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Rare Diseases in Oto-Rhino-Laryngology, Head and Neck Surgery

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ABSTRACT

Rare diseases pose multiple challenges for patients, relatives, physicians, nursing staff, and therapists. Their rarity impedes research and treatments due to medical and economical reasons. Many diseases in the field otorhinolaryngology, head and neck surgery are rare diseases due to their low prevalence. The initiation of the right management processes requires knowledge about diagnostics, resources (like centers, networks and registries), about specifics of the physician-patient relationship, follow-up care, including communication with family doctors and the role of self-help groups. Of special interest for university hospitals and our scientific society are the specific aspects of research including European networks and research funding, information management, public relations, education, training, financing, and regulations like orphan drugs and clinical trials in small populations.

Contents

1. Introduction

Rare disease diagnosis and therapy present major challenges for all people involved, including the affected patients, their relatives, and the medical, therapeutic, and nursing staff. Rare diseases represent a very heterogenic group. The majority (~80 %) of orphan diseases are at least partly related to genetic aspects. They often lead to symptoms with childhood onset and exhibit a chronic course, and are rarely curable. Rare diseases are also characterized by particular regulatory, economic, and research-related aspects. By definition, rare diseases affect a low number of patients, making it difficult to conduct trials due to the wide distribution of patients suffering from a given disease.

Rare diseases are extremely challenging in terms of both diagnosis and therapy. Affected patients often need interdisciplinary care provided by a team of experts, and their treatment typically requires specific qualifications, skills, and equipment. Additionally, they may have special needs regarding the doctor–patient relationship, in terms of "shared decision making" [1] and communication with physicians who will provide further treatment. Moreover, the optimal methods for good treatment and care are often unclear. These factors contribute to delayed diagnoses, and patients' feelings of isolation. However, in recent years, rare diseases have been increasingly the focus of public attention [2].

Many typical diseases encountered in the field of oto-rhino-laryngology, head and neck surgery are considered rare diseases based on their prevalence. As this discipline is mainly defined by the affected body region (head and neck), it frequently overlaps with other disciplines, and oto-rhino-laryngologists inevitably encounter manifestations of rare diseases. Notably, the first manifestations of rare diseases are commonly in the head and neck area. Thus, oto-rhino-laryngologists must be familiar with rare ENT-specific diseases. They should have knowledge about the diagnostics; the available resources (e. g. centers, networks, and registries); the particularities of the doctor–patient relationship and follow-up, including communication with family doctors; and the role of self-help and support groups. For university medical professionals and the scientific community, areas of specific interest may include the particularities of this field of research, including European networking and research funding, information management, public outreach, teaching and education, and the regulatory aspects (orphan drugs).

2. Definition

The specific definition of a rare disease (also called orphan diseases) varies among different countries. In the European Union (EU), a disease is considered rare when it affects no more than 5 of 10 000 people (50:100 000 or 1:2000). In contrast, a rare disease is defined by a maximum prevalence of 1:1500 people (7.5 per 10 000 people) in the United States (US), 1:2500 (4 per 10 000) in Japan, 1:10 000 in Australia, and even 1:100 000 in Switzerland [2, 3]. In the EU, most rare diseases affect only one person or even less per 100 000 people. However, about 5000–8000 different rare diseases affect an overall total of 27–36 million people in the EU, i. e. 6–8 % of the EU population. In Germany alone, about 4–6 million people live with rare diseases.

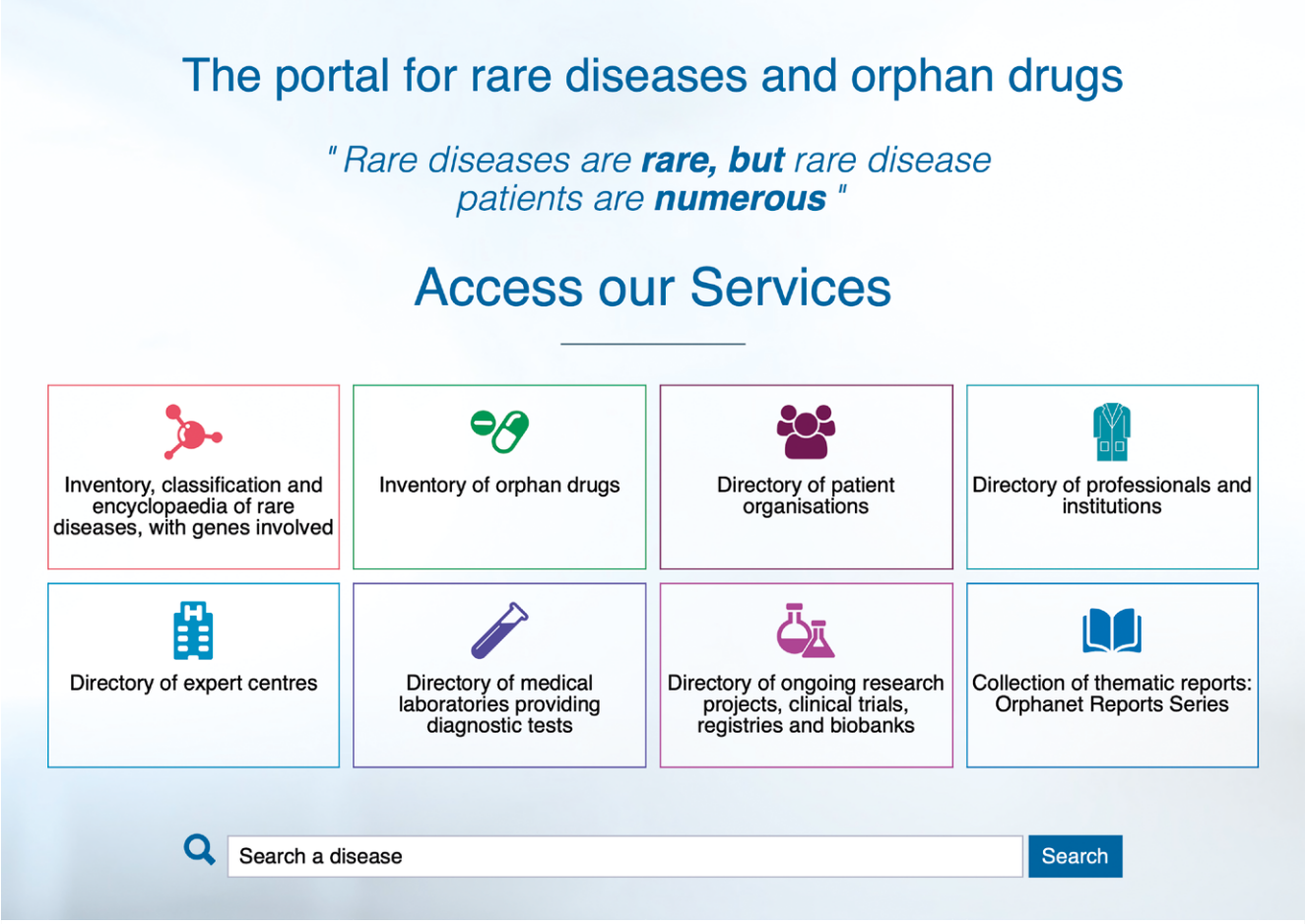
Notably, the term of "Orphan" is also used to describe diseases and therapies (e. g. "Orphan Drugs") that are actually rather common (e. g. many tropical diseases) but which are neglected due to economic reasons, including the absence of economic incentives to develop therapies. However, these diseases will not be discussed in the present article.

3. Orphanet

Orphanet is a database summarizing the available resources relating to rare diseases and medications for rare disease treatment (so-called orphan drugs), created with the stated goal of "gathering and improving knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases". Orphanet aims to provide high-quality information about rare diseases, and to ensure equal knowledge access for all stakeholders. Orphanet also maintains the Orphanet rare disease nomenclature (**ORPHA code**), which is essential for improving the visibility of rare diseases in health and research information systems" [4]. Orphanet was established in 1997 in France by the French National Institute for Health and Medical Research (INSERM). In 2000, this initiative became a European endeavor, supported by grants from the European Union.

Specifically, Orphanet provides [4, 5] (▶ **Fig. 1**) the following: an inventory, classification, and encyclopedia of rare diseases with associated genes; information about drugs for rare diseases (orphan drugs); a list of self-help organizations; a list of experts and institutions, as well as expert centers; a list of medical labs offering diagnostic services; a list of current research projects, clinical trials, registries, and biobanks; and a collection of specific articles (Orphanet report series). The Orphanet database can be used to look up diseases, clinical signs and symptoms, classifications, genes, and handicaps (activity impairments regarding daily life or their functional consequences) associated with rare diseases. The functional Orphanet thesaurus is based on the ICF classification of the World Health Organization (International Classification of Functioning, Disability and Health – Children and Youth, ICF-CY, WHO 2007). The Orphanet nomenclature contains a "heterogeneous typology of entities of decreasing extension, including: groups of disorders, disorders, and sub-types. A disorder in the database can be a disease, a malformation syndrome, a clinical syndrome, a morphological or a biological anomaly or a particular clinical situation (in the course of a disorder). They are organized into groups and further divided into clinical, etiological or histopathological subtypes" [4]. When seeking information about a rare disease, search criteria can include the disease name, ORPHAcode, gene symbol/name, OMIM or MIM number ("Online Mendelian Inheritance in Man", a database registering the human genes and their mutations), or International Classification of Disease (ICD)-10 code.

Orphanet also provides access to an encyclopedia of rare diseases for experts, comprising a series of expert-authored and peer-reviewed information, including "Review Articles, clinical practice guidelines, diagnostic criteria, guidance for genetic testing, Practical Genetics, clinical genetics review, emergency guidelines, anesthesia guidelines, disability factsheets, and summary information on the disease in a language other than the seven languages of Orphanet" [4]. For professionals and patients, Orphanet provides in-



▶ **Fig. 1** The internet opeing page of Orphanet, the portal for rare diseases and orphan drugs.

formation about self-help groups (patient organizations, umbrella organizations, and alliances) that specialize in a certain disease or disease groups, which may be sorted geographically (according to country, region, or city.)

In 2019, a cooperation was forged between Orphanet and the "International Clinical Trials Registry Platform" (ICTRP) – Registry of the World Health Organization (https://www.who.int/ictrp/en/). Incorporation of the Orphanet registry has significantly improved the identification of clinical trials for rare diseases for ICTRP users (http://apps.who.int/trialsearch/).

Finally, the "Orphanet Report Series" is a published series of reports that are available as downloads, with different focuses covering the whole spectrum of rare diseases. These reports include the following topics: list of rare diseases, epidemiological report with available prevalence data, list of orphan drugs, overview of available registries for rare diseases in Europe, annual activity report, list of relevant (research) infrastructures in Europe, results of the Orphanet survey regarding user satisfaction, and a list of all experts who have contributed to the contents of the Orphanet database [4].

3.1 Orphanet Journal of Rare Diseases

The "Orphanet Journal of Rare Diseases" is the official journal of Orphanet, founded in 2006, and published by BioMed Central (SpringerNature) "Open Access". It specifically focuses on research regarding rare diseases, including review articles and clinical trials, as well as articles on public health and orphan drugs.

4. Orphan Drugs

Since 1983, the term orphan drug has been used to define medications applied for the treatment of rare diseases. In this terminology, "Orphan Drug" refers to the above-mentioned definition of rare/orphan diseases, based on varying prevalence rates in different regions. In addition to the definition of rare diseases based on prevalence, the term orphan drug also applies to drugs lacking economic profitability. Due to the small market and correspondingly low sales during legal patent protection — combined with high development costs — orphan drugs are not of great interest to the pharmaceutical industry. This is also the case for drugs intended for a market with low purchase power, as is typical of diseases that are common in poorer countries, particularly tropical diseases; however, this use of the term will not be discussed in the present article.

To promote and develop orphan drugs, the political authorities in the US issued the "Orphan Drug Act" (ODA) in 1983 [6]. The main incentive provided to pharmaceutical industries is the right of exclusive marketing (7 years under the ODA). Additionally, the ODA provides research funding for companies and academic research groups, and reduced fees in the approval process and tax reductions, while drugs for rare diseases are under evaluation for therapeutic potential. In the context of the Orphan Disease Act of the US Food and Drug Administration (FDA), the "Orphan Drug Designation" programs include the "Humanitarian Use Device (HUD) Designation", the "Orphan Products Clinical Trials Grants", the "Pediatric Device Consortia (PDC) Grant", and the "Orphan Products Natural History Grants". Since their introduction, these programs have promoted a significant increase in the field of developing drugs for rare disease treatment. In the US, this includes the market introduction of over 600 orphan drugs since the start of the program [7].

In 2000, the European Union implemented the "Orphan Medicinal Product Regulation", with the aims of defining a common procedure for the designation of drugs as orphan drugs, and creating incentives for orphan drug research, development, and distribution. Within the European Medicines Agency (EMA), the Committee for Orphan Medicinal Products (COMP) regularly issues recommendations for acknowledging the status of "Orphan Drug". An application for designation of a medicinal product as an orphan medicinal product may be submitted if the sponsor can establish that a medicinal product is intended for the diagnosis, prevention, or treatment of a life-threatening or chronically debilitating condition that 1) affects no more than five in 10 000 persons in the community; or 2) that without incentives it is unlikely that the marketing of the medicinal product in the community would generate sufficient return to justify the necessary investment. Additionally, the applicant must demonstrate that the community presently has no satisfactory method of diagnosis, prevention, or treatment of the condition in question, or if such a method exists, that the medicinal product will be of significant benefit to those affected by that condition [8]. Upon approval of an orphan drug in the EU registry, the applicant has market exclusiveness for the approved indication for 10 years. Additionally, the application fees are partially remitted to the pharmaceutical company, and other important cost savings may be achieved by the simplified approval procedure. The drugs with orphan status approved in the EU are listed in the Orphanet database, and published in the "Lists of medicinal products for rare diseases in Europe".

According to the act on the restructuring of the medicines market (AMNOG) of 2010, additional benefit from an approved drug must be confirmed. However, since orphan drug approval is only issued when the disease is rare and no adequate therapy already exists, the necessity of confirming an additional benefit of an orphan drug may be neglected. This facilitation only applies to drugs that have a low turnover due to their approval for rare diseases. It does not apply to pharmaceutical companies that have achieved a turnover of over 50 million Euro with their orphan drug, in which case, the confirmation of additional benefit must be submitted. The requirement of proving an additional benefit might be one reason why the FDA has approved more oncological drugs compared to the EMA, particularly for subgroups of oncological diseases with higher prevalence [9].

Controversies have arisen regarding "undesired side effects" of the regulatory and funding programs in the context of orphan drug development. There is the possibility of manipulation ("gaming the system") for profit maximization [10]. The increasing number of approved orphan diseases may include biomarker-defined subgroups of non-orphan diseases, particularly in the field of oncology [11]. Reports have described the use of piecemeal tactics for non-orphan diseases with the aim of achieving drug approvals by exploiting the competitive advantages in the context of the orphan drug status [12, 13]. Reduced research and development costs (smaller clinical trials or observational studies), accelerated review processes at the approval authorities, reduced or minimal competition, and other aspects have led to a situation where orphan drugs rank among the most expensive and most lucrative drugs on the world market [14]. Therefore, the incentive systems will have to be reviewed.

5. Clinical Trials and Biometric Aspects

From a biometric perspective, the development of therapies for rare diseases encounters numerous problems regarding the performance of clinical trials as a precondition for therapy approval. Complicating factors include the low disease prevalence, heterogeneity of the patient populations, geographical dispersion, and high percentage of pediatric patients. Clinical trials for rare diseases usually include very small numbers of patients, presenting challenges regarding an efficient study design and specific biometric methods for outcome analysis with limited populations. In general, in the ethical assessment of any clinical trial, one must evaluate the biometric quality with regards to study design, calculation of case numbers, and statistical analysis, as methodologically poor research in humans must be considered unethical [15].

Most statistical design and analysis methods for clinical trials have been developed and evaluated for study populations of at least several hundred patients. These methods are not always suitable for therapy evaluation when the sample size is small — as is naturally the case for orphan diseases. It is unknown whether there is a specific cut-off value for sample sizes, below which standard methods can no longer be considered adequate. Therefore, current investigations use statistical methods to assure that high significance is achieved in small patient populations. Such methods include, for example, the inclusion of multiple or composite endpoints for conclusions regarding therapeutic effects, which may improve the statistical power of biometric tests [16, 17].

In the context of orphan diseases, **real-world evidence** (RWE) trials are another possible means of coping with the natural problems of randomized clinical trials, which still represent the gold standard of clinical research. In medicine, real evidence refers to evidence from observational data that are collected during clinical routine, outside of the setting of randomized clinical trials. Analysis of real-world data may support the benefit assessment of drugs used in the context of rare diseases. Data availability has been improved by progressive digitization [18, 19], suggesting that in the future real-world evidence will play a major role in the development, benefit assessment, and regulatory processes (approval) of therapies for orphan diseases [20–23].

Even if the common guidelines for clinical trial conduction (e. g. ICH guidelines) also apply for clinical trials of rare diseases, the EMA

and the committee for Medicinal Products for Human Use (CHMP) have developed and published specific guidelines for the performance of clinical trials with small study populations: **EMA/CHMP guideline on clinical trials in small populations**[24]. Additionally, the **International Rare Diseases Consortium** (IRDiRC) has issued recommendations developed by a task force for clinical trials in small populations (**Small Population Clinical Trials Task Force, SPCT**) [25, 26].

6. Ethical Aspects

Based on the four medico-ethical principles of Beauchamp and Childress [27], and in the context of decision making and weighing in the context of rare diseases, we must observe the patient's right of autonomy (autonomy principle), the principle of avoiding damage (non-maleficence, "primum non nocere"), the principle of care (support, beneficence), and the principle of justice. The decision of how much a society should spend on investigations of orphan diseases and their therapies represents a moral dilemma. On one hand, these diseases affect only a small percentage of the individuals in a society. From a utilitarian perspective, the allocation of major resources for rare diseases is morally wrong because it does not maximize the aggregated overall benefit, i. e. the sum of welfare of all individuals in a society. On the other hand, society has a moral obligation to not abandon those people who are affected by an incurable orphan disease. Additionally, the medical field has the professional obligation of scientific progress, i. e. to increase our knowledge about diseases and their therapies. Hence, with regard to **justice**, the different principles contradict each other, depending on the standpoint from which they are assessed [28].

A recent example is the discussion about the world's most expensive drug to date — Zolgensma (onasemnogene abeparvovec) — produced by the Swiss pharmaceutical company Novartis. Gene therapy with Zolgensma slows muscle loss in severe spinal muscular atrophy (SMA1), which originates from an inherited homozygous defect in the SMN1 gene. Based on gene therapy by means of an adenoviral vector, Zolgensma leads to the integration of a functioning variant of the SMN1 gene into the spinal cord motoneurons, supporting their survival and maintenance of their function. Our knowledge of the benefit of Zolgensma is mainly based on a small trial including 12 children, of whom the majority achieved head control, and two-thirds can sit without support. Twenty-four months after application, all children were still alive [29]. In 2020, the European Medicines Agency approved the drug. The costs for the singular gene therapy amount to about 2 million Euro, and this so-called "value-based pricing" has been the subject of controversial discussions. According to the producers, single therapies that approach the genetic cause of a disease require different assessment compared to chronic therapies. In Germany, this gene therapy will go through the necessary benefit assessment process, according to AMNOG, during the upcoming months. It is of particular medico-ethical, political, and medico-economic relevance that the medication was originally developed in non-profit and donation-funded labs in the USA and France [30].

The **utilitarian point of view**, in the sense of maximizing the common welfare, is the basis of economic evaluation for prioritization in health politics. However, there is no full consensus regarding which values must be maximized. One typical measure is the so-called loss of healthy life years (disability-adjusted life years; DALY). The DALY concept was first presented in 1993 by the World Bank, and is intended to measure the importance of different diseases for the society, including the efficiency of interventions (prevention and treatment), as "economic unit per DALY gained" [31]. Besides the principle of maximization, there is also the indigence and equality principle. According to the definition, each single rare disease does not frequently occur; however, the entirety of rare diseases affects a relatively high number of people. Thus, Gericke and co-authors asked two relevant questions [28]: "What level of resources should be devoted to orphan disease research overall?" and "What level of resources should be allocated to each individual disease?". Further problems in the context of economic assessment arise regarding the allocation of resources for research purposes, due to the extreme uncertainty regarding success or benefit. The minimal market needed to arouse industry interest in developing an orphan drug is estimated as 100 million US dollars [32], and it is probably actually much higher.

Besides the utilitarian point of view, there is also a **legal claim**. This is mentioned, for example, in the Charter of Fundamental Rights of the EU regarding access to medical care and the right of medical service within the context of the respective national law. However, strictly speaking, this does not affect the right or the claim of research funding for presently non-existing therapies [28]. In terms of the **principle of care (support, beneficence)**, the requirements of provision and weighing apply for the actors, as well as the balance of service, risk, and costs.

The concept of **non-abandonment** applies to the field of rare diseases since they are neglected due to the low or absent economic incentives for research and development—at least without governmental incentives. The different levels of political and social efforts described in this article, which aim to increase knowledge about rare diseases and to improve the diagnosis, care, and treatment of patients suffering from rare diseases, must be assessed in the context of non-abandonment. These various moral obligations require (financial) support of the investigation of orphan diseases and their therapies, including the development of orphan drugs, on multiple levels [28]. The success of these political and social activities is clearly confirmed by the significantly increased number of approved medicines for the treatment of rare diseases [7].

Nonetheless, many ethical aspects and challenges in the field of rare diseases remain unsolved. Many issues are related to the different standards and rules in various countries, and could be improved by stronger international and global approaches. The composition of the decision-making bodies plays an important role in terms of weighing and solving ethical dilemmas, and in fairly distributing resources [33]. Advances in DNA sequencing, and current developments in genome editing and genome surgery (e. g. the CRISPR/Cas method, and in vivo gene therapy using adenoviral vectors) will likely introduce new medico-ethical challenges, including in the field of orphan diseases [34–37].

7. Legal Aspects and Outpatient Specialist Care[1]

Few legal regulations exist regarding the topic of rare diseases. In fact, rare diseases are explicitly mentioned only in in Germany in §116b of the 5th Social Security Code (SGB V), in the context of regulating the outpatient specialist care. Since rare diseases are defined only based on their prevalence, there is no limitation to severe courses. Thus, a suspected diagnosis is sufficient to gain access to specialist treatment [38].

Rare diseases are also relevant in the context of so-called **off-label use**, i. e. when medicines are applied for indications that are not included in the current approval. Such applications are only allowed in exceptional cases — at least with regards to statutory health insurances — and the presence of an extremely rare disease that cannot be systematically investigated is considered as such an exception. This is cited in the settled case-law of the BSG (see BSG judgement dated March 19, 2002 – B 1 KR 37/00 R, NJW 2003, 460), and in the so-called "Nikolaus judgement" of the Federal Constitutional Court (Bundesverfassungsgericht). According to the guiding principle, it is incompatible with the fundamental rights (Art. 2 Abs. 1 GG) combined with the welfare state principle (Art. 2 Abs. 2 Satz 1 GG) to exclude patients with statutory health insurance from deliberately chosen medical treatment of a life-threatening or regularly lethal disease for which generally acknowledged medical standard therapy is not available, if there is a reasonable prospect of a cure or a noticeable positive effect on the disease course (BVerfG, Judgement dated December 6, 2005–1 BvR 347/98, NJW 2006, 891). According to these requirements, § 31 Abs. 1 S. 4 SGB V states that in single medically justified cases, physicians may prescribe medicines that are actually excluded from specific medical care [39, 40].

Finally, the question has been raised about the **liability in cases of non-recognition of a rare disease**. Jurisdiction has decided that a (hospital) doctor is not liable for diagnostic errors of diseases that are practically not encountered (OLG Koblenz, Judgement dated January 27, 2014–5 U 1383/13, MedR 2015, 38 ff).

8. German National Action Alliance for People with Rare Diseases (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen; NAMSE)

The National Alliance for People with Rare Diseases (NAMSE) in Germany was founded in 2010 as an association of the Federal Ministry of Health, the Federal Ministry of Education and Research, and the Alliance of Chronic Rare Diseases (Allianz Chronischer Seltener Erkrankungen, ACHSE), together with 25 partners (exclusively umbrella organizations and associations of the most important actors in healthcare), by adopting a common declaration as a coordination and communication institution. This alliance was formed with the objective of initiating better healthcare for patients with rare diseases based on already existing structures and European experiences. It pools existing initiatives, networks researchers, and physicians, and summarizes information for physicians and patients (www.namse.de).

Since 2011, the Federal Ministry of Education and Research (BMBF) has also contributed to the **International Rare Diseases Research Consortium (IRDiRC)** with promotion of national associations for rare diseases, which was founded by the European Commission and the US National Institute of Health (NIH). Contributors to the IRDiRC comprise over 50 international partners, including research funding organizations like the BMBF, patient associations, and industry partners. Also in 2011, the "GKV Versorgungsstrukturgesetz" (Healthcare Structures Act) introduced **outpatient specialist care** (Ambulante spezialfachärztliche Versorgung, ASV) with §116b SGB V. This is a new healthcare sector in which panel physicians and hospital outpatient departments care for patients according to standardized requirements.

In 2014, the central information platform on rare diseases, called **ZIPSE**, was established to provide quality-assured knowledge and information about rare diseases to patients and their relatives, as well as to medical, therapeutic, and nursing staff (www.portal-se.de). This platform does not provide primary information, but rather links to already existing and quality-assured proposals regarding rare diseases, such as Orphanet, ACHSE, SE atlas, and centers for rare diseases.

In 2013, NAMSE published a national action plan including 52 proposed measures to coordinate and organize future action of the German healthcare and social system in the context of rare diseases. This plan describes a three-stage center model. The criteria for type A centers (reference centers) and type B centers (centers of expertise) were established and operationalized by a NAMSE task force, and published by the partners in 2014.

One element of NAMSE is a project called the **Open Source Registry System for Rare Diseases (OSSE)**, which is funded by the German Federal Ministry of Health. The aim of this project is to allow patient associations, hospitals, researchers, and other involved people to establish patient registries using an open-source software, which will lead to strengthening the national registry landscape. In the context of OSSE, a minimal dataset was developed, which has since been replaced by an EU version. This dataset should be the basis for all participating registries, to allow and foster the retrievability of and the exchange with registries (www.osse-register.de).

Since 2009, **centers for rare diseases** have been established at German University Hospitals, which are committed to the healthcare of patients with orphan diseases. One action of NAMSE is the provision of the **healthcare atlas for people with rare diseases** (Versorgungsatlas für Menschen mit seltenen Erkrankungen, **se-atlas**). This internet portal offers information and a comprehensive overview of healthcare possibilities and self-help organizations for people with rare diseases, their relatives, physicians, non-medical staff, and the general public. Links are available regarding centers for rare diseases in Germany, an overview of umbrella institutions, an overview of certified institutions, and an overview of **European reference networks (ERN)** (www.se-atlas.de)

For rare diseases within the field of oto-rhino-laryngology, head and neck surgery, the European Reference Network for craniofacial anomalies and ear, nose, and neck disorders is a relevant examp-

[1] The chapter on legal aspects was mainly created by Dr. jur. Carina Dorneck, M.mel., Faculty of Law, Martin Luther University Halle-Wittenberg.

le (https://ern-cranio.eu). The topic of rare diseases has also been integrated into the national competence-based catalog of learning targets of medicine (NKLM) and dental medicine, the new licensing regulations for physicians, the healthcare strengthening act of the statutory health insurances regarding the development of enabling regulations for university outpatient departments (§ 117 SGB V), and the Hospital Structure Act with consideration of specific tasks for hospital centers due to particular provisions. The Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) has decided that special tasks must be financed via center supplements because they are services for patients from other hospitals (e. g. interdisciplinary boards) or overarching tasks (e. g. keeping and evaluating registries). Since 2016, high-throughput sequencing for diagnostics of rare diseases has been included in the general assessment standard (Einheitlicher Bewertungsmaßstab, EBM). With the sample dataset of 2020, the DIMDI published standardized codes for rare diseases. Beside the alpha ID code and the ICD-10 code, they also contain the so-called ORPHAcode from Orphanet. In 2020, the BfArM published the alpha ID SE version for 2021, containing the respective ORPHAcode from Orphanet for a large number of the rare disease entries. The 2021 version includes 8043 diagnoses with ORPHA code.

Another project that was established by the Federal Ministry of Health as part of NAMSE is the **central information portal about rare diseases** (Zentrales Informationsportal über seltene Erkrankungen, ZIPSE). At the end of 2019, this project was taken over by the Foundation of Health Knowledge (Stiftung Gesundheitswissen). Here, patients and relatives can find an overview of the medical, therapeutic, and nursing service providers in the field of rare diseases. Quality-assured information, particularly concerning diagnostics, therapy, self-help, healthcare institutions, research, and registries, are listed according to specific criteria (adapted from https://www.portal-se.de/ziele).

9. Alliance of Chronic Rare Diseases (Allianz chronischer seltener Erkrankungen, ACHSE)

ACHSE is a network of self-help organizations, which is intended to be a voice, multiplier, and mediator to address the needs and problems of patients with rare diseases. It promotes knowledge about these diseases within the population, and among interested representatives, physicians, and therapists. ACHSE tasks include the support of patients and relatives, networking of physicians and therapists, research funding, sensitization of the public, representation of political interests, and improvement of information and knowledge management (adapted from www.achse-online.de). Moreover, the ACHSE participates in the annual "**Rare Disease Day**", which is an international day dedicated to rare diseases on the last day in February (www.rarediseaseday.org). This campaign primarily addresses the general public, politicians and healthcare politicians, industry representatives, researchers, therapists, and all people who are interested in rare diseases.

10. Research and Research Funding

Investigating rare diseases can lead to insights regarding fundamental biomedical processes and correlations, and the discovery of knowledge that is also essential for identifying causes and origins of frequently occurring diseases. In 1657, William Harvey wrote that "… Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. …" [41]. Researchers, pharmaceutical industries, and sponsors have long understood that scientific experience related to the investigation of rare diseases provides benefits in the context of frequent diseases, and useful knowledge about their mechanisms and therapies. This is largely because many orphan diseases result from single gene mutations, allowing scientists to observe the sequelae of gene defects, as they could in a well-controlled experiment. A good example is the investigation of familial hypercholesterinemia, which led to the development of statins [28].

For the clinical and patient-oriented investigation of rare diseases, it is extremely important to work in supra-regional or international structures. In this context, **disease registries** play a central role. A disease registry with clear quality criteria regarding completeness may serve as a basis for the generation of evidence through high-quality clinical trials, particularly non-randomized trials.

Among the projects in the field of orphan diseases that are funded by different institutions in Germany, about half are related to rare cancer diseases. Projects related to rare genetic diseases are the second most prevalent. At this time, comprehensive data are not available regarding the resources provided in Germany for the investigation of orphan diseases and the systematic assessment of all research activities.

Since 2013, the **Federal Ministry for Education and Research** (Bundesministerium für Bildung und Forschung, BMBF) has fostered national research associations for rare diseases. The activities of these associations are focused on information about disease origins, as well as diagnosis and therapy research. They cover a broad spectrum of rare diseases, including immunology, developmental disorders, kidney diseases, nervous system diseases, and metabolic disorders. The organization particularly focuses on funding projects oriented towards translation. In February 2018, the BMBF published a guideline regarding the promotion of translation-based projects in the field of rare diseases.

The BMBF and the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) participate in the **European Joint Program on Rare diseases (EJP RD)**. This program receives financial support from the EU, and entails the cooperation of 130 institutions from 35 countries to create a comprehensive sustainable research ecosystem from 2019–2024, with the aim of establishing improved coordination and feedback between research, healthcare, and medical innovation. In addition to the coordinated access to data, training activities, and accelerated translation — international research funding is an integral part of this program. It comprises the promotion of networking meetings for knowledge exchange, and the cooperation of industry and academia to work on specific research challenges as well as transnational research associations. For the latter, the contributing 31 research sponsors from 23 countries have expanded their activities initiated in E-Rare. BMBF and DFG participated in the first two publications from 2019 and

2020, and two additional publications are planned (adapted from www.namse.de).

In 2021, the **innovation fund** of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) will promote guideline projects on rare diseases. The funding occurs in two different ways. On one hand, the innovation fund promotes the creation or updating of complete guidelines. On the other hand, the fund supports evidence-based research of the institute of quality and efficiency in healthcare (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) in the context of single clinically relevant issues regarding guidelines.

The **International Rare Diseases Research Consortium (IRDiRC)** includes governmental and non-profit organizations, pharmaceutic and biotechnological companies, and an umbrella organization for patient interests and scientists with the objective of promoting investigations of rare diseases worldwide. In 2017, the IRDiRC formulated a vision for research regarding rare diseases. By 2027, all patients suffering from known orphan diseases should obtain an accurate diagnosis, healthcare, and available therapies within one year after their first medical consultation. Additionally, 1000 new treatment approaches should be approved—particularly for the rare diseases for which therapy options are not presently available [42].

Furthermore, several foundations provide funding for the investigation of rare diseases. One example is the **Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen** (www.elhks.de) that fosters improved medical care for people with orphan diseases via targeted research funding. This foundation mainly addresses relevant challenges associated with new approaches to quality-assured molecular genetic diagnostics, acceleration of the development of specific therapies, and the expansion of expert networks. The annual Eva Luise Köhler Research Award is one of the most established awards in this research field.

11. Conclusion

Rare diseases are particularly challenging in terms of diagnostics, pre-clinical and clinical research, interdisciplinary and multiprofessional management, and adequate funding—including for accounting, coding, and regulatory aspects. They often entail specific requirements in the context of the physician–patient relationship, follow-up, and communication with co-treating physicians. Moreover, orphan diseases represent a medico-ethical challenge, particularly in the context of allocation in terms of healthcare and research. It is highly important to establish funding for information management and public relations efforts, as well as for training and education and conscious research — including national and international networking, registry creation and maintenance, and the establishment of clinical centers. Additionally, self-help plays an important role in the well-being of patients and their relatives. They often have the best knowledge about their diseases, and it may be helpful to combine this knowledge with the expertise of service providers.

In light of the manifold challenges, over recent years, good results have been achieved through politically, academically, and self-help established activities, with contributions of different stakeholders. However, many issues are still present and require our attention and commitment, in order to diagnose rare diseases without unnecessary delay, and to provide our patients with access to adequate treatment in suitable centers.

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Conflict of interest

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