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Universal Social Protection for Catastrophic Diseases in Argentina: A Policy Simulation

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INTRODUCTION

There are some diseases that affect fewer people but require a significant share of the health system's resources. They are called Catastrophic Diseases (CD) because of their economic impact on the patients and those on whom the financial burden falls (patients, families, and the health system). There are several studies that have described the consequences and distinctive features of these pathologies.[2]

In Argentina, The National Survey on Health Spending and Utilization, 2010, estimated that approximately 6 percent of households have health expenses that exceed 34 percent of their income. However, the economic impact is even greater for the health system as a whole and for health providers who have to finance medication and health services to cover CD, either due to legal obligations or judicial decisions.

It is possible to identify at least six different types of financing and coverage for CD in Argentina (Tobar, 2010b). However, even though the affected find answers in the health system, these responses are fragmented and inequitable.

Against this, our hypothesis is that the creation of a National Insurance for Catastrophic Diseases (NICAD) would allow universal coverage and homogenizing protection against these diseases at a lower cost.

This policy option may face the challenges of economic sustainability, quality, and care equity that the coverage of these pathologies generates for the health system. In this context, our initiative aims to generate evidence to support the creation of the NICAD by demonstrating its technical feasibility and economic efficiency.

For this purpose, this policy simulation first defines and describes the main features of CD. Second, it identifies types of coverage and financing CD in Argentina. Third, it briefly presents experiences from other countries. Fourth, it describes a set of policy options for the coverage of these diseases. Fifth, it justifies why the creation of National Insurance is the most appropriate policy option in the Argentinean context. Sixth, it selects a set of pathologies to be covered, calculates total cost per pathology (medication and treatment per patient, per year), and estimates the cost of implementation of the NICAD. Finally, it simulates its implementation in four alternative scenarios, each with different strategies for lowering spending, specifically on medication.

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[2] Tobar, F. (2010 a). "¿Qué aprendimos sobre la cobertura de enfermedades de alto costo?", in Tobar, F. *¿Qué aprendimos de las reformas de salud?*, Buenos Aires, Ediciones Fundación Sanatorio Güemes; Xu, K. et al. (2003). "Household catastrophic health expenditure: A multicountry analysis", *Lancet* 362, No. 9378; Xu, K. et al. (2007). "Protecting households from catastrophic health spending", *Health Affairs,* 26, No. 4; Wyszewianski, L. (1986). "Families with catastrophic health care expenditures", *Health Service Research,* December, United States; Aedo, C. (1996). "Los problemas de salud del adulto mayor y las enfermedades catastróficas", en *Estudios Públicos,* No. 63, Chile; Beebe, J. (1988). "Medicare reimbursement and regression to the mean", *Health Care Financing Review,* No. 9, United States; Fondo Nacional de Recursos (2010). "Política y gestión de la cobertura de medicamentos de alto costo", *Publicación Técnica ,* No. 13, Montevideo, Uruguay.

Since there is no similar study in Argentina, outcomes and results of this policy simulation and costing exercise are innovative and a very useful input for decision-makers.

WHAT ARE CATASTROPHIC DISEASES?

There is a limited set of low-prevalence but high-cost diseases which require increasing amounts of resources. They are called catastrophic diseases (CD) due to the economic impact on the patients and those who finance their treatment (patients, families, and the health system).

Beyond its formal definition, these diseases share certain characteristics that distinguish them from other diseases and therefore require a special approach.

The literature highlights the following features of CD. It shows the negative economic impact that these diseases may cause and how they affect the sustainability of health systems.
- They involve high-cost treatments. From an epidemiological perspective, these diseases are not a priority because of their low prevalence. Yet, from an economic point of view, they involve high-cost treatments that exceed the threshold considered normal. They have a deep impact on household budgets, driving them to financial insolvency and, therefore, poverty. Ke Xu defined catastrophic diseases as those whose treatment involves a direct cost equal to or greater than 40 percent of household income (Xu, 2003). This definition was then used by the WHO and by various studies (Wyszewianski, 1986). One of them, based on national household expenditure surveys from 89 countries (which represent 89 percent of world population), concludes that about 150 million people each year undergo a catastrophic impact on their household budgets for those (their relatives or themselves) suffering from diseases that require expensive treatments. Of these, about 100 million fall below the poverty line, and within these, 90 million live in developing countries (Xu, 2007).
- They have a different expenditure curve. The usual expenditure for people with a particular disease shows the phenomenon of regression to the mean: they spend more in the first year and less in later years. The evolution of catastrophic diseases is extremely slow, and this behavior is termed "slow reversion to the mean" (Beebe, 1988). Although these diseases require highly complex procedures to diagnose and/or treat, drugs are usually the main component of the high expenditure: not only because of their high cost, but also because it is a chronic requirement.
- Households are unable to finance them. From a financial perspective, it is unthinkable that this expenditure can be covered by patients' finances; yet, other sources of funding may become a potential threat to the financial sustainability of the whole system.
- It is a problem that affects both rich and poor (Xu, 2003). There is a mistaken belief that these diseases are more prevalent in developed societies and, therefore, have low priority in the public agenda of developing countries. However, the evidence gathered from cross-sectional studies shows that household expenditure on health

is affected by catastrophic diseases much more in low-income than in high-income countries (Padrón, 2003).

- There is a trend toward increasing catastrophic expenditure in health systems. The reason for this rests on the high rate of innovation prompted by these diseases. They are a profitable opportunity for drugs research and the development sector.
- Within the catastrophic expenditures, a group of high-cost drugs (HCD) is the main component. The mere use of these drugs transforms a disease into a CD. They create a growing market across the world in terms of quantity, but much more so in turnover. The average price of these drugs also tends to rise, and there is a significant inelasticity of price in the demand. These drugs represent the weakest point in health systems as they absorb increasing portions of their resources.

Hence, this set of diseases that involves expensive treatments and HCD begins to influence the sustainability of health systems. Its growing economic weight requires public policies and strategies to manage coverage increasing expenditure and to reduce inequality in treatment.

Due to their unique characteristics, these diseases constitute a conundrum that could increase the inefficiencies and inequities of health systems. In this sense, the State's inaction would generate, on the one hand, an inefficient allocation of the financial resources available for health and, on the other, unequal and inadequate treatment to patients due to the financial implications of those treatments.

HOW ARE THESE CATASTROPHIC DISEASES COVERED IN ARGENTINA?

In Argentina, CD coverage is low and heterogeneous. It is not precisely defined in the Compulsory Medical Program (PMO by its acronym in Spanish) that establishes the healthcare obligation of Private Medical Insurances and National Social Insurances (NSI). Meanwhile, the provincial health ministries try to tackle the demands of patients with catastrophic diseases (only for those who have no formal insurance), but they do so in isolation and in a disjointed manner. In all cases, the financiers suffer the impact of treatment these diseases, mainly due to the high cost of the drugs involved.

In this context, at least six different types of financing and coverage of CD are currently being implemented in Argentina.[3] They are briefly described here.

National Social Insurances
National Social Insurances (NSI) are tied to formal employment and are funded by contributions from employees and employers (3 percent and 6 percent of payroll, respectively). Currently, there are around 300 NSI in Argentina, responsible for the coverage of almost 18 million people.

Even though it is mandatory for them to cover a minimum package of medical health services, i.e. the Compulsory Medical Program, this plan does not explicitly define most of the coverage related to CD.

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[3] This section is based on Tobar (2010 b).

Although the total number of people covered by these insurances is very high, not all the insurances can put together an adequate risk pool to cover CD.[4] In this context, the Special Programs Administration (APE by its acronym in Spanish) was created in 1998 to confront this financial problem and compensate the significant costs generated by these diseases. The APE was a national decentralized agency that administered subsidies to NSI.[5]

Theoretically, the APE acted as a reinsurance of CD for these institutions. However, these subsidies in fact were not based on defined rules, nor automatically delivered. In part, this lack of transparency, and the conflicts that were built around it, encouraged the recent changes in this program.

Lately, the APE was absorbed by the Superintendency of Health Services (SSS by its acronym in Spanish), which duties are temporary and primarily for ensuring proper monitoring and enforcement of the essential functions of the State, and to achieve efficiency in public administration (Decree 1198/12). The Decree also sets a deadline (90 days) for the SSS to submit a proposal for the Agency's organizational structure. This can be an opportunity to implement new social protections against CD.

Provincial Social Insurances
There are 24 Provincial Social Insurances (PSI) in Argentina. Together they cover around 6.4 million people and their members pay a monthly contribution for coverage. As they are not clustered in a single regulatory framework; these insurances have different regulations and different characteristics regarding to size, levels of contribution,[6] financial solvency, and type of coverage provided.

In order to provide medical services associated with CD, as well as high- cost drugs, these Provincial Insurances recruit medical services and set up agreements with pharmacies and laboratories (drug stores). However, in addition to their monthly contributions, patients often also have to pay for access to medical care and drugs required for CD treatment.

Besides, the Provincial Social Insurances are constantly forced to comply with judicial pronouncements and, therefore, to expand their coverage.

Federal Health Program
The Federal Health Program (PROFE by its acronym in Spanish) was created to ensure healthcare coverage to non-contributory pension beneficiaries. Although it is a national program under the Ministry of Health of the Nation, its implementation is provincial.

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[4] On the one hand, there are 32 social insurances that have at least 100,000 beneficiaries each (together they cover more than 76 percent of all NSI beneficiaries). On the other hand, there are 95 social insurances with fewer than 5,000 beneficiaries (Superintendencia de Servicios de Salud - Superintendency of Health Services).

[5] APE's resources came from the Solidarity Redistribution Fund. These resources were allocated to subsidies distribution to finance high-complexity services and medications.

[6] Wage contribution levels differ from one PSI to another. While in Chubut the provincial insurance requires 7 percent of payroll, the local social insurance in the City of Buenos Aires requires 14 percent of payroll (Tobar, F. 2010 b).

As two-thirds of beneficiaries enter this program when they receive a disability certificate, this program has a higher incidence of CD than among the general population. About 3 percent of PROFE beneficiaries suffer from CD. Therefore, medical care of these diseases involves three-quarters of the program's budget.

To address this situation, the program incorporated a reinsurance mechanism for catastrophic diseases, called High Cost and Low Incidence Program (PACBI by its acronym in Spanish).[7] In addition, the program hires --from the central level and directly from suppliers--other high-cost care services to ensure equal coverage in terms of access and quality.

Private Medical Insurances
There are more than 500 Private Medical Insurances that provide coverage to about 6 million people. However, due to supply contracts that these insurances establish with the medical companies, about 75 percent of them (4 million) come from National Social Insurances. They are funded by fees provided voluntarily by families or companies.

The law (24.754) requires private medical companies to ensure coverage of the Compulsory Medical Program (PMO). They are also permanently under pressure from their members and constantly forced to comply with judicial pronouncements to expand coverage vertically.

Like the Social Insurances, most Private Medical Insurances do not have their own medical services. Therefore, they set up agreements with private suppliers to provide care to beneficiaries. Meanwhile, the provision of drugs is organized through agreements with pharmacies and specialized laboratories. Thus, they can access to list prices and negotiate reduced rates.

Again, as in Social Insurances, the beneficiaries pay a monthly fee to Private Medical Insurance, but often depending on the plan they adopt, they also have to pay for the medical services. Usually, this does not apply to high-cost drugs. In most cases, CD drugs are funded entirely by private insurances.

Public Health Programs and Services
Aside from these models, Argentina has vertical programs from the National and Provincial Ministry of Health that are also oriented to providing and financing healthcare for CD.

These programs centrally purchase drugs and supplies and then transfer them to provincial ministries and/or to the local services referents for the treatment of such diseases.

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[7] The PACBI is constituted through the retention of a monthly per capita contribution that the Department of National Medical Benefit transfers to the provinces. It only disburses the corresponding refunds once the province provides documentation that proves effective healthcare provision for CD.

The National Ministry of Health receives funding from the National Central Budget and acquires the necessary drugs and supplies through public purchases. Then, the providers hand them over to the provincial ministries who further distribute them amongst the hospitals. Some provinces also acquire them through public purchasing to complement purchasing from the national government.

Direct payment to households
Patients suffering from CD and their families also make direct payments towards health services and drugs.

Preliminary results from the National Health Expenditure based on the Metropolitan Area of Buenos Aires establish that 6.02 percent households spend around 34 percent of household income on health (Tobar, 2012).

EXPERIENCES AND LESSONS LEARNED FROM OTHER COUNTRIES

Catastrophic Diseases are a concern all over the world. In this context, some Latin American countries have begun to implement public policies against CD.

Although most Latin American countries have addressed the problem of CD from within their public policy agenda, Uruguay is probably the most outstanding case. The National Resources Fund in Uruguay, created in 1980, has gradually become a national CD insurance that (a) provides universal coverage to these low-incidence, high-cost pathologies, (b) accredits providers, and (c) defines and monitors treatment protocols for these diseases, ensuring that all citizens receive the same healthcare.[8]

Meanwhile, in Chile, private insurances contribute to a fund for reinsurance against CD. However, the most important response in Chile has been the policy of Explicit Health Guarantees (EHG). As part of this policy, a group of pathologies has been protocolized (most of them catastrophic) in order to provide equal access and quality protection to the different population groups. To achieve this, the state subsidizes the provision of EHG for low-income populations.

In Brazil a set of high-cost diseases was also positively discriminated. This began with HIV/AIDS, but later coverage was extended to a broader set of pathologies whose funding remains the State's responsibility. This enables centralized purchase of HCD and economies of scale. As a result, universal coverage for a number of CD (such as chronic renal failure, HIV, Gaucher disease, immunosuppressed, etc.) has been achieved. This universal insurance follows protocols for diagnosis and treatment. These CD are not covered by private health insurances because coverage is guaranteed by the State.

In Colombia these diseases were not part of the Compulsory Health Plan. Therefore, the institutions in charge of health protection (Health Promotion Entities [HPE]) may request the Solidarity and Guarantee Fund (FOSYGA) for a refund for CD coverage. This

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[8] Law No. 16.343. *Highly specialized medical institutes*. Published on January 11, 1993. Uruguay.

went against social security sustainability. As a result, the health reform act (Law No. 1438, 2010) included a set of measures related to CD coverage, such as the creation of an Institute for Health Technology Assessment, a review of the Compulsory Health Plan, and the introduction of a special regulatory regime for biotech and high-cost drugs.

PUBLIC POLICY OPTIONS FOR THE COVERAGE OF CATASTROPHIC DISEASES[9]

In Argentina, the degree of inequality in CD coverage and its increased economic weight requires adequate public policy implementation.

It is possible to distinguish a set of policy options to promote protection against CD. The following are four public policy alternatives with different capacities to reduce catastrophic expenses:

Diagram 1. Public policy options for the coverage of Catastrophic Diseases
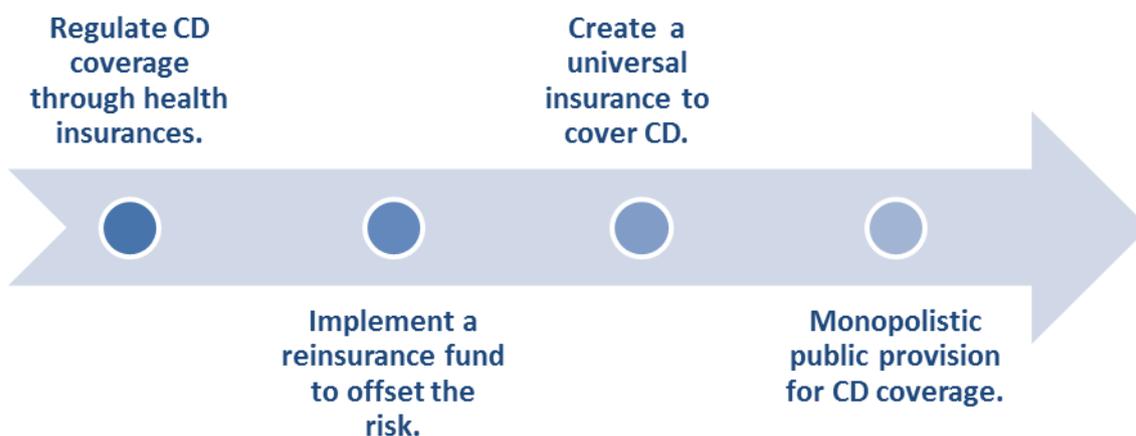
Regulate CD coverage through health insurances

Insurance is a mechanism to reduce uncertainty by transferring the risk of casualty to a third party who therefore receives a payment in advance. The sustainability of the insurance requires assembling a group of insured people so that individual risks are consolidated into a set or pool of risk.

There are three key conditions to ensure a proper risk pool: the number of people insured; the cost of diseases (treatment and drugs); and the incidence of the pathologies. The greater the number of people covered, the lower the incidence and the higher the costs involved, the better the performance of the health insurance as a social protection mechanism (Martínez, 2010).

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[9] This section is based on Tobar (2010 b).

The limitations of this policy are that it achieves universality only if the coverage of health insurance does; it is difficult to achieve equal and quality protection among the different insurances; the vertical expansion of the coverage tends to occur more often due to judicial proceedings than to healthcare decisions; and, it is hardly sustainable if an adequate risk pool is not achieved.

Implement a reinsurance fund to offset the risk

This mechanism allows the insurer to transfer part of the risks taken and reduce its possible loss. In other words, it is an insurance hired by an insurer. It is enforced by regulating the operation of health insurance: they are forced to cover healthcare for CD, and are required to contribute to a reinsurance to cover catastrophic expenses.

The advantage of this instrument is that it solves the lack of an adequate risk pool, because the reinsurance, by grouping several insurances, creates the conditions for a proper operation. Its weaknesses are that, on the one hand, it increases the transaction costs, and, on the other, it does not include mechanisms to rationalize and control catastrophic spending.

Create a universal insurance to cover CD

From the perspective of insurance, this alternative involves exempting health insurance from covering the risks associated with CD, as these pathologies would be universally covered by public insurance.

In this case there would be no refund to funders. Instead, goods and healthcare services for these diseases will be provided by a new, non-state public entity. This entity will certify providers, hire services, centrally purchase medicines and supplies, define healthcare protocols, and audit results.

This proposal is based on the model of the National Resource Fund of Uruguay. In this document, this policy option will be investigated and promoted.

Monopolistic public provision for CD coverage

This public policy involves the provision of goods and services related to CD coverage directly from the State, rather than delegating care to private providers. This is a vertical integration model, because the State is the one that provides, finances, and standardizes care. Its implementation requires the use of public health services and the centralized purchase of HCD and supplies needed for CD coverage.

This model allows economies of scale and enables the delivery of health services according to the needs of the population (previously defined in accordance with health criteria). However, its performance has the same restrictions that affect public healthcare services: lack of incentives and sanctions to ensure both access and quality.

WHY SHOULD A UNIVERSAL INSURANCE TO COVER CATASTROPHIC DISEASES BE IMPLEMENTED?

A universal insurance to cover CD would permit positive discrimination to explicitly approach catastrophic pathologies. This alternative involves exempting healthcare insurances (Private and Social Insurances) from covering risks related to catastrophic diseases. By contrast, these pathologies would begin to be universally covered by the new public and unique insurance (NICAD) that will be able to prioritize treatments and implement mechanisms to ensure and verify their performance.

This strategy would permit an increase in access to health services in a sufficient, appropriate, and timely manner; ensure the quality of services for all; increase the predictability of expenditures; and facilitate the regulation of the health services provided. As a result, this universal insurance would help to solve both efficiency and equity problems simultaneously: efficiency, because it could rationalize the expenses, and equity because it could help ensure access to and quality of healthcare for the entire population.

The aim of this mechanism is not only to cover all the inhabitants. It is also intended to verify that health services are provided in a proper form (it explicitly guarantees a healthcare protocol for the citizen). This way, the strategy also solves the problems of the variation in the quality of health services provided.

Essentially, NICAD promotes a universal response that will consolidate the right of every inhabitant of Argentina to get proper assistance against CD. In addition, this proposal fulfills the following requirements, which makes it the best choice in the Argentinean context:

- Effectiveness: it is based on evidence-based medicine and its progress, reducing variability in clinical practices, and implementing provision models that are adequate to needs.
- Efficacy: it regulates the shift from demand of goods and services towards an adaptation of provision of sanitary to the needs of the population.
- Efficiency: it creates an adequate risk pool and economies of scale in the acquisition of high-cost drugs and the hiring of high-end medical services.
- Equality: it may improve equality in the system through the provision of similar healthcare services, regardless of income level or the type of coverage of the patient.
- Financial sustainability: the generation of a risk pool that fits the coverage of these diseases constitutes a more efficient response than individual ones.
- Gradual evolution: Progressive incorporation of population (horizontal coverage) and protections (vertical coverage).
- Quality: it may achieve more equal, adequate, and secure healthcare services.
- Sustainability: It incorporates population and protection in a progressive way. Once results, in terms of efficiency, are achieved, it may extend coverage and contain costs.

Creating an insurance that covers CD involves setting up a social or public institution that acts as the single purchaser of goods and services related to these diseases. It

requires relying on stable funding sources, whether social contributions or fiscal resources.

The instrument to implement this policy option will be a Federal CD Fund, whose function will be to finance highly specialized medical services with proven effectiveness. This Federal Fund will allow the entire population of the country equal access to specialized health services, and will ensure that procedures are carried out under conditions of economic and financial sustainability. The Fund will receive contributions from the National Ministry of Health and from other social and private insurances. For these latter, adherence will be voluntary and contributions will be based on the number of people under its coverage.

This funding model, through stable and independent sources, will avoid the use of additional payments which act as a barrier to health access and which drive patients and their families to financial insolvency and eventually to poverty.

The implementation of NICAD must be done in stages. The ultimate aim is to achieve universal coverage, but the work should start from the public sector to prioritize access and coverage of those who currently have no formal coverage (Social and Private Insurances) or are insured by the Federal Health Program (PROFE).

Second, it should attempt to progressively integrate Provincial Social Insurances (PSI) and their beneficiaries into the National Insurance scheme. This way, coverage will move toward a more universal and homogeneous model. Thereafter, NICAD and the Federal Fund will be consolidated. Each type of coverage must contribute to this Fund according to the number of people it covers.

Third, it should permit National Social Insurances and Private Medical Insurances to join NICAD. Although this will not be mandatory, it would be desirable as they would get equal coverage for their catastrophic patients at a lower, more stable and more predictable cost.

Diagram 2 summarizes the NICAD operating scheme.

Diagram 2. National Insurance for Catastrophic Diseases (NICAD): Operational Scheme
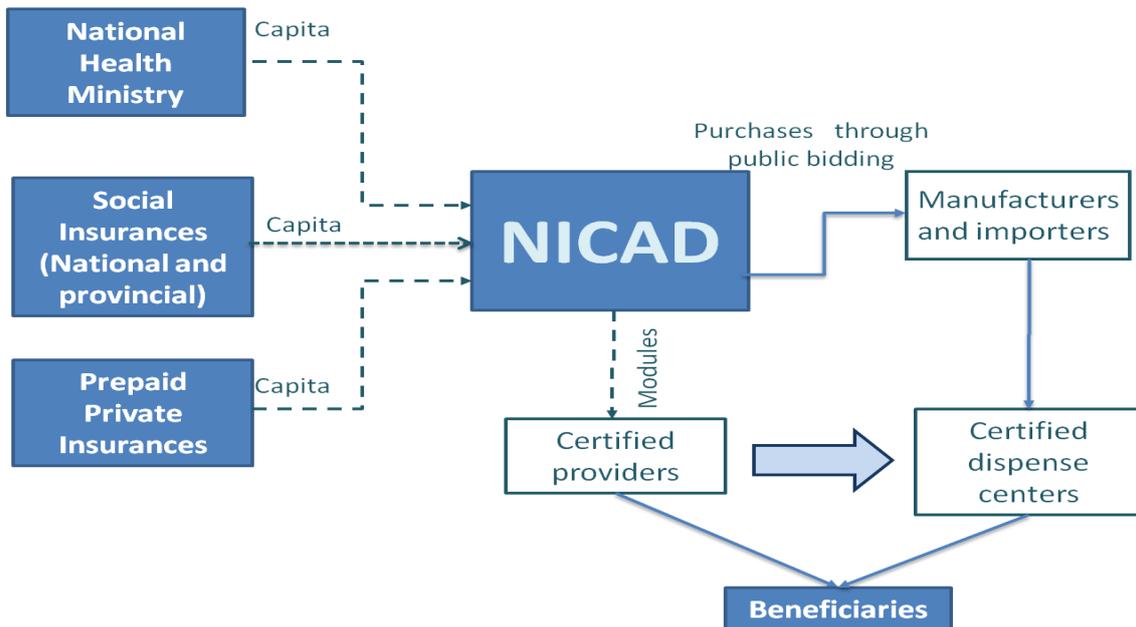
ALTERNATIVE SCENARIOS FOR THE IMPLEMENTATION OF NATIONAL INSURANCE FOR CATASTROPHIC DISEASES

After evaluating different strategies to address the problem of CD, and once the most adequate public policy option in the Argentinean context is selected (Universal Insurance), it is appropriate to evaluate its feasibility and efficiency, both in economic and financial terms.

For this purpose, we calculate total cost per pathology (medication and treatment per patient, per year) for a set of pathologies, and estimate the cost of implementing this National Insurance. We then analyze alternative scenarios of implementation of NICAD. Each scenario involves different cost-reducing strategies.

Methodology
To calculate the expenditure on the operational costs of the NICAD, we first chose a set of pathologies to cover. Second, we analyzed and selected treatment protocols for those diseases. We then estimated the annual average cost for each pharmacological treatment.

The simulation focused on pharmacological treatment because it is the main component of costs and best explains the increase in CD treatment prices. Finally, we included costs for diagnosis and medical services.

1. Selection of pathologies to be covered in the first stage of NICAD

After discussions with several stakeholders,[10] we made a list of pathologies to be covered by the NICAD in its first stage: Gaucher's disease, Fabry disease, Pompe disease, Crohn's disease, cystic fibrosis, diseases with growth hormone treatment and treatment of chronic renal failure (CKD), post-transplant immunosuppression, HIV/AIDS, hemophilia, multiple sclerosis, multiple myeloma, tumors in the central nervous system, hepatitis C, leukaemia and gastrointestinal stromal tumor (GIST),and breast, kidney, and colorectal cancers.

2. Evaluation of available treatment guidelines for the CD chosen

From both national and international sources, we have identified treatment protocols and guidelines available in different governmental web pages, as well as agencies for health technology assessment and clinical epidemiology. Some are worth mentioning: National Institute for Clinical Excellence in England, United States Preventive Task Force Services, and Canadian Task Force Services.

Additionally, we went through open access and restricted journals, such as the *New England Journal of Medicine*, *Journal of the American Medical Association*, *The Lancet, Journal of the American Family Association* and *British Medical Association,* catalogued publications at Medline, LILACS, and OVID. We have also analyzed the systematic reviews and the meta-analysis available at the Cochrane Collaboration.

The information on incidence, prevalence, morbidity and mortality, follow up, treatment, and complications of health issues was obtained from different web pages and statistical departments of different countries, as well as from international organizations (WHO/PAHO), patients, and the resources of medical institutions. Although most of the information can be found in the bibliography of this document, some other estimations were needed to complete missing data: e.g. distribution and incidence of choice of treatment for those diseases with more than one alternative.

On the topic of treatment, these diseases involve recommendations with diverse degrees of scientific evidence. Certain pathologies require a single high-cost drug (HCD), while others may need more than one, as well as other drugs needed for treatment.

3. Determining the average annual cost of pharmacological treatment[11]

The estimation of the average annual cost was based on the unit cost of medication involved, and the average dosage recommended for each disease. In those cases where medication is related to the patient's weight, we used as reference a standard adult weight of 70 kilograms and with a body surface of 1.73 square meters. In the case of pediatric patients, the reference was a child of 30 kilograms and a body surface of 0.6 square meters. Data was processed and set up in comparative tables.

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[10] We held meetings with officials from the Ministry of Health and other public agencies, and with representatives of social health insurances and private companies.

[11] For this research, the benchmark price of diagnosis and medical services is from the Autonomous City of Buenos Aires (capital city of Argentina) and the Province of Buenos Aires. However, there may be price variability between regions.

Next, we describe the process undertaken to determine those costs:
a. We made a selection of medications involved in the treatment of each disease, when treatment includes several drugs.
b. We identified all commercial brands for each medication available in Argentina, the form (vial, pill or syrup) in which they were available, and their prices. In order to do so, we studied secondary sources: *Manual Farmaceutico Kairos* and *Alfabeta*. The prices of certain drugs were available from the pharmaceutical companies directly, since they were not available in the pharmaceutical manual. These included: Genzyme (Myozyme, Fabrizyme, Cerezyme), Roche (Pegasys, Transtuzumab), Lazar (Talidomida). However, we were not able to get information from Novartis (Imitanib) and Janssen-Cilag (Bortezomid) and had to resort to other published papers.
c. Determining price per unit and each form in which they were available. The unit was defined as vial, pill or syrup according to its form. Even though treatments often follow international units (IU), our unit was established by soliciting documents because cost data was mostly provided by purchasing departments.
d. Estimating the average cost of treatment. To make the estimate we have considered one year of treatment, regardless of the fact that many illnesses take up to two years, such as oncological pathologies, and all forms in which each drug is available. Within that, drug forms with a price update period of more than two years in the *Kairos* or *Alfabeta* manuals were excluded.
e. Calculation of extreme (low and high) costs of treatment. We took into account the lowest and the highest costs for available treatment in those cases where multiple forms of a drug were available.
f. Establishing a weighted average cost, low and high, for each pathology. We applied usage rates for each treatment scheme and their cost.

$$\text{Weighted average cost} = F_1 \times C_1 + F_2 \times C_2 + \ldots + F_n \times C_n$$

In this equation, F is the usage rate of a specific treatment, and C, the cost of that treatment.

Limitations of this method
The approximation of the total cost of the diseases was based on secondary sources, and the percentage of costs associated with drugs was fixed. In fact, we calculated the cost of all medications. For other services, the percentage was based on literature. For those cases where no information was available or was outdated by more than four years, the percentage was estimated with 50 percent approximation.

The definition of treatment schemes when estimating the pharmacological treatment costs and some high-cost services --such as dialysis in CKD and spinal cord transplant in leukaemia and multiple myeloma--was based on international recommendations and specialized bibliography (except for HIV/AIDS, hepatitis C, and chronic renal failure, which have specific protocols published by the Ministry of Health).

Table 1 describes the assumptions made for estimating costs per pathology.

Table 1. Assumptions made and limitation for each disease, 2011

Disease	Assumptions	Limitations
Gaucher	• An average patient weight of 45kg (average weight for 50 PROFE[12] patients is 42kg). • Price of medication was informed by Genzyme. • Highest cost component is medication: it was assumed at 85%	• Cost of treatment can be overestimated because price of medication was considered without any discount.
Fabry	• Number of cases match international bibliography. • Price of medication was informed by Genzyme. • Total cost of treatment was calculated considering that medication represents 50%.	• Lack of data on patients undergoing treatment. • Cost of treatment can be overestimated because price of medication was considered without discount.
Pompe	• As data on patients does not exist, an arbitrary number of cases was considered. • Price of medication was informed by Genzyme. • Total cost of treatment was calculated considering that medication represents 50%.	• Lack of data on patients undergoing treatment. • Cost of treatment can be overestimated because price of medication was considered without any discount.
Crohn	• It was assumed that 2% of patients need high-cost treatment: 2/3 using infliximab and 1/3 using adalimumab. • It was considered as public sector the total PROFE´s provision. • Medication represents 33% of the cost (27% for biological monoclonal therapies) and hospitalization represents 57% (Casellas, 2010).	• Lack of data on patients undergoing treatment.
Cystic Fibrosis	• Number of estimated treated patients: 1,000-1,500 (150 at Garrahan Hospital, 250 at Sor Ludovica, and 1,000 at all other hospitals). Between 1,000 and 1,200 patients would require treatment. • 45% of patients under treatment require tobramycin. • Total cost of treatment was calculated considering that medication represents 50%.	• Lack of a list of beneficiaries that allows an estimation of prevalence with low error.

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[12] Federal Health Program. The main objective of this program is to ensure healthcare coverage to non-contributory pension beneficiaries affiliated to PROFE.

Disease	Assumptions	Limitations
Treatments with growth hormone	• The number of patients to cover arises from considering that 48% of the population has public health coverage. • Total cost of treatment was calculated considering that medication represents 50%.	• Lack of a list of beneficiaries that allows an estimation of prevalence with low error.
Chronic Renal Failure	• Dialysis treatment and other services were considered.	
Chronic Renal Failure – CKD – post-transplant (Immunosuppression)	• Equal frequency for all treatments and with a single drug (no combinations) was assumed. • Total cost of treatment was calculated considering that medication represents 50%.	
HIV/AIDS	• The purchasing price for Ministry of Health was considered for first, second, and third-line schemes. • Total cost of treatment was calculated considering that antiretroviral medication represents 89% (Basombrio, 2003).	
Hemophilia	• Total cost of treatment was calculated considering: 85% in factors, 8% in medical consults, and 2.3% in other medication.	
Multiple sclerosis	• All patients will need treatment at some point. Interferon would be used in 80% of cases. • It was assumed that 50% of patients would be using REBIF NF and 50% Blastoferon. • Medication represents 40% of annual cost and hospitalization represents 35%.	
Multiple Myeloma	• Prices for talidomida (Lazar) and bortesomid (Janssen-Cilag) were sourced from laboratories and are retail prices. • Total cost of treatment was calculated considering that medication represents 50%.	• Cost of treatment can be overestimated because price of medication was considered without any type of discount.

Disease	Assumptions	Limitations
Tumors in nervous central system	• Incidence of bevazucimab with irinotecan because of unwanted response or recurrence in 10% of patients. • Total cost of treatment was calculated considering that medication represents 50%.	
Hepatitis C	• Interchangeability between both pegylated interferons available in the market was assumed. • Total cost of treatment was calculated considering that medication represents 50%.	• Lack of case registry.
Leukaemia	• We considered leukaemia in children and teenagers. It was calculated a dosage for children (30 kg or0.6 m2). • Total cost of treatment was calculated considering that medication represents 50%.	
GIST	• Price of mesilato de imatinib (Glivec) was obtained from the article by J. Chareau, "Medicamentos de Alto costo", published in August 2011. • Total cost of treatment was calculated considering that medication represents 50%.	
Breast cancer	• Price of trastuzumab was given by laboratories and is the retail price. • Total cost of treatment was calculated considering that medication represents 50%.	• Cost of treatment can be overestimated because price of medication was considered without any type of discount.
Kidney cancer	• Total cost of treatment was calculated considering that medication represents 50%.	
Colorectal cancer	• Total cost of treatment was calculated considering that medication represents 50%. In Spain it represents 53% of treatments with cituximab, and 22% of traditional treatments (Carnero Gómez, 2005).	

Results

The costing exercise enabled us to calculate total cost per pathology-- medication and treatment per patient, per year (Section 7.1)--and simulate the operating expenses of the NICAD in four alternative scenarios of implementation (Section 7.2).

7.1 Cost of each pathology in the current model

Table 2 presents the highest and lowest costs of the primary medication per pathology, and Table 3 shows the average annual cost of medication per patient, and the total cost of treatment per patient, per year.

Table 2. Selected Catastrophic Diseases
Highest and lowest annual cost for the primary medication per patient (US$), 2011

Pathology	Lowest cost	Highest cost
1. Gaucher	317.363	317.363
2. Fabry	245.024	245.024
3. Pompe	286.043	286.043
4. Crohn	49.162	226.341
5. Cystic fibrosis	46.536	53.070
6. Treatments with growth hormone	28.784	75.310
7. Chronic renal failure – CKD – dialysis	-----------	-----------
8. Chronic renal failure – CKD – post- transplant	4.808	193.561
9. HIV/AIDS	602	2.988
10. Hemophilia	513.636	675.362
11. Multiple sclerosis	102.220	114.233
12. Multiple myeloma	16.336	16.544
13. Tumors in the nervous system	19.130	45.055
14. Hepatitis C	20.748	28.101
15. Leukaemia	3.900	4.903
16. GIST	90.964	90.964
17. Breast cancer	13.839	23.490
18. Kidney cancer	153.794	169.377
19. Colorectal cancer	29.535	41.231

Source: CIPPEC, based on data from Genzyme and *Kairos* manual.

Table 3. Selected Catastrophic Diseases. Average annual cost of medication, and total annual cost of treatment per patient (US$), 2011.

Pathology	Average annual cost of medication	Total annual cost of treatment
1. Gaucher	317.363	373.368
2. Fabry	245.024	490.048
3. Pompe	286.043	572.087
4. Crohn	167.281	619.560
5. Cystic fibrosis	49.897	99.795
6. Treatments with growth hormone	57.039	114.078
7. Chronic renal failure – CKD – dialysis	----------	13.571
8. Chronic renal failure – CKD – post- transplant	22.658	45.315
9. HIV/AIDS	1.798	2.020
10. Hemophilia	479.314	563.899
11. Multiple sclerosis	108.078	216.157
12. Multiple myeloma	12.600	31.499
13. Tumors in the nervous system	65.652	131.304
14. Hepatitis C	24.404	48.809
15. Leukaemia	4.283	8.565
16. GIST	90.964	181.928
17. Breast cancer	18.240	36.479
18. Kidney cancer	163.133	326.266
19.Colorectal cancer	54.036	108.071

Source: CIPPEC.

In addition to drugs, some diseases require to consider two kinds of high-cost services. Table 4 presents average cost per patient, and total annual spending on spinal cord transplants (for acute linfoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia, and multiple myeloma) and dialysis (for chronic renal failure).

Table 4. Selected Catastrophic Diseases. Average cost per patient and total annual spending on spinal cord transplants of each pathology, and dialysis (US$), 2011

Transplant treatments	Patients under treatment	Average cost	Annual spending for all patients
Transplants			
Acute linfoblastic leukaemia	240	$ 20.000	$ 4.800.000
Acute myeloid leukaemia	113	$ 20.000	$ 2.260.000
Chronic myeloid leukaemia	105	$ 20.000	$ 2.100.000
Multiple myeloma	523	$ 16.459	$ 8.608.012
Dialysis			
Chronic renal failure	26.355	$ 13.571	$ 357.675.000

Source: CIPPEC.

Annexure 1 shows how this data was arrived at, per pathology.

7.2 Simulation of the operational spending of a National Insurance for Catastrophic Diseases (NICAD)

The information obtained from the costing exercise enabled us to simulate the operating expenses of the NICAD in four alternative scenarios of implementation.

The proposal relies on the following assumptions:

1. Universal insurance for the population of Argentina (40 million people) against the subset of catastrophic pathologies selected.
2. Cost reduction due to rationalization of facilities; incorporation of protocols for treatments, and economies of scale.
3. Additionally, savings will be made by choosing the cheapest therapy options (for those treatments where there is more than one price option).
4. Cost reduction by introducing economies of scale in hiring and acquisitions. Aggregated and centralized purchases could result in lower prices, even in cases of monopolistic products.

The most relevant factor in the construction of universal insurance for CD is medication. Taking this into consideration, four alternative scenarios were outlined in order to make a detailed analysis (the first assumption is maintained in all scenarios).

Scenario #1

In the first scenario, the insurance would reach universal coverage of the 19 diseases by extending the current model of Social Insurances and Private Insurances to the entire population.[13] That is, a model that does not introduce protocol definitions and reimburses treatments at retail prices.

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[13] According to the latest national census, Argentina has 40,117,096 inhabitants (National Population and Housing Census, 2010. INDEC)

At this initial stage, the National Insurance would spend US$ 3.210 million in medication (per year). This comes from multiplying unit costs --Table 3, first column-- and the estimated prevalence for each disease --Table 6, second column--. Total annual expenditure in medication per pathology for this scenario is presented in the third column of Table 6.

Scenario #2

This scenario assumed centralized purchase of all products. This should produce economies of scale and reduce intermediate costs.

In order to estimate the possible economies of scale, we extrapolated current laws from Brazil, where all public acquisitions require at least 24.69 percent discount on the price set by laboratories.[14] Although it seems to be a simplistic solution, such a discount on all medication is, according to previous studies, a sensible and realistic option.[15]

On the other hand, in order to estimate the reductions in intermediate costs, we relied on previous investigations that focused on the analysis of the components of medication pricing in Argentina. Our research showed that retail price equivalent to 151 percent of laboratory output price (ISALUD, 1999), or that the laboratory output price was equivalent to 66 percent of the retail price.

Simultaneously using both factors to adjust prices, the potential discount could be about 50 percent. Annual expenditure on medication per pathology in this scenario is presented in the fourth column of Table 6. As we can see, National Insurance would spend US$ 1605,20 million in medications (per year).

Scenario #3

For this scenario we considered VAT (21 percent) exemption in the price of high-cost drugs (HCD). This is possible by buying medications through international organizations (exempt from VAT), or by creating an appropriate legal framework that allows it.

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[14] "In Brazil, the current policy on price controls is carried out by the Medicine Market Regulatory Commission, which defines the price at which the products enter the market and the readjustments on them. In July 2007, the Health Ministry decided to guarantee a minimum reduction of around 24.69% in the Price of 146 products bought by the Single Health System SHS (directly by the Ministry or at the provincial or municipal level). Among others were included: those medications needed to treat Parkinson's Disease, Alzheimer, Multiple Sclerosis, Rheumatoid Arthritis, HIV/AIDS, Cancer and other diseases that require continuous use of drugs (additionally considering high cost 'exceptional' drugs, usually used for low prevalence diseases). In 2007, the SHS has spent around US$ 800 millions" (Cabral de Barros, 2008).

[15] From the analysis of 21 acquisition processes, it has been proved that by centralizing public expenditure of drugs at the national level, the National Government in Argentina gets discounts up to 90 percent on the market price (Tobar, 2011). This applies to generic drugs, in which competitive supply usually lowers prices.

This same paper analyzed the weight that involves competition on prices and it concludes that every time you double the number of providers, it could be obtained at a price 12.7 percent lower. However, as in this case they are monopolistic or oligopolistic medications, there is no significant scope for improving savings.

However, in another recent study (Tobar, 2012), it has been verified that in Argentina, high-cost drugs are sold at prices above those prevailing in other Mercosur countries. We could assume that centralized purchasing would allow both discounts and the cheapest prices. Thus, assuming a discount of 24.69 percent from the laboratory's starting price is therefore relatively conservative. However, it is convenient to assume this discount because the legislation in Brazil is based on extensive research of acquisitions, and because this benchmark has proved to be sustainable over time.

From a fiscal point of view, this involves the State reversing the collection of VAT included in these medications. Nevertheless, in this case it is a distorted collection. On the one hand because there is no moral abuse in the consumption of HCD, and on the other because Argentina is the second country in the world in terms of tax burden through medications (Table 5). In several Latin American countries, such as Peru and even Brazil, there are lists of protected high-cost drugs that are exempt.

To ensure that such savings will not be absorbed by the laboratories, this measure could be supplemented by the internationalization of drug purchase. This means purchasing through international competitive bidding, using control prices (witness prices) obtained from countries procuring at the lowest price.

Table 5. Tax burden applied to medications. Selected countries. 2011

Brazil	33,8
Argentina	**21**
Austria	20
Perú	18
Chile	18
Germany	16
El Salvador	13
Uruguay	12
Average - Latin America countries	**10,07**
Italy	10
Greece	7,5
Finland	7,5
Turkey	7,5
Belgium	6
Holland	6
Average- industrialized countries	**5,8**
Portugal	5
Japan	5
Paraguay	5
Spain	4
Switzerland	2,5
France	2
United Kingdom	0
Canada	0
Sweden	0
US	0
Nicaragua	0
Panamá	0
Colombia	0
Mexico	0
Venezuela	0

Source: CIPPEC.

The annual expenditure on medications per pathology for Scenario 3 can be seen in the fifth column of Table 6. As shown, in this case the National Insurance expenditure would be US$ 2536,10 million on drugs for catastrophic patients.

Scenario #4

In contrast to the previous three, this scenario gathers all the potential savings mentioned before. Therefore, to savings achieved through centralized purchasing (Scenario 2) and tax exemptions (Scenario 3), this scenario adds potential cost reductions through prescription and purchase rationalization.

For those treatments where there is more than one price option, this scenario considered the decline in spending by selecting the cheapest therapy options. This choice, combined with reductions achieved by economies of scale and exemption from taxes such as VAT, leads to the maximum savings scenario. In this case, the National Insurance would spend US$ 811,6 million in medications (per year).

Table 6 presents the estimated costs per pathology. It also shows annual spending on medication by NICAD in alternative scenarios. Finally, the last rows present, for each scenario, the annual and monthly per capita cost for the implementation of NICAD. This information is based on current dollar prices.

Table 6. Annual spending on medications by NICAD, per pathology.
Alternative scenarios (in million US$).

Pathology	Estimated number of patients	Annual spending in medications Scenario #1	Scenario #2	Scenario #3	Scenario #4
1. Gaucher	160	50,8	25,4	40,1	9,8
2. Fabry	85	20,8	10,4	16,5	6
3. Pompe	6	1,7	0,9	1,4	0,3
4. Crohn	320	53,5	26,8	42,3	4,6
5. Cystic fibrosis	1.200	59,9	29,9	47,3	16,2
6. Treatments with growth hormone	624	35,6	17,8	28,1	5,2
7. Chronic renal failure – CKD – Dialysis	26.355				
8. Chronic renal failure – CKD – post-transplant	1.880	42,6	21,3	33,7	2,6
9. HIV/AIDS	41.000	73,7	36,9	58,2	9,5
10. Hemophilia	2.100	1006,6	503,3	795,2	291,9
11. Multiple sclerosis	6.500	702,5	351,3	555	192,7
12. Multiple myeloma	1.600	20,2	10,1	15,9	5,8
13. Tumors in the nervous system	865	56,8	28,4	44,9	10

14. Hepatitis C	525	12,8	6,4	10,1	3,2
15. Leukaemia	3000	12,8	6,4	10,1	3,4
16. GIST	18	1,63	0,8	1,3	0,5
17. Breast cancer	18.717	341,4	170,7	269,7	75,1
18. Kidney cancer	750	122,3	61,2	96,7	33,5
19. Colorectal cancer	11.000	594,4	297,2	469,6	141,3
Total Cost		**3210,0**	**1605,2**	**2536,1**	**811,6**
Annual per capita cost	**40.117.096**[16]	**80,02**	**40,01**	**63,22**	**20,23**
Monthly per capita cost		**6,67**	**3,33**	**5,27**	**1,69**

Source: Developed by CIPPEC.

Briefly summarized, in Scenario 1, where universal insurance for the pathologies selected would be achieved by extending the current provision model of Social Insurances and Private Insurances, the National Insurance would spend US$ 3.210 million in medication (per year).

In Scenario 2, this cost would be reduced by 50 percent (US$ 1605,20 million) through centralized purchasing, and, in Scenario 3, the spending would decrease by 21 percent (US$ 2536,10 millions) with a tax exemption strategy.

Finally, Scenario 4 is the one that results in maximum savings. It not only takes into account all the previous savings, but also reduces costs by prescription and purchase rationalization. In this case, the National Insurance would reduce spending on medications by 75 percent (US$ 811,6 million). Thus, the cost of Scenario 4 is just a quarter of Scenario 1.

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[16] Total population, National Population and Housing Census, 2010, INDEC.

**Chart 1. Annual spending on medications by NICAD.
Alternative scenarios (In million US$)**
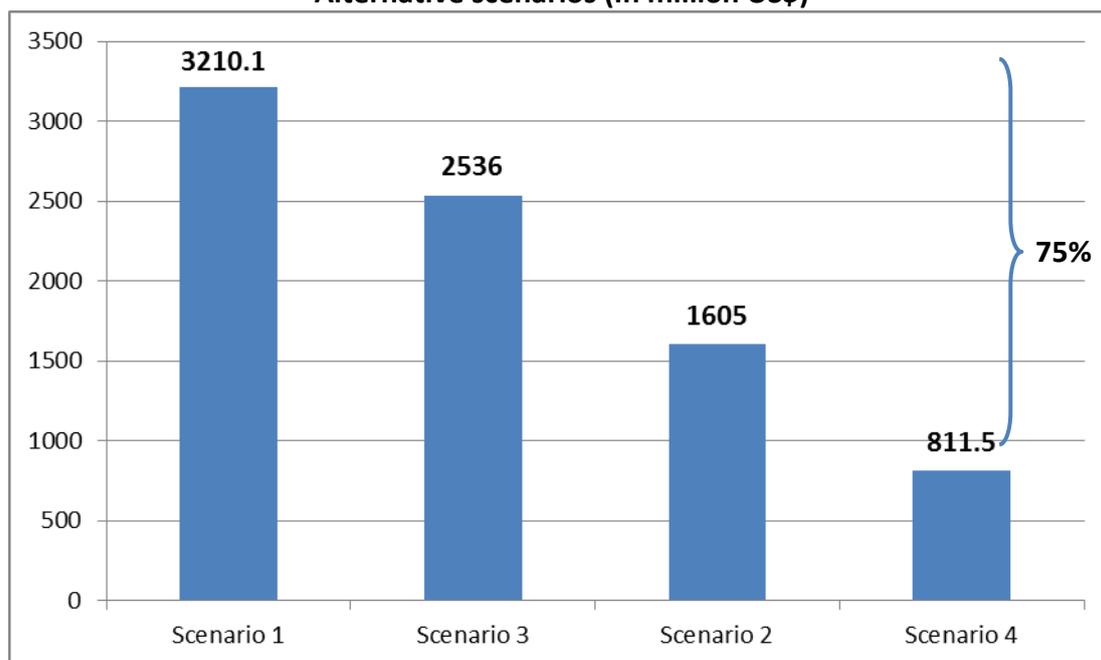
Source: Developed by CIPPEC.

CONCLUSION

Catastrophic diseases are a growing challenge for health systems as the high costs involved in their treatment affect the sustainability of systems. In a context of limited resources, this means that more resources are being allocated to these low-prevalence diseases at the expense of other healthcare interventions that reach a wider population.

As mentioned, there is no explicit and equal coverage against these risks in Argentina. There are only isolated and disparate answers. In this regard, National Social Insurances have a reinsurance system to finance CD coverage, but in fact it is not working as expected and is currently being revised. Private Medical Insurances are forced to cover these diseases through judicial pronouncements that constantly threaten their financial sustainability. Meanwhile, provincial health ministries try to meet the demands of patients with no health insurance coverage, but they do so in isolation and unsystematically.

Therefore, Argentina has a varied coverage against the risk of CD, but this is inequitable and unsustainable in the long term. In this context, National Social Insurances and Private Medical Insurances, that cover about 60 percent of the population (INDEC, 2010), are the most vulnerable from a financial perspective.

To address this policy challenge, this paper presents the National Insurance for Catastrophic Diseases (NICAD) as the most appropriate policy option in the Argentinean context. In this regard, the study shows that the NICAD would be able to solve both the equity challenge (in terms of access and quality), and the efficiency challenge (in terms of financial sustainability).

This document presents the benefits of the NICAD in alternative scenarios of implementation. Between Scenario 1, that represents the current coverage provided by the National Social Insurances and Private Medical Insurances, and Scenario 4, that includes all the NICAD benefits, the NICAD would be able to cut costs by 75 percent, especially on medication.

This means that if the NICAD operates at full strength, i.e. provides quality and equal coverage to the whole population, it will cost less than some current insurances (National Social Insurances and Private Medical Insurances). This is evident from the analysis of the monthly per capita cost: National Social Insurances and Private Medical Insurances currently pay US$ 6,67 per person, while the NICAD would reduce this cost to US$ 1,69.

These results indicate the technical feasibility and economic efficiency of this public policy option. In this sense, it is an important academic contribution and generates evidence for its potential implementation.

Nevertheless, it still remains to analyze its political viability. The Argentinean health system is fragmented; it is composed of a large number of actors, and is strained by conflicting interests. This technical contribution would surely be strengthened by other studies that focus on the analysis of the political viability of this measure.

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Annex 1. Details according to pathology

Gaucher Disease

This is considered a rare disease, mostly prevalent among the Ashkenazi Jewish population. It is caused by a deficiency of glucocerebrosidase. Its prevalence is estimated at 1 case per 250,000 inhabitants, and its incidence is 1 in 18 million people per year.[17] In the US[18] there are 20,000 cases of this disease, and 30,000 cases are estimated worldwide. In Argentina 300 cases are estimated, and 51 of them are covered by PROFE.

Patients are classified into three types according to signs and symptoms. Type I is the most common (about 90 percent of cases), and is the only one for which there is evidence regarding the effectiveness of treatment with imiglucerase.

Age of onset of symptoms is variable, from early infancy to adulthood, with cases that never presented clinical manifestations. By the most common mutation presentation, the average age of onset of symptoms is 30 years.[19]

For a patient weighing 70 kg and requiring a dose of 60 IU (30-60 IU), the average annual cost of treatment with imiglucerase (cerezyme from Genzyme) is US$ 423,150. Although this is the most frequently used dosage, the literature shows different positions in this regard. However, it is recommended that the lowest dose that controls symptoms is best.

An analysis of the population treated under PROFE reveals a cost of about US$ 230,000 per patient. This is because the average weight of patients treated is 45 kg. There are wide variations in treatment costs associated with small adjustments to clinical management. For example, if the dose is adjusted from 60 IU to 30 IU for a 70 kg patient, the annual cost would be US$ 211,000 against US$ 423,000 for a 60 IU dose treatment. This shows the importance of clinical variability, which is a fundamental component in the implementation of Catastrophic Illness Insurance.[20] The retail price of the product has been acquired from Genzyme since it is not published in the pharmacists' manuals for regular consultation in pharmacies.

Fabry Disease

This disease, caused by a deficiency of alpha-galactosidase A (Genzyme Fabrazyme R), is included within the group of inherited metabolic diseases of lysosomal storage.[21]
It is the second most common disease after Gaucher, with a prevalence of 1/17,000--1/11,7000 in Caucasian men.[22] Current life expectancy among afflicted males is around 48 years.

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As it occurs in most of the cases of rare diseases, there is a significant delay in diagnosis—an average of 14 years between the onset of symptoms and the actual diagnosis.[23] The treatment for this disease is agalsidase A and B. In children below 7 years of age,[24] the safety and efficacy of the treatment has not yet been established.

The average annual cost of treatment is close to one million pesos.

Pompe Disease

This is an inherited metabolic disease (autosomal recessive) that is extremely rare, included in inborn errors of metabolism.[25] It belongs to the group glycogenosis, diseases caused by deposition or accumulation of glycogen.

Its prevalence is estimated at 5,000-1,000 people,[26] an overall incidence of 1/40,000 live births, and 1/138,000 in classic childhood disease and 1/57,000 in late disease. The mean age at diagnosis is 4.7 months.[27]

The HCD used to treat Pompe disease is alpha-glucosidase A (MyozymeR Genzyme). The average annual cost of treatment is US$ 190,000.

Crohn's Disease

This disease, as well as ulcerative colitis, is also known as inflammatory bowel disease. Its cause is unknown and it has a chronic course. It peaks between the second and third decades of life, and again around 70 to 80 years. The prevalence varies in different countries.

Although Crohn's disease can be located anywhere from the mouth to the anus, most symptomatic patients can be classified into three anatomical groups:[28]
1. Small bowel disease only (30 – 40 percent)
2. Small intestine and large intestine disease (40 – 55 percent)
3. With colitis only (15 – 25 percent)

Between 50 and 80 percent of patients with the disease will require surgery at some point of its evolution.

High-cost drugs used for its treatment include infliximab and adalimumab for cases of severe illness and / or refractory to standard treatments[29] (5-sulfazalasina, mesalasina, corticosteroids, azathioprine, methotrexate). Both drugs are also used to manage diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic

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arthritis. The average annual cost of adalimumab is 4 to 6 times cheaper than infliximab (Table 1 A).

A Spanish study[30] has shown that drugs accounted for 33 percent of costs (27 percent by monoclonal biologic therapies), and hospitalizations for 57 percent (4,500 Euros per patient, per year).

Table 1 A. Crohn's disease. Average annual cost of primary medication. Argentina, 2011. (US$)

Drug	Trade name	Laboratory	Price in Argentina per Unit	Average Annual Cost
Infliximab	Remicade	Schering Pl	8.128 US$	950.632,2 US$
Adalimumab	Humira	Abbott	5.083 US$	206.479,2 US$

Source: Developed by CIPPEC based on prices and *Kairos* Manual and *Charreau* J. (High cost drugs, August 2011).

Cystic Fibrosis

Also known as pancreas fibrocystic disease, it is the most common autosomal recessive lethal disease among Caucasians.

Its prevalence is estimated at 30,000 (US), and its incidence is 1 in 2,000 or 3,000 live births and 1 in 30 healthy carriers.[31]

The age at diagnosis is around 2 years and life expectancy has increased notoriously in recent years, and stands now at 37 years of life. The two high-cost drugs for treatment are alpha dornase and tobramycin aerosolized.

Unlike alfa dornase, which is produced by one laboratory, tobramycin is produced in seven laboratories, thus making it a competitive market (Table 2 A). It is observed that the difference between the more expensive and less expensive treatment is 30 percent.

The annual cost of treatment with tobramycin was estimated at US$ 200,000 on average.

In 2010, eight laboratories produced the aerosolized form of tobramycin[32] (Table 2 A). But comparing 2010 with 2011, it was found that two laboratories no longer featured in the *Kairos* manual and three of them have not updated their prices over the past three years, suggesting that they are off the market. Consequently, this market turned uncompetitive in a year. Available forms are Tetrafarm, Teva Tuteur and LKM, which suffered a price increase of 13, 15, and 21 percent, last year. If we consider only the

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[30] Asellas, F. & Panés, J. y cols (2010). "Costes médicos directos de la enfermedad de Crohn en España", *PharmacoEconomics* - Spanish Research Articles, 7 (1): 38-46.
[31] Segal, Edgardo. (1999). Consenso de Fibrosis Quística. *Arch. Argent. Pediatr,* 97 (3):188.
[32] Tobar, F. (2011). "Medicamentos de alto costo en Argentina"- IEPS- Segundo Informe de investigación- Medicamentos & Salud- revisado el 15 de Mayo del en
http://www.apm.org.ar/es/cultura/ieps_2do_informe_medicamentos_y_salud.pdf-

cost of these three treatments, the difference between the more expensive treatment and the cheaper one is 23 percent. [33]

Table 2 A. Aerosolized tobramycin.
Different trade shows and annual cost of treatment in Argentina, 2011. (ARG$)

Trade name	Laboratory	Price in Argentina Pesos	Average Annual Cost of Treatment Pesos
		2011	2011
Pulmozyme	Roche	1.253	76.197
Alveoterol	Tetrafarm	40.659	265.010
Belbarmicina INL	Quim Luar	28.600	186.411
Pulbronkal	Permatec	24.098	157.067
Tobi	Teva Tuteur	50.016	325.997
Tobramicina Cassara	Cassara	29.400	191.625
Tuberbut	LKM	45.472	296.380

Source: CIPPEC's calculations based on data from *Kairos* manual.
Note (1): the unit price is calculated based on the price listed in the Kairos manual. It was considered the submissions of forms with 56 blisters. Only three laboratories have forms of 28 (Tetrafarm, Quim Luar, and DOSA). (2) The calculation was carried out based on 600 mg / day with 28 days' treatment, alternating with a break of 28 days.

Growth Hormone Deficiency
The growth hormone is produced by the pituitary gland and is essential for growth in children. Deficit leads to delayed growth.
Replacement therapy is promoted in the following clinical situations:
- Children with growth hormone deficiency.
- Children with idiopathic short stature (controversial).
- Chronic renal failure in children who have had a transplant.
- Turner syndrome
- Prader-Willi Syndrome

The deficit is a common cause of short stature in children. Up to 25 percent patients with three or more standard deviations below the mean for age are deficit in this hormone.[34]

Having defined such a deficit and the need for replacement therapy, the results should be re-evaluated periodically, and in cases of poor response, treatment should be suspended.

Based on the need for reassessment before continuing treatment, the treatment duration is variable, on average a period of 10 years.

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[33] Hamilton, G. (2011). "Enfermedades Catastróficas- Escenarios posibles para el gasto total en a Fibrosis Quística", Asociación de Economía de la Salud- Argentina.
[34] Analysis of the different presentations available from Human Growth Hormone. Available at www.iecs.org.ar

Somatotropin treatment is provided by six laboratories and the gap between the most expensive option is 2 to 3 times more than the cheapest (Table 3 A), with changes in the cost of treatment being between 73 and 180 thousand pesos/year, in consonance with the price in pharmacies.

Table 3 A. Growth hormone.
Trade names and average annual cost of treatment. Argentina, 2011. (ARG$)

Trade name	Laboratory	Average annual cost of treatment (Pesos) 2011
Biotropín	IVAX	136.445
Genotropin	Pfizer	164.073
Genotropin	Pfizer	164.073
HHT	Sidus	73.543
Hutrope	Eli Lilly	161.788
		161.781
Norditropin nordiflex	Novo Nordisk	154.855
		154.874
		154.873
		135.605
		135.654
		135.654
		135.654
Saizen	Merck Serono	186.474
Saizen 8 mg Click Easy		192.418

Source: CIPPEC's calculations based on the pharmacist manual *Kairos*.
(1) The treatment is based on units, some forms are in units and others are in milligrams (1mg = 3 IU). Prices are based on the *Kairos* manual, and treatment was evaluated for children with an average weight of 30 kg.

With regard to clinical variability, some professionals argue that the trademark used at the start of the treatment must be continued throughout, but there is limited scientific evidence that supports this.

Chronic Renal Failure
Chronic kidney disease (CKD) worsens slowly over time. There might not be any symptoms in the initial stages, and the loss of function usually takes months or years to occur. It might be so slow that symptoms do not occur until kidney function is less than one-tenth of the normal.

The final stage of chronic kidney disease is called renal disease (ESRD). The kidneys fail and the patient needs dialysis or a kidney transplant.

Chronic kidney disease and ESRD affect more than two out of every 1,000 people in the United States. Diabetes and hypertension are the two most common causes for this.

Many other diseases and conditions can damage the kidneys, including:
- Problems related to the kidney arteries
- Congenital anomalies of the kidneys (such as polycystic kidney)
- Some drugs and toxic chemicals
- Autoimmune disorders (such as lupus erythematosus and scleroderma)
- Injury or trauma
- Glomerulonephritis
- Kidney stones and infection
- Reflux nephropathy

It is worth highlighting two stages: pre- and post-renal transplantation. In the first, the patient requires dialysis, and in the second, immunosuppressive medication.
The annual cost of coverage by dialysis is close to US$ 60,000 per year, and the main providers of dialysis services in Argentina are Fresenius Medical Care Dialysis and Confederation of Argentine Centers.

After renal transplantation, immunosuppressive therapy is essential to prevent rejection of the transplanted organ.

There are many approved drugs for this purpose, and are used in combination to increase the effectiveness of treatment. The most commonly used combination includes prednisone + an antimetabolite (azathioprine, mycophenolate) + a calcineurin inhibitor (cyclosporine, tacrolimus).

The high-cost drugs involved in this treatment are:
- Micofenolato
- Tacrolimus
- Everolimus
- Sirolimus
- OKT3 (monoclonal antilymphocyte)
- ATG (polyclonal antilymphocyte)

Of the four, two are manufactured in a single laboratory (Table 4 A).

Table 4 A. Immunosuppressive treatments. Trade name in tablets and average annual cost of treatment. Argentina, 2011. (ARG$)

Drug	Trade name	Presentation	Laboratory	Price in Argentina 2011 Pesos	Average annual cost 2011 Pesos
Tacrolimus	Prograf	0,5 mg X 50	Gador	817	125.246,10
		1 mg X100		2.516,87	96.459,04
		5 mg X50		6.300,64	96.588,81
		0,5 X50		1.060,61	812.957,57
	Prograf XL	1 X 50		776,95	119.106,44
		5X 50		1.197,29	91.772,28
		0,5X 50		5.987,28	91.785,00
	Tacroninmun	1X 100	LKM	484	74.197,20
		5X 50		1.492	57.180,90
		0,5 X100		3.730	57.180,90
		0,5X 50		559	428.473,50
	Litacro 0,5	1X100	DOSA	1.237,11	94.824,48
		1X50		650	99.645,00
	Litacro 1	250 X100		2.120	81.249,00
		500X 50		1.060	81.249,00
Mycophenolate	Cellcept	500X 50	Roche	979,12	21.442,73
		250X 100		979,12	21.442,73
	Imuxgen	500 X 50	Bioprofarma	1.005,4	22.018,26
	Mycophenolate Mofetil Varifarma	500 X 50	Varifarma	818,15	17.917,49
		500X 40		818,15	17.917,49
	Mycophenolate Mofetil 500	500 X 50	Sandoz	933,2	20.437,08
	Mycoldosa 500	500 X 60	DOSA	786,5	21.530,44
		180 X120		922	20.191,80
		360 X 120		1.128,5	20.595,13
	Myfortic	0,25 X60	Novartis	1.390,48	35.244,81
		0,5X 60		2.780,85	35.243,41
Everolimus	Certican	0,75X 60	Novartis	1.599,64	87.580,29
		0,5 mg X 50		3.199,34	87.581,93
		1 mg X100		4.798,99	87.581,57
Sirolimus	Rapamune	1mg X 60	Wyeth	4.954,21	60.276,22
		2mg X 30		4.954,21	60.276,22

Source: CIPPEC's calculations based on pharmacist manual *Kairos*.

HIV / AIDS

The prevalence of HIV in the population of Argentina is less than 1 percent, although there are population groups in which this prevalence exceeds 5 percent. It is estimated that 130,000 people are affected by the virus, although only half of them are aware of their status. Among those who do know, the vast majority are monitored: 41,000 people receive antiretroviral medication, of whom two-thirds get it from the Ministry of Health. **Table 5 A** reflects the age distribution of those affected by the virus, and among them, those who are being treated by the State at the national level.

Table 5 A. HIV / AIDS. Distribution by age group. Argentina, 2011.

Age group	Patients under the National AIDS program	In the
Under 14 years	899	1.271
15 to 50 years	23.200	32.800
Over 50 years	4.901	6.929
Total	29.000	41.000

Source: CIPPEC's calculations based on data from the Ministry of Health. "Análisis de utilización de Fármacos antiretrovirales en Argentina". OPS Ministerio Salud Argentina. 2011. Available at http://publicaciones.ops.org.ar/publicaciones/otras%20pub/UtilizacionRetroviralesArg.pdf

There are three different lines of treatment with therapeutic alternatives depending on viral resistance and the clinical conditions of each patient. It is estimated that 63 percent of patients receive a first line of treatment, 33 percent a second line or a first-line protease inhibitor, and 4 percent a third line or salvage therapy.[35]

Table 6 A. HIV / AIDS.
Percentage of expenditure on account by stage. Argentina, 2011

Concept	Stadiums			
	A	B	C	All
Practices	0.25	0.46	0.92	0,58
Consultations	0.44	0.42	0.47	0,44
Days of hospitalization	1.78	4.99	15.70	8,24
CD4	0.55	0.40	0.37	0,42
Viral load	1.58	1.03	0.76	1,08
Antiretroviral drugs	95.4	92.7	81.78	89,25

Source: Basombrio et al. (2003). Guide to procedures with therapeutic alternatives and their economic impact on outpatient treatment and hospitalization of people living with HIV / AIDS. Editions Isalud. Buenos Aires.

The first line consists of patterns composed of any combination of nucleoside or nucleotide analogues with efavirenz or nevirapine, and diagrams composed solely of nucleoside / nucleotide (e.g. AZT/3TC/ABC). The **second line** consists of the schemas

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[35] Ministerio de Salud-"Análisis de utilización de Fármacos antiretrovirales en Argentina" OPS-Ministerio Salud-Argentina-2011-Available at
http://publicaciones.ops.org.ar/publicaciones/otras%20pub/U1.03tilizacionRetroviralesArg.pdf

that contain the following antiretrovirals (but do not contain any antiretroviral considered third-line or "rescue"): nelfinavir, saquinavir (with or without ritonavir), indinavir (with or without ritonavir), atazanavir (with or without ritonavir), lopinavir / ritonavir, fosamprenavir (with or without ritonavir). Finally, the **third-line** contains the following antiretrovirals: darunavir (with or without ritonavir), tipranavir (with or without ritonavir), etravirine, maraviroc, raltegravir, Enfuvirtide, or schemes with four or more antiretrovirals (excluding ritonavir). In the case of HIV / AIDS, 89 percent of the cost of treatment is on antiretroviral drugs (Table 6 A).

Hemophilia

This is an X-linked genetic disorder. There are typically two types of hemophilia: Type A, deficiency of clotting factor VIII, and Type B, factor IX deficiency. The incidence of hemophilia A is 8.9 per 100,000 men[36] (women transfer the disease, but only rarely have the clinical form). Instead, hemophilia B has an incidence of approximately one-fifth of A. In Argentina about 2,100 men are afflicted with the disease. Among hemophiliacs, about 630 would also have Hepatitis C, and 67 would have HIV.[37]

The treatment aims to reduce the frequency and extent of bleeding which may occur spontaneously or following trauma. Intraartricuar bleeding (hemarthrosis) is common. The treatment could use concentrates of factor VII and IX with various levels of purification, as well as recombinant products, including Kogenate, Bioclate, Helixate, and Recombinate. In Argentina, they represent 23 percent of treatment for hemophilia A and 10 percent for hemophilia B.[38]

In addition, desmopressin (DDAVP), a synthetic analogue of an antidiuretic hormone is also use. It is useful in treating individuals with mild hemophilia A, with a factor VIII level of 5 percent or greater. In these patients, the use of desmopressin significantly reduces the need for coagulation factors.[39] In Argentina, 1.30 International Units of factor VIII were used per capita per year (in 2004). The same source reports the use of 29,110 units of factor VIII for hemophilia person per year.[40]

Table 7 A. Hemophilia. Distribution costs in the treatment of hemophilia A and B for adults and children. Argentina, 2011. (ARG$)

	Frequency of patients	Middle Cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Hemophilia A adults	0,70	2.283.970	2.520.917	3.327.979
Hemophilia A children	0,17	1.110.976	1.152.531	1.505.588
Hemophilia B adults	0,09	2.003.265	1.720.925	2.191.492
Hemophilia B children	0,03	872.131	751.128	952.800
Weighted cost of treatment	1,00	2.013.120	2.157.272	2.836.521

Source: CIPPEC.

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[36] Stonebraker, Jeffrey S. & Paula, H. B. Bolton-Maggs (2010). "A study of variations in the reported hemophilia A prevalence around the world, *Hemophilia,* 16, 20–32.
[37] World Federation of Hemophilia Report on the Annual Global Survey 2009. Marzo 2011.
[38] World Federation of Hemophilia Report on the Annual Global Survey 2009. Marzo 2011.
[39] Mannuccio, P. (1998). "La Desmopresina (DDAVP) en el tratamiento de los trastornos de la coagulación: Los primeros 20 años", *Tratamiento de la hemofilia*, February.
[40] Jeffrey S. Stonebraker & Mark Brooker (2010)."A study of reported factor viii use around the world", *Haemophilia,* 16, 33–46.

It is possible to achieve price reductions between 21 and 25 percent just by choosing the most economical treatment option in both hemophilia A and B, in children and adults. Note that in this calculation, treatment options for public production were not considered (Table 7 A).

Multiple Sclerosis

Multiple sclerosis has an incidence of 18.5 cases per 100,000 population. It has a currently estimated prevalence of about 6,500 people with the disease. The average age of onset of the disease in Argentina is 24.5 years.

It usually progresses by outbreaks and the symptomatology derives from axonal demyelination foci. In 85 percent cases, patients suffer flares and remissions, which evolve towards the secondary form, while 10 to 15 percent suffer from the primary progressive form.[41]

Regarding its treatment, the outbreaks are usually treated with ACTH or corticosteroids. Annual rates of reported outbreaks vary, averaging 0.5 outbreaks per person per year.

New drugs approved for the treatment of MS are interferon B and glatiramer acetate (copolymer).[42]

Interferon B is useful in approximately 80 percent of patients with periods of exacerbation and remission and secondary progressive forms.[43] Both IFN and copolymer are included among the treatments subsidized by the SAP (APE).

Interferon can be a1 or b1. The first has two drugs on the market: blastoferón (Sidus) and NF rebif (Merck Serono); the second has just one, recombinant betaferon (Bayer). Interferon b is used in Scheme 1, a1 in Scheme 2, and copolymer is used in Scheme 3. The price decreases by half from one scheme to another (Table 8 A).

Table 8 A. Multiple sclerosis. Cost distribution of the different treatment schedules. Argentina, 2011. (ARG$)

	Frequency of patients	Middle cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Schedule 1	0,5	295.923	295.672	296.206
Schedule 2	0,3	89.999	65.747	115.454
Schedule 3	0,2	68.006	67.906	68.119
Weighted cost of treatment		453.929	429.325	479.780

Source: CIPPEC.

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[41] Ministerio de Salud de Chile (2008). "Guía Clínica de Esclerosis Múltiple". Santiago de Chile.

[42] Sánchez López, A.J. & García Merino, A. (2011). "Protocolo terapéutico de la esclerosis múltiple". *Medicine*, 10.

[43] Correale J., Patrucco L., y cols. "Consenso sobre el uso de drogas inmunomoduladoras en el tratamiento de la esclerosis múltiple en Argentina" Area de enfermedades desmielinizantes de la Sociedad Neurológica Argentina.

Multiple Myeloma

This is a neoplastic disease of the bone marrow, affecting approximately 1 in 25,000 people per year. About 15 percent of patients die in the first three years, and another 15 percent each year thereafter.[44]

The mean age at diagnosis is 68 years, and 37 percent of those affected are under 65, which is considered the age limit for candidates for a bone marrow transplant.[45] A number of studies have shown that myeloablative chemotherapy based on the use of high-dose intravenous melphalan and autologous bone marrow transplantation (ABMT) improves complete remission rates and increases survival. This has positioned ABMT as the standard treatment in young patients. In patients over 65 years, or those who are not candidates for transplantation for other reasons, the combination of melphalan, prednisone, and thalidomide is often used. In recent years, the use of drugs that were originally reserved only for refractory disease or relapse has increased, as is the case with bortezomib and lenalidomide.[46]

A European study[47] of costs involved showed that medication represents 40 percent of the annual cost per patient with multiple myeloma, while admissions account for 35 percent. The same study reported an incidence of bone marrow transplant autologous 0.2 per patient per year.

Despite having at least three different treatment regimens (Table 9 A), there is a variation of just 2 percent between the lowest and highest price.

Table 9 A. Multiple myeloma. Distribution costs (low, medium, and high), of the different treatment schedules. Argentina, 2011. (ARG$)

	Frequency	Medium cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Transplants	**0,33**	69.127	68.611	69.485
Scheme 1	**0,335**	5.960	5.188	6.352
Scheme 2 (relapse)	**0,1675**	196.715	195.943	197.107
Scheme 3	**0,1675**	3.040	2.268	3.432
Weighted cost of treatment with medication alone		52.919	52.147	53.311
Weighted costs of treatment		**58.268**	**57.580**	**58.648**

Source: CIPPEC.

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[44] Principios de Medicina Interna. Harrison. 16th Edition. 2010.

[45] Palumbo, A. (2011)."Multiple Myeloma". *N Engl J Med,* 364:1046-60.

[46] Hrusovsky, I., Emmerich, B. (2010). "Bortezomib retreatment in relapsed multiple myeloma - results from a retrospective multicentre survey in Germany and Switzerland". *Oncology*, 79(3-4):247-54. Epub 2011. March 3.

[47] Koleva, D. (2011). "Healthcare costs of multiple myeloma: an Italian study". *European Journal of Cancer Care*, 20, 330–336.

Central Nervous System Tumors

Among the cancers of the central nervous system in adults, glial tumors account for 50 to 60 percent of all primary brain tumors, meningiomas account for 25 percent, neurinomas about 10 percent, and the rest constitute a variety of tumors.

The brain is more likely to have a tumor metastatic from other sites than primary neoplasms. The most common primary brain tumors are astrocytic tumors, of which the more aggressive variant is glioblastoma multiforme, which has a median survival rate without treatment from four to six months. Its peak incidence is between 50 and 70 years of age.[48] The incidence as estimated by the International Agency for Research on Cancer is 1,442 new cases per year.

With radiation treatment, the observed median survival was 29 weeks. The combined treatment of radiotherapy (six weeks) and temozolomide (six months) showed a 26 percent survival rate at two years, with a mean survival of 16 months.[49] [50] [51]

A percentage of those with poor response or recurrence received bevacizumab with irinotecan, but evidence of their effectiveness is still controversial[52] (Table 10 A).

Table 10 A. Glioblastoma. Different treatment regimens. Argentina, 2011.

	Drug	Dose
Therapy scheme	Temozolomide	75 mg per m2 per day for 6 six weeks, followed by Temozolomide monotherapy 200 mg per m2 per day for 5 days every month for six months
Rescue scheme	Irinotecan	340 mg/m2 or 125 mg/m2 for 3 or 4 months
	Bevacizumab	10 mg per kg of body weight every 2 weeks

Source: CIPPEC.

In the case of meningioma, the treatment of choice is complete surgical resection. However, in some cases of complex location (such as the base of the skull), it cannot be removed by traditional surgery. In these cases, radiosurgery is used, either by radiation or gamma knife stereotactic.[53] In a large sample it was found that of 10,000 patients with meningioma, 82 percent had undergone surgery, of whom 28 percent had received total resection or radical (without subsequent radiation therapy), and 72 percent partial resection (in need of subsequent radiotherapy). Less than 10 percent of meningiomas are histologically malignant.[54]

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[48] Díaz V. & Yáñez, A. (2006). "Tendencia de la mortalidad por tumores cerebrales malignos en Chile. Análisis de tasas". *Rev. chil. neuro-psiquiatr*, vol.44, no. 4 dic.

[49] Jaramillo, S., Osorio, W., Espitia, J. C. (2010). "Avances en el tratamiento del glioblastoma multiforme". *Univ. Méd. Bogotá* (Colombia), 51 (2): 186-203, April-June.

[50] DeAngelis, L.M. (2005). "Chemotherapy for brain tumors--a new beginning". *N Engl J Med* 352 (10): 1036-8.

[51] Stupp, R., Dietrich, P.Y., Ostermann, Kraljevic S., et al. (2002). "Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide". *J Clin Oncol,* 20 (5): 1375-82.

[52] Buie, L. & Valgus, J. (2008). "Bevacizumab: a treatment option for recurrent glioblastoma multiforme". *Ann Pharmacother.* October, 42(10):1486-90. Epub September 2.

[53] Plasencia, A., Berti, A., y cols (2008). "Radiocirugía Esterotáctica del Meningioma Intracraneal". *Revista Peruana de Neurocirugía,* Vol. 3, No. 2 April-June.

[54] McCarthy, B.J. & Davis, F. (1998). "Factors associated with survival in patients with meningioma". *J Neurosurg*, May, 88(5):831-9.

Table 11 A. Glioblastoma. Distribution costs low, medium and high of the different treatment schedules. Argentina, 2011.

	Medium cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Therapy scheme	162.348	89.276	210.256
Rescue scheme	1.296.267	875.714	1.545.260
Average costs weighted by the frequency of treatment	275.739	167.919	343.756

Source: CIPPEC.

There is a 51 percent difference between the most expensive and the least expensive option (Table 11 A).

Hepatitis C
Hepatitis C has a poorly defined incidence in our country. An ANLIS document suggests 0.64 percent prevalence of infection in the blood donor population. [55]

It is worth highlighting that this donor population is highly selected and not representative of the general population. Countries with complete epidemiological data have shown that the prevalence of HCV is three to six times higher in general population than in volunteer blood donors. In Argentina, serological surveys of adult general population show a range of prevalence from 2.8 to 5.6 percent.[56]

In a serological survey carried out in Cordoba,[57] prevalence was as follows: genotype 1: 38 percent, genotype 2: 55 percent, and genotype 3: 5 percent. However, various studies differ on the seroprevalence of different genotypes. For example, another Argentinean study reported 70 percent of genotype 1, 21.9 percent of genotype 2, and 7.3 percent of genotype 3.[58]

The disease usually has an asymptomatic period of 15 to 30 years, and reduces life expectancy by about seven years.[59]
Treatment of patients with genotype 1 should be for a period of 48 weeks with full doses of peginterferon alfa-2b or peginterferon alfa-2a linked to ribavirin.[60] [61] Patients with genotypes 2 and 3 can be treated for 24 weeks.[62]
Pegylated interferon is produced by two laboratories. Although when introduced in the market doses were weight-adjusted, currently Roche recommends two doses: one for

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[55] Consenso Argentino de Hepatitis C. Conclusiones. Publicación de la Sociedad Argentina para el Estudio de las Enfermedades del Hígado. 2000.

[56] Quarleri, J. & Robertson ,B. y cols (1998). "Genomic and phylogenetic analysis of hepatitis C virus strains from Argentina". *Medicina* (Buenos Aires), 58: 153-9.

[57] Re V., Lampe, E., y cols (2003). "Hepatitis C virus genotypes in Cordoba, Argentina. Unexpected high prevalence of genotype 2". *Medicina* (Buenos Aires), 63: 205-210.

[58] Findor J., Sorda J. y cols (1999). "Distribución de los genotipos del virus de la hepatitis C en una población argentina de drogadictos endovenosos". *Medicina*, Vol. 59, No.1.

[59] Seeff, L.B. (2002). "Natural history of chronic hepatitis C". *Hepatology,* 36:S35-46.

[60] Mangia, A., Santoro R., et al. (2005). "Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3". *N Engl J Med,* 352:2609-2617.

[61] Ministerio de Salud de Chile (2010). "Manejo de la infección por virus de la hepatitis C". Serie Guías Clínicas.

[62] Butt, A., Wang, X., et al. (2009). "Effect of hepatitis C virus and its treatment on survival". *Hepatology,* 50:387-392.

patients over 70 kg and another for patients below that weight. Instead, Schering continues to suggest the weight-adjusted doses (Table 12 A).

Table 12 A. Drugs. Average, low and high costs for the treatment of hepatitis C in Argentina, 2011. (ARG$)

	Frequency of patients (1)	Medium cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Genotype 1 Scheme	0,55	132.256	112.440	152.287
Genotype 2 and 3 Scheme	0,45	66.128	56.220	76.144
Weighted average cost based on the frequency of the scheme	1	102.498	87.141	118.023

Source: CIPPEC.

It is possible to achieve a 15 percent discount by choosing the lower cost option as compared to the average cost. The price variation when considering the higher price option is 27 percent.

Leukaemia in Children and Adolescents

Leukaemia is the most common cancer in children: affects 35 to 40 percent of patients with cancer under 15 years of age.[63] It is estimated that there are approximately 3,000 new cases per year in Argentina.[64] Acute leukaemia is the most common in children and acute lymphoblastic leukaemia (ALL) accounts for 80 percent of all cases at that age. About 15 percent are acute myeloid leukaemia (AML), and less than 5 percent are chronic myeloid.[65] The annual incidence of leukaemia in children in Argentina is 4 cases per 100,000 children under 15 years.[66]

Treatment of patients with ALL is adapted to the risk of patient diagnosis and comprises three phases: induction, intensification (consolidation), and maintenance. The overall duration is a minimum of two years. Prognostic factors are age and leukocyte count at diagnosis, genotype of leukemic cells, and the initial response to treatment. These are the most accepted parameters in setting risk groups.[67] Based on these factors, four risk groups have been identified that receive different treatments in increasing intensity:

Low risk (35 percent): The long-term survival of this group is greater than 90 percent. Intermediate risk (45 percent): This group has a long-term survival of around 75 percent.

High risk (10 percent): The survival of this group is around 60 percent as treatment is much more intense than in others.

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[63] Lassaletta, Atienza A. (2004). "Leucemias. Leucemia Linfoblástica Aguda". *Pediatr Integral*, VIII(5):435-442.
[64] Ministerio de Salud de la Nación (2010). "Cuándo sospechar Cáncer en un niño".
[65] Campbell M., Ferreiro C., y cols (1999). "Leucemia linfoblástica aguda. Características al diagnóstico en 100 niños". *Rev. Chil. Pediatr*, v.70, n.4, Santiago, July.
[66] The Globocan Project. 2008
[67] Torpy J. (2009). "Leucemia linfoblástica aguda". *JAMA*, January 28, Vol. 301, No. 4.

Very high risk (10 percent): These children are candidates for allogeneic bone marrow transplant at the first remission. The survival of this group is around 35 percent, which has improved in patients who have access to allogeneic transplantation.

The drugs used include vincristine, methotrexate, cytarabine, mercaptopurine, cyclophosphamide, and dexamethasone. Intrathecal chemotherapy is also performed.[68]

Treatment of AML (15 percent) is performed induction with cytarabine associated with daunorubicin or idarubicin, with or without etoposide.[69] [70] After remission, consolidation and intensification is performed with high-dose cytarabine, anthracyclines, and, in some cases, etoposide. Bone marrow transplantation is recommended in the group of patients considered high risk, and/or those who show poor response to treatment or relapse. They are estimated to be 50 percent, of which 25 percent account for bone marrow transplant. In chronic myeloid leukaemia (3 percent to 5 percent), bone marrow transplantation from a matched sibling is considered curative and is recommended as the first line therapy.[71] Imatinib mesylate is the HCD recommended as second line of therapy in the absence of a donor family.[72]

The variation between the lowest cost and the average cost is 5 percent, considering both drugs and transplantation (Table 13 A).

Table 13 A. Leukaemia in children and adolescents. Average, low and high costs for drug treatment and transplants, Argentina, 2011. (ARG$)

Treatments	Frequency of patients treated	Average cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
ALL	0,73	14.278	12.364	17.383
ALL Transplant	0,08	84.000	84.000	84.000
AML	0,14	17.617	17.529	17.781
AML transplant	0,02	336	336	336
CML	0,03	199.211	199.211	199.211
CML Transplant	0,04	84.000	84.000	84.000
Weighted cost of treatments		24.618	23.208	26.907
Weighted cost of treatment only with medication		17.987	16.381	20.592

Source: CIPPEC.

[68] Universidad Católica de Chile (2011). "Protocolo de tratamiento de Leucemia Linfoblástica en niños y adolescentes", accessed September 20, 2011 in
http://contacto.med.puc.cl/oncologia_pediatrica/PDF/protocolo_leucemia.pdf
[69] **Instituto Nacional del cáncer "Tratamiento de la leucemia mieloide aguda recién diagnosticada"** (2011). Available at http://www.cancer.gov/espanol/pdq/tratamiento/LMAinfantil/HealthProfessional/page5
[70] Tomizawa D., Tabuchi K. et al. (2007). "Repetitive cycles of high-dose cytarabine are effective for childhood acute myeloid leukaemia: long-term outcome of the children with AML treated on two consecutive trials of Tokyo Children's Cancer Study Group". *Pediatr Blood Cancer*, August, 49(2):127-32.
[71] Ministerio de Salud de Chile (2010). "Guías Clínicas. Leucemia en Personas Menores de 15 años".
[72] Pavón Morán V. & Hernández Ramírez, P. y cols (2005). "Imatinib en leucemia mieloide crónica". Revista Cubana Hematol Inmunol Hemoter, v.21 n.3, Ciudad de la Habana sep.-dic.

Considering only drug prices, the variation between average cost and low cost is 8 percent and 20 percent.

Variation rates are lower than in other cases despite the fact that 50 percent of the drugs have more than one supplier; but as there are fewer than six labs, the fluctuation of prices is limited (Table 14 A).

Table 14 A. Leukaemia in children and adolescents. Number of providers drug laboratories. Argentina, 2011.

Drug	Number of presentations	Number of laboratories
Cyclophosphamide	10	6
Cytarabine	12	5
Daunorubicin	1	1-GP Pharm
Dexamethasone	1	1-Cassara
Etoposide	1	1-Microsules
Hydrocortisone	10	5
L-asparaginase	1	1-Filaxis
Mercaptopurine	1	1-Filaxis
Imatinib mesylate	1	1-Novartis
Methylprednisolone	3	3
Methotrexate	12	4
Vincristine	3	3

Source: CIPPEC

Gastrointestinal Stromal Tumor – GIST

This is a group of tumors with an incidence of approximately 10 to 20 cases per million, representing only 0.1 to 3 percent of all gastrointestinal tumors. They can be located anywhere in the gastrointestinal tract, as well as mesentery or retroperitoneum.

Seventy percent are located in the stomach, 20 to 30 percent in the small intestine, and 7 percent in the anorectal region. Seventy to 80 percent of GISTs are benign. They affect patients over 50 years and may be discovered incidentally.[73]

Computed tomography (CT), especially the one with multiple detectors, is the method of choice for the detection and categorization of these tumors, and in a number of cases, 31 percent of patients received a PET scan at some stage of the disease.[74]

The treatment is surgical resection. But the presence of metastases at diagnosis implies the need for chemotherapy. In one of the reported series, 23 percent of patients had metastatic disease at diagnosis, half in the liver and the other half in the

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[73] Oyanedel R. & Brien A. y cols (2008). "Tumores del estroma gastrointestinal (GIST), un particular tipo de neoplasia". *Revista Médica Chile,* 136: 921-929.

[74] Racioppi M., Borgas C., y cols (2007). "Impacto del PET-CT en la reestadificación y manejo de los tumores del estroma gastrointestinal (GIST)". Departamento de Diagnóstico por Imágenes del Hospital Italiano de Buenos Aires. Buenos Aires, October 24.

peritoneum. In an Argentinean study, 19 of 54 patients (35 percent) presented metastases at diagnosis.[75]

Regarding treatment options, radiotherapy is not useful since these are radioresistant tumors. Conventional systemic chemotherapy too was not effective, although it checked low response rates to doxorubicin and dacarbazine. Imatinib mesylate (Glivec) in combination with surgery has dramatically changed the prognosis of patients with metastasis, at least doubling survival from less than 12 months to over two years.[76]

The cost of treatment per year is $ 382,050. Sixty GIST cases are estimated per year (10 and 20 cases per million), of which about 18 would need treatment with Glivec, resulting in an annual expenditure of $ 6,876,884.

Breast cancer
Breast cancer is most prevalent form of cancer among the women of Argentina. The International Agency for Research on Cancer has estimated its incidence at 74 cases per 100,000 women per year. This number begins to rise from the age of 40 and finds its peak around 75.[77]

In 2008, there were 18,717 new cases and 5,200 deaths from this disease, with a mortality rate of 22.4 age-adjusted per 100,000 women.[78] In turn, a study of disease burden in Argentina showed that this cancer is responsible for more than 6 percent of premature life years lost (Disability Adjusted Life Years or DALY) in females.[79]

Ninety-five percent cases are invasive carcinomas, of which 80 to 85 percent are ductal. A study of the kinds of initial tumors at the clinical stage showed that 6.7 percent of patients were classified as tumors in situ (0), 43.5 percent as early carcinomas (I-IIA), 42.3 percent as locally advanced tumors (IIB-IIIC), and 7.3 percent as carcinomas metastatic (IV).[80]
Almost all cases of ductal carcinoma in situ are treated with conservative surgery followed by radiotherapy.[81] The classical model of chemotherapy consists of cyclophosphamide, doxorubicin, and 5-fluorouracil, and, where appropriate, adding paclitaxel.

All pre-menopausal women with estrogen and progesterone receptor positive should receive tamoxifen,[82] [83] and women who overexpress the HER-2 gene are potential

[75] Oyanedel R., Brien A. y cols (2005). "Tumor Estromal Gastrointestinal (GIST): formas de presentación". *Rev Chil Radiol,* 11(1):13-18.
[76] NHS (2009). "Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours" NICE Technology Appraisal Guidance.
[77] Viniegra M. & Paolino M. (2010). "Cáncer de mama en Argentina: organización, cobertura y calidad de las acciones de prevención y control. Informe final julio 2010: diagnóstico de situación del Programa Nacional y Programas Provinciales. OPS.
[78] The GLOBOCAN Project. Year 2008. Accessed http://globocan.iarc.fr/
[79] Ministerio de Salud de la Nación. "Estudio de carga de enfermedad de La Argentina". 2010.
[80] Angarita F., Acuña S. y cols (2010). "Presentación inicial de las pacientes con diagnóstico de cáncer de seno en el Centro Javeriano de Oncología, Hospital Universitario San Ignacio". *Revista Colombiana de Cirugia*, 25, 19-26.
[81] Zulaica V. (2009). "Cáncer de mama". Fisterra. *Guias Clínicas,* 9 (37).
[82] Ministerio de Salud de Chile (2010). "Guía Clínica. Cáncer de Mama".
[83] Maughan K., Lutterbie M. y cols (2010). "Treatment of Breast Cancer". *Am Fam Physician*, 81(11).

candidates for the HCD trastuzumab. The incidence of overexpression varies but is estimated at 20 to 30 percent.

Table 15 A. Breast cancer. Costs of different treatment regimens.
Argentina, 2011. (ARG$)

	Frequency of patients	Average cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Scheme 1 - In situ Ductal	0,10	1.093	690	1.957
Scheme 2 - Stages I and II Invasive early	0,40	91.838	68.334	119.893
Scheme 3 - Locally Advanced	0,40	89.137	67.273	114.514
Scheme 4 - Stage IV or recurrent	0,10	41.077	38.129	47.004
Average cost of schemes	1	76.607	58.124	98.659

Source: CIPPEC.

In analyzing cost variances (Table 15 A), the highest percentage is observed in Diagram 1 (65 percent), but in Schemes 2 and 3, in which the reduction is about 40 percent, this represents a saving of almost $ 50,000 per treatment per year.

Kidney Cancer

Kidney cancer is the sixth most common cancer among men in Argentina. The International Agency for Research on Cancer has estimated its incidence at 9.4 cases per 100,000 men per year, with a mortality of 5.3 per 100,000 per year. In women, the estimated incidence is 3.4 per 100,000, and mortality of 1.9 per 100,000. Among both sexes, about 3,000 new cases of kidney cancer are diagnosed each year.[84]

This cancer occurs most often between 55 and 66 years. The most common type in adults is clear cell renal carcinoma (80 percent), followed by papillary carcinoma (10 to 15 percent).[85]

Stages 1 (9 percent of the styles), 2 (39 percent) and 3 (16 percent) are mostly treated with surgery (partial nephrectomy or total), and in some cases, radiotherapy and/or renal artery embolization. In stage 4 (20 to 25 percent), chemotherapy drugs and immunotherapy are also used.[86]

Treatment with IL-2 was the first to be approved as immunotherapy. Its toxicity is very high, so there are very few candidates for its indication. However, it is the only treatment that showed remission at this stage (8 to 10 percent). In cases where treatment was tolerated (20 to 30 percent of patients), its duration is approximately 1 year.

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[84] The GLOBOCAN Project. Accessed http://globocan.iarc.fr/
[85] Academia Nacional de Medicina "Consenso Nacional Inter-Sociedades para el diagnóstico y tratamiento de las neoplasias renales parenquimatosas del adulto". Argentina. 2010
[86] Ljungberg B., Cowan, N. y cols (2007). "Guias Clínicas en Carcinoma Renal". *Eur Urol*, Jun, 51(6):1502-10.

Sunitinib and bevacizumab[87] with a-2 + IFN 2nd are HCDs used in treatment. Everolimus is used as a second line.[88] [89]

Table 16 A. Kidney cancer. Average, low and high cost of the different patterns of drug treatments. Argentina, 2011. (ARG$)

	High Cost Medication used	Frequency of patients	Average cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Scheme 1 (a)	IL2	0,12	339.984	260.476	385.296
Scheme 1 (b)	IL2+ Everolimus	0,28	488.175	408.667	533.487
Scheme 2 (a)	Sunitinib	0,12	989.584	987.292	994.143
Scheme 2 (b)	Sunitinib+ Everolimus	0,18	1.137.776	1.135.484	1.142.335
Scheme 3 (a)	Bevacizumab	0,12	524.824	502.382	547.266
Scheme 3(b)	Bevacizumab+ Everolimus	0,18	673.016	650.574	695.457
Weighted costs		**1**	**685.159**	**645.935**	**711.383**

Source: CIPPEC.

It is only the choice of starting treatment with sunitinib or bevacizumab (**Table 16 A**) that represents a difference of $ 450 000 per year per treatment.

Colon-Rectal Cancer
Cancer of the colon and rectum is the third most common in both men and women. It has an incidence of 11,000 cases per year, accounting for 20 percent of cancer incidence in both sexes. Moreover, mortality is 6,930 deaths per year, accounting for 11.8 percent of cancer mortality in both sexes.[90]

The 5-year survival in stage I is 90 percent, in stage II 70-80 percent, stage III between 40-70 percent, and stage IV 10 percent.[91]

Stage I is surgically treated and almost completely cured.

Adjuvant chemotherapy is a clear indication in stage III, indicating the FOLFOX scheme. In stage II, however, adjuvant chemotherapy indication is not clearly defined, reserved for those with poor prognosis. In stage IV, the drugs that have had effect include oxaliplatin, irinotecan, 5-fluoroulacilo, and capecitabine. We have also developed

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[87] Frampton, J.E., Keating, G.M. (2008). "Bevacizumab: in first-line treatment of advanced and/or metastatic renal cell Carcinoma". *BioDrugs*, 22(2):113-20.
[88] Motzer R. & Escudier, B. (2008). "Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial". *Lancet.* August 9, 372(9637):449-56.
[89] Llarena Ibarguren R. (2009). "Tratamiento del cáncer renal metastásico: vigencia de la Inmunoterapia". *Actas Urológicas Españolas,* 33(5):584-592.
[90] The GLOBOCAN Project. Accessed http://globocan.iarc.fr/
[91] Academia Nacional de Medicina. "Consenso Argentino para la prevención del cáncer colorectal. 2004" http://www.acamedbai.org.ar/pagina/academia/consenso%20colorrectal.htm

biological therapies such as monoclonal antibodies, bevacizumab and cetuximab. The preferred schemes are FOLFOX and FOLFIRI.[92][93]

Stage IV with potentially resectable liver metastases can be treated with neoadjuvant chemotherapy followed by surgery of the primary tumor and metastases. Solitary pulmonary metastases may also be considered potentially surgical.[94]

In stage IV, 20 percent patients show metastases[95]. Among other drugs, cetuximab and bevacizumab are the HCDs that are in use in this latter stage of the disease.

The scheme used in distant metastatic disease is about 3.5 times more expensive than the scheme used in localized disease. Choosing the cheapest treatment option allows a lower cost of 18 percent compared with average costs, and 29 percent with higher treatment costs (Table 17 A).

Table 17 A. Colon and rectal cancer. Average, low and high costs of primary drug treatment. Argentina, 2011. (ARG$)

	Adjusted frequency of treatments	Average cost (Pesos)	Low cost (Pesos)	High cost (Pesos)
Located Scheme	0,133	160.226	145.507	180.798
Scheme III Folfox node metastasis	0,294	160.226	145.507	180.798
Scheme III FOLFIRI node metastasis	0,294	207.563	127.865	272.459
Scheme IV Metastatic distance Folfox	0,056	160.226	145.507	180.798
Scheme IV Metastatic distance Folfox + 2 line	0,056	457.847	413.101	489.516
Scheme IV Metastatic distance FOLFIRI	0,056	223.948	162.905	257.686
Scheme IV Metastatic distance FOLFIRI + 2 line	0,056	501.040	432.111	544.156
Scheme IV Metastatic distance XELOX	0,028	252.898	252.898	252.898
Scheme IV Metastatic distance XELOX + 2 line	0,028	551.583	527.098	568.453
Costs of treatment weighted by frequency		**226.950,13**	**185.980,30**	**262.479,60**

Source: CIPPEC.

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[92] Fernandez Calvo O., y cols "Cáncer de Cólon" Guias Clínicas Fisterra 2009;9
[93] National Cancer Institute. Colon Cancer Treatment.
http://www.cancer.gov/cancertopics/pdq/treatment/colon/HealthProfessional/page9
[94] Thierry A., Boni C., et al. (2004). "Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC)". *NEJM*, June 3, 350:2343-2351.
[95] Cappell M. (2005). "The pathophysiology, clinical presentation, and diagnosis of colon cancer and adenomatous polyps". *Med Clin N Am,* 89.