tr/TusadData/userfiles/file/ATS%20idiopathicpulmonary-fibrosis.pdf. [Accessed: December 2021].
103. [Online]. Available: https://www.pahssc.org.tr/hastalik/4/pulmoner-arteriyel-hipertansiyon-pah-nedir. [Accessed: December 2021].
104. [Online]. Available: https://kosuyolueah.saglik.gov.tr/TR,418055/pulmoner-hipertansiyon-nedir.html. [Accessed: December 2021].
105. [Online]. Available: https://www.thd.org.tr/thdData/userfiles/file/ORAK%20HUCRELI%20ANEMI.pdf. [Accessed: December 2021].
106. Republic of Turkey Ministry of Health General Directorate of Public Health, «Premarital Hemoglobinopathy Screening Program».
107. Republic of Turkey Ministry of Health, «Hemoglobinopathy Control Program from Hereditary Blood Diseases and Regulation on Diagnosis and Treatment Centers,» Official Gazette, October 24, 2022.
108. D. Loukopoulos, "Haemoglobinopathies in Greece: prevention programme over the past 35 years," Indian J Med Res., 2011 Oct;134(4):572-6. PMID: 22089622; PMCID: PMC3237258.
109. E. Landfeldt, "Consanguinity and autosomal recessive neuromuscular diseases," Developmental Medicine & Child Neurology, vol. 58, no. 8, pp. 796-797, 2016.
110. SSI, «Social Security Institution Communiqué Amending the Healthcare Implementation Communiqué,» Official Gazette, January 11, 2020.
111. The National Clinical Programme for Rare Diseases, "Model of Care for Transition from Paediatric to Adult Healthcare Providers in Rare Diseases," July 2018.

112. [Online]. Available: https://www.turkiyeklinikleri.com/article/en-dunyada-ve-ulkemizde-kistik-fibrozishastaligi- 47919.html . [Accessed: December 2021].
113. The Turkish Pediatric Respiratory Diseases and Cystic Fibrosis Society, «Cystic Fibrosis Registry of Turkey (CFRT) 2019 data».
114. European Cystic Fibrosis Society, "ECFS Patient Registry Annual Data Report," 2019.
115. [Online]. Available: https://rarediseases.org/rare-diseases/mucopolysaccharidoses/ . [Accessed: December 2021].
116. SSI, «Social Security Institution Communiqué Amending the Healthcare Implementation Communiqué,» 31853 Official Gazette, June 1, 2022.
117. [Online]. Available: www.rarediseases.org. [Accessed: December 2021].
118. [Online]. Available: www.orpha.net. [Accessed: December 2021].
119. H. Bajwa and W. Azhar, Niemann-Pick Disease. [Updated 2021 Jul 18]., In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 Jan.
120. [Online]. Available: https://www.ninds.nih.gov/. [Accessed: December 2021].
121. S. E. Bianconi, D. I. Hammond, N. Y. Farhat and et al, "Evaluation of age of death in Niemann-Pick disease, type C: Utility of disease support group websites to understand natural history," Mol Genet Metab. 2019;126(4):466-469. doi:10.1016/j.ymgme.2019.02.004.
122. [Online]. Available: https://www.inpda.org/. [Accessed: December 2021].
123. General Directorate of Public Health Department of Child and Adolescent Health, [Online]. Available: https://hsgm.saglik.gov.tr/tr/cocukergen-tp-liste/hemoglobinopati-kontrol-program%C4%B1.html. [Accessed: November 2021].
124. Republic of Turkey Ministry of Health General Directorate of Health Services, "Health Strategy and Action Plan for Rare Diseases 2023-2027," 2022.

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