

# Rare disease burden of care and the economic impact on citizens in Germany, France and Italy

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## Executive summary

Over 7000 types of rare diseases have been identified, with one study suggesting that there may be as many as 10 876 rare diseases.<sup>1</sup> About 80% of rare diseases are of genetic origin, and 70% manifest in childhood. Globally, 400 million people have a rare disease.<sup>2</sup> No treatment is available for most rare diseases (as many as 95%).

Rare diseases present a societal concern owing to difficulties and delays in diagnosis, a lack of treatment availability, investment risk in developing treatments and the need for reliable regulatory and access conditions.<sup>3</sup> Up to 36 million people in the European Union (EU) live with a rare disease; some ultra-rare diseases affect only a handful of patients while other rare diseases affect several hundred thousand people.<sup>4</sup> Delayed diagnosis often complicates therapeutic options because rare diseases are progressive,<sup>3</sup> leading to loss of function, and the systemic impact may be permanent in the absence of early intervention.

Chiesi Global Rare Diseases, with support from IQVIA, set out to quantify the societal impact relative to the significant unmet needs of patients with rare diseases, first in the US and now in Europe. This paper reports on the direct, indirect and mortality-related costs for 23 rare diseases across five therapeutic areas in three EU member states (i.e. Germany, France and Italy). We benchmarked these costs against those for high-prevalence diseases such as diabetes, cardiovascular disease, Alzheimer's disease, arthritis and certain cancers. We explored the burden when treatment is available and provided a scenario analysis to show what the cost would have been if there were no effective treatment available for those diseases.

We found that indirect costs for the 23 rare diseases included averaged 29% of the total burden when treatment was available and increased to an average of 45% when no treatment was available. These data suggest that the availability of treatment creates positive value and alleviates financial strain on families and healthcare systems.

We present these data with the hope that stakeholders will act with urgency and optimism to enact policies that increase access to therapeutics. We also hope that the findings in our study can support patients and patient representatives, as well as policy-makers and other stakeholders in understanding the extent to which rare conditions affect individuals, society, and healthcare systems.

Comprehensive plans and meaningful societal support should be provided to patients with a rare disease and their families. We encourage further exploration, and hope that the next European Partnership for Rare Diseases, financed by the EU and its member states, will focus on the acute gap in research and treatments further, and on the totality of its impact.<sup>5</sup>

## Key findings

### ***The cost burden on families affected by a rare disease is significant***

The average burden for the high-prevalence diseases we used as a benchmark was €7000 per patient per year (PPPY).<sup>6</sup> In comparison, the average burden of the rare diseases we explored was €107 000 PPPY, which equates to an increase of more than 15 times.

Of this PPPY burden, indirect costs for the 23 rare diseases were found to average 29% of the total burden when treatment is available, rising to an average of 45% when no treatment is available. Significantly, most of these indirect costs (e.g. caregiver burden, home changes and costs of secondary treatments, travelling and accommodation) are borne by families.

### ***The availability of treatment creates positive value and alleviates financial strain on families and the healthcare systems assessed***






We directionally estimated that without any treatment options available, the overall burden PPPY would increase by 28% across the 23 diseases in focus. Furthermore, accelerating access to treatments for rare diseases has the potential to move the burden away from families and to mitigate incremental cost increases over time based on the savings they deliver.

## Methodology and analysis

### ***Building a database of representative therapeutic areas***

The 23 rare diseases (Figure 1) were selected from a variety of lists and the extensive literature review conducted for our US Burden of Rare Diseases report in 2021.<sup>7</sup> The included therapy areas and selected diseases were based on a review of more than 500 published articles and also lists in relevant databases including Orphanet and those produced by the National Organization for Rare Disorders as well as the Genetic and Rare Diseases Information Centre and other bodies of the US National Institutes of Health. The selections were also directly discussed with the IQVIA centres of excellence, several US based patient advocacy groups, and therapy area experts from 15 international institutions. The selected diseases and corresponding therapy areas were based on several criteria, including the degree of unmet need, relative importance to US-based patient advocacy groups, interest in the scientific community, prevalence and apparent burden of disease. Together, the 23 rare diseases selected affect approximately 227 000 people in Germany, France and Italy.

**Figure 1.** Summary of selected rare diseases

 <b>Metabolic disorders</b>	 <b>Haematological disorders</b>	 <b>Immunological disorders</b>	 <b>Congenital disorders</b>	 <b>Neurological disorders</b>
<ul style="list-style-type: none"><li>• Fabry disease</li><li>• Gaucher disease type I</li><li>• Mucopolysaccharidosis (Hunter, Hurler)</li><li>• Ornithine transcarbamylase deficiency</li><li>• Phenylketonuria</li></ul>	<ul style="list-style-type: none"><li>• Acquired aplastic anaemia</li><li>• Acute intermittent porphyria</li><li>• Atypical haemolytic uremic syndrome</li><li>• Beta thalassaemia major</li><li>• Sickle cell disease</li></ul>	<ul style="list-style-type: none"><li>• Autoimmune encephalitis</li><li>• Common variable immune deficiency</li><li>• Juvenile idiopathic arthritis</li><li>• Myasthenia gravis</li><li>• Pemphigus vulgaris</li></ul>	<ul style="list-style-type: none"><li>• Angelman syndrome</li><li>• Christianson syndrome</li><li>• Deletion 5p</li><li>• Fragile X syndrome</li></ul>	<ul style="list-style-type: none"><li>• Amyotrophic lateral sclerosis</li><li>• Ataxia telangiectasia</li><li>• Duchenne muscular dystrophy</li><li>• Early onset familial Alzheimer's disease</li></ul>

## Evaluating healthcare costs

Costs of care (Table 1) associated with the selected 23 rare diseases were explored through research of health economic reports, health technology assessment (HTA) reports and peer reviewed publications. Additional insights were gained from interviews conducted with physicians, rare disease specialists and experts in health economics. The overall cost burden was evaluated across three categories.

- **Direct costs** including the costs of treatment, medical procedures, hospitalizations, physician visits and home healthcare, and also other medical costs.
- **Indirect costs** including patient and caregiver productivity loss, work loss, home changes, travelling and accommodation for medical visits.
- **Mortality costs** based on the value of statistical life and the difference between average life expectancy and that for people with a rare disease.

**Table 1.** Cost categories included in the analysis

	Direct costs	Indirect costs	Mortality costs
<b>Definition</b>	<ul style="list-style-type: none"> <li>• All direct costs related to medical care</li> <li>• This burden is often assumed by patients and payers</li> </ul>	<ul style="list-style-type: none"> <li>• All indirect costs related to a specific condition</li> <li>• Economic burden derived mainly from patient and caregiver productivity losses</li> </ul>	<ul style="list-style-type: none"> <li>• Estimated VSL adjusted to patient lifespan:               <ul style="list-style-type: none"> <li>– €5 300 000 per life in Germany<sup>8</sup></li> <li>– €4 700 000 per life in France<sup>8</sup></li> <li>– €3 800 000 per life to reduce the risk by one in Italy<sup>8</sup></li> </ul> </li> </ul>
<b>Cost summary</b>	<ul style="list-style-type: none"> <li>• Prescription drugs</li> <li>• Medical procedures (e.g. dialysis)</li> <li>• Hospitalization (inpatient)</li> <li>• Hospitalization (outpatient)</li> <li>• Home healthcare</li> <li>• Professional services (e.g. nurse visits)</li> </ul>	<ul style="list-style-type: none"> <li>• Patient productivity loss</li> <li>• Caregiver burden</li> <li>• Home changes</li> <li>• Cost of secondary treatments</li> <li>• Travelling and accommodation costs</li> </ul>	<ul style="list-style-type: none"> <li>• Sum of all cash flows not generated by a patient because of an earlier-than-average death due to rare disease</li> </ul>
<b>Source</b>	<ul style="list-style-type: none"> <li>• PAGs</li> <li>• EU health economic reports and peer-reviewed publications</li> <li>• EU HTA reports</li> <li>• Expert interviews (physicians, specialists and health economic experts)</li> </ul>		<ul style="list-style-type: none"> <li>• EU health economic reports</li> </ul>

EU, European Union; HTA, health technology assessment; PAG, patient advocacy group; VSL, value of statistical life.

In Europe, high-prevalence chronic diseases are one of the major causes of morbidity and mortality, with approximately 35% of the European population reported to have a long standing (chronic) health problem.<sup>9</sup> Combined, high-prevalence diseases account for 70-80% of the costs of healthcare systems. Estimates of the total cost burden associated with 24 high-prevalence diseases (including diabetes, cardiovascular diseases, Alzheimer's disease, arthritis and certain cancers) were used for benchmark comparisons with the rare disease burden. These costs ranged from €3400 PPPY to €16 720 PPPY, with an average of €7000 PPPY.<sup>6</sup>

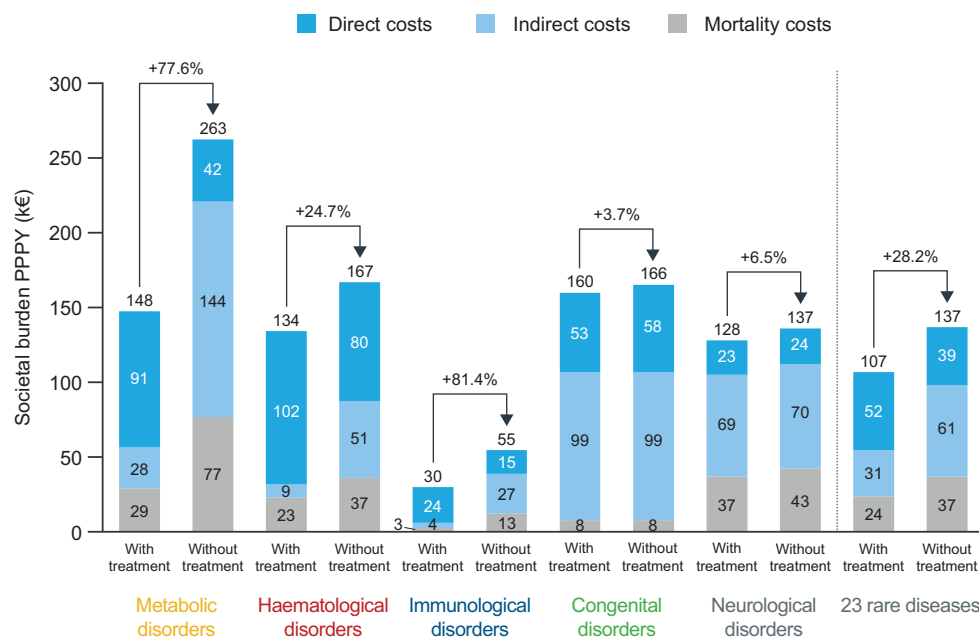
## Results

### Rare disease therapy areas display mixed cost profiles

Several factors affected overall cost profiles relating to the chosen therapy areas (Figure 2). These factors highlight ongoing challenges for rare disease drug developers and for patients and their families.

In metabolic diseases, enzyme replacement therapies slow down and limit progression of disease, but consistent treatment leads to a high proportion of direct costs. Several treatment options exist for the five haematological disorders in focus, with the economic burden being driven by concomitant treatments and some targeted therapies (e.g. eculizumab for atypical haemolytic uraemic syndrome). In immunological disorders, the lack of targeted, curative therapies coupled with a low quality of life leads to high unmet needs for patients despite comparatively lower economic burden compared with other therapeutic areas. In congenital diseases, patients generally do not achieve autonomy and require lifelong support leading to significant unmet needs for patients and their families. Finally, there are minimal treatment options available for patients with neurological disorders, who experience progressive neurodegeneration and a low quality of life.

**Figure 2.** Burden of disease PPPY (k€)<sup>a</sup> across selected rare diseases with and without treatment



<sup>a</sup>Please note that some totals do not match because of rounding.

PPPY, per patient per year.

### Scenario analysis assessing cost burden if treatment was not available

In our scenario analysis, we found that in most cases, compared with when treatment was available, without any treatment options available, the overall burden PPPY increased. Averaging the positive and negative scenarios, the overall percentage increase in costs was 28.2% across the 23 diseases in focus (Figure 2). Importantly, this is likely to be an underestimate because it does not consider the psychosocial aspects of disease management, both on patients and on caregivers.

In metabolic diseases the burden increased by 77.6% without treatment, primarily driven by reduced life expectancy without enzyme replacement therapies and the potential need for 24/7 care in mental-health facilities for patients with phenylketonuria (Figure 2). Haematological disease burden increased by 24.7% without treatment because patients would require additional care and would miss more work, driving greater productivity loss (Figure 2). Across immunological disorders, the burden increased by 81.4% without treatment because of productivity losses associated with the high burden of care that patients would require (Figure 2).

Across the congenital diseases assessed, the burden increased by 3.7% without treatment because there are currently no disease-modifying treatment options available, only basic treatments to manage symptoms such as epilepsy and attention deficit hyperactivity disorder (Figure 2). In neurological diseases, the burden increased 6.5% without treatment because patients are likely to experience accelerated neurodegeneration requiring more healthcare professional visits and hospitalizations (Figure 2).

**Additional perspectives to consider**

***The case for greater patient centrality in value assessments***

Significant burdens (e.g. patient productivity loss, caregiver burden, home changes and costs of secondary treatments, travelling and accommodation) are borne by citizens affected by rare diseases and their families. There is a need to factor in a degree of flexibility in the assessment of orphan drugs because many national assessments are designed to look at cost-effectiveness without sufficiently factoring in rarity and the need for flexibility in the production of evidence before and after marketing authorization.<sup>10-13</sup>

Although some flexibility already exists, there is much room for improvement and alignment in the way qualitative assessment and uncertainty related to orphan drugs are considered. Patient engagement in decision-making, however, remains a major unmet need across the markets we assessed (Table 2).<sup>14</sup> Examples that could be followed or adapted include Patient and Clinician Engagement meetings used in Scotland<sup>15</sup> or the Summary of Information for Patients used by the UK National Institute for Health and Care Excellence.<sup>16</sup>

There has also been increasing support for developing and implementing so-called value frameworks, which capture benefits beyond health gains traditionally measured in HTA procedures (such as the quality-adjusted life-year, or QALY).<sup>11-13</sup> Implementing a pan-EU HTA for orphan diseases by 2028 should be a step in the right direction to standardize and homogenize processes in the EU.<sup>17</sup> We hope for our data to contribute to a growing trend and body of evidence that aims to broaden the assessment of value of OMPs for citizens and society, with active patient involvement in the decision-making process.

**Table 2.** Summary of orphan pathways in selected countries<sup>11-14,18-20</sup>

EU member state	HTA approach to OMPs
Germany	<ul style="list-style-type: none"> <li>• Special regulation for ODs in the context of the early benefit assessment if costs lower than €30 million per year</li> <li>• Surrogate parameters are viewed critically and accepted only in individual cases</li> <li>• Patient involvement: Limited to presenting to but not voting in assessment committee</li> </ul>
France	<ul style="list-style-type: none"> <li>• Additional benefit is considered proven if the clinical demonstration matches with HAS methodology (HTA Committee). There is no specificity or exemption in terms of requirements for OMP</li> <li>• Early access procedures are available for all innovative drugs in unmet need situations</li> <li>• Accelerated HTA procedures are only available for cost-effective drugs</li> <li>• Patient involvement at the present stage: Limited to a written contribution in the HTA dossier</li> </ul>
Italy	<ul style="list-style-type: none"> <li>• No additional benefit based on a specific cost-effectiveness threshold</li> <li>• Innovation fund available for certain drugs – OMPs fulfilling a certain degree of unmet need and therapeutic advantage combination are eligible</li> <li>• Budget impact is a key consideration. No explicit process for incorporating societal preferences or sustainability of innovation in rare diseases</li> <li>• Patient involvement at present stage: Limited/Absent</li> </ul>

EU, European Union; HAS, Haute Autorité de Santé; HTA, health technology assessment; MA, marketing authorization; OMP, orphan medicinal product.

## Implications and recommendations

The United Nations Sustainable Development Goal 3 aims to “ensure healthy lives and well being for all at all ages”. However, the lack of resources and funding in the rare disease space makes it difficult for patients with a rare disease to have the same access to and opportunity for healthy lives and well-being as patients with a high-prevalence disease.<sup>12</sup> In an attempt to address these issues, we provide four recommendations (Figure 3), each addressing an implication derived from our study.

**IMPLICATION 1:** the impact of the 23 rare diseases is substantial, and families affected by any of these diseases shoulder an inequitable burden compared with patients with one or more high-prevalence conditions. Furthermore, accelerating access to treatment via expedited mechanisms of pricing and reimbursement has the potential to mitigate incremental cost increases over time based on the PPPY savings they deliver.

**RECOMMENDATION 1:** recommit to collaboration and coordination that will improve research and innovation,<sup>21</sup> bringing together multidisciplinary expertise to leverage advancements in technology to their fullest extent, leading to more available treatments for people living with a rare disease.

**IMPLICATION 2:** the impact of rare diseases is higher in the absence of treatment than in its presence, with a particular effect on indirect costs, with substantial repercussions on patients’ personal and financial health. Indeed, our results showed that rare disease treatments create value for society and move the burden away from patients and to healthcare systems, which are better equipped to shoulder it.

**RECOMMENDATION 2:** reaffirm the fundamental importance of the voice of patients and caregivers, by placing their experience of diagnosis, access to treatment and ongoing care at the centre of decision-making and ensure their views are heard and represented at every opportunity and discussion.

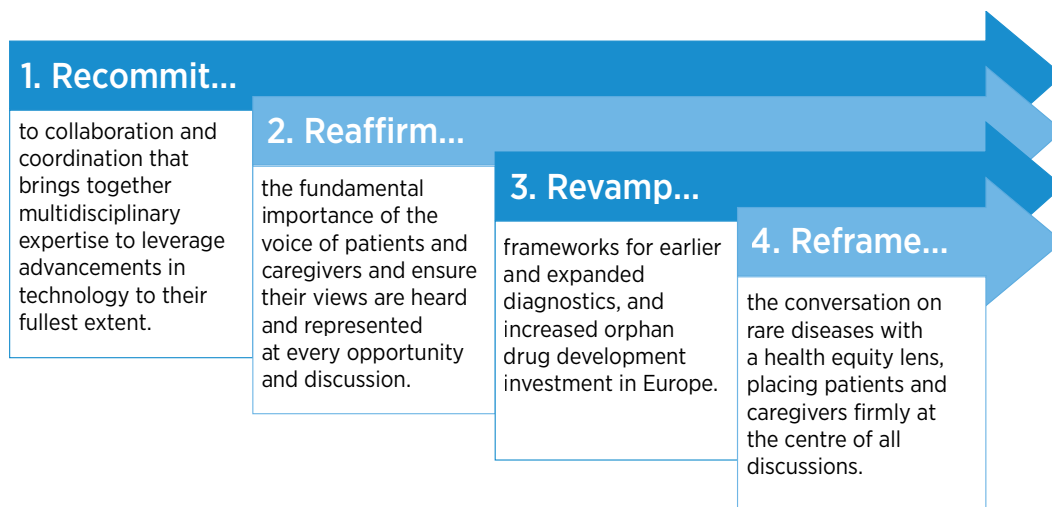
**IMPLICATION 3:** opportunities for investment in rare diseases are strong globally, but Europe is not leading when compared with the US and China.<sup>22</sup>

**RECOMMENDATION 3:** revamp frameworks for earlier and expanded diagnostics, and increased orphan drug development investment in Europe.

**IMPLICATION 4:** there is no sustainable movement towards equity without increasing patient engagement and leading from the patient perspective.

**RECOMMENDATION 4:** reframe the conversation on rare diseases with a health equity lens, placing the patients and caregivers firmly at the centre of all discussions.

**Figure 3.** Recommendation summary



## **Conclusion: A way forward**

Advances in technology, such as genomics and big data, have enabled researchers to better understand the underlying causes of rare diseases, which in turn has led to an increase in funding for research and development of treatments. In this context, revision of European pharmaceutical legislation should also contribute to enhancing competitiveness and stimulating continuous innovation in Europe, including technology for the early diagnosis of rare diseases.

On a national level, payers should consider the burden of rare diseases and adopt more flexible payment models to allow for timely access to therapies. Future research that supports the value equation should also include the calculation of intangible burdens such as stigmatization and depression.

The data we have developed opens the door to a more granular way of thinking about rare diseases, which takes into account positive and negative societal aspects of rare diseases and how to resolve them in future policies and societal commitments. Indeed, accelerating access to treatments for rare diseases has the potential to move the burden away from families and to mitigate incremental cost increases over time based on the savings they deliver.

We urge all stakeholders, including payers, patients, industry, academia, healthcare providers, policy-makers and regulators, to come together in partnership, committing to finding shared solutions that improve the quality of life and outcomes for all patients. Improving funding, access and innovation in the rare disease space will not only serve to achieve the goals set forth by the United Nations but will also help to create positive value and bring down the overarching economic costs that rare diseases impose on families and healthcare systems.

## **Authors and funding**

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## References

1. Haendel M, Vasilevsky N, Unni D et al. How many rare diseases are there? *Nat Rev Drug Discov* 2020;19:77–78.
2. Global Genes. Rare disease facts. Available from: <https://globalgenes.org/rare-disease-facts/> (Accessed 4 October 2023).
3. Nestler-Parr S, Korchagina D, Toumi M et al. Challenges in research and health technology assessment of rare disease technologies: report of the ISPOR Rare Disease Special Interest Group. *Value Health* 2018;21:493–500.
4. European Commission. Rare diseases. Available from: [https://health.ec.europa.eu/non-communicable-diseases/expert-group-public-health/rare-diseases\\_en#:~:text=There%20are%20more%20than%206000,70%25%20already%20start%20in%20childhood](https://health.ec.europa.eu/non-communicable-diseases/expert-group-public-health/rare-diseases_en#:~:text=There%20are%20more%20than%206000,70%25%20already%20start%20in%20childhood) (Accessed 4 October 2023).
5. European Commission. Draft proposal for a European Partnership under Horizon Europe: rare diseases. 2022. Available from: [https://research-and-innovation.ec.europa.eu/system/files/2022-02/ec\\_rtd\\_he-partnerships-rare-diseases.pdf](https://research-and-innovation.ec.europa.eu/system/files/2022-02/ec_rtd_he-partnerships-rare-diseases.pdf) (Accessed 10 October 2023).
6. Meersens. Chronic diseases, who will pay the bill? Available from: <https://meersens.com/chronic-diseases-who-will-pay-the-bill/?lang=en> (Accessed 9 October 2023).
7. Chiesi Global Rare Diseases. The burden of rare diseases: an economic evaluation. 2022. Available from: [https://chiesirarediseases.com/assets/pdf/chiesiglobalrarediseases.whitepaper-feb.-2022\\_production-proof.pdf](https://chiesirarediseases.com/assets/pdf/chiesiglobalrarediseases.whitepaper-feb.-2022_production-proof.pdf) (Accessed 9 October 2023).
8. Sweis NJ. Revisiting the value of a statistical life: an international approach during COVID-19. 2022;24:259-72.
9. Eurostat. Self-perceived health statistics. 2022. Available from: [https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Self-perceived\\_health\\_statistics&oldid=509628](https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Self-perceived_health_statistics&oldid=509628) (Accessed 09 October 2023).
10. Annemans L, Ayme S, Le Cam Y et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). *Orphanet J Rare Dis* 2017;12:50.
11. Czech M, Baran-Kooiker A, Atikeler K et al. A review of rare disease policies and orphan drug reimbursement systems in 12 Eurasian countries. *Front Public Health* 2019;7:416.
12. Ollendorf DA, Chapman RH, Pearson SD. Evaluating and valuing drugs for rare conditions: no easy answers. *Value Health* 2018;21:547-552.
13. Stafinski T, Glennie J, Young A, Menon D. HTA decision-making for drugs for rare diseases: comparison of processes across countries. *Orphanet J Rare Dis* 2022;17:258.
14. Balvanyos J, Nicod E, Hutchings A on behalf of the ORPH-VAL Working Group. ORPH-VAL principles in practice: Comparison of alignment of five European P&R systems. 2019. Available from: <https://www.orph-val.org/> (Accessed 10 October 2023).
15. Nicod E, Whittal A, Drummond M, Facey K. International variations in the appraisal of drugs for rare diseases; what are the main lessons? [abstract] *Value Health* 2019;22 Suppl3:S855.
16. National Institute for Health and Care Excellence. Summary of Information for Patients. 2021. Available from: <https://www.nice.org.uk/guidance/GID-TA10656/documents/committee-papers-2#:~:text=Why%20should%20I%20use%20a,about%20the%20medicine%20under%20review> (Accessed 10 October 2023).
17. IQVIA. The Future of EU HTA. 2022. Available from: <https://www.iqvia.com/form-pages/general?redirectUrl=%2f-%2fmedia%2fiqvia%2fpdfs%2flibrary%2fwhite-papers%2fthe-future-of-eu-hta.pdf&title=The+future+of+EU+HTA> (Accessed 16 October 2023).
18. Kawalec P, Sagan A, Pilc A. The correlation between HTA recommendations and reimbursement status of orphan drugs in Europe. *Orphanet J Rare Dis* 2016;11:122.
19. Lee D, McCarthy G, Saeed O et al. The challenge for orphan drugs remains: three case studies demonstrating the impact of changes to NICE methods and processes and alternative mechanisms to value orphan products. *Pharmacocon Open* 2023;7:175-187.
20. Malinowski KP, Kawalec P, Trabka W et al. Health technology assessment and reimbursement policy for oncology orphan drugs in Central and Eastern Europe. *Orphanet J Rare Dis* 2020;15:277.
21. European Commission, Directorate-General for Research, Innovation. Collaboration – a key to unlock the challenges of rare diseases research: Publications Office of the European Union. 2021.
22. European Federation of Pharmaceutical Industries and Associations (EFPIA). Factors affecting the location of biopharmaceutical investments and implications for European policy priorities. 2022. Available from: <https://www.efpia.eu/media/676753/cra-efpia-investment-location-final-report.pdf> (Accessed 10 October 2023).