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Horizon scanning and drug expenditure for rare diseases: three-year predictive model in Italy 2025–2027

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Abstract

Background and objective In recent years, spending on orphan drugs in Italy has seen a significant rise. The analysis aims to estimate future spending for medicines for rare diseases (RDs) in Italy.

Methods A forecasting model was developed over a three-year time frame. New drugs were selected according to specific criteria, using Biomedtracker and clinical trial databases. For each therapeutic indication, comparators were identified to estimate the average cost per patient. Overall expenditure was projected by applying prevalence data to the eligible population, and considering expected drug uptake trends over the study period. Additionally, a deterministic sensitivity analysis was performed to assess the influence of price fluctuations on total pharmaceutical spending.

Results Overall, a total of 137 pipeline drugs for RDs were identified, covering 74 indications. The model estimated a total spending on RD treatments equal to €2.08 billion in 2024, corresponding to an average cost of €24,777 per patient. The projection indicates an increase by 1.9% in 2025, 4.0% in 2026, and 7.1% in 2027 compared to 2024. Focusing on orphan designation drugs ($n=115$), the 2024 expenditure was estimated at €1.93 billion, with an average patient cost of €22,984. The introduction of new orphan drugs is expected to drive further increases in spending by 1.1% in 2025, 2.2% in 2026, and 3.7% in 2027.

Conclusions The results underscore the growing financial impact of orphan drugs on Italy's healthcare budget. This analysis offers a quantitative projection of the resources required to ensure continued access to innovative therapies for RDs.

Keywords Forecast model, Rare diseases, Orphan drugs, Pharmaceutical expenditure, Horizon scanning

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Introduction

Rising healthcare costs increasingly challenge European healthcare systems [1]. Over the past two decades, data show an increase in expenditure and consumption of drugs in Europe [2–4], and this is particularly true for rare diseases (RDs) [5]. In Italy, the National Health Service (NHS) drug expenditure in 2022 was € 23.5 billion (+ 5.5% vs. 2021) [6]. Of these, € 1.98 billion in 2022 were for orphan drugs (+ 29.0% compared to 2021) [7]. Among the drugs that generate the highest resource absorption in our country, those for the treatment of genetic diseases, lymphomas, myelomas, and other onco-haematological conditions, which account for more than 50% of the total expenditure on orphan drugs and more than 60% of total consumption, should certainly be mentioned [7].

In a context of growing economic pressure, forecasting and planning pharmaceutical expenditure have become a crucial element for ensuring the sustainability of national healthcare systems [8]. To support this need, several forecasting methods have been developed, among which two are most commonly used. The first approach involves extrapolating future trends from pharmaceutical companies' financial data, particularly reported sales figures. However, these forecasts are usually presented at a global level, since sales data are rarely disaggregated by region. This limits their relevance for policymakers in areas such as Europe, where pharmaceutical markets differ significantly from those in the United States and Asia [8].

The second methodology, used by some international consultancy firms, employs proprietary audited data from pharmacies and hospitals worldwide [8].

While these models enable expenditure forecasting, they rarely account for uncertainty, making them inadequate for a rapidly evolving drugs' market where future developments are difficult to predict. Moreover, the review of these models revealed the presence of a limited number of studies that comprehensively model the entire process, including the savings from off-patent products and the additional costs associated with new branded medicines at the drug level [9]. Additionally, forecasts on pharmaceutical expenditure use economic models mainly based on (1) analyses of historical time series [10]; (2) average growth rates by therapeutic macro-areas and evaluations of effects that may change the trend of the health expenditure (patent expirations, entry of new drugs with relevant impact), with or without inclusion of elements of uncertainty in the reference scenarios [11]; (3) the breakdown of expenditure growth into its components of prices (entry of new higher-priced drugs and patent expiries), consumption and mix (shift of prescription in favour of more or less drugs within the same therapeutic class) [12].

Such models are suitable for aggregate pharmaceutical expenditure forecast, but are not applicable on specific drugs, for which it is necessary to:

- identify the place in therapy and therapeutic alternatives, estimating new drugs target population and the market penetration.
- determine the price of the new drugs.

This evaluation may happen by considering data of drugs already launched for the same indication, with adjustments based on the incremental value of the drug or similar drugs in absence of therapeutic alternatives, or through simulation models of prescribing behaviour based on information between clinicians [13].

Despite some notable examples, such as the forecasting approach developed in the Italian region of Piemonte - based on Horizon Scanning, target population analysis, therapeutic positioning, analogue-based price simulations, and projected market dynamics [14] - these remain isolated initiatives. Currently, there is a lack of standardized and replicable forecasting models tailored to innovative and orphan drugs, especially at a national level.

This highlights a significant gap: existing forecasting tools are either too generic or too aggregate to support timely, informed, and locally relevant planning for the arrival of high-impact, innovative drugs—especially for RDs. A comprehensive, drug-level forecasting model that integrates Horizon Scanning, epidemiological data, therapeutic positioning, price estimation, and uptake projections—while also incorporating uncertainty—is still missing.

The present work sets two important and complex objectives to:

1. Analyse the drugs for RDs currently in the approval phase at the European Medicines Agency (EMA) level that are arriving in Italy between 2025 and 2027.
2. Develop a model for forecasting the pharmaceutical expenditure for the NHS over a three-year horizon.

Methods

The forecast analysis was developed using a 3-year forecast model (2025–2027) adopting the Italian NHS perspective. The model was built following six methodological steps [9, 15] (Fig. 1):

Step 1–3. Identification of new drugs and/or new indication and cost Estimation of comparators

The identification of new drug's indication was developed using the *Biomedtracker* database (an independent database that analyses drugs in development or developed starting from the Food and Drug Administration (FDA)

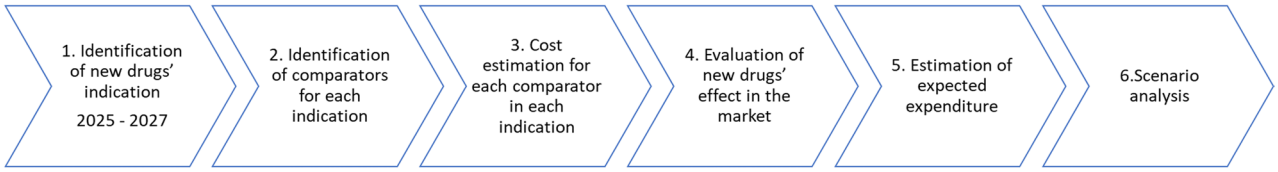

Fig. 1 Methodological steps used to build the model

approval process through to approval in EMA) supplemented with other sources, such as the European Union Clinical Trials Register [16], ClinicalTrials.gov [17] and Datamonitor reports [18]. The Biomedtracker database reports a likelihood of approval derived from the combination of the baseline value and analyst assessment. A 70% threshold was applied to select drugs in the analysis. This percentage was validated through consultation with national experts in drug evaluation, pricing, and market access [19].

Drugs arriving in 2025

For the year 2025, all drugs for RDs approved in Europe as of December 2024 were considered, excluding those already approved in Italy. It was hypothesized that RD drugs approved in Europe have a median approval time in Italy of 463 days [20].

Drugs arriving in 2026

For 2026, drugs for RDs that have undergone the BLA (Biologics License Application) or NDA (New Drug Application) procedure in the USA as of December 2024. It was assumed that these drugs have a median approval time in Europe of 277 days [21].

Drugs arriving in 2027

For the year 2027, all drugs for RDs in Phase III as of December 2024 with a probability of 70% were considered, as for the previous year, with the same median approval of 277 days.

After identifying the reference comparators (Standard of Care – SoC), therapeutic costs borne by the NHS were estimated for each specific indication following three main steps:

1. Drugs prices reimbursed by the NHS: the therapeutic cost of comparators was obtained considering the regional tender ex-factory price for each package, referred to the most recent regional tender, as proxy for the ex-factory price net of the confidential discount [22]. In absence of the regional tender price, the net ex-factory price was considered [23].
2. Expected dosage for each therapy: for the cost of each comparator, the expected dosage in the Summary-of-Product-Characteristics was considered, and in absence of this information, the median Progression-Free-Survival (PFS). When the PFS was also absent, the median duration of treatment shown in the clinical study was considered. In case of total absence of information and in presence of chronic disease, an annual treatment cost was computed. Median values were used instead of mean values due to the unavailability of mean data in the sources consulted. While mean values are generally preferred for cost analyses, the median was considered the most reliable measure in this context.
3. Follow-up standardization: For the disease for which the treatment is projected throughout the patient's life, the cost was applied to each year of the expenditure forecast. In addition, in the presence of add-on therapies, the therapeutic cost included also the cost of drugs to be taken in combination. For the treatment cost, a weight of 70 kg and a BSA of 1.72 m^2 were considered. These assumptions are in line with Italian Medicines Agency (Agenzia Italiana del Farmaco – AIFA) guidelines [24].

Step 4. Evaluation of the effects of new indication in the market

The next step was to estimate the potential effect of new drugs on the overall pharmaceutical expenditure once they reached the market. Given the limited availability of final, published results from clinical trials at the time of analysis, the model was based on assumptions informed by expert opinion.

1. Innovation effect: the first effect was associated with new drugs that were considered an innovation for the specific indication. The first assumption was to include in this group all those drugs currently under the EMA Fast track and Priority Medicines (PRIME) procedures or/and recognised as drugs with a significant clinical contribution. For this specific drug category, it was assumed that all the patients treated with this innovation generate a greater cost of + 15% (range + 10% - +20%) compared to the average cost of comparators with the

same indication. This is an assumption about the premium price accepted by AIFA in the negotiation phase.

2. Competition/price erosion effect: for the residual drugs for RDs which were not included in the first category and were not biosimilars or generics, the model assumed a therapeutic cost reduction of −15% (Range − 20%/−10%) compared to the average cost of comparators with the same indication. This effect was assumed as an effect of price negotiation which promotes the drug competition among drugs with comparable efficacy. For these patients, the model assumed that in the same year, this reduction would be propagated over a further 20% of patients treated with other drugs.
3. Biosimilar/generic effect: in this case, the model assumed that with the commercialization of a new biosimilar/generic drug of a specific indication, treated patients with the originator would have a reduction of the average cost of therapy of −80% (Range − 80% - −33%), reflecting on 100% of treated patients. It should be noted that biosimilars/generics were only included in the analysis if they fell within a therapeutic area in which there were not already biosimilars or generics of the same molecule and in the same indication.
4. Orphan drugs: for drugs with no real comparators, a zero cost was considered until the entry of the new drug and a pure incremental expenditure from the year of reimbursement of the latter.

Step 5. Estimation of the expected impact on volumes and uptake

To estimate the expected pharmaceutical expenditure, the following steps were followed:

A Epidemiological estimation of patients with RDs on the Italian context.

Prevalence and incidence estimations were retrieved from the literature for each indication considered, preferring, if available, data from the Italian population. However, the number of subjects considered at this stage was highly overestimated due to necessary correction factors that had to be considered:

- diagnosis rate of prevalent/incident patients.
- patients who might refuse treatment with target drugs.
- treatment compliance.
- lack of centres or availability of space in centres.
- other access-related factors.

For each indication, specific assumptions (validated by experts) were developed. Additionally, the model assumed that, in the base case, the number of treated patients would remain unchanged over the three years of the considered time horizon.

B Annual uptake of new drugs considered for the indication under analysis.

For the definition of the drug uptake during the 3 years of the time horizon considered and for each indication, an opinion from clinicians and experts involved was required. Dealing with RDs, where the data availability was limited, the uptake percentage during the time horizon was estimated starting from the identification of three different clusters:

- indications with prevalence/incidence lower than 500 patients.
- indications with prevalence/incidence between 500 and 3,000 patients.
- indications with prevalence/incidence greater than 3,000 patients.

The pharmaceutical expenditure prediction model assumed that the total uptakes during three years would differ in relation to the drug's cluster and the presence or absence of treatments already reimbursed in Italy (Table 1). For example, for a drug whose indication has a prevalence/incidence lower than 500 patients, without any competitors, the uptake would be equal to 20%, 35%, and 50%, during the next three subsequent years after estimated approval respectively. Otherwise, it would have an uptake of 15%, 25%, and 35% if there were no competitors. Specifically, it was assumed that with the presence of other treatments already reimbursed, the uptake of the new drug could require more time and not ensure the complete absorption of patients during the three years. On the other hand, without any competitors, even if the uptake would be more significant, it could not absorb all patients (e.g. different timing of drugs for market access across Italian regions, lack of treatment availability, difficulties in accessing treatment).

The RDs included in the model were aggregated in the following Therapeutic Areas (Table 1):

Table 1 Drug uptake by cluster

Prevalence/Incidence < 500 patients	Year 1	Year 2	Year 3
Absence of reimbursed treatments	20%	35%	50%
Presence of reimbursed treatments	15%	25%	35%
Prevalence/Incidence between 500 and 3,000 patients	Year 1	Year 2	Year 3
Absence of reimbursed treatments	10%	20%	35%
Presence of reimbursed treatments	5%	12%	20%
Prevalence/Incidence >3,000 patients	Year 1	Year 2	Year 3
Absence of reimbursed treatments	7%	15%	30%
Presence of reimbursed treatments	3%	7%	15%

(1) Autoimmune/immunology; (2) Cardiovascular; (3) Dermatology; (4) Endocrinology; (5) Haematology; (6) Gastroenterology (Non-inflammatory intestinal disease); (7) Infectious disease; (8) Metabolism; (9) Neurology; (10) Oncology (liquid and solid) (Oncology and onco-haematology); 11) Renal disease; 12) Respiratory disease.

The detailed list of each pathology is reported in the annex (Table S1).

Step 6: scenario analysis

Once the population and cost parameters were defined, the model estimated the annual pharmaceutical expenditure by multiplying the expected number of patients treated with each drug - both the SoC and new treatments negotiated at the AIFA level - by their respective treatment costs. The analysis compared forecasted expenditures across the three-year period under different scenarios, evaluating both absolute and relative changes in spending. To test the robustness of these projections, a deterministic sensitivity analysis was conducted. This included two components: the first assessed the impact of hypothetical price fluctuations over time, while the second evaluated how specific market dynamics - such as innovation premiums, price erosion due to competition, and the introduction of biosimilars or generics - might influence expenditure trends.

In the first analysis, it was considered an increment and reduction of prices equal to 15% in 2024, while it was assumed that drug prices could undergo a slight increase or a reduction of 1% in 2025, 2% in 2026, and 4% in 2027.

In the second analysis, the main effects were identified with experts' support, which could have influenced the health expenditure trend. These effects include innovation, competition/price erosion, as well as the entry of biosimilar and generic drugs, with their respective percentage variations detailed in step 4.

Table 2 Distribution of molecules by year of commercialization in Italy

Therapeutic area	2025	2026	2027	Totale
Autoimmune/immunology	6	9	1	16
Cardiovascular	2	2		4
Dermatology			1	1
Endocrinology	4	4		8
Haematology	9	5	18	32
Gastroenterology*		1		1
Infectious disease	1			1
Metabolism	8	10		18
Neurology	4	3	1	8
Oncology (liquid and solid) ^	24	19		43
Renal disease	3			3
Respiratory disease		1	1	2
Total	**61**	**54**	**22**	**137**

*Non-inflammatory intestinal disease

^Oncology and onco-haematology

Results

The analysis considered 137 new drugs for RDs likely to be reimbursed during the period 2025–2027, for a total of 74 indications. 113 drugs obtained the orphan designation. The therapeutic areas with the highest prevalence were the oncologic/onco-haematological, haematologic and metabolic areas. Notably, haematology is expected to play a particularly significant role by 2027, reflecting an increasing trend over the forecast period (Table 2).

The analysis shows that over the next 3 years, only about 17% will bring a significant level of innovation (24 out of 137), compared to just one new biosimilar/generic drug (in an indication where no other drugs are present).

Moreover, given 137 new drugs and 74 indications under evaluation, 174 competitors were identified. The model considers a total of 83,921 patients treated with the total drugs under examination, with an average treatment cost for the period 2024–2027 ranging between approximately € 25,000 and € 27,000. The data show a significant increase in the number of patients treated compared to the previous year (about 40,000 per year), while simultaneously reflecting a decrease in the average treatment cost.

In 2024, the total expenditure associated with drugs for RDs, considering both the number of prevalent patients and the scenario with tender prices, was equal to € 2.08 billion, with an average cost per treated patient equal to € 24,777. The market access of new drugs would generate a pharmaceutical expenditure of € 2.12 billion (in 2025), € 2.16 billion (in 2026), and € 2.23 billion (in 2027), and an average cost per treated patient of € 25,243, € 25,757, € 26,536, respectively in 2025, 2026 and 2027. The increase of expenditure during years, compared to the year 2024, will be equal to + 1.9%, + 4.0%, and + 7.1% in 2025, 2026, and 2027 respectively (Fig. 2).

Considering only the 115 drugs with orphan designation in the scenario with regional tender prices and estimating a number of prevalent patients treated equal to 83,921 in all three years, pharmaceutical expenditure in 2024 was € 1.93 with an average cost per treated patient of € 22,984. In this case as well, the market entry of new orphan drugs would generate pharmaceutical expenditure of about € 1.95 billion (in 2025), € 1.97 billion (in 2026), and almost € 2 billion (in 2027), with an average cost per treated patient of € 23,244, € 23,497, and € 23,824, respectively, in 2025, 2026, and 2027. The increase in expenditure over the years of the time horizon compared to 2024 was found to be + 1.1%, + 2.2%, and + 3.7%, respectively, in 2025, 2026, and 2027 (Fig. 2).

It is highlighted that in both groups, oncology (solid and liquid) and neurology represent the two largest areas

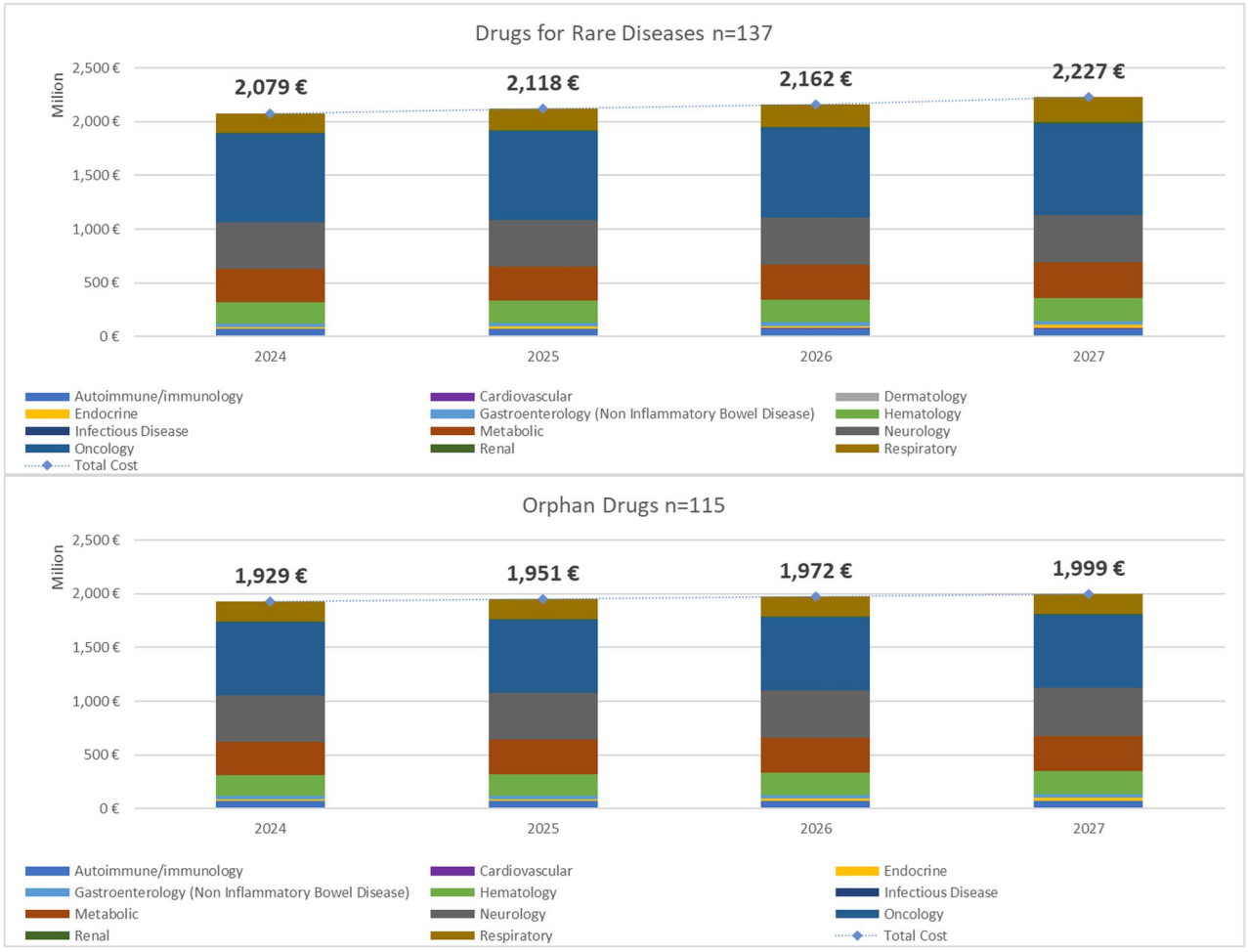

Fig. 2 Pharmaceutical expenditure in millions 2024–2027 (rare diseases, $n = 137$ and orphan drugs, $n = 115$)

of expenditure. When considering all drugs for RDs, oncology accounts for 39.6% of pharmaceutical spending, and neurology for 20.9%. However, when considering only orphan drugs, these areas represent 35.3% and 22.5% of pharmaceutical spending, respectively. It is worth noting that dermatology is the only area that does not have orphan drugs and, therefore, is not included in the graphs and associated tables.

Sensitivity analysis

Given the assumptions introduced in the model and the variability of the main parameters, Fig. 3 presents the spending forecasts and estimated confidence intervals based on the model parameters at the national level. Figure 3 shows that, in the base case (solid line), the growth in spending on drugs for RDs over the 3 years of analysis could be approximately € 148 million, while for orphan drugs alone, this would reach around € 70 million in the third year.

Figure 4 shows the results of the sensitivity analysis, highlighting how spending might change compared to the estimates for 2024, with the introduction of new therapies. The analysis considers the three key effects explained in the methods. Assuming that the cost estimation analysis for 2024 is realistic and that the various potential effects mentioned above are respected, the introduction of the RD drugs considered in this analysis could generate a maximum increase of approximately € 326 million over three years (+15.7%). Among the scenarios considered in the analysis, a minimum increase of just under € 14 million (+0.7%) is also estimated, which accounts for the combined effects of both competition and new biosimilar/generic drugs introduction, effectively offsetting the innovation effect (Fig. 4). The analysis generates a very wide range due to the high uncertainty associated with the model's 2- and 3-year forecasts and the access of drugs. The same analysis (Fig. 4) presented for orphan drugs shows a lower maximum absolute increase, which reaches approximately € 221 million in the third year (+11.5%), with a potential decrease of around € 40 million (–2.1%) due to the erosion effect and the biosimilar. This increase is moderated, compared to

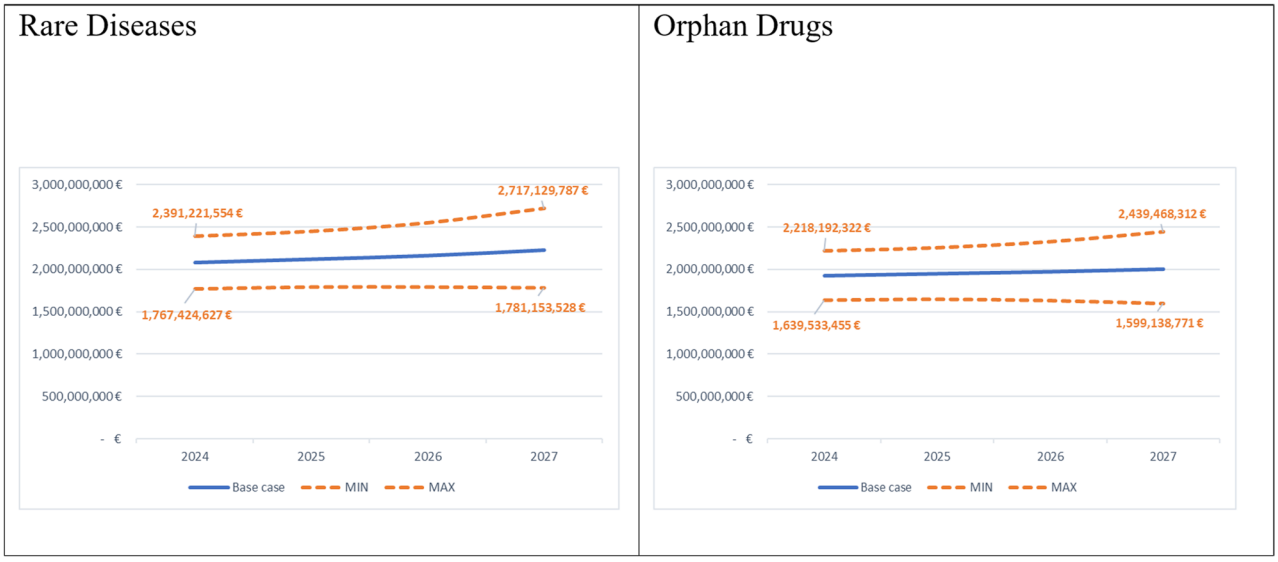

Fig. 3 Sensitivity analysis: Estimates of pharmaceutical expenditure according to prices - Italy 2024–2027

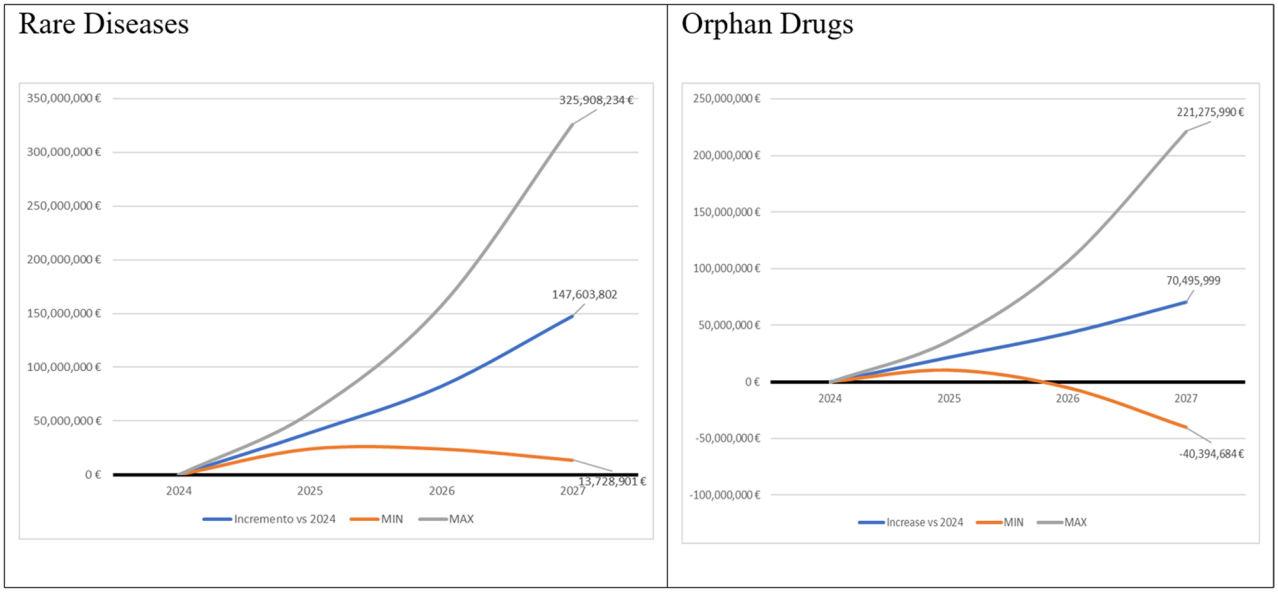

Fig. 4 Sensitivity analysis: Estimates of pharmaceutical expenditure - Italy 2024–2027

the overall indications in the analysis, by the different structure of the indications and the introduction of the biosimilar, as described earlier.

Discussion

This analysis pursued ambitious objectives and sought to address key research questions for Italy at national level. The analysis identified 137 new drugs under development and approval, intended to treat 74 different RD indications. These 137 drugs were selected among those most likely to be reimbursed during the observation period and to impact pharmaceutical spending. The distribution of these drugs by year of commercialization and by therapeutic area highlights a significant concentration in the oncology/onco-haematology sector, followed by areas such as neurology and metabolism. The predictive model developed estimates that the introduction of new drugs for RDs could result in an increase in spending over three years ranging from a minimum of +€14 million (+0.7%) to a maximum of approximately +€326 million (+15.7%) compared to 2024.

A study conducted in Europe by Urbinati et al. 2014 [15] aimed to build a model to assess the net effect generated by the entrance of new patented drugs versus drugs with expired patent, with a forecast horizon of 5 years (2012–2016). This study [15] shares with our work the

objective of forecasting pharmaceutical expenditure in light of upcoming drug entries, including orphan and innovative medicines. Their model, applied to several European countries, estimated the net budget impact, highlighting the potential for overall expenditure reduction in certain national contexts. Unlike our analysis, however, their approach was primarily oriented toward estimating macroeconomic balances at the national level, without a specific focus on RDs or a detailed breakdown of uptake dynamics, cost structures, and innovation effects. Our model builds on that forecasting tradition, but with a narrower therapeutic scope and a higher granularity, specifically tailored to support planning within the Italian NHS by quantifying the expected impact of future RD therapies, both orphan and non-orphan, over a three-year period.

In the Italian context, a relevant contribution was provided by Manea et al. 2023 [25], who conducted a regional-level budget impact analysis focused on non-oncological RD drugs using real-world data from the Veneto Region. Their study provided a detailed snapshot of the expenditure structure for orphan and non-orphan drugs within a single regional health system, based on actual consumption and administrative records. While this approach offers valuable insights into spending dynamics at the local level, it remains limited in its geographical scope and does not attempt to forecast future trends or incorporate drugs currently in development. Our work complements and expands upon this perspective by adopting a national forecasting approach that includes both oncological and non-oncological RDs, integrates epidemiological projections, and simulates the future budget impact of therapies not yet available on the market. By doing so, it aims to support long-term planning efforts at the national and regional levels, bridging the gap between retrospective expenditure analyses and prospective strategic forecasting.

Overall and, if compared with existing literature, the results of this study highlight the impact of new drugs for RDs on pharmaceutical expenditure, providing a quantitative estimate of resources required for the access of these drugs in Italy. Through a transparent and practical methodological approach, based on updated epidemiological data and realistic market scenarios, the model provided valuable estimates on the evolution of pharmaceutical spending. These estimates represent a crucial tool for the resource planning and management by the Italian NHS, allowing for the optimal allocation of funds to ensure accessibility to new treatments.

As with all modelling approaches, this analysis has limitations to consider. First of all, the selection of drugs may not necessarily reflect the actual timing of national approvals. Price negotiation and reimbursement timelines in Italy could cause delays in the commercialization of the drugs included in the analysis and extend the estimated economic consequences beyond the base year (2024). However, the introduction dynamics of new drugs in patient treatment were considered conservatively to account for the likely delays during this phase of agency stabilization. A second limitation concerns the epidemiological estimates considered in the analysis. Efforts were made to obtain the most robust and recent information available in the literature, but many assumptions were based on expert opinion, rendering the epidemiological analysis uncertain. In this case, however, the sensitivity analysis attempted to account for the variability underlying these estimates, providing interval impact assessments that could represent plausible spending impact estimates. Moreover, the relative incremental analysis compared to 2024 does not suffer from this bias, considering a constant amount treated over the years with SoC or new indications.

Another limitation concerns the scope of the model. First, it focuses solely on pharmaceutical spending without accounting the potential effects on patient health outcomes or the broader impact on the overall healthcare budget and indirect costs. Additionally, any assumptions about the health outcomes that innovation will bring to treated patients was not considered. Aspects such as quality of life, organizational consequences, and spending on other direct and indirect cost items are determining variables in the economic evaluation of new healthcare technologies. This part will undoubtedly be the subject of future analyses, which will further clarify the impact of innovation on the considered conditions. Despite the previously discussed limitations, the data presented are unique at the national level and represent a strategic tool for the planning and management of resources by the NHS and the Regional Health Services.

Conclusions

In conclusion, given the limited evidence available at both national and international levels, this work makes a significant and innovative contribution to the future forecast of pharmaceutical expenditure for RDs. By evaluating comparator costs and the potential introduction of new therapies, this study provides valuable insights into the resources required to support expenditure on these drugs. Furthermore, the model could represent a crucial tool for supporting healthcare policy decisions in better allocate resources, as long as planning systems involve specific clinical pathway, guaranteeing a solid network between stakeholders such as patients, policymakers, clinicians, and pharmaceutical companies.

The possibility of conducting sub-analyses by indication and achieving greater granularity in the assumptions could be a further development of this model, offering a valuable forecasting and healthcare planning tool.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-025-00699-4.

Supplementary Material 1.

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Authors' contributions

AM, DC, GG, AA and MB contributed to the acquisition and analysis of data for the implementation of the predictive model. RB, MG, CL, FL, PC and CJ contributed to the interpretation of data. All authors contributed to the drafting and revision of the manuscript.

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Data availability

The datasets used and/or during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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