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Reviews

Rare cancers—Rarity as a cost and value argument

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ABSTRACT

Here is a paradox in medicine: rare diseases are unusual, but developing a rare disease is quite frequent. This is also true for rare forms of cancer. Almost every 20th person in the world suffers from a rare disease, and about one quarter of all new diagnosed cancers belong to rare cancers. The downside of rare diseases for patients is the difficulty to find the right institution for their treatment, for health care payers it is the costly treatments, and for medical professionals their limited knowledge if they are not specialized in the disease in question. On the other hand, the upside for clinical researchers is that rare diseases are beneficial for their scientific careers, as many clinical and scientific questions are still open. The advantages for the pharmaceutical industry are the premium prices, the special governmental programs to stimulate research, and achieving a dominant position in a small market. To sum up, rare cancers are important for all stakeholders in medical care and deserve more attention from public health research.
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Contents

1. Rare diseases are quite frequent

About 7000–8000 of the 30,000 known diseases are rare diseases, also commonly known as orphan diseases [1]. The European Union (EU) defines a rare disease as having a prevalence of less than 500 cases per million people [2]. In contrast, rare diseases in other countries are defined through different prevalence rates: e.g., in United States (US) 750, in Japan 400, and in Australia 120 patients per million people [3].

It seems paradoxical that, while the patient population for each rare condition is small, the aggregate population of people living with a rare disease is large. Moreover, many people living with a rare disease do not know that they are ill, or they search unsuccessfully for a diagnosis or therapy. The prevalence of all rare diseases is approximately 5%, with about 400 million rare disease patients worldwide. In the EU, 27–36 million people suffer from rare diseases. In the US, where there are approximately 25 million citizens with rare diseases, the estimated prevalence is similar to that in the EU [4]. In Germany alone, approximately 4 million patients suffer from a rare disease [5]. This generates a paradox of rarity: suffering from a rare disease is actually quite common.

One of the most common and well-known rare diseases is cystic fibrosis (CF) or mucoviscidosis. CF has a prevalence of 500 in a million in Europe and is a complex lifelong chronic disease caused by genetic mutations. Like in CF, in 80% of rare diseases, a gene defect causes the condition. In most cases, CF affects multiple organ systems. The average life expectancy for patients with CF has increased from only a few months in the 1950s to 30–50 years nowadays. In Germany, there are about 8000 patients living with diagnosed CF. In contrast to CF, ribose-5-phosphate isomerase deficiency is

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the rarest disease in the world, with only one known case. Therefore, researchers need to be cautious when formulating general statements on rare diseases.

Clinical research has developed very effective treatments for many rare diseases in recent years. However, many of these are quite costly. For instance, the lifetime costs of treating a patient with type 1 Gaucher's disease in a Dutch setting is 5,716,473 Euro [6]. For many other diseases, a symptomatic or no treatment is available.

In contrast to rare diseases in general, the definition of rare cancers is based on incidence instead of prevalence because prevalence can be a misleading indicator of rarity for disorders that occur infrequently. In the EU, cancers are commonly classed as rare when they have an incidence of ≤60 per million people per year [7]. However, the US National Cancer Institute defines rare cancers as having an incidence rate of 150 per million people per year. About 22–27% of all diagnosed cancers are rare (22% of all annual cancer diagnosis in the EU [7]), and they cause about one quarter of all deaths by cancer [8–10]. Similar to rare diseases in general, it is useful to distinguish between "frequent rare cancers" such as stomach, head, and neck cancer and "rare rare cancers" such as eye cancer. Clinical research has developed individualized medical concepts to treat rare carcinoids. However, these concepts lead to high, and in some cases very high, treatment costs for patients. Moreover, personalized medicine and increasingly sophisticated molecular pathology lead to new challenges for developing and price setting of orphan products.

In this paper, we discuss the public health and economic challenges posed by rare diseases. We also draw attention to the specific challenges that rare forms of cancer present for health care systems and clinical and public health research, and in particular the assessment of value for innovative treatments for rare cancers, and the role of precision medicine and targeted therapies.

2. Rare diseases from an economic point of view

In the well-known article "The Voluntary Exchange Theory of Public Economy" [11], published in 1939 by Richard Musgrave, the responsibilities of a government are structured into three major "branches": the stabilization of the economy, (re)distribution, and achievement of an efficient allocation of resources. This conceptual division of the responsibilities of governments can also be transferred to health care systems. From an economic viewpoint, we can identify three major tasks for health care systems. Firstly, high-quality health care has to be provided consistently and appropriately to all patients in a country (stabilization). Consequently, people should not face disadvantages in the health care system because of the rarity of their diseases; more precisely, all patients should have equal access to health care facilities. The system should prioritize those who have the largest needs, and accordingly, the financing scheme of the health care system should pursue society's equity values (distribution). Health services should function effectively, and the health care system should use the scarce resources efficiently in order to maximize the wellbeing of patients (allocation). These are precisely the economic challenges of health policy in all countries, and they apply to the treatment of rare diseases in particular.

3. Challenges for the health care system posed by rare diseases in general

Rare diseases pose a number of challenges for health care systems. From a dual economic and organizational point of view, the following six issues can be formulated:

1. In many cases, the diagnosis of rare diseases is very difficult due to their rarity and heterogeneity. The majority of physicians have little or no experience with these disorders, e.g. rare childhood or rare eye cancer. Educational efforts and better information systems can help both physicians be more sensitive towards rare diseases and patients to reduce their time-consuming odyssey through the health care system. Patients often get neither the correct treatment nor a name for their illness. An accelerated and improved diagnosis through the use of novel diagnostic technologies based on genome sequencing methods could reduce health-related suffering and the underuse and misuse of health care resources. However, at this time, genome sequencing is very costly.
2. Because the number of rare disease patients is small, the question is how to organize appropriate care for these patients. Specifically, the health care system needs to create specialized outpatient care units. These centers should have close contact with medical universities to incorporate the recent innovations into the treatment of patients with rare diseases.
3. The distribution of specialized centers has to be decided by health care payers. They should consider whether the implementation of a few centers in each country or large region, or even only one center, is more suitable to serve rare disease patients. The EU has developed criteria to establish European Reference Networks (ERN) for rare diseases. The legal framework for creating a system of ERN was established with EU Article 12 of Directive 2011/24/EU [12]. To ensure the efficiency of health systems and access to high-quality health care, these networks should be able to collaborate, coordinate, and share their knowledge across borders. However, up to now, evidence regarding the efficiency and validation of organization models for complex networks such as ERN is missing. Furthermore, cross-border financing for ERN is challenging.
4. In many cases, the treatment of rare diseases is extremely costly. The cost of orphan drugs alone absorbs a significant and growing part of health care budgets due to the increasing number of declared orphan drugs with high prices. The budget impact of orphan drugs in Sweden and France was analyzed by British researchers using a dynamic forecasting model [13]. In 2013, orphan drugs amounted to 2.7% of the total drug expenditures in Sweden and 3.2% in France. By 2020, these costs are expected to reach 4.1% in Sweden and 4.9% in France [13]. Society in general and health care payers in particular need to decide how much they are willing to pay for the treatment of rare diseases. A macroeconomic allocation dilemma has resulted from having limited resources: if society's spending on the treatment of rare diseases increases, the resources for the treatment of more common diseases need to decrease.
5. Without special regulations and incentives, pharmaceutical companies will spend less money on the research and development of drugs used in the treatment of patients with rare diseases. This is due to the small market for these highly specialized drugs, given the low number of patients in comparison to broader indications, such as asthma, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, coronary heart disease (CHD), depression, and dementia [14]. National and supra-national organizations have imposed incentive schemes to stimulate research on the treatment of rare diseases. Since 2003, the European Commission, for instance, has approved 111 drugs as orphan drugs (including 6 anti-cancer drugs) in the EU [15]. These drugs go through a facilitated registration process. In general, after the licensing of a new drug, a health care payers' organization or a public institution decide on its pricing and reimbursement. This "fourth hurdle" has been imposed by many countries in the last years (Australia in 1987, Canada in 1994, and England in 1999). In 2011, Germany introduced its fourth

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hurdle with the Act on the Reform of the Market for Medical Products (AMNOG) in relation to price regulation. In all of these regulations for pricing and reimbursement, orphan drugs have a special status. For instance, in Germany, drugs with a market turnover of less than 50 million euros receive orphan drug status; therefore, companies can negotiate premium benefits with the Federal Association of Sickness Funds (e.g. companies do not have to provide an approval of additional benefit of the orphan drug).

6. The special status of orphan drugs has had an effect, and currently, pharmaceutical companies allocate 40% of their spending in biomedical research to research and development of cancer drugs [16] to treat, in many instances, cancers classed as rare diseases. The authors of a study for the German Federal Ministry of Health forecasted that the authorities would approve 30 to 50 new cancer drugs in Europe within the following five to seven years [17]. Moreover, pharmaceutical companies need incentives to conduct 'salami slicing'. Thereby, cancer indications are divided into smaller orphan sections, which are often based on genetic discrepancies of the tumor, so that pharmaceutical companies can use the benefits of the orphan drug legislation. A discussion is needed on whether this poses perverse incentives or not. For instance, in the US, launch prices of anticancer drugs increased substantially over time. On the one hand, it seems that the low number of persons that suffer from a certain disease is an argument for a higher rate. On the other hand, value-based pricing or clinical benefit concepts can set a more output-oriented incentive: The higher the additional value of the new drug compared to the second best alternative, the higher the sale price. Particular for orphan drugs, there is often no (second best) alternative treatment available, which makes the price setting process difficult. However, the concept of value-based pricing does not take into account the cost for the supplier to develop and market a product, which are normally higher for orphan drugs than for common drugs. Otherwise, high prices may just reflect the perverse incentives explained by the power of some stakeholders in the process of allocating public expenditures. In the context of molecular diagnostics and targeted therapies, which may lead to a situation when all diseases are rare diseases, this difficult discussion will become even more important.

In summary, research and heath care organization for rare diseases have been strongly debated topics among all stakeholders. For instance, many actions in the past few years aimed at improving the treatment of patients with rare diseases were initiated by the EU, such as a concerted action plan known as EUROPLAN (European Project for Rare Diseases National Plans Development). Additionally, an expert commission for rare diseases named EUCERD (European Union Committee of Experts on Rare Diseases) has been founded, which provides advice to the European Commission and assists the Commission in international cooperation's. Overall, in the EU the implementation and initiation of national concerted action plans has been conducted in all member states. In the USA, an Orphan Drug Act was imposed, which covers both rare and non-rare diseases "for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug" [18]. For several years, there has been an ongoing debate on orphan drug policies and their reimbursement [9,14,19,20], [21]. Nonetheless, the global issue remains: what are the costs and benefits of worldwide activities ushered in to increase the awareness of rare diseases and to provide incentives to increase spending on research and development of treatments for these patients?

4. Challenges for the health care system posed by rare cancers

In addition to the above challenges presented by rare diseases in general, rare cancers pose additional challenges for the health care system.

1. Rare cancers are difficult to study due to the low patient numbers, poor diagnostic precision, and therapeutic mismanagement [8,22]. If available, historical and non-controlled studies are the basis for many of the standard treatments for rare cancers [23]. Hence, scientific societies and research networks in the area of rare cancers are essential for the development of new clinical and healthcare research in this field. With a particular focus on the progress of molecular biology and the increasing division of rare cancers into even rarer subgroups, international and intercontinental collaborations are necessary in order to conduct large trials in a subset of rare cancers. Extensive research is needed in the area of healthcare and therapy for rare cancers, as well as research in diagnostic accuracy, which presents challenges. Nevertheless, for all implemented specialized structures a long-term financial solution has to be ensured, as financial uncertainties can lead to an inhibition in the expansion of health care services.
2. The introduction of molecular techniques and genomic analysis as a diagnostic approach has led to the discovery of cancer variants. In the pre-molecular era, these variants may have represented a subset of a more common cancer. However, in the molecular, genomic, and post-genomic era these variants may represent several rare cancer subtypes. Taken to its extreme, this classification shift will be the basis for personalized medicine [24]. Although the technological opportunities for large-scale genotyping and the discovery of rare variants are available, cost constraints exist and inhibit a more substantial expansion of these methods [25]. To treat every variant of rare cancer as a singular clinical entity, new, non-conventional study designs and research methods might be necessary to enable at least some low-level evidence-based health care [26]. From a health economic viewpoint, there is a tradeoff between the very high costs of personalized medicine, as well as the high costs of the development of subtype-specific drugs, and the availability of effective treatment options for small subgroups of rare cancers.
3. Reference networks and specialized care units can help to improve the management of patients and quality of care in the field of rare cancers. Knowledge among physicians about treatment options and management of rare cancers is often very limited [8]. As suggested earlier in relation to healthcare for rare diseases, health care systems need to create reference centers and specialized care units for rare cancers to avoid therapeutic mismanagement, delays in diagnostic due to poor diagnostic precision, and difficulties in accessing information [23]. Reference networks improve the access to clinical trials for patients with rare cancers, and enable the gathering of exhaustive data about small populations [8], [23]. Nonetheless, specialized health care structures need sufficient financial resources.
4. Biobanks and registries for rare cancers are crucial for medical research. Population-based registries provide fundamental data on incidence, prevalence, and survival rates of rare cancers [7]. The development of new treatment options in rare cancers has increased considerably through medical research using biobanks. Both registries and biobanks, however, need to consider data protection aspects and ethical principles [27]. Registries and biobanks are especially important for medical research in rare pediatric cancers. In developed countries, pediatric cancer is still the primary cause of death by disease among

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children [28]. Particularly for rare pediatric cancers, medical advances and research using biobanks and registers can increase the chance of cure.

5. New research methods are needed because of the increasing stratification of cancers. Conventional, powerful trial designs, like a hypothesis-testing randomized controlled trial with treatment comparisons, require large numbers of patients, and for many rare cancers, such quality evidence is not available. The existing evidence consists mainly of retrospective case series and case reports [26], [29]. For small study populations, Bayesian-design trials may help generate some evidence. Additionally, clinical studies should incorporate quality of life as an outcome measure and patients preferences as an endpoint [27]. To ensure that patients with rare cancers receive appropriate healthcare, research has to develop new, pragmatic, efficient, and economical treatment options.
6. The development of new drugs for rare cancer faces several challenges and needs. Substantial evidence and safety approval is needed for all drugs, irrespective of their indication's rarity. For rare indications, all available data should be used in order to establish the efficacy of an intervention, which can be achieved through formal collaborations among reference centers [27], [30]. However, incentives for the development of orphan drugs by pharmaceutical companies are also necessary. Additionally, drug repositioning can be an efficient approach to drug discovery for rare cancers [31].

A comprehensive and overall task for all stakeholders is the generation of evidence-based information about rare cancers. RARECARE is a scientific research program on rare cancers in Europe to estimate the burden of rare cancers in Europe and to improve the quality of the data on rare cancers [32]. Society's goal is to ensure that patients with rare cancers do not face disadvantages in the health care system. Still, because of the rarity and heterogeneity of these diseases, healthcare costs can be extremely high [33].

5. Challenges for orphan drugs' price setting

A highly debated question is, if prices for innovative drugs to treat rare cancer patients are too high or too low. If prices are too high, payers pay too much relatively to other health services and give an incentive to pharmaceutical industry to spend too much for research and development (R&D). If reimbursement prices are too low, there are no incentives to develop drugs for the treatment of patient with rare diseases.

Prices in general have different functions, among others an allocative and a distributional function. Prices on a "normal market" reflect the consumer's willingness to pay, the production cost of the suppliers, the scarcity of the goods and the market structure, e.g. the number of suppliers and consumers and the form of competition (monopoly, oligopoly etc.). In reality, "normal markets" are rare. Modern economies show more of the "the winner gets all" markets. That means, the leading supplier can realize an extraordinary profit, while others do not receive a sufficient market share to survive in the long run. Typical "the winner gets all" markets are markets of the new economy and social media networks (e.g. Facebook, Google).

The market for health services is distorted by third party payers and supplier induced demands: The patient is the consumer, but doesn't pay and doesn't decide, the doctor decides the drug consumption, but does not pay either, and the health insurance pays without being the consumer nor the decision maker. This threefold segmented consumer side leads to the necessity that health insurers have to determine an appropriate price schedule for innovative drugs for rare cancer treatment, which gives enough incentives to the pharmaceutical industry to invest in R&D. However, these incentives should not be so strong, that R&D on rare disease drugs are not profitably any more. On the other hand, prices should be "fair", e.g. should lead to acceptable profit margins.

Different concepts are used in industrialized countries to solve these challenges. For instance, the National Health System (NHS) has used a concept of profit control for pharmaceutical companies. Through this the cost of the pharmaceutical suppliers were taken into account. Later on the NHS was one of the first health care systems which switched to a value based pricing concept. Other countries, like Germany, apply clinical benefit concepts, such as the comparative effectiveness of a drug, whereby the comparator is the best alternative current therapy. The effectiveness is measured in clinical outcome measures or survival rates. However, orphan drugs (defined with a revenue less than 50 million euros) are excluded from this process in Germany. That is why prices are the result of negotiations between the federal association of sickness funds and the pharmaceutical companies. Recently, France has adopted the NHS-approach by measuring the outcome of a therapy from the patient's perspective with the quality adjusted life year (QALY) concept.

All concepts have their pro and cons. The pros are that all concepts work and cover some of the aspects, which would play a role in the price setting in "free markets". The cons are that the concepts do not take into account the cost for the supplier to develop and market a product. It also does not consider the consumer's willingness to pay, e.g. patients. If the QALY gain due to a new drug in general (or in comparison to other drugs) is linear correlated with the willingness to pay (or additional willingness to pay) of the patients is an open question.

6. Patient and physicians reported outcomes about rare diseases

In a research project for the Federal Government of Germany, we asked patients suffering from rare diseases what factors they considered important for an appropriate treatment of their disease. The competence of the physician was identified as the most important factor, followed by excellent information, and easy access to medical aid. The importance of different health care aspects for patients with rare diseases is shown in Table 1. Surprisingly, it was not important for patients whether the treatment centers were close to their homes or not, as patients, if necessary, can arrange access for treatment outside the country [5].

Additionally, the therapy for cancer patients should involve patient preferences. For instance, the Center of Health Economics Research Hannover (CHERH) conducted a study on the preferences of patients with lung and colon cancer in Germany. The authors concluded that the overall survival is the most important attribute of a patient's treatment [34]. A nationwide survey in Korea analyzed the oncologist perspective on rare cancers and identified difficulties in treatment, a lack of guidelines and treatment options, and reimbursement issues for the physicians. Moreover, oncologists showed moderate preferences for high-volume centers and encouragement of off-label treatments [35]. These two examples show that sometimes the preferences of patients and oncologists are different from what might be assumed. In addition, oncologists do not always anticipate patients' preferences correctly.

7. Conclusion

From an economic viewpoint, health care systems should strive to achieve three goals, which are extremely difficult particularly in relation to rare diseases:

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Table 1
Importance of different health care aspects for patients with rare diseases.

How important are the following aspects of treatment of your disease?						
N = 47	*Very important*	*Important*	*Neutral*	*Less important*	*Unimportant*	*No information*
Close to home healthcare	12.8%	25,5%	36,2%	17,0	2,1	6,4
High level of expertise of the medical direction	85,1%	10,6%	0,0%	0,0%	0,0%	4,3%
Timely appointment	29,8%	46,8%	10,6%	8,5%	0,0%	4,3%
Good cooperation between medical and non-medical caregiver	44,7%	25,5%	17,0%	4,3%	0,0%	8,5%
Good collaboration with family doctor	46,8%	38,3%	6,4%	4,3%	0,0%	4,2%
Unchanging key contacts	40,4%	48,9%	6,4%	0,0%	0,0%	4,3%
Early access to diagnostic tools	42,6%	40,4%	4,3%	4,3%	4,3%	4,1%
Psychological care for patients and relatives	51,1%	34,0%	8,5%	2,1%	0,0%	4,3%
Fast access to new drugs	34,0%	29,8%	17,0%	8,5%	4,3%	6,4%
Availability of specially trained non-medical therapists	42,6%	29,8%	19,1%	2,1%	0,0%	6,4%
Easy access to aid	57,4%	23,4%	6,4%	6,4%	2,1%	4,3%
Information about new treatment options	61,7%	31,9%	2,1%	0,0%	0,0%	4,3%
Information about treatment centers	55,3%	31,9%	2,1%	0,0%	%0,0	10,7%
Access of treatment options outside Germany	12,8%	21,3%	36,2%	12,8%	10,6%	6,3%
Others	0,0%	0,0%	6,4%	0,0%	0,0%	93,6%

a) efficient production of health care
b) just distribution of resources
c) stable financing.

Because the number of patients suffering from rare diseases is large and the treatments are costly, these conditions pose an extraordinary financial and organizational challenge for health care payers. Furthermore, the treatment of these patients can be extremely difficult due to the heterogeneity of the diseases; in fact, for many of them, no effective therapy exists. Because of the rarity of these conditions, health care systems need to provide incentives to stimulate research for developing appropriate treatments. However, if unlimited budget resources were to be spent on rare diseases, this would increase the overall health care costs or, due to limited resources, lead to shortcomings in the provision of standard healthcare. The overarching goal is to provide high-quality care and meet patients' needs. A decisive approach can be the development of a network of high-competence centers for patients with rare diseases. Moreover, a critical review of the reimbursement system in healthcare is needed. Furthermore, comprehensive information systems for rare diseases can help both physicians and patients. The lack of high-quality information on the diagnosis and treatment of rare diseases in general, and particularly of rare cancers, is still apparent in many countries. The EU has provided an umbrella regulation to improve the treatment of rare disease patients, whose implementation is an ongoing process.

We think that new concepts for defining the prices for drugs for rare diseases in general and rare cancers in particular have to be developed. This is even more needed, if individualized medicine concepts come in place due to the development of genetic testing. The criteria have to be transparent and known ex ante to the suppliers. The prices must be fair and fit with the overall remuneration schedules for health services and goods. Non-public price negotiations between payers and suppliers do not fulfil this requirement. To develop those pricing schemes, science has to develop better concepts to measure patient preferences and benefit. The cost to develop new drugs must be transparent. In addition, we have to understand better the relationship between quality of life, risk and willingness to pay.

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