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

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Abstract

We find ourselves in a fortunate yet challenging situation: we have access to more beneficial health technologies than we can afford to finance. However, this increased availability, coupled with an ageing population and epidemiological changes, is straining health spending worldwide. To ensure that higher spending actually maximizes benefits, it is crucial for this growth to be sustainable, to not divert resources from other important investments and to be in line with the goals of the health system. Given limited resources, allocating funds to one technology means forgoing allocation to others. Like many Latin American countries, Colombia grapples with the financial burden of covering high-cost drugs—some of which are highly-effective, while others show reduced clinical effectiveness. Each of these drugs carries an opportunity cost in terms of the health gains lost by allocating these resources elsewhere.

To achieve this, we analyzed ten drugs selected based on their significant budgetary impact or high cost per case. These drugs were oncologic, for autoimmune and orphan diseases, and one for diabetes. In Colombia, financing these drugs instead of the best available alternatives results in an additional cost of US$453 million for the duration of treatments for all current recipients. The quality adjusted life years (QALY) provided by these technologies average (per patient and for the duration of the treatments) is less than a year of perfect health (0.73 QALY). Alternatively, if these resources were redirected to expand and enhance existing health system services, the net gain would amount to 88,000 life years in perfect health.

In other words, defunding certain services to finance the ten selected high-cost drugs would result in Colombians losing 88,000 life years of perfect health. In this article, we aim to quantify the opportunity cost of financing high-cost drugs in Colombia.

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

Key words: Health spending, public health spending, medicines, pricing, priority setting, pharmaceutical policies, pharmaceuticals, procurement, policies, efficiency, spending, prioritization, resources, health, generic drugs, healthy living, cost-effectiveness

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

The Case of Colombia

Catalina Gutiérrez • Santiago Palacio
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IDB

SUMMARY

» **We find ourselves in a fortunate yet challenging situation: we have access to more beneficial health technologies than we can afford to finance.** However, this increased availability, coupled with an ageing population and epidemiological changes, is straining health spending worldwide. To ensure that higher spending actually maximizes benefits, it is crucial for this growth to be sustainable, to not divert resources from other important investments and to be in line with the goals of the health system. Given limited resources, allocating funds to one technology means forgoing allocation to others. Like many Latin American countries, Colombia grapples with the financial burden of covering high-cost drugs—some of which are highly-effective, while others show reduced clinical effectiveness. Each of these drugs carries an opportunity cost in terms of the health gains lost by allocating these resources elsewhere.

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INTRODUCTION

- **Health spending is increasing worldwide due to epidemiological and demographical changes, and also due to the emergence of new and increasingly expensive health technologies.** This is straining public budgets. Latin America and the Caribbean (LAC) is also experiencing this trend: over the past two decades, health spending has grown from 6.6 to 7.9 percent of GDP, and by 2030 it is expected to increase by another 2 points of GDP (Lorenzoni *et al.*, 2019).

- To ensure these health investments are actually beneficial, it is crucial for them to be sustainable, to not displace other important investments and to be cost-effective. General cost-cutting measures might control spending growth, but if they cut important services they can reduce access to healthcare and negatively affect overall population health. On the other hand, **improving resource allocation and reducing waste can help control costs while delivering better value.**

- **This is especially important given that there are still gaps in the coverage of essential health services.** According to the Universal Health Coverage (UHC) tracking project, Latin American countries have less access to essential health services for communicable diseases. Their UHC index average is 65 over 100, compared to 85 for high-income countries[2]. Other key UHC indicators also show gaps: 13 percent of women do not have access to four prenatal care visits, and 55 percent of people with HIV lack access to anti-retroviral therapy[3].

- **To make informed fund allocation decisions it is important to analyze the potential impact of specific policies aimed at improving efficiency.** Two promising policies that have not been fully explored in this region are closing gaps in essential services (rather than spending on high-cost drugs with limited or uncertain effectiveness) and increasing the use of generic instead of branded drugs in both public and private markets.

- **This article focuses on the first policy:** evaluating opportunity costs in order to advocate for necessary policy changes and inform decision-making, especially regarding the coverage and pricing of high-cost drugs. When deciding where to allocate public resources, it is not just about cost-effectiveness and improving overall population health; other criteria, just as equity and social preferences, also play important roles. But it is essential to understand and quantify the health impact of funding high-cost drugs with uncertain or limited effectiveness. Knowing the opportunity cost in terms of life years lost (or lived with reduced quality) is crucial for the courts, patients, citizens and the medical community to make informed decisions with a full understanding of their consequences.

- **In this context, this article highlights the opportunity cost for Colombia of funding high-cost, cutting-edge drugs**—some that may have a reduced or uncertain effectiveness—by examining ten drugs with high treatments costs or with a substantial budgetary impact due to widespread use. (Annex 1 provides details on how we selected these drugs).

1. BASIC ELEMENTS OF THE ORGANIZATION OF THE COLOMBIAN HEALTH SYSTEM AND DRUG FINANCING

Colombia's healthcare system consists of two main insurance regimes: the contributive and the subsidized (for those financially unable to contribute).

- **Both regimes are financed with citizen contributions and additional budgetary resources.** Currently, 95 percent of the population is covered by one of these regimes. An additional 4 percent is insured under special regimes (such as those for teachers, armed forces and police), and about 1 percent of the population remains uninsured. Within the subsidized and contributive regimes, benefit plans are managed by firms known as EAPBs (*empresas administradoras del plan de beneficio*), which act as insurers and managers of resources and services for their members. Citizens have the option to choose an EAPB within their regime. Each EAPB receives a premium per member known as the Payment Unit per Capitation (UPC, *unidad de pago por capitación*), which varies based on age, gender and region of residence. EAPBs are responsible for covering an explicit benefit plan (PBS, *plan de beneficios en salud*), which includes most healthcare technologies available in Colombia, including drugs, supplies, professional services, diagnostics, care services and prevention and promotion services that are not provided collectively.

- **In 2015, a statutory reform established health as an autonomous fundamental right,** allowing access to technologies not covered by the benefit plan, regardless of cost or effectiveness[4]. Colombian citizens can access these additional benefits not covered by their explicit benefits plan through special requests from an attending physician or by a court order. These benefits are covered through the maximum budgets –a sum assigned to the EAPBs. This predominantly covers high-cost drugs, but may also cover supplies such as special lenses and support services (caregivers, diapers, transport, lodging and nutritional supplements, among others).

- **This statutory law permits the exclusion of certain technologies from public financing.** To be excluded, services or treatment must meet certain explicit criteria: having cosmetic purposes, being experimental, lacking scientific evidence on their effectiveness or safety, not being authorized by the health agency or being provided overseas. However, in some cases the courts have granted exceptions for experimental treatments, those provided overseas or those of a cosmetic nature that have not been approved by a competent authority. In practice, this means that Colombians can access all services and technologies if prescribed by an attending physician or a judge[5].

- Additionally, despite price regulation for drugs in concentrated markets, **EAPBs can negotiate the prices of drugs they acquire individually.** However, a fragmented market reduces their negotiating power as well as the system's ability to secure prices lower than the ceilings established by regulation.

- **In 2019, drug spending represented 19 percent of public health spending in Colombia (11.2 trillion pesos), exceeding the Organisation for Economic Co-operation and Development (OECD) average** of 12 to 15 percent per country. Nearly half of Colombia's public health spending in drugs is attributed to drugs not included in the explicit plan.

2. CONCEPTUAL FRAMEWORK

Allocating scarce healthcare resources necessarily means not funding treatments that could potentially benefit some individuals to finance treatments for others.

Allan Williams, one of the pioneers of economic evaluation, states it eloquently: "Technological advance has put us in the fortunate, though painful, situation of having at our disposal more beneficial activities than we can finance (...) The explicit decision of allocating resources to a patient is inevitably the implicit decision of denying it to another." These decisions are inevitable because needs are unlimited and resources are not. The question is how to make those decisions so that they are fair and acceptable.

One of the aims of health systems is to achieve the highest possible health level for their entire population. It is thus reasonable to allocate resources with efficiency criteria; that is, so that investments result in the highest number of healthy life years for the population[6].

The economic evaluation of technologies provides tools that make it possible to estimate the health gained or lost with each health investment in a technical, transparent and objective way. Technology evaluation compares two alternative courses of action both in terms of their costs and their consequences (Drummond, Sculpher *et al.*, 2015). These tools help answer questions such as: Is it justifiable to invest a certain amount for a certain health gain? How much population health is gained or lost with a given investment, considering that there are alternative uses for those resources? Is this the best use of resources? The cost-effectiveness threshold, incremental cost-effectiveness ratio and net health gains are three of the economic evaluation tools used to answer those questions and quantify an investment's opportunity cost.

A health technology's **opportunity cost** is simply the healthy life years lost due to the services that must be cut back or not delivered to have the funds necessary to finance it. In simpler terms, it is what is given up when a decision is made. A positive opportunity cost shows a good decision was made, whereas a negative opportunity cost indicates that a different decision would have been better.

The **incremental cost-effectiveness ratio (ICER)** allows the comparison of two technologies in terms of their costs and the health benefits they provide. Health benefits are generally measured in Quality Adjusted Life Years (QALY). One QALY is one life year lived in perfect health. **The ICER is calculated as:**

$$\frac{ICER = C_{hcd} - C_a}{QALY_{hcd} - QALY_a} \qquad (1)$$

For the purposes of this article, sub-index *hcd* refers to a high-cost drug, *a* is the best therapeutic alternative offered by the health system, *C* is the unit cost (for example, annual cost of the treatment per person) and QALY are the quality-adjusted life years provided by the technologies. In this case, if a high-cost drug is more expensive and provides less life years in health than the alternative, it is obvious that the best decision would be not to finance it; in this case, the ICER would be negative.

Frequently, a new technology is more expensive and more effective than the alternative, and thus has a positive ICER. Is it justifiable to invest resources in the new technology to achieve that additional health gain or not? To answer that question, we need to be able to compare the ICER with a reference number over which an intervention would not be acceptable (because the cost for each healthy life year is too high) and under which it would be considered cost-effective.

A reference value often used is the **cost-effectiveness threshold (CET).** The CET is the average price or cost at which the system is producing a healthy life year[7]. **The threshold is an indicator of how much health is bought with every dollar invested in a health system.** If a technology's ICER is higher than the threshold, it means it produces a healthy life year at a higher cost than the health system as a whole. Displacing health system resources to finance the new technology thus results in the loss of healthy life years[8]. Several countries –such as the United Kingdom, Ireland and China– use the CET to support decisions on what is covered with public resources.

The ICER informs whether the new technology is cost-effective compared to the threshold but does not tell you how much health is gained or lost if health system resources are redirected to finance it. **The net health gains** quantify the additional QALY that are lost or gained.

Starting from the cost-effectiveness threshold, the new technology's net benefit is calculated as:

$$NHB = (QALY_{hcd} - QALY_{a}) \quad * \quad \frac{N - (C_{hcd} - C_{a})}{CET} \qquad (2)$$

Health gain of the new technology

Health loss due to defunding other technologies

where the sub-index *hcd* is the high-cost drug, *a* is the therapeutic alternative, *C* is the annual treatment cost per person, *N* is the target population and CET is the cost-effectiveness threshold. The first term captures the total health gained and the second the loss. **If the NHB is positive, the high-cost drug produces more population health, whereas if it is negative population health decreases.**

3. METHODOLOGY

This article calculates the opportunity cost of financing high-cost drugs for Colombia.

The opportunity cost of high-cost drugs was calculated using equations (1) and (2). The QALY gained or lost and the ICER of each drug is estimated and then compared to the threshold. The cost-effectiveness threshold comes from Espinosa *et al.*, (2022), which applies the methodology used in several countries to estimate the threshold for Colombia. The authors find that the CET in Colombia equals 86 percent of the per capita GDP, which would equal COP 19.8 million for 2021.

To estimate the net benefit, we must identify the technology at hand, the therapeutic alternative to the high-cost drug, the costs and QALY provided by both options and the target population of the drug being evaluated. **In the next section, we provide the information sources used for each variable.** In section 3.2, we discuss our definition of a high-cost drug and describe the criteria and methods used to select the ten drugs we evaluated.

3.1 INFORMATION SOURCES

In this section, we present the information sources that we used. In annexes 2 and 3, we describe in further detail the sources used for each drug and for the different estimates.

3.1.1 Prices and Quantities

SISMED. SISMED (*Sistema de Información de Precios de Medicamentos*, Drug Prices Information System), managed by the CNPMDM (*Comisión Nacional de Precios de Medicamentos y Dispositivos Médicos*, National Commission for Drug and Medical Device Prices), collects information related to the marketing of all drugs in Colombia. This system reports total sales, prices and unites sold, making it possible to analyze data disaggregating by active ingredient, commercial presentation and marketing channel.

Transactions in SISMED are divided into two channels: commercial and institutional. The institutional channel registers transactions for all drugs with the wording "institutional use" in their label and that are financed by the Sistema General de Seguridad Social en Salud (SGSSS, General Social Security in Health System). For this article, we utilize sales and prices recorded in the institutional channel at the laboratory and active ingredient levels for the years 2020 and 2021[9].

MIPRES. As of 2019, the health professionals who prescribe drugs that are not included in the PBS must submit a request through the MIPRES application to the patient's EAPB. This request includes the member's identity, active ingredient prescribed, quantities prescribed, health condition (CIE-10) and billing information, among other data. These benefits are financed with a resource fund known as "maximum budgets" (*presupuestos máximos*) that are given to the EAPBs to cover and manage benefits not included in the PBS. The health ministry uses the MIPRES information to determine this budget. For the purposes of this article, we used the records as of March 31, 2022, which relate to deliveries from January 2020 through December 2021.

Sufficiency database. The health ministry uses the Sufficiency (*Suficiencia*) database for the sufficiency study to calculate the annual value of the UPC. This database is created from the information that the EAPBs of both the contributive and subsidized regimes report to the ministry regarding the technologies and services provided to their members throughout an entire year. It covers the socio-demographic information of their members, the health services they required during the year, their associated diagnosis (CIE-10), drugs delivered, quantities dispensed, drug prices, number of services provided and the membership regime, among other variables.

For this article, we used the information reported from 2017 through 2019.

Pricentric database[10]. The Pricentric database is a private information source that collects the prices of the highest-cost drugs marketed worldwide. It is based on information collected in several countries by health agencies and public and private price sources, such as pharmaceutical companies. This database includes data disaggregated by commercial brand regarding such variables as annual treatment cost, indication, duration, defined daily dosages, drug's date of approval, net price, list price, discounts and reimbursements. It collects the 50 brands with the highest treatment cost per patient per year in Colombia (which correspond to 40 active ingredients). For this article, we used the database for 2021.

3.1.2 Quality-Adjusted Life Years

The Cost-Effectiveness Analysis Registry (CEA) is a database of more than 10,000 cost-utility studies published from 1976 to the present on a wide variety of diseases and treatments measuring the health effects in terms of QALY. This registry collects information from academic papers published after being subject to a standardized review process. Data is collected for more than 40 variables per 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.

3.1.3. Target Population

To calculate the opportunity cost of covering high-cost drugs we need to determine the quantity of people that receive or could receive each drug. This can be calculated starting from the number of people who currently receive the drug or the total number of people who could potentially obtain it.

The information on the number of people who receive a given drug in Colombia, for the years 2020 and 2021, was obtained from the MIPRES database. To estimate the number of potential recipients, we utilized information on the prevalence of the condition treated by the drug.

Prevalence is basically derived from three sources:

1. **The first is the "Global Burden of Disease Study 2019"** (Global Burden of Disease Collaborative Network, 2021), which estimates prevalence for a great number of diseases, by age range and disaggregated to 4 CIE-10 digits.
2. **The second source is the information of the High-Cost Account (CAC, Cuenta de Alto Costo).** CAC is a fund-account that manages the risk adjustment of the basic premium (UPC) according to the high-cost cases of each EAPB, in order to reassign resources to those EAPBs with a higher number of patients having these conditions. CAC collects information on patients who require high-cost care. CAC annually publishes reports for six high-cost diseases with information on the number of people reported by the health promotion entities (EPS for *entidades promotoras de salud*), including condition, disease stage and health results. The diseases covered by CAC are hemophilia, cancer, rheumatoid arthritis, HIV, hepatitis C and chronic renal disease.
3. **The third information source is the Global Cancer Observatory (GLOBOCAN).** It collects information on prevalence, incidence and mortality of the most common cancer types for several countries. In cases without prevalence information, we resorted to academic papers published in national or international journals.

3.2 SELECTING THE DRUGS TO EVALUATE AND THEIR COMPARISONS

There is no current international consensus on the definition of "high-cost drugs."

The Pan American Health Organization (PAHO) has established certain criteria to identify high-cost drugs, including an absence of therapeutic alternatives, those that serve orphan diseases, diseases with high mortality risk, innovative drugs, high prices and administration complexity, among others (Pan American Health Organization, 2010).

Meanwhile, in more local contexts, objective measures have been proposed to define high-cost drugs from the basis of fixed amounts over which a drug would be considered part of this category. In Brazil, for example, they are defined as those whose monthly value exceeds the minimum wage. Additionally, the English health system defines a series of criteria by which a drug is considered

to be high-cost and, thus, not covered with the national payment-for-results fee. These criteria include high unit cost, high annual treatment cost, an annual impact of over 1.5 million pounds and that they are delivered in a reduced number of specialized centers[11].

In Colombia, there is neither a definition of high-cost drugs nor an explicit list that groups them together. **To select the drugs for our analysis we followed a combined strategy that considered:**

1. **The budgetary impact measured** as the spending on one drug as a share of the total spending on drugs financed with public resources in a period of up to five years.

2. **Drugs with the highest cost per patient per year and the highest annual average treatment cost.** This produced a list of fifteen prioritized drugs. (Annex 1 describes this process in further detail).

The next step was to associate each drug to the different pathologies for which it is used. We then identified conditions for which there were economic evaluations in the CEA Registry. When the CEA Registry returned more than one paper, we chose the one most contextual to Colombia (for example, Latin American countries), with a longer time frame and/or that had the minimum necessary information needed to estimate the opportunity cost.

We did not find studies for five of the fifteen prioritized drugs. This can be an indicator that there is no evidence on the drug's effectiveness other than that provided by the industry[12]. In these cases, we discarded the drug from our analysis. On the other hand, two of the fifteen drugs we identified were comparable to each other. In this case, we chose for our analysis the one with the highest annual cost per patient. Lastly, we identified an additional drug to complete our list of ten drugs to analyze. The drugs we identified absorb close to 16 percent of the total spending on drugs not covered by the UPC in one year (COP 840,000 million for all conditions); this does not include plasmatic factor VIII and abatacept, which are financed with UPC resources and whose combined spending represents close to 2 percent of the total spending on drugs financed through this fund (just over COP 80,000 million).

3.3 ESTIMATING QALY AND COSTS AND DETERMINING TARGET POPULATION

For each treatment, both for the high-cost drug and its comparison, we considered the drug's cost, its application costs when applicable and the costs associated to adverse events and complications.

We used two different strategies to estimate the costs associated with the treatment of each HCD and its comparison. For drug cost, we used the annual per capita spending recorded in MIPRES for the condition under analysis (by CIE-10 code). This information was contrasted with the treatment cost constructed from the drug prices reported in SISMED and the dosage indicated in the academic paper. In the results section of this article, we discuss the cases in which the treatment costs derived from these methodologies were significantly different.

To estimate the costs of application and those originating from medical complications, we used the ratio between those costs and the drug cost per patient per year reported in the academic paper. This ratio was applied to the annual treatment cost per person estimated for Colombia[13].

Our last step was to identify the number of people who need treatment, for which we used two strategies. The **first** used the number of people reported in the MIPRES database as consuming either the HCD or its comparison. The **second** used the condition's prevalence in the general population from the sources described in section 3.2. (Annex 2 details the prevalence information sources).

Finally, we verified if the selected drugs had a health registry entry for the selected condition. All selected drugs, except aflibercept and its comparison abatacept, have health registry entries for their conditions. Both aflibercept and abatacept are used *off-label*[14].

Table 1 presents the drugs selected for analysis, their comparisons, indications and target populations. Annex 2 presents the specific information sources used for QALY, costs and prevalence. The selected drugs are heterogeneous regarding the type of condition they treat, their action mechanism, the reason for which they were classified as high-cost and, as we shall see, the degree of competition in the market.

The selected drugs are oncologic, immunosuppressive or serve orphan diseases (and an anti-diabetic). Adalimumab, liraglutide, abatacept and aflibercept are included because, although they have a moderate annual treatment cost, the total cost is high due to the large number of people who use them. Recombinant coagulation factors VIII have both a high treatment price and a large number of users. The remaining drugs were included because they are among the 20 drugs with the highest annual treatment cost per person.

For patients with spinal muscular atrophy and paroxysmal nocturnal hemoglobinuria, there are no alternative pharmacological treatments to nusinersen and eculizumab, respectively, apart from palliative care. They also do not have biosimilars. Three of the selected drugs do have biosimilar competition –lenalidomide, recombinant factor VIII and adalimumab– as do other drugs in the same therapeutic class. The other seven drugs still enjoy exclusivity in the marktplace[15]. **These are important differences, as we shall see, to design policies that can increase spending efficiency.**

TABLE 1 Drugs selected for analysis

High-cost drug and active ingredient	Therapeutic group	Analyzed condition and indication	Prevalence in Colombia and target population	Commercial brands registered in Colombia	Comparison (active ingredient)
Liraglutide	Anti-diabetic	Second-line treatment for patients with type 2 diabetes mellitus	1.2 million adults	Victoza ®	Metformin + glimepiride
Abatacept	Immunosuppressive	Second- or third-line treatment for moderate to severe rheumatoid arthritis (RA)	8,816, women aged 55 to 64	Orencia®	Continue monotherapy with metrotexate
Lenalidomide + dexamethasone	Oncologic	First-line treatment for patients with multiple myeloma not suitable for autologous stem-cell transplantation	1,670 Average diagnostic age: 70	Revlimid® Ladevidina® Domide® Lenoside®	Bortezomib + melphalan + prednisone
Adalimumab	Immunosuppressive	Second-line treatment for patients over 16 with moderate or severe ulcerative colitis	10,802 Average age of prevalent cases: 40	Humira® Amgevita®	Corticosteroids + aminosalicylates thiopurines
Ibrutinib	Oncologic	First-line of treatment for chronic lymphocytic leukemia (CLL) for patients intolerant to chemotherapy	Prevalence of acute lymphocytic leukemia: 580 to 2,092 Median diagnostic age: 70	Imbruvica®	Obituzimab + chlorambucil
Nusinersen	Other drugs for musculoskeletal system disorders	First-line of treatment for patients with 5q spinal muscular atrophy type 1	Prevalence: 0.1 / 100,000 inhabitants[16] Age: less or equal to 6 months	Spinraza®	Standard care
Aflibercept	Anti-neovascularization agents	Age-related macular degeneration	People over 55 with possible case of ARMC in Colombia: 393,756[17]	Eylia®	Bevacizumab (Avastin®)
Eculizumab	Selective immunomodulator	Paroxysmal nocturnal hemoglobinuria (PNH)	Prevalence: 1/100,000 inhabitants[18] 511 cases	Soliris ®	Standard care
Plasmatic / human factor VIII	Blood coagulation factors	Type A hemophilia	2,160 According to CAC, prevalence of 4.29 / 100,000 inhabitants	Feiba®, Haemoctin®, (among others)	Recombinant factor VIII
Pembrolizumab	Anti-neoplastic agents	First-line of treatment for metastatic melanoma	Prevalence: 8.88 cases / 100,000 inhabitants. From prevalence data and a percentage of cases in stage 3 of 27.7%	Keytruda®	Ipilimumab (Yervoy®)

4. RESULTS

4.1 OPPORTUNITY COST OF FINANCING HIGH-COST DRUGS

Tables 2 and 3 summarize the costs and QALY for the base scenario. The base scenario uses the number of people who are under treatment and the average spending per person recorded in the MIPRES database. In other words, it reflects the clinical practice currently observed in Colombia. Eight of the drugs under study are more costly and more effective than their comparison, with additional contributions in quality-adjusted life years of 0.04 to 1.49 additional life years for the treatment duration. Pembrolizumab is less costly and more effective than its comparison, while the plasmatic factor is costlier and less effective than its comparison[19]. **The additional cost of eculizumab and nusinersen is over COP 470 million (US$120,000) per patient per year; this reflects their**

TABLE 2 **Annual treatment costs per person, number of users, and annual and total cost for the health system in 2021[20]**

Drug	Annual treatment cost per person, in 2021 COP (MIPRES)			People (D)	Annual cost for the health system (CxD) Million pesos	Health system cost for the duration of the treatment[21] Million pesos (net present value)
	HCD (A)	Comparison (B)	Difference (C=A-B)			
Nusinersen[22]	668,515,195	134,572,481	533,942,715	42	22,426	247,803
Eculizumab	506,054,702	32,616,823	473,437,879	102	48,291	464,573
Ibrutinib	107,525,944	46,854,040	60,671,904	168	10,193	326,247
Pembrolizumab	106,420,491	117,946,956	(11,526,465)	168	- 1,936	-15,705
Plasmatic factor VIII[23]	75,569,103	64,967,760	10,601,343	1,283	13,602	13,601
Lenalidomide	38,501,993	18,644,947	19,857,046	3,146	62,470	377,085
Aflibercept	7,876,663	1,566,903	6,309,760	5,856	36,950	341,884
Abatacept	6,849,977	711,941	6,138,036	1,365	8,378	126,799
Adalimumab[24]	6,483,732	1,254,712	5,229,019	569	2,975	60,148
Liraglutide	2,296,521	342,272	1,954,249	10,562	20,640	91,796
Total				**23,261**	**223,988**	**2,034,233**

Source: authors' calculations based on MIPRES, Sufficiency study and academic papers (see Annex 2).

TABLE 3 QALY gained for the duration of the treatment per person and health system total

Drug	People (A)	Total QALY per person with discount			Total QALY gained for the duration of the treatments (A x D)
		HCD (B)	Comparison (C)	Difference (D=B-C)	
Lenalidomide	3,146	4.26	2.79	1.47	4,624.62
Liraglutide	10,562	10.25	10.02	0.23	2,429.26
Abatacept	1,365	1.25	1.10	1.43	1,951.95
Ibrutinib	168	8.32	6.84	1.49	250.32
Aflibercept	5,856	1.38	1.34	0.04	234.24
Eculizumab	102	8.39	7.31	1.08	110.16
Adalimumab[25]	569	4.10	3.91	0.18	102.42
Nusinersen[26]	42	1.85	0.42	1.43	60.06
Pembrolizumab	168	1.68	1.36	0.32	53.76
Plasmatic factor VIII[27]	1,283	0.62	0.78	(0.16)	-205.28
Total	**23,261**				**9,611.51**

dominant positions in the market, inasmuch as they are the only available treatments.

It is important to highlight that these results refer only to the analyzed condition. Some drugs treat multiple conditions and these results cannot be extrapolated to them. **A drug can be cost-effective for the treatment of one condition and not for the treatment of another.**

From Table 2 and Table 3, we can see that Colombia incurs additional spending of approximately COP 224,000 million annually in these ten drugs (US$59 million). If we estimate the cost for the duration of the treatment and the number of people treated, the additional cost amounts to 2 trillion pesos (US$543 million); this begets around 9,600 QALY distributed among approximately 23,000 people for the duration of the treatment or the patients' lives[28], **which is equal to five additional months of life in perfect health per patient.**

Table 4 presents the opportunity cost and the cost-effectiveness of the treatments in the base scenario. There is no direct relation between the opportunity cost and the incremental cost-effectiveness ratio (ICER). For example, liraglutide has an ICER 90 percent higher than the Colombian cost-effectiveness threshold. Even so, the number of people using it implies that financing this drug instead of its alternative results in 2,199 quality-adjusted life years that are not gained. On the other hand, the cost of adalimumab is 14 times the cost-effectiveness threshold, but the number of persons using it is substantially lower, so a smaller number of QALY is lost. This illustrates the importance of taking into account not just the ICER but also the opportunity cost for decision making.

Treatment price is not directly related to the average cost-effectiveness ratio. For example, the two most important treatments, nusinersen and eculizumab, have a higher cost-effectiveness than other drugs with lower costs per person. This is because these two treatments have the highest incremental benefits.

The drugs with the highest opportunity costs are eculizumab (30,000 QALY), aflibercept (17,000 QALY), ibrutinib (16,000 QALY) and nusinersen (9,500 QALY). Aflibercept's high opportunity cost results from the drug's low efficacy;

TABLE 4 Opportunity cost of financing high-cost drugs in Colombia, 2021

Drug	Condition	ICER in 2021 COP	ICER as a share of the CET	Opportunity cost in QALY
Eculizumab	Paroxysmal nocturnal hemoglobinuria	5.463.039.285	275,5	(30.235)
Aflibercept	Macular degeneration	1.423.947.251	71,8	(16.999)
Ibrutinib	Acute lymphocytic leukemia	1.303.322.450	65,7	(16.200)
Nusinersen	Spinal muscular atrophy	3.185.062.699	160,6	(9.586)
Lenalidomide	Multiple myeloma	81.538.634	3,9	(7.052)
Abatacept	Adult rheumatoid arthritis	64.960.304	3,3	(4.442)
Liraglutide	Diabetes type II	37.787.925	1,9	(2.199)
Adalimumab	Ulcerative colitis	276.707.048	14.0	(1.336)
Plasmatic factor VIII	Hemophilia	HCD is dominated	NA	(891)
Pembrolizumab	Chronic lymphocytic leukemia	HCD dominates	NA	846
Total				**(88.095)**

Source: authors' calculations based on MIPRES database and Pricentric, 2021.

it provides just 0.04 QALY compared to the alternative, which equals 14 additional life days in perfect health. It is worth highlighting that this drug's use is *off-label*. On the other hand, ibrutinib's opportunity cost results mainly from its high cost, given that it has the highest contribution of additional QALY among those we analyzed.

If the resources used to finance high-cost drugs had been used to cover other health services with average cost-effectiveness, Colombia could have gained 88,000 QALY. In other terms, if financing these drugs meant the country defunded other services, 88,000 QALY were lost[29].

These results reflect the opportunity cost under the observed clinical practice and for the current coverage of these drugs. It is not unusual for the observed cost to be lower than the normative cost; that is, what it would cost if the drugs were dispensed according to the clinical guides. This could be because patients do not claim all prescribed drugs, because doctors temporarily suspend treatments following patient intolerance, etc. Likewise, the number of patients treated can differ from the treatment's target population, either because the entire population is not covered or because the drug is being given to a higher number of patients. For example, doctors and patients may use the drug as the first-line treatment when the guidelines suggest using it as a second-line treatment.

4.1.1. Normative Opportunity Cost

In a second exercise, we estimated the normative opportunity cost for a subgroup of drugs; that is, the opportunity cost if the drugs were given to everyone who needed them according to indications.

This could also be described as the potential opportunity cost Colombia could incur if it financed the analyzed HCDs.

Table 5 shows the treatment cost according to the indicated dosages. There is great price variability for the same drug in the Colombian market. To estimate the annual treatment cost, we used the quantity-weighted average price. **In most cases, the normative cost was higher than the cost observed in clinical practice.**

Under this scenario, pembrolizumab would cease to be less costly than its comparison. That is, we observe that clinical practice has altered the cost relationship between these two drugs. This change could be attributed to price factors or to the possibility that patients prescribed this drug may not be receiving the complete treatment as per clinical guidelines.

Table 5 also shows the estimated prevalence for the conditions served by HCDs. Prevalence was estimated by considering that not all patients who suffer a condition are candidates for treatment. The prevalence of lenalidomide, for example, corresponds to patients with multiple myeloma who are not transplant candidates. Annex 2 describes these sub-populations in further detail.

As could have been expected, the potential population is substantially higher than the population currently receiving the drug[30]. The case of aflibercept is illustrative: while macular degeneration incidence in the population aged 45 to 85 is 8 percent (393,000), only 5,826 Colombians who face this condition receive the drug. The difference could be explained by the drug's low clinical effectiveness, or by the fact that it is *off-label* for the treatment of macular degeneration. At a cost of over COP 13 million a year per patient, the generalized usage of this drug would have a significant budgetary impact for a very small gain in clinical and QALY terms. **Hence the importance of including cost-effectiveness, opportunity cost and budgetary impact considerations in decisions concerning coverage and price-setting.**

As we have commented, patients and doctors are liable to interrupt treatments due to secondary effects, lack of effectiveness, complications or preferences. Patients may also fail to adhere to the treatment[31]. Even so, the cost difference between the two scenarios warrants a follow up on the use of these high-cost treatments: incomplete treatments seldom achieve expected results, yet the spending is still incurred.

TABLE 5 **Additional cost of high-cost drugs and prevalence of the condition in Colombia, 2021**

Drug	Annual treatment cost per person in 2021 COP (SISMED)			People (prevalence)
	HCD	Comparison	Difference	
Nusinersen	1,504,586,211	134,572,481	1,370,013,731	123
Eculizumab	1,019,814,276	32,616,823	987,197,453	510
Pembrolizumab	376,133,333	216,710,500	159,422,833	1,239
Plasmatic factor VIII	361,235,351	60,843,439	300,391,912	2,160
Ibrutinib	196,524,802	68,295,651	128,229,151	1,483
Lenalidomide	29,608,047	24,894,728	4,713,319	1,670
Abatacept	29,452,982	234,000	29,218,982	8,816
Aflibercept	13,174,690	1,833,395	11,341,295	393,756
Liraglutide	11,811,321	827,887	10,983,434	1,207,409
Adalimumab	4,979,528	963,623	4,015,905	8,641

Source: authors' calculations based on the price database reported in SISMED, 2021.

Table 6 presents the potential opportunity cost derived from the normative exercise. For the drugs we analyzed, the opportunity cost amounts to 5.6 million QALY. As was to be expected, this number is higher than the observed opportunity cost. In other words, if all patients who are candidates for the drugs were to receive them according to the clinical indications and at the observed market prices, the opportunity cost of HCDs could be up to 60 times higher.

Aflibercept and liraglutide account for 81 percent of the opportunity cost. Both have a significant potential population and reduced benefits compared to their alternatives. Liraglutide was analyzed as an additional first-line treatment for the population where monotherapy loses its efficacy. The results show that the gains from this practice are reduced in relation to their costs. Using liraglutide as a second- or third-line treatment, or only in patients with certain conditions (obesity), as recommended by the Colombian clinical practice guide, would reduce the potential opportunity cost.

In the case of plasmatic factor VIII, 33,000 QALY would be lost in an alternative that is both costlier and less effective.

4.2 PRICE VARIATIONS AND THEIR IMPACT ON OPPORTUNITY COST

In Colombia, the bulk of high-cost drugs have a regulated maximum selling price; even so, there are important price differences below the maximum authorized prices.

Table 7 shows the price ranges observed for some of the HCDs or for their therapeutic alternatives. Variations range from 9 to 873 percent.

TABLE 6 **Potential opportunity cost of financing high-cost drugs, 2021**

Drug	Condition	ICER (2021 COP)	ICER as a share of the cost-effectiveness threshold	Opportunity cost (QALY)
Liraglutide	Diabetes type II	145,161,285	7	(2,580,802)
Aflibercept	Macular degeneration	2,559,432,679	129	(2,067,331)
Eculizumab	Paroxysmal nocturnal hemoglobinuria	11,391,353,986	574	(316,131)
Ibrutinib	Acute lymphocytic leukemia	2,505,378,336	126	(276,935)
Abatacept	Adult rheumatoid arthritis	277,092,025	14	(162,035)
Pembrolizumab	Chronic lymphocytic leukemia	4,040,818,703	204	(80,369)
Nusinersen	Spinal muscular atrophy	8,172,374,134	412	(72,305)
Plasmatic factor VIII	Hemophilia	Dominated	NA	(33,063)
Adalimumab	Ulcerative colitis	212,511,941	11	(15,222)
Lenalidomide	Multiple myeloma	35,592,921	2	(1,951)
Total				**(5,606,144)**

Source: authors' calculations based on the price database reported in SISMED, 2021.

TABLE 7 Price variations for certain drugs, 2021

Drug	Minimum price per mg (COP)	Maximum price per mg (COP)	Difference (%)
Bortezomib	51,703	502,907	873 %
Prednisone	10	41	298 %
Lenalidomide[32]	7,419	22,082	198 %
Recombinant coagulation factors VIII	692	1,744	152 %
Metformin + Glimepiride[33]	369,4	590	60 %
Adalimumab	15,768	19,470	23 %
Bevacizumab	7,239	8,766	21 %
Dexamethasone	1,180	1,288	9 %

Source: authors' calculations based on the price database reported in SISMED, 2021.

TABLE 8 Incremental cost-effectiveness ratio and opportunity cost for lenalidomide according to price variations, 2021

Drug	ICER (COP)	ICER as a share of the cost-effectiveness threshold	Opportunity cost (QALY)
Lenalidomide, base price	35,592,921	1.70	(1,951)
Lenalidomide, minimum price	16,789,908	0.8	376
Adalimumab, base price	212,511,941	10.7	(15,222)
Adalimumab, generic price	176,934,456	8.9	(12,411)

Source: authors' calculations based on the price database reported in SISMED, 2021.

These variations imply that, in some cases, it would be possible to improve incremental cost-effectiveness using the lowest price recorded in the market. The case of lenalidomide is illustrative. If the lowest reported prices were used for both drugs –the HCD and its comparison– lenalidomide would be cost effective and would imply a net health gain of 376 QALY. That is, with the lowest prices lenalidomide dominates its comparison by being both more effective and less costly (Table 8).

The alternative treatment to lenalidomide, bortezomib, also has significant price dispersion: Velcade® (the branded drug) costs nearly 5 times more than the average of equivalent generics. Replicating the same exercise, we found that the opportunity cost of financing lenalidomide would increase 70 percent if bortezomib were acquired at the lowest price and lenalidomide at the highest price, going from a loss of 1,951 QALY to a loss of 3,205 QALY.

The opportunity cost of adalimumab would be reduced by slightly over 3,000 QALY if we were to compare it to the biosimilar alternative. This drug serves several other autoimmune diseases –with varying degrees of effectiveness– that affect a significant number of people; thus, it is one of the drugs that generate the highest budget expense, deserving a specific strategy to achieve lower prices.

Similarly, if price reductions could be achieved for drugs that have no competition, they could be more cost-effective and not result in loss of QALY. For example, liraglutide would be more effective and less costly than the alternative in the treatment of type 2 diabetes if its price were reduced by 30 percent.

In other cases, suppliers sell very close to the maximum selling price (MSP) set by the CNPMDM; that is the case for ipilimumab and liraglutide. The maximum price is estimated to be in the 25th percentile of prices from a 17-country sample. In other words, the regulated price in Colombia is not the lowest among the countries used as a reference. It is generally higher than prices in Australia, Brazil, Mexico and Panama, which means there might be space for additional price reductions[34].

For some drugs we found that the MSP is more than 50 percent higher than the selling prices recorded in SISMED in 2021. For example, Bortemix® of 3.5 of Lafrancol has a MSP of COP 2,269,831 while its average selling price was COP 180,962. Table 9 shows some of these price comparisons, either by mg or IU (for factor VIII).

These differences can be explained by two reasons: generic drugs could have emerged on those markets; or the EAPBs and the IPSs might have negotiated the drugs' acquisition prices directly with providers and distributors at a lower price than de MSP. **This suggests that the methodology to set MSP could be revised to achieve lower prices.**

TABLE 9 **SISMED prices compared with regulated prices for certain high-cost drugs, 2021**

Drug	Average price, SISMED, 2021, per mg / IU	Maximum sale price by Circular 12 of 2021	Difference (%)
Bortezomib	119,636	648,523	442 %
Lenalidomide[35]	3,488	36,162	168 %
Obinutuzumab	5,101	12,664	148 %
Adalimumab	18,539	32,000	73 %
Recombinant factor VIII	1,085	1,729	59 %

Source: authors' calculations based on the price database reported in SISMED, 2021 and CNPMDM Circular 12 of 2021.

5. LIMITATIONS

This article illustrates the potential opportunity cost that Colombia incurs when it finances high-cost drugs, some of which have reduced additional effectiveness relative to their comparisons.

These results are subject to available information. While rigorously researched, this article does not claim to be an economic evaluation for making decisions on the coverage of the analyzed drugs. For example, we did not use national information to estimate the costs of complications and secondary effects, but rather extrapolated those from international information. Additionally, we used only one study to obtain the QALY provided by the HCDs and their comparisons. **In any case, the assumptions we used do not change the main conclusions: HCDs have opportunity costs in terms of QALY that should be considered.**

Estimating the QALY gained and the total cost of a treatment is not without difficulties. On the one hand, the results are sensitive to the underlying assumptions, which include: discount rate; clinical action taken when effectiveness is lost, which can be either suspend all treatment or proceed to a second- or third-line treatment; the time frame of the study (lifelong, 5 years, 10 years); and the QALY provided by each drug. The use of QALY as a measure of gain is not without controversy, either.

Even so, there are mechanisms to incorporate uncertainty into the estimations, and more countries are using technology evaluations, including economic and budgetary impact evaluations, to support their coverage decisions.

Additionally, it often is not a case of one alternative or the other but rather that some patients exhaust options as treatments lose their therapeutic effectiveness. **This highlights the importance of setting fair prices related to the QALY provided and their opportunity cost, as well as establishing clear rules on when a treatment is initiated, when it is suspended and if it is prescribed as a first-, second- or third-line treatment.**

6. CONCLUSIONS AND RECOMMENDATIONS

6.1 CONCLUSIONS

Every decision to allocate resources has an opportunity cost in terms of life years gained or lost.

This article reveals that **Colombia spends nearly COP 244 billion annually to fund ten high-cost drugs instead of opting for more affordable alternatives.**

An annual expense of COP 224,000 million (US$59 million), accumulated over the duration of patient treatments, translates to an additional cost of 2 trillion pesos (US$543 million). If these funds were distributed across the entire health system to enhance and expand existing services, Colombians would gain a total of 88,000 life years of perfect health. Another way to visualize this impact: 8,800 individuals would gain 10 years of perfect health. **Conversely, if financing these drugs defunds more effective services, the country loses 88,000 healthy life years.**

The choice of which drugs to finance is crucial, even among high-cost options, as demonstrated by cases like ipilimumab and pembrolizumab for melanoma treatment. Prioritizing one over the other can result in a gain or loss of up to 846 life years of perfect health (under observed clinical conditions) or up to 80,000 life years if administered according to the drug's indications.

Colombia experiences for several active ingredients, such as lenalidomide, ample price variability for the same product. If the country purchased the entire supply at a lower market price, lenalidomide would outperform its therapeutic alternative by being less costly and more effective for treating multiple myeloma.

While incremental cost-effectiveness and opportunity cost are not the sole criteria for determining coverage, they provide valuable decision-making information. For instance, liraglutide could be more effective and cost less than alternatives for type 2 diabetes if its price were reduced by 30 percent. Similarly, lenalidomide would dominate its comparison if acquired at the lower market price. This is especially pertinent considering the potential increase in utilization of these drugs for the analyzed conditions, which could substantially raise their budgetary impact as they become more widespread. In contrast, available evidence indicates that aflibercept would have minimal incremental effectiveness in macular degeneration treatment, equivalent to just 14 additional days of life in perfect health, with an opportunity cost of nearly 17,000 QALY.

6.2 RECOMMENDATIONS

There are tools available to help reduce the budgetary impact and opportunity cost associated with high-cost drugs.

The effectiveness of these strategies can vary depending on the type of drug, number of alternatives in the market and the nature of the disease. While Colombia already has a price control scheme based on international references, it falls short of achieving efficient health spending. There are several alternatives the country could explore to improve its approach.

One effective step could be to establish a list of high-cost drugs based on price and budgetary impact, and conduct economic evaluations to assess their opportunity cost and incremental cost-effectiveness. **This analysis should be integrated into policy decision-making and communicated clearly to all audiences for consultation, including non-specialized audiences.**

Implementing intelligent procurement mechanisms for drugs that exert significant pressure on the system is of paramount importance to the region. As demonstrated in this article, opportunity costs can be substantial. Given budget constraints, changes in the epidemiological profiles and the growing influx of innovative therapies, health systems cannot continue purchasing drugs indiscriminately, especially those associated with high financial costs or those with clinical uncertainty.

Managed Entry Agreements (MEA) between drug producers and payers play a pivotal role in addressing these challenges.

To implement effective MEAs, a comprehensive strategy is required:

1. **Prioritization:** Using all drugs analyzed in this article as a pilot.
2. **Rigorous negotiation:** This includes conducting economic evaluations, assessing budgetary impacts, defining clinical outcomes to payment conditions and designing operational-clinical pathways for optimal technology use.
3. **Monitoring and collecting data:** Tracking patient-level data.
4. **Evaluation of outcomes:** It is essential to assess the results of these agreements.

In monopolistic markets where drugs demonstrate effective therapeutic outcomes but come with substantial costs, such as liraglutide, financial arrangements like discounts, price/volume agreements or budgetary limits should be considered. Conversely, drugs with high clinical uncertainty, such as nusinersen, may require agreements based on performance, shared risk or evidence-based results tied to outcomes. (Brazil has negotiated a comparable agreement for nusinersen, although this policy's impact has not been evaluated yet).

Managed Entry Agreements (MEA) can mitigate opportunity costs derived from the acquisition of innovative drugs that exert more pressure on the health system, aiming to purchase health outcomes and reduce uncertainty.

Colombia has made progress in developing a legal framework and operational model for MEAs, although official approval is still pending. Despite technical and political challenges, **LAC should move toward centralized regional procurement to enhance bargaining power and secure lower prices.** The PAHO has already demonstrated success with this approach for anti-retroviral drugs to treat hepatitis C.

For markets with limited alternatives, adopting inverse tenders could help lower costs for drugs like adalimumab and lenalidomide. This strategy, utilized in New Zealand, allows only the lowest-priced drug supplier to receive financing. The selected supplier can negotiate directly with the EAPBs and IPSs for acquisition of the drug at the price stipulated in the tender.

In markets where the patent for innovative drugs has expired and the active ingredient has alternatives with varying prices (like with recombinant factor VIII and lenalidomide), competition could be achieved by inviting more competitors into the market. Improving transaction transparency for IPSs or EAPBs with distributors or suppliers could also help. This could involve publishing purchase prices and profit margins across the distribution chain.

Colombia has the necessary information, but it is not currently organized in an easily accessible manner nor is it effectively communicated. Moreover, this information is not routinely used to set price or coverage policies. **Expediting processes to approve and promote the entry of generic drugs or biosimilars could also contribute to price reduction for high-cost drugs.**

Physicians play a critical role in substituting higher-cost drugs with more affordable alternatives. However, they often lack information on price differences and opportunity costs. Providing price data and disseminating information through medical societies could facilitate more informed decision-making.

Clear guidelines for treatment initiation and termination should be established and communicated to physicians, as has been done for nusinersen in Colombia. Scientific societies should contribute to these guidelines, considering budgetary impacts and opportunity costs.

Implementing a clinical monitoring system for patients receiving high-cost drugs, similar to the CAC's approach for diseases like hemophilia or certain kinds of cancer, could optimize resource utilization and improve health outcomes.

Price control for drugs with active patents requires multifaceted strategies. While international price references are valuable, price regulation must be more aggressive to prevent inflated prices. For some drugs, the national price was below the 25th percentile of the international reference price before regulation. However, the MSP is consistently established based on the last reference, resulting in a maximum price that exceeds the market price, which has been seen in the cases of recombinant factor VIII and ibrutinib.

In these situations, using an MSP based on international prices can have unintended incentives for pharmaceutical companies, prompting them to practice the "bat effect" (sticking close to the maximum price). Additionally, Colombian price regulations currently rely on international price references for branded drugs, even in markets where generic alternatives are available. Thus, the maximum price ends up being considerably higher than the prices of generic drugs.

All of these factors suggest that Colombia should take comprehensive action on prices. In the short term, monitoring drugs with MSPs exceeding national prices can prevent unjustified price hikes. It is also crucial to revise the price regulation methodology to include prices of generics in competitive markets, not just international prices of branded drugs. Additionally, setting the MSP as the lower of the international reference price or the nationally observed price would align Colombia's price policy with its goals of efficiently allocating public resources for drug procurement.

A strategy to consider, particularly for monopolistic markets, is to establish prices based on therapeutic value.

Colombia has taken steps in this direction, although new regulations are still pending approval.

Vincent Rajkumar (2020) posits that countries "should be more willing to use compulsory licensing to lower the cost of specific prescription drugs when negotiations with drug manufacturers on reasonable pricing fail or encounter unacceptable delays. This process permitted under the Doha declaration of 2001, allows countries to override patent protection and issue a license to manufacture and distribute a given prescription drug at low cost in the interest of public health." Colombia has already adopted this path in one instance, as has Brazil.

Lastly, Colombia must address the ethical implications of covering all prescriptions regardless of efficacy. **Funding drugs with limited clinical effectiveness and high opportunity costs should be discouraged, and their coverage reconsidered.**

ANNEX 1. SELECTION OF DRUGS CONSIDERED AS HIGH-COST

To select the drugs for this article we started by with the following lists.

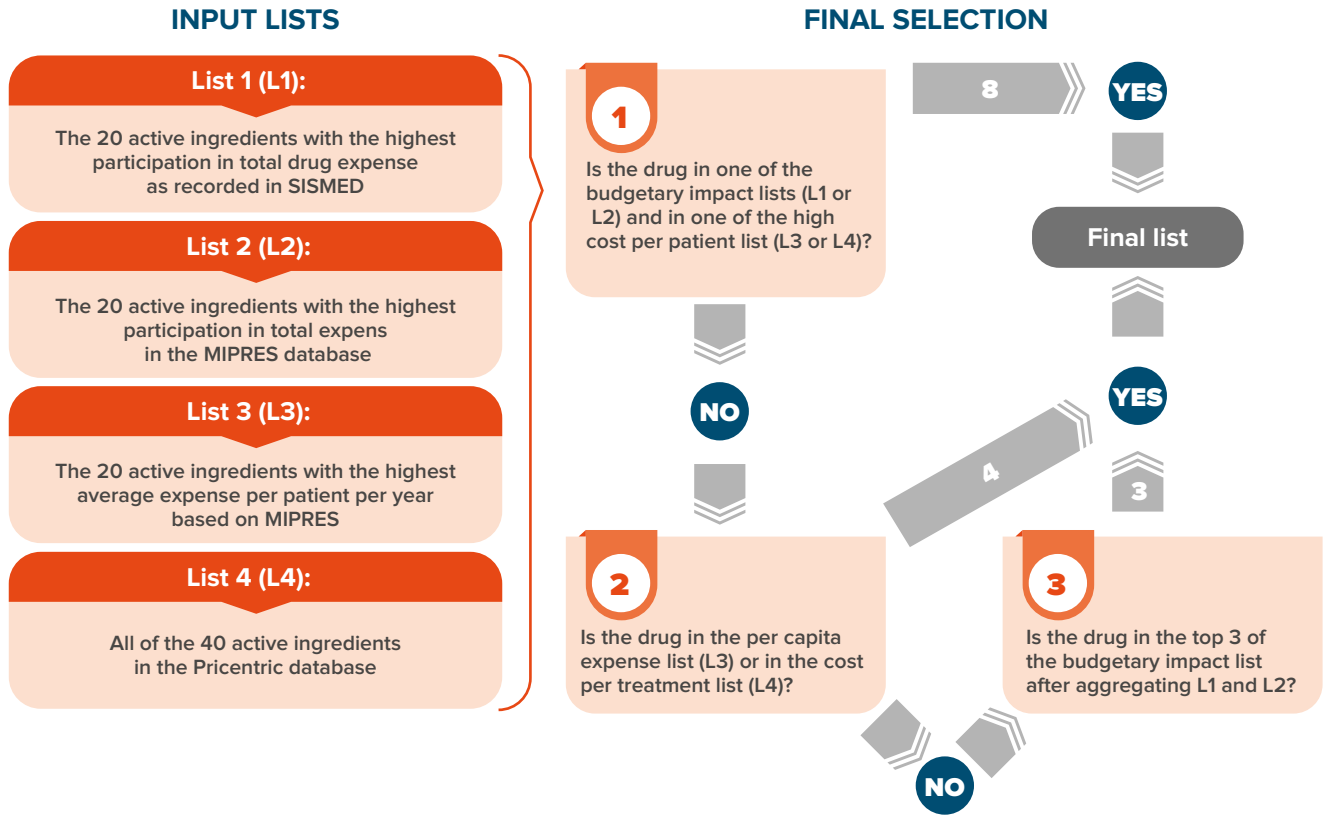
- **List 1:** the 20 active ingredients with the highest participation in total drug spending, as recorded in SISMED.
- **List 2:** the 20 active ingredients with the highest participation in total spending in the MIPRES database.
- **List 3:** the 20 active ingredients with the highest average spending per patient per year based on MIPRES[36].
- **List 4:** all of the 40 active ingredients in the Pricentric database.

Final selection

Starting with those four lists, the final selection was made according to the following outline (as illustrated in Figure 1):

1. **We selected those active ingredients which, having been included in either list 1 or 2, were also included in either list 3 or 4.** That is, we selected drugs which have a high budgetary impact and a high expense/cost per patient per year. This operation yielded eight active ingredients fulfilling both conditions.
2. **We selected the active ingredients included both in list 3 and 4;** that is, those associated with a high expense/cost per person per year. This operation yielded four drugs.
3. **Of the active ingredients included both in list 1 and list 2** –that is, those associated with a high impact in the total drug expense– and that had not been included in the two previous steps, we selected the three active ingredients with the highest participation in total drug expense.
4. **The next step was associating each drug with the pathologies for which the analysis was to be conducted.** First, we identified the conditions for which the drug's marketing is authorized in Colombia. Then, we used the WHO's list of essential drugs to verify that none of the selected drugs was included as essential for a particular condition (since the WHO has already considered their costs to be justified in relation to their benefits).
5. **We identified all the available economic studies in the Tufts database analyzing the drugs' cost-effectiveness for any of the conditions resulting from step 4.** Drugs for which no information was found were discarded.

FIGURE 1 Diagram of the selection of the final list of high-cost drugs in Colombia



Source: authors' elaboration.

ANNEX 2. SOURCES OF INFORMATION USED AND USE GIVEN

TABLE A2 Sources of information used and use given (1 of 2)

	Reported information	Use for the study	Period
SISMED	Total sales, prices and units sold by active ingredient, commercial presentation and marketing channel (institutional or private).	Prices reported in SISMED were used to: estimate treatment costs in the normative scenario; study the impact of price variation in opportunity costs.	2020-2021.
MIPRES	Information on prescription of drugs not included in the PBS and, thus, covered through the maximum budgets system. Includes member identities, prescribed active ingredient, quantities prescribed, health condition (CIE-10) and billing information, among other variables.	The prices, number of patients and quantities sold reported by MIPRES were used to estimate the drugs' opportunity costs and cost-effectiveness under the observed clinical practice. MIPRES data were also used to identify the higher cost drugs in terms of budgetary impact and cost per patient per year.	March 31, 2022 cut; relates to deliveries made January 2020 through December 2021.
Sufficiency database	Information on the benefits included in the PBS. Covers the socio-demographic information of members, the health services they required during the year, the associated diagnosis (CIE-10), the drugs provided, quantities provided, drug prices, number of services provided and affiliation regime, among other variables.	The information was used to identify the highest cost drugs in terms of budgetary impact and cost per patient per year. As expected, the cost per patient per year for the benefits included in the benefit plan –and thus reported in this database– was always below de costs per patient per year of the benefits not included in the plan and reported in the MIPRES database.	2019.
Pricentric database	Prices of the highest cost drugs marketed worldwide, for several countries, and based on the information collected by health agencies and public and private sources, such as pharmaceutical companies. This includes data disaggregated by commercial brand on annual cost of treatment, indication, duration, defined daily dosage, drug's date of approval, net price, list price, discounts and reimbursements. Collects the 50 brands with higher cost per treatment per patient per year in Colombia (which correspond to 40 active ingredients).	The information of cost per patient per year was used to select the ten high-cost drugs, following the methodology described in Annex 1.	2021.

TABLE A2 Sources of information used and use given (2 of 2)

	Reported information	Use for the study	Period
The Tufts Cost-Effectiveness Analysis Registry	Includes 10,000 cost-utility analyses related to a wide variety of diseases and treatments published since 1976. It collects information on academic papers published after being subject to a standardized review process.	QALY provided by the 10 selected technologies and their comparisons.	Several years.
Global Burden of Disease Study 2019	Estimated prevalence for a great number of diseases, by age range and disaggregated to 4 CIE-10 digits.	Prevalence of diseases not available in CAC or Globocan.	2019.
High Cost Account (CAC)	Information on the number of persons reported by the EPSs with a condition, disease stage and health results for six diseases: hemophilia, some cancers, rheumatoid arthritis, HIV, hepatitis C and chronic renal disease.	Prevalence of hemophilia, rheumatoid arthritis and some cancers.	2021.
Global Cancer Observatory	Information on prevalence, incidence and mortality of the main types of cancers for several countries across the world.	Prevalence of some cancers.	2021.

ANNEX 3. SOURCES FOR PREVALENCE AND QALY, AND ANALIZED TIME FRAME

Sources for prevalence:

- **Liraglutide** and abatacept, Institute of Health Metrics Evaluation, Global Burden of Diseases.
- **Lenalidomide,** Global Cancer Observatory.
- **Adalimumab,** Fernández-Ávila, D. and Bernal-Macías, S., (2020).
- **Ibrutinib,** High Cost Account, prevalence of other lymphocytic leukemia; and MIPRES database, people with CLL.
- **The percentage of patients who do not respond to first-line treatment,** or who belong to a severity or age subgroup, is sourced from various academic sources or DANE population estimates.

TABLE A3 Source for prevalence and QALY and analyzed time frame

Drug	Time frame	Discount rate	Source for costs	Source for QALY and country of analysis
Liraglutide	Lifetime	3 %	Maximum budgets database (MIPRES).	Roussel, R., Martinez L. *et al.* (2016). France.
Abatacept (1)	Lifetime	3 %	Maximum budgets database (MIPRES).	Yuang, Y. and Trivedi, D., (2010). United States.
Abatacept (2)	Lifetime	3 %	Built based on SISMED price database and dosage indicated in the study and confirmed in GPC.	Yuang, Y. and Trivedi, D., (2010).
Lenalidomide	Lifetime	3 %	Maximum budgets for lenalidomide and bortezomib, SISMED for melphalan and prednisone.	Usmani, S. Z. and Cavenagh, J. D. (2016). United States.
Adalimumab	10 years	5 %	SISMED for adalimumab. The comparison was built keeping constant the price ratio observed in the publication.	Beilman, C. L. and Thanh, N. X. (2016). Canada.
Ibrutinib				
Nusinersen	7 years	3 %	Maximum budgets database (MIPRES) for nusinersen. The comparison was built keeping constant the price ratio observed in the publication.	Thokala *et al*. (2020). United States.
Aflibercept	8 years	3 %	Maximum budgets database (MIPRES).	Brown *et al.* (2020). United States.
Eculizumab	20 years	5 %	Maximum budgets database (MIPRES) for eculizumab. The comparison was built keeping constant the price ratio observed in the publication.	Cruz *et al.* (2021). Brazil.
Recombinant factor VIII	1 year	N.A.	Pricentric.	Lotfi *et al.* (2020). Iran.
Pembrolizumab	10 years	4 %	Maximum budgets database (MIPRES).	Pike *et al.* (2017). Norway.

NOTES

[1] The authors would like to especially thank the officials of the Dirección de Regulación de Beneficios, Costos y Tarifas del Aseguramiento (Insurance Benefit, Cost and Fee Regulation Direction) at Colombia's Ministerio de Salud y Protección Social (Health and Social Protection Ministry) for the support to obtain the data and solving multiple doubts regarding the information.

[2] Tracking universal health coverage: 2021 Global Monitoring Report. Geneva, WHO 2021. https://www.who.int/data/monitoring-universal-health-coverage.

[3] Tracking universal health coverage: 2021 Global Monitoring Report. Geneva, WHO 2021. https://www.who.int/data/monitoring-universal-health-coverage.

[4] Law 1751 of 2015, Health Statutes.

[5] Aguirre, C., "Tendencias de la jurisprudencia constitucional colombiana sobre exclusiones del plan de beneficios en salud", in *Revista de la Facultad de Derecho y Ciencias Políticas*. ISSN: 2390-0016 (online) / Vol. 49 / No. 130 / PP. 102 - 124 January - June 2019 / Universidad CES, Medellín, Colombia.

[6] This is not the only criteria. Other criteria to be taken into account include equity (give more to those in a disadvantaged situation), inter-generational justice (not jeopardizing the welfare of future generations through unlimited indebtedness) and sustainability (not jeopardizing a country's economic stability). Having said that, there is ample consensus that resources should be allocated efficiently.

[7] Gains can also be measured in life years gained, disability-adjusted life years (DALY) avoided, etc.

[8] There are other interpretations of the cost-effectiveness threshold. The definition we use here is consistent with the methodology used to estimate it: the elasticity to expense of health gains.

[9] We use laboratories' primary sale transactions to avoid double accounting.

[10] Pricentric data for Colombia were obtained through an agreement between the IADB and Tufts University.

[11] https://www.gov.uk/government/news/high-cost-drugs.

[12] We found no economic studies at the Tufts registry for elosulfase alfa, idursulfase, galsulfase alglucosidase alfa and imiglucerase, which are in the first, third, fourth, sixth and seventh position in the highest cost per treatment per year ranking of drugs. This suggests that there are no economic studies available for these drugs that have not been financed by the industry and meet the quality standards of the CEA Registry.

[13] The costs of application, complications and secondary effects comprise a very low share of total treatment costs, which means this assumption should not significantly impact our main conclusions.

[14] There are five products registered in Invima as bevacizumab but with no indication "on the label". However, according to the Health and Social Protection Ministry's Usos No Incluidos en el Registro Sanitario (UNIRS, Uses Not Included in the Health Registry) of November 5, 2021, bevacizumab is approved for the use in the "Treatment of adult patients with macular degeneration". UNIRS is a mechanism used by the ministry to approve the *off-label* use of certain drugs.

[15] A biosimilar to liraglutide is expected to enter the world market toward 2023. The existence of a biosimilar or generic competition was verified with the FDA's *Purple Book*, Drug Bank and the Generics and Biosimilars Initiative (GaBI). Saxenda has another branded drug with the same active ingredient and the same presentation but it only has an authorized record for weight loss, and both have similar prices.

[16] Tansgrud, S. E. and Halvorsen, S. (1989), "Child Neuromuscular Disease in Southern Norway". *Acta Pædiatrica*, 78: 100-103. https://doi.org/10.1111/j.1651-2227.1989.tb10894.x.

[17] Updated with DANE 2018 population information database and prevalence obtained from Rodríguez, F., Vergara, O. and Ocampo, H., "Guías de manejo de la degeneración macular relacionada con la edad - neovascularización coroidea". 2. 2009;42:128–49.

[18] Consulted at https://www.orpha.net.

[19] To select the drugs for analysis, we considered not only the individual cost but also the budgetary impact. This explains why pembrolizumab ends up with a lower annual cost than its comparison.

[20] Abatacept and liraglutide data is from 2020 deflated to 2021, because we could not find information for them or their comparisons for 2021. We deflated using the pharmaceutical products index.

[21] Treatment durations used for this study go from one year through the patient's remaining lifetime, depending on the drug, and is subject to the time frame analyzed in the clinical study (see Annex 3). The figure is expressed in net present value.

[22] The cost of palliative care was estimated based on the ratio found in the studies between the cost of the drug and that of standard care; that ratio was multiplied by the cost of the drug in Colombia.

[23] The costs of plasmatic factor VIII and its comparison, as well as those of abatacept and its comparison, were calculated based in the sufficiency database, since they are drugs financed with UPC resources.

[24] The cost of systemic therapies was estimated using the cost ratio included in Beilman *et al*., (2016) and the treatment value per person observed in MIPRES.

[25] The cost of systemic therapies was estimated using the cost ratio included in Beilman *et al*., (2016) and the treatment value per person observed in MIPRES.

[26] The cost of palliative care was estimated based on the ratio found in the studies between the cost of the drug and that of standard care; that ratio was multiplied by the cost of the drug in Colombia.

[27] The costs of plasmatic factor VIII and its comparison, as well as those of abatacept and its comparison, were calculated based in the Sufficiency database, since they are drugs financed with UPC resources.

[28] These values were obtained by multiplying the number of people in each treatment by the annual cost differential. The same operation was conducted to obtain the QALY. The total number of beneficiaries is the sum of the people who receive each treatment, assuming that no person presents more than one of the conditions we analyze.

[29] The gains in QALY are not strictly commeasurable because not all studies use the same time frame. Even so, the addition provides an approximation to the QALY obtained in the aggregate.

[30] The exception is lenalidomide, which may reflect a conservative estimation of the number of individuals ineligible for transplantation, or the drug's utilization in patients who are transplant candidates but opt for treatment with the biological product preferred by the physician or the patient.

[31] For example, for nusinersen –with an expense of COP 27,800 million– we found that, on average, patients who were given this drug did not even reach three doses during a year, when the prescription schedules four loading doses during the first 63 days and one maintenance dose every four months afterward. However, clinical practice guidance recommends suspending treatment if certain effectiveness goals are not reached.

[32] Corresponds to drug lenalidomide (25 mg), solid presentation for oral application.

[33] Corresponds to drug metformin and glimepiride (4 mg), solid presentation for oral application.

[34] Prior experience of the authors who have participated in price regulation processes.

[35] The relevant market for lenalidomide in this calculation is 25 mg, solid presentation for oral application.

[36] We used the same procedure with data from the sufficiency database. However, the spending per patient per year found in that database was always below the one recorded in the MIPRES database.

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