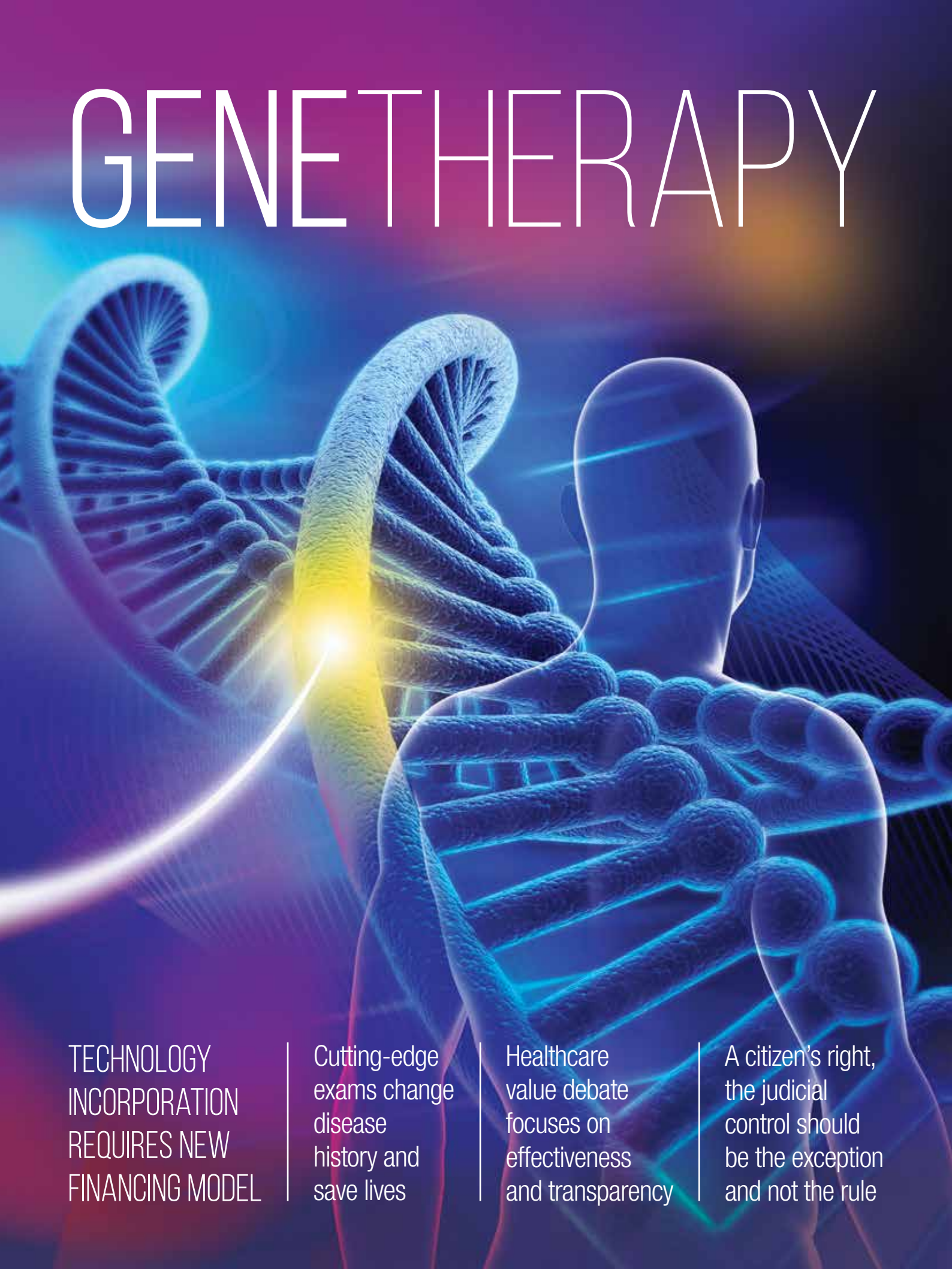
GENE THERAPY



TECHNOLOGY INCORPORATION REQUIRES NEW FINANCING MODEL

Cutting-edge exams change disease history and save lives

Healthcare value debate focuses on effectiveness and transparency

A citizen's right, the judicial control should be the exception and not the rule

Over the past decade, advances in genetics and biotechnology have allowed the pharmaceutical industry to develop gene and cell therapies that are revolutionizing the treatment of rare and ultra-rare diseases, as well as cancers previously viewed as uncurable.

These groundbreaking treatments open new cure perspectives for patients and physicians. Nevertheless, since they still come with a high cost, an in-depth debate about the best ways to evaluate, fund, and incorporate these therapies into the national public and private health care systems is necessary.

In the Gene and Advanced Therapies: Creating Value in the Patient Journey and in the Health System Forum, held by the Syndicate of the Pharmaceutical Industries (Sindusfarma) and the National Health Surveillance Agency (Anvisa) on October 23 and 24, 2019, in the agency's auditorium in Brasilia, public managers, physicians, national and international researchers, congressmen, and healthcare leaders shared experiences in Brazil and in other countries. They discussed various aspects related to the theme, such as regulation, clinical research, diagnosis, legislation, financing, and sustainability of the system.

EDITORIAL

GENETHERAPY

GENE AND ADVANCED THERAPIES:
Creating Value in the Patient Journey
and the Health System

October 23 and 24, 2019
Anvisa Auditorium – Brasilia

HELD AND ORGANIZED BY

SINDUSFARMA

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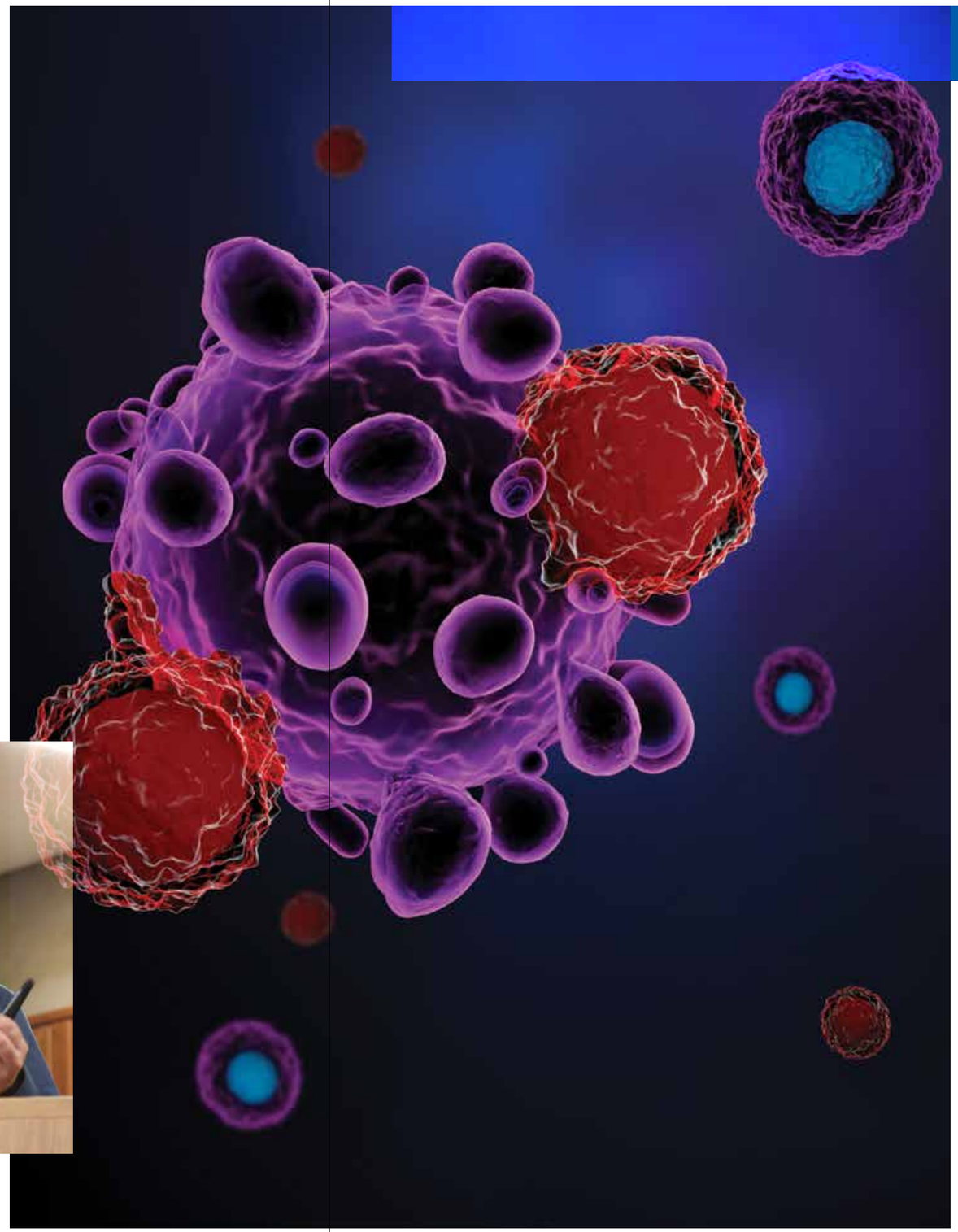
CONTENTS

GENE THERAPIES: A REVOLUTION ON THE WAY

Advanced medicine allows us to glimpse a new world order in healthcare. With technology, it is possible to reprogram DNA to fight hitherto incurable diseases

GUILHERME BALDO, PROFESSOR OF THE FEDERAL UNIVERSITY OF RIO GRANDE DO SUL



Great expectations have been created from the complete mapping of the human genome. Currently, we live in the moment when the results of such work are beginning to emerge through accurate diagnoses and treatments against diseases previously considered incurable.

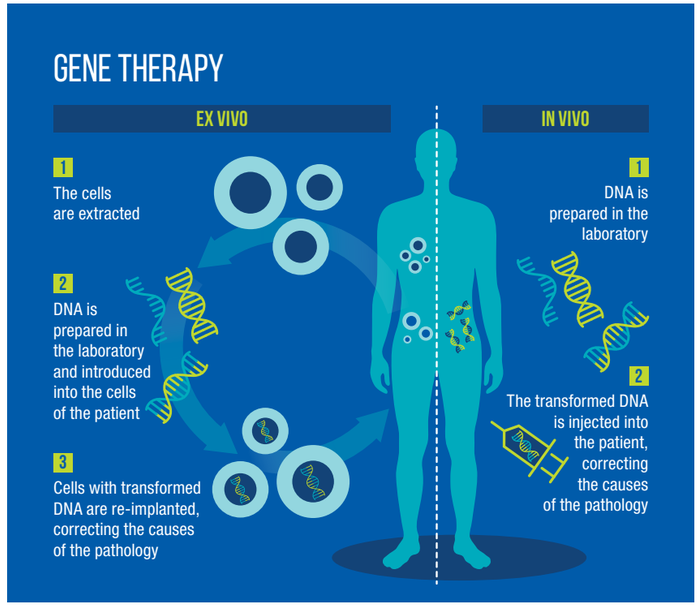
"In the last five years, advanced therapies have leaped globally speaking. Today, all major pharmaceutical industries develop protocols in the area. In the coming years, we will have at least 25 products approved for various diseases," says Guilherme Baldo, professor at the Federal University of Rio Grande do Sul.

Advanced therapies are biological products obtained from human cells and tissues that have undergone a manufacturing process. One of them is cell therapy – which uses whole cells to cure a disease like bone marrow transplantation, for example – and gene therapy, whose differential is the introduction of DNA or RNA into the cell to correct or replace defective genes that hinder the full functioning of the body.

The techniques are independent – one does not supplant the other, and they often

overlap. Both focus on the potential for single-dose healing for rare, severe diseases that, without the help of new technologies, lead to death or require ongoing, usually lifelong treatment.

Americans pioneered in this field, laying the pillars of knowledge that currently guide the work of hundreds of laboratories and research centers around the world. French and Italian scientists also occupy leading positions in this crusade. “Brazil cannot stand still on this matter. It is a large investment conditioned on many biosafety protocols, but a vital one,” says Baldo.



HOW IT WORKS

There are different ways to introduce functional genes – capable of reversing the picture of some diseases or stimulating the immune system – within cells. You can either insert a normal gene to replace a non-functional gene or modify an anomalous gene.

There are two ways of exchanging and repairing a gene:

- **ex vivo** – researchers remove the patient’s cells, modify or replace the gene in the laboratory, and then reinsert the transformed cell into the patient’s body (the best-known example is called CAR-T).
- **in vivo** – genetic material is altered directly in the patient’s body.

In both cases, the big challenge is to find vectors capable of transferring DNA efficiently. This is because genetic material must cross the entire plasma membrane of the cell and reach the correct position – otherwise, it may lead to an adverse response from the body, such as unexpected mutations, for example. In other words, a carrier that protects the gene until delivery to its destination is required.

Modified in the laboratory, they lose their harmful character and receive the DNA that must be inserted into the target cells. By infecting them, they carry with them one or more copies of the altered gene, returning to the body the normalization of some hitherto inefficient processes.

A lot of research is underway to improve the delivery of the molecule to the recipient cell. The need stems from the fact that, although they lose their pathogenicity, viral vectors can elicit an immune system response that renders therapy ineffective.

Another key point is correct addressing since the vector can lead to insertional mutagenesis by accidentally entering an undue region – when genetic material interferes with elements that regulate cell reproduction – resulting in tumors.

One of these new pathways is gene editing, which consists of using a protein that can break DNA at a precise point and, at the time of the break, insert into it the material that will replace the anomalous gene, eliminating the use of vector and reducing the risk of deviations. While in the classic form, there is a degree of uncertainty about where the genetic product will be inserted, editing allows taking a specific mutation and insert another gene in that place.

> GENE THERAPY REPROGRAMS THE BODY TO FIGHT THE DISEASE DIRECTLY. YOU ALTER OR REPLACE THE DEFICIENT GENE TO NORMALIZE CELLULAR FUNCTIONS.”
>
> GUILHERME BALDO

CUSTOMIZATION

Given their multiple applications, gene therapies will surely bring a revolution in the healthcare system. However, because they use unique information about the characteristics of each recipient, there are doubts about how to enable access to the population, since they treat each patient individually.

“Although a vector or patient’s cell is needed to carry the genetic content, a new product is not necessarily created for each patient. Modification is the same for all who have a particular disease. As a result, in the future it will be possible to achieve some scale and, consequently, reduce the cost of treatments,” says Baldo.

In the future, new technologies are expected to provide a cure for several diseases that result from the misbehavior of a gene, including inherited and acquired diseases such as tumors, lethal virus infections, and cardiac conditions, among others.

> The biggest conclusion of the genome project was to explain that the complexity of the human being lies in the coding.”
>
> CAROLINA FISCHINGER
> Geneticist Physician

CAR-T THERAPY

In early October, the Brazilian media disclosed the news of a patient with terminal lymphoma who got rid of cancer symptoms thanks to unprecedented treatment in Latin America. A 64-year-old man underwent one of the most advanced approaches to gene medicine so far: CAR-T – the acronym for chimeric T-cell antigen receptors.

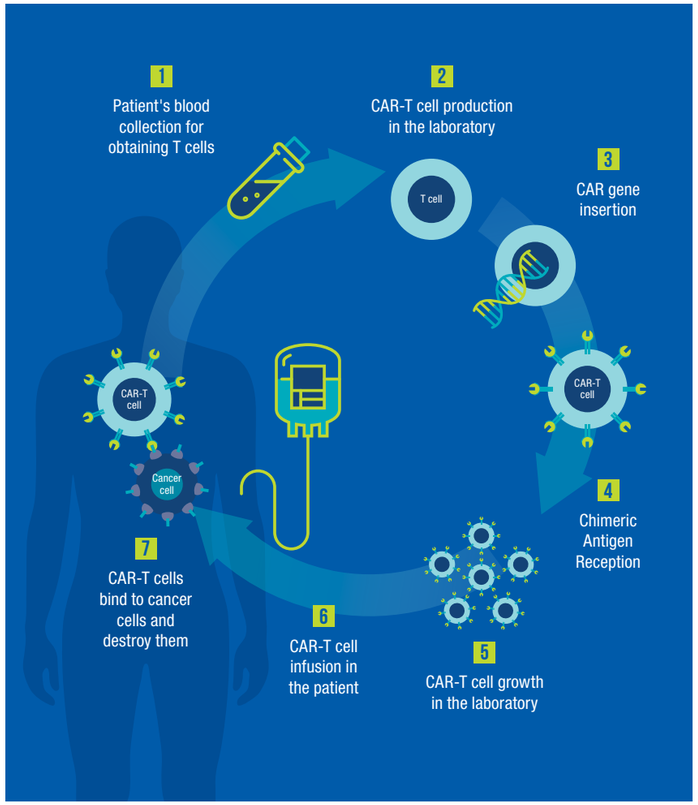
It is a procedure that combines cell therapy, gene therapy, and immunotherapy and has been applied for the treatment of hematologic cancers, such as lymphomas and leukemias. Extracted from the patient, T cells — called the immune system's warhorse because of their role in driving the immune response and killing pathogen-infected cells — are engineered in the laboratory to fight the tumor.

This modeling uses unarmed viruses that carry chimeric receptors, that is, synthetic molecules designed to induce T cells to recognize tumor cells. Once reprogrammed, the T cells are inserted back into the patient and attack cancer.

"CAR-T was considered worldwide as the most innovative therapy of the past year. But it is not risk-free, so it needs to be performed in highly complex centers," says Angelo Maiolino, director of the Brazilian Association of Hematology, Hemotherapy, and Cell Therapy (ABHH).

Among the adverse reactions that treatment can trigger is cytokine release syndrome (fever and low blood pressure in the days following administration, when the body's defense begins to fight off malignant cells), as well as neurological toxicity.

Moreover, it is important to keep in mind that since it is a recent and expensive technology, it is used when the possibilities for conventional treatment have been exhausted. According to Maiolino, physicians are applying CAR-T in patients with very advanced diseases, which implies a potentially lower success rate. "Still, the results are very good, with a global response between 50 to 100% percent," he says. Additionally, there is the prospect that incorporating this therapy into previous lines of treatment further increases the perceived effectiveness of outcome.



HOPE FOR 13 MILLION BRAZILIANS

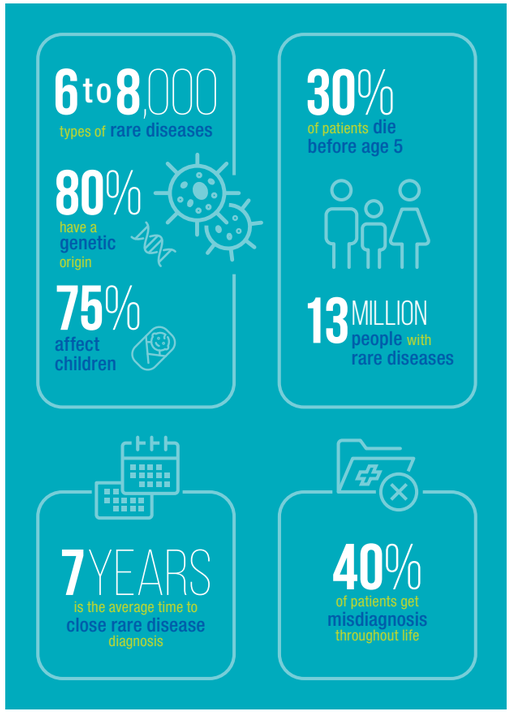
Degenerative and disabling in most cases, rare diseases are targeted for treatments that correct defective genes

Rare diseases are priority targets for advanced therapies. Usually chronic, progressive, and disabling, these diseases mainly affect children, and most do not have medical treatment. According to the Ministry of Health, a disease is classified as rare when it has an incidence of up to 65 cases per 100,000 inhabitants. It is estimated that 13 million Brazilians are affected by these diseases.

It's a high number, as it's the diversity of conditions associated with it. There are six to eight thousand types of rare diseases in the world, according to the World Health Organization (WHO) – 80% of them are of genetic origin. The others result from environmental, infectious, and immunological causes, among others.

The prevalence of gene therapy research focused on rare diseases is explained by the innovative character of the treatments. Fear of significant adverse effects restricted the initial use of this technology to patients with no other chance of cure. "Treatments today are safer, but genetic diseases are still the focus, especially because of the high cost of treatments," says geneticist Guilherme Baldo.

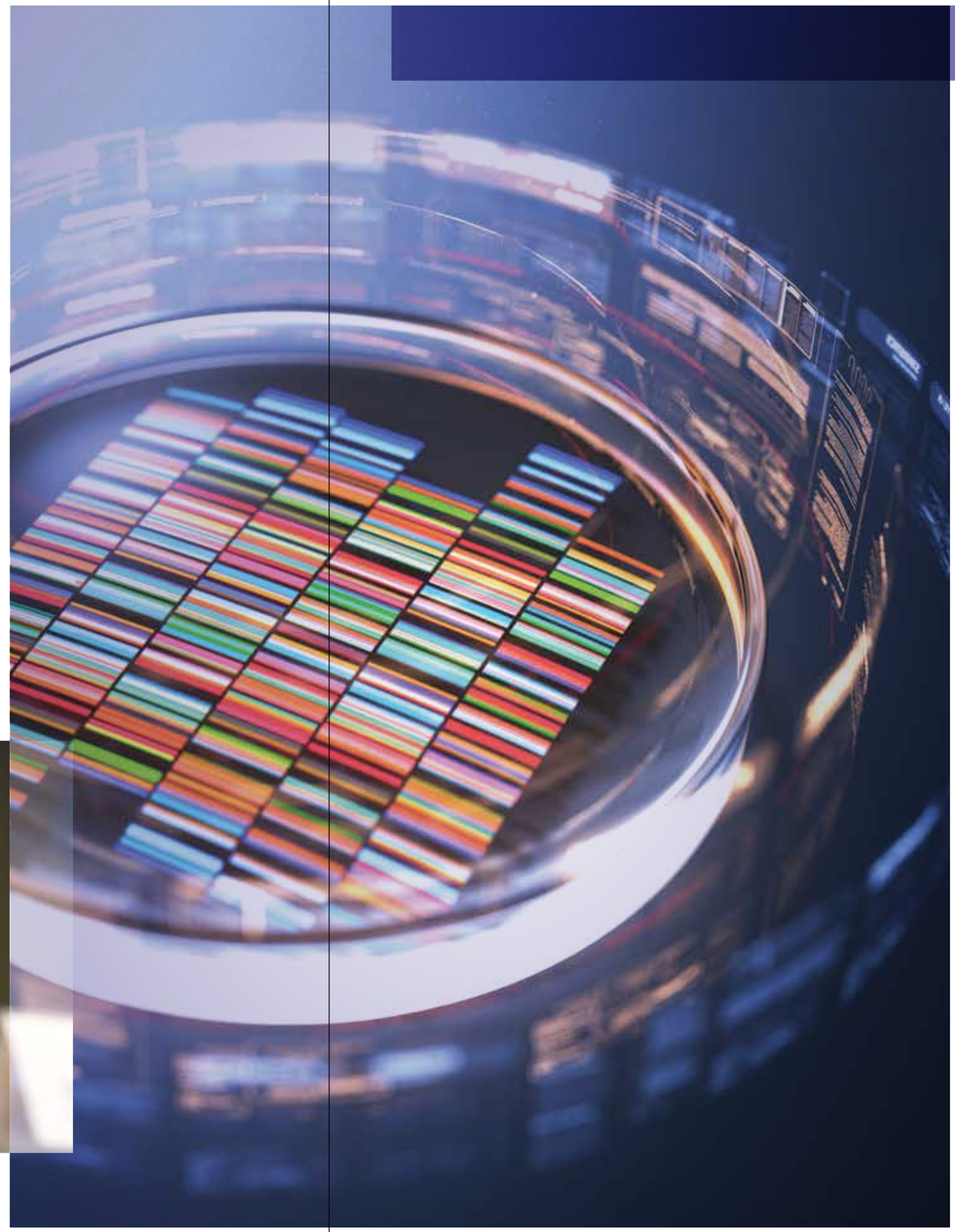
"Treating a patient with gene therapy costs around 1 million to 2 million US dollars today. This does not make it a viable choice for diseases that already have cheaper solutions," says Baldo. In the case of rare diseases, however, such reasoning is reversed. A patient suffering from mucopolysaccharidoses, for example, costs 1 million reais per year for a lifetime because he or she needs to replace an enzyme – not produced by the body – in the hospital once a week. Gene therapy can solve this kind of problem with a single intervention.



GENETIC INFORMATION CAN TRANSFORM CLINICAL DECISIONS

Detecting the disorder early in life increases the patient's chances. State-of-the-art exams guarantee a greater possibility of treatment success

WAGNER BARATELA,
GENETICIST PHYSICIAN



Featured by a wide range of signs and symptoms, rare diseases are difficult to diagnose, leading to the late discovery in many cases. Indeed, it contributes to the high rate of patients who die before five years of age (30%). Detecting the disorder early in life can change the history of the disorder and increase the chances of the patient.

"The diagnosis is fundamental, and we have evolved a lot in this area in recent years. We can now map by genetic analysis diseases that required us to order invasive tests such as muscle biopsy to investigate muscle dysphorias," says geneticist Carolina Fischinger.

The information that cutting-edge exams offer transforms clinical decisions. And not just for rare diseases. Some cancer situations may be more likely to be correct when the evaluation is accompanied by molecular tests to define the medical's conduct.

In the case of rare diseases, it is possible to know which specific mutation caused the symptoms and then opt for the best treatment. "We are living in a promising moment, but it is important to point out, especially to families, that there is still a long way to go," says geneticist Wagner Baratela.

DAVID SCHLESINGER,
DIRECTOR OF LABORATORY
EXPERT IN GENETIC TESTING

EXOME SEQUENCING

Today, among the most robust genetic examinations, there is complete sequencing of the exome, which scans the entire coding region of the human genome for changes. It can detect the genes responsible for complex diseases and solve uncertain cases. It is incorporated into SUS as the first line of diagnosis of intellectual disability.

Price, however, is a strong barrier to its use. "When it appeared, the exome was performed for around 6,000 US dollars. Today it costs about $ 1,000 reais. The idea is to make the diagnosis of rare diseases faster, more accurate, and more accessible," says David Schlesinger, neurologist, and director of the Mendelics genetics laboratory.

Reality shows that the value is still far from allowing access to all Brazilians in need. "Availability by the SUS [public healthcare system] is extremely limited, and parents are unable to pay – they ask the church for help to pay for the exam," says Mara Lucia Schmitz

The exome is recognized as one of the most important tools for genetic research today and needs to be present in medical indications, but it requires a complex interpretation of results and does not rule out clinical analysis. "You have to know what to look for, so the diagnosis should always start with patient evaluation. The test cannot be a crutch for physicians," says geneticist Baratela.

THERE IS ALWAYS A PATIENT FACING A TECHNOLOGICAL BREAKTHROUGH

CARMELA GRINDLER, TECHNICAL DIRECTOR OF HEALTHCARE,
SECRETARY OF HEALTH OF THE STATE OF SÃO PAULO

Gene therapies are a great promise for complex diseases, which explains the high expectation created around positive outcomes. But from the perspective of patients and their familiar context, there is a very important gain that predates the clinical outcome.

"Medicine has risen to a degree never reached, but there is always a patient facing a physician," says geneticist Carolina Fischinger. She emphasizes the benefits of genetic evaluation, which allows finding the causal diagnosis, even when it is not accompanied by alternative treatment. "For parents, it is very important to know what motivated their child's illness," she says.

Neurologist Mara Lucia Schmitz reinforces the importance of accurate diagnosis to support family members emotionally. "Often, the parents' despair comes from not understanding what is going on with their child. The definition of the disease helps to alleviate distress. They stop pilgrimage through doctor's offices looking for answers and start to face the situation in another way," she says.

Diagnosing is not enough, though: it is necessary to implement public policies capable of reducing the social impact brought by these diseases. According to Carmela Grindler, Technical Director of Healthcare of the São Paulo State Secretariat, 80% of the families in which the occurrence of some disorder considered rare occur are headed by women. They frequently lose their employability due to the number of work absences caused by the child's illness.

"They are annihilated families. Assistance is no concession. It is a human right. And these women should not be humiliated, begging for the treatment of their children. They are Brazilian and entitled to high-cost gene therapy. It is not only who can afford who is entitled [to treatment]. We all have children, grandchildren – 30% of rare diseases are spontaneous mutations; we all have a right," she says.

Another important point in the social approach is the inclusion of patients of rare diseases. They need employability to fund themselves. Carmela Grindler highlights the need to ensure dignity for those who will not have effective change with the new treatments: "Has anyone been more productive in life than Stephen Hawking? It is not possible to judge human beings by their degree of disability or dependence. You have to look at what they represent."

APPOINTMENTS' WAITING TIME MAKES TREATMENTS UNFEASIBLE

Advanced medicine requires skilled facilities. There are now only eight referral hospitals for the care of rare disease patients in Brazil

Two years is the waiting time for a child to get an appointment at the Center for the Treatment of Complex Diseases of Hospital Pequeno Príncipe, Paraná. Many die before being treated or receive a late diagnosis when disease progression precludes any possibility of therapy.

The huge demand is explained by the fact that there are only eight hospitals qualified as a reference for the care of rare disease patients in Brazil. There is no way to serve them all. "We received patients from all over the country. Medical appointments are difficult, taking at least one hour for the doctor to understand what is affecting the patient. It is impossible to curb the wait", says Mara Lucia Schmitz, the physician responsible for the center.

Furthermore, it goes the same way in other states. With only one center of reference approved by the Ministry of Health, the state of São Paulo awaits the government's authorization to put into operation seven ready-made state-of-art centers. "We need to extend specialized care. The healthcare system does not serve the patient who has a rare disease. If the signals are not clear, they go through the service and wander from doctor to doctor to treat the symptoms," says Carmela Grindler, technical director of Healthcare of the São Paulo State Secretariat.

Once the patient is diagnosed, and with a possibility of treatment, the struggle for obtaining high-cost medication begins. The judicial path – or judicialization – has been a means of access, but it is still not a guarantee, according to Schmitz, because government delivery sometimes fails. "The lack of medicine at the right moment can lead to metabolic crises and cause a child who could be normal becomes one with special needs," she says.

Similarly, the lack of training because of the absence of centers of reference. Some treatments reach the patient by injections in the brain; others are inserted into the spinal cord; the administration route varies according to the disease, but the converging point is that they always require specific care. "The procedure is as important as the medicine, we need qualified centers," says Antoine Daher, president of Casa Hunter, an entity focused on rare disease patients.

MARA LUCIA SCHMITZ, PHYSICIAN RESPONSIBLE FOR THE CENTER FOR THE TREATMENT OF COMPLEX DISEASES, HOSPITAL PEQUENO PRÍNCIPE, PARANÁ

ANTOINE DAHER,
PRESIDENT OF CASA HUNTER

GABRIELA TANNUS,
GENE THERAPY FORUM MODERATOR

DEVELOPMENT OF NEW THERAPIES ADVANCES IN THE WORLD

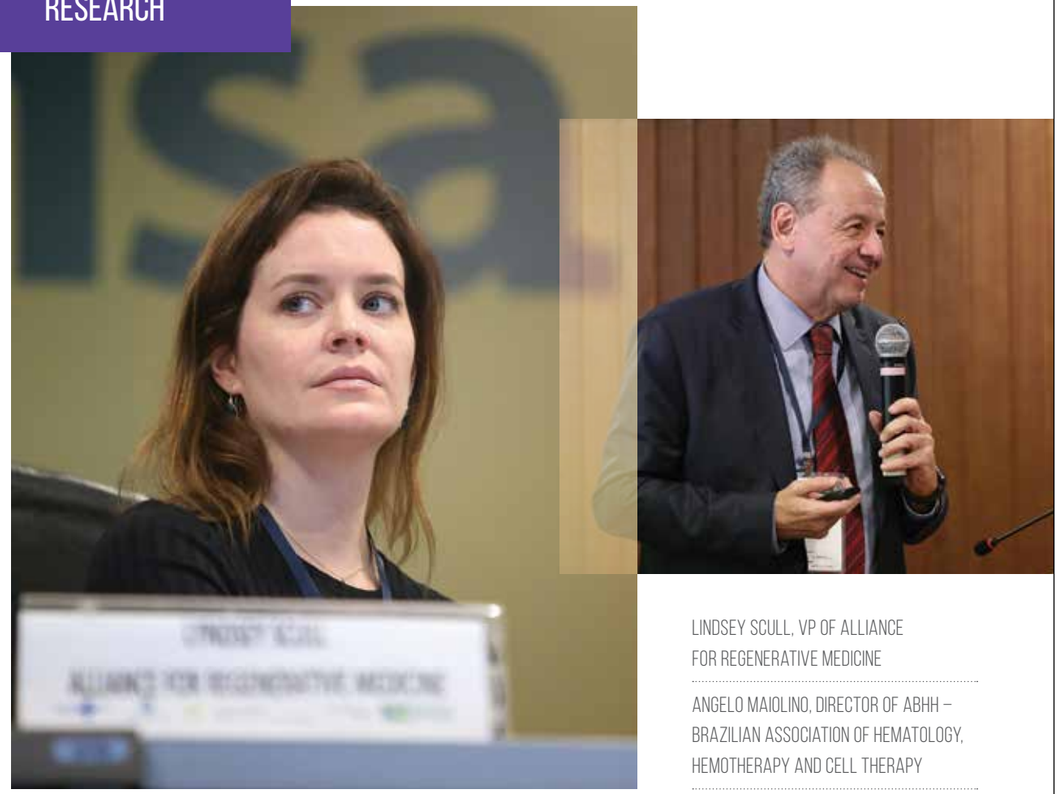
Prospects are encouraging: More than 30 billion US dollars have been invested in advanced medicine since 2016 – and results are starting to emerge

JONAS SAUTE, GENETICIST PHYSICIAN OF HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

There are now 953 companies in the world developing advanced medicine, including those working with gene therapy, cell therapy, and tissue engineering development. The figures are from the Alliance for Regenerative Medicine, headquartered in Washington, DC. (USA), and follows the development of advanced therapies across the planet.

The organization estimates that 32.7 billion US dollars have been invested in the development of new treatments from early 2016 until now. At the onset, there were about 700 clinical trials in progress. Currently, there are 1,071, of which 96 in phase 3, i.e. the final stage to reach the market.

Prospects are encouraging, according to the Alliance for Regenerative Medicine. “Last year was decisive. No less than 13.1 billion US dollars have been invested in the industry, and 2019 is on track to reach or exceed this level,” says Lindsey Scull, VP of Communications. According to her, even companies that are not yet profitable are on investor radars because of the potential of their research.



LINDSEY SCULL, VP OF ALLIANCE FOR REGENERATIVE MEDICINE

ANGELO MAIOLINO, DIRECTOR OF ABHH – BRAZILIAN ASSOCIATION OF HEMATOLOGY, HEMOTHERAPY AND CELL THERAPY

In Brazil, scientists working in the area estimate that the country is far from being able to take advantage of these resources. “We are very late; we lack equipped centers that meet all biosafety protocols and can provide critical services for clinical research. We do not have funds to study, and we depend on the interest of the pharmaceutical industry to go ahead,” says Guilherme Baldo, professor at the Federal University of Rio Grande do Sul.

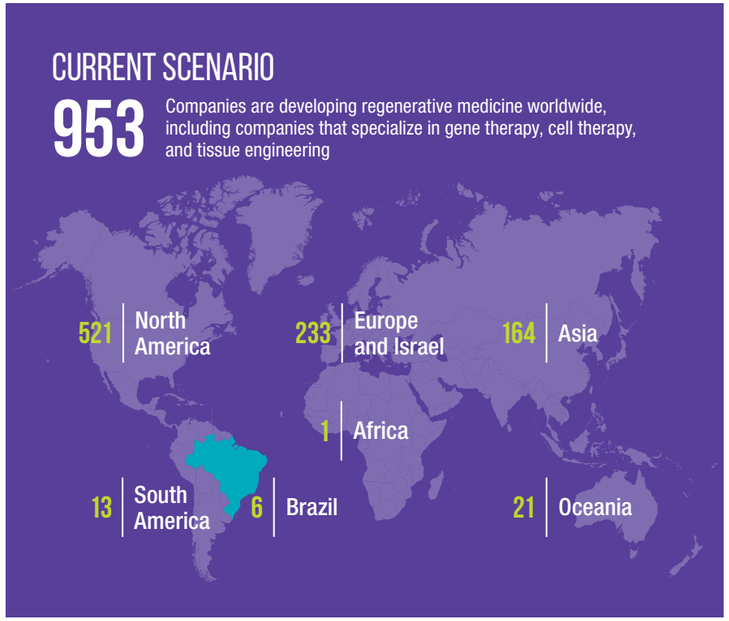
Significantly, the result of the lack of investment increasingly restricts access to the benefits of new technologies. “Everything is done in developed countries and arrives here for an impractical price. If we researched in Brazil, it would be easier to incorporate them into the healthcare system, and we would know better the effectiveness of each medication,” says Jonas Saute, a geneticist at the Hospital de Clínicas de Porto Alegre.

Bruno Abreu, Sindusfarma’s director of Market and Legal Affairs, sees the alignment of research groups with industry as fundamental. “We have a horizon of 40 to 60 new gene therapies to be launched by 2030. In fact, this a spinning machine: having medicines on the market also allows the industry to fund future research,” he says.

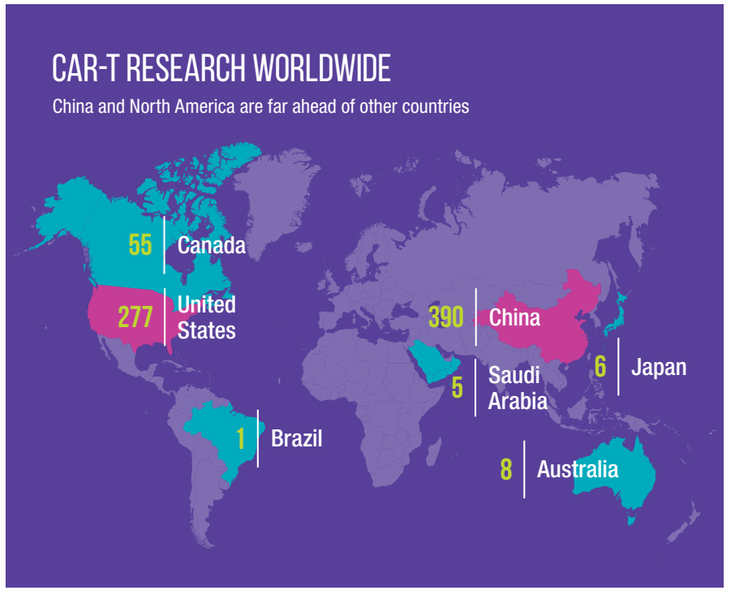
We are no lacking capable scientists. “Our professionals are top-notch,” says Antoine Daher, president of Casa Hunter, a support organization for patients of rare diseases. “Gene therapy in a few years will be a tool to treat all kinds of diseases, not just rare ones. If we invest in research, we will have national patents, and this will help to ensure the sustainability of the system”, he says.

Despite all the difficulties, Brazil has a well-developed basis In some areas, such as the processes involving the CAR-T therapy, whose path is very promising, according to Angelo Maiolino, director of the Brazilian Association of Hematology, Hemotherapy, and Cell Therapy (ABHH). “We are evolving very fast, so we strongly need more industry clinical trials in our centers. We have full conditions to make it happen,” he says.

> “WE NEED TO HAVE OUR CLINICAL RESEARCH – IT IS MANDATORY, THIS SHIP HAS ALREADY SAILED.”
>
> ANGELO MAIOLINO



Source: Alliance for Regenerative Medicine



Source: https://clinicaltrials.gov & http://www.chictr.org.cn

“BRAZILIANS WILL NOT BE LAB RATS”

For Anvisa, technical assessment of patient risks is a priority to establish a modern regulatory framework for Advanced Therapy Products

Saving lives, permanently curing diseases without treatment beforehand, improving the quality of patients’ lives: the real perspectives of gene therapies allow us to glimpse a new world order in healthcare. But the size of the ambition is in proportion to the challenges. Efficiency, risks, and high costs are some of the questions that stand in the way of this almost utopian future and demand the mobilization of all those involved in the sector.

Among these points of attention is the technical risk assessment, a priority of the National Health Surveillance Agency (Anvisa), an authority linked to the Ministry of Health. “Patient safety must be preserved – the Brazilian population will not be guinea-pigs,”, says William Dib, president of the entity at the head of the mission to establish a regulatory framework for Advanced Therapy Products (ATP).

The work in progress is under the responsibility of the Blood, Tissues, Cells, and Organs Management office, linked to Anvisa. João Batista da Silva Júnior, the area manager, emphasizes this imperative view in the process of registering advanced products and therapies. “A therapeutic product cannot be made available to humans without having a whole headroom in preclinical studies,” he says. “The balance between risk and benefit is the motto of our work.”

WILLIAM DIB,
DIRECTOR-PRESIDENT OF ANVISA

ROSANA MASTELLARO, DIRECTOR OF REGULATORY AFFAIRS OF SINDUSFARMA

JOÃO BATISTA DA SILVA JÚNIOR,
RESPONSIBLE FOR BLOOD, TISSUE, CELLS AND ORGANS MANAGEMENT AT ANVISA

Silva Junior points out that the discussion at Anvisa occurs since 2012, with an important milestone in 2018, when the agency published two norms that conceptualize these products in the country: the introduction of mechanisms of good practices in cells (RDC 214 in the Brazilian acronym) and the definition of procedures and regulatory requirements for conducting clinical trials with advanced therapy products in Brazil (RDC 260).

“The international experience shows that the regulatory agency needs to be very close to developers at this time,” says Silva Junior. He uses the United States as an example.

“If you look at a product’s history, it is being discussed by the agency five or six years during development. It facilitates the process. When the dossier is submitted for approval, everything goes faster.”

Sindusfarma’s director of Regulatory Affairs, Rosana Mastellaro, believes Anvisa is on the right track. “Having regulation for these products puts Anvisa at a level similar to other leading regulatory authorities, such as FDA, Europe’s EMA, and Japan’s PMDA,” she says. “Having clinical research in the country will bring opportunity and hope for treatment and often cure for our population.

REGULATORY CONVERGENCE

The United States holds the largest number of advanced therapy product records in the world today. They have 16 records, considering the inclusion of umbilical cord cells, which is not done in other countries. Without them, that number drops to eight – the same as Europe. Far ahead is South Korea, with 14 records; India and Japan have four; Canada, two; and Australia and China, one.

Currently, Brazil has one product for gene therapy for the treatment of hereditary retinal dystrophy under analysis. Cooperation with other countries is crucial. "We follow an international model because this development is global. We need to understand this properly so that we can make Brazil develop in this area with the same quality and competitiveness," says Silva Junior. Although the standards are convergent, he points out that this does not mean a world standardization.

Last August, Anvisa submitted the theme of gene therapy to public consultation (document reference CP 706), and the results are expected to emerge in early 2020. Four types of registration are being proposed: complete, simplified, conditional approval, and, exceptionally, with a registration waiver (see image). At first, priority would be given to products developed in clinical trials in the country.

RECORDS PROPOSED BY ANVISA

CLASS I (SIMPLIFIED)	UPON RECEIPT, AND IF THE PRIORITY CATEGORY IS VERIFIED, ANVISA WILL HAVE 120 DAYS TO COMMENT. THE VALIDITY OF THE REGISTRATION WOULD BE 5 YEARS, WITH THE POSSIBILITY OF RENEWAL.
CLASS II (COMPLETE)	MORE EXTENSIVE DOCUMENTATION AND STUDIES ARE REQUIRED FOR CASES THAT DO NOT QUALIFY AS PRIORITIES. UPON RECEIPT, ANVISA WILL HAVE 365 DAYS TO COMMENT. THE VALIDITY WOULD ALSO BE 5 YEARS, RENEWABLE.
CLASS III (UNDER CONDITIONAL APPROVAL)	USE IN SERIOUS DEBILITATING CONDITION, IN THE ABSENCE OF COMPARABLE ALTERNATIVE THERAPY. ANVISA WILL HAVE 180 DAYS TO COMMENT. THE VALIDITY WOULD BE ONE YEAR, WITH THE POSSIBILITY OF RENEWAL UP TO FIVE YEARS.
REGISTRATION WAIVER	IT APPLIES TO PRODUCTS DEVELOPED FOR SPECIFIC PATIENTS, FOR TREATMENT OF DISEASES WITHOUT ALTERNATIVE THERAPY IN THE COUNTRY AND UNDER IMMINENT LIFE-THREATENING CONDITIONS. ANVISA WILL HAVE 30 DAYS TO COMMENT.

CLINICAL TESTS SINCE RDC260 (2018)

3 APPROVED
In vivo gene therapy in the areas of Hematology and Neurology (global sponsor)

5 UNDER APPROVAL
Advanced Cell Therapy in Orthopedic (national sponsor)

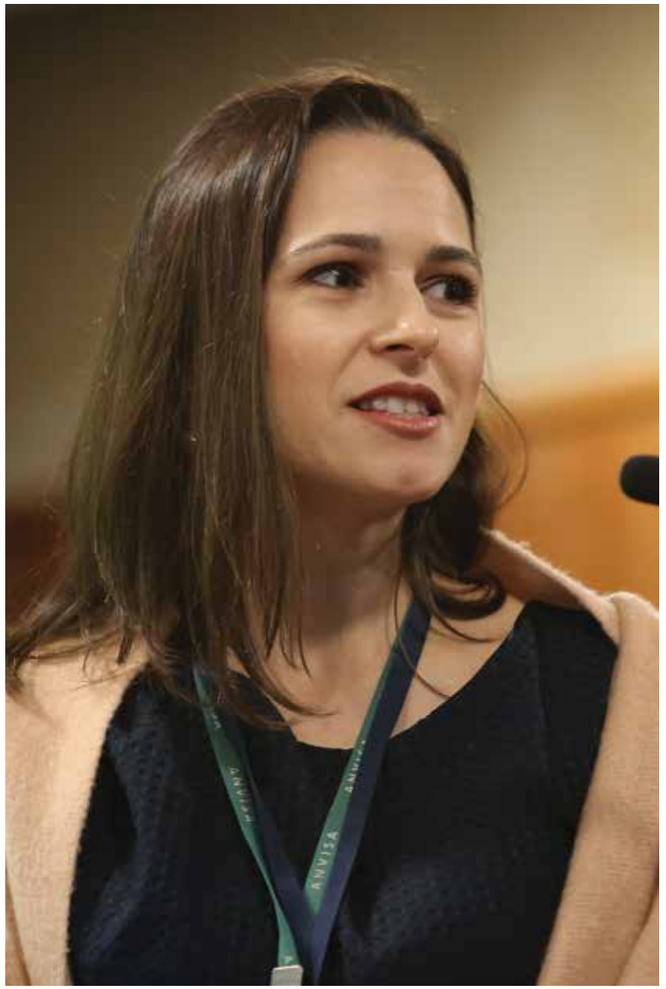
3 UNDER ANALYSIS
In vivo gene therapy and ex vivo gene therapy in Ophthalmology and Oncology (global sponsor)

2 REJECTED
In vivo gene therapy

AUTHORIZATION REQUIREMENTS

All companies involved in manufacturing an advanced therapy product shall comply with Good Manufacturing Practice as set forth in RDC 214, documented in clinical and non-clinical reports.

CLASS I	Report of all non-clinical and clinical studies performed with the product, which may be given priority in cases of rare, neglected, emerging or reemerging disease, public health emergencies or serious debilitating conditions, and where no alternative is available. available therapy.
CLASS II	Report of all non-clinical and clinical studies performed with the product, as well as quality dossier, in the cases provided for in Art. 23 of Chapter V of CP 706.
CLASS III	Report of all non-clinical and clinical studies performed with the product, as well as full schedule of clinical studies yet to be performed for efficacy, package leaflet, and medical information re-evaluations.
REGISTRATION WAIVER	Notification to Anvisa with information on use and prior clinical experience with the product and available non-clinical and clinical data information. The product is not marketable.



DEFINITION OF PRICES NEEDS TO GO ALONG WITH MODERNIZATION

Challenges for implementing new technologies include decreasing the high tax burden on medicines and ending the pricing model

PRISCILA GEBRIM, OF THE MEDICINES MARKET REGULATION CHAMBER (CMED)

The emergence of new medical technologies represents a global challenge related to the economic viability of treatments and medicines. In Brazil, they evidenced old and known problems, which made the discussion unavoidable in our current reality. "The bar has gone up a lot," says Bruno Abreu, director of Market and Law Affairs at Sindusfarma, for whom two of the major problems are the tax burden and the archaic model of pricing and control.

Abreu points out that the Medicines Market Regulation Chamber (CMED), an interministerial body of the Sanitary Surveillance Agency (Anvisa), was born in 2003 and was expected to last only one year but it lasts until today. The entity's Resolution No. 2 was disclosed in 2004, establishing, until today, the legal framework for the pricing of products. Since then, there have been several attempts to review this resolution, to no avail. There is a retry currently in progress, but it is delayed.

"Resolution 2 was very modern when it came out, but today it does not respond to the needs of the sector," he says. "It is completely out of step with new technologies." CMED's Priscila Gebrim Louly recognizes the lag. "By the current regulation, gene therapies will be treated as new drugs, and should go through all the stages provided for in pricing," she says, also noting that new technologies are within the scope of the ongoing review.

TAXES VS. INVESTMENTS

Another bottleneck pointed out by Bruno Abreu is the fact that Brazil is the country that charges the most taxes on medicines in the world. The figures can reach 31.3% of high-cost medicines in Brazil, while the international average is 6%. Argentine comes second, with 21%. "Countries that are similar to us, like Mexico, have a zero tax policy," he says. Moreover, tax exemption is not uncommon: it exists in the United States, Colombia, Canada, and Venezuela, among others.

"We are breaking a very important knowledge barrier," says Nelson Mussolini, Sindusfarma's Executive President. "We need to know how governments are going to treat this new way of saving lives, of bringing people into a productive environment."

> "In Germany, the evaluation of gene therapy products is based on relevant evidence for the patient: mortality, morbidity, quality of life and side effects, always considering the severity of the disease."

MERIEM BOUSLOUK-MARX
Drug Incorporation Specialist

DATA TRANSPARENCY IS A PREMISE FOR MEASURING COSTS

For experts, focus on the definition of healthcare value should not be on the remuneration of the services provided, but on the patients' quality of life

CESAR ABICALAFFE, PRESIDENT OF THE BRAZILIAN INSTITUTE OF VALUE IN HEALTH (IBRAVS)

The measurement of healthcare value – fundamental to the public and private sectors – is crucial for advanced therapies because of their high cost. Most experts today argue that the focus on defining this value should not be on the remuneration of the services provided, but on patients, their experience, and quality of life. First and foremost, transparency in the data is required to integrate the user into this process.

"The bottom line of the concept of value is precisely getting a healthcare system that can effectively deliver results, clinical outcomes, to patients. But obviously with an adequate cost to make this delivery", says Cesar Abicalaffe, president of the Brazilian Institute of Health Value (IBRAVS). The challenge is huge.

Worldwide, the concept of Value-Based Healthcare (VBHC) is ahead of this trend. Its creator, Michel Porter, professor and researcher at Harvard University, rightly starts from the need to contain the high costs of healthcare, proposing a new relationship between everyone involved in the system – industry, financiers, providers, and patients. One of its pillars is the transition from the procedure-based payment model to the clinical outcome payment obtained.

"One of the great features of the value concept is precisely the transfer of risk to industry and the service provider," says Abicalaffe. "For the system to find new treatment alternatives, contractual arrangements for sharing risks." He believes this would be a way to lessen existing uncertainties when incorporating new technology and unlocking funding.

A key point is the transparency. According to Abicalaffe, it involves measuring the performance and performance of service providers, something that is a reality in other countries, but not in Brazil. The difficulty is not only technical, as our healthcare data are poor, but also political. "Imagine ranking doctors and hospitals," says Abicalaffe, predicting the backlash from those involved.

HEALTHCARE SCORE VALUE

Taking into account, on the one hand, the prospects for economic gain of industry, financiers and service providers, and, on the other, patient experience, IBRAVS has been developing a possible specific methodology for the Brazilian reality. It will enable both the implementation of new technologies such as genetics and the access of the public to them.

Still in tests, the EVS (Healthcare Value Score in the Brazilian acronym) is an attempt to create a multidimensional basis with composite metrics that combine standardized indicators (see box). Hence the need to have accurate data on the clinical condition of patients and definition of care lines. This is critical not only for management and treatment but also for enabling risk-sharing contracts.

"It is possible to have an EVS for the clinical staff of a hospital, for the cooperative physicians of an organization, or an illness. But everything has to do with how the indicators between quality and cost are composed," he says. Through a formula, one can measure the indicators in isolation, know which ones are good and bad, and ultimately have a unique index.

In the proposed model, there is a greater weight for quality, precisely to meet the need to share risks among all involved in the system. "The application of this is not easy because we're breaking a paradigm. The traditional model is centered on service providers, and we need to focus on the patient. It takes a lot of work."

HOW IT WORKS

EVS is obtained from a set of indicators, standardized for the Brazilian market, which translate into the following equation:

$$EVS = [IQ \times p + IC \times (1-p)] \times 0{,}05$$

IQ QUALITY INDEX

Unique composite indicator from 0 to 100 generated from the grouping of indicators such as structure, process efficiency, results. Each of these aspects has its own score, also from 0 to 100, and the result indicators add up to at least 70% of the IQ. Applying the quality p weight (from 0 to 1) in total, the weight of the IQ in the equation will mean 70%.

IC COST INDEX

Unique composite indicator from 0 to 100 generated from other indicators related to the cost of producing services depending on the perspective of return, different for the financier and service provider. Applying the quality p weighting in total, the IQ weight in the equation will mean 30%.

P WEIGHT QUALITY (0 TO 1)

JEREMY SCHAFER, OF THE
PRECISION FOR VALUE AND HEALTH

TERRITORIALITY

In the public system, which serves 75% of the Brazilian population, the challenge is similar, but with important differences. Joselito Pedrosa, Healthcare Management consultant, points out that Brazil is the only country in the world with more than 100 million inhabitants to have an integrated universal healthcare system. In this reality, other variables must enter the value definition account.

"There is the perspective of the doctor, the healthcare provider, which is very different from that of the public manager in different parts of the country," he says. "Territoriality is a weighting factor. (…) The value in [the state of] Rio Grande do Sul will be different from [the state of] Acre, as it is different between the population of the East Zone and Morumbi [regions in the city of São Paulo]". According to him, a fundamental aspect to consider is the differences in infrastructure between these different places, which radically changes the perspective of the patient.

Notably, information asymmetry among stakeholders, especially on the part of users, is another complicating factor for the correct measurement of the results. The result is an excess of tables as negotiating tools. "The remuneration model is bankrupt; it benefits someone that we do not know yet, but it does not benefit the whole system and its users. Everyone loses." Pedrosa also says that the speed of technology poses more challenges. "By the time you finish analyzing a process of incorporating a product into healthcare, there's another newer technology knocking on the door."

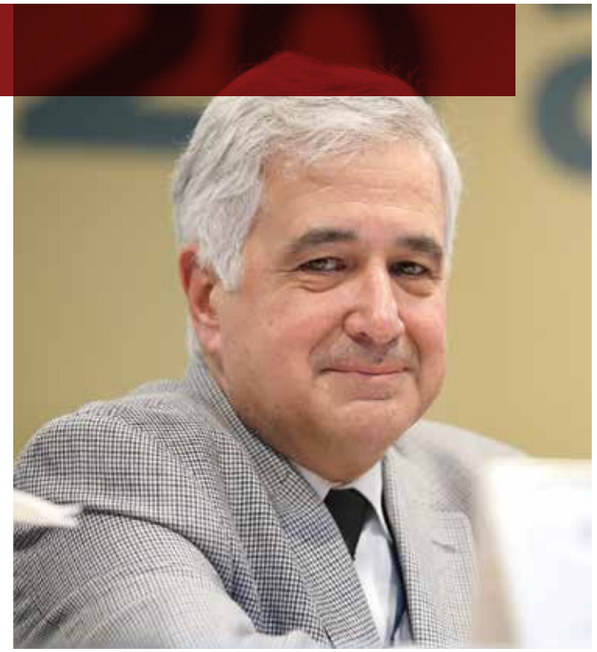
FINANCING INFORMATION

In the case of advanced therapies, there is another obstacle: because they are new technologies, the data are always insufficient to evaluate the cost-effectiveness of products. "In traditional therapies, it is easy to predict what might happen in the long run, but it doesn't happen with gene therapy," says Jeremy Schafer of Precision for Value and Health. Schafer points out that this is a complicating factor in short-term financing models, as in the US and in several countries.

"Significant upfront costs can deplete financial resources before benefits are realized," he says. In Brazil, the uncertainties about the efficacy – and safety – of these new therapies are also an issue that is imposed by the current pricing criteria.

Priscila Gebrim Louly of the Medicines Market Regulation Chamber (CMED) says the entity's regulatory framework is already under review. "These are very costly therapies worldwide. The challenge is how to set a fair price from the industry, patient, and investor perspective," she says.

SHARE OF RISKS INCREASES POSSIBILITIES



ANDRÉ CEZAR MÉDICI,
HEALTH ECONOMIST OF THE WORLD BANK

Gene therapies represent not only a paradigm disruption in the treatment of disease but also in the business models of the pharmaceutical industry, according to André Cezar Médici, health economist at the World Bank. He says that new financing models are needed in this new reality.

"Allocative efficiency is very much the logic by which pharmaceutical companies work today," explains Medici. "The price of the product or service offered must reflect the marginal costs of production, i.e. the opportunity cost. If we prioritize allocative efficiency, companies may find it difficult to achieve an adequate risk-adjusted return on investment because R&D costs will not be recovered."

To illustrate the scale of the problem, Medici uses numbers from the United States, where estimates point to investments between 1.3 billion and 2.6 billion US dollars for the development of a biological agent, cheaper than the genetic one. But the maximum can reach $ 5 billion, taking into account the failures in the process. The pharma Merck, for example, claims that 75% of its costs of R&D correspond to failures. A returnless and discouraging cost.

In fact, with the prospect of cure, companies need to think about long-term return models compared to palliative treatments that may eventually consume even greater resources throughout the patient's life. This is of special consideration in universal public systems with the SUS. "In the insurance healthcare market, however, we have a problem. Savings may not be rewarded because patients can simply switch operators," he says.

Alternatives designed to solve these dilemmas include the risk-sharing model, in which patients or insurers-providers do not pay if therapy fails to produce the expected clinical outcome. Pharmaceutical companies assume part of the risks and costs if results are not achieved. "This model has been successfully used in France and Spain to manage the costs of some drugs, and Medicare in the United States already uses such arrangements to cover the lymphoblastic leukemia gene."

The latter, according to Medici, makes gene therapies the main candidates for value-based pricing. "Value-based pricing must come from the perspective of the patient and society and take into account the net benefit of gene therapy throughout the individual's life," he says.

TECHNOLOGY INCORPORATION REQUIRES NEW HEALTHCARE MANAGEMENT

Today's rigid system is unable to absorb advanced therapies, which require accurate measurement of benefits and sustainable agreements

The radical change in the way we treat disease still has a long and complex way to go. All the issues involved in the current debate around new technologies – cost, financing models, regulation, and clinical research – concur and converge on one key point of this transformation: the need to make advanced therapies products economically viable, ensuring the population's access to them.

"There is no point in having the technology available and not accessible," says Denizar Vianna, secretary of Science, Technology, and Strategic Inputs at the Ministry of Health. To overcome this breakdown, it is essential to start by changing the system itself, which today cannot incorporate these new treatments.

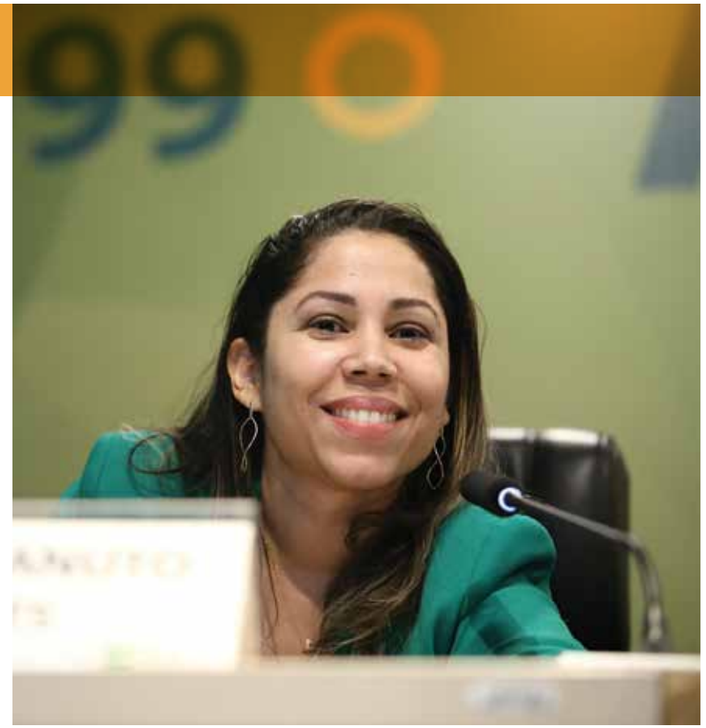
"We need to change the financing model," he says, stressing that a "management shift" at the Ministry is mandatory. "Either we have changed, or we will continue to put out fires." The numbers weigh. "Is the SUS missing money? Yes, and we have to discuss this. But we have to make better use of available resources, and for that we need to be innovative in the financing."

Sindusfarma's Executive President, Nelson Mussolini, says that gene therapy is a step towards the future, but recognizes that making it accessible is not an easy matter and will require much debate. "We need to define how governments will address this new way of saving lives, recovering people and bringing them into the production environment, he says. "I always say that medicine is an investment, the state cannot regard it as an expense; it is much better to have productive people than in hospitals."

Anvisa's Director-President, William Dib, agrees. "It is necessary to find a common ground in which everyone wins so that the population can obtain this treatment safely and with quality."

Although expensive, these new therapies can reduce costs as they would save on current treatments that require hospitalizations and procedures throughout the patient's life. But the lack of data is once again a complication. "Not even the United States has achieved a cost-benefit ratio that meets this market," says Jeremy Schafer of Precision Value & Health. "The industry needs to offer parameters to prove that the product really works, and who is paying needs to insist on these indicators."

To evaluate is, in fact, the great challenge of incorporating new technologies. In Brazil, this task is under the responsibility of the National Commission for the Incorporation of Technologies in SUS (Conitec), a collegiate body chaired by Secretariat of Science, Technology, Innovation, and Strategic Inputs, with 13



DENIZAR VIANNA, SECRETARY OF SCIENCE, TECHNOLOGY, AND STRATEGIC INPUTS OF THE MINISTRY OF HEALTH

VANIA CANUTO, DIRECTOR OF TECHNOLOGY MANAGEMENT

OTAVIO BERWANGE, DIRECTOR OF ACADEMIC RESEARCH OFFICE (ARO) OF HOSPITAL ALBERT EINSTEIN

representatives from the other secretariats of the Ministry of Health.

One of the goals of Conitec is to accurately measure the benefits of gene therapies while drawing up new financing arrangements that can make them feasible. “Few healthcare technology assessment bodies have established specific pathways or requirements for gene therapy products,” says Vania Canuto, the agency’s director. “Agencies are used to evaluating randomized controlled trials, and in such cases, such studies are not feasible.”

SUS AND ANS

In addition to innovation with the development of new methodologies, there are other demands on the path under debate in Brazilian society and the world. “The question is not only how to face the high cost of these therapies, but also how to modernize the SUS,” says Antoine Daher, president of Casa Hunter. “And this cannot be attributed solely to the Ministry of Health. Otherwise, we will collapse.”

The issue to be faced, therefore, is to design a new sustainable healthcare model for Brazil. “We have to be partners. In the future, the formula of the Ministry of Health and the operators as buyers and the industry as sellers will no longer work,” says Daher. He asks for greater participation of patient organizations in cost-benefit assessments for technology incorporation.

Schafer reports that one of the major problems in the United States is that most people are in the private system, where the user can change its insurance model at any time – which inhibits operators’ interest in cover the costs of these new treatments as they would not be compensated for by the end of long treatments.

In Brazil, the National Supplementary Health Agency (ANS) faces the same obstacle. Moreover, there are additional difficulties regarding the regulatory mechanisms of the country. “We need a new model,” says Rogério Scarabel, director of the National Agency for Supplementary Health (ANS). “We have several payers, with different sizes. Of the 733 operators in Brazil, 447 have up to 20,000 lives. We need to discuss the economic impact.”

“The solution of the problem – and that is a big problem – it is a shared one,” says Bruno Abreu, director of Market and Law Affairs at Sindusfarma, which follows Scarabel in need to update the regulatory mechanisms, with more transparency and involvement of society. “The solution also goes through culture changes. When we have a big challenge like this, we need to take advantage of it. It is an opportunity window that we cannot afford to miss,” he says.

PILOT PROJECT

In the path of innovation, the first step has already been taken. This year, the Ministry of Health implemented a risk-sharing financing pilot project, which is currently the alternative that most mobilizes attention among experts in the sector. “It is an agreement based on expectation of patients’ range, on medium-term clinical outcomes of follow-up of these patients, which will provide us with the monitoring of the results,” says Denizar Vianna, Secretary of Science, Technology, and Strategic Inputs at the Ministry of Health.

On the horizon is the measurement of the effectiveness and effectiveness of treatments, which today are not part of Conitec’s structure in evaluating the incorporation of therapies and drugs – and which are fundamental for the subsequent definition of their value, enabling financing and, consequently, access.

The pilot project has been run in partnership by the Ministry of Health and the Academic Research Office (ARO) of the Hospital Albert Einstein, in São Paulo. The idea is to generate real-world evidence – post-registration data using costing, administrative, and outcome data reported by patients and physicians.

“We are taking care to define the methodological results from a clinical study and real-world data from a given technology to prove its day-to-day benefit and facilitate decision-making.” This is a key point of the risk-sharing model. “The idea is to evaluate the outcome in the real world and partially pay only for how much is achieved with patient follow-up,” says Jonas Sauté, a physician who works at the Medical Genetics, Neurology, and Internal Medicine at the Hospital de Clínicas de Porto Alegre. “If the patient has improved 10%, this is the amount I have to pay for the medication, for example. But for that the metrics are key.”

RULES'S ARCHAISM HAMPERS PARTNERSHIPS

Old-fashioned, bureaucratic, and unsuitable for the healthcare sector, legislation regulating government procurement makes access to new technologies unfeasible

RENATA CURY,
HEALTHCARE LAW SPECIALIST

FERNANDO MENDES GARCIA NETO,
DIRECTOR OF ANVISA

NELSON MUSSOLINI, ALESSANDRA BASTOS AND DENIZAR VIANNA

"If we do not change the existing system – bound, legalistic, bureaucratic – we will not be able to fund innovative therapies." The statement by Denizar Vianna, Secretary of Science, Technology, and Strategic Inputs at the Ministry of Health, opens up a key issue. On the agenda is the urgent need to reform current legislation to meet the new times.

This issue clearly illustrates the obligation to use the Bidding Law (1993) for government procurement of medicines. "It's a law designed to hire infrastructure works, made for another type of market, and we use it in healthcare," says the secretary. Moreover, the lag extends to other mechanisms in the sector.

Sindusfarma's director of Market and Legal Affairs, Bruno Abreu, agrees. "Legislation has to keep up with the innovative spirit of new technologies coming to allow them to be incorporated into healthcare systems with agility, transparency, and legal certainty." Alessandra Bastos, Anvisa's director, recalls that the municipality is bound by a 1976 law that defines what medicine is.

Notably, archaism is the most visible aspect of a model that needs deep adjustments. "Brazil has one of the few universal healthcare access systems that make a single, initial purchase, and pays everything on entry. It has no other subsequent bonus and penalty mechanism based on results," says Denizar Vianna. It is good for negotiating price with the manufactures, but it prevents the implementation of financing alternatives for gene therapies.

The final adoption of the risk-sharing model – which has been gaining momentum in the world for the incorporation of advanced therapies – finds this obstacle since it provides precisely for the payment by clinical outcome – a solution to face the high costs. "Risk-sharing establishes possibilities for partnerships between the public and private sectors, which were once almost antagonistic," says Renata Cury, a Healthcare Law specialist.

"A Swedish study shows how the risk-sharing payment system is more valuable and saves money for a developing country," says Cury. Titled The End of the International Reference Pricing System? (2015), the study signed by teachers Ulf Persson and Bengt Jönsson reaches this conclusion by comparing the new model and the traditional one, which is based on the International Reference Price for setting prices for medicines.

Nevertheless, there are legal obstacles that prevent contractual arrangements in this regard. The inadequacy of the Bidding Law, highlighted by Denizar Vianna, is again at the core of the problem, providing that contracts will last only one year in the vast majority of cases. "We need to change. "We need to relax the rules," says Renata Cury.

COST DOUBLES WHEN ACCESS COMES BY COURT ORDER

In addition to the public budget bleeding, expenses with lawsuits establish a framework of uncertainty that impacts prices throughout the chain

The technical, administrative, and financial complexities surrounding advanced therapies are accompanied by a peculiar difficulty in Brazil. Data from the Federal Attorney General's Office show that the expenses of the Ministry of Health with the judicialization of the sector last year represented 1.3 billion reais for the public coffers. When we add the spending of states and municipalities, the value will jump to around 7 billion reais. "It is the Brazilian uniqueness of judicialization," says Denizar Vianna, Secretary of Science, Technology, and Inputs Strategies of the Ministry of Health.

In addition to budget bleed, unforeseen spending establishes a framework of uncertainty that impacts the entire chain, increasing prices, and hampering planning efforts. "Judicialization is not good for anyone," says Bruno Abreu, Sindusfarma's director of Market and Legal Affairs. "Industry needs predictability and legal certainty."

Nevertheless, it is a fact that the judicial route ends up being the only alternative today for the rare patient who needs high-cost drugs, without production scale, or not registered in the country. "It is a citizen's right to go to court, but that should be the exception, not the rule," says Vianna.

BRUNO ABREU, DIRECTOR OF MARKET AND LEGAL AFFAIRS AT SINDUSFARMA

JOSELITO PEDROSA, HEALTH MANAGEMENT CONSULTANT

Weighting finds support again in numbers. "The average value for a patient with a rare disease case ranges from 45 to 55 times compared to other patients with a lawsuit," says Carmela Grindler, Technical Director of Health at the São Paulo State Department of Health.

Measures restricting judicialization are on the agenda at the Federal Supreme Court. For the sector, it is urgent to adjust the rules of price regulation and incorporation. "We now have processes under review that go well beyond the 90-day deadline," says Bruno Abreu. Also, he says that the problem derives largely from CMED's regulatory pricing model. "Only officially the medicines do not enter the system, because they end up entering the court, in a much more expensive route. The government no longer buys at the factory price in these cases, and ends up buying at retail value, which is sometimes double the original amount."

Joselito Pedrosa, Health Management consultant, agrees. "If we use all the money spent on court on other fronts and change the logic of payments – for clinical outcome, for example – the problem of rare diseases will be partially solved."

RARE DISEASES IN THE CONGRESS

"Congressmen are more aware of working to ensure a better life for Brazilians suffering from difficult diseases," says Deputy Diego Garcia (PODE-PR), rapporteur of the Chamber's Special Subcommittee on Rare Diseases. One of the subcommittee's work axes is to gather real data on rare diseases. "We want to know who the patients are, where they are, what kind of disorder they have, what kind of care they can count on," he says.

Garcia argues that from this assessment, it will be possible to establish effective laws. "Today, several proposals are being made in Congress about rare diseases, but there is no point in advancing on paper and have no results in practice," he says. According to him, the difficulty is such that some states cannot ensure even the obligatory Guthrie test.

CROSS-SECTORAL DIALOGUE IS VITAL FOR FINDING SUSTAINABILITY

Government, industry, service providers, patient associations, and scientists agree that access to new technologies depends on the participation of all

The entry of new technologies in Brazil, especially genetics, goes necessarily through a change in the country's health management. But that is not enough. Government, the pharmaceutical industry, service providers, patient associations, and scientists are unanimous in their diagnosis that, because of its complexity, the construction of a new model will only be viable with the participation of all.

Brazil cannot put aside new technologies, given the provisions of the Federal Constitution, which enshrines the universal right to health," says Sindusfarma's Executive President Nelson Mussolini. "As a society, we need to quickly organize and look for formulas to cope with this investment in people's lives. We must not forget that people with health generate wealth for the country!".

NELSON MUSSOLINI,
EXECUTIVE PRESIDENT OF SINDUSFARMA

ROGERIO SCARABEL, DIRECTOR OF THE NATIONAL SUPPLEMENTARY HEALTH AGENCY (ANS)

"We have to sit down together and look for alternatives to fund these new therapies because we can't simply skip treatments because of their high costs," says geneticist Carolina Fischinger. Among the urgent needs is the expansion of specialized centers, the promotion of clinical research, and the modernization of pricing and financing processes to make the system sustainable.

"Physicians and the government have to work together to overcome the price challenge," says Antoine Daher, president of Casa Hunter. "We need to do more partnerships with the industry, bring technology to Brazil. SUS spends millions on inefficient treatments because it does not diagnose correctly and, therefore, does not treat properly. It's money that goes down the drain," he says. "We have to be partners; no one can solve it alone."

The charge is echoed in the federal government. "We are trying to move forward to meet this challenge with an agency model that is more independent in technology assessment, that brings patient organizations into decision-making, because one way to legitimize the decision is to bring the various actors in the process," says Denizar Vianna, Secretary of Science, Technology and Strategic Inputs at the Ministry of Health.

Alessandra Bastos, director of the Health Surveillance Agency (Anvisa), says the agency's aims at working with those involved in the sector in this process, not for them. "For is only for one person – for the citizen, for the patient, for the sick. The academia has to work with the Ministry [of Health], with Anvisa, with the productive sector."

MOBILIZATION IN GOVERNMENT SECTORS

Within the federal government's reach, there is also an effort to meet this demand, according to Raphael Correia, responsible for the General Coordination of People with Rare Diseases in the Ministry of Women, Family, and Human Rights. Correia says that he works closely with the Ministry of Health to ensure the expansion of patient care and to ensure that the rights established by law reach the people who need it. "Our eyes are not only on the patient but also on the family, always greatly affected by the problem."

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