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Patient-Level Costing, Strategic Reimbursement, and Budget-Constrained Coverage in Rare Diseases: A TDABC-Based Analysis of Severe Haemophilia A

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Abstract

Rare-disease treatment financing is challenging because high-cost therapies, clinical need, and budget constraints create interdependent decisions among manufacturers, public payers, and healthcare providers. This article combines patient-level time-driven activity-based costing (TDABC) with a sequential reimbursement benchmark and a fixed-budget coverage analysis for severe haemophilia A. Using institutional pathway data and a representative clinical profile, the study estimates an annual treatment cost of EUR 105,429.14 for the representative patient, of which EUR 98,514.04, or 93.4%, corresponds to pharmaceutical expenditure. TDABC is used to identify the clinical and operational resources consumed throughout the treatment pathway and the practical capacity allocated to its delivery. The analytical model then translates the resulting cost structure into reimbursement, provider-adoption, and population-coverage conditions. The results show that treatment feasibility and budget-constrained coverage are driven primarily by drug price, body weight, dose intensity, and administration frequency, while non-drug operational costs have a comparatively limited effect. The article contributes by connecting institution-specific patient-level costing with the interdependent implications of treatment cost for manufacturers, payers, providers, and patient access. The framework provides a transparent reimbursement benchmark rather than a complete bargaining model and supports affordability, budget-impact, and treatment-capacity assessments in rare diseases.

Keywords: haemophilia A; TDABC; patient-level costing; game theory; reimbursement; budget-constrained coverage

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1. Introduction

Rare diseases place disproportionate pressure on health systems because they combine clinical urgency, low prevalence, and high treatment costs. This creates a setting in which access decisions are not purely clinical, but also strategic, as manufacturers, public payers, and healthcare providers operate under different objectives and constraints.

At the same time, healthcare organisations increasingly require patient-level cost evidence to support treatment adoption, budget planning, and reimbursement negotiations. In severe haemophilia A, annual treatment cost is dominated by therapy-related variables, particularly price per international unit, dose intensity, body weight, and administration frequency, while other operational components account for a comparatively small share of total cost. The representative-patient TDABC estimate amounts to EUR 105,429.14 per year, of which EUR 98,514.04 corresponds to pharmaceutical expenditure, representing 93.4% of total cost.

These cost characteristics are highly relevant not only for internal management accounting, but also for the external strategic problem of reimbursement design. Patient-level TDABC evidence should therefore be interpreted not merely as a descriptive costing exercise, but as an analytical input into the strategic interaction between manufacturers, payers, and providers. The central question addressed in this article is thus not only how much treatment costs, but also how cost structure shapes reimbursement feasibility and treatment coverage under binding public budget constraints.

This article contributes in three ways. First, it provides patient-level TDABC evidence for severe haemophilia A in Portugal, a rare-disease setting in which robust micro-costing evidence remains limited. Second, it translates this costing evidence into a transparent reimbursement-feasibility benchmark, showing how drug price, non-drug treatment cost, operational burden, and provider mission benefit enter the minimum reimbursement condition. Third, it extends the costing evidence to a budget-constrained coverage setting, not as a full strategic equilibrium model, but as a policy-oriented framework for assessing treatment capacity, exclusion risk, and the sensitivity of coverage to drug-related cost drivers.

This framing also positions the article within two intersecting research streams. The first concerns patient-level costing and TDABC in healthcare, where micro-costing is used to reveal the resource implications of clinical pathways. The second concerns game-theoretic analyses of healthcare and pharmaceutical decision-making, where access, pricing, subsidy, and treatment decisions are modelled as interdependent strategic choices. Prior game-theoretic work has examined interactions among patients, pharmaceutical firms, donors, vaccine developers, and drug developers in disease contraction and recovery settings (Hausken & Ncube, 2020, 2022). Karunadasa and Sieberg (2024) show that healthcare payment systems and insurance coverage shape provider behaviour, service provision, and patient welfare, highlighting the importance of financial incentives in healthcare delivery. Ganzfried (2024) applies a Stackelberg equilibrium framework to cancer treatment, showing how sequential leader–follower structures can be used to model clinical decision-making. Soltanolkottabi et al. (2020) further demonstrate how game-theoretic models can support public health policy by linking individual behaviour, disease dynamics, and policy-relevant outcomes. These studies support the use of game-theoretic tools in healthcare contexts, while the present article contributes by combining institution-specific TDABC evidence with a reimbursement-feasibility and budget-constrained coverage benchmark for a rare-disease treatment pathway.

Accordingly, the article should be read primarily as a TDABC-based patient-level costing study with a transparent analytical extension, rather than as a full theory of rare-disease reimbursement bargaining. The strategic model is deliberately parsimonious and is used to translate empirically observed cost components into reimbursement and coverage constraints.

Although drug expenditure represents 93.4% of total annual cost, the use of TDABC remains relevant for three reasons. First, it provides a transparent patient-level decomposition of the entire care pathway rather than measuring pharmaceutical expenditure alone. Second, it identifies the time, capacity, and cost of the clinical and operational resources

required to deliver treatment. Third, it distinguishes drug-related expenditure from provider-side resource consumption and the proportion of practical capacity allocated to the treatment pathway, thereby supporting reimbursement and operational-capacity analysis. Accordingly, TDABC is not presented as the main explanation for total cost variation, which is predominantly pharmaceutical, but as the patient-level costing architecture that makes the full treatment pathway and its provider-side implications visible.

The central motivation for the study is therefore to connect three decision levels that are usually examined separately: patient-level resource consumption, reimbursement feasibility, and population coverage under a fixed budget. The novelty does not lie in proposing a new TDABC method or a complete bargaining theory. Rather, it lies in using institution-specific patient-level costing evidence to define both a reimbursement frontier and a budget-constrained coverage frontier in a rare-disease setting.

2. Background and Related Literature

2.1. Costing Systems and Patient-Level Costing in Healthcare

Healthcare costing systems provide information to support resource allocation, operational management, reimbursement, and treatment-planning decisions. Their usefulness depends not only on the availability of expenditure data, but also on the ability to associate costs with the patients, services, activities, and clinical pathways that consume the underlying resources. This distinction is particularly important in healthcare because aggregate accounting information may identify total expenditure without explaining how resources are consumed across activities or individual care pathways.

Healthcare costs may be classified as direct or indirect according to their relationship with the relevant cost object. Direct costs can be traced directly to a patient, treatment, procedure, or clinical episode, as in the case of pharmaceuticals, medical consumables, or externally provided diagnostic procedures. Indirect costs relate to resources shared across activities or patients, including administrative support, facilities, equipment, and certain categories of clinical and non-clinical staff. These costs require an allocation criterion, and the choice of that criterion may affect the resulting estimate of patient- or service-level cost.

Micro-costing and patient-level costing seek to overcome the limitations of highly aggregated costing systems by identifying the resources consumed throughout the care pathway and assigning their costs to the corresponding patient, procedure, or treatment episode. These approaches are particularly useful when patients follow different pathways, require different levels of clinical intensity, or consume resources in ways that are not adequately reflected in average tariffs or departmental cost allocations. Patient-level costing can therefore provide a more transparent basis for comparing treatment pathways, identifying cost drivers, and assessing the financial implications of clinical and reimbursement decisions.

Activity-based costing (ABC) assigns resource costs to activities and subsequently assigns activity costs to cost objects through cost drivers that seek to reflect the causal relationship between resource consumption and the relevant patient, service, or procedure. ABC is especially useful when indirect costs are significant and conventional allocation methods may distort the economic representation of the activities and services provided. However, traditional ABC systems can be demanding to implement and maintain because they require multiple activity cost pools, extensive data collection, and regular updating of cost-driver information (Cooper & Kaplan, 1988).

Time-driven activity-based costing (TDABC) simplifies this process by relying primarily on two parameters: the cost of supplying resource capacity and the time required to perform each activity. The method calculates a capacity cost rate for each resource and applies that rate to the estimated time consumed by the patient or activity (Kaplan & Anderson, 2004). In healthcare, this structure allows the cost of a clinical pathway to be

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reconstructed from the resources, time requirements, consumables, pharmaceuticals, and external services associated with care delivery (Kaplan & Porter, 2011).

Systematic reviews show that TDABC has been applied in multiple healthcare settings to estimate patient- and pathway-level costs, identify variation in resource consumption, and support value-based healthcare initiatives (Keel et al., 2017; Etges et al., 2020). However, the relevance of TDABC does not depend exclusively on indirect costs representing the largest share of total expenditure. Even when direct pharmaceutical expenditure dominates total cost, TDABC can remain useful by providing a complete decomposition of the care pathway, distinguishing drug-related expenditure from provider-side resource consumption and identifying the capacity implications associated with treatment delivery.

This distinction is central to the present study. In severe haemophilia A, pharmaceutical expenditure is expected to dominate annual treatment cost. TDABC is therefore not used on the assumption that indirect cost allocation explains most of the total cost variation. Instead, it provides the patient-level costing architecture needed to measure the complete treatment pathway, identify the clinical and operational resources required for delivery, and distinguish the pharmaceutical component from the provider-side cost and capacity consequences of treatment.

2.2. TDABC Applications, Capacity Measurement, and Healthcare Decision-Making

The capacity cost rate is a central parameter of TDABC. It represents the cost of supplying one unit of practical resource capacity and is normally expressed as a cost per minute. It is determined by dividing the cost of supplying a resource by the resource's practical capacity. Practical capacity differs from theoretical capacity because it excludes expected periods of unavailability, including breaks, training, leave, maintenance, preparation time, and other operational interruptions.

The cost assigned to an activity is obtained by multiplying the capacity cost rate of each resource by the time required to perform that activity. Direct consumables, pharmaceuticals, and externally provided services may then be added separately. Annual patient-level cost is subsequently obtained by combining the cost of each activity with its expected frequency throughout the annual treatment pathway.

An additional contribution of TDABC is its ability to distinguish between capacity supplied, capacity consumed, and capacity remaining unused. Used capacity corresponds to the time assigned to the activities included in the relevant care pathway, whereas unused capacity represents the difference between practical capacity and the capacity consumed. The cost of unused capacity may then be estimated by applying the relevant capacity cost rate to the unused resource time. However, when a resource supports multiple patient groups or clinical pathways, capacity not assigned to the pathway under analysis cannot automatically be classified as unused capacity. Establishing actual unused capacity requires information on the complete set of activities performed by that resource.

This information is relevant for healthcare management because aggregate expenditure alone does not reveal whether resources are overloaded, adequately used, or available but underutilised. Capacity measurement can therefore support resource planning, process redesign, and the identification of operational constraints affecting treatment delivery.

TDABC may also use time equations to represent variation in the time required to perform an activity according to patient, procedural, or clinical characteristics. Time equations are particularly useful when the same general activity has multiple variants or when resource consumption depends on identifiable complexity factors. However, complex time equations require sufficiently detailed observations to estimate the incremental time associated with each conditional characteristic. Where such data are unavailable, activity-

specific time estimates may provide a more transparent and empirically defensible alternative, provided that the assumptions and limitations are clearly disclosed.

In healthcare settings, the value of TDABC therefore extends beyond the calculation of a single patient cost. It can reveal the resource structure of the care pathway, support process redesign, identify capacity constraints, and provide operational evidence for treatment-planning and reimbursement discussions. Nevertheless, its accuracy depends on the quality of resource-cost information, practical-capacity assumptions, activity-time estimates, and clinical-frequency data. Estimates based on professional validation rather than automated time capture may introduce measurement uncertainty, while the use of average patient profiles may conceal heterogeneity in treatment intensity and resource consumption.

Accordingly, TDABC results should not automatically be interpreted as exact measurements of the cost of every individual patient. They should be viewed as structured patient-level estimates that make the underlying assumptions transparent and allow the principal operational and clinical cost drivers to be identified. In the present study, this role is particularly important because the resulting cost estimate is subsequently used as an empirical input into reimbursement-feasibility and budget-constrained coverage analyses.

2.3. Severe Haemophilia A: Cost Drivers and Financing Pressure

Severe haemophilia A is a rare bleeding disorder associated with substantial clinical complexity and financial burden. Patients require continued monitoring and prophylactic treatment to prevent or control bleeding episodes, and the annual treatment burden depends on the therapeutic regimen, pharmaceutical price, dose intensity, body weight, administration frequency, bleeding risk, and individual treatment response.

Existing European and Portuguese studies have documented the substantial cost of haemophilia treatment. Rocha et al. (2015) examined treatment costs and healthcare-resource utilisation among patients with haemophilia, while Café et al. (2019) assessed the health and economic burden of haemophilia A in Portugal. O'Hara et al. (2017), through the CHESS study, provided broader European evidence on the cost of severe haemophilia. Although these studies differ in perspective, sample, treatment period, and cost components, they consistently identify pharmaceutical expenditure as the principal component of the economic burden associated with severe haemophilia.

The evolution of haemophilia treatment further complicates comparison across studies. New pharmaceutical alternatives may improve clinical outcomes, reduce bleeding frequency, and facilitate patient self-administration, but they may also involve higher acquisition costs than historical treatment regimens. Consequently, reimbursement decisions based solely on previous cost estimates or aggregate tariffs may fail to reflect the current economic structure of treatment.

Patient heterogeneity is an important source of cost variability. Annual pharmaceutical expenditure may vary according to body weight, prescribed dose per kilogram, administration frequency, bleeding history, treatment response, and the presence of inhibitors. These factors imply that the expected cost of treatment cannot always be represented adequately by a single deterministic value. Even when an average patient-level estimate is useful for planning, the underlying variability should be considered in reimbursement and budget-impact analysis.

The concentration of total expenditure in the pharmaceutical component has two important implications. First, changes in price per international unit, dose intensity, body weight, or administration frequency may influence annual cost much more strongly than changes in administrative, equipment, or routine follow-up expenditure. Second,

relatively small changes in expected annual drug expenditure may materially affect the number of patients who can be treated under a fixed public budget.

This problem is especially relevant in rare disease financing. Rare diseases often combine high per-patient costs, small eligible populations, limited longitudinal evidence, and strong ethical pressure to provide access. These characteristics challenge conventional reimbursement frameworks because a treatment may be clinically appropriate and individually reimbursable but still create significant affordability and coverage pressure at population level (Rittenhouse & Nicod, 2024).

The financing problem therefore extends beyond measuring the cost of an individual treatment pathway. It also involves determining whether the observed cost is compatible with payer valuation, provider capacity, available public budgets, and the number of clinically eligible patients. Patient-level costing provides the empirical foundation for this assessment, but reimbursement and coverage remain strategic decisions involving actors with different incentives and constraints.

2.4. Game Theory, Reimbursement, and Coverage Decisions

Game theory provides a framework for analysing situations in which the outcome of one actor's decision depends on the choices made by other actors. This characteristic is directly relevant to pharmaceutical reimbursement, where access to treatment results from the interaction between manufacturers, public payers, healthcare providers and in more complex settings, patients, regulators, donors, and health technology assessment bodies.

The manufacturer seeks to obtain a price that compensates production, development, and commercial risk while preserving access to the reimbursed market. The payer must balance the expected health or social value of treatment against affordability, opportunity cost, and the budgetary consequences of reimbursement. The healthcare provider seeks to ensure patient access but must also consider whether reimbursement is sufficient to cover pharmaceutical expenditure, clinical resources, operational burden, and the internal capacity required to deliver the treatment pathway.

Previous game-theoretical research has analysed healthcare access and pharmaceutical decisions from different perspectives. Hausken and Ncube (2020) model strategic interaction among individuals, the pharmaceutical industry, donors, and disease dynamics, showing that drug availability, subsidies, purchase decisions, and recovery outcomes are mutually dependent. Hausken and Ncube (2022) extend this reasoning to competition between vaccine and pharmaceutical companies, demonstrating how development, production, purchase, and subsidy decisions may interact to generate different access outcomes.

Other studies have examined the role of incentives, payment mechanisms, and sequential decisions in healthcare. Wettstein and Boes (2020) analyse the effect of reimbursement negotiations on pharmaceutical cost and availability. Olsder et al. (2023) examine subsidy, pricing, and payment mechanisms intended to improve access to rare-disease treatments. Karunadasa and Sieberg (2024) show how payment systems and insurance coverage influence provider behaviour and service provision, while Ganzfried (2024) demonstrates the application of a Stackelberg equilibrium structure to sequential decision-making in cancer treatment.

These studies show that healthcare access is not determined by cost or clinical value in isolation. Pricing decisions affect payer affordability; reimbursement decisions affect provider adoption; and provider capacity may affect whether nominally reimbursed treatment can be delivered sustainably. Public-budget constraints add another layer because an individually feasible reimbursement decision may still reduce the number of patients who can be covered at population level.

Nevertheless, existing game-theoretic studies generally do not incorporate institution-specific patient-level costing evidence directly into the reimbursement condition. Conversely, TDABC studies provide granular estimates of patient- and pathway-level resource consumption but often stop at cost measurement, process analysis, or operational improvement. The relationship between micro-costing evidence, strategic reimbursement feasibility, and aggregate treatment capacity therefore remains insufficiently developed.

The present article uses a sequential manufacturer–payer–provider model to translate patient-level costing evidence into a transparent reimbursement threshold. The strategic framework is deliberately parsimonious. It is not intended to represent the full complexity of pharmaceutical negotiation, which may involve confidential discounts, alternative treatments, repeated bargaining, asymmetric information, regulatory constraints, outcome uncertainty, and different contractual arrangements. Instead, it provides a benchmark showing how the observed cost structure constrains the reimbursement and adoption decision.

The fixed-budget extension complements this strategic analysis by translating expected annual cost per patient into aggregate treatment capacity. This distinction is important: the sequential game analyses whether treatment can be reimbursed and adopted for an individual patient, whereas the fixed-budget calculation examines how many eligible patients can be covered under a finite annual budget. Together, these perspectives connect manufacturer pricing, payer reimbursement, provider feasibility, and patient access.

2.5. Research Gap and Positioning

The literature reviewed identifies three related but insufficiently integrated research streams. The first concerns patient-level costing and TDABC in healthcare, which provide detailed evidence on the resource consumption and cost of clinical pathways. The second concerns the economic burden of severe haemophilia A, which establishes the importance of pharmaceutical expenditure and treatment intensity. The third concerns game-theoretic and reimbursement models, which examine strategic interaction among pharmaceutical firms, payers, providers, patients, and other healthcare actors.

However, healthcare TDABC studies generally do not translate institution-specific patient-level costs into formal reimbursement-feasibility and budget-constrained coverage conditions. Haemophilia cost studies identify substantial expenditure but usually do not model how the resulting cost structure affects manufacturer, payer, and provider decisions. Game-theoretic reimbursement studies model strategic interaction but are not normally calibrated using detailed patient-level evidence from a complete clinical pathway.

Table 1 positions the present article relative to selected published studies and identifies the specific gap addressed by the analysis.

Table 1. Comparison with selected related studies.

Study	Context and Main Focus	Method	Main Drivers	Treatment of Uncertainty	Relationship with the Present Study
Rocha et al. (2015)	Haemophilia treatment costs and resource utilisation	Empirical cost analysis	Treatment utilisation and direct medical costs	Limited	Provides Portuguese cost evidence but does not connect patient-level costs with reimbursement thresholds
O'Hara et al. (2017)	Economic burden of severe haemophilia in Europe	Multi-country cost study	Treatment regimen and healthcare-resource use	Variation across	Provides broader European evidence but not

				patients and countries	an institution-specific TDABC model
Keel et al. (2017)	TDABC applications in healthcare	Systematic literature review	Time, resources, practical capacity, and activity costs	Discussed across reviewed studies	Establishes the relevance of TDABC but does not develop a reimbursement or coverage model
Etges et al. (2020)	TDABC and value-based healthcare	Systematic review	Patient-level costs and care-pathway resource consumption	Heterogeneous across studies	Supports patient-level costing but generally stops before strategic reimbursement modelling
Hausken and Ncube (2020)	Disease contraction, pharmaceuticals, and donor decisions	Multi-period game-theoretic model	Drug availability, subsidies, purchases, and recovery	Strategic and dynamic	Provides a broader strategic model but is not calibrated with institutional patient-level costing evidence
Hausken and Ncube (2022)	Competition between vaccine and pharmaceutical firms	Game-theoretic model	Development, production, competition, subsidies, and access	Strategic scenarios	Models pharmaceutical competition but does not include provider-level treatment costs
Wettstein and Boes (2020)	Pharmaceutical reimbursement negotiations	Experimental reimbursement analysis	Negotiation, cost, price, and availability	Experimental variation	Examines reimbursement behaviour but does not include a complete patient-level pathway cost
Olsder et al. (2023)	Access to rare-disease treatments	Subsidy, pricing, and payment-scheme analysis	Price, subsidy, payment design, and access	Alternative policy schemes	Closely related to rare-disease access but not based on institutional TDABC evidence
Karunadasa and Sieberg (2024)	Payment systems, insurance, and provider behaviour	Medically framed real-effort experiment	Coverage, payment, provider effort, and welfare	Experimental scenarios	Supports the importance of payment incentives but does not calibrate reimbursement with patient-level costs
Present study	Severe haemophilia A treatment, reimbursement feasibility, and budget-constrained coverage	Patient-level TDABC, sequential benchmark game, and fixed-budget analysis	Drug price, body weight, dose, administration frequency, non-drug cost, operational burden, and annual budget	Deterministic sensitivity and scenario analysis	Connects institution-specific patient-level costing with manufacturer, payer, provider, and coverage implications

The contribution of this article lies at the intersection of these research streams. First, it provides an institution-specific patient-level cost estimate for severe haemophilia A using a TDABC architecture that incorporates activity times, practical capacity, capacity cost rates, direct expenditure, and provider-side operational resources. Second, it translates the resulting cost structure into a sequential reimbursement-feasibility condition involving the manufacturer, public payer, and healthcare provider. Third, it extends the patient-level estimate to a fixed-budget setting in which annual treatment cost determines the number of patients who can be covered.

The novelty of the article is therefore not the development of a complete theory of pharmaceutical bargaining. Rather, it lies in the operational use of patient-level costing evidence to define two related frontiers: the reimbursement frontier determining whether treatment can be financed and adopted for an individual patient, and the coverage frontier determining how many patients can be treated under a binding annual budget.

The empirical and analytical components are deliberately connected. The TDABC model identifies the observed cost structure and provider-side resource implications; the sequential model converts those costs into reimbursement and adoption conditions; and the fixed-budget extension translates expected cost per patient into aggregate coverage capacity. This sequence provides a transparent bridge between management accounting, reimbursement decision-making, and rare-disease access under scarcity.

3. Materials and Methods

3.1. Empirical Costing Component

The empirical component relies on institutional data from the Santa Maria Local Health Unit (ULSSM) concerning the treatment pathway for severe haemophilia A over a one-year horizon. The TDABC model follows the seven-step healthcare framework proposed by Kaplan and Porter: pathology selection, value-chain definition, process mapping, identification of resources, estimation of time consumption, estimation of resource supply cost and practical capacity, and calculation of annual cost per patient. Resource estimates were obtained from institutional records, reference tariffs, operational information supplied by the hospital, and time estimates validated with clinical staff.

Table 2 identifies the source, reference period, purpose, and validation procedure associated with each major empirical input used in the patient-level costing model. This distinction is important because the model combines directly observed institutional data, externally defined reference values, clinical treatment parameters, and operational estimates validated by healthcare professionals.

Table 2. Data sources and parameter construction.

Data Element	Source	Period	Use in the Model	Validation
Staff annual cost	ULSSM payroll/management accounting records	2024–2025	CCR numerator	Institutional records
Equipment acquisition/depreciation	ULSSM records or market/reference values	2024–2025	Equipment CCR	Documentary validation
Practical capacity	Work schedules and methodological assumptions	2024–2025	CCR denominator	80% HR; 85% equipment
Activity times	Clinical interviews/process validation	September 2025–May 2026	Time allocation	Medical and nursing validation
Drug price	Hospital pharmacy data	2025	Direct drug cost	Pharmacy records
Dose and frequency	Clinical pathway/WFH guidance	2024–2025	Annual drug consumption	Clinical validation
Bleeding incidence	Institutional operational data	2024–2025	Expected bleeding cost	Institutional data
External services	Portuguese tariffs/internal values	2024–2025	Direct external costs	Official/institutional sources
Overheads/External Supplies and Services (FSE)	Annual ULSSM FSE divided by the total number of patients treated	2024–2025	Allocation of support and operating expenditure to the patient pathway	Reconciled with institutional accounting information and the allocation basis used in the study

All monetary values are reported in 2025 euros. Inputs referring to 2024–2025, 2025, and 2025–2026 were combined without inflation adjustment because they relate to a short

and overlapping data-collection period. This should be considered when interpreting the cost estimate.

TDABC Calculation Procedure

For each clinical and technological resource r, the capacity cost rate was calculated as:

$$CCR_r = \frac{Cost\ of\ supplying\ resource\ r}{Practical\ capacity\ of\ resource\ r} \quad (1)$$

where CCR_r denotes the capacity cost rate of resource r. Practical capacity differs from theoretical capacity because it excludes expected periods of unavailability, including breaks, training, leave, maintenance, preparation time, and other operational interruptions.

Practical capacity was estimated at 80% of theoretical capacity for human resources and 85% for equipment, reflecting breaks, training, maintenance, and other periods of expected unavailability. The cost assigned to activity a was then calculated as:

$$Activity\ Cost_a = \sum_r CCR_r \times t_{ar} + Direct\ Consumables_a + Externally\ Provided\ Services_a \quad (2)$$

where t_{ar} denotes the estimated number of minutes of resource r consumed by activity a. Annual patient-level cost was obtained by multiplying the cost of each activity by its expected annual frequency and summing across the complete care pathway:

$$Annual\ Patient\ Cost = \sum_a Activity\ Cost_a \times Frequency_a \quad (3)$$

The detailed activity-level TDABC calculations, including the pathway stages, resources involved, time estimates, annual frequencies, capacity cost rates, consumables, pharmaceutical expenditure, external services, overhead allocation, and resulting activity-level costs, are provided in the Supplementary Materials.

Used capacity for each resource was estimated as the total annual minutes assigned to the severe haemophilia A pathway. To ensure consistency between resource supply and resource consumption, both practical capacity and pathway-specific resource use were expressed on an annual basis. Capacity not allocated to the severe haemophilia A pathway was calculated as:

$$Capacity\ Not\ Allocated\ to\ the\ severe\ haemophilia\ A\ Pathway = Annual\ Practical\ Capacity_r - Capacity\ Used\ by\ the\ severe\ haemophilia\ A\ Pathway_r$$

This measure represents the proportion of each resource's annual practical capacity that is not assigned to the severe haemophilia A pathway. It should not be interpreted as unused capacity because the human and technological resources included in the model also support other patients and clinical pathways. Estimating actual unused capacity would require information on the complete set of activities performed by each resource. Accordingly, the capacity results are interpreted as pathway-specific capacity-allocation measures rather than as estimates of total hospital resource utilisation or unused capacity.

The TDABC architecture reconstructs costs at the patient-pathway level. However, the pharmaceutical-cost component is based on a representative patient profile rather than on separately observed annual pharmaceutical consumption for each of the 92 patients. The resulting estimate should therefore be interpreted as a representative-patient TDABC estimate. It does not capture the full heterogeneity associated with age, individual body weight, inhibitor status, product choice, treatment response, bleeding history, or patient-specific prophylactic regimens.

The model uses activity-specific time estimates rather than complex time equations. This choice reflects the relatively standardised treatment pathway modelled in the institutional setting and the absence of sufficiently granular patient-level observations to estimate conditional time equations. Where patient heterogeneity affects treatment cost, it is represented through explicit clinical and economic parameters—such as body weight, dose intensity, administration frequency, and bleeding incidence—rather than through unobserved time-equation coefficients. The absence of more complex time equations represents a limitation of the current model and an opportunity for future research using individual patient-level data.

Table 3 reports the annual practical capacity, capacity cost rates, and capacity allocated to the severe haemophilia A pathway for each human-resource category. Monthly practical capacity was annualised to ensure consistency with the annual treatment-pathway workload calculated for the 92 patients included in the institutional analysis. Capacity utilisation therefore represents the proportion of each resource category's annual practical capacity consumed by the severe haemophilia A pathway.

Table 3. Human-resource capacity, capacity cost rates, and capacity allocated to the severe haemophilia A pathway.

Resource Category	Number of Professionals	Annual Cost (€)	Capacity per Professional (min/Year)	Total Capacity (min/Year)	CCR (€/min)	Pathway Capacity Used (min/Year)	Pathway Utilisation (%)	Capacity Allocated Elsewhere (min/Year)
Pathway Physicians	3	545,911.06	132,480	397,440	1.3736	40,890	10.3%	356,550
Pathway Nurses	7	334,981.66	88,320	618,240	0.5418	32,170	5.2%	586,070
Pathway Healthcare assistants	7	128,193.80	88,320	618,240	0.2074	7350	1.2%	610,890
Administrative staff	1	16,802.45	88,320	88,320	0.1902	3060	3.5%	85,260
Other-specialty physicians	1	26,576.53	88,320	88,320	0.3009	11,040	12.5%	77,280
Total human resources	19	1,052,465.50	—	1,810,560	—	94,510	5.2%	1,716,050

The severe haemophilia A pathway uses 94,510 min of the 1,810,560 minutes of annual practical human-resource capacity included in the model, corresponding to 5.2%. The highest pathway-specific utilisation is observed for other-specialty physicians, at 12.5%, followed by physicians, at 10.3%. Utilisation is lower for nurses, administrative staff, and healthcare assistants. These figures should not be interpreted as total hospital resource-utilisation rates because the remaining capacity may be used in the treatment of other conditions and patients. Accordingly, the final column is described as capacity not allocated to the severe haemophilia A pathway rather than unused capacity. Table 4 presents the corresponding practical-capacity, capacity-cost-rate, and pathway-utilization results for the technological resources included in the TDABC model.

Table 4. Technological-resource capacity and utilisation by the severe haemophilia A pathway.

Technological Resource	Number of Units	Annual Equipment Cost (€)	Total Capacity (min/Year)	CCR (€/min)	Pathway Capacity Used (min/Year)	Pathway Utilisation (%)	Capacity Allocated Elsewhere (min/Year)
Computer 1	8	233.33	1,175,040	0.000199	24,460	2.08%	1,150,580
Mobile phone	4	10.00	587,520	0.000017	5640	0.96%	581,880
Printer	4	78.75	587,520	0.000134	1256	0.21%	586,264
Vital-signs monitor	2	150.00	293,760	0.000511	552	0.19%	293,208
Thermometer	1	1.00	172,800	0.000006	460	0.27%	172,340
BMTest machine	1	187.50	172,800	0.001085	460	0.27%	172,340
Zebra printer	2	78.75	293,760	0.000268	490	0.17%	293,270
Measuring tape	2	12.50	293,760	0.000043	368	0.13%	293,392
Scale with stadiometer	2	62.50	293,760	0.000213	460	0.16%	293,300
Examination table	2	312.50	293,760	0.001064	1380	0.47%	292,380

The severe haemophilia A pathway consumes 35,526 min of the 4,164,480 min of annual technological-resource capacity represented in the model, corresponding to 0.85%. Computer 1 has the highest pathway-specific utilisation rate, at 2.08%, while all the remaining technological resources are below 1%. These results indicate that the pathway places limited pressure on the technological resources included in the TDABC model. However, the remaining capacity should not be classified automatically as unused capacity, because the same equipment supports other patients and clinical pathways.

3.2. Game-Theoretic Component

To transform patient-level costing into a benchmark reimbursement framework, this article models treatment financing as a sequential game involving three actors: the manufacturer, the public payer, and the healthcare provider. This extension is justified by the empirical cost structure of severe haemophilia A, in which annual treatment cost is highly concentrated in the drug component and is therefore directly affected by pricing and treatment-intensity choices.

The manufacturer, denoted by M, chooses the annual drug price per patient, $p \geq 0$, interpreted as the strategic price relevant to the reimbursement negotiation. This variable is conceptually distinct from the annual provider-level drug expenditure observed in the institutional data, which may reflect procurement arrangements, confidential discounts, and other institutional conditions.

The public payer, denoted by P, chooses a reimbursement transfer $T \geq 0$. The healthcare provider, denoted by H, decides whether to adopt the treatment pathway, with $A \in \{0, 1\}$, where $A = 1$ denotes treatment adoption and $A = 0$ denotes non-adoption. This timing reflects the institutional logic of rare-disease financing: price is set or defended by the manufacturer, reimbursement is then assessed by the payer, and treatment can only be operationally sustained by the provider if the financial and operational conditions are met.

Let $c_M \geq 0$ denote the manufacturer's annual production cost per patient. Let $k > 0$ denote the provider's annual non-drug cost of treatment, as estimated by the TDABC model. Let $\gamma \geq 0$ denote an operational congestion or overload penalty borne by the provider, reflecting implementation burden, localised physician overload, or other internal frictions associated with treatment delivery. Let $\delta \geq 0$ denote the provider's mission-

related benefit from ensuring treatment access and let $V \geq 0$ denote the payer's gross value from reimbursing treatment, which may be interpreted as the social or institutional value attributed to patient access.

If treatment is adopted, the players' payoffs are given by:

$$\pi_M = (p - c_M)A, \tag{4}$$

$$\pi_P = (V - T)A, \tag{5}$$

$$\pi_H = (T - p - k - \gamma + \delta)A. \tag{6}$$

Equation (4) states that the manufacturer obtains the difference between the annual drug price and the annual production cost only when the treatment pathway is adopted. Equation (5) states that the payer obtains the gross institutional or social value of treatment access net of the reimbursement transfer only when reimbursement leads to adoption. Equation (6) defines the provider's payoff from treatment adoption as the reimbursement transfer net of the drug price, non-drug treatment cost, and operational burden, plus the mission-related benefit associated with ensuring patient access. The provider adopts the treatment pathway when this payoff is non-negative. If A = 0, all payoffs are equal to zero. The solution concept is subgame-perfect equilibrium, obtained by backward induction. The strategic logic is straightforward: the manufacturer prefers a higher price conditional on adoption; the payer values access but wishes to minimise fiscal cost; and the provider adopts only if reimbursement is sufficient to cover the drug price, non-drug treatment cost, and any operational burden net of mission benefit.

This framework allows patient-level TDABC evidence to be embedded directly into a reimbursement game. Instead of treating costing as a purely descriptive exercise, the model uses cost information to identify the conditions under which treatment adoption is financially viable for the provider and acceptable to the payer. In this way, costing becomes an input into strategic decision-making under budget pressure.

The model is intentionally stylized. The linear payoff structure is used to make the reimbursement threshold analytically transparent and to show how the TDABC cost components enter the adoption condition. It does not model bargaining power, uncertainty, repeated negotiation, asymmetric information, alternative treatments, heterogeneous patients, or alternative reimbursement contracts. These elements are important in real reimbursement settings but are kept outside the baseline model so that the link between the empirical costing evidence and the reimbursement threshold can be isolated. Section 5 discusses how relaxing these assumptions would change the strategic interpretation of the results.

3.3. Baseline Calibration

The game is calibrated using the annual patient-level cost estimate obtained from the TDABC model for severe haemophilia A. The baseline annual total cost per patient is C = EUR 105,429.14. Of this amount, D = EUR 98,514.04 corresponds to the observed annual provider-level drug expenditure per patient, while k = EUR 6915.10 corresponds to the annual non-drug treatment cost. Accordingly, the empirical cost decomposition is expressed as $C = D + k$.

To make the baseline calibration numerically reproducible, the annual provider-level drug expenditure was decomposed into regular prophylactic consumption, one supervised administration included in the annual pathway, and expected drug use associated with bleeding-related care. The baseline acquisition price per international unit was EUR 0.4453925, the representative patient body weight was 70 kg, the prescribed dose was 30 IU/kg, and the prophylactic regimen included two administrations per week over 52

weeks, consistent with the clinical pathway and the World Federation of Haemophilia guidance (Srivastava et al., 2020). Institutional data indicated that 30 of the 92 patients required bleeding-related care during the reference period. In the absence of patient-level information on the number of additional administrations associated with each episode, the ratio $30/92$ is used as an approximation of the expected bleeding-related administration component. This assumes one additional administration for each patient requiring bleeding-related care and may therefore understate pharmaceutical consumption when multiple episodes or administrations occur. This assumption is acknowledged as a limitation of the analysis.

The cost per administration was calculated as:

$$Cost\ per\ Administration = q \times w \times d, \tag{7}$$

where q denotes the acquisition price per international unit, w denotes the representative patient body weight in kilograms, and d denotes the prescribed dose in international units per kilogram per administration. Using the baseline values:

$$Cost\ per\ Administration = 0.4453925 \times 70 \times 30 = EUR\ 935.32425. \tag{8}$$

Annual expenditure on regular prophylaxis was calculated as:

$$D_{prophylaxis} = q \times w \times d \times f \times s, \tag{9}$$

where f denotes the number of prophylactic administrations per week and s denotes the number of treatment weeks per year. Therefore:

$$D_{prophylaxis} = 0.4453925 \times 70 \times 30 \times 2 \times 52 = EUR\ 97{,}273.72. \tag{10}$$

Total annual provider-level drug expenditure was calculated as:

$$= D_{prophylaxis} + D_{supervised} + D_{bleeding}, \tag{11}$$

where the drug expenditure associated with one supervised administration was:

$$D_{supervised} = q \times w \times d = EUR 935.32, \tag{12}$$

and expected bleeding-related drug expenditure was:

$$D_{bleeding} = q \times w \times d \times \frac{30}{92} = EUR\ 305.00. \tag{13}$$

Consequently:

$$D = 97{,}273.72 + 935.32 + 305.00 = EUR\ 98{,}514.04. \tag{14}$$

The resulting value represents annual pharmaceutical expenditure from the provider perspective. It should not be interpreted as the manufacturer's production cost, net transaction price, or profit-generating revenue.

The annual non-drug treatment cost was calculated as:

$$k = C - D, \tag{15}$$

$$k = 105{,}429.14 - 98{,}514.04 = EUR\ 6915.10. \tag{16}$$

Accordingly, total annual patient-level cost was:

$$C = D + k, \tag{17}$$

$$C = 98{,}514.04 + 6915.10 = EUR\ 105{,}429.14. \tag{18}$$

The baseline clinical and economic inputs used to estimate annual drug expenditure are summarised in Table 5.

Table 5. Baseline clinical and economic inputs used to estimate annual drug expenditure.

Parameter	Symbol	Baseline Value	Unit	Source
Acquisition price per international unit	q	0.4453925	EUR/IU	ULSSM hospital pharmacy data
Representative patient body weight	w	70	kg	Institutional clinical profile
Dose intensity	d	30	IU/kg/administration	Clinical pathway and WFH guidance
Cost per administration	qwd	935.32425	EUR/administration	Calculated value
Prophylactic administration frequency	f	2	administrations/week	Clinical pathway
Annual treatment horizon	s	52	weeks/year	Model assumption
Annual prophylactic administrations	$f \times s$	104	administrations/year	Calculated value
Regular annual prophylactic expenditure	$D_{\text{prophylaxis}}$	97,273.72	EUR/patient/year	Calculated value
Supervised administration included in the annual pathway	—	1	administration/year	Institutional care pathway
Drug expenditure associated with the supervised administration	$D_{\text{supervised}}$	935.32	EUR/patient/year	Calculated value
Probability of bleeding-related care	—	30/92 = 32.61%	probability	Institutional data
Expected bleeding-related drug expenditure	D_{bleeding}	305.00	EUR/patient/year	Calculated value
Total annual provider-level drug expenditure	D	98,514.04	EUR/patient/year	Calculated value

The parameters and cost components above were obtained from the original TDABC model and supporting project documentation developed by Cardoso (2026).

The baseline prophylactic regimen comprises 104 administrations per year and generates regular annual pharmaceutical expenditure of EUR 97,273.72. The model additionally includes one supervised administration valued at EUR 935.32 and expected bleeding-related drug expenditure of EUR 305.00. The latter is obtained by weighting the cost of one additional administration by the institutional probability of bleeding-related care of 32.61%. These three components generate total annual provider-level drug expenditure of EUR 98,514.04.

To complete the TDABC reconciliation, Table 6 reports the annual cost by pathway stage and separates the pharmaceutical and non-drug components. The self-administration stage amounts to EUR 97,699.08, comprising EUR 97,273.72 in regular prophylactic drug expenditure and EUR 425.36 in non-drug costs. The stage-level amounts reconcile to an annual treatment cost of EUR 105,429.14 for the representative patient, including EUR 98,514.04 in pharmaceutical expenditure and EUR 6915.10 in non-drug expenditure.

Table 6. Reconciliation of annual treatment cost by pathway stage and cost component.

Pathway Stage	Total Stage Cost (EUR)	Pharmaceutical Component (EUR)	Non-Drug Component (EUR)
Diagnosis	685.49	0.00	685.49
Routine follow-up	5502.22	935.32	4566.90
Self-administration	97,699.08	97,273.72	425.36
Bleeding-related care	1062.70	305.00	757.70
Overheads/FSE	479.65	0.00	479.65
Total	105,429.14	98,514.04	6915.10

The reconciliation separates pharmaceutical expenditure from the clinical, operational, external-service, and overhead costs included in the annual care pathway. Drug expenditure incorporated within individual pathway stages is classified under D and

excluded from k, thereby preventing double counting. The resulting decomposition reproduces the annual treatment cost of EUR 105,429.14 for the representative patient.

Because confidential discounts, procurement arrangements, manufacturer production costs, and the net transaction price received by the manufacturer are not observed, D is used as the empirical drug-cost anchor and should not be interpreted as a direct estimate of the manufacturer's transaction price, production cost, or profit margin. In the strategic model, p remains the price variable chosen by the manufacturer, whereas D represents the provider-level pharmaceutical expenditure observed in the institutional data.

The empirical cost structure further shows that pharmaceutical expenditure represents 93.4% of total annual cost. At pathway-stage level, diagnosis accounts for EUR 685.49, routine follow-up for EUR 5502.22, self-administration for EUR 97,699.08, bleeding-related care for EUR 1062.70, and allocated overheads/External Supplies and Services (FSE) for EUR 479.65. The routine follow-up, self-administration, and bleeding-related totals include pharmaceutical components that are classified under D and excluded from k in the drug–non-drug cost decomposition. These results imply that marginal changes in internal operational costs are unlikely to shift the reimbursement-feasibility frontier as strongly as changes in drug price and treatment-intensity variables. Accordingly, the strategic reimbursement space is shaped primarily by the price and utilisation profile of the therapy.

The TDABC model also provides operational information on the resources assigned to the severe haemophilia A pathway. The annual institutional pathway for the 92 patients included in the analysis consumes an estimated 94,510 min of human-resource capacity and 35,526 min of technological-resource capacity. These values correspond to approximately 5.2% of the annual practical capacity of human resources and 0.85% of the annual practical capacity of technological resources included in the model. Capacity allocation is not evenly distributed across resource categories: the pathway accounts for 10.3% of the annual practical capacity of pathway physicians, 12.5% of other-specialty physicians, 5.2% of pathway nurses, 3.5% of administrative staff, and 1.2% of healthcare assistants. These percentages represent capacity allocated specifically to the severe haemophilia A pathway and should not be interpreted as total hospital resource-utilisation rates, since the same resources also support other patients and clinical pathways. Although the pathway uses a limited proportion of aggregate annual practical capacity, the operational-burden parameter γ is retained as a scenario-based variable to represent potential implementation frictions, coordination requirements, or localised constraints that are not directly measured by the pathway-specific capacity-allocation figures.

For consistency across all deterministic sensitivity scenarios, annual total treatment cost was calculated using the following compact expression:

$$C(q, w, d, f, b) = k + qwd(52f + 1 + b). \quad (19)$$

Here, k denotes annual non-drug treatment cost, q denotes the acquisition price per international unit, w denotes representative patient body weight, d denotes dose intensity per administration, f denotes the number of prophylactic administrations per week, and b denotes the expected bleeding-related administration component. Each one-way sensitivity scenario varies only the parameter under examination while holding all remaining parameters constant.

Deterministic sensitivity analysis shows that annual cost per patient is highly sensitive to therapy-related variables. Since all pharmaceutical expenditure components are linear in the price per international unit, body weight, and dose intensity, these parameters were varied while holding the annual non-drug treatment cost constant at EUR 6915.10. A 10% decrease in the price per international unit reduces annual cost from EUR 105,429.14 to EUR 95,577.74, whereas a 10% increase raises annual cost to EUR 115,280.55.

Reducing representative body weight from 70 kg to 60 kg lowers annual cost to EUR 91,355.71, while increasing body weight to 80 kg raises annual cost to EUR 119,502.58. Reducing dose intensity from 30 IU/kg to 10 IU/kg lowers annual cost to EUR 39,753.11, whereas increasing dose intensity to 40 IU/kg raises annual cost to EUR 138,267.16. Increasing administration frequency from two to three prophylactic administrations per week raises annual cost to EUR 154,066.00. By contrast, changes in the probability of bleeding-related care have only a limited effect on annual cost. These results reinforce the conclusion that reimbursement feasibility and budget-constrained coverage are primarily driven by drug-related parameters.

For the strategic model, the total annual expected cost per patient may therefore be written as

$$C(\theta) = D(\theta) + k(\theta), \tag{20}$$

where $D(\theta)$ denotes the expected annual provider-level drug expenditure and $k(\theta)$ denotes the expected annual non-drug treatment cost. The vector θ includes the clinically and economically relevant parameters affecting treatment expenditure, such as price per international unit, body weight, dose intensity, administration frequency, and bleeding-related activity.

To avoid interpreting unobserved strategic parameters as empirically estimated quantities, the calibration distinguishes between directly observed TDABC parameters and scenario-based parameters. The drug cost, non-drug treatment cost, and annual total cost are obtained from the institutional TDABC model. By contrast, payer valuation, manufacturer production cost, provider mission benefit, operational burden, annual budget, and number of eligible patients are not directly observed in the hospital costing data. These parameters are therefore treated as scenario variables. This distinction is important because the purpose of the model is not to estimate the full bargaining environment, but to show how the empirically observed cost structure constrains reimbursement feasibility and coverage capacity. Table 7 summarizes the observed TDABC parameters and the scenario-based strategic variables used in the calibration.

Table 7. Calibration of observed TDABC parameters and scenario-based strategic variables.

Parameter	Meaning	Baseline/Scenario Value	Source/Status
D	Observed annual provider-level drug expenditure per patient	EUR 98,514.04	TDABC estimate
k	Annual non-drug treatment cost	EUR 6915.10	TDABC estimate
$C = D + k$	Annual total cost per patient	EUR 105,429.14	TDABC estimate
γ	Provider operational burden	Scenario: EUR 0/EUR 5000	Not directly observed; scenario-based
δ	Provider mission-related benefit	Scenario: EUR 0/EUR 3000	Not directly observed; scenario-based
V	Payer gross valuation of treatment access	Scenario-based	Not directly observed
c_M	Manufacturer annual production cost	Not estimated	Not observable from provider data
B	Annual payer budget	Scenario: EUR 1 million/2 million/5 million/10 million	Scenario-based
$\bar{N}$	Clinically eligible patients	Scenario-based or institutional input	To be specified if available

The values assigned to γ, δ, and B are illustrative stress-test values rather than empirically estimated quantities. The operational-burden scenario of EUR 5000 corresponds to approximately 72.3% of the baseline non-drug treatment cost k, while the mission-

benefit scenario of EUR 3000 corresponds to approximately 43.4% of k. These values are used to represent economically material changes in provider-side conditions and should not be interpreted as observed monetary estimates. The annual budget levels of EUR 1 million, EUR 2 million, EUR 5 million, and EUR 10 million were selected to illustrate how the coverage frontier scales across alternative payer capacities. No claim is made that these values reproduce the actual disease-specific payer budget, the provider's monetary valuation of its mission, or an empirically observed operational burden.

Because manufacturer production cost is not observable from provider-level data, the numerical scenarios focus on reimbursement feasibility and coverage capacity rather than on estimating manufacturer profit. The condition $p \geq c_M$ is maintained as a feasibility condition for manufacturer participation, but c_M is not interpreted as an empirically calibrated parameter.

Because the purpose of the formal model is to provide a benchmark rather than a complete bargaining environment, the propositions below should be interpreted as threshold results derived from the TDABC-calibrated cost structure.

3.4. Equilibrium Characterisation: Mathematical Propositions and Proofs

Throughout, ties are assumed to be resolved in favour of treatment adoption and reimbursement whenever a player is indifferent between acting and not acting. This tie-breaking convention is adopted as an access-favouring analytical rule. It allows reimbursement and adoption to occur when the payer or provider is exactly indifferent. Under an alternative convention in which indifference leads to non-reimbursement or non-adoption, the boundary price may not be attainable. In that case, the manufacturer would need to choose a price arbitrarily close to the boundary, such as $p = p^* - \varepsilon$, for $\varepsilon > 0$. The underlying feasibility frontier remains unchanged, although exact extraction of the full surplus is no longer guaranteed.

Proposition 1 (Provider adoption rule)**.** *Given p and T, the provider adopts the treatment pathway if and only if*

$$T \geq p + k + \gamma - \delta \tag{21}$$

Proof. At stage 3, the provider compares the payoff from adoption with the payoff from non-adoption. If A = 1, the provider obtains

$$\pi_H = T - p - k - \gamma + \delta \tag{22}$$

If A = 0, the provider obtains 0. Hence, adoption is optimal if and only if

$$T - p - k - \gamma + \delta \geq 0, \tag{23}$$

which is equivalent to

$$T \geq p + k + \gamma - \delta. \tag{24}$$

Under the tie-breaking rule, equality also leads to adoption. □

Proposition 2 (Payer reimbursement rule)**.** *For any price p announced by the manufacturer, the payer's optimal reimbursement transfer is*

$$T^*(p) = \begin{cases} \max\{0, p + k + \gamma - \delta\}, \text{if } V \geq \max\{0, p + k + \gamma - \delta\}, \\ 0, otherwise. \end{cases} \tag{25}$$

Proof. By Proposition 1, the provider adopts if

$$T \geq p + k + \gamma - \delta. \tag{26}$$

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Since reimbursement transfers are constrained by $T \geq 0$, the minimum feasible transfer that induces adoption is:

$$T(p) = \max\{0, p + k + \gamma - \delta\}. \quad (27)$$

If the payer wishes to induce adoption, any transfer above this threshold strictly reduces the payer's payoff. Therefore, conditional on reimbursement and adoption, the payer chooses:

$$T^*(p) = \max\{0, p + k + \gamma - \delta\}. \quad (28)$$

The payer's resulting payoff is

$$V - \max\{0, p + k + \gamma - \delta\}. \quad (29)$$

Reimbursement and adoption are therefore optimal if and only if:

$$V \geq \max\{0, p + k + \gamma - \delta\}. \quad (30)$$

Otherwise, the payer does not provide a positive reimbursement transfer. If $p + k + \gamma - \delta > 0$, this results in non-adoption. If $p + k + \gamma - \delta \leq 0$, the provider is willing to adopt at $T = 0$. □

Proposition 3 (Subgame-perfect equilibrium)**.** *Suppose*

$$V \geq c_M + k + \gamma - \delta. \quad (31)$$

Then the game has a pure-strategy subgame-perfect equilibrium given by

$$p^* = V - k - \gamma + \delta,\ T^* = V,\ A^* = 1. \quad (32)$$

In this equilibrium, the manufacturer captures the entire net surplus compatible with treatment adoption, while the payer and provider obtain zero net payoff.

Proof. By Proposition 2, reimbursement and adoption occur if and only if

$$V \geq p + k + \gamma - \delta. \quad (33)$$

From the manufacturer's perspective, any price above

$$V - k - \gamma + \delta \quad (34)$$

yields no reimbursement and therefore zero payoff, while any price at or below that threshold yields reimbursement and adoption. Since the manufacturer's payoff under adoption is

$$\pi_M = p - c_M, \quad (35)$$

it is strictly increasing in p. The manufacturer therefore sets the highest price consistent with reimbursement, namely

$$p^* = V - k - \gamma + \delta. \quad (36)$$

Substituting p^* into the payer's optimal transfer rule yields

$$T^* = p^* + k + \gamma - \delta = V. \quad (37)$$

By Proposition 1, the provider then adopts. The equilibrium payoffs follow immediately:

$$\pi_p^* = V - T^* = 0, \quad (38)$$

$$\pi_H^* = T^* - p^* - k - \gamma + \delta = 0, \quad (39)$$

https://doi.org/10.3390/g17050046

$$\pi_M^* = p^* - c_M = V - k - \gamma + \delta - c_M. \quad (40)$$

The condition

$$V \geq c_M + k + \gamma - \delta \quad (41)$$

ensures that the manufacturer's equilibrium payoff is non-negative. □

If $V < c_M + k + \gamma - \delta$, the manufacturer cannot choose a price that both induces reimbursement and covers its production cost. The resulting equilibrium therefore involves no reimbursement and no adoption. At $V = c_M + k + \gamma - \delta$, adoption at $p^* = c_M$ gives the manufacturer a zero payoff. Under the access-favouring tie-breaking convention adopted in this study, the manufacturer selects the price that supports reimbursement and adoption. Without this first-stage tie-breaking convention, the boundary case admits multiple equilibria, since the manufacturer is indifferent between adoption at a zero payoff and prices that result in no adoption.

Proposition 4 (Comparative statics of the equilibrium price)**.** *Whenever the equilibrium of Proposition 3 exists, the equilibrium manufacturer price satisfies*

$$\frac{\partial p*}{\partial V} = 1, \ \frac{\partial p*}{\partial \delta} = 1, \ \frac{\partial p*}{\partial k} = -1, \text{ and } \frac{\partial p*}{\partial \gamma} = -1. \quad (42)$$

The effect of the provider's mission benefit δ depends on whether the manufacturer's price is held fixed. For a fixed price p, a higher δ lowers reimbursement transfer required to induce provider adoption. When p is endogenous, however, the equilibrium expression implies that the manufacturer may increase p^* one-for-one with δ. These two comparative-static exercises should therefore be interpreted separately.

Proof. From Proposition 3,

$$p^* = V - k - \gamma + \delta. \quad (43)$$

Differentiating directly with respect to each parameter yields the stated comparative statics. The equilibrium price rises one-for-one with the payer's valuation V and the provider's mission benefit δ, and falls one-for-one with non-drug cost k and the operational penalty γ. □

The empirical calibration below requires an explicit distinction between the strategic price variable p and the observed provider-level drug expenditure D. The institutional data identify D, but do not reveal the manufacturer's net transaction price, production cost, confidential discounts, or contractual rebates. Therefore, for illustrative calibration only, D is used as an empirical anchor for p. This assumption does not imply that provider-level drug expenditure is identical to the manufacturer's net price or revenue.

Corollary 1 (Observed-expenditure feasibility benchmark)**.** *For illustrative calibration, suppose that the strategic drug-price variable p is anchored to the observed provider-level drug expenditure D = EUR 98,514.04. Under this assumption, treatment is reimbursed and adopted if and only if*

$$V \geq 105{,}429.14 + \gamma - \delta. \quad (44)$$

Equivalently, the maximum annual drug-expenditure level compatible with reimbursement under the benchmark assumptions is

$$p^* = V - 6915.10 - \gamma + \delta. \quad (45)$$

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Proof. The result follows Proposition 3 after substituting the empirical TDABC values into the equilibrium condition. Since total annual cost is C = 105,429.14 and the non-drug component is k = 6915.10, the reimbursement feasibility condition becomes

$$V \geq C + \gamma - \delta. \tag{46}$$

Likewise, the equilibrium price threshold becomes

$$p^* = V - k - \gamma + \delta = V - 6915.10 - \gamma + \delta. \tag{47}$$

These numerical expressions depend on the illustrative anchoring assumption $p = D$. Without that assumption, the general reimbursement condition remains $V \geq p + k + \gamma - \delta$. □

Corollary 2 (Sensitivity of the reimbursement frontier)**.** *Let* $V_{\min}$ *denote the minimum payer valuation required for reimbursement and adoption. Under the observed-expenditure feasibility benchmark, changes in drug-related parameters shift* $V_{\min}$ *one-for-one with the resulting change in annual total treatment cost.*

A 10% decrease in the price per international unit reduces V_{min} *by EUR 9851.40, whereas a 10% increase raises it by EUR 9851.40. Reducing representative body weight from 70 kg to 60 kg lowers* V_{min} *by EUR 14,073.43, while increasing body weight to 80 kg raises it by EUR 14,073.44. Reducing dose intensity from 30 IU/kg to 10 IU/kg lowers* V_{min} *by EUR 65,676.03, whereas increasing dose intensity to 40 IU/kg raises it by EUR 32,838.01. Increasing prophylactic administration frequency from two to three administrations per week raises* V_{min} *by EUR 48,636.86. Changes in the probability of bleeding-related care produce comparatively limited changes in* V_{min}.

Proof. Under the observed-expenditure feasibility benchmark, the minimum payer valuation required for reimbursement is:

$$V_{min} = C(\theta) + \gamma - \delta. \tag{48}$$

Holding γ and δ constant, any change in annual total treatment cost $C(\theta)$ shifts $V_{\min}$ by the same amount. The numerical implications therefore follow directly from the internally consistent deterministic sensitivity analysis of the TDABC model. □

The equilibrium characterisation shows that the strategic reimbursement space is governed primarily by the drug component of cost and only secondarily by the non-drug treatment pathway. This is fully consistent with the empirical finding that drug expenditure accounts for 93.4% of total annual cost. The benchmark implication is that pricing and treatment-intensity assumptions dominate the reimbursement frontier, whereas moderate variation in bleeding-related activity has limited impact on the feasibility of adoption.

3.5. Fixed-Budget Extension: Budget-Constrained Treatment Capacity

The baseline sequential game identifies whether treatment can be reimbursed and adopted for one patient at a given price-cost configuration. However, rare-disease financing also involves an aggregate budget question: even if treatment is individually reimbursable, the payer may still be unable to cover all clinically eligible patients when the annual public budget is fixed. To capture this institutional feature, the model is extended to include an annual payer budget B > 0.

Let C(θ) denote the expected annual cost per treated patient under treatment profile θ, where θ includes variables shown by the TDABC model to be most relevant for cost: price per international unit, body weight, dose intensity, weekly administration frequency, and expected bleeding-related treatment burden. Assume first that clinically eligible patients are homogeneous in expected benefit and expected cost. The payer's problem is then

to maximise the number of treated patients subject to the annual budget constraint. Formally, the coverage problem is

$$\max_{N \in Z_{\geq 0}} N \tag{49}$$

subject to

$$NC(\theta) \leq B, 0 \leq N \leq \bar{N} \tag{50}$$

Allowing $N = 0$ ensures feasibility when the annual budget is below the cost of treating one patient.

The fixed-budget extension should be interpreted as an accounting-based coverage implication of the TDABC estimate rather than as an additional strategic equilibrium result. Its purpose is to translate the annual patient-level cost into a treatment-capacity constraint faced by the payer. This distinction is important because the expression B/C(θ) is not, by itself, a game-theoretic result; it is a budget-feasibility implication of the calibrated cost per patient.

Proposition 5 (Optimal treatment capacity under a fixed budget)**.** *Let $B > 0$ be the payer's fixed annual budget, let $C(\theta) > 0$ denote the expected annual treatment cost per patient, and let $\bar{N}$ denote the number of clinically eligible patients. If the payer seeks to maximise the number of treated patients, the optimal number of patients covered is:*

$$N^*(B, \theta) = \min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}. \tag{51}$$

Proof. The payer chooses the largest feasible integer N that satisfies both the budget constraint and the eligible population constraint:

$$NC(\theta) \leq B. \tag{52}$$

and

$$0 \leq N \leq \bar{N}, N \in Z_{\geq 0}. \tag{53}$$

The budget constraint implies:

$$N \leq \left\lfloor \frac{B}{C(\theta)} \right\rfloor. \tag{54}$$

Since the number of treated patients cannot exceed the number of clinically eligible patients, the largest feasible integer satisfying both constraints is:

$$N^*(B, \theta) = \min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}. \tag{55}$$

□

Let $\bar{N}$ denote the number of clinically eligible patients. Full treatment coverage is feasible if and only if the annual budget is sufficient to finance the expected cost of all eligible patients. This immediately yields the following result.

Corollary 3 (Coverage frontier and exclusion set)**.** *Full treatment coverage is feasible if and only if:*

$$B \geq \bar{N}C(\theta). \tag{56}$$

The number of clinically eligible patients who remain untreated is:

$$E^*(B,\theta) = \bar{N} - N^*(B,\theta) = \max\left\{0, \bar{N} - \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}. \quad (57)$$

Proof. Full coverage requires sufficient budget to finance all clinically eligible patients. Therefore, full coverage is feasible if and only if:

$$B \geq \bar{N}C(\theta). \quad (58)$$

The number of untreated clinically eligible patients is the difference between the eligible population and the optimal number of patients covered:

$$E^*(B,\theta) = \bar{N} - N^*(B,\theta), \quad (59)$$

Substituting the optimal coverage rule from Proposition 5 gives:

$$E^*(B,\theta) = \bar{N} - \min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\} = \max\left\{0, \bar{N} - \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}. \quad (60)$$

□

This extension allows the model to speak directly to the policy problem of rationing under scarcity. Treatment access is no longer determined only by whether one patient can be reimbursed, but also by whether the aggregate budget can support the total number of eligible patients under a given treatment profile. In this sense, TDABC evidence determines not only the reimbursement threshold, but also the system-wide treatment capacity.

Proposition 6 (Comparative statics of optimal coverage)**.** *Suppose that* $C(\theta)$ *is increasing in the drug price per international unit, body weight, dose intensity, weekly administration frequency, and expected bleeding-related treatment intensity. Then optimal coverage,*

$$N^*(B,\theta) = \min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}, \quad (61)$$

is weakly decreasing in each of these variables.

Proof. An increase in any parameter that raises $C(\theta)$ reduces, or leaves unchanged, the budget-feasible number of treatment slots:

$$\left\lfloor \frac{B}{C(\theta)} \right\rfloor \quad (62)$$

Since optimal coverage is the minimum between the number of clinically eligible patients and the number of treatment slots supported by the budget, an increase in $C(\theta)$ cannot increase $N^*(B,\theta)$. Therefore, optimal coverage is weakly decreasing in each cost-increasing parameter. □

The fixed-budget extension is especially important in this empirical setting because the main determinants of annual cost are also the main determinants of treatment capacity. Since the drug component dominates total cost, even moderate increases in price per international unit, average body weight, dose intensity, or administration frequency can materially reduce the number of patients that the payer is able to cover within a fixed annual budget. By contrast, changes in bleeding incidence shift the aggregate coverage capacity only marginally.

3.6. Heterogeneous Patients and Priority-Weighted Coverage

The homogeneous-patient assumption is restrictive in rare-disease reimbursement because eligible patients may differ in severity, expected treatment benefit, bleeding risk, treatment response, and urgency of access. To address this limitation, the budget

extension can be generalised to a priority-weighted coverage problem. Let i = 1, …, $\bar{N}$ index clinically eligible patients. Each patient *i* is associated with an expected annual treatment cost Ci(θ) and a priority or health-benefit weight wi ≥ 0, reflecting severity, expected clinical benefit, urgency, or other criteria defined by the payer or HTA process. The payer chooses xi ∈ {0, 1}, where xi = 1 if patient *i* is covered and xi = 0 otherwise.

The priority-weighted coverage problem is:

$$\max \sum w_i \times x_i \tag{63}$$

subject to

$$\sum C_i(\theta) x_i \leq B, \tag{64}$$

$$x_i \epsilon \{0,1\} \tag{65}$$

As a homogeneous special case, when all eligible patients have the same expected annual cost and no differential priority weights, coverage is given by:

$$N^*(B,\theta) = min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\} \tag{66}$$

When patients differ in expected annual cost or priority weight, no single floor-ratio formula generally characterises the optimal solution.

When patients differ in expected cost or priority weight, however, the payer must decide not only how many patients can be treated, but also which patients should be prioritised under the available budget.

This extension is directly relevant to rare-disease policy because it connects patient-level costing with prioritisation, welfare criteria, and HTA decision-making. It also provides a natural route for incorporating patient heterogeneity, alternative treatment pathways, and value-based reimbursement rules in future versions of the model.

3.7. Computational Implementation and Complexity

The baseline TDABC calibration and sequential reimbursement benchmark are analytically tractable and do not require iterative numerical optimisation. For A activities and R resource categories, the activity-costing stage has computational complexity of approximately $O(AR)$, because each activity cost is obtained by aggregating the resource-time products associated with that activity. The homogeneous fixed-budget extension is calculated in constant time once expected annual cost per patient is known. The heterogeneous priority-weighted extension corresponds to a 0–1 knapsack problem and is therefore NP-hard in its general form. However, the present article introduces this extension conceptually and does not solve a large-scale empirical instance. Future stochastic implementations using Monte Carlo simulation would have complexity increasing approximately linearly with the number of simulations and evaluated patient profiles.

4. Results

Using the representative clinical profile, the patient-level TDABC architecture estimates an annual treatment cost of EUR 105,429.14 for the representative patient. The cost is decomposed into diagnosis, routine follow-up, self-administration of medication, bleeding-related care, and allocated overheads/FSE. Drug expenditure amounts to EUR 98,514.04, representing 93.4% of total annual cost. The remaining non-drug cost corresponds to the clinical, operational, and supporting resources required throughout the treatment pathway. This concentration shows that the financial sustainability of treatment is driven primarily by pharmaceutical expenditure, although the TDABC analysis remains

relevant for identifying provider-side resource consumption and the proportion of practical capacity allocated to the severe haemophilia A pathway.

The second result is analytical. In the sequential reimbursement game, treatment adoption is feasible only if the payer's valuation satisfies the condition

$$V \geq p + k + \gamma - \delta. \tag{67}$$

Equivalently, the highest manufacturer price that can be sustained in equilibrium is

$$p^* = V - k - \gamma + \delta. \tag{68}$$

Because this threshold follows from a linear benchmark specification, it should be interpreted as a first-order reimbursement condition rather than as a complete representation of real-world negotiation. Its value is to demonstrate how the empirical TDABC cost structure constrains the strategic space available to the payer, provider, and manufacturer. More complex institutional arrangements may shift the distribution of surplus, but they would still need to confront the same underlying cost frontier.

This shows that patient-level cost evidence matters strategically because it defines both the lower bound of provider acceptance and the upper bound of payer tolerance. In the calibrated setting, the reimbursement frontier is governed primarily by the therapy price and by the variables that determine drug use intensity.

The third result concerns budget-constrained treatment capacity. Once the payer's annual budget is fixed at B, the effective number of clinically eligible patients that can be treated is

$$N^*(B, \theta) = min\left\{\bar{N}, \left\lfloor \frac{B}{C(\theta)} \right\rfloor\right\}. \tag{69}$$

This result transforms the TDABC model from a patient-level costing tool into an aggregate coverage model. A treatment regime with a lower annual expected cost per patient expands the number of patients who can be covered within a fixed budget, whereas a more intensive or more expensive treatment regime compresses the feasible treatment set.

The sensitivity analysis shows how the coverage frontier changes when the treatment profile varies. A 10% increase in the price per international unit raises annual cost by EUR 9851.40 per patient, from EUR 105,429.14 to EUR 115,280.55. Increasing prophylactic administration frequency from two to three times per week raises annual cost to EUR 154,066.00, substantially reducing the number of patients who can be financed under a fixed budget. Higher body weight and dose intensity similarly tighten the feasible coverage set. By contrast, changes in the probability of bleeding-related care have only a limited effect on annual cost and aggregate coverage capacity.

The provider-side capacity findings provide an operational complement to the patient-level cost estimate. The severe haemophilia A pathway accounts for approximately 5.2% of the annual practical capacity of human resources and 0.85% of the annual practical capacity of technological resources included in the analysis. Among human resources, the highest pathway-specific capacity shares are observed for other-specialty physicians and physicians, at 12.5% and 10.3%, respectively. These results do not indicate overall hospital underutilization or excess capacity, because the healthcare professionals and equipment included in the model also support other patients and clinical pathways. Instead, they quantify the proportion of annual practical capacity specifically attributable to the severe haemophilia A pathway.

Taken together, the results indicate that severe haemophilia A reimbursement is governed by a narrow strategic margin. The treatment can be clinically justified and operationally deliverable yet still become financially unsustainable if the drug component moves upward or if the treatment regime intensifies. Conversely, reductions in price per

international unit or treatment intensity do not merely improve the economics of one patient; they also expand the number of patients that can be covered when the payer faces a fixed annual budget.

The effects of treatment-cost variability are interdependent across the three institutional perspectives. From the manufacturer's perspective, a higher drug price may increase revenue conditional on reimbursement, but it also reduces the range of payer valuations compatible with market access. From the payer's perspective, higher price, dose intensity, body weight, or administration frequency increases expenditure per patient and reduces the number of patients covered under a fixed budget. From the provider's perspective, the same changes increase the reimbursement transfer required to finance treatment delivery, while non-drug cost and operational burden affect the minimum transfer compatible with adoption. Consequently, drug-related cost variation simultaneously affects manufacturer participation, payer affordability, provider feasibility, and population coverage.

4.1. Reimbursement-Feasibility Scenarios

Table 8 reports illustrative reimbursement-feasibility scenarios based on the calibrated TDABC cost structure. These scenarios are not intended to estimate the payer's true valuation or the provider's mission benefit. Instead, they show how the reimbursement condition changes when operational burden and mission-related benefit are introduced explicitly. Under the baseline benchmark, with $\gamma = 0$ and $\delta = 0$, reimbursement is feasible if V is at least equal to the annual total cost per patient, EUR 105,429.14. Introducing an operational burden of EUR 5000 increases the minimum payer valuation required for reimbursement to EUR 110,429.14. If a mission-related benefit of EUR 3000 partially offsets this burden, the minimum payer valuation decreases to EUR 107,429.14.

Because several strategic parameters are not observable from provider-level TDABC data, the numerical results should be interpreted as illustrative scenarios rather than as empirical estimates of payer valuation, manufacturer cost, or provider mission benefit. Their role is to show how the calibrated cost structure affects reimbursement feasibility under alternative institutional assumptions.

Table 8. Illustrative reimbursement-feasibility scenarios under alternative provider-side assumptions.

Scenario	V	γ	δ	Minimum Valuation Required	Reimbursement Feasible?	Maximum Compatible Drug Price
Baseline benchmark	105,429.14	0	0	105,429.14	Yes	98,514.04
Operational burden	110,429.14	5000	0	110,429.14	Yes	98,514.04
Mission benefit partly offsets burden	107,429.14	5000	3000	107,429.14	Yes	98,514.04
Insufficient payer valuation	100,429.14	0	0	105,429.14	No	Not applicable
Higher payer valuation	115,429.14	5000	3000	107,429.14	Yes	106,514.04

The scenarios show that the model does not estimate a unique reimbursement price; rather, it identifies the reimbursement feasibility frontier associated with different institutional assumptions. When payer valuation is below the TDABC-based cost threshold, reimbursement does not occur in the benchmark model. When payer valuation exceeds the threshold, the surplus can support reimbursement and adoption. The main empirical insight is that the frontier is anchored by the drug component, because non-drug cost represents only EUR 6915.10 of the annual total cost.

4.2. Budget-Constrained Coverage Scenarios

Table 9 translates the baseline annual cost per patient into budget-feasible treatment capacity under alternative annual budget scenarios. At the baseline annual cost of EUR 105,429.14 per patient, a budget of EUR 1 million supports nine treatment slots, EUR 2 million supports 18 treatment slots, EUR 5 million supports 47 treatment slots, and EUR 10 million supports 94 treatment slots. However, when the clinically eligible population is limited to 92 patients, effective coverage under the EUR 10 million scenario is capped at 92 patients.

Table 9. Budget-feasible treatment capacity and effective coverage under alternative annual budget levels.

Annual Budget B	Annual Cost per Patient C	Budget-Feasible Treatment Slots	Effective Coverage if $\bar{N} = 92$
EUR 1,000,000	EUR 105,429.14	9	9
EUR 2,000,000	EUR 105,429.14	18	18
EUR 5,000,000	EUR 105,429.14	47	47
EUR 10,000,000	EUR 105,429.14	94	92

Table 10 further shows how budget-feasible treatment capacity and effective coverage change under alternative treatment profiles, assuming an illustrative annual budget of EUR 5 million and a clinically eligible population of 92 patients. The results show that treatment capacity is highly sensitive to drug-related parameters. A lower dose intensity substantially expands the number of treatment slots supported by the budget, whereas higher dose intensity or administration frequency sharply reduces treatment capacity. However, effective coverage cannot exceed the clinically eligible population, even when the budget would support a larger number of treatment slots.

Table 10. Sensitivity of budget-feasible treatment capacity and effective coverage to alternative treatment-cost scenarios under a EUR 5 million budget.

Treatment-Cost Scenario	Annual Cost per Patient	Budget-Feasible Treatment Slots	Effective Coverage if $\bar{N} = 92$
Price per IU −10%	EUR 95,577.74	52	52
Baseline	EUR 105,429.14	47	47
Price per IU +10%	EUR 115,280.55	43	43
Weight 60 kg	EUR 91,355.71	54	54
Weight 80 kg	EUR 119,502.58	41	41
Dose 10 IU/kg	EUR 39,753.11	125	92
Dose 40 IU/kg	EUR 138,267.16	36	36
3 administrations/week	EUR 154,066.00	32	32

Relative to the baseline, a 10% increase in the price per international unit raises annual cost per patient from EUR 105,429.14 to EUR 115,280.55 and reduces budget-feasible treatment capacity from 47 to 43 patients. This corresponds to four fewer treatment slots, or approximately 8.5% of baseline capacity. A 10% decrease in the price per international unit reduces annual cost to EUR 95,577.74 and increases budget-feasible capacity to 52 patients, creating five additional treatment slots. Increasing prophylactic administration frequency from two to three times per week raises annual cost to EUR 154,066.00 and reduces capacity from 47 to 32 patients, a decline of 15 treatment slots, or approximately 31.9%. Dose intensity generates the widest sensitivity range. At 10 IU/kg, the annual budget supports 125 treatment slots, although effective coverage is capped at 92 patients

when the eligible population is $\bar{N} = 92$. At 40 IU/kg, annual cost rises to EUR 138,267.16 and budget-feasible capacity falls to 36 patients.

These scenarios should not be interpreted as clinically interchangeable treatment options. They are one-way sensitivity tests intended to show how treatment-intensity assumptions propagate through annual patient cost, reimbursement requirements, and payer coverage capacity. Any change in dose or administration frequency must remain clinically appropriate and cannot be justified by cost considerations alone.

The stakeholder effects are interdependent. Higher price or treatment intensity may increase pharmaceutical expenditure per treated patient, but it also raises payer budget impact, increases the financing required by the provider, and reduces population coverage. Conversely, lower expenditure expands the feasible coverage set but may affect manufacturer participation and remain compatible with clinical effectiveness.

5. Discussion

This article addresses a broader decision problem than conventional costing studies. Patient-level TDABC identifies the expected annual cost of treatment, but the real policy problem in rare diseases is strategic rather than purely descriptive. Manufacturers influence the price dimension of treatment; payers must decide whether and how much to reimburse under finite fiscal capacity; and providers must determine whether access can be sustained given internal clinical workload and operational constraints. By embedding patient-level cost evidence in a sequential game and then extending the framework to a fixed-budget coverage problem, the article shows how management accounting can contribute directly to reimbursement design and treatment rationing under scarcity.

A central contribution of the article is to show that not all components of cost have equal strategic relevance. The empirical TDABC model demonstrates that treatment cost is overwhelmingly driven by the drug component, while non-drug costs represent a relatively small share of the annual burden. This implies that reimbursement feasibility and population-level coverage should be analysed first and foremost through the lens of drug price, dose assumptions, administration frequency, and patient profile. From a managerial and policy perspective, marginal efficiency gains in diagnosis or follow-up remain useful, but they are unlikely to shift the sustainability frontier as strongly as negotiations over pharmaceutical pricing and treatment regime.

The fixed-budget extension is particularly relevant for publicly funded healthcare systems. A therapy may satisfy the reimbursement condition for one patient and remain unsustainable at the population level if the expected annual cost per patient is too high relative to the total available budget. This distinction between individual reimbursement feasibility and aggregate treatment capacity is especially important in rare diseases, where per-patient cost is high and eligible populations, though small in absolute terms, may still exceed the financing room created by a fixed public budget. The model provides a first-order way to organise the frontier between treatment access and exclusion.

The article also contributes methodologically by linking TDABC to game theory in a way that is directly interpretable for healthcare decision-making. TDABC supplies the micro-costing foundation, identifying the structure and sensitivity of patient-level expenditure. The sequential game then translates this costing evidence into a reimbursement condition. The budget extension adds a further layer by converting per-patient cost into a system-level coverage constraint. This sequence—from costing to reimbursement to coverage—provides a more complete analytical framework than either costing analysis or stylized bargaining models considered in isolation.

5.1. Implications for HTA, Value-Based Pricing, and Managed Entry Agreements

The findings have implications for health technology assessment (HTA), value-based pricing, and managed entry agreements in rare diseases. In rare-disease settings, reimbursement decisions are often made under high clinical uncertainty, small patient populations, high per-patient cost, and strong ethical pressure for access. The TDABC evidence presented in this article does not replace cost-effectiveness analysis or formal HTA appraisal, but it provides an operational cost foundation that can inform affordability assessments, budget-impact analysis, and reimbursement negotiations.

From a value-based pricing perspective, the results show that the reimbursement discussion should not focus only on whether the treatment generates clinical value, but also on whether the annual cost profile is compatible with the payer's budget and the provider's operational capacity. Because drug expenditure accounts for 93.4% of annual cost in the calibrated pathway, price per international unit, dose intensity, body weight, and administration frequency are the variables most likely to affect affordability and population coverage.

The model also helps identify where managed entry agreements could be relevant. Financial-based agreements, such as expenditure caps, price-volume agreements, or confidential discounts, would directly shift the drug-price component and therefore the reimbursement frontier. Outcome-based agreements, such as pay-for-performance, coverage with evidence development, or conditional treatment continuation, would be especially relevant when clinical effectiveness, eligible population size, or long-term budget impact are uncertain. In this sense, the TDABC model can provide the cost baseline against which alternative reimbursement contracts are assessed.

However, the present model does not estimate the optimal managed entry agreement. It identifies the cost and coverage conditions that such agreements would need to address. Future research could therefore combine patient-level TDABC evidence with outcome data, patient heterogeneity, and explicit contract design to evaluate whether value-based or risk-sharing arrangements improve both access and sustainability.

The interpretation of the formal results should therefore be deliberately modest. The backward-induction model is useful because it translates the TDABC estimate into a reimbursement threshold, but it does not claim that real-world reimbursement is determined by a single linear transfer rule. In practice, reimbursement negotiations involve incomplete information, institutional bargaining power, legal and regulatory constraints, confidential discounts, multi-period reassessment, and uncertainty about clinical outcomes and eligible population size. The value of the model is to provide a transparent benchmark against which these more complex arrangements can be interpreted.

Several limitations should nevertheless be acknowledged. First, empirical evidence is drawn from a single institutional setting, which limits external generalizability. Second, the game-theoretic specification is deliberately stylized: the equilibrium condition, comparative statics, and reimbursement threshold follow from a linear payoff structure designed to isolate the role of patient-level cost evidence. The model does not include explicit bargaining, uncertainty, repeated negotiation, asymmetric information, alternative treatments, heterogeneous patients, or different reimbursement contracts. These omissions mean that the strategic component should be interpreted as a benchmark for reimbursement feasibility rather than as a complete institutional model of rare-disease contracting. Third, some of the activity-time estimates in the TDABC model rely on professional validation and process mapping rather than automated time capture, which introduces measurement uncertainty. In addition, the capacity analysis measures the proportion of practical capacity allocated to the severe haemophilia A pathway rather than the total utilisation of each resource across the hospital. Because comprehensive information on the other clinical pathways supported by these resources was not available, the analysis does not

estimate actual unused capacity. Nevertheless, the main conclusion remains consistent across the empirical costing analysis and the formal reimbursement benchmark: treatment sustainability is driven primarily by the drug-related component of cost.

Future research could extend the model in several directions. One possibility would be to allow heterogeneous patients, so that coverage decisions are based not only on cost but also on expected health benefit, severity, treatment response, or priority weighting. Another would be to move from a one-shot sequential game to an explicit bargaining or repeated-negotiation framework in which price, reimbursement, risk-sharing, and continuation decisions are jointly determined over time. A third possibility would be to introduce uncertainty and asymmetrical information about treatment effectiveness, budget impact, eligible population size, or provider capacity. A fourth extension would compare alternative treatments and reimbursement contracts, including outcome-based agreements, expenditure caps, volume-price agreements, or shared-risk contracts. These extensions would strengthen the bridge between management accounting, health economics, and strategic decision theory.

5.2. Open Research Directions

Several open research directions emerge from this benchmark framework. First, future models should incorporate explicit bargaining between manufacturers and payers, allowing price and reimbursement transfers to be jointly determined rather than sequentially imposed. Second, uncertainty should be introduced regarding clinical effectiveness, eligible population size, budget impact, and long-term outcomes, since these dimensions are central in rare-disease reimbursement. Third, patient heterogeneity should be modelled more fully by allowing patients to differ in severity, expected benefit, treatment response, bleeding risk, and expected annual cost. Fourth, future research should compare alternative reimbursement contracts, including outcome-based agreements, expenditure caps, price-volume agreements, and managed entry agreements. Finally, repeated negotiation and reassessment over time could be incorporated to reflect real-world reimbursement processes, where prices, evidence, and coverage decisions evolve as new clinical and economic information become available.

6. Conclusions

This article demonstrates how institution-specific patient-level TDABC evidence can be translated into reimbursement-feasibility and budget-constrained coverage implications in severe haemophilia A. The representative-patient TDABC estimate amounts to EUR 105,429.14 per year, of which EUR 98,514.04, or 93.4%, corresponds to pharmaceutical expenditure. Although drug expenditure dominates total cost, TDABC remains relevant for identifying the clinical and operational resources consumed throughout the patient pathway and the proportion of practical capacity allocated to treatment delivery. The sequential benchmark shows how drug price, non-drug treatment cost, operational burden, and provider mission benefit affect the reimbursement and adoption frontier, while the fixed-budget extension demonstrates how annual cost per patient determines population coverage. The main contribution of the article therefore lies in connecting patient-level costing with the interdependent implications of treatment cost for manufacturers, payers, providers, and patient access under binding budget constraints.

The analysis is subject to several limitations. The empirical evidence derives from a single institutional setting, some activity-time estimates rely on professional validation and process mapping rather than automated time capture, and the capacity analysis measures the proportion of practical capacity allocated to the severe haemophilia A pathway rather than total hospital resource utilisation or actual unused capacity. In addition, the strategic parameters not observable in the institutional data are examined through

illustrative scenarios, and the benchmark model excludes explicit bargaining, asymmetric information, repeated negotiation, alternative treatments, outcome uncertainty, and detailed patient heterogeneity. Future research should extend the framework using individual patient-level observations, probabilistic sensitivity analysis, alternative treatment pathways, and explicit reimbursement contracts. These extensions would allow treatment-cost uncertainty, patient prioritisation, and risk-sharing arrangements to be incorporated more fully into reimbursement and coverage decisions.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/g17050046/s1. The supplementary activity-level TDABC calculation workbook contains the pathway-stage and activity definitions, resources involved, time estimates, annual frequencies, capacity cost rates, consumables, pharmaceutical expenditure, external services, overhead allocation, and resulting activity-level costs used to obtain the representative-patient estimate.

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Data Availability Statement: The empirical costing evidence used in this study derives from institutional data provided by the Santa Maria Local Health Unit (ULSSM). Due to institutional and confidentiality restrictions, the raw data are not publicly available. Aggregated data supporting the findings may be made available by the corresponding author upon reasonable request and subject to institutional approval.

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References

Café, A., Carvalho, M., Crato, M., Faria, M., Kjollerstrom, P., Oliveira, C., Pinto, P. R., Salvado, R., dos Santos, A. A., & Silva, C. (2019). Haemophilia A: Health and economic burden of a rare disease in Portugal. *Orphanet Journal of Rare Diseases*, *14*, 211.

Cardoso, T.J.L. (2026). *Custo do tratamento da hemofilia a grave na ULSSM* [Master's thesis, ISEG-Lisbon School of Economics and Management].

Cooper, R., & Kaplan, R. S. (1988). Measure costs right: Make the right decisions. *Harvard Business Review*, *66*, 96–103.

Etges, A. P. B. S., Ruschel, K. B., Polanczyk, C. A., & Urman, R. D. (2020). Advances in value-based healthcare by the application of time-driven activity-based costing for inpatient management: A systematic review. *Value in Health*, *23*, 812–823.

Ganzfried, S. (2024). Computing Stackelberg equilibrium for cancer treatment. *Games*, *15*(6), 45. https://doi.org/10.3390/g15060045.

Hausken, K., & Ncube, M. (2020). Game theoretic analysis of persons, the pharmaceutical industry, and donors in disease contraction and recovery. *Humanities and Social Sciences Communications*, *7*, 150. https://doi.org/10.1057/s41599-020-00626-4.

Hausken, K., & Ncube, M. (2022). A game theoretic analysis of competition between vaccine and drug companies during disease contraction and recovery. *Medical Decision Making*, *42*(5), 571–586. https://doi.org/10.1177/0272989X211053563.

Kaplan, R. S., & Anderson, S. R. (2004). Time-driven activity-based costing. *Harvard Business Review*, *82*, 131–138.

Kaplan, R. S., & Porter, M. E. (2011). How to solve the cost crisis in health care. *Harvard Business Review*, *89*, 46–64.

Karunadasa, M., & Sieberg, K. K. (2024). Payment systems, insurance, and agency problems in healthcare: A medically framed real-effort experiment. *Games*, *15*(4), 23. https://doi.org/10.3390/g15040023.

Keel, G., Savage, C., Rafiq, M., & Mazzocato, P. (2017). Time-driven activity-based costing in health care: A systematic review of the literature. *Health Policy*, *121*, 755–763.

O'Hara, J., Hughes, D., Camp, C., Burke, T., Carroll, L., & Diego, D. A. G. (2017). The cost of severe haemophilia in Europe: The CHESS study. *Orphanet Journal of Rare Diseases*, *12*, 106.

Olsder, W., Martagan, T., & Tang, C. S. (2023). Improving access to rare disease treatments: Subsidy, pricing, and payment schemes. *Management Science*, *69*(9), 5256–5274.

Rittenhouse, B. E., & Nicod, E. (2024). Rare diseases: Economic evaluation and policy considerations. *Value Health 27*(12), 1635–1636.

Rocha, P., Carvalho, M., Lopes, M., & Araújo, F. (2015). Costs and utilization of treatment in patients with hemophilia. *BMC Health Services Research*, *15*, 484.

Soltanolkottabi, M., Ben-Arieh, D., & Wu, C.-H. (2020). Game theoretic modeling of infectious disease transmission with delayed emergence of symptoms. *Games*, *11*(2), 20. https://doi.org/10.3390/g11020020.

Srivastava, A., Santagostino, E., Dougall, A., Kitchen, S., Sutherland, M., Pipe, S. W., Carcao, M., Mahlangu, J., Ragni, M. V., Windyga, J., Llinás, A., Goddard, N. J., Mohan, R., Poonnoose, P. M., Feldman, B. M., Lewis, S. Z., van den Berg, H. M., Pierce, G. F., & the WFH Guidelines for the Management of Hemophilia Panelists and Co-Authors. (2020). WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*, *26*, 1–158.

Wettstein, D. J., & Boes, S. (2020). The impact of reimbursement negotiations on cost and availability of new pharmaceuticals: Evidence from an online experiment. *Health Economics Review*, *10*, 13.