e-ISSN 2594-2166 Medicina y ética, vol. 37 núm. 3, July-September, 2026

Rare diseases, therapeutic equity and human dignity: ethical challenges of scientific innovation in Mexico

Las enfermedades raras, la equidad terapéutica y la dignidad humana: desafíos éticos de la innovación científica en México

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CÓMO CITAR: Ocampo-Ortega, S. A., Villafaña Rauda, S., Espinosa Sánchez, A., Izquierdo Vega, J. A., Aranda Domínguez, J., Trejo Tovar, M. F. (2026). Rare diseases, therapeutic equity and human dignity: ethical challenges of scientific innovation in Mexico. *Medicina y ética, vol. 37, núm. 3.* DOI: https://doi.org/10.36105/mye.2026v37n3.02

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https://doi.org/10.36105/mye.2026v37n3.02

Abstract

Rare diseases (RD) pose a clinical, social, and ethical challenge: their low individual prevalence contrasts with a significant population-level burden, prolonged diagnostic delays, a heavy family burden, and limited treatment options in most cases. The emergence of gene therapy and certain other advanced therapies, including those based on gene silencing or modification and other highly personalized (N-of-1) approaches—opens opportunities for patients with no alternatives, but increases clinical uncertainty and highlights gaps in our regulatory frameworks. Objective: To analyze, through a literature review and a

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Received:	Sent for review:	Accepted:	Published:
10.30.2025	11.04.2025	01.07.2026	07.02.2026

normative bioethical analysis, the implications of biomedical innovation for therapeutic equity and human dignity in Mexico. Methodology: A documentary review of biomedical and bioethical literature, along with a comparative examination of international regulatory frameworks and applicable Mexican regulations. Results: Tensions are identified between beneficence and non-maleficence, autonomy and distributive justice, as well as specific gaps regarding exceptional access and the monitoring of highly personalized interventions. Conclusion: Mexico has relevant regulatory foundations, but requires explicit guidelines, streamlined procedures, and ethical safeguards that reduce inequality, prevent the provision of interventions without evidence, and promote responsible access to innovation.

Keywords: rare diseases; bioethics; gene therapy; right to try.

1. Introduction

Rare diseases (RD) pose a challenge to public health and clinical ethics due to their heterogeneity, diagnostic delays, and the limited availability of diagnostic and therapeutic resources. A disease is considered rare when it affects fewer than 5 people per 10,000 inhabitants (1). However, low epidemiological prevalence should not diminish its relevance: the "diagnostic odyssey" can last for years and entails substantial psychosocial, economic, and family impacts. On the other hand, the aggregate impact of RDs is high, and unlike what one might think when studying them separately, collectively more than 6,000 rare diseases have been described, affecting approximately 3.5–5.9% of the global population; furthermore, 70% are of genetic origin and have an onset in childhood; most are chronic, progressive, disabling, and life-threatening. Despite this, nearly 95% of these conditions lack approved treatments, which limits therapeutic options and may lead to the pursuit of unvalidated interventions (2–5).

The burden of RDs falls not only on patients but also on their families and healthcare systems, generating a significant impact in

https://doi.org/10.36105/mye.2026v37n3.02

terms of costs, loss of productivity, and the demand for long-term care that the patient will likely require, affecting the quality of life of both the patient and their caregivers. Consequently, RDs must be a public health priority, with comprehensive policies that ensure equitable access to diagnosis, research, therapeutic innovation, and social support, especially in low- and middle-income countries where gaps in care are most pronounced (5,6).

In Mexico, a study by the Mexican Social Security Institute (IMSS) reported that 4.3% of the patients evaluated had a rare disease, considering only those included in the official national list, which reinforces that, when analyzed collectively, their prevalence is not marginal (7). Complementarily, the Mexican Registry of Rare Diseases (ReMexER) —first year, 2022–2023— estimated that between 6 and 8 million people in the country (4.6–6.2% of the population) live with one of the more than 6,000 rare diseases described globally (8).

In addition to the therapeutic gap, there is a problem of visibility: the label of "rare" can contribute to a lack of public policies focused on the diagnosis, research, and treatment of these types of diseases. This leads to significant delays in diagnosis, with periods ranging from 5 to 10 years depending on the literature and the age group in question. Furthermore, only about 5% of these diseases have approved treatments, which means that in most cases, they are highly disabling —even fatal— conditions with no therapeutic hope and mortality rates that can reach up to 30%. As a result, many RDs lead to disability, complications, and catastrophic costs for families; in this context, there is a clear need for specific public policies and regulatory frameworks capable of addressing the unique characteristics of these conditions (9,10).

Given the lack of therapeutic options for most of these patients, medical research in the field of rare diseases becomes indispensable for reducing health inequalities, as a large portion of this population has been unable to receive specific treatments precisely because they do not exist. Consequently, effective mechanisms of health equity are required to guarantee access to timely diagnoses and innovative

https://doi.org/10.36105/mye.2026v37n3.02

interventions. In this regard, research and technological development should not be guided solely by commercial criteria linked to the prevalence or market potential of a disease, but rather governed by fundamental ethical principles. Furthermore, today there is a real opportunity, through technologies such as gene therapy, to offer personalized treatments for the first time that could specifically benefit many of these patients; therefore, hindering their development through ambiguous or insufficient regulatory frameworks is tantamount to slowing progress toward health equity.

A relevant example of this is technologies derived from projects such as whole-exome sequencing (WES) and whole-genome sequencing (WGS). The Human Genome Project was a public, non-profit initiative funded primarily by the U.S. Department of Energy and the National Institutes of Health (NIH), with a budget of approximately $3 billion and the participation of international organizations such as the Wellcome Trust in the United Kingdom, as well as various research centers in Europe and Asia. This collective investment made it possible to map the complete sequence of the human genome and laid the groundwork for the development of technologies that are now essential for shortening diagnosis times for rare diseases by facilitating the identification of causative genes and previously unknown variants. This demonstrates that large-scale biomedical research can generate universal benefits that transcend commercial interests and contribute directly to therapeutic justice (11,12).

In the field of rare diseases, where commercial incentives are limited and individual prevalence is low, biomedical research often progresses slowly. This lack of interest in the part of industry is also reflected in limited, insufficient, or even nonexistent regulatory frameworks that fail to address the real needs of these populations. In the absence of a market that drives the development of specific regulations for advanced therapies, health regulation lags behind and contributes to perpetuating inequity in access to diagnosis and treatment. This situation is particularly critical in Latin American coun-

https://doi.org/10.36105/mye.2026v37n3.02

tries and other low- and middle-income regions, where regulatory weaknesses hinder the growth of translational research and make it difficult for scientific advances to translate into concrete clinical applications that benefit those living with rare diseases (13,14).

In this context, gene therapy has emerged as one of the most promising strategies, offering therapeutic alternatives for previously untreatable diseases. Traditionally, Latin American countries have not developed specific regulatory frameworks to generate innovative drugs due to high costs, the complexity of clinical phases, and the limited infrastructure required to produce and evaluate treatments in clinical trials of traditional medications. This lack of regulation also reflects the region's marginal participation in the global development of pharmacological therapies (13,14).

However, this landscape is beginning to change with the advent of highly personalized interventions, including those targeting very small populations or even a single individual. In these scenarios, traditional clinical trial models —designed to demonstrate efficacy and safety in large populations— lose some of their applicability, because the intervention is intended for a single patient rather than a population. Consequently, the costs and timelines associated with lengthy clinical phases, as well as rigid regulatory frameworks designed for conventional therapies, may no longer be necessary or relevant in their traditional form. Although research remains costly, the possibility of substantially reducing the "transition" from development to implementation makes it more feasible for middle-income countries to drive translational research and generate therapies that can be used in a personalized manner, even when the local pharmaceutical industry for the development of innovative drugs is not yet fully established. This opens a tangible path for innovation tailored to local needs, particularly for people who currently lack therapeutic alternatives because their genetically based conditions previously lacked the technology for treatment, or because the disease has low prevalence. All of this, however, requires the establishment of clear and adequate regulatory frameworks that ensure safety, methodological rigor, and

https://doi.org/10.36105/mye.2026v37n3.02

ethical oversight, as well as building trust and encouraging the participation of local researchers by offering a feasible and transparent pathway to develop solutions with a direct impact on their own population (14).

This new paradigm not only helps drive local scientific development but also strengthens the effective recognition of patient autonomy by opening up the possibility that, after receiving complete, understandable, and accurate information about expected benefits, risks, uncertainties, and available alternatives, each person can freely decide whether or not to participate in an experimental intervention under clear, transparent, and supervised ethical conditions. In the case of gene therapies specifically designed for the causal variant or pathogenic mechanism of a patient (or an extremely small population), it is not possible to predict their clinical effectiveness with certainty, and it is also often difficult to generate robust evidence of long-term toxicity using conventional methods, precisely because there are no large cohorts or extended observation periods prior to their use. However, for many serious rare diseases, these interventions may represent the only available therapeutic option. Therefore, when the patient explicitly understands this uncertainty —including the possibility of no benefit and the existence of unknown risks— and still considers that the intervention aligns with their values, life plan, and needs, there should be easily accessible mechanisms that allow their decision to be respected, without compromising bioethics.

For those living with rare diseases, potential access to gene therapies represents not only a technological advance: it constitutes a vindication of their dignity, because it shifts the historical logic that has placed them on the margins of innovation —not due to a lack of clinical need, but because of their low prevalence and limited profitability, as well as the lack of technology that previously existed to treat these diseases— and recognizes them as people of equal moral worth, with enforceable rights, allowing them to actively participate in the development of treatments for their condition. Speaking of dignity here is not a rhetorical device: it implies affirming that

https://doi.org/10.36105/mye.2026v37n3.02

their lives and suffering matter, that their condition does not make them dispensable "statistical exceptions," and that the healthcare and scientific systems have obligations toward them, even if market incentives are insufficient. Within this framework, dignity is expressed in the practical prohibition against treating them as means —as mere sources of data or anecdotal cases— and in the demand to treat them as ends in themselves: individuals with a history, expectations, and a life plan that deserves consideration.

This demand also translates into the concrete recognition of these individuals' right not to be excluded from the benefits of scientific progress. When the sole reason for not developing or offering an intervention is that it is not economically "feasible," a form of structural inequity is entrenched in which therapeutic opportunity depends on market size rather than clinical need. Added to this is the fact that, even though the technical possibility of developing potential treatments exists today, the absence of a clear legal framework and operational access pathways —for both researchers and patients— can become an unjustified obstacle that violates their rights and perpetuates exclusion. Gene therapy, by opening the possibility of personalized interventions or those targeted at very small populations, challenges this dependency and restores a principle of health justice: innovation must also be directed toward those who have historically been neglected by industry and by conventional development models. In this sense, potential access to these therapies can be understood as a form of moral and health-related redress in the face of repeated exclusion.

In practice, this means recognizing the patient's right to explore reasonable options when effective treatments are unavailable, not to be dismissed out of hand, and to actively participate in decisions affecting their own body and future. Dignity is linked here to autonomy: allowing the person to decide, based on existing information about the development and without coercion, is to recognize their capacity to deliberate on risks, benefits, and uncertainties; it is to accept that the patient is not a passive recipient of external decisions,

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but a moral agent capable of consenting to or rejecting an intervention in accordance with their values. At the same time, it also implies recognizing their right to truth and transparency: providing honest information about what is known and what is not known and supporting the decision.

Consequently, the challenge is not to choose between bioethics and autonomy, but to articulate both: regulatory and governance frameworks that ensure informed consent, independent risk–benefit assessment, oversight by ethics committees, monitoring plans, reporting of adverse events, and criteria for transparency and traceability. In this way, patients are protected from abuse or unjustified exposure, but the uncertainty inherent in these therapies is also prevented from becoming a barrier that effectively denies or delays the right of those who have no alternatives and who, of their own free will, wish to seek treatment through such interventions.

At this point, the debate naturally fits into translational medicine, understood as a systematic, bidirectional process through which findings from basic biomedical research are transformed into clinical and public health applications with a direct impact on patients and society. This approach seeks to bridge the gap between the laboratory and clinical practice, facilitating the development of evidence-based diagnostics, therapies, and interventions (15).

Within this framework, although gene therapy constitutes one of the most promising tools in contemporary biomedicine, its responsible implementation faces particular challenges; the decisive obstacle is not necessarily replicating the classic pathway of extensive clinical phases, but rather having regulations that enable clear, agile, and risk-proportionate development and access pathways. This does not imply reducing ethical or scientific standards but rather reorienting them toward safeguards appropriate for scenarios of high uncertainty: explicit criteria for quality and traceability, independent evaluation of the risk–benefit balance, strengthened informed consent, and mandatory follow-up plans. In this regard, recent experiences —such as gene therapy treatments for sickle cell disease (SCD) developed in

https://doi.org/10.36105/mye.2026v37n3.02

the United States— have demonstrated transformative potential, but have also highlighted that, without operational regulatory frameworks, innovation can become inaccessible or unfeasible, especially in countries where the disease burden is highest (16). Therefore, rather than multiplying bureaucratic procedures designed for conventional therapies, the challenge lies in building regulatory mechanisms that allow these interventions to be developed and implemented with administrative efficiency, without compromising safety, methodological rigor, and ethical oversight.

When such frameworks are absent or ambiguous, clinical uncertainty increases and the expansion of parallel markets is encouraged, including the proliferation of unapproved or insufficiently supervised interventions. An example of this is the growing phenomenon of medical tourism or advanced therapy tourism, where patients travel to countries with more developed infrastructure to access experimental treatments unavailable in their home countries. These practices exacerbate global inequities in access to innovation, as only those with financial resources can afford these trips; furthermore, the risks include serious complications, lack of follow-up, inadequate information, and a lack of institutional accountability mechanisms (16,17).

Given this landscape, it is essential to propose comprehensive strategies aimed at strengthening local capacity for research, regulation, and clinical care, in order to ensure that the implementation of gene therapies is ethical, equitable, and sustainable in middle-income countries. This entails designing specific regulatory pathways for highly personalized therapies that reduce unnecessary administrative friction but, at the same time, mandate critical safeguards: independent ethical review, product transparency and traceability, structured clinical monitoring, and long-term surveillance, so that therapeutic hope does not translate into unprotected exposure to risk (16).

Furthermore, the development of protocols for highly personalized therapies —capable of maintaining rigorous standards of quality, safety, and therapeutic plausibility even when targeting a very small number of patients or even a single individual— has demonstrated

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that it is possible to establish more efficient evaluation and access pathways than those of traditional models, without compromising essential bioethical safeguards. An example of this is Milasen, an antisense therapy designed in 2019 to treat Mila Makovec, a girl diagnosed with a unique and fatal variant of neuronal ceroid lipofuscinosis type 7 (CLN7). CLN7 is a form of neuronal ceroid lipofuscinosis (NCL), also known as Batten disease, caused by mutations in the MFSD8 gene (17). It is a rare, hereditary, neurodegenerative disease that typically begins in childhood and is characterized by progressive vision loss, cognitive decline, severe epileptic seizures, and diminished motor skills due to the pathological accumulation of lipopigments in neurons; its clinical course is usually rapid, and in many cases, life expectancy does not extend beyond early adolescence.

Exceptionally, the team led by Dr. Timothy Yu at Boston Children's Hospital succeeded in developing a personalized therapy for Mila within approximately 11 months, from the genetic identification of the defect to the administration of the drug. This milestone demonstrated that, when effective regulatory pathways, adequate informed consent, and ethical oversight are in place, it is possible to design and implement highly individualized interventions for rare or even unique diseases, generating useful clinical evidence under supervised conditions (18). Cases like this show that regulation should not be understood solely as a system of restrictions, but as an enabling infrastructure: when it offers clear, predictable procedures that are proportionate to the risk, it accelerates the translation of biomedical findings into real-world clinical applications.

This case also invites reflection on the principle of equality, reminding us that not only high-prevalence diseases deserve research and treatment: every person, regardless of the rarity of their condition, has the same right to receive care, access innovation, and, at the very least, attempt a treatment. Consequently, regulatory frameworks should aim to ensure equity in access to advanced therapies, without the population frequency of a disease determining the available therapeutic opportunities (19).

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Unlike the case of Milasen in the United States —where close collaboration between researchers, family members, treating physicians, and regulatory authorities enabled, through the FDA's expanded access program, the design, development, and administration of an individualized therapy under rigorous ethical and scientific criteria— this intervention was achieved in a short period: just 11 months from molecular diagnosis to drug administration, a timeframe unthinkable in traditional clinical research models. The speed and dynamism of this process demonstrated that conventional regulatory structures —based on sequential phases, large cohorts, and long evaluation periods— are not viable for these cases.

But it also demonstrates that institutional alternatives exist that allow for swift action without compromising oversight and traceability (20). This precedent also spurred the development of specific regulatory guidelines for N-of-1 therapies based on antisense oligonucleotides, with the aim of providing a clearer, more flexible, and ethically robust framework for evaluating highly personalized interventions, recognizing that traditional clinical trials cannot adequately address these needs (20).

Within this same continuum of regulatory solutions, expanded access and the Right to Try are two mechanisms designed to offer therapeutic alternatives to patients with serious illnesses who have exhausted conventional options. Expanded access, formalized by the FDA since the 1980s, allows for the use of experimental interventions when there is reasonable clinical justification and an ethical and regulatory review process is guaranteed. Under this framework, protocols must be evaluated by an Institutional Review Board (IRB) and authorized by the FDA, ensuring technical oversight, traceability, and patient protection; furthermore, it boasts approval rates exceeding 99% and relatively short decision-making times, making it a viable option for individuals without comparable therapeutic alternatives (20,34).

For its part, the Right to Try reduces the administrative burden by eliminating the need for prior FDA approval and mandatory IRB

https://doi.org/10.36105/mye.2026v37n3.02

review, allowing for faster access to experimental drugs. However, it can only be applied to drugs that have completed Phase I clinical trials, which provides a minimum threshold of safety information, though insufficient to guarantee their efficacy or long-term effects. In this mechanism, speed and patient autonomy take center stage, which can be relevant when time is critically limited and there are potentially promising options in early stages (34).

For middle-income countries, this point is strategic: having clear, proportionate, and feasible regulatory pathways could allow not only the adoption of innovations developed in other contexts but also the building of local capacities for research, manufacturing, clinical evaluation, and monitoring, with the aim of developing technologies and drugs tailored to their own epidemiological needs and historically underserved populations. In other words, appropriate regulation not only protects; it also enables the possibility of being at the forefront and of transforming local science into clinical benefits for the population (20,24,25).

This paradigm shift requires a deeper examination of the ethical foundations underpinning the possibility of offering advanced therapies, particularly highly personalized ones, to patients with rare or unique diseases who lack treatment options. In this regard, it is essential to incorporate the concepts of therapeutic equity and human dignity as guiding principles of any emerging regulatory framework.

Therapeutic equity is understood as the moral and health-related obligation to correct avoidable and unjust inequalities in access to health technologies and therapeutic opportunities. Equity is not merely a technical criterion, but an ethical imperative that demands directing resources and policies toward those facing the greatest obstacles to achieving the highest possible level of health, while avoiding both intentional and structural discrimination. From this perspective, the low prevalence of a disease cannot justify the exclusion of patients from biomedical innovation processes or from access to advanced interventions. (21).

For its part, human dignity can be understood as a principle that affirms the inherent and inalienable value of every person simply

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by virtue of being human and which, at the legal-normative level, translates into a foundation for recognizing rights, imposing duties, and establishing limits on clinical, scientific, and state action. In this sense, human dignity functions as a guiding criterion for decision-making and the assignment of responsibilities, particularly in contexts of vulnerability, where the risk of harm, exclusion, or arbitrariness increases (22,23).

To avoid ambiguities, we distinguish between: (a) ontological dignity, understood as the intrinsic, unconditional, and non-gradable value of the person —independent of their state of health, capabilities, or social utility—; and (b) human dignity in the normative sense, conceived as an operational principle that translates that value into practical criteria to guide bioethical deliberation, regulation, and the design of public policies. In the remainder of the text, we will use "human dignity" to refer to the normative principle, explicitly specifying when we are referring to its ontological dimension (22,23).

In operational terms, this implies that no life should be treated as expendable for economic reasons and that the State must assume an active responsibility —moral and, in many contexts, also legal— to reduce avoidable inequalities through concrete actions: strengthening timely diagnosis, supporting translational research capabilities, ensuring specialized care networks, and creating institutional conditions for the development of and access to advanced therapies.

Ensuring that dignity and equity goes beyond merely stating principles; it requires the effective operation of a set of coordinated systems. This requires clear regulatory frameworks proportionate to the risk that enable pathways for development and access to highly personalized therapies; ethics committees with the technical capacity to evaluate scenarios of high uncertainty; infrastructure for traceability, pharmacovigilance, and long-term follow-up; and financing and prioritization mechanisms that prevent access from depending exclusively on the ability to pay or the ability to travel. Integrating therapeutic equity and human dignity as guiding principles, therefore, strengthens the moral legitimacy of scientific innovation and

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guides public policies that ensure that, in countries such as Mexico, the prevalence of a disease does not become synonymous with clinical neglect, regulatory exclusion, or structural barriers to accessing technologies developed within or outside the country (25).

2. Methodology

This study is a narrative review with a qualitative bioethical and regulatory analysis, aimed at examining the ethical challenges associated with the research and development of advanced therapies—including gene therapy and personalized treatments—in the context of rare diseases in Mexico. The design is based on a documentary study of scientific, regulatory, philosophical, and public policy sources, with the aim of offering a structured and critical reflection on the principles that should guide biomedical innovation in highly vulnerable populations. This is not a systematic review aimed at synthesizing clinical effects, but rather a documentary and conceptual analysis that integrates evidence, regulatory frameworks, and bioethical deliberation.

2.1. Type of Study

A conceptual and normative analysis was developed, characteristic of bioethical research, which does not involve intervention with human subjects and utilizes analytical frameworks derived from:

- Principled bioethics
- Bioethics of ontological dignity
- Therapeutic equity in public health

2.2. Selection and sources of information

The literature review included four categories:

https://doi.org/10.36105/mye.2026v37n3.02

1. Biomedical and bioethical literature: scientific articles on prevalence, diagnosis, gene therapy, N-of-1 studies, and works on bioethical principles focused on the topic.
2. International regulatory frameworks: FDA (expanded access), Right to Try, EMA (compassionate use), CIOMS, and the Declaration of Helsinki (2024 version).
3. Mexican regulations: Constitution, General Health Law, Regulations of the General Health Law on Health Research (RLGSMIS), Regulations on Health Supplies, and NOM-012-SSA3-2012, in addition to applicable administrative provisions and criteria (COFEPRIS, CONBIOÉTICA, etc.).

The sources were selected based on conceptual relevance, currency, institutional authority, and relevance to the regulatory analysis of the Mexican case.

Search strategy and selection criteria

A structured search was conducted in PubMed/MEDLINE, supplemented by a targeted review of regulatory documents and guidelines (e.g., Declaration of Helsinki, CIOMS, FDA/EMA, COFEPRIS, and the Ministry of Health). Combinations of terms in Spanish and English related to rare diseases, orphan drugs, advanced therapies, exceptional access, and the regulatory framework were used: "enfermedades raras/rare diseases," "medicamentos huérfanos/orphan drugs," "terapia génica/gene therapy," "N-of-1," "oligonucleótidos antisentido/ antisense oligonucleotides", "compassionate use", "expanded access", "Right to Try", "therapeutic equity", "human dignity", "Mexico", "General Health Law", "Research Regulations", and "COFEPRIS". Priority was given to literature and regulations in effect through October 2025.

Articles, reviews, and official sources directly relevant to the following were included: (i) advanced and highly personalized therapies (e.g., gene therapy, ASO/siRNA, N-of-1 approaches), (ii) compassionate use/expanded access/Right to Try, and (iii) bioethical prin-

https://doi.org/10.36105/mye.2026v37n3.02

ciples and applicable regulatory standards in Mexico. Promotional materials, editorials lacking a substantive argument, reports without traceable sources, duplicates, and documents without an explicit connection to the manuscript's objective were excluded.

As this is a narrative review, a systematic review protocol was not followed; consequently, the findings are interpreted as a critical synthesis guided by bioethical and regulatory relevance.

2.3. Analytical Procedure

The analysis was conducted at three levels:

i. Descriptive Level: The scientific and clinical challenges of rare diseases were characterized.
ii. Normative level: We analyzed certain interpretations of national and international legal frameworks and their applicability to emerging therapies and vulnerable populations, in addition to identifying and highlighting the regulatory gaps that persist in these areas.
iii. Bioethical level: Certain ethical dilemmas were identified and analyzed using classical principles (autonomy, beneficence, justice), contemporary theories (therapeutic equity), and the human dignity approach.

The process included a comparative analysis of international experiences and the structural conditions of the Mexican regulatory system, with the aim of identifying regulatory gaps and proposing applicable guidelines.

2.4. Scope and Limitations

This study does not aim to develop clinical recommendations or evaluate the therapeutic efficacy of specific interventions of any kind. Its main purpose is to initiate an informed debate on the ethical challenges posed by advanced and personalized therapies in the

https://doi.org/10.36105/mye.2026v37n3.02

field of rare diseases in Mexico, as well as to offer some preliminary analytical criteria that may guide the development of public policies, regulatory frameworks, and institutional strategies in this area in the future.

Our analysis is based on the scientific, bioethical, and regulatory literature available as of October 2025, and on the regulations in force as of that date. Given its conceptual focus, the study does not replace the need for more in-depth and specialized evaluations, which must involve experts in health regulation, biomedical law, health economics, pharmacovigilance, translational science, and public policy design. A comprehensive approach will require inter-institutional and multidisciplinary deliberative processes that exceed the scope of this article.

Although the study focuses on the Mexican context, the bioethical principles and regulatory elements discussed here may be useful for other countries with similar regulatory structures and institutional capacities. In this sense, the work aims to stimulate reflection, promote interdisciplinary dialogue, and contribute to the collective construction of an ethical agenda for biomedical innovation in rare diseases, rather than offering definitive or exhaustive guidelines.

3. Regulatory Framework in Mexico

Access to therapeutic innovation in the context of rare diseases must be analyzed within the framework of Mexican regulations and from a perspective that places the individual at the center of therapeutic decisions. The Political Constitution of the United Mexican States, in Article 4, recognizes the right to health protection as a fundamental human right of all persons, establishing the State's responsibility to create the necessary conditions to guarantee access to medical services and medications without distinction. Therefore, we consider it essential that this right be fully guaranteed also for people living with rare diseases (Political Constitution of the United Mexican States, Art. 4, 1917/2025) (26).

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Similarly, the General Health Law (LGS) establishes in Articles 1 and 2 that health protection must be guided by principles of equity, quality, and respect for the individual, recognizing health not only as an individual good but also as a social good; this conception requires placing the individual and their dignity at the center of all health policy. In the specific case of rare diseases, the current possibility of developing innovative therapies for those who previously had no options at all opens up a horizon of hope, but it also raises the ethical imperative to regulate and facilitate fair access to these technologies. Within this framework, the LGS provides two relevant provisions: on the one hand, Article 102 empowers the Ministry of Health to authorize the use of drugs or materials in humans when there is insufficient evidence of efficacy (or when changes to indications are sought), requiring supporting documentation and the submission of a protocol (application, pharmacological and preclinical information, prior clinical studies if available, protocol, and letter of institutional acceptance), and even contemplates the possibility of an opinion from an "authorized third party" that triggers a maximum resolution period of 30 business days; in operational terms, this establishes an authorization framework based on documentation and protocol, closer to a research/validation scheme than to a case-by-case access "program." On the other hand, Article 103 allows a physician to use therapeutic or diagnostic resources "under investigation" on a sick person when there is a well-founded possibility of saving a life, restoring health, or alleviating suffering, always with written informed consent and in compliance with applicable requirements; however, it functions as a clinical exception centered on the medical act and consent, without detailing uniform eligibility criteria, minimum thresholds of evidence, streamlined authorization pathways, standardized follow-up protocols, or standardized institutional responsibilities, which can result in variability among institutions and administrative burdens designed for conventional therapies.

Similarly, the General Health Law (LGS) recognizes among its objectives the development of education and scientific and technological research for health, which constitutes not only a technical

https://doi.org/10.36105/mye.2026v37n3.02

means but also a moral responsibility oriented toward serving the common good and caring for human life (General Health Law, arts. 1, 2, 102, and 103, 1984/2024) (27).

Furthermore, Article 17 Bis of the General Health Law grants the Federal Commission for Protection against Health Risks (COFEPRIS) the authority to authorize, regulate, and monitor drugs, including those in the research phase. This is particularly relevant for gene therapies in rare diseases, where the lack of effective treatments makes access to innovation an ethical imperative linked to patient dignity, understood as an intrinsic value that demands respect and protection (General Health Law, Art. 17, 1984/2024) (27).

4. Analysis

In Mexico, there is no unified framework known as "compassionate use" with detailed guidelines equivalent to those of the FDA or the EMA. However, there are regulatory bases that allow for exceptional pathways in limited circumstances. On the one hand, the Health Supplies Regulation (RIS) provides mechanisms for importing medications for special treatments of low-incidence diseases and for medications without health registration (RIS, Art. 196) (29). On the other hand, Title V of the General Health Law (LGS) and the RLGSMIS contain provisions for the use of therapeutic or diagnostic resources under investigation and for the authorization of clinical research, always with written informed consent, committee oversight, and monitoring by the competent health authority (27,28).

If an innovative drug were developed and produced entirely in Mexico, the applicable framework would not be the RIS, but rather the General Health Law (arts. 96–103) and its regulations on research (RLGSMIS), in addition to Mexican Official Standard NOM-012-SSA3-2012, which regulates research in human subjects. This framework permits the use of unregistered drugs within authorized clinical trials, provided there is a protocol approved by Research and

https://doi.org/10.36105/mye.2026v37n3.02

Research Ethics Committees and authorization from COFEPRIS. Likewise, the LGS provides for exceptional cases of therapeutic or diagnostic use "under investigation" in a sick patient (Art. 103), with written informed consent and compliance with applicable requirements. Thus, while Article 196 of the RIS provides a basis for access via importation for special treatments, in the case of domestically developed products, the legitimate pathway is defined as "investigational drug," with ethical, scientific, and regulatory traceability (27,29,30).

However, when attempting to apply this general framework to exceptional access pathways and highly personalized therapies, significant regulatory and operational tensions arise. In practice, Article 103 (therapeutic or diagnostic use "under investigation") operates as a case-by-case clinical exception rather than a general access pathway, as it does not define a standardized procedure that clearly outlines the minimum requirements, eligibility criteria, and monitoring obligations. By failing to establish explicit evidence thresholds, uniform selection criteria (e.g., severity, absence of alternatives, biological plausibility), or a consistent monitoring and pharmacovigilance framework, its implementation is heavily dependent on local interpretations and institutional capacity, favoring discretionary decisions and unequal outcomes across institutions.

This design contrasts with the logic of more formalized mechanisms such as expanded access or the Right to Try, which—despite significant differences among themselves—function as explicit pathways: they define more precisely who can access them, under what clinical conditions, what safeguards must be met, and how patient traceability and follow-up are ensured. In other words, they do not depend solely on the exception of the medical act, but on a procedural framework that reduces administrative uncertainty and guides clinicians and researchers on "what to do" and "how to do it" in scenarios of therapeutic urgency. In Mexico, the absence of a fully operational equivalent pathway can lead to a paradox: even when the intervention is scientifically plausible and clinically urgent,

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access remains subject to procedural gaps, institutional heterogeneity, and documentation burdens that are not designed for N-of-1 therapies. This not only increases variability and the risk of inequity but may also discourage the local development of these technologies by heightening regulatory uncertainty regarding timelines, requirements, and responsibilities, thereby limiting the potential to transform biomedical innovation into effective treatments for populations lacking therapeutic alternatives.

In turn, Article 102 presupposes a framework based on standardized protocols and progressive evidence; when applied to ultra-personalized interventions (e.g., N-of-1 or individualized genomic therapies), this requirement is difficult to implement without friction, as "robust" evidence in the classical sense may be impractical within clinical timelines, turning the documentation burden into delays precisely where urgency and rarity demand agile yet fully traceable decisions.

These limitations are exacerbated by structural issues: the absence of explicit regulation on compassionate use creates gaps that necessitate analogical interpretations, hindering uniform and expedited application; furthermore, slow administrative procedures delay timely access to potentially beneficial options.

Internationally, there are formalized guidelines regulating compassionate access and expanded access for patients without therapeutic alternatives. In the United States, the FDA has established specific procedures for the Expanded Access Program, which allow the use of investigational drugs based on criteria of severity, reasonable risk, and independent ethical approval (30). In the European Union, the European Medicines Agency (EMA) has issued guidelines for Compassionate Use Programs (31), aimed at ensuring safe, equitable, and regulated access for rare diseases or life-threatening conditions. For its part, the Council for International Organizations of Medical Sciences (CIOMS) Guidelines do not directly regulate compassionate use or expanded access, but they establish essential ethical principles that should guide any intervention involving

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unapproved or investigational products. These guidelines emphasize the obligation to conduct a proportionate assessment of risks and benefits, ensure clear and understandable informed consent, apply additional protections for vulnerable patients, and maintain transparent mechanisms for ethical oversight—including independent review and scientific justification of the intervention—to ensure that patient well-being takes precedence over regulatory or commercial interests. (32). The absence of equivalent guidelines in Mexico highlights the need to move toward explicit regulatory frameworks that provide legal and ethical certainty for both patients and researchers.

The existence of clear regulatory frameworks in Mexico is essential. In this regard, the National IRB Guidelines state that Institutional Review Boards (IRBs) must be autonomous, institutional, interdisciplinary, and advisory bodies responsible for carefully evaluating protocols involving human subjects. Their role includes critically reviewing the potential risks and benefits of the project, ensuring clear and understandable informed consent, protecting the dignity and rights of participants, especially vulnerable populations—and ensuring continuous monitoring of the effects of approved interventions (32).

In this regard, national regulations already provide for a robust ethical oversight system (through the IRBs), with criteria regarding risk proportionality, scientific relevance, protection of human dignity, and safeguards for vulnerable groups—which is particularly relevant in protocols targeting rare diseases or high-risk interventions, where therapeutic urgency and structural vulnerability require prudent, transparent, deliberate, and person-centered decisions (33).

The mechanisms described seek to balance the principle of beneficence—providing access to a potentially useful treatment—with that of non-maleficence—avoiding unnecessary risks—always within the framework of respect for the patient's dignity and autonomy. In this regard, it is vital that the Mexican government develop clearer and more accessible legal and institutional frameworks for research centers and academic institutions, enabling these institutions to manage requests for access to experimental treatments in a streamlined and supported manner, in accordance with the principle of

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distributive justice, thereby ensuring that no patient is excluded from therapeutic options due to bureaucratic or structural limitations.

International experience offers useful alternatives; for example, in the United States, the "Right to Try" framework reinforces patient autonomy by allowing patients to exhaust potential therapeutic options in situations where no treatment is available and their lives are in danger, even without the direct involvement of the regulatory authority.

This model, though not without criticism, highlights the need for flexible, person-centered mechanisms that recognize in every human being an inviolable ontological dignity and the capacity to make rational decisions when traditional therapeutic options have been exhausted (34).

Finally, such frameworks not only open the door to individual access but also allow academic and institutional research centers—whose interest lies more in social welfare than in commercial profitability—to actively participate in advancing translational research. Their contribution could be decisive in addressing complex health problems, especially in a country like Mexico, where public investment in science is limited and social needs are pressing. In this context, the discussion surrounding concepts such as the Right to Try takes on ethical and normative relevance, as it is not merely about protecting but also about enabling the right to access the latest therapeutic advances.

5. Universal ethical principles in rare disease research

Research on rare diseases (RD) requires particular ethical attention, stemming not only from low prevalence and limited evidence but also from the context of social and clinical vulnerability in which patients often find themselves. The design of protocols in this field must be guided by universal bioethical principles—respect for autonomy, beneficence, non-maleficence, and justice—within the framework of classical principlism. These principles take on special

https://doi.org/10.36105/mye.2026v37n3.02

relevance when applied to populations historically rendered invisible by health systems and, therefore, exposed to risks of exclusion, inequity, and instrumental use.

International bodies such as the Declaration of Helsinki—whose most recent revision in October 2024 explicitly incorporates, for the first time, guidelines for genetic interventions, gene therapies, and other emerging biomedical technologies —and the CIOMS guidelines have established regulatory frameworks for research involving human subjects, emphasizing the need to ensure scientific relevance, a proportionate assessment of the risk-benefit balance, fair selection of participants, robust informed consent, and independent ethical oversight. The 2024 version emphasizes that, in studies involving genetic technologies —especially when long-term effects are uncertain—researchers must ensure enhanced mechanisms for continuous follow-up, post-intervention surveillance, transparency in risk communication, and the obligation to scientifically justify any participant exposure to interventions whose safety profile is not fully characterized. It also establishes that participants must clearly understand the experimental nature of these therapies, the possibility of unpredictable outcomes, and the need for strict risk mitigation protocols.

However, the particularities of rare diseases, including therapeutic urgency, a scarcity of alternatives, and the methodological complexity of clinical trials with small populations, require further reflection on how these principles should be interpreted and applied in practice, especially in contexts where limited evidence and clinical pressure can generate significant ethical dilemmas (35,36).

The emergence of technologies such as gene therapy —defined as the targeted transfer of genetic material to modify gene expression and correct mutations or restore altered biological functions— has transformed the therapeutic landscape for many previously incurable diseases. This approach includes strategies based on viral vectors (AAV, lentiviral, and retroviral), gene editing, and antisense oligonucleotides, each with specific efficacy and risk profiles. As noted by the New England Journal of Medicine, since 2016 at least six

https://doi.org/10.36105/mye.2026v37n3.02

gene therapies have been approved by the FDA and the EMA, covering cancer, β-thalassemia, retinal dystrophies, severe immunodeficiencies, and spinal muscular atrophy, while more than 800 clinical programs remain in development for monogenic diseases previously lacking therapeutic options, some of which are classified as ER (37,38).

In this context, the principle of justice takes on particular significance, but today it must also be understood as a layered form of justice that acknowledges inequities in access to advanced therapies within systems such as Mexico's. Without explicit equity policies and ethical oversight, the development of these technologies may exacerbate preexisting disparities. Incorporating gene therapy into a national ethical agenda requires not only oversight of research but also a commitment to ensuring fair, safe, transparent, and patient-centered access, recognizing the clinical and social uniqueness of each patient in the era of precision medicine.

Likewise, the emergence of regulatory proposals such as the Right to Try, which recognize patients' right to access experimental treatments when no approved options exist, opens a new field of bioethical analysis. These schemes, while seeking to expand autonomy, require explicit criteria for scientific evaluation, ethical review proportional to the risk, and effective safeguards against commercial exploitation, misinformation, or institutional neglect during follow-up.

In the context of ER with no approved treatments and a serious or potentially fatal prognosis, ethical deliberation can be grounded in principles such as the lesser evil and double-effect action; however, in light of recent approaches to the principle of harm and identity-related paternalism, its justification takes on new nuances. Based on these approaches, when a medical decision entails a significant risk of causing serious harm to the patient's "future self"—especially if that future individual may be psychologically distinct from the current self— the classic distinction between harm to oneself and harm to others becomes blurred. From this perspective, avoiding a potentially beneficial treatment may not only constitute an imprudent

https://doi.org/10.36105/mye.2026v37n3.02

choice but could be morally equivalent to allowing harm to another person (42,44).

In this sense, the principle of the lesser evil allows for the selection of an experimental intervention that, despite its risks, represents a less harmful alternative than the natural progression of the disease —which must be well documented— or than the total absence of therapeutic options, as is often the case in these conditions. Complementarily, the principle of double effect remains useful for evaluating actions with both positive and negative consequences, provided that the primary intention is the patient's benefit and there is proportionality between risks and benefits. However, it is suggested that, in certain circumstances, there may be a moral obligation to prevent a patient from refusing interventions that would prevent severe harm to their future self, especially when such refusal is based on erroneous information or unfounded beliefs and when the anticipated harm is significant (42–44).

In gene therapies and experimental treatments —whose potential benefit may lie on a time horizon associated with substantial changes in the patient's future psychological identity— ethical assessment must consider not only current autonomy but also the protection of that future individual. This reinforces a dynamic interpretation of traditional bioethical principles: they remain essential but must be applied while acknowledging the complexity introduced by vulnerability, scientific uncertainty, and the responsibility to prevent foreseeable serious harm. Thus, contemporary ethical frameworks favor an approach that balances autonomy, harm prevention, and responsible access to emerging interventions, promoting prudent, transparent, and socially responsible decisions (39).

6. Proposal for ethical and regulatory guidelines to strengthen research on rare diseases in Mexico

The consolidation of robust ethics in rare disease research in Mexico cannot depend solely on isolated efforts by researchers, commit-

https://doi.org/10.36105/mye.2026v37n3.02

tees, or associations. A gradual and consistent structural change is required, aligned with feasible regulatory frameworks that are consistent with our institutional capacities, yet simultaneously incorporating explicit political commitments to equity, social participation, and access to biomedical innovation. In particular, it is essential to have clear and operational regulations —in line with existing international frameworks— that allow for the rapid, traceable, and bioethically supervised development and use of advanced therapies, especially when it comes to highly personalized interventions for patients with no therapeutic alternatives. Based on the ethical and regulatory analysis presented, the following guidelines applicable to our context are proposed:

First, it is necessary to develop a specific regulatory framework for advanced therapies and experimental treatments to be applied to patients with no alternatives, particularly in rare diseases. This framework should draw on international experiences such as expanded access, compassionate use, and schemes like the Right to Try—not as models to be copied uncritically, but as evidence that it is possible to establish explicit, agile pathways proportionate to the risk while preserving essential safeguards (ethical review, traceability, monitoring, and accountability). This framework must be adapted to the Mexican legal system —or that of countries seeking to incorporate these technologies— and developed through inter-institutional collaboration, involving COFEPRIS, CONBIOÉTICA, national health institutes, public universities, and patient organizations (associations, foundations, etc.). Furthermore, it must be grounded in principles of justice, scientific evidence, protection of rights, human dignity, and informed autonomy. Its purpose would be to establish clear, predictable, and streamlined procedures for requests for compassionate or expanded access, preventing regulatory uncertainty and disproportionate bureaucracy from becoming a structural barrier to innovation and care.

Second, it is essential to strengthen and consolidate the national registry of rare diseases, structured to accurately identify the target population, moving beyond partial initiatives, and to be inclusive of

https://doi.org/10.36105/mye.2026v37n3.02

all diseases classified as rare. Although there have been advances such as the Mexican Registry of Patients with Rare Diseases (ReMeXER) and an expanded catalog of recognized diseases, there is still not fully institutionalized, public, mandatory, and interoperable system across institutions that centralizes the registry and makes it accessible.

A national registry should ensure equitable territorial coverage and data connectivity and incorporate official natural history programs and standardized genomic databases. This infrastructure would not only facilitate translational research but would also serve as the foundation for the development of and access to personalized therapies, including gene therapies, under conditions of greater distributive justice; additionally, it would improve the design, targeting, and evaluation of public policies in this area.

Third, we propose strengthening research ethics committees through ongoing training in bioethics applied to emerging technologies (gene therapy, gene editing, N-of-1 studies, compassionate use), ensuring their autonomy, interdisciplinary diversity, and deliberative capacity. The integration of these committees into national networks —coordinated or endorsed by CONBIOÉTICA— would help harmonize criteria, share best practices, and provide support to centers with less experience. In the case of rare diseases, where structural vulnerability is high, these committees should have specific guidelines for evaluating protocols with high uncertainty and therapeutic urgency, without losing sight of the ethical principles already outlined (33).

Fourth, it is a priority to establish a specific public fund for research on rare diseases, with funding lines dedicated to: the development of gene therapies and other advanced therapies, the strengthening of genomic diagnostic platforms, technology transfer, and the local development of vectors and precision medicine tools. These funds should be accessible to academic institutions, public hospitals, and civil society organizations, with transparent allocation mechanisms and evaluation criteria that include not only scientific productivity but also social impact and territorial equity.

https://doi.org/10.36105/mye.2026v37n3.02

Fifth, it is necessary to systematically incorporate the equity perspective at all levels of scientific and health decision-making. This implies including geographic, cultural, and socioeconomic criteria in the selection of participants, in the location of clinical trial centers, and in the distribution of benefits derived from research. From this perspective, justice cannot be reduced to formal equality of opportunity but must be oriented toward correcting historical inequalities, prioritizing communities and regions that have been systematically excluded from access to biomedical innovation.

Finally, the meaningful participation of patient and family organizations must be strengthened, not merely as passive beneficiaries, but as strategic actors in the design of public policies, the evaluation of health technologies, the ethical oversight of research protocols, and the development of culturally relevant informed consent materials. International experience shows that the most advanced models —such as European alliances or WHO technical groups— actively incorporate patient associations into research governance. Adapting this approach to the Mexican context would allow for the development of a truly inclusive ethics framework, where people living with rare diseases participate in decisions that affect their lives, their therapeutic prospects, and their quality of life.

7. Conclusions

Research on rare diseases poses one of the most pressing and complex bioethical dilemmas in medicine: how to ensure that scientific innovation reaches those who, for decades, have been excluded from biomedical progress not due to a lack of clinical need, but because of the absence of available technology and insufficient incentives to develop it.

In the face of diseases that affect few but have a profound and sustained impact, the ethical response cannot be indifference or passive waiting, but rather deliberate action guided by justice, equity, and collective responsibility.

https://doi.org/10.36105/mye.2026v37n3.02

At the international level, initiatives aimed at harmonizing policies on research, diagnosis, and therapeutic access for rare diseases have recently been consolidated. Among these, the European Rare Diseases Research Alliance (ERDERA) stands out, focused on strengthening research networks, standardizing clinical and genomic data, and promoting common criteria for equitable access to advanced therapies in Europe. In parallel, the World Health Organization established a Technical Group on Rare Diseases in 2024–2025, whose proposals —presented at its May 2025 meeting— focus on improving registry systems, promoting early diagnosis, ensuring sustainable financing for innovative therapies, and fostering regulatory frameworks accessible to middle-income countries (40, 41).

While these international strategies represent a valuable benchmark and a desirable goal, their implementation in Mexico faces significant structural limitations. The advent of technologies such as gene therapy opens unprecedented possibilities for patients with previously untreatable diseases; however, their incorporation into the national health system is hindered by regulatory lag, lack of access to timely diagnosis, institutional concentration of capabilities, and the absence of specific public policies for rare diseases. In this scenario, bioethics is indispensable not only to protect rights but also to enable responsible pathways to innovation: adapting global recommendations to a context marked by historical inequalities and still-insufficient infrastructure requires clear frameworks —proportional to the risk and fully traceable— that prevent both neglect and improvisation.

Therefore, it is essential to open the debate on how Mexico could adopt exceptional access mechanisms comparable to those already operating internationally —including schemes such as the Right to Try, under clear regulation and with rigorous ethical and scientific criteria— as a legitimate pathway to expand access to experimental treatments for severe or currently untreatable conditions. This is not about weakening regulations, but about making it operational and proportionate in scenarios where inaction can also be unjust. Respect for autonomy and the right to try therapeutic options must go

https://doi.org/10.36105/mye.2026v37n3.02

hand in hand with robust safeguards, independent ethical oversight, transparency regarding uncertainty, and informed support, including obligations for follow-up and accountability.

This article has argued that inclusive ethics in rare disease research demands more than good intentions: it requires policy decisions, agile regulatory structures, fair funding, meaningful patient involvement, and a scientific culture committed to the common good. Equity is not merely an abstract principle, but a concrete guide for directing the distribution of opportunities, risks, and benefits in the design and execution of science, preventing innovation from widening existing gaps.

21st-century bioethics must not fear innovation, but it must demand responsibility, transparency, and solidarity from it. Only in this way can we build a science that serves everyone, especially those who have historically been excluded from the benefits of biomedical progress.

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