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What is the Opportunity-Cost of Financing High-Cost Drugs? The Case of the Dominican Republic

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Abstract

In the last decades, there has been a remarkable increase in therapeutic innovations, many of which have significantly improved life expectancy and quality of life for populations. However, they have also placed pressure on health systems, increasing the need to prioritize interventions in line with the goals of those systems.

Determining coverage and financing in solidarity-based systems with limited resources is a complex challenge. To make this task easier, analytical methods have been developed over the last two decades to quantify intervention benefits and determine the extent to which an investment provides value in terms of the systems' goals, beginning with reducing mortality and improving quality of life.

In this context, the evaluation of health technologies and the economic evaluation of health technologies have played an important role in informing decisions regarding their coverage. Firstly, there is a need to prove the clinical and therapeutic benefits of these technologies (and to quantify them). Secondly, there is a consensus that understanding a technology's value requires evaluating it in the context of all alternative possible uses in the system to the resources it demands. In other words, the additional Benefit must be compared to its opportunity cost, defined as the health benefits foregone by investing resources in that technology instead of another within the system.

This article quantifies the opportunity cost, in terms of population health, of the coverage and purchases of high-cost drugs for the Dominican Republic. After this introduction, in section 2 we present the country's drug coverage context; in section 3 we discuss the methodology used to estimate the opportunity cost; in section 4 we present the evaluation results; and in section 5 we provide our main conclusions and lessons learned.

Keywords: Oportunity Cost, Health Financing, Health Systems, Project Procurement Health, Public policy, Dominican Republic, Research, Efficiency, Public Resources, Spending Efficiency, Health expenditure, Evaluation, Coverage, Investment.

JEL Codes: H10, H11, H21, H30, H51, H61, I1

WHAT IS THE OPPORTUNITY COST OF FINANCING HIGH-COST DRUGS?

The case of the Dominican Republic

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INTRODUCTION

- **In the last decades, there has been a remarkable increase in therapeutic innovations, many of which have significantly improved life expectancy and quality of life for populations.** However, they have also placed pressure on health systems, increasing the need to prioritize interventions in line with the goals of those systems.

- Determining coverage and financing in solidarity-based systems with limited resources is a complex challenge. To make this task easier, analytical methods have been developed over the last two decades to quantify intervention benefits and determine the extent to which an investment provides value in terms of the systems' goals, beginning with reducing mortality and improving quality of life.

- In this context, the evaluation of health technologies and the economic evaluation of health technologies have played an important role in informing decisions regarding their coverage. Firstly, there is a need to prove the clinical and therapeutic benefits of these technologies (and to quantify them). Secondly, there is a consensus that understanding a technology's value requires evaluating it in the context of all alternative possible uses in the system to the resources it demands. **In other words, the additional benefit must be compared to its opportunity cost, defined as the health benefits foregone by investing resources in that technology instead of another within the system.**

- This article quantifies the opportunity cost, in terms of population health, of the coverage and purchases of high-cost drugs for the Dominican Republic. After this introduction, in section 2 we present the country's drug coverage context; in section 3 we discuss the methodology used to estimate the opportunity cost; in section 4 we present the evaluation results; and in section 5 we provide our main conclusions and lessons learned.

1. EXECUTIVE SUMMARY

We find ourselves in the fortunate situation of having treatment options available that were unimaginable just a few decades ago.

» **At the same time, this, together with an ageing population and epidemiological changes, is putting pressure on health expenditures in countries around the world.** Given that resources are finite, allocating resources to one technology necessarily means *not* allocating them to others.

» **As with every other country in the world, the Dominican Republic faces the financial pressure of covering high-cost drugs.** Certain high-cost medications represent significant advances in the treatment of specific conditions, while others have limited clinical efficacy compared to existing alternatives. All of them might have an opportunity cost in terms of the health not gained or not. This article illustrates what that opportunity cost could be, estimating it for a sample of ten high-cost drugs currently covered by the Dominican health system.

» **The opportunity cost was estimated with two methodologies.** We first used the standard methodology: comparing the costs and benefits of high-cost drugs to the cost-effectiveness threshold. The second methodology estimates the opportunity cost in terms of the health gains that would result from reallocating those resources to closing the gaps in essential services.

» **Financing these drugs instead of the best therapeutic alternatives available in the country implies an additional cost of US$154 million for the duration of the treatments for all those receiving them.** The total number of quality-adjusted life years (QALY) provided by these technologies, on average per patient and for the duration of the treatment, is less than one year in perfect health (0.83 QALY). Using the threshold method, we conclude that if those resources were allocated to expand the services available in the system, the net gain would be 35,000 life years in perfect health. If the resources were allocated to cover the gaps in detecting and screening for cervical cancer (54 percent) and in detecting and non-pharmacologically managing diabetes patients (61 percent), the whole gap in cervical cancer detection and 46 percent of the gap in diabetes could be bridged, with a net health gain of 136,000 life years in perfect health.

2. CONTEXT: COVERAGE OF HIGH-COST DRUGS

The Dominican Republic is a country of 10.8 million inhabitants (Oficina Nacional de Estadística, National Statistics Office, (ONE). 2020 Census). Its population's life expectancy is 74 years and its per capita GDP in 2022, according to its Central Bank, was US$10.532 (current dollars) (Banco Central de República Dominicana, n.d.).

The Dominican health system is organized into three financing systems: (i) the subsidized system, which covers the population with no payment capacity; (ii) the contributive system, for those with formal employment; and (iii) the subsidized contributive system, for those with payment capacity and without formal employment. The subsidized system has a public insurer, SENASA. The contributive system is funded by contributions from employers and employees, and is made up by health risk insurers (*aseguradoras de riesgo de salud*, ARS) that may be public, private or self-managed. All of them are under the regulation and supervision of the Superintendencia de Salud y Riesgos Laborales (SISALRIL, Health and Labor Risk Superintendence).

The number of insured Dominicans has grown. Currently the system has ample reach. It covers 98 percent of the population (10.6 million people in 2022), of which the contributive system covers 4.8 million (ADARS, 2022). Regarding drug coverage, the PDSS explicitly includes the coverage of outpatient drugs. Financial coverage is structured with maximum limits per member per year; the basic plan covers 70 percent of drug costs in the contributive system, and 100 percent in the subsidized system. Additionally, the basic plan includes some high-cost drugs.

Besides the Plan Básico de Salud's (Basic Health Plan) drug coverage, the Dominican Republic has the **Programa de Medicamentos de Alto Costo y Ayudas Médicas (High-cost Drug and Medical Help Program - PMAC)**. PMAC serves 14,000 users, independently of their system membership. PMAC is managed by the Health Ministry and invests approximately RD$4.4 billion (US$815 million) per year to procure drugs, which is approximately 4 percent of public expenditure in health[2]. The program covers drugs not included in the PDSS or that, being covered, are unaffordable –especially for low-income workers– given financial coverage limits and user co-pays. The program covered 113 drugs (see tables 13 and 14 in Annex 1). This article's analysis precisely focuses on these PMAC-covered drugs.

3. METHODOLOGICAL CONSIDERATIONS

HIGH-COST DRUGS (HCD)

Although there is no internationally accepted definition of a "high-cost drug" (HCD), prices and the economic effort required for patients and other health system actors to buy them are common denominators. Besides prices, inter-governmental organizations such as the Pan American Health Organization (PAHO) mention other identifying indicators, including an absence of therapeutic alternatives, those that serve orphan or high-mortality diseases, innovative drugs and those that present administrative complexity (Pan American Health Organization, 2010). Additionally, they are generally marketed in monopolistic or oligopolistic contexts, or are legally protected under patents.

Unlike other countries, the Dominican Republic has a list of high-cost drugs that are covered, known as PMAC. Although this list has not been established through previously defined, explicit criteria, upon studying it, we can conclude that the main criterion for inclusion is their economic impact on families. This list, as it stood in 2022, was the starting point for the identification of the high-cost drugs we evaluated in this article (see tables 13 and 14, Annex 1).

From the list of 113 HCDs listed by the PMAC, we selected ten molecules for this study. They follow these criteria: (i) unit price; (ii) frequency of use; (iii) number of therapeutic alternatives available for each HCD; (iv) availability of information on patients, units and prices; and (v) degree of relevance according to experts[3].

In Table 1, we present the ten selected molecules. The therapeutic areas they serve are: cancer (6 molecules), autoimmune diseases (2 molecules), multiple sclerosis (1 molecule) and rare diseases (1 molecule for Fabry disease). For eight of the ten molecules, there is no generic or biosimilar substitute (the exceptions are regorafenib and etanercept, for which biosimilars exist).

TABLE 1 HCDs selected for opportunity cost evaluation

Molecule description	Health condition	Brand (innovative)	Groups	Generic or biosimilar in Dominican Republic	Generic or biosimilar in the world	Comparison molecules (same indications)
Pembrolizumab	Cancer (immunotherapy: multiple indications)	Keytruda	High-cost – with alternatives	NO	NO	Other PD-L1 (atezolizumab, nivolumab)
Atezolizumab	Cancer (immunotherapy: multiple indications)	Tecentriq	High-cost – with alternatives	NO	NO	Other PD-L1 (pembrolizumab, nivolumab)
Etanercept	Autoimmune diseases	Enbrel	High-cost – with alternatives	NO	YES	Anti-TNFs (adalimumab, infliximab, cetuximab, golimumab)
Golimumab	Autoimmune diseases	Simponi	High-cost – with alternatives	NO	NO	Anti-TNFs (adalimumab, etanercept, cetuximab, golimumab)
Palbociclib	Cancer (breast HER2-)	Ibrance	High-cost – few alternatives	NO	NO	CDK 4/6 inhibitors (ribociclib)
Regorafenib	Cancer (colon + other indications)	Stivarga	High-cost – few alternatives	NO	YES	Tyrosine kinase inhibitors
Enzalutamida	Prostate cancer	Xtandi	High-cost – few alternatives	NO	NO	Abiraterona, apalutamide and daralutamide
Sorafenib	Renal carcinoma + other indications	Nexavar	High-cost – few alternatives	NO	NO	Tyrosine kinase inhibitors
Ocrelizumab	Multiple sclerosis	Ocrevus	High-cost – few alternatives	NO	NO	RRMS (many options), primary progressive (no options)
Agalsidasa Beta	Fabry disease	Fabrazyme (Genzyme)	Few alternatives	NO	NO	Agalsidasa ALFA

Source: authors' elaboration.

METHODOLOGY FOR THE OPPORTUNITY COST ESTIMATION FOR HCD COVERAGE

In this article, we define opportunity cost as the health gains *not* obtained for having invested in the technology versus investing in the best alternative available within the system (gold standard therapy). To estimate opportunity cost, we chose the following two methods:

1. **Method 1:** opportunity cost estimation following the cost-effectiveness threshold estimated for the Dominican Republic.

2. **Method 2:** opportunity cost estimation compared to closing the gaps in highly cost-effective essential services.

Method 1: opportunity cost estimation following the cost-effectiveness threshold

The cost-effectiveness threshold method is currently the most common used to estimate opportunity cost. The cost effectiveness threshold represents the average cost of generating one quality-adjusted life year in the Dominican health system. This approach compares the cost of the evaluated technology's incremental gain (incremental cost-effectiveness ratio or ICER) with the cost-effectiveness threshold. This yields the opportunity cost per each treated case, which is then multiplied by the number of treated people to obtain the total opportunity cost. In contexts where there is a budget restriction or limits to the growth of health investment, this threshold is a good proxy of the health gains lost due to the displacement of existing services to cover and finance the cost of new technologies (Sculpher, 2012) (Paulden, 2016). If the cost of generating a QALY by the evaluated technology is higher than the average cost of generating a QALY in the health system, there is an opportunity cost. That is, the system generates less health by investing in the evaluated technology rather than in the system average.

To quantify the amount of health lost or gained, we use net health gains (NHG). The NHG compares the additional QALY provided by a technology to the QALY that would be generated if those resources were to be invested in the health system. Put another way, the NHG shows how much health is lost if it were necessary to defund certain services to finance a given technology. The NHG is calculated as:

$$NHG = (QALY_x - QALY_a) * N - \frac{(C_x - C_a)}{CET} * N$$

where "QALY" refers to the quality-adjusted life years generated by the technology, the sub-index "x" refers to the evaluated technology, "a" refers to the alternative technology, "C" refers to the technology's total cost, "N" to the number of treated people and "CET" is the cost-effectiveness threshold. The first term corresponds to the total health gains obtained by financing technology x compared to a. The second term shows how much health could be obtained if the difference in costs between technology a and technology x were to be invested in the health system.

To estimate the NHG we used the cost-effectiveness threshold estimated in 2023 by Riascos in terms of QALY (Riascos, 2023). According to that study, the cost-effectiveness threshold (average estimation) in terms of QALY is US$4,108 (2022), equal to 39 percent of the country's per capita GDP. That is to say that, **on average, generating a quality-adjusted life year in the Dominican Republic has a cost of US$4,108**[4]. In Table 14, Annex 1, we detail the steps taken to obtain these results.

Estimating the opportunity cost using the standard estimation methodology has its limitations. The most important of them is probably the assumption of the health system's technical efficiency. That is, if the decision-makers face information deficiencies, market power in price setting or limitations for defunding services, the system and the initial resource allocation may be inefficient. In that case, the technical efficiency assumption would not hold, underestimating the real opportunity cost[5].

The risk of underestimation is higher in low- and medium-income countries that still have coverage gaps for essential services. Allocating resources to high-cost technologies when these gaps persist not only contradicts ethical principles like equity (WHO, 2014); it also goes against the health system's main goals of increasing population health and life expectancy and improving quality of life. Thus, in this article we propose an original way, additional to the threshold method, to estimate the opportunity cost that takes into account the existence of gaps in essential services[6].

Method 2: opportunity cost estimation compared to closing the gaps in highly cost-effective essential services

This second approach calculates the opportunity cost expressed in the prospective purchase of essential goods and services for which there are still effective coverage gaps. This approach involves estimating the health gains which would be obtained if the resources necessary to finance the HCDs were instead used to close coverage gaps in highly cost-effective essential services. This approach lifts the system's technical and allocative efficiency assumptions, and incorporates the aspect of population coverage into the analysis. In other words, it integrates the concept that expanding coverage in average or low priority interventions when the system has not reached universal coverage in high priority interventions is inefficient and increases inequity.

The drawback of this exercise is that it needs very detailed information, which is not always available. It must define essential services, have a cost-effectiveness ratio for each of them, understand which population would require those essential services and know effectively which population accesses them, as well as the cost of providing them. In countries that have not reached universal coverage in essential services, it is important to obtain the necessary information needed to estimate the opportunity cost of covering high-cost drugs, which may sometimes have limited effectiveness, before expanding population coverage of highly cost-effective interventions.

To estimate the health gains of closing the gaps in these services, we conducted a non-systematic search of papers on the cost-effectiveness of essential services, measured in terms of QALY. From these articles we selected the reported (QALYi,j) where sub-index "i" refers to the service (i=cervical cancer detection, diabetes detection and management); and sub-index "j" refers to the country for which the calculation is reported in the original study.

The incremental cost-effectiveness index of service "i" in the Dominican Republic, which is to say the cost of producing a QALY by screening for cervical cancer or detecting and managing diabetes, is calculated as

$$ICER_{i,\,DR} = \frac{\text{unit cost}_{i,\,DR}}{QALY_{i,\,j}}$$

and the opportunity cost for the Dominican Republic, that is, the net health gain of covering the gaps, is calculated as

$$NHB_{i,\,DR} = (QALT_x - QALY_a) - \frac{\text{total cost of closing the gap}_{,\,DR}}{ICER_{i,\,DR}}$$

The methodology we followed for the specific case of the ten HCDs is further explained in section 4.

INFORMATION SOURCES USED TO ESTIMATE THE OPPORTUNITY COST

To conduct our estimation, we used the following information sources.

1. **IADB database for updating the Dominican Republic's benefits plan.** The IADB has been working with the Dominican Republic to update the social security in health system's benefits plan. As part of that process, it has collected information on costs, benefits and gaps in essential health services and the prevalence of the associated conditions. With this information we can calculate the QALY attributable to closing the gaps in these services and how much it would cost to do so.

2. **Outpatient drug prices and quantities database provided by IQVIA.** This is a worldwide standardized database that collects all commercial transactions at some point in the pharmaceutical distribution chain. It collects monthly price and quantity data, with information on the laboratory that produces and distributes the drug, brand, presentation, molecules grouped by ATC-4, market type, product type and concentration, among other variables. In the Dominican Republic, outpatient drug dispensation, also called "retail," differs from that of HCDs. Thus, this source's data is not complete.

3. **SISALRIL institutional purchases database.** List of prices gathered by SISALRIL for high-cost drugs. Internal information with average purchase price of drugs included in the PMAC high-cost drugs program.

4. **Tufts database of cost-effectiveness studies.** The Cost-Effectiveness Analysis Registry (CEA) is a complete database of over 10,000 cost-effectiveness analyses on a wide variety of diseases and treatments published from 1976 to the present day. The Registry collects information from academic papers published after being subject to a standardized review protocol. These analyses approach a wide variety of diseases and treatments; all of them measure health effects in terms of QALY. The database collects information on more than 40

variables for each paper. The registry is managed by Tufts University's Center for Evaluation of Value and Risk in Health (CEVR). We obtained the QALY for each drug and its comparison from this registry.

5. **Global Burden of Disease Study.** To estimate the gaps in essential services we used the prevalence reported in the Global Burden of Disease Study 2019 (GBD, 2019), which has information on prevalence for several countries disaggregated by CIE-10 code.

6. **SISALRIL costs study.** To cost the essential services baskets, we used the information on prices provided by the Superintendencia de Salud y Riesgos Laborales (SISALRIL). To determine the health services baskets and the frequency of both interventions, we utilized information from the pilot study that collected this data to update the benefits package in 2020, incorporating information up to 2022 prices[7].

4. ESTIMATION OF THE OPPORTUNITY COST FOR HIGH-COST DRUGS IN THE DOMINICAN REPUBLIC

METHOD 1: ESTIMATION OF THE QALY GAINED (LOST) BY COVERAGE OF SELECTED HCDS USING THE COST-EFFECTIVENESS THRESHOLD METHOD

This section presents the estimation of the NHG (equation 1) for the HCDs under analysis, and the steps followed to obtain the variables that make up that equation.

Obtaining incremental QALY

To calculate incremental QALY (QALYx - QALYa), we used studies from Tufts University to gather the following information for each analyzed molecule: (i) QALY provided by the HCD; (ii) QALY provided by the comparison; (iii) treatment duration under the molecule under study; (iv) treatment duration under the comparison; (v) cost-effectiveness ratio; and (vi) molecule price.

Table 2 presents a summary of each molecule in the study: target population of the intervention, intervention analyzed, comparison (gold standard treatment) and estimated incremental QALY for the analyzed intervention relative to its comparison. In the cases where the gold standard treatment involved two molecules, we estimated for both of them –for example, the gold standard for breast cancer treatment includes both letrozole and fulvestrant. For our analysis, we used the average incremental gains reported in the studies[8].

Regarding the incremental health gains provided by each of the analyzed treatments, as shown in Table 2, they are all less than two life years in perfect health, except for the treatment of multiple sclerosis with ocrelizumab. Eight of the ten molecules show health gains that are less than one life year in perfect health. In some cases, such as in metastatic colon cancer, such gains fail to reach one month in perfect health. This is important because, although some new high-cost drugs contribute significantly to improve population health, others provide a marginal benefit relative to the comparison therapies.

TABLE 2 Incremental QALY of the evaluated interventions

Active ingredients	Population	Indication	Intervention	Comparison	Result: incremental QALY
Agalsidasa beta	Patients with symptomatic Fabry disease	Fabry disease	Agalsidasa beta	Standard medical care	0.03
Palbociclib	Patients with advanced breast cancer	Breast cancer	Palbociclib + letrozole	Letrozole Fulvestrant	0.70
Pembrolizumab	Patients with non-small cell lung cancer in 1st line of treatment	Non-small cell lung cancer	Pembrolizumab in 1st line of treatment	Chemotherapy + platinums (carboplatin - cisplatin) Docetaxel	0.69
Sorafenib	Patients with renal cancer in 2nd line of treatment	Renal cancer	Sorafenib	Supportive care	0.25
Etanercept	Patients with active rheumatoid arthritis	Psoriatic arthritis	Etanercept	Conventional treatment (DMARD and NSAID)	1.74
Golimumab	Patients with active rheumatoid arthritis	Psoriatic arthritis	Golimumab	Conventional treatment (DMARD and NSAID)	1.90
Enzalutamida	mCRPC patients chemotherapy-naive	Prostate cancer	Enzalutamida	Docetaxel	0.37
Ocrelizumab	RRMS patients with mild to moderate disability	Multiple sclerosis	Ocrelizumab	Beta-interferon	0.66
Atezolizumab	Non-small cell lung cancer [1L with PD-L1]	Non-small cell lung cancer	Atezolizumab	Platinum-based doublet chemotherapy or docetaxel	1.12
Regorafenib	Metastatic colon cancer	Colon cancer	Regorafenib	Supportive care	0.03

Source: authors' elaboration.

Estimation of incremental costs

To estimate incremental costs (Cx - Ca), we first estimated annual cost and then the net present value of the total cost, which depends on the duration of the treatment as well as the patients' life expectancy.

We estimated the annual treatment cost in the Dominican Republic for each high-cost molecule and its comparison. Subsequently, we calculated the incremental cost, defined as the difference between the cost of the intervention (analyzed molecule) and its comparison (gold standard treatment). In cases where the gold standard treatment involved two molecules, we used the average cost of the comparisons.

To estimate the total direct cost, we calculated the cost per case per year, then multiplied it by the total number of patients who would require said treatment according to medical protocols.

To calculate the cost per case, we included only the cost of acquiring and administrating the molecules for the specified timeframe and frequency defined by the protocols. In cases where such protocols were unavailable, we relied on information from the drugs' prospectuses. We did not include adverse effects, complementary treatments, admissions or comorbilities[9].

In all cases, we assumed 100 percent adherence and compliance with treatment protocols. The prices we used are the purchases made via tender by the Health Ministry (MSAL). As Table 3 shows, the prices obtained via tender are, on average, lower than the market prices collected by a SISALRIL study.

Table 3 shows the estimation of the average annual cost per case, estimated number of current cases under treatment and the total estimated expenditure on the analyzed molecules. Annually, the expenditure (at net present value) equals US$67 million for 1,807 patients.

Once we estimated the annual cost, we calculated the net present value of the therapy's total cost for the duration of the treatment. The data needed for this estimation included the average treatment duration and the discount rate, which we obtained in the mentioned publications.

Table 4 shows the estimations of the total treatment cost per case for the treatment's duration for each intervention-comparison and the incremental cost, defined as the difference between the net present value of the per case cost of the intervention and its comparison. The total incremental cost for the selected HCD relative to its comparison is US$154,680,199 for the duration of the treatment for the 14,577 covered patients. This is the incremental expenditure the health system incurs during all treatments in the patients' lives. Of this investment, 22 percent corresponds to palbociclib, a molecule for the treatment of advanced breast cancer, followed by Golimumab, used for the treatment of psoriatic arthritis.

TABLE 3 Annual costs per case and total annual cost of selected HCDs

Active ingredient and presentation	MSAL tender price	SISLRIL reference price	Annual cost per case MSAL price	Number of estimated annual covered cases	Total annual cost with current coverage (at MSAL prices)
PALBOCICLIB 100 mg - 125 mg - 75 mg	6,414	7,683	64,135	348	22,319,135
PEMBROLIZUMAB 100 mg / 4 ml	4,194	5,445	72,703	153	11,123,626
ENZALUTAMIDA 40 mg	3,869	4,571	27,082	263	7,122,689
REGORAFENIB	6,998	7,415	251,917	25	6,297,936
GOLIMUMAB 50 mg / 1 ml	1,255	1,255	15,063	370	5,573,239
ATEZOLIZUMAB 1200 mg / 20 ml	6,991	8,001	83,889	62	5,201,092
ETANERCEPT 50 mg / 20 ml	840	1,340	10,077	442	4,454,085
OCRELIZUMAB 300 mg / 10 ml	8,028	8,119	32,114	97	3,115,019
SORAFENIB 200 mg	2,895	4,023	37,630	45	1,693,337
AGALSIDASA BETA 35 mg / 10 ml	4,814	8,001	115,537	2	231,074
Total				**1,807**	**67,131,232**

Source: authors' elaboration.

TABLE 4 Net present value and incremental cost of the interventions' direct costs

Commercial brand	Active ingredient and presentation	Complete treatment cost per case (net present value)	Comparison cost per case (net present value)	Incremental cost per case (net present value)	Total incremental cost (net present value) (incremental cost per case * number of cases)	Share of HCD total cost
Ibrance	PALBOCICLIB 100 mg - 125 mg - 75 mg	104,062	4,668	99,394	34,589,137	22,4%
Simponi	GOLIMUMAB 50 mg / 1 ml	93,900	9,492	84,408	31,231,026	20,2%
Enbrel	ETANERCEPT 50 mg / 20 ml	55,642	8,408	49,629	21,935,975	14,2%
Ocrevus	OCRELIZUMAB 300 mg / 10 ml	259,872	49,376	210,496	20,418,142	13,2%
Keytruda	PEMBROLIZUMAB 100 mg / 4 ml	106,765	2,504	104,262	15,952,012	10,3%
Xtandi	ENZALUTAMIDA 40 mg	38,723	1,887	36,836	9,687,934	6,3%
Tecentriq	ATEZOLIZUMAB 1200 mg / 20 ml	166,913	8,691	158,222	9,809,778	6,3%
Fabrazyme	AGALSIDASA BETA 35 mg / 10 ml	3,905,005	90,000	3,815,005	7,630,011	4,9%
Stivarga	REGORAFENIB	102,901	0	102,901	2,572,525	1,7%
Nexavar	SORAFENIB 200 mg	18,970	0	18,970	853,660	0,6%
				Total incremental cost	**154,680,199**	**100%**

Source: authors' elaboration.

Estimation of the opportunity cost using the cost-effectiveness threshold

To estimate the opportunity cost as the **NHG of covering the HCDs**[10], we used the estimation of the net present value of the incremental QALY obtained in section 4.1.1, the net present value of the incremental costs presented in section 4.1.2 and the cost-effectiveness threshold estimated by Riascos *et al*. (2023).

The NHG results are shown in Table 5. As the table shows, the opportunity cost of covering the ten high-cost molecules we analyzed has a negative impact on the system's efficiency. The opportunity cost for a CET of US$4,108 per QALY is estimated at 35,258 QALY, with an interval of 28,240 QALY to 40,835 QALY, depending on the studies used for the estimation.

Conceptually, those numbers show the QALY that are *not* obtained by the system if resources must be reallocated to finance the analyzed HCDs[11]. As expected, a higher cost-effectiveness threshold (lower average health system productivity) yields a lower opportunity cost.

Table 5 shows that three HCDs, palbociblib, golimumab and ocrelizumab, represent 56 percent of the total opportunity cost; and five HCDs concentrate 80 percent of it, palbociblib, golimumab, ocrelizumab, etanercept and pembrolizumab. The pathologies associated with these drugs are chronic diseases (breast cancer, psoriatic arthritis, multiple sclerosis and lung cancer) of a significant prevalence and the drugs are used in second- or third-line treatments with a limited impact on survival and quality of life, which is part of the reason for their high opportunity costs.

The three HCDs with a lower impact in total opportunity cost are sorafenib, regorafenib and algasidase beta. Together, they account for 8 percent of the opportunity cost. These molecules have a smaller aggregate impact because they treat a smaller amount of patients, but they also have a lower value per dollar (Table 5). Sorafenib is a high-cost drug for second-line treatment of kidney cancer; the incremental QALY it provides relative to its comparison (supportive care) is three months in perfect health. The number of patients who reach that stage and are covered (45 patients) is very small compared to those of the other cancers analyzed. Regorafenib is a HCD for metastatic colon cancer. Its opportunity cost comes from the scant health gains it provides in terms of QALY: 11 additional days in perfect health. Lastly, algasidase beta is a HCD for Fabry disease, which is classified as a rare or low-incidence disease. Only two patients are being covered for this disease, and the drug provides 0.7 QALY.

These results are very robust to changes in the value of the threshold and to the gains in QALY reported in the various studies. Table 6 shows the opportunity cost using the upper and lower bounds of the threshold estimated by Riascos *et al*. (2023). Table 6 also shows the opportunity cost using the minimum and maximum QALY values reported in the literature. For the lower bound of the CET (US$3,445 per QALY), the average opportunity cost increases to 42,452 QALY, with an interval of 33,939 to 49,266 QALY. With the highest CET value the opportunity cost decreases to between 26,286 and 37,946 QALY, with an average of 32,792 QALY.

To complete our analysis, we added the value per dollar invested in the Dominican Republic for each of the ten HCDs (Table 7). To that end, we estimated the cost-effectiveness ratio of each molecule and listed them as such. As can be seen, the least cost-effective HCD is algasidase beta, which has a cost-effectiveness ratio more than 1,000 times the CET. The same applies for regorafenib.

The best cost-effectiveness is for etanercept, whose ICER is 7 times the CET. The rest of the molecules are over ten times higher than the threshold. Apart from the opportunity cost, the value per dollar invested provided by each molecule is very important both for coverage decisions and price negotiations.

TABLE 5 Estimation of the opportunity cost using the threshold method and a threshold estimation of US$4,108

Indication	Commercial brand	Active ingredient and presentation	Net gain per treated patient at MSAL prices, net present value (QALY)			Total net gain (net present value)		
			MIN	AVG	MAX	MIN	AVG	MAX
Breast cancer	IBRANCE	PALBOCICLIB 100 mg - 125 mg - 75 mg	-20.92	-23.50	-25.02	-7,280.64	-8,176.88	-8,706.22
Psoriatic arthritis	SIMPONI	GOLIMUMAB 50 mg / 1 ml	-18.51	-18.64	-18.78	-6,848.42	-6,898.12	-6,947.82
Relapsing-remitting multiple sclerosis	OCREVUS	OCRELIZUMAB 300 mg / 10 ml	-25.45	-49.43	-80.21	-2,468.43	-4,795.08	-7,779.98
Psoriatic arthritis	ENBREL	ETANERCEPT 50 mg / 20 ml	-7.70	-9.93	-11.05	-3,401.61	-4,390.02	-4,886.00
Non-small cell lung cancer (NSCLC)	KEYTRUDA	PEMBROLIZUMAB 100 mg / 4 ml	-8.07	-24.34	-32.80	-1,234.19	-3,723.77	-5,018.70
Non-small cell lung cancer (NSCLC)	TECENTRIQ	ATEZOLIZUMAB 1200 mg / 20 ml	-33.92	-37.66	-40.68	-2,103.09	-2,335.21	-2,522.27
Prostate cancer	XTANDI	ENZALUTAMIDA 40 mg	-8.60	-8.60	-8.60	-2,260.89	-2,260.89	-2,260.89
Endocrine disorders (Fabry disease)	FABRAZYME	AGALSIDASA BETA 35 mg / 10 ml	-928.04	-928.04	-928.04	-1,856.07	-1,856.07	-1,856.07
Colon cancer	STIVARGA	REGORAFENIB	-24.34	-25.03	-25.72	-608.38	-625.64	-642.89
Renal cancer	NEXAVAR	SORAFENIB 200 mg	-3.96	-4.36	-4.77	-178.13	-196.34	-214.56
Opportunity cost for the Dominican system of covering the ten molecules						**-28,239.86**	**-35,258.03**	**-40,835.39**

Source: authors' elaboration.

TABLE 6 Sensitivity analysis of the opportunity cost with the threshold method

Net gain (in AVC)	Threshold (CET) dollars per QALY			
		3,445	4,108	4,398
Gain per patient identified in the literature	Min	-49,266	-40,835	-37,943
	Average	-42,452	-35,258	-32,790
	Max	-33,939	-28,240	-26,285

Source: authors' elaboration.

TABLE 7 Estimation of the cost-effectiveness ratio for the Dominican Republic, in dollars

HCD	Condition	Incremental treatment cost per case	Additional QALY per treatment (avg.)	Incremental cost-effectiveness ratio (ICER)	ICER / CE threshold ratio	Net gain per patient
Agalsidasa beta	Endocrine disorders (Fabry disease)	3,815,005	0.70	5,450,007.85	1,326.77	-928.04
Regorafenib	Colon cancer	102,901	0.03	4,116,040.74	1,002.02	-25.03
Ocrelizumab	Relapsing-remitting multiple sclerosis	210,496	1.81	116,296.30	28.31	-49.43
Pembrolizumab	Non-small cell lung cancer (NSCLC)	104,262	1.04	99,931.16	24.33	-24.34
Palbociclib	Breast cancer	99,394	0.70	141,991.53	34.57	-23.50
Atezolizumab	Non-small cell lung cancer (NSCLC)	158,222	0.85	185,416.66	45.14	-37.66
Enzalutamida	Prostate cancer	36,836	0.37	99,289.08	24.17	-8.60
Sorafenib	Renal cancer	18,970	0.26	74,393.00	18.11	-4.36
Golimumab	Psoriatic arthritis	84,408	1.91	44,308.75	10.79	-18.64
Etanercept	Psoriatic arthritis	49,629	1.74	28,563.40	6.95	-10.34

Source: authors' elaboration.

METHOD 2: ESTIMATION OF THE QALY GAINED (LOST) BY COVERAGE OF THE SELECTED HCDS RELATIVE TO CLOSING THE GAPS IN THE EFFECTIVE COVERAGE OF ESSENTIAL SERVICES

In this section, we present the method used to estimate the opportunity cost in terms of QALY gained by closing gaps in effective coverage. For this exercise, we followed the steps presented in Table 16, Annex 2, which also shows the information required and sources used.

We selected two interventions included in the first priority group of the DCP3 study. One is the timely detection of cervical cancer, a health condition with a high probability of recovery if detected and treated in a timely fashion. It is estimated that this disease produces over 658 deaths and 21,000 disability-adjusted life years (DALY) lost per year in the Dominican Republic (GBD 2019), which could be reduced with timely diagnostic and treatment interventions. The other is an intervention for the detection and non-pharmacological management of type 2 diabetes, one of the health conditions with the highest burden of disease in the Dominican Republic. According to GBD data, the burden of this disease reaches 50,576 DALY and is linked to 1,300 annual deaths. Thus, the two selected interventions are: (i) timely detection of cervical cancer through visual inspection or tests such as the Papanicolaou; and (ii) the detection and non-pharmacological management of diabetes among at-risk adults, including glucose control, arterial pressure and lipid management and constant feet care.

Information exists on the gaps in effective coverage and the cost of the baskets of services needed (see section on sources) for both interventions. For 2022, the gap in the timely detection of cervical cancer is 54 percent, and that of the timely and comprehensive detection and non-pharmacological management of diabetic patients is 61 percent.

Estimation of the incremental QALY

Having identified these two high-priority interventions, and since DCP3 does not report QALY but rather DALY, we conducted a non-systematic search for cost-effectiveness studies on the QALY gained by similar interventions in other countries. We selected studies that were better adjusted in terms of intervention, population and comparison, and whose results were adjusted to the question under study (PICOT question). We then calculated the QALY that could be gained if universal coverage were to be reached in both services. For diabetes, we selected Herman *et al*. (2005) and for cervical cancer we selected Chauchan *et al*. (2020). The incremental QALY generated by the interventions are shown in Table 8.

Estimation of the incremental cost

We computed the annual normative cost per case for providing each intervention in the Dominican Republic. To achieve this, we identified the goods and services to be included in the intervention and adhered to the usage regulations from the local care protocols. To cost each service basket, we used 2022 market prices. Tables 21 and 24 in Annex 4 provide further details on the baskets.

Having estimated the normative cost per case, we proceeded to estimate the normative cost under universal coverage and current coverage. To that end we estimated the number of people who would require the intervention according to normative and epidemiological data (need), and subsequently, we applied the current coverage percentage.

For the cervical cancer prevention basket, need was calculated for the target population, defined through expert local judgment as all women aged 30 through 49. To calculate current demand, we estimated an average coverage of 46 percent, derived from the information in the SISALRIL databases regarding the conduction of the Papanicolaou test. For the diabetes basket, we used the prevalence of diabetes as reported by the 2019 Global Burden of Disease 2019 study. For the normative cost, we estimated current demand (utilization) of the interventions. For current demand, we estimated an average coverage of 39 percent, calculated from the information in the SISALRIL databases for the glycated hemoglobin test.

Table 9 presents the per case and total normative costs, incremental cost and financing gap to reach universal coverage. Although it is true that reaching 100 percent coverage is not plausible, the exercise seeks to illustrate the importance of conducting these investments to close gaps in effective coverage.

Closing the gaps in the coverage of these two interventions would have an additional annual cost of US$21,828,743, of which the cervical cancer intervention accounts for US$3,740,564 and the type 2 diabetes intervention accounts for US$18,088,179. Since the timeframes for these studies are 10 and 20 years, respectively, the net present value of the additional investment needed in those timeframes are estimated at US$301,014,202 (US$31,907,767 for cervical cancer and US$269,106,434 for type 2 diabetes).

Estimation of the opportunity cost using the method of bridging gaps

To estimate the opportunity cost with this method, we used equations 2 and 3, as outlined in section 3. Tables 10 and 11 present the results of these estimations.

Table 10 presents the ICER estimation for both interventions using the incremental QALY obtained from the literature and the local cost of the intervention. The ICER for the cervical cancer intervention was estimated at US$910 per QALY, and that of timely detection and management of type 2 diabetes was estimated at US$1,288 per QALY. Both ratios are well below even the lower bound of the cost-effectiveness threshold for the Dominican Republic (US$2,722 per QALY). In other words, closing the gaps in the coverage of these essential interventions would generate a health gain for Dominicans bigger than that generated on average by the system.

TABLE 8 Incremental QALY of the selected interventions

Intervention	Population	Comparison	Result: incremental QALY*	Duration	Source
Timely detection for cervical cancer with visual inspection or tests such as Papanicolaou	Women over 30 years	Treatment	0.09	10 years	Herman et al. (2005)
Diabetes detection and management among at-risk adults, including glucose control, arterial pressure and lipids management and constant feet care	Over 18 years glucose-intolerant population	Placebo	0.57	20 years	Cauchan et al. (2020)

Source: authors' elaboration.

TABLE 9 Annual estimated financial gap to reach universal coverage

Intervention	Health condition (1)	Target population (2)	Need (number of cases expected to require intervention according to prevalence and incidence) (3)	Current coverage (number of cases currently receiving intervention) (4)	Annual normative cost per incremental case (5)	Timeframe (6)	Normative incremental cost per case, net present value (7)	Normative incremental cost, net present value (7) *((3)-(4))
Timely detection for cervical cancer with visual inspection or tests such as Papanicolaou	Cervical-uterine cancer	Women over 30 years	728,571	336,067	$9,53	10 years	$81.3	$31,907,767
Diabetes detection and management among at-risk adults, including glucose control, arterial pressure and lipids management and constant feet care	Type 2 diabetes	Over 18 years glucose-intolerant population	600,745	234,290	$49.36	20 years	$734.3	$269,106,434

Source: authors' elaboration.

TABLE 10 Potential gains in QALY of closing the coverage gap

Intervention	QALY per case, net present value	Cost per case, net present value	Estimated ICER for the Dominican Republic	HCD resources reallocated to essential interventions	QALY gained by HCD resource reallocation
Timely detection for cervical cancer with visual inspection or tests such as Papanicolaou	0.09	81.29	910.33	$31,907,767	35,051
Diabetes detection and management among at-risk adults, including glucose control, arterial pressure and lipids management and constant feet care	0.57	734.35	1,288.34	$269,106,434	95,295
Total				**$154.680.199**	**130.346**

Source: authors' elaboration.

Table 11 presents the net health gains from financing HCDs compared to that of financing the bridging the gaps in effective coverage, disaggregating by each drug. For this calculation, we listed the HCDs in a "league table", in a decreasing ICER order. Then, the additional budget needed to cover each HCD –US$154,680,199 in Table 5– was successively allocated to cover the gaps until it was exhausted. Closing the gap for the timely detection of cervical cancer intervention requires an additional investment of US$31,907,767, which equals the coverage of all patients who receive regorafenib and algasidase beta, and a fraction of those who receive palbociclib. This leaves US$122,772,432 available to cover the gap to detect and manage diabetes. With the resources used to cover the ten HCDs, the Dominican Republic could close the entire gap in timely detection of cervical cancer and 46 percent of the gap in diabetes detection.

The QALY provided by closing these gaps are calculated as the amount allocated to cover each gap divided by the respective intervention's ICER (second term of equation 3), which results in a gain of 130,346 QALY. These QALY are compared with the incremental QALY generated by HCDs: 2,459. The difference between the QALY provided by the HCDs and those provided by closing the gaps is the opportunity cost. **The opportunity cost of financing HCDs compared to closing the effective coverage gap in the interventions we studied, thus, is estimated at 127,887 QALY *not* gained by the Dominican health system.**

As expected, the opportunity cost calculated with the method of bridging the gaps in effective coverage of essential interventions is significantly higher than the one estimated using the cost-effectiveness threshold. This is a very important result: in low- and medium-income countries that still have significant gaps in the coverage of essential treatments, estimating the opportunity cost with standard methodology could underestimate the true opportunity cost of coverage decisions.

TABLE 11 Estimation of the opportunity cost of reallocating resources to close essential services gaps

HCD	Condition	HCDs incremental cost-effectiveness ratio	Total additional QALY	Treatment incremental cost	Aggregate budget per intervention	Comparison intervention	Essential services incremental cost-effectiveness ratio	Percentage of gap covered by resource reallocation	Close of gap QALY	Net health benefits of resource reallocation
Agalsidasa beta	Endocrine disorders (Fabry disease)	5,450,007	1.4	7,630,011	7,630,011	Cervical cancer detection	910.33	100%	8,382	-8,380
Regorafenib	Colon cancer	4,116,040	0.6	2,572,525	10,202,536				2,826	-2,825
Atezolizumab	Non-small cell lung cancer (NSCLC)	185,416	52.9	9,809,778	20,012,314				10,776	-10,723
Palbociclib	Breast cancer	141,991	243.6	11,895,453	31,907,767				13,067	-12,824
Palbociclib	Breast cancer	141,991	243.6	22,693,684	22,693,684	Diabetes detection and management	1,288.34	46%	17,615	-17,371
Ocrelizumab	Relapsing-remitting multiple sclerosis	116,296	175.6	20,418,142	43,111,825				15,848	-15,673
Pembrolizumab	Non-small cell lung cancer (NSCLC)	99,931	159.6	15,952,012	59,063,837				12,382	-12,222
Enzalutamida	Prostate cancer	99,289	97.6	9,687,934	68,751,771				7,513	-7,422
Sorafenib	Renal cancer	74,393	11.5	853,660	69,605,431				663	-651
Golimumab	Psoriatic arthritis	44,309	704.9	31,231,026	100,836,456				24,241	-23,536
Etanercept	Psoriatic arthritis	28,563	768.0	21,935,975	122,772,432				17,027	-16,259
Total costs, QALY and net health benefit			2.459	154,680,199					130,346	-127,887

Source: authors' elaboration.

5. SUMMARY AND CONCLUSIONS

A key goal of health systems is to increase population health while improving life expectancy and quality of life. To reach this goal, systems are organized to provide goods and services to advance, prevent, diagnose and help people recover from health issues.

To provide these goods and services, systems face limited resources available to finance them. The explicit prioritization of resources based on available evidence is increasingly needed in a world with growing needs and increasingly sophisticated and costly technologies. Cost-effectiveness analysis plays a key role in this context, as it helps understand the health consequences of different resource allocation alternatives.

This article presented the estimation of the opportunity cost of financing ten high-cost drugs in the Dominican Republic. We used two alternative methodologies: the standard methodology of net health gains using the system's cost-effectiveness threshold (CET) as a proxy of average health production per dollar invested in the system; and an alternative methodology that calculated the net health gains by comparing the cost-effectiveness ratios of essential interventions that are highly cost-efficient and have not yet reached universal coverage. For this article, we studied the timely detection of cervical cancer and the detection and management of type 2 diabetes.

The ten drugs we analyzed annually require close to US$67 million and serve 1,807 patients. Using either methodology, the net health gain estimations for financing these ten high-cost drugs indicate that they represent high-opportunity cost interventions in terms of population health. With the cost-effectiveness threshold methodology, and for the average system productivity resulting in a threshold of US$4,108 per QALY, the opportunity cost was estimated at 28,240 to 40,385 QALY. With the methodology of closing the gaps in population coverage, that opportunity cost more than doubles to 127,887 QALY.

As expected, this suggests that in countries with gaps in essential services, the traditional threshold methodology may significantly underestimate the opportunity cost. These results highlight the importance of considering the existence of gaps in essential services when evaluating the opportunity cost to include new technologies in benefits plans. At a methodological level, this is an invitation to adapt standard methods of economic evaluation and opportunity cost estimation in low- and middle-income countries that often have gaps in the coverage of highly cost-effective services.

The high opportunity cost is explained not only by the prices but also by the low gains provided by some of the drugs in terms of population health, as well as the number of people requiring these therapies. For example, algasidase beta has the highest cost per patient per year. However, given the small number of patients with Fabry disease (2 patients), this molecule's impact in total opportunity cost is limited.

Studying the value per investment of each molecule by estimating the ICER for the Dominican Republic allowed us to rank the molecules relative to the health value they provide per dollar invested in them. The range of this variation for the ten molecules is very wide. Two molecules, algasidase beta and regorafenib, have ICERs over 1,000 times that of the country's CET.

One observation from this analysis is that affordability can be derived from allocating resources and devising strategies to achieve price reductions.

In some cases, the price differences observed between the financing subsystems are considerable, and this gap could be reduced with joint procurement strategies. In other cases, alternatives could be explored, such as shared risk when there is uncertainty on the molecule's effectiveness. Finally, it is key to consider that increasing benefit coverage of technologies with limited effectiveness, when a country still has not achieved universal coverage of highly cost-effective essential interventions, has a direct impact on total population health.

ANNEX 1. LIST OF HIGH-COST DRUGS

TABLE 13
(1 of 2)

MSAL list of high-cost drugs included in PDSS

DRUG / INTERNATIONAL NONPROPRIETARY NAME (INN)	SPECIALTY	PATHOLOGY	PDSS
LEUPRORELIN ACETATE 7.5 MG/ML/VIAL	Endocrinology	Cancer (breast)	YES
SOMATROPINE 5.3 MG/ 1 ML (16 UI)	Endocrinology	Precocious puberty	YES
COAGULATION FACTOR VIII 500 UI / 100 ML	Hematology	Type A hemophilia	YES
HUMAN IMMUNOGLOBULIN 5 G	Neurology	Neurological	YES
SUNITINIB MALATE 12.5 MG	Oncology	Cancer (gastrointestinal, renal, pancreatic)	YES
SUNITINIB MALATE 25 MG	Oncology	Cancer (gastrointestinal, renal, pancreatic)	YES
ZOLEDRONIC ACID 4 MG /5ML	Oncology	Cancer (breast)	YES
BEVACIZUMAB 100 MG / 4 ML	Oncology	Cancer (colon, breast)	YES
BEVACIZUMAB 400 MG / 16 ML	Oncology	Cancer (colon, breast)	YES
CETUXIMAB 100 MG / ML	Oncology	Cancer (colon, neck)	YES
CAPECITABINE 500 MG/	Oncology	Cancer (breast)	YES
LAPATINIB DITOSYLATE 250 MG	Oncology	Cancer (breast)	YES
LETROZOLE 2,5 MG	Oncology	Cancer (breast)	YES
TRASTUZUMAB 600 MG / 5 ML	Oncology	Cancer (breast)	YES
FULVESTRANT 250 MG/ 5 ML	Oncology	Cancer (breast)	YES
PERTUZUMAB 420 MG / 14 ML	Oncology	Cancer (breast)	YES
GOSERELINE ACETATE 10.8 MG / IMPLANT	Oncology	Cancer (prostate, breast)	YES
ABIRATERONE ACETATE ABIRATERONA 250 MG	Oncology	Cancer (prostate)	YES
ABIRATERONE ACETATE 500 MG	Oncology	Cancer (prostate)	YES
GOSERELINE ACETATE 36 MG / PROLONGED RELEASE IMPLANT	Oncology	Cancer (prostate)	YES
BICALUTAMIDE 50 MG	Oncology	Cancer (prostate)	YES
ERLOTINIB 150 MG	Oncology	Cancer (lung)	YES

TABLE 13
(2 of 2)

MSAL list of high-cost drugs included in PDSS

DRUG / INTERNATIONAL NONPROPRIETARY NAME (INN)	SPECIALTY	PATHOLOGY	PDSS
DASATINIB 100 MG	Oncology	Chronic myeloid leukemia	YES
IMATINIB 400 MG	Oncology	Chronic myeloid leukemia	YES
RITUXIMAB 1,400 MG 11.7 ML	Oncology	Non-Hodgkin lymphoma	YES
IBRUTINIB 140 MG	Oncology	Mantle cell lymphoma	YES
IBRUTINIB 420 MG	Oncology	Mantle cell lymphoma	YES
IBRUTINIB 560 MG	Oncology	Mantle cell lymphoma	YES
BORTEZOMIB 3,5 MG	Oncology	Multiple myeloma	YES
LENALIDOMIDA 25 MG	Oncology	Multiple myeloma	YES
TEMOZOLAMIDE 100 MG	Oncology	Brain tumor	YES
RITUXIMAB 100 MG / 10 ML	Rheumatism / Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	YES
RITUXIMAB 500 MG /50 ML	Rheumatism / Non-Hodgkin lymphoma	Non-Hodgkin lymphoma	YES
ZOLEDRONIC ACID 5 MG / 100 ML	Rheumatism	Osteoporosis	YES
SODIUM MICOFENOLATE 360 MG	Transplant	Cancer (breast)	YES
VALGANICICLOVIR HYDROCHLORIDE 450 MG	Transplant	Transplant	YES
BASILIXIMAB 20 MG	Transplant	Transplant	YES
CICLOSPORINE 100 MG/ ML	Transplant	Transplant	YES
EVEROLIMUS 0,50 MG	Transplant	Transplant	YES
EVEROLIMUS 0,75 MG	Transplant	Transplant	YES
MYCOPHENOLATE MOFETIL 500 MG	Transplant	Transplant	YES
TACROLIMUS XL 1 MG	Transplant	Transplant	YES
TACROLIMUS XL 5 MG	Transplant	Transplant	YES
SIROLIMUS 1 MG	Transplant	Transplant	YES
TACROLIMUS 0,5 MG	Transplant	Transplant	YES
TACROLIMUS 1 MG	Transplant	Transplant	YES
TACROLIMUS XL 0,5 MG	Transplant	Transplant	YES
ANTITHYMOCYTE IMMUNOGLOBULIN RABBIT 25 MG	Transplant	Transplant (aplastic anemia)	YES

TABLE 14
(1 of 3)

MSAL list of high-cost drugs not included in the PDSS

DRUG / INTERNATIONAL NONPROPRIETARY NAME (INN)	SPECIALTY	PATHOLOGY	PDSS
RECOMBINANT HUMAN EPIDERMIC GROWTH FACTOR	Endocrinology	Diabetic foot	No
USTEKINUMAB 130 MG / 26 ML	Gastroenterology	Chrohn's disease / colitis	No
USTEKINUMAB 45 MG / 0,5 ML	Gastroenterology	Chrohn's disease / colitis	No
USTEKINUMAB 90 MG / 1 ML	Gastroenterology	Chrohn's disease / colitis	No
SOFOSBUVIR 400 MG/ VELPATASVIR 100 MG	Gastroenterology	Virus hepatitis C	No
EMICIZUMAB 105 MG	Hematology	Hemophilia	No
EMICIZUMAB 30 MG / 1 ML	Hematology	Hemophilia	No
ANTI-INHIBITOR COAGULANT COMPLEX 500 UF	Hematology	Hemophilia anti-inhibitors	No
BLOOD COAGULATION FACTOR IX 500 UI	Hematology	Type B hemophilia	No
DEFERASIROX 500 MG	Hematology	Excess iron	No
ELTROMBOPAG 25 MG	Hematology	Primary immune thrombocytopenia	No
MALIZUMAB 150 MG / ML	Pulmonology	Severe asthma / hives	No
DORNASA ALFA 2.5 MG / 2.5 ML	Pulmonology	Cystic fibrosis	No
PIRFENIDONE 267 MG	Pulmonology	Pulmonary fibrosis	No
BOSETAN 125 MG	Pulmonology	Pulmonary hypertension	No
RIOCIGUAT 1 MG	Pulmonology	Pulmonary hypertension	No
RIOCIGUAT 1,5 MG	Pulmonology	Pulmonary hypertension	No
RIOCIGUAT 2 MG	Pulmonology	Pulmonary hypertension	No
RIOCIGUAT 2,5 MG	Pulmonology	Pulmonary hypertension	No
OCRELIZUMAB 300 MG / 10 ML	Neurology	Primary progressive multiple sclerosis	No
RILUZOLE 50 MG	Neurology	Amyotrophic lateral sclerosis	No
GLATIRAMER ACETATE 40 MG / 1 ML	Neurology	Relapsing remitting multiple sclerosis	No
CALDRIBINE 10 MG	Neurology	Relapsing remitting multiple sclerosis	No
FINCOLIMOD 0,5 MG	Neurology	Relapsing remitting multiple sclerosis	No
INTERFERON BETA 1 A 44 MCG / 0.5 ML	Neurology	Relapsing remitting multiple sclerosis	No
INTERFERON BETA 1 B 250 MCG / ML (8.0 MILLION UL)	Neurology	Relapsing remitting multiple sclerosis	No

TABLE 14
(2 of 3)

MSAL list of high-cost drugs not included in the PDSS

DRUG / INTERNATIONAL NONPROPRIETARY NAME (INN)	SPECIALTY	PATHOLOGY	PDSS
TERIFLUNOMIDE 14 MG	Neurology	Relapsing remitting multiple sclerosis	No
AGALSIDASE BETA 35 MG	Neurology / hereditary	Fabry disease	No
IMIGLUCERASE 400 U	Neurology / hereditary	Gaucher disease	No
GALSUFASE 5 MG / 5 ML (1MG / 1ML)	Neurology / hereditary	Mucopolysaccharidosis IV	No
PEMBROLIZUMAB 100 MG / 4 ML	Oncology	Cancer (melanoma)	No
OCTREOTIDE 20 MG / 2 ML	Oncology	Cancer (gastric, acromegaly)	No
SORAFENIB TOSILATE 200 MG	Oncology	Cancer (liver, renal, thyroid)	No
PALBOCICLIB 100 MG	Oncology	Cancer (breast, negative HER2)	No
PALBOCICLIB 125 MG	Oncology	Cancer (breast, negative HER2)	No
PALBOCICLIB 75 MG	Oncology	Cancer (breast, negative HER2)	No
RIBOCICLIB 200 MG	Oncology	Cancer (breast, negative HER2)	No
ENZALUTAMIDE 40 MG	Oncology	Cancer (prostate, metastatic)	No
OSIMERTINIB MESILATE 80 MG	Oncology	Cancer (lung)	No
ATEZOLIZUMAB 1,200 MG / 20 ML	Oncology	Cancer (lung, breast triple negative)	No
REGORAFENIB 40 MG	Oncology	Cancer (CCR, GI, liver)	No
OBINUTUZUMAB 1,000 MG / 40 ML	Oncology	Chronic lymphocytic leukemia	No
NILOTINIB 200 MG	Oncology	Chronic myeloid leukemia	No
BENDAMUSTINE HYDROCHLORYDE 100 MG / VIAL	Oncology	CLL, non-Hodgkins L, multiple myeloma	No
DARATUMUMAB 400 MG/20 ML	Oncology	Multiple myeloma	No
FILGASTRIM 300 MCG / 0.5 ML	Oncology	Neutropenia	No
AZACITIDINE 100 MG / VIAL	Oncology	Myelodysplastic syndrome	No
PALIPERIDONE PALMITATE 100 MG	Psychiatry	Schizophrenia	No
PALIPERIDONE PALMITATE 150 MG	Psychiatry	Schizophrenia	No
PALIPERIDONE PALMITATE 75 MG	Psychiatry	Schizophrenia	No
INFLIXIMAB 100 MG / RENSIME	Rheumatism / gastrointestinal	Rheumatism / gastro	No
INFLIXIMAB 100 MG / VIAL REMICADE	Rheumatism / gastrointestinal	Rheumatism / gastro	No

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MSAL list of high-cost drugs not included in the PDSS

DRUG / INTERNATIONAL NONPROPRIETARY NAME (INN)	SPECIALTY	PATHOLOGY	PDSS
GOLIMUMAB 50 MG / 1 ML	Rheumatism / Non-Hodgkin lymphoma	Psoriasis / ulcerative colitis	No
TOFACITINIB XR CITRATE 11 MG	Rheumatism	Rheumatoid arthritis	No
TERIPARATIDE 250 MCG / 2.4 ML	Rheumatism	Osteoporosis	No
GUSELKUMAB 100 MG / 1 ML	Rheumatism	Psoriasis	No
SECUKINUMAB 150 MG	Rheumatism	Psoriasis	No
TOCILIZUMAB 162 MG / 0.9 ML	Rheumatism	Rheumatisms	No
TOCILIZUMAB 200 MG / 10 ML	Rheumatism	Rheumatisms	No
TOCILIZUMAB 80 MG / 4 ML	Rheumatism	Rheumatisms	No
ETANERCEPT 25 MG / ML	Rheumatism	Rheumatisms / gastro	No
ETANERCEPT 50 MG / ML	Rheumatism	Rheumatisms / gastro	No
ADALIMUMAB 40 MG /0,4 ML	Rheumatism / gastro	Rheumatisms / gastro	No
TOCILIZUMAB 400 MG	Pulmonology	COVID	No
REGEN-COV (CASIRIVIMAB/IMDEVIMAB)	COVID	COVID	No
REMDESIVIR 100MG	COVID	COVID	No

ANNEX 2. METHODOLOGY USED TO ESTIMATE OPPORTUNITY COST (DETAIL)

The following table presents, step-by-step, the methodology used to obtain the opportunity cost of covering high-cost drugs.

TABLE 15 Steps followed to estimate the opportunity cost using the threshold methodology

STEP	INFORMATION REQUIRED	INFORMATION SOURCE USED
STEP 1: definition of the PICOT question (population, intervention, comparison, outcome, time) for each of the selected molecules.	PICOT by expert judgment for each analyzed molecule.	Expert judgment.
STEP 2: revision of cost-effectiveness economic literature to identify the published articles which would answer, with data for other countries, the PICOT question.	Cost-effectiveness studies.	Tufts database.
STEP 3: obtaining the information of health gains and costs from the original study.	QALY provided by the intervention and the comparison. Treatment duration under intervention and comparison. Cost-effectiveness ratio. Intervention price.	Cost-effectiveness studies selected from Tufts database.
STEP 4: estimation of the direct coverage costs of HCDs in the Dominican Republic.	Unit prices of analyzed drugs. Quantities purchased of analyzed drugs. Number of patients who require the analyzed drug. Analyzed drug's management protocol.	IQVIA database. SISALRIL institutional purchases database. Estimate of number of patients of PMAC program.
STEP 5: estimation of the opportunity cost of HCDs.	Net present value of the treatment costs. Cost-effectiveness threshold.	Determination of the cost-effectiveness threshold for the Dominican Republic study.

TABLE 16 **Steps followed to estimate the opportunity cost using the methodology of closing effective coverage gaps**

STEP	INFORMATION REQUIRED	INFORMATION SOURCE USED
STEP 1: obtaining incremental QALY for the selected essential interventions.	List of essential services. Cost-effectiveness studies. Identification of cost-effectiveness studies that answer PICOT question for each of the interventions. Obtaining information of health gains and costs from the original study.	DCP3. Tufts database.
STEP 2: estimation of incremental costs. **STEP 2.1:** estimation of need of essential services based on epidemiological data (prevalence and incidence).	Prevalence, incidence and use frequency rates according to norm or expert judgment for each service.	Global Burden of Disease.
STEP 2.2: estimation of use rate of essential services based on observed data.	Use rate for each service in the Dominican Republic.	Local expert judgment.
STEP 2.3: calculation of effective coverage gaps.	Difference of need rate and use rate for each service.	
STEP 2.4: estimation of normative costs using need rate (universal coverage) and use rate.	Unit prices for each service, units needed for each service under the assumption of universal coverage and current coverage.	
STEP 2.5: estimation of finance gap to reach universal coverage.	Cost difference under current and desired coverage.	
STEP 3: estimation of opportunity cost.		

ANNEX 3. SUMMARY OF STUDIES USED

TABLE 17
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Summary of studies used

Molecule	Health condition	Year	Country	Study	Authors
Agalsidasa beta	Endocrine disorders (Fabry disease)	2013	Germany	Cost-effectiveness of enzyme replacement therapy for Fabry disease	Rombach
Palbociclib	Breast cancer	2016	Switzerland	Palbociclib as a first-line treatment in oestrogen receptor-positive, HER2-negative, advanced breast cancer not cost-effective with current pricing: a health economic analysis of the Swiss Group for Clinical Cancer Research (SAKK)	K Matter-Walstra et al.
Palbociclib	Breast cancer	2017	United States	Cost-effectiveness of Palbociclib in Hormone Receptor-Positive Advanced Breast Cancer	H. Mamiya1, et al.
Palbociclib	Breast cancer	2017	Canada	Palbociclib in hormone receptor positive advanced breast cancer	J. Raphael et al.
Pembrolizumab	Non-small cell lung cancer (NSCLC)	2018	United Kingdom	First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective	Xiaohan Hu & Joel W. Hay
Pembrolizumab	Non-small cell lung cancer (NSCLC)	2018	United States	Cost-effectiveness of pembrolizumab as first-line therapy for advanced non small	Mina Georgievaa, et al.
Pembrolizumab	Non-small cell lung cancer (NSCLC)	2017	United States	The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC	Aguiar et al.
Sorafenib	Renal carcinoma	2009	United Kingdom	Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma	Martin Hoyle
Sorafenib	Renal carcinoma	2010	United Kingdom	Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation	J Thomson Coon
Etanercept	Psoriatic arthritis	2011	United Kingdom	Cost effectiveness of golimumab for the treatment of active psoriatic arthritis	Ewen Cummins et al.
Etanercept	Psoriatic arthritis	2014	United Kingdom	Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic	Matthew Richard Cawson et al.

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Summary of studies used

Molecule	Health condition	Year	Country	Study	Authors
Etanercept	Psoriatic arthritis	2006	United Kingdom	Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis	N. J. Bansback1, et al.
Etanercept	Psoriatic arthritis	2011	United Kingdom	Modelling the cost-effectiveness of biologic treatments for psoriatic arthritis	Laura Bojke1, et al.
Golimumab	Psoriatic arthritis	2011	United Kingdom	Cost effectiveness of golimumab for the treatment of active psoriatic arthritis	Ewen Cummins et al.
Golimumab	Psoriatic arthritis	2014	United Kingdom	Systematic review, network meta-analysis and economic evaluation of biological therapy for the management of active psoriatic	Matthew Richard Cawson et al.
Enzalutamida	Prostate cancer	2021	Japan	Cost-effectiveness analysis of enzalutamide for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer in Japan	Hiroyuki Okumura
Ocrelizumab	Relapsing remitting multiple sclerosis	2017	United States	Incremental net monetary benefit of ocrelizumab relative to subcutaneous interferon β-1a	Melissa A. Frasco
Ocrelizumab	Relapsing remitting multiple sclerosis	2017	United States	Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis	Hongbo Yang
Ocrelizumab	Relapsing remitting multiple sclerosis	2018	United States	Disease-Modifying Therapies for Relapsing–Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis	Marita Zimmermann
Ocrelizumab	Primary progressive multiple sclerosis	2018	United States	Disease-Modifying Therapies for Relapsing–Remitting and Primary Progressive Multiple Sclerosis: A Cost-Utility Analysis	Marita Zimmermann
Atezolizumab	Non-small cell lung cancer (NSCLC)	2021	United States, United States, China	First-Line Atezolizumab for Metastatic NSCLC with High PD-L1 Expression: A United States-Based Cost-Effectiveness Analysis	Ye Peng
Atezolizumab	Non-small cell lung cancer (NSCLC)	2021	United States	First-Line Atezolizumab for Metastatic NSCLC with High PD-L1 Expression: A United States-Based Cost-Effectiveness Analysis	Ye Peng
Atezolizumab	Non-small cell lung cancer (NSCLC)	2021	China	Cost-Effectiveness Analysis of Atezolizumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer With Different PD-L1 Expression Status	Guoqiang Liu

TABLE 17
(3 of 3)

Summary of studies used

Molecule	Health condition	Year	Country	Study	Authors
Atezolizumab	Non-small cell lung cancer (NSCLC)	2020	United States	Cost-effectiveness of atezolizumab plus chemotherapy for advanced non-small-cell lung cancer	Shen Li
Regorafenib	Colon cancer	2018	United States	Cost-Effectiveness Analysis of Regorafenib and TAS-102 in Refractory Metastatic Colorectal Cancer in the United States	Sang Kyu Cho
Regorafenib	Colon cancer	2015	United States	Cost-Effectiveness Analysis of Regorafenib for Metastatic Colorectal Cancer	Daniel A. Goldstein

TABLE 18 Parameters used in the opportunity cost estimations; values and source

Intervention	Year	Country	Author	Timeframe	QALY interv.	QALY comp.	Increm. QALY	Interv. treatment duration	Original study ICER (QALY)	Currency
Agalsidase beta	2013	Germany	Rombach	Lifetime	32.1	31.3	0.70	47.50	5,500,000 -750,0000	Euro
Palbociclib	2016	Switzerland	K Matter-Walstra et al.	Lifetime	3.33	2.19	1.14	1.68	301,227	CHF
Palbociclib	2017	United States	H. Mamiya1, et al.	Lifetime	2.13	1.82	0.32	1.68	768,498	US$
Palbociclib	2017	Canada	J. Raphael et al.	Lifetime	3.43	2.21	1.22	1.68	131,988	US$
Palbociclib	2017	United States	H. Mamiya1, et al.	Lifetime	1.46	1.34	0.12	0.77	918,166	US$
Pembrolizumab	2018	U.K.	Xiaohan Hu & Joel W. Hay	Lifetime	1.93	0.71	0.83	0.52	86,913	Pounds
Pembrolizumab	2018	United States	Mina Georgievaa et al.	Lifetime	1.8	1.06	0.74	0.52	52,000	Pounds
Pembrolizumab	2017	United States	Aguiar et al.	5 years	0.92	0.57	0.35	0.52	98,421	US$
Sorafenib	2009	U.K.	Martin Hoyle	10 years	1.18	0.91	0.27	0.55	75,398	Pounds
Sorafenib	2010	U.K.	J Thomson Coon	10 years	1.15	0.91	0.24	0.46	102,498	Pounds
Etanercept	2011	U.K.	Ewen Cummins et al.	Lifetime	7.69	5.44	2.25	na	16,811	Pounds
Etanercept	2014	U.K.	Matthew Richard Cawson et al.	40 years	7.2	5.2	2.00	na	28,917	Pounds
Etanercept	2006	U.K.	N. J. Bansback1, et al.	10 years	4.49	3.67	0.82	na	28,189	Pounds
Etanercept	2011	U.K.	Laura Bojke1, et al.	40 years	7.12	5.24	1.88	na	18,000	Pounds
Golimumab	2011	U.K.	Ewen Cummins et al.	Lifetime	7.21	5.3	1.91	na	16,811	Pounds
Golimumab	2014	U.K.	Matthew Richard Cawson et al.	40 years	7.1	5.2	1.90	na	17,435	Pounds
Enzalutamide	2021	Japan	Hiroyuki Okumura	10 years	2.34	1.969	0.37	na	85,899	US$
Ocrelizumab	2017	United States	Melissa A. Frasco	30 years	11.29	10.46	0.83	na	Cost saver	US$
Ocrelizumab	2017	United States	Hongbo Yang	20 years	6.83	6.27	0.56	na	Cost saver	US$
Ocrelizumab	2018	United States	Marita Zimmermann	Lifetime	10.94	5.67	5.27	10.94	166,338	US$
Ocrelizumab	2018	United States	Marita Zimmermann	Lifetime	3.33	2.75	0.58	3.33	648,799	US$
Atezolizumab	2021	United States	Ye Peng	Lifetime	2.17	0.85	1.32	1.80	170,144	US$
Atezolizumab	2021	China	Guoqiang Liu	Lifetime	1.8	0.88	0.92	2.17	123,778	
Regorafenib	2018	United States	Sang Kyu Cho	5 years	0.397	0.339	0.06	0.40	395,223	US$
Regorafenib	2015	United States	Daniel A. Goldstein	Lifetime	0.42	0.38	0.04	0.42	975,954	US$

TABLA 19
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Parameters used to estimate annual cost per case

Indication	Commercial brand	Product and presentation	Presentation	Concentration	Recommended dosage	Application	Use (the Dominican Republic technical notes)
Fabry disease	FABRAZYME (GENZYME)	AGALSIDASA BETA	Agalsidase beta 35 mg / 10 ml	35 mg	70 mg	Every two weeks	The recommend dose of Fabrazyme is 1 mg/kg of body weight, administered once every two weeks by intravenous perfusion.
Breast cancer	IBRANCE	PALBOCICLIB	Palbociclib 100 mg - 125 mg - 75 mg	125 mg	125 mg	Once a day	Daily dose is for 21 consecutive days; then 7 days off and restart. Continue while patient obtains clinical benefit or until unacceptable toxicity appears. 125 mg daily recommended dose. 75 mg/day reduced minimum dose in case of adverse effects.
Non-small cell lung cancer (NSCLC)	KEYTRUDA	PEMBROLIZUMAB	Pembrolizumab 100 mg / 4 ml	100 mg / 4 ml	200 mg	Every 3 to 6 weeks	Recommended dose of Keytruda in adults is 200 mg every 3 to 6 weeks administered by intravenous perfusion during 30 minutes.
Psoriatic arthritis	ENBREL	ETANERCEPT	Etanercept 50 mg / 20 ml	50 mg / 20 ml	50 mg	Once a week	Recommended dose of Enbrel is 25 mg administered twice a week or 50 mg administered once a week. For all indications, available data suggest that clinical response is generally obtained within the first 12 weeks of treatment.
Psoriatic arthritis	SIMPONI	GOLIMUMAB	Golimumab 50 mg / 1 ml	50 mg /0,5 ml	50 mg	Once a month	Subcutaneous injection. 50 mg administered by subcutaneous injection one a month, in the same day each month.
Carcinoma renal	NEXAVAR	SORAFENIB 200 mg	Caja con 112 comprimidos	200 mg	800 mg	Twice a day	Recommended dose of sorafenib Teva in adults is two 200 mg pills twice a day. This equals a daily dose of 800 mg or four pills a day.

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(2 of 2)

Parameters used to estimate annual cost per case

Indication	Commercial brand	Product and presentation	Presentation	Concentration	Recommended dosage	Aplication	Use (the Dominican Republic technical notes)
Prostate cancer	XTANDI	ENZALUTAMIDA 40 mg	Soft gel capsules. Box of 112 capsules	40 mg	160 mg	Four capsules per day	Recommended dose is 160 mg: four 40 mg film covered capsules or two 80 mg capsules taken at the same time, once a day.
Relapsing-remitting multiple sclerosis	OCREVUS	OCRELIZUMAB 300 mg / 10 ml	Solution for perfusion	300 mg/ 10 ml	600 mg	Cada 6 meses	Initial dose is 600 mg administered in two separate intravenous perfusions. First a 300 mg perfusion followed by a second 300 mg perfusion two weeks later. (Table 1). Following dosage: from then on, doses of Ocrevus are administered in single 600 mg doses by intravenous perfusion, six months after the first perfusion of the initial dose. A minimal interval of 5 months must be preserved between Ocrevus doses.
Non-small cell lung cancer (NSCLC)	TECENTRIQ	ATEZOLIZUMAB 1.200 mg / 20 ml	Concentrate for solution for infusion	1,200 mg/ 20 ml	1,200 mg	Every three weeks	Tecentriq monotherapy: recommended dose of atezolizumab is 1,200 mg administered intravenously every three weeks.

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Estimation of the net present value of the incremental cost

Intervention	Comparison	Country in which study was conducted	Study timeframe	Study intervention years	Study discount rate	Annual cost per case of intervention, at MSAL prices	Intervention cost (net present value)	Comparison cost at local prices (net present value)	Net present value of the incremental cost per case
Agalsidase alfa or agalsidase beta	Standard medical care	Dutch population	Lifetime	47.50	1.5%	117,526.67	3,972,258.37	90,000.00	3,882,258.37
Palbociclib + letrozole	Letrozole	Switzerland	Lifetime (all)	1.68	0.0%	65,240.00	109,820.68	511.61	109,309.07
Palbociclib + letrozole	Letrozole	United States	Lifetime	1.68	3.0%	65,240.00	105,557.67	511.61	105,046.06
Palbociclib + letrozole	Letrozole	Canada	Lifetime	1.68	5.0%	65,240.00	102,685.25	511.61	102,173.65
Palbociclib + letrozole	Fulvestrant	United States	Lifetime	1.68	3%	65,240.00	105,353.79	17,137.56	88,216.23
Pembrolizumab in first-line of treatment	Platinum - or chemotherapy with carboplatin-cisplatin	United Kingdom	Lifetime	2.00	4%	73,955.56	140,492.95	2,655.00	137,837.95
Pembrolizumab in first-line of treatment	Platinum - or chemotherapy with carboplatin-cisplatin	United Kingdom	Lifetime	2.00	0.0%	73,955.56	147,911.12	2,655.00	145,256.12
Pembrolizumab in first-line of treatment	Docetaxel patients without PD-L1	United States	5 years	0.52	4%	73,955.56	37,408.19	2,201.50	35,206.69
Etanercept	Management with DMARDs and NSAIDs	United Kingdom (4)	Lifetime	7.69	4%	10,250.67	68,078.02	10,112.65	57,965.37
Etanercept	Management with DMARDs and NSAIDs	United Kingdom (4)	40 years	7.20	4%	10,250.67	64,256.54	9,544.99	54,711.56

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Estimation of the net present value of the incremental cost

Intervention	Comparison	Country in which study was conducted	Study timeframe	Study intervention years	Study discount rate	Annual cost per case of intervention, at MSAL prices	Intervention cost (net present value)	Comparison cost at local prices (net present value)	Net present value of the incremental cost per case
Etanercept	Management with DMARDs and NSAIDs	United Kingdom (4)	10 years	4.49	4%	10,250.67	41,917.70	6,226.66	35,691.03
Etanercept	Management with DMARDs and NSAIDs	United Kingdom (4)	40 years	7.12	4%	10,250.67	63,626.49	9,451.40	54,175.09
Golimumab	Management with DMARDs and NSAIDs	United Kingdom (2)	Lifetime, 40 years	7.21	4%	15,322.22	96,165.25	9,556.67	86,608.58
Golimumab	Management with DMARDs and NSAIDs	United Kingdom (2)	Lifetime, 40 years	7.10	4%	15,322.22	94,870.08	9,427.96	85,442.13
Sorafenib	Supportive care	United Kingdom (2)	10 years (2)	0.55	0%	38,277.78	21,051.15	-	21,051.15
Sorafenib	Supportive care	United Kingdom (2)	10 years (2)	0.46	0%	38,277.78	17,542.70	-	17,542.70
Enzalutamida	Docetaxel	Japan	10 years	1.43	0%	27,548.89	39,390.13	1,886.98	37,503.15
Ocrelizumab	Beta-interferon	United States	30 years, 20 years	11.29	0%	32,666.67	368,580.14	123,075.68	245,504.46
Ocrelizumab	Beta-interferon	United States	30 years, 20 years	6.83	0%	32,666.67	222,895.44	74,428.88	148,466.56
Ocrelizumab	Supportive care	United States	Lifetime	10.94	0%	32,666.67	357,160.07	-	357,160.07
Ocrelizumab	Supportive care	United States	Lifetime	3.33	0%	32,666.67	108,756.45	-	108,756.45

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Estimation of the net present value of the incremental cost

Intervention	Comparison	Country in which study was conducted	Study timeframe	Study intervention years	Study discount rate	Annual cost per case of intervention, at MSAL prices	Intervention cost (net present value)	Comparison cost at local prices (net present value)	Net present value of the incremental cost per case
Atezolizumab	Platinum o docetaxel	United States, United States, China	10 years, lifetime, lifetime	2.00	0%	85,333.33	170,641.07	8,734.69	161,906.38
Atezolizumab	Platinum	United States	Lifetime	2.17	0%	85,333.33	185,143.99	9,477.06	175,666.93
Atezolizumab	Chemtherapy	China	Lifetime	1.80	0%	85,333.33	153,578.50	7,861.30	145,717.20
Regorafenib	Supportive care	United States	5 years, lifetime	0.40	0%	256,256.00	101,726.53	-	101,726.53
Regorafenib	Supportive care	United States	5 years, lifetime	0.42	0%	256,256.00	107,619.88	-	107,619.88

ANNEX 5. BASKETS OF PROVISION WHICH MAKE UP THE ESSENTIAL INTERVENTIONS

TABLE 21 Provision basket for cervical cancer

Intervention	Description (clinical guide /dosage)	Source for description	Level of care	Service type	Note on assigned provision
Timely detection of cervical cancer through visual inspection or tests such as the Papanicolaou	Guidance and information exchange	Control Integral de Cáncer Cervicouterino, Guía de Prácticas Esenciales, OPS/OMS. 2016	Primary level of care	Guidance	General medical consultation
	Cytology (Papanicolaou frotis) Screening of all women 30-49 years old or liquid base cytology (LBC)		Primary level of care	Pathologic anatomy	Basic stain study in vaginal cytology, tumoral and/or functional
	HPV tests Screening of all women 30-49 years old or liquid base cytology (LBC)		Primary level of care	Laboratory	HPV tests
	Screening of all women 30-49 years old or liquid-based cytology (LBC)		Primary level of care	Pharmaceutical (active ingredient)	Acetic acid

TABLE 22
(1 of 2)

Provision basket for diagnosis and management of type 2 diabetes

Intervention	Description (clinical guide /dosage)	Source for description	Health care level	Service type	Note on assigned provision
Detection and management of diabetes among at-risk adults, including glucose control, arterial pressure and lipid management and constant feet care.	General consultation	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	Primary and secondary level	Consultation	General medicine consultation
	Endocrinology consultation	Guia AIAD sobre Diagnóstico, control tratamiento de Diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	Secondary and tertiary level	Consultation	Specialized medicine consultation
	Glucose level	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	Primary and secondary level	Laboratory	Glucose, O'Sullivan test +
	Oral glucose tolerance test	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	Secondary and tertiary level	Laboratory	Glucose, tolerance curve +
	Calcium	Expert opinion	All three levels	Laboratory	Calcium by colorimetry *+
	Chlorine	Expert opinion	All three levels	Laboratory	Chlorine [Chloride]
	Magnesium	Expert opinion	All three levels	Laboratory	Magnesium+
	Phosphorous	Expert opinion	All three levels	Laboratory	Inorganic phosphorous [phosphates]
	Potassium	Expert opinion	All three levels	Laboratory	Potassium +
	Sodium	Expert opinion	All three levels	Laboratory	Sodium+
	Serum creatinine	Expert opinion	All three levels	Laboratory	Creatinine in serum, urine or other
	Microalbuminuria	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	All three levels	Laboratory	Albumin

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(2 of 2)

Provision basket for diagnosis and management of type 2 diabetes

Intervention	Description (clinical guide /dosage)	Source for description	Health care level	Service type	Note on assigned provision
Detection and management of diabetes among at-risk adults, including glucose control, arterial pressure and lipid management and constant feet care.	Glycated hemoglobin test HBA1c	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	All three levels	Laboratory	Glycated hemoglobin by monoclonal antibodies
	VDRL	Expert opinion	All three levels	Laboratory	Serology [non treponemic test] VDRL in serum or CSF & * +
	HDL	Expert opinion	All three levels	Laboratory	High-density cholesterol [HDL]
	LDL	Expert opinion	All three levels	Laboratory	Enzymatic low-level cholesterol [LDL]
	Total cholesterol	Expert opinion	All three levels	Laboratory	Total cholesterol
	Triglycerides	Expert opinion	All three levels	Laboratory	Triglycerides +
	Non-mydriatic eye fundus	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	Secondary and tertiary level	Procedure	Non-mydriatic eye fundus
	Electrocardiogram	Guía AIAD sobre Diagnóstico, control y tratamiento de diabetes tipo 2 en Medicina Basada en la Evidencia, 2019	All three levels	Procedure	High-resolution electrocardiogram [late potentials study] +

TABLE 23 **Provision basket for cervical cancer; timely detection for cervical cancer through visual inspection or tests such as Papanicolaou**

Description (clinical guide/dosage)	Health care level	Service type	Note on assigned provision	Relative frequency	Unit cost RS (pesos 2022)
Guidance and information exchange	Primary level	Guidance	General medicine consultation	1	222
Cytology (Papanicolaou frotis). Screening of all women 30-49 years old or liquid base cytology (LBC)	Primary level	Pathologic anatomy	Basic stain study in vaginal cytology, tumoral and/or functional	0.8	159
Screening of all women 30-49 years old or liquid base cytology (LBC)	Primary level	Pharmacological (active ingredients)	Acetic acid	0.4	70

TABLE 24 **Provision basket for type 2 diabetes; detection and management of diabetes among at-risk adults, including glucose control, arterial pressure and lipid management and constant feet care**

Description (clinical guide/dosage)	Health care level	Service type	Note on assigned provision	Relative frequency	Unit cost RS (pesos 2022)
General consultation	Primary and secondary level	Consultation	General medicine consultation	1	221.6
Endocrinology consultation	Secondary and tertiary level	Consultation	Specialized medicine consultation	0.9	221.4
Glucose level	Primary and secondary level	Laboratory	Glucose, O'Sullivan test +	1	134.7
Oral glucose tolerance test	Secondary and tertiary level	Laboratory	Glucose, tolerance test+	0.5	52.8
Calcium	All three levels	Laboratory	Calcium by colorimetry *+	0.5	53.6
Chlorine	All three levels	Laboratory	Chlorine [Chloride]	0.5	58.6
Magnesium	All three levels	Laboratory	Magnesium+	0.5	64.2
Phosphorous	All three levels	Laboratory	Inorganic phosphorous [phosphates]	0.5	57.3
Potassium	All three levels	Laboratory	Potassium +	0.5	73.3
Sodium	All three levels	Laboratory	Sodium+	0.5	67.4
Serum creatinine	All three levels	Laboratory	Creatinine in serum, urine or other	0.5	46.9
Microalbuminuria	All three levels	Laboratory	Albumin	0.5	48.7
Glycated hemoglobin test HBA1c	All three levels	Laboratory	Glycated hemoglobin by monoclonal antibodies	0.7	110.8
VDRL	All three levels	Laboratory	Serology [non treponemic test] VDRL in serum or CSF & * +	0.01	0.9
HDL	All three levels	Laboratory	High-density cholesterol [HDL]	1	85.3
LDL	All three levels	Laboratory	Enzymatic low-level cholesterol [LDL]	1	85.4
Total cholesterol	All three levels	Laboratory	Total cholesterol	1	77.4
Triglycerides	All three levels	Laboratory	Triglycerides +	1	78.4
Non-mydriatic eye fundus	Secondary and tertiary level	Procedure	Non-mydriatic eye fundus	1	840.0
Electrocardiogram	All three levels	Procedure	High-resolution electrocardiogram [late potentials study] +	0.5	88.4

NOTES

[1] The authors would like to especially thank the teams at the Ministerio de Salud de República Dominicana and the team at SISALRIL, who provided key support for this study. The authors, however, are exclusively responsible for the results and the opinions contained in the study.

[2] The public health expenditure for 2019 was RD$118,384 million. Source: World Bank.

[3] The selection of the drugs started with the 48 exclusive PMAC molecules (listed in Annex 1). They were grouped according to three explicit criteria: (a) high-cost molecules with few alternatives (just one or two); (b) high-cost molecules with alternatives (more than three); and (c) rare diseases with few alternatives. By therapeutic alternatives we understand different molecules that have the same indication and that could be understood as substitute. From the second group we pre-selected just one or two molecules with the same indication and the same action mechanism with the intention of covering different pathologies and indications. From this list we conducted an ad-hoc selection process. We first discarded those for which we found no information on QALY, prices or number of patients; and those for which there were more than two generic or biosimilar alternatives (in order to focus our analysis on drugs with few generic or biosimilar alternatives). At this stage we had selected a total of thirteen molecules which were qualitatively analyzed by a group of decision makers. From that analysis we included four molecules which were not included (two because of their high price and two for their high frequency) and discarded three molecules. Finally, these lists were cross-referenced with the average PMAC prices, and we made a ranking with final adjustments in which we prioritized ten molecules (eight of them are among the costliest and two are included for their high frequency). It should be made clear, though, that while we prioritized high prices, the final selection included examples of the three original clusters.

[4] The exchange rate used for the conversion was 54,93 Dominican pesos per dollar. Source: Banco de la República de República Dominicana.

[5] For more on this subject, readers could consult (Eckerman 2014), (Pekarsky, 2012) and the methodological note that is part of this series.

[6] The methodology applied for the specific case of the selected HCDs is presented with further detail in section 4.1.

[7] The information source for price indexes and exchange rates is the World Bank up to 2021. For 2022 we used information from the Banco de la República de República Dominicana.

[8] This means assuming, for the breast cancer example, that 50 percent of the population which requires treatment substitutes the HCD for a comparison (letrozole) and 50 percent resorts to the other comparison (fulveztrant). In another example, the target population for algasidase beta comprises those diagnosed with symptomatic Fabry disease. The intervention molecule is algasidase beta, and the comparison is standard medical care. The incremental QALY reported for the study, for treatment with algasidase beta relative to standard medical care, is 0.70 life years in perfect health per treated patient. (For further methodological details, refer to the accompanying methodological note).

[9] The cost of purchasing the high-cost drugs generally amounts to 90 percent of the total cost, which means that not including the other costs, as those derived from adverse effects and complications, should not significantly alter the results.

[10] Estimated following equation 1, as detailed in section 3.

[11] This value is not annual, but rather corresponds to all the period in which the patients are alive and receiving treatment.

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