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## Systematic Review

# Budgetary Impact and Cost Drivers of Drugs for Rare and Ultrarare Diseases

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### ABSTRACT

**Objectives:** To review recent studies reporting health care expenditures (budgetary impact) for orphan medicinal products (OMPs) in Europe and to contribute to our understanding of the cost drivers of nononcological OMPs by means of an empirical analysis in Germany. **Methods:** A systematic search for relevant studies on rare diseases was conducted in PubMed and Embase (until December 2016). In addition, annual treatment costs of nononcological OMPs in Germany were analyzed with respect to five explanatory variables: total prevalence of disease, prevalence with added benefit, availability of alternative treatments for the same indication, extent/probability of treatment benefit, and evidence for a treatment effect on mortality. **Results:** A total of nine studies with specific estimates of the budget impact of OMPs for a total of 11 countries were identified; one study addressed specifically ultrarare diseases. Annual per-capita spending for OMPs ranges from €1.32 in Latvia to €16 in France.

Per-patient annual treatment costs vary between €27,811 and €1,647,627 in Germany. On the basis of the German data set, the regression analysis shows that log prevalence has a significant inverse relationship with log annual treatment cost. In this model, doubling the prevalence leads to a 43% decrease in annual treatment cost. **Conclusions:** Despite per-patient annual treatment costs ranging up to several hundreds of thousands of euros for some OMPs, per-capita spending for OMPs is relatively small. In this study an inverse relationship between prevalence and annual treatment costs was found.

**Keywords:** budgetary impact, drug prices, orphan medicinal products, prevalence, rare diseases, ultrarare diseases.

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## Introduction

In many jurisdictions, including the United States, the European Union (EU), Japan, and Australia, legislation has been adopted to encourage the development of treatments for rare or “orphan” diseases. Under this legislation, developers and manufacturers of so-called orphan drugs used to treat orphan diseases benefit from a range of incentives, including reduced or waived licensing fees, extended market exclusivity periods and, in the United States and Japan, tax relief on development costs [1–3].

The introduction of regulation for rare disorders has contributed to the rise of research and development efforts, leading to increasing availability of effective treatments for rare disorders [4]. From the perspective of the biopharmaceutical industry, orphan medicinal products (OMPs) are now attractive investment opportunities [5–7]. At the same time, however, in many cases the use of drugs for rare disorders has been associated with high annual

acquisition costs per patient, and “the five most expensive drugs in the world” [8] all happen to be medications for ultrarare diseases (URDs).

Fixed costs of research and development are largely independent from sales volume or for that matter from the very small number of patients affected with a rare disorder. Consequently, one should expect an inverse correlation between drug acquisition costs per patient and the prevalence of the target condition (in line with, e.g., [9]).

Against this background, concerns have been raised that drugs for orphan disorders “may impose substantial increasing costs to the healthcare system” [10], to the point that these costs may become “unsustainable, even for health services that have met them hitherto” [4]. Many of the technologies in question do not meet broadly used benchmarks for cost-effectiveness, for example, incremental costs per quality-adjusted life-year gained of €50,000 (e.g., [11–13]), and sometimes cost-effectiveness data

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<https://doi.org/10.1016/j.jval.2017.10.015>

are not available at all (cf. [14]). As a result, recent debate has focused on the appropriateness and usefulness of conventional cost-effectiveness analysis as a tool to determine the “value for money” offered by OMPs [13,15–17]. Accordingly, in many jurisdictions OMPs are exempted from formal health economic analysis (e.g., in some cases in the Netherlands), follow specific processes, or receive positive reimbursement decisions despite indications of costs per quality-adjusted life-year higher than deemed acceptable in other areas (e.g., [18–21]).

As the prevalence of conditions displays a continuous pattern, attempts to separate “orphan” and “ultra-orphan” from “normal” conditions are somewhat arbitrary exercises. Nevertheless, orphan disorders have been defined by the US and EU legislations. In the United States, these are diseases with a prevalence of fewer than 200,000 affected persons; in the EU, prevalence must be fewer than 5 per 10,000 (or <0.05%) of the population.

The National Institute for Health and Care Excellence in the United Kingdom introduced a definition of ultra-orphan drugs that it applied to drugs with indications for conditions with a prevalence of less than 1 per 50,000 persons initially in 2005, and then subsequently less than 100 patients in England in the recently updated Highly Specialised Technologies appraisal process in 2013. Similarly, the recent EU Clinical Trials Directive [22] defined URDs as “severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000.”

In Australia, the Pharmaceutical Benefits Advisory Committee often considers URD drugs within the context of the Life Saving Drugs Program [23]. It remains to be seen whether such programs provide sufficient incentives to develop products and reverse possible trends toward an increasing number of companies focusing on more prevalent orphans and fewer in the “very rare” category [24].

The objective of the present article was 1) to review recent studies reporting health care expenditures (budgetary impact) for drugs for orphan diseases (including URDs) in Europe and 2) to contribute to our understanding of the drivers of acquisition costs of OMPs by means of an empirical analysis. Specifically, we searched for variables explaining costs of OMPs as negotiated between manufacturers and representatives of the German statutory health insurance. We particularly aimed at confirming the theoretical relationship between disease prevalence and drug costs empirically. This should be of interest given the lack of transparency of and very limited research on the pricing of OMPs [25,26] and, in particular, drugs for URDs.

For the cost driver analysis we focused on the German market, which is the largest European market in terms of pharmaceutical production and sales [27]. Specifically, we analyzed OMPs that had completed an early benefit assessment in Germany (see [Appendix in Supplemental Materials](http://dx.doi.org/10.1016/j.jval.2017.10.015) found at <http://dx.doi.org/10.1016/j.jval.2017.10.015> for details of the benefit assessment process in Germany). We chose to focus on nononcological diseases because our dependent variable, which is annual treatment costs, does not fit oncology drugs well because the application of oncology drugs is often based on a limited number of cycles or time to treatment progression.

## Methods

### Budgetary Impact of OMPs

We conducted a systematic search for relevant full-text articles on rare diseases (including URDs) in PubMed and Embase (until December 2016), using the search algorithm “orphan drugs AND (budget impact OR spending).” Studies with data from outside Europe and those reporting individual-level but not

population-level cost data were excluded. When estimates were reported over a multiyear period, we took the latest one.

Local currencies were converted into euros on the basis of the exchange rate at the time of the study in question. To calculate per-capita cost, we used population data of the study year in question from the World Bank [28].

### Drivers of Cost per Patient for OMPs

#### Data sources

We included all pharmaceuticals that were classified as OMPs by the Federal Joint Committee, had completed an early benefit assessment by the end of 2016, and were not withdrawn from the German market. Drugs had to be approved by the European Commission in a nononcological indication. We analyzed annual treatment costs with respect to five explanatory variables: total prevalence of the disease (continuous), prevalence with added benefit (continuous), extent/probability of benefit (discrete), effect on mortality (discrete), and availability of alternative treatments for the same indication (discrete). Variables are explained in the following sections.

**Annual treatment costs.** Information on annual treatment costs before price negotiation between a manufacturer and the National Association of the Statutory Health Insurance Funds was obtained from the official resolution document issued by the German decision-making body, the Joint Federal Committee (or *Gemeinsamer Bundesausschuss* [G-BA]). If unavailable from this source, data were retrieved from assessments by the German health technology assessment agency, the Institute for Quality and Efficiency in Health Care (cf. also [Appendix in Supplemental Materials](#)). In cases in which several dosing regimens were reported (e.g., on the basis of age or weight), we took the average of the upper and lower bounds of annual treatment costs. In a sensitivity analysis representing a conservative scenario, we used upper bounds only.

To arrive at the annual treatment cost after price negotiation between a manufacturer and the National Association of the Statutory Health Insurance Funds, we determined the negotiated rebate as listed in the Lauer-Taxe® as a percentage of the manufacturer’s asking price and applied this percentage to the annual treatment cost before negotiation. For drugs for which negotiation results were unavailable (e.g., because negotiations were still ongoing or prices were being set by the arbitration body), we applied the average rebate of drugs with available information.

**Prevalence.** When possible, we used prevalence data gathered by Orphanet [29] or else the assessment reports by the European Medicines Agency. For OMPs with an indication for more than one rare disease (i.e., pasireotide and riociguat), we determined the sum of prevalence rates.

In addition to total prevalence, we included the size of the population expected to have an added benefit in the German statutory health insurance system. The size of the population with expected benefit is supposed to be smaller than the total prevalence because it takes into consideration, among others, contraindications, age restrictions, and lack of access to treatment, for example, because patients may not be detected. For example, in Germany less than 200 patients with type 1 Gaucher disease were treated in 2009 [30], whereas total prevalence data [31] suggest the patient population to be about 800. Nevertheless, estimates on the population size with expected benefit are subject to large uncertainty and therefore still justify a concomitant consideration of total prevalence estimates. As a source of the population size with expected benefit, we used estimates by

the Institute for Quality and Efficiency in Health Care and the G-BA. In case only ranges were published, we took the average of the upper and lower bounds.

**Size/probability of benefit.** On the basis of the early benefit appraisal by the G-BA, we used a dummy variable to distinguish between “nonquantifiable” and “minor” additional benefit (other benefit categories did not apply in our sample with the exception of one patient subgroup for ivacaftor). To this end, we used information from the official G-BA resolution documents.

**Effect on mortality.** On the basis of the early benefit appraisal by the G-BA, we used a dummy variable to categorize mortality reduction either as statistically significant or not.

**Availability of alternative treatments.** We introduced a dummy variable to account for a satisfactory alternative method authorized in the EU for the treatment of the condition. To this end, we used information from the European Medicines Agency.

### Data analysis

We used the method of ordinary least squares for estimating the parameters in a linear regression model with and without logarithmic transformation. All independent variables were categorical except for prevalence, which was continuous. To detect multicollinearity among the explanatory variables, we constructed a correlation matrix and two-way contingency tables (the latter apply only to categorical variables) and calculated the variance inflation factors, which measure how much multicollinearity has increased the variance of a slope estimate [32], as well. We considered P values of less than 0.05 to be statistically significant.

Because the aim of our regression was to explain and not to predict annual treatment costs, we did not develop a parsimonious model based on stepwise elimination. All analyses were performed using STATA version 11.0 (StataCorp, College Station, TX).

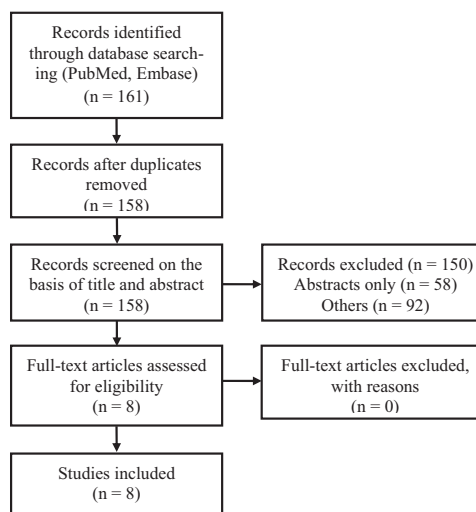
## Results

### Budgetary Impact of OMPs

On the basis of the PubMed and Embase search described earlier, from a total of 161 hits we identified eight studies with specific estimates of the budget impact for a total of 10 countries (Fig. 1; see also Appendix Table A1 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.10.015> [33–40]).

Two estimates related to all European countries and the Eurozone countries, respectively. Six studies determined budget impact on the basis of actual sales and cost data, thus incorporating uptake of drugs implicitly. Two studies [33,34] projected their estimates on the basis of a model that explicitly considered drug uptake. One study [33] focused specifically on ultra-orphan drugs. None of the studies included costs of 1) treating side effects; 2) costs of drug-related services such as counseling, monitoring, and testing; 3) savings from a reduction in morbidity; and 4) life extension costs.

As Appendix Table A1 in Supplemental Materials suggests [33–40], estimates vary from country to country and even for a single country (France [37,38]). For example, the percentage of pharmaceutical expenditure spent on orphan drugs ranges from 0.8% in Latvia to 7.8% in Bulgaria. Annual per-capita spending on orphan drugs ranges from €1.32 in Latvia (2014; own calculation based on Logviss et al. [39]) to €20.23 in France (2012; own calculation based on Hutchings et al. [38]). Projected future share of spending for orphan drugs ranges, on the basis of the few studies from which such projections were available, from 4% in



**Fig. 1 – PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.**

Sweden (year 2020) to 5% in France (year 2020), translating into annual per-capita expenditures between €25 (or €2.10 per person-month) in Sweden (2020) and €30 (or €2.48 per person-month) in France (2020; own calculation based on Hutchings et al. [38]). Furthermore, estimates are lower for ultra-orphan drugs than for orphan drugs Table 1.

### Drivers of Cost per Patient for OMPs

We found 21 drugs for nononcological indications that had been appraised by the Federal Joint Committee by the end of December 2016. Ataluren was excluded from the analysis because the manufacturer opted for withdrawing it from the German market. Only two drugs (pasireotide and riociguat) were approved for two indications. The final sample of 20 OMPs includes 11 ultra-orphan drugs. Summary data are provided in Table 2 (for details, see Appendix, Table A2). For eight drugs, negotiations were still ongoing or prices were being set by the arbitration body, thus mandating to apply an average rebate of drugs with available information.

In the correlation matrix (not shown) the highest correlation was found between total prevalence and prevalence with added benefit ( $r = 0.68$ ). Therefore, we included only total prevalence in the main model and considered treated prevalence in a sensitivity analysis. The  $\chi^2$  contingency table analysis showed no significant relationships, indicating absence of multicollinearity between categorical variables. Similarly, all variance inflation factors were lower than the conventional cutoff of 10.

**Table 1 – Summary of studies on budget impact of (ultra-)orphan drugs in Europe (n = 13 estimates).**

|   | Mean (range)                             |
|---|--|
| Annual budget impact (€)                  | 677,975,264<br>(2,641,727–4,620,000,000) |
| Pharmaceutical expenditure (%)            | 2.7 (0.7–7.8)                            |
| Annual per-capita spending (€)            | 8.41 (1.32–20.23)                        |
| Type of study<br>(% decision model)       | 15                                       |
| Consideration of substitution effects (%) | 0  |
| Consideration of uptake (%)               | 15                                       |

**Table 2 – Summary of nononcological orphan medicinal products included in the analysis (n = 20).**

|  | Mean (range)                  |
|--|-------------------------------|
| Prevalence per 100,000 persons   | 5.7 (0.2–30)                  |
| Population with expected benefit in the German statutory health insurance system | 1712 (18–7550)                |
| Availability of alternative treatments (% yes)                                   | 55                            |
| Effect on mortality (% yes)  | 40                            |
| Annual treatment cost (€)  | 296,881<br>(27,811–1,647,627) |
| Extent/probability of benefit (% nonquantifiable)                                | 60                            |

In addition to conducting a regression analysis on the basis of untransformed variables (Table 3), we transformed some of the variables in additional analyses. The logarithm of annual treatment costs was taken given that histogram, box plot, quantile-quantile plot, and normal probability plot suggested right skewness of the data (the Shapiro-Wilk test was also statistically significant at  $P < 0.001$ ). For total prevalence and prevalence with added benefit, the Shapiro-Wilk test was also significant ( $P < 0.001$ ) and again histogram, box plot, quantile-quantile plot, and normal probability plot suggested right skewness of the data. Therefore, we took the logarithm of the prevalence data as well.

In the regression specifications, only (log) population size (prevalence with added benefit) was found to be significant. There is an inverse relationship with untransformed and log-transformed annual treatment costs (Tables 4 and 5). According to the log-log specification, doubling the prevalence leads to a 30% decrease in annual treatment cost. The adjusted  $R^2$  for this model is 0.33. Using log total prevalence as opposed to log population size yields a similar result, that is, a significant inverse relationship with log annual treatment cost. In this model, doubling the treated prevalence leads to a 43% decrease in annual treatment cost. Using only upper bounds of annual treatment cost as the dependent variable leads to a smaller (15%) and nonsignificant decrease in annual treatment cost for doubling the prevalence with added benefit.

## Discussion

There are two potentially competing criteria that payers may use to make pricing and reimbursement decisions for the treatment of rare diseases: the cost-effectiveness ratio considering incremental costs per patient and the budgetary impact. The budgetary impact often represents the primary concern of policymakers and payers (cf. [41]), and it is usually addressed by means of budgetary impact analyses (BIAs). BIAs reflect aggregate spending

on OMPs, or on the category of URD drugs, and typically are a function of acquisition costs per unit and utilization. The notion of “affordability” is frequently used in the context of BIAs and conceptually implies the existence of a fixed (or at least limited) health care budget.

Empirically, participants in studies measuring public preferences have been found to be reluctant to accept that the decision to cover a program for orphan disorders inevitably leads to the loss of access to effective care of a much larger number of common-disease patients [42]. Citizens often prefer reallocating spending from other public programs to health care to avoid rationing (e.g., [42–44]).

Several studies estimated the budget impact of orphan and ultra-orphan drugs in Europe. Our search identified the studies presented in Appendix Table A1 in Supplemental Materials. Two studies predicted that future spending on orphan drugs would reach a plateau at 4% to 5% of total pharmaceutical expenditure by the year 2020 [34,38], thereafter growing at a rate not faster than the total market. This effect was expected to be largely driven by the anticipated expiry of market exclusivity for many OMPs.

Only one study specifically addressed ultra-orphan drugs; it predicted that spending for drugs for nononcological URDs might reach 1.4% of the total European pharmaceutical expenditures by 2021 assuming a 1.1% annual growth of total pharmaceutical expenditures in Europe [33]. The authors concluded that their analyses did not support concerns about an uncontrolled growth in expenditures for URD drugs. Nevertheless, they recommended “continuously monitoring the budget impact in order to provide an input into rational policy making.” If projected spending in Europe for nononcological URD drugs was related to current population figures, the data cited would translate into €4.04 per person-year or €0.34 per person-month. The question, of course, remains whether this is an unreasonably high amount given the relatively small number of patients benefitting or is it a modest and justified social transfer ensuring that patients unfortunate enough to suffer from a URD are not abandoned and left behind [45].

One approach to empirically address this issue might be to systematically measure the social willingness to pay or, in the case of a national health scheme, the willingness to be taxed to cover the population by the health scheme. Methods to measure social preferences for, as a proxy for social value of, access to health care programs have been proposed (e.g., [46–48]). Their use was advocated by health economists and health technology assessment experts on grounds of normative considerations and an in-depth review of the broader literature on “empirical ethics” [13,17,49,50]. Recently, Richardson et al. [51] provided direct empirical evidence supporting sharing health care resources with small numbers of severely ill patients, even if services were not cost-effective. They concluded that the wish to share “per se [... may have] been obscured in studies that focus upon cost per patient rather than the cost per person sharing the cost” [51].

Because unit costs are one of the variables determining the budgetary impact of an OMP, understanding the drivers of unit

**Table 3 – Regression model using untransformed variables (the dependent variable is annual treatment cost).**

|                       | Coefficient | SE        | 95% CI                  | t statistic | P value |
|-----------------------|-------------|-----------|-------------------------|-------------|---------|
| Population size       | −71.26209   | 45.96751  | −169.2395 to 26.71533   | −1.55       | 0.142   |
| Mortality             | 184,413     | 206,265.6 | −255,231.8 to 624,057.7 | 0.89        | 0.385   |
| Added benefit         | 127,824     | 174,042   | −243,137.8 to 498,785.8 | 0.73        | 0.474   |
| Alternative treatment | −247,553.1  | 165,948.9 | −601,264.7 to 106,158.6 | −1.49       | 0.156   |
| Constant              | 404,589.7   | 185,553.7 | 9,091.398 to 800,087.9  | 2.18        | 0.046   |

CI, confidence interval; SE, standard error.



**Table 4 – Regression model using log annual treatment costs as the dependent variable.**

|                       | Coefficient | SE        | 95% CI                  | t statistic | P value |
|-----------------------|-------------|-----------|-------------------------|-------------|---------|
| Population size       | −0.0003326  | 0.0001139 | 0.0005752 to −0.0000899 | −2.92       | 0.011   |
| Mortality             | 0.1637585   | 0.5108981 | −0.925195 to 1.252712   | 0.32        | 0.753   |
| Added benefit         | 0.5057849   | 0.4310837 | −0.4130482 to 1.424618  | 1.17        | 0.259   |
| Alternative treatment | −0.5505641  | 0.4110378 | −1.426671 to 0.3255423  | −1.34       | 0.200   |
| Constant              | 12.4476     | 0.4595968 | 11.46799 to 13.4272     | 27.08       | 0.000   |

CI, confidence interval; SE, standard error.

costs will be of interest even in the context of a social value framework relying on “social” (often nonselfish) preferences beyond individual utility maximization. After all, social preferences for the treatment of orphan disorders may be shaped by an understanding of the cost drivers. We intended to describe empirically identifiable variables, hereby hoping to contribute to future informed debate about reasonable OMP price regulation. A few previous studies analyzed the factors that explain prices of drugs for rare and ultrarare diseases [13,25,52,53]. By far the most comprehensive and sophisticated analysis was published recently by Picavet et al. [54]. Using data on annual treatment costs of 59 orphan drugs from six European countries (Belgium, the Netherlands, Czech Republic, France, Italy, and the United Kingdom), the study identified three predictors of lower annual treatment costs: availability of other treatment indications (“repurposed orphan drugs”) (yes/no), oral administration (yes/no), and availability of alternative treatments for the same indication (yes/no). Furthermore, four predictors were found to be associated with higher annual treatment costs: availability of multiple orphan indications as a proxy for the size of the “potential treatment population” or prevalence, improvement in survival (yes/no), improvement in quality of life (yes/no), and treatment duration of 6 months and more (yes/no). In addition, the study attempted to determine the impact of nononcological diseases and URDs on annual treatment costs but found no significant relationship.

Perhaps the most surprising finding was the lack of an inverse relationship between the availability of multiple orphan indications and the annual treatment cost. The authors justified this finding by arguing that orphan drug prices are determined on the basis of the prevalence of the first indication and that launch prices for the first indication are unlikely to be reviewed after subsequent approval(s) in further indications. This argumentation then presupposes that the relationship between prevalence and costs depends on whether the orphan drug has been approved for two or more indications. The relationship between prevalence and annual treatment costs is usually considered to be inverse on the basis of the assumption of largely fixed research and development costs (i.e., costs are assumed to be independent from sales volume) [33]. From reading the literature, prevalence is therefore usually held to be the most important predictor. This relationship between prevalence and annual

treatment costs has also been confirmed empirically in univariate analyses [25,55,56]. Because the trend in the six countries analyzed by Picavet et al. [54] was positive for URDs versus no URDs, it cannot be excluded that prevalence as a continuous variable (as opposed to the dichotomous indicator of URD used by Picavet et al.) would have yielded a significant result. Furthermore, because the study by Picavet et al. did not include interaction terms, it is not clear whether the aforementioned seven significant predictors are transferable to nononcological diseases.

In contrast to the study by Picavet et al. [54], we find that lower prevalence is associated with higher annual treatment costs in a log specification. Thus, we are able to confirm previous analyses and intuition [9,13,25,33,53,55,56]. Also, in contrast to Picavet et al. [54], we could not show that availability of alternative treatments for the same indication or improvement in survival had a significant impact on treatment costs. Yet, we cannot exclude that a larger sample would have had more power to detect additional significant relationships. In contrast to Picavet et al., we did not include availability of other treatment indications and treatment duration as further explanatory variables because only two drugs (pasireotide and riociguat) had more than one indication and only two drugs (alipogentiparovec and isavuconazole) were not labeled for continuous treatment.

Despite its plausible results, our study is not without limitations. First, estimates on budget impact obtained from the systematic review are from different time periods and are expected to change over time because of launching of new and more expensive drugs while expecting expiry of market exclusivity for others (this could explain the different estimates on orphan drug spending in France). Therefore, these studies reflect only temporary spending. Second, for patients who receive continuous treatment (beyond 1 year), the annual treatment cost represents an underestimate. In the case of alipogentiparovec, the underestimation is partially compensated by a minor overestimation from including the cost of nondrug services in the annual treatment costs because the latter was not clearly separable. Furthermore, one may object that average annual treatment costs as used in our regression model may differ in the real world because physicians may deviate from recommended dosing schemes or because patient characteristics are different than assumed at the time of price negotiation. Yet, it is important to point out that our goal was to explain drug costs as negotiated

**Table 5 – Regression model using log population size and log annual treatment costs.**

|                       | Coefficient | SE        | 95% CI                   | t statistic | P value |
|-----------------------|-------------|-----------|--------------------------|-------------|---------|
| Log population size   | −0.3019365  | 0.1409484 | −0.6023609 to −0.0015121 | −2.14       | 0.049   |
| Mortality             | −0.2691135  | 0.4979712 | −1.330514 to 0.7922869   | −0.54       | 0.597   |
| Added benefit         | 0.7436814   | 0.4567575 | −0.2298741 to 1.717237   | 1.63        | 0.124   |
| Alternative treatment | −0.454449   | 0.4601457 | −1.435226 to 0.5263283   | −0.99       | 0.339   |
| Constant              | 13.77697    | 0.9246476 | 11.80613 to 15.74781     | 14.90       | 0.000   |

CI, confidence interval; SE, standard error.

between manufacturers and representatives of the statutory health insurance. In contrast, information on actual treatment cost is hardly available at the time of negotiation and therefore unlikely to carry any weight in explaining prices.

The data included in this study do not allow calculating cost-effectiveness ratios; yet, the mean annual treatment cost of €296,881 suggests that health gains in the order of several (quality-adjusted) life-years were needed for drugs to be considered cost-effective by conventional standards. Underlying this value judgment is the standard utilitarian perspective suggesting that the goal of collectively financed health schemes is to maximize population health gains (valued on the basis of individual, selfish preferences) within the available resource constraints. Drugs for URDs would therefore hardly receive priority (e.g., [10,15,57]).

The empirical ethics literature (e.g., [13,16,49–51]) suggests that a utilitarian approach may be in serious conflict with prevailing social norms and preferences. In this context, we believe it is worth pointing out that on a per-capita basis, spending for orphan drugs is generally low as found by our literature search (see [Appendix Table A1 in Supplemental Materials](#)), currently running at €1.50 for nononcological URD drugs in Europe (projected to rise to €4.04 in 2021 assuming unchanged population size) and a current maximum of €20.23 per year for orphan drugs in France (projected to plateau at €30 in 2020 on the basis of Hutchings et al. [38]).

Ultimately, this conflict can be traced back to fundamental value judgments, and for this reason, it is not necessarily clear which of the two criteria—incremental costs per patient or budgetary impact—ought to be given priority. Although standard health economic evaluations rely on a utilitarian framework, stronger emphasis on social value judgments might lead to a greater role for budget impact and social willingness to pay—an emerging paradigm that will deserve (and require) further in-depth analysis, deliberation, and empirical research [13,48–51].

## Conclusions

In the present study, an inverse relationship between prevalence and annual treatment costs was found specifically for drugs for nononcological URDs. Annual treatment costs per patient may run into several hundreds of thousands of euros for some of the URD drugs. Accordingly, many drugs for URDs cannot meet conventional benchmarks for cost-effectiveness. Yet, a review of budget impact studies suggests that URD drugs are and will remain affordable, because annual spending per capita seems relatively small. Thus, present and future funding decisions will depend more on social value judgments than on individual cost per patient treated.

## Acknowledgment

We thank Dr Mohit Jain for valuable suggestions. All conclusions and any errors are the sole responsibility of the authors.

Source of financial support: Parts of this study were financially supported by BioMarin (London) under an unrestricted educational grant policy.

## Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at <http://dx.doi.org/10.1016/j.jval.2017.10.015> or, if a hard copy of article, at [www.valueinhealthjournal.com/issues](http://www.valueinhealthjournal.com/issues) (select volume, issue, and article).

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