Age reprogramming: Innovations and ethical considerations for prolonged longevity (Review)

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Received December 4, 2024; Accepted March 14, 2025

DOI: 10.3892/br.2025.1974

Abstract. Age reprogramming and cellular rejuvenation therapies are revolutionizing the approach to aging and age-related diseases. These ground-breaking interventions target fundamental biological processes, including genomic instability, telomere attrition, and mitochondrial dysfunction, to restore cellular function and delay the onset of degenerative conditions. Emerging strategies such as epigenetic reprogramming, gene editing, stem cell therapy, and senolytic drugs show immense promise in extending health spans and potentially reversing aspects of aging. Despite marked progress in preclinical studies and early-stage clinical trials, translating these therapies into practical healthcare solutions presents significant challenges. Key issues include ensuring safety, optimizing delivery mechanisms, overcoming regulatory barriers, and addressing high costs. Moreover, ethical and economic considerations, such as equitable access and societal impacts, must be carefully addressed to prevent widening health disparities. The present review examines the current state of cellular rejuvenation research, highlighting both scientific advancements and the complex challenges associated with these therapies. With interdisciplinary collaboration, robust ethical frameworks, and scalable technological innovations, these therapies have the potential to transform healthcare. By shifting the focus from disease management to proactive health preservation, they offer a future where aging becomes a manageable and equitable process.

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Key words: age reprogramming, rejuvenation, epigenetic, gene editing, stem cell therapy, senolytics, CRISPR, ethics

1. Introduction

Aging is a fundamental biological process, yet it remains one of the most complex and pressing challenges for modern healthcare and society. The global aging population is increasing at an unprecedented rate. According to the United Nations, by 2050, 1 in 6 people will be over the age of 65, compared to just 1 in 11 in 2019 (1,2). This demographic shift is accompanied by a surge in age-related diseases, including cardiovascular disorders, cancer, neurodegenerative diseases, and diabetes, which collectively account for >70% of global mortality. The economic impact is equally staggering, with healthcare costs for elderly populations expected to markedly escalate, placing immense strain on public health systems, social security frameworks, and family resources (3). These statistics underscore the urgent need for innovative strategies to address the biological drivers of aging and its associated diseases.

Age reprogramming represents a transformative frontier in modern medicine, offering ground-breaking solutions to the multifaceted challenges posed by aging. As the aging process drives a cascade of cellular and molecular changes that underlie numerous chronic and degenerative diseases, targeting these fundamental mechanisms has become a critical focus for advancing healthcare (4). Age reprogramming therapies aim to address the biological hallmarks of aging, including genomic instability, epigenetic alterations, mitochondrial dysfunction, cellular senescence, and telomere attrition (5,6). By intervening in these core processes, these therapies aspire to restore cellular health, enhance function, and build resilience against age-related decline (7).

Recent scientific breakthroughs have advanced the field of age reprogramming from conceptual exploration to actionable innovation. Techniques such as epigenetic reprogramming, which modifies gene expression patterns without altering the underlying DNA sequence, have shown the potential to reverse cellular aging markers (8,9). The use of Yamanaka factors

[octamer-binding protein 4 (Oct4), SRY-box transcription factor 2 (Sox2), Kruppel-like factor 4 (Klf4), and c-Myc] to reprogram somatic cells has been particularly ground-breaking, enabling cells to regain a youthful phenotype while preserving their specialized identity (6,10). This discovery paves the way for novel therapeutic strategies to address conditions such as neurodegenerative diseases, cardiovascular disorders, and cancer (11,12).

Gene editing is another powerful tool in the age reprogramming arsenal. Technologies such as CRISPR-Cas9 offer unparalleled precision in modifying genes associated with aging, allowing scientists to enhance DNA repair mechanisms, deactivate genes driving cellular senescence, or correct mutations that accelerate degeneration (13,14).

These advancements are not only transforming the scientific understanding of aging but also challenging societal norms and expectations. By moving beyond traditional approaches that focus on managing symptoms of age-related diseases, age reprogramming offers a proactive pathway to extend health span, the period of life spent in good health (3).

Despite its transformative potential, the journey to realizing age reprogramming therapies faces significant challenges. Scientific hurdles include ensuring the safety and efficacy of these interventions, particularly given the complexity of cellular and molecular mechanisms involved in aging. Current delivery systems, such as viral vectors and nanoparticles (15), require substantial refinement to achieve precision targeting of aging cells without affecting healthy tissues (16). Furthermore, the translation of preclinical successes to human applications is fraught with regulatory and logistical barriers. Rigorous clinical trials, ethical frameworks, and comprehensive safety evaluations are essential to build public trust and ensure the responsible deployment of these therapies (17).

The societal and ethical implications of age reprogramming are profound, particularly regarding the risk of unequal access, which could exacerbate health disparities both within and between nations. The high costs associated with developing and implementing these therapies may limit their availability to affluent populations, further widening socio-economic divides. Additionally, extended health spans will necessitate coordinated adjustments to workforce dynamics, retirement policies, and social services to ensure sustainable and equitable integration (18,19).

The present review analyzes the scientific innovations underpinning age reprogramming and cellular rejuvenation, exploring their potential to revolutionize medicine and redefine human aging. It also examines the multifaceted challenges (scientific, economic, ethical, and societal) that must be addressed to ensure these therapies benefit humanity equitably and sustainably.

2. Current status of cell regeneration research

Cell regeneration research, particularly in the context of age reprogramming, has made significant strides in recent years. This field involves innovative strategies to reverse or halt the biological processes that lead to aging and age-related diseases. The current status of this research includes several key areas of focus: Epigenetic reprogramming, gene editing, stem cell therapy, and senolytic drugs.

Epigenetic reprogramming refers to the process of modifying gene expression patterns without altering the underlying DNA sequence. This ground-breaking approach leverages the inherent plasticity of the cell to reset its biological state, effectively reversing markers of cellular aging and restoring a youthful gene expression profile. Unlike genetic modification, which directly edits DNA, epigenetic reprogramming operates through mechanisms such as DNA methylation, histone modifications, and chromatin remodelling. These changes influence how genes are turned on or off, offering a non-invasive way to rejuvenate cells and enhance their functional capacity (20,21).

One of the most promising strategies in epigenetic reprogramming involves the use of Yamanaka factors, Oct4, Sox2, Klf4, and c-Myc (6,22). Initially discovered as a method to induce somatic cells into pluripotent stem cells [induced pluripotent stem cells (iPSCs)], this technique has since evolved to allow partial reprogramming. In this process, cells regain numerous youthful characteristics without losing their specialized identity (23). This balance is critical for therapeutic applications, as it ensures that rejuvenated cells can still perform their original functions. The ability to restore cellular health without erasing its identity holds immense potential for treating a variety of age-related conditions, including neurodegenerative diseases, cardiovascular disorders, and certain types of cancer.

The work of Bruno *et al* (24) on the Oct4 regulatory network highlights the role of chromatin modifiers, ten-eleven translocation 1 and Jumonji domain-containing protein 2A, in enhancing reprogramming efficiency and reducing variability. Their mechanistic model emphasizes that targeted recruitment of these epigenetic factors significantly impacts the success of cellular reprogramming. This study not only confirms the importance of epigenetic regulators but also provides a computational framework for optimizing reprogramming protocols, paving the way for more precise and predictable stem cell generation strategies.

The research by Kaemena *et al* (25) identifies KRAB zinc finger protein 266 (ZFP266) as a major inhibitor of iPSC generation (25). Through CRISPR/Cas9 knockout screening, they revealed how ZFP266 impedes chromatin opening by binding to short interspersed nuclear elements (SINEs), suppressing reprogramming factors such as Oct4, Sox2, and Klf4. This research underscores the significance of chromatin accessibility in reprogramming and offers a novel avenue for enhancing iPSC efficiency by targeting reprogramming roadblocks. Their innovative approach of converting ZFP266 from an inhibitor to a facilitator by modifying its co-suppressor domains highlights the potential for reprogramming-specific protein engineering.

The study by Wang *et al* (26) on the nucleosome remodeling deacetylase (NuRD) complex and spalt like transcription factor 4 (Sall4) further enriches our understanding of chromatin remodeling during early reprogramming (26). Their findings suggest that Sall4, in collaboration with the NuRD complex, plays a crucial role in closing open chromatin regions that encode genes resistant to reprogramming. This chromatin closing is essential for successful somatic reprogramming. Importantly, their identification of the Sall4-NuRD axis as a critical component of reprogramming adds a layer of complexity to our knowledge of cell fate control, demonstrating the intricate interplay between transcription factors and chromatin-modifying complexes.

The investigation of Xie *et al* (27) into the role of ring finger protein 40 (RNF40) highlights how this histone H2B ubiquitin-protein ligase facilitates early stages of iPSC reprogramming by promoting epigenetic modifications such as H2B monoubiquitination (27). The findings of the study which revealed that RNF40 indirectly regulates enhancer of zeste 2 polycomb repressive complex 2 subunit, a polycomb repressive complex component, provide a deeper understanding of how bivalent chromatin marks are resolved during reprogramming. This research establishes RNF40 as a central mediator of the epigenetic transitions required for pluripotency, offering insights into manipulating histone modifications for improved reprogramming outcomes (27).

A study by Müller *et al* (28) investigated M-phase phoshoprotein 8 (MPP8), an epigenetic protein crucial for maintaining the ground-state pluripotency of mouse embryonic stem cells. The findings demonstrated that MPP8 operates independently of detectable H3K9me3 levels to repress long interspesed nuclear element-1 and protect the hypomethylated pluripotent state (28). This highlights the versatility and complexity of epigenetic regulators in sustaining pluripotency and provides new insights into non-canonical pathways of chromatin regulation in stem cell biology.

Finally, a study by Srinivasan *et al* (29) on striatin interacting protein 2 (Strip2) identified this protein as a regulator of pluripotency and differentiation by interacting with the NuRD/TRIM28/HDACs/SETDB1 histone methyltransferase complex (29). Their discovery that Strip2 binds to DNA motifs akin to KRAB-ZFPs and modulates DNA methylation adds a new dimension to our understanding of how pluripotency and differentiation are controlled. By linking Strip2 to both pluripotency maintenance and differentiation processes, the study provides a potential target for fine-tuning stem cell behavior in regenerative medicine (29).

In addition to epigenetic reprogramming using Yamanaka factors for rejuvenation therapy, CRISPR technology introduces a revolutionary approach to enhance both the efficiency and safety of this process (30,31). While Yamanaka factors have shown immense promise in resetting cellular aging markers and restoring youthful gene expression profiles, challenges such as incomplete reprogramming, tumorigenic risks, and off-target effects remain significant barriers to clinical application. CRISPR, with its precise genome-editing capabilities, offers an innovative solution to address these limitations by enabling highly targeted modifications at the genetic and epigenetic levels (32).

CRISPR can be also used to fine-tune the expression of Yamanaka factors, ensuring that their activation occurs in a controlled and transient manner. This reduces the risk of over-activation, which can lead to tumorigenesis or loss of cellular identity. Additionally, CRISPR-based tools such as CRISPR-dead Cas9 (dCas9) fused with epigenetic modifiers provide the ability to activate or suppress specific genes without introducing permanent changes to the DNA sequence (33,34). This allows researchers to induce rejuvenation effects by selectively targeting aging-related pathways while minimizing unintended consequences.

Stem cell therapy involves using stem cells to repair or replace damaged tissues (35,36). This approach is being explored for its potential to rejuvenate tissues and organs affected by aging. By leveraging the regenerative capacity of stem cells, researchers aim to restore tissue function and delay the onset of degenerative conditions (37,38). Previous studies have shown promising results with stem cell therapy in animal models (49-41).

In clinical settings, these therapies are being tested for their safety and efficacy. Early-stage clinical trials have shown promising results, but significant challenges remain, including refining delivery mechanisms and overcoming regulatory hurdles (42). For instance, viral vectors and nanoparticles are being developed to ensure precise targeting of aging cells without affecting healthy tissues (43). Recent studies have emphasized the importance of developing safe and effective delivery systems for gene editing and stem cell therapies (44,45).

The regeneration research holds significant promise for transforming our approach to aging and age-related diseases. By targeting the fundamental biological processes that drive aging, these therapies have the potential to extend health span and improve quality of life. However, addressing the scientific, economic, and ethical challenges associated with these innovations will be crucial for their successful implementation in both clinical and experimental settings.

3. Healthcare cost implications

Age reprogramming and longevity therapies could lead to both increased and decreased healthcare costs, depending on their efficacy, accessibility, and implementation (46,47). If successful, longevity therapies could lead to substantial long-term savings by reducing the financial burden of age-related diseases. Chronic conditions such as heart disease, dementia, diabetes, and arthritis are among the leading contributors to healthcare expenses globally (5,48). By targeting the underlying mechanisms that drive these conditions, longevity therapies have the potential to mitigate or even eliminate the need for costly interventions, surgeries, and long-term care typically associated with aging populations.

For instance, senolytic drugs designed to selectively eliminate senescent cells may significantly decrease the inflammatory environment that underpins multiple age-related diseases (5,49). By investing in preventative measures, healthcare systems could shift from a reactive approach, where resources are spent on treating diseases, to a proactive strategy focused on maintaining health and wellness, ultimately leading to a more sustainable financial model.

Conversely, the development and implementation of age reprogramming therapies are burdened by significant upfront costs, posing a substantial challenge to their widespread adoption (46). Advanced technologies such as CRISPR gene editing, sophisticated stem cell-based treatments, mitochondrial rejuvenation techniques, and senolytic interventions are at the cutting edge of biotechnology (50-54). However, these innovations come with inherent complexities that drive up costs at every stage of development and deployment.

The research and refinement of such therapies require access to specialized laboratory facilities equipped with state-of-the-art technologies. These include high-throughput sequencing platforms, precision gene-editing tools, and cell culture systems capable of handling complex biological

manipulations. Moreover, their operation demands a highly skilled workforce, including molecular biologists, bioengineers, clinical researchers, and regulatory specialists, whose expertise comes at a premium (53). The recruitment, training, and retention of such personnel further add to the financial burden.

In addition to technological and human resource demands, the regulatory oversight required to ensure safety and efficacy significantly escalates costs. These therapies often involve manipulating fundamental biological mechanisms, necessitating rigorous preclinical testing, comprehensive clinical trials (7), and extensive safety evaluations to meet regulatory standards (17). Compliance with these regulations requires long timelines, substantial financial investment, and meticulous documentation, further straining budgets (54).

Another major contributor to high costs is the manufacturing and delivery process. Producing personalized therapies, such as gene-edited cells or tailored stem cell treatments, often involves intricate and time-consuming protocols that are challenging to scale. Technologies such as viral vectors or nanoparticles for precise delivery of therapeutic agents also require optimization to ensure specificity, stability, and minimal off-target effects (53). These production challenges lead to high per-unit costs, particularly in the early stages when economies of scale have not been achieved.

All these factors create financial barriers that make these therapies initially accessible only to affluent individuals or well-resourced healthcare systems (3). Without targeted efforts to reduce costs such as investing in scalable manufacturing technologies, developing universal treatment platforms, or fostering public-private partnerships, the benefits of age reprogramming risk being confined to a privileged minority. Addressing these economic hurdles will be critical to ensuring that these ground-breaking innovations achieve their full potential to improve health and extend longevity for all.

As a result, healthcare systems may face increased economic strain, particularly if these therapies are initially available only to a select segment of the population or if they require significant out-of-pocket expenses for patients. Governments and healthcare providers will need to carefully weigh the potential long-term savings from reduced disease burden against the immediate financial implications of implementing these new therapies (55). This could lead to difficult decisions about resource allocation, possibly diverting funds from other critical healthcare areas. A detailed picture of the healthcare cost implications associated with age reprogramming therapies, linking each aspect to its financial impact on healthcare systems is provided in Table I.

The introduction of longevity therapies will also create new pressures on insurance providers and publicly funded healthcare systems (56). Key questions will arise regarding the coverage of these treatments: Should longevity therapies be classified as essential healthcare services, warranting funding through public health insurance, or should they be considered elective procedures, requiring individuals to cover costs out-of-pocket?

The resolution of these questions will necessitate a careful examination of the balance between personal and collective responsibility in healthcare financing. As these therapies become more widely available, the ethical implications of access and equity in healthcare will come to the forefront. Policymakers will need to consider the potential for exacerbating health disparities if only wealthier individuals can afford these advanced treatments, while also addressing the need for inclusive frameworks that ensure equitable access to innovative healthcare solutions (57).

While age reprogramming and longevity therapies hold the promise of reducing long-term healthcare costs by preventing age-related diseases, their development and implementation come with significant upfront expenses and potential challenges for insurance coverage and equity (58). A balanced approach that considers both immediate costs and long-term savings will be essential for navigating this evolving landscape in healthcare.

4. Accessibility and inequality in longevity therapies

The accessibility of longevity therapies presents a significant challenge, with the potential to exacerbate existing social and economic inequalities. If these treatments remain available only to a privileged segment of the population, they could deepen disparities in healthcare access, economic opportunities, and overall quality of life. The high cost of developing and administering age-reprogramming therapies is likely to restrict their initial availability to wealthier individuals and nations, creating a scenario where only the affluent benefit from extended health spans and prolonged productivity. This raises ethical concerns about the equitable distribution of healthcare resources and the societal consequences of a growing gap between those who can afford longevity interventions and those who cannot.

On a global scale, disparities in access to longevity therapies may widen the health divide between high-income and low-income countries. Numerous developing nations already face significant healthcare challenges, including limited resources, inadequate infrastructure, and competing priorities such as infectious disease management and maternal health. Integrating advanced longevity treatments into these healthcare systems may prove financially and logistically overwhelming, further marginalizing populations that already struggle with basic medical care. Without targeted efforts to address these disparities, a 'longevity divide' could emerge, where wealthier nations reap the benefits of life-extending therapies while less affluent regions remain burdened by preventable age-related diseases.

The equitable distribution of healthcare resources is a fundamental ethical principle that could come under scrutiny with the introduction of longevity therapies (55). The ethical debate surrounding longevity therapies extends beyond affordability to the broader issue of healthcare prioritization. Policymakers must navigate difficult decisions about resource allocation, balancing investments in extending lifespan with the pressing need to improve primary healthcare services. In low- and middle-income countries, where healthcare funding is already constrained, prioritizing longevity treatments over fundamental health needs could widen inequities in care. A thoughtful approach is required to ensure that advancements in aging research complement, rather than overshadow, essential healthcare initiatives (Fig. 1).

Table I. Healthcare cost implications associated with age reprogramming therapies.

Aspect	Description	Implications	Healthcare cost implications	(Refs.)
Potential for cost savings	Targeting underlying mechanisms of age-related diseases (such as heart disease, dementia, diabetes) to reduce reliance on interventions, surgeries, and long-term care.	Shifts healthcare focus from reactive treatment to preventative wellness strategies, potentially saving billions globally.	Long-term reductions in healthcare expenses associated with managing chronic and age-related diseases.	(3,5)
Senolytic drugs	Designed to clear senescent cells, reducing systemic inflammation and slowing the progression of multiple age-related conditions.	Promotes healthier aging populations, lowering healthcare costs tied to treating inflammation-driven diseases such as arthritis and cardiovascular disorders.	Cost savings from reduced treatment requirements for inflammation-related conditions and improved patient outcomes.	(5,49)
High upfront costs	Advanced technologies (such as CRISPR, stem cell therapies, mitochondrial rejuvenation) require specialized equipment, expert personnel, and rigorous research processes.	Limits early adoption to affluent individuals or nations, creating barriers to widespread access.	Significant initial investments for research, development, and infrastructure setup, delaying cost-efficiency benefits.	(46)
Technological demands	Reliance on cutting-edge tools (such as gene-editing platforms, cell culture systems) and highly skilled professionals (molecular biologists, bioengineers, clinicians).	Increases operational expenses for research and development, delaying widespread availability.	High operational costs drive up therapy prices, affecting affordability and scalability.	(53)
Regulatory compliance	Extensive clinical trials, safety evaluations, and adherence to strict regulatory frameworks to ensure efficacy and public trust.	Adds financial and time burdens, requiring long-term investments to navigate complex approval processes.	Raises the overall cost of bringing therapies to market, impacting initial accessibility and affordability.	(7,17)
Manufacturing challenges	Personalized therapies including gene-edited cells and stem cell treatments involve intricate, time-consuming protocols and costly delivery systems (for example, viral vectors).	Scaling production while maintaining affordability is difficult, leading to high per-unit costs and limited accessibility in early stages.	Increases per-unit costs, particularly in early phases, until scalable and cost-efficient production methods are developed.	(53)
Healthcare system strain	High initial costs for implementing therapies could divert resources from other critical healthcare areas or require significant out-of-pocket expenses for patients.	Risks overburdening publicly funded systems and creating inequities unless offset by future savings from reduced disease prevalence.	Short-term budgetary strain on healthcare systems, requiring careful allocation of resources.	(55)

Table I. Continued.

Aspect	Description	Implications	Healthcare cost implications	(Refs.)
Insurance and funding dilemmas	Uncertainty over whether longevity therapies should be covered by public health insurance or considered elective treatments requiring private funding.	Raises ethical and economic questions about equitable access and the prioritization of healthcare funding for innovative therapies.	Potential increases in insurance premiums and out-of-pocket costs for patients, affecting affordability and coverage scope.	(56)
Equity and accessibility	Without interventions such as public-private partnerships, universal platforms, and scalable production, access may remain restricted to affluent populations or nations.	Exacerbates health disparities globally, creating a 'longevity divide' that leaves underprivileged groups without access to transformative therapies.	Limits the broader economic benefits of healthier populations if access remains exclusive to certain socio-economic groups.	(57)
Ethical and policy frameworks	Policymakers must address questions concerning access, affordability, and balancing resources between innovative therapies and essential healthcare needs.	Equitable distribution frameworks are essential to ensure that these therapies benefit all socio-economic groups and reduce societal divides.	Investment in inclusive policies could balance short-term costs with long-term societal and economic benefits of healthier aging populations.	(17)
Long-term impact	Potential to lower costs by preventing age-related diseases vs. high initial investments for research, production, and infrastructure.	A sustainable balance is needed to offset short-term financial strain with long-term savings, creating a healthier aging population and reducing economic burdens.	Significant potential for long-term healthcare savings by reducing treatment needs for chronic diseases and improving workforce productivity.	(19)

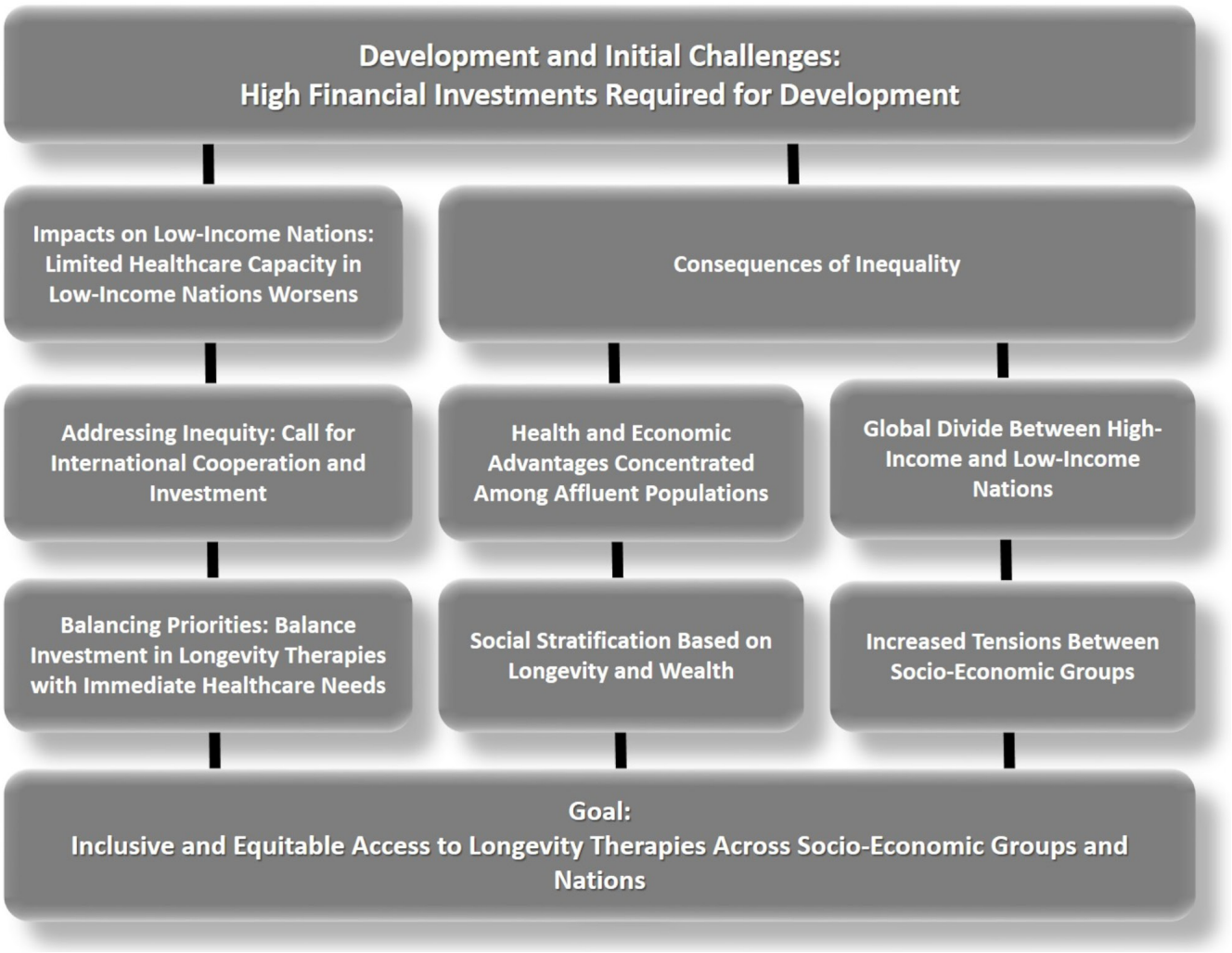

Figure 1. Problems of accessibility and inequality in anti-aging and longevity therapies.

Economic disparities also shape access within individual nations. Even in wealthier countries with strong healthcare systems, longevity therapies may initially be restricted to those who can afford them, creating a tiered healthcare landscape where extended health and vitality become privileges of the wealthy. This could reinforce social stratification, as those with access to these therapies gain prolonged economic and social advantages, further entrenching inequalities in wealth, employment, and quality of life. Middle-income nations face a unique challenge, possessing some capacity to adopt longevity therapies but often at the cost of diverting resources from other critical healthcare areas. The long-term consequences of such trade-offs require careful consideration to prevent the deepening of existing health inequities (55,59).

Moreover, the disparities also influence the global adoption of longevity therapies in healthcare systems, economic resources, regulatory frameworks, and cultural norms across different countries (Table II). Cultural and societal factors further influence the acceptance and implementation of longevity therapies. In some societies, aging is viewed as a natural process, and efforts to extend lifespan may be met with skepticism or resistance. Conversely, cultures that prioritize youthfulness and productivity may be more receptive to these treatments, influencing policy decisions and funding allocations. These differences highlight the need for culturally sensitive approaches to longevity research and implementation, ensuring that interventions align with societal values and ethical considerations.

Addressing these problems requires a multifaceted approach. Public-private partnerships, tiered pricing models, and subsidized healthcare programs could help make longevity therapies more widely accessible. Additionally, fostering research and innovation within middle- and low-income countries could reduce dependence on external providers and ensure that treatments are tailored to local healthcare needs. International collaboration and policy frameworks promoting equitable distribution will be essential in preventing longevity therapies from becoming tools of exclusivity.

Ultimately, ensuring fair access to longevity therapies is not just a matter of medical innovation but of ethical and social responsibility. Without proactive measures to bridge the gap, these treatments could reinforce existing inequalities rather than serving as tools for global health improvement. A comprehensive strategy that integrates affordability, infrastructure development, and ethical healthcare policies is necessary to ensure that longevity advancements benefit all segments of society, regardless of economic status or geographic location.

Table II. Global disparities in healthcare and implications for longevity therapies.

Metric	High-income nations	Low-income nations	Implications for longevity therapies
Healthcare expenditure per capita	5,000-12,000 USD (for example, USA, Germany, Japan)	50-150 USD (for example, Sub-Saharan Africa, South Asia)	High costs of longevity therapies are prohibitive in low-income settings, limiting adoption and innovation.
Percentage of GDP spent on healthcare	10-17%	3-6%	Lower budget allocation restricts funding for anti-aging research and access to therapies.
Access to advanced biotechnologies	Widely available (including CRISPR, stem cell clinical trials)	Rare or non-existent	Lack of access to cutting-edge biotechnologies perpetuates inequality in health outcomes.
Life expectancy	80-85 years	55-65 years	Existing gaps in longevity could widen further without equitable deployment of anti-aging interventions.
Availability of trained healthcare workers	30-50 per 10,000 individuals	1-5 per 10,000 individuals	Insufficient personnel in low-income nations limits the capacity to deliver complex treatments.
Healthcare infrastructure	Advanced hospitals, research centres, labs	Basic care facilities with limited diagnostic tools	Complex therapies requiring advanced infrastructure remain inaccessible in resource-limited settings.
Public spending on aging research	1 billion USD+ annually (including NIH, EU funding programs)	<10 million USD annually	Low investment prevents development of localized therapies and limits participation in global research collaborations.
Health equity index (WHO)	0.8-0.95	0.2-0.4	Inequitable healthcare systems hinder the fair distribution of longevity benefits.
Availability of anti-aging therapies	Widespread in clinical trials and early applications	Rare or experimental at best	Limited access results in a ‘longevity divide’, concentrating benefits in affluent regions.

5. Ethical considerations in genetic interventions for longevity

The prospect of employing genetic interventions to enhance longevity brings forth a complex landscape of ethical questions that must be carefully navigated. These questions encompass the scope of genetic modifications, their safety, and the broader social implications that may arise from their implementation (60). As we stand on the brink of revolutionary advancements in genetic therapies, it is imperative to consider the ethical ramifications that accompany these technologies.

One of the most ethically contentious aspects of longevity therapy is the potential for germline editing, altering genes in such a way that these changes can be inherited by future generations. Unlike somatic cell editing, which affects only the individual receiving the treatment, germline editing would pass genetic modifications to offspring, raising profound ethical concerns regarding consent, unintended consequences, and the long-term impact on human evolution (61).

While germline editing could theoretically shield future generations from age-related diseases, it carries significant risks of unforeseen genetic complications, which may not manifest until many years later (62). The inability to obtain consent from future generations introduces a moral dilemma: Are we justified in making irreversible changes to the human genome without the approval of those who will be affected? Furthermore, the potential for germline editing to create a form of genetic determinism raises additional ethical concerns, as the implications of modifying traits related to health, longevity, and possibly even intelligence or physical ability must be considered.

Longevity therapies challenge societal notions of natural aging and what it means to grow old. Some ethicists contend that interfering with the biological aging process represents a fundamental shift in healthcare thus transforming it from a tool for treating diseases into an enhancement technology aimed at extending life beyond natural limits (62). This distinction is crucial, as it provokes questions about the ethical implications of prioritizing treatments that extend life in ways that deviate from biological norms. The summary on the ethical considerations and solutions in genetic interventions for longevity and rejuvenation therapy are provided in Table III.

The potential for creating a biologically privileged class raises concerns about social fragmentation. If only certain segments of the population can afford or access longevity therapies, a divide may emerge between those who undergo age reprogramming and those who do not. This disparity could lead to a society where health and longevity become markers of privilege, further entrenching existing social inequalities. The ethical implications of creating enhanced individuals must be critically examined, particularly in terms of fairness and justice within society.

A critical ethical consideration in the realm of longevity therapies is the issue of informed consent and individual autonomy. Individuals must retain the right to decide whether or not to undergo these treatments, particularly given the associated risks and unknowns, especially during the early stages of these therapies. Upholding ethical standards requires ensuring that patients are fully informed about potential risks, including side effects and long-term consequences that may not yet be understood (58).

Moreover, as longevity therapies become more commonplace, society must respect the rights of individuals to decline these treatments without facing societal pressure, stigma, or discrimination (Fig. 2). Ensuring that personal autonomy is preserved in the face of potential societal norms promoting longevity as a desirable goal is essential for maintaining ethical integrity in healthcare. The ethical framework surrounding informed consent must adapt to address the nuances of these therapies, ensuring that individuals make choices based on comprehensive information and without coercion (62).

The extension of human health span and potential lifespan raises crucial questions regarding the environmental and societal impacts of a growing population of healthy, long-lived individuals (63). While a healthier elderly population could alleviate some economic burdens on healthcare systems, it may simultaneously exert increased pressures on essential resources such as housing, employment, and social services.

Moreover, longer lifespans could have significant environmental implications. Extended consumption patterns could contribute to resource depletion and environmental degradation, necessitating thoughtful planning to mitigate these effects. As we consider the societal changes that accompany a population with an extended health span, it is vital to ensure that longevity therapies do not inadvertently create new challenges. Integrating sustainability into the discussion of longevity therapies will be essential to fostering an equitable and healthy future for all individuals (60,64).

The genetic interventions introduce a host of ethical considerations that must be meticulously examined (65,66). Addressing the complexities of germline editing, the redefinition of natural aging, informed consent, and the broader societal impacts will be critical to navigating the ethical landscape of these emerging technologies (58). The complex ethical dimensions of gene intervention for aging and cellular rejuvenation therapies, emphasizing the need for careful regulation, informed consent, and equitable access to these ground-breaking but potentially controversial treatments is illustrated in Table IV.

Steps toward international ethical alignment could include creating a globally recognized body, akin to the World Health Organization (WHO), to oversee genetic interventions and longevity therapies. This body could develop universal guidelines defining permissible applications of germline editing, enforce strict regulatory standards, and foster cooperation between countries. Agreements such as the UNESCO Universal Declaration on Bioethics and Human Rights could serve as a foundation for establishing these principles (67,68). Additionally, such a framework should emphasize equitable access to these therapies, ensuring that advancements benefit global populations rather than a privileged few.

6. Future directions in age reprogramming research

Future research in age reprogramming holds the promise of addressing critical challenges in aging and advancing healthcare into a new era. One of the most promising areas of investigation is targeted mitochondrial editing. Mitochondrial dysfunction, a hallmark of aging, contributes to reduced energy production, oxidative stress, and the progression of age-related diseases. Precise editing of mitochondrial DNA using advanced

Table III. Ethical considerations and solutions in genetic interventions for longevity.

Aspect	Description	Ethical concerns	Proposed solutions
Scope of genetic modifications	Genetic interventions, including somatic and germline editing, aim to address aging by modifying biological processes.	Risks of unintended consequences, unforeseen genetic complications, and irreversible impacts on human evolution.	Conduct rigorous safety testing, establish robust ethical oversight, and involve public discourse to ensure responsible applications.
Germline editing	Alters inheritable genes to potentially prevent age-related diseases in future generations.	Raises concerns about consent from future generations, unforeseen long-term consequences, and risks of genetic determinism (modifying non-health traits).	Limit germline editing to essential health interventions; develop international guidelines and enforce strict regulatory controls.
Redefinition of natural aging	Longevity therapies challenge aging as a natural process, treating it as a condition that can be managed or reversed.	Raises questions about disrupting biological norms, redefining aging, and prioritizing enhancements over natural health trajectories.	Promote ethical discussions about the societal perception of aging and ensure alignment with cultural and moral values.
Social stratification	Access to longevity therapies may create a privileged class with significant health and lifespan advantages.	Risk of widening socio-economic divides, reinforcing inequities, and fostering societal tensions between those who can and cannot afford these therapies.	Implement equitable pricing models, public-private partnerships, and subsidies to ensure broader access for underserved populations.
Informed consent and autonomy	Ensures individuals can decide whether to undergo therapies with full knowledge of risks and benefits.	Challenges in communicating complex risks, societal pressures to conform, and potential stigma for those who choose to opt out.	Establish transparent consent processes, enhance public education, and safeguard individual rights to refuse therapies without discrimination.
Environmental impacts	Extended lifespans may increase demand for resources such as housing, food, and energy, intensifying ecological strain.	Risk of overburdening environmental resources, contributing to depletion, and exacerbating global inequalities in access to essentials.	Integrate sustainability into longevity strategies, promote eco-friendly practices, and ensure resource-conscious planning in policy design.
Societal implications	A growing population of healthy, long-lived individuals could disrupt workforce dynamics and retirement systems.	Strains on healthcare, pensions, and social services; risks of generational inequalities and conflicts over resource allocation.	Adapt workforce structures, introduce flexible retirement policies, and ensure fair distribution of resources to maintain intergenerational equity.
Sustainability	Balancing the benefits of extended healthspans with societal and ecological demands.	Ethical dilemmas of extending life without adequately addressing resource needs and long-term environmental impacts.	Align longevity advancements with sustainability goals, ensuring therapies support global ecological and social well-being.
Justice and fairness	Ensures fair access to therapies across socio-economic groups and nations.	Risk of exclusive access for affluent populations or countries, leaving marginalized groups without benefits of longevity therapies.	Establish global frameworks for equitable access, incentivize affordable production, and support low-income nations with healthcare infrastructure.
Ethical governance	Development of transparent and inclusive guidelines to regulate genetic interventions for longevity.	Risks of misuse, inequities, and inadequate accountability in deploying advanced therapies.	Form interdisciplinary coalitions to set ethical standards, ensure global oversight, and continuously evaluate societal impacts.

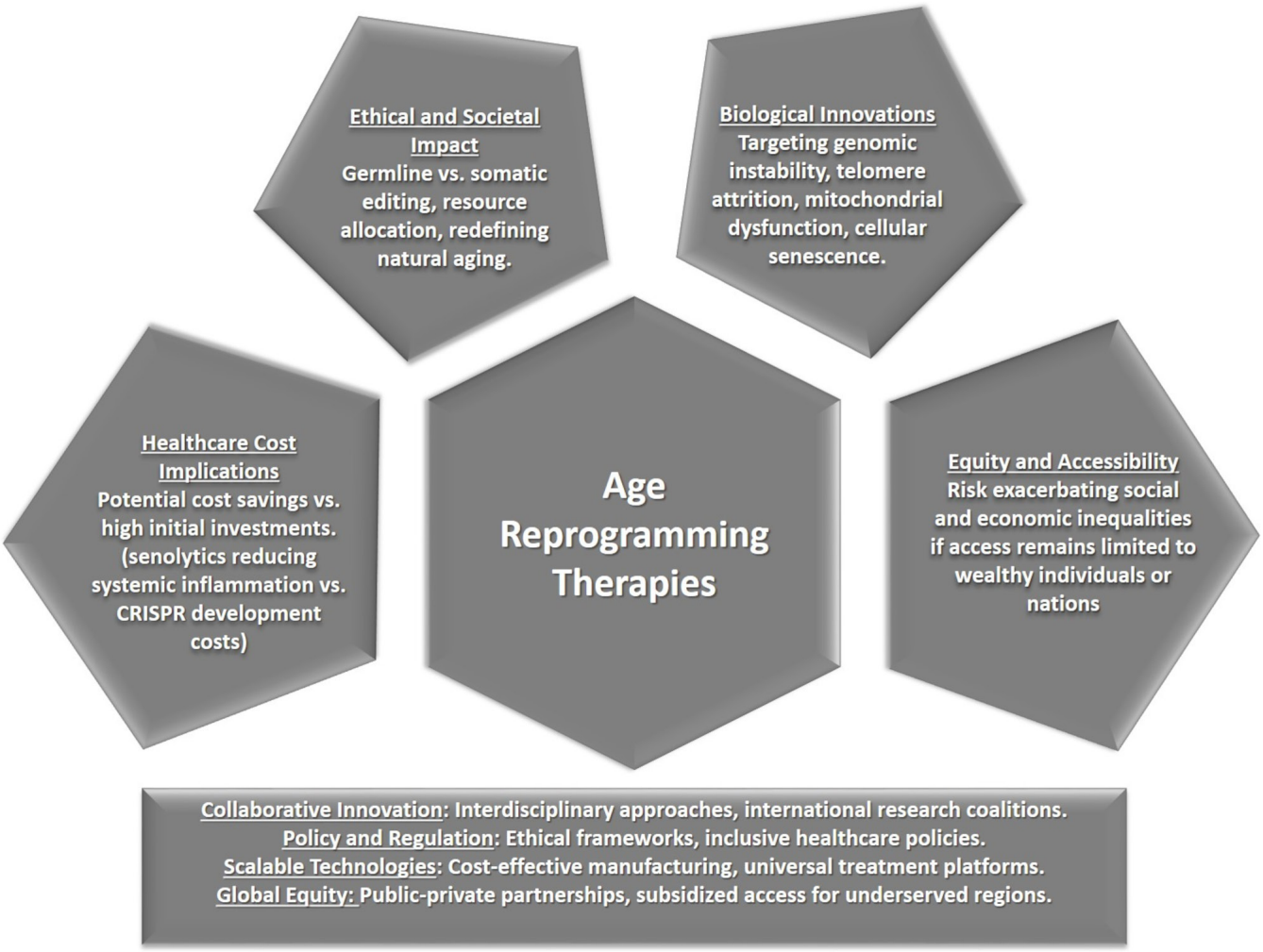

Figure 2. Main aspects of age reprogramming therapies in context of the ethical and socio-economic impacts.

CRISPR-based tools, such as mitoCRISPR, could correct mutations, restore energy metabolism, and reduce oxidative damage in aging tissues (69). Combining mitochondrial editing with therapies that promote mitochondrial biogenesis and balanced fission-fusion cycles could offer a comprehensive approach to improving cellular health and longevity (70,71).

Another critical avenue of research is stem cell rejuvenation for neurodegenerative conditions, which pose significant challenges in aging populations. Neurodegenerative diseases including Alzheimer's and Parkinson's could be addressed by leveraging reprogrammed neural stem cells derived through techniques such as partial reprogramming or iPSCs (72,73). These cells have the potential to restore neural plasticity and replenish lost or damaged neurons, offering hope for regeneration in affected brain regions. Pairing these approaches with extracellular vesicle-based delivery systems may enhance therapeutic outcomes by improving the integration of stem cells and reducing inflammation in neural tissues.

To optimize these therapies, the development of reliable and minimally invasive biomarkers is essential. Biomarkers that reflect biological age and therapeutic efficacy, such as circulating DNA methylation patterns, telomere length, or mitochondrial health indicators, could enable precise monitoring of therapeutic progress. Artificial intelligence (AI)-driven analyses of multi-omics datasets, encompassing genomics, proteomics, and metabolomics, could accelerate the discovery and validation of such biomarkers, ensuring their effective application in clinical settings.

Epigenetic reprogramming tools also remain a cornerstone of age-reprogramming research. Yamanaka factors have shown great potential for reversing cellular aging, but future efforts should focus on refining these tools to achieve controlled and reversible reprogramming without inducing tumorigenicity or loss of cell identity (74,75). Transient delivery of reprogramming factors through advanced techniques, such as nanoparticles or gene-editing technologies, could improve safety and precision, paving the way for broader clinical applications (6).

Another promising direction involves gene therapies targeting immune senescence. The aging immune system, which becomes less effective at fighting infections and more prone to chronic inflammation, could benefit from interventions aimed at rejuvenating immune function. For example, modifying pathways involved in T-cell regeneration or reducing pro-inflammatory cytokines could enhance immune resilience in older adults (76). Combining such strategies with senolytics or senomorphics could further improve outcomes by reducing systemic inflammation (77,78).

Table IV. Ethical issues and impact of gene intervention in rejuvenation therapy on individuals.

Ethical Issues	Description	Potential impacts on individuals	Solutions
Health risks	Risks related to the safety and unintended effects of genetic interventions.	On-target risks: Potential tumorigenesis from prolonged activation of Yamanaka factors. Off-target risks: CRISPR may unintentionally alter genes unrelated to aging, leading to unpredictable health issues.	Need in extensive preclinical testing and phased clinical trials to ensure safety. Implement robust monitoring systems for long-term follow-up.
Equity of access	Unequal availability of therapies based on socioeconomic status or geographic location.	Wealthier individuals may benefit disproportionately, leading to a healthcare gap. Limited access for underprivileged populations could exacerbate inequalities.	Develop public-private partnerships to subsidize treatments for low-income populations. Prioritize global collaborations to ensure equitable distribution.
Autonomy rights	The right of individuals to make informed decisions about undergoing genetic intervention.	Individuals may feel pressured to adopt therapies due to societal or familial expectations. Lack of adequate information could hinder fully informed consent.	Create clear educational campaigns to explain risks, benefits, and alternatives. Ensure counselling services are available to address societal or familial pressures.
Informed consent	The necessity of clear and thorough communication about risks and benefits to participants.	Complex scientific details may confuse patients, leading to uninformed decisions. Ethical concerns arise if therapies are applied without clear, long-term safety data.	Simplify consent processes with layperson-friendly explanations. Require third-party oversight to ensure consent forms are properly reviewed and understood.
Intergenerational impacts	Genetic changes that may unintentionally affect future generations if germline cells are altered.	Children of treated individuals might inherit unintended modifications. Raises ethical questions about altering human biology without consent from future generations.	Prohibit germline editing until safety is proven and public consensus is reached. Focus on somatic cell therapies that do not affect future generations.
Psychological effects	Potential mental and social impacts of rejuvenation therapies.	Increased pressure to maintain ‘youthful’ traits could cause psychological stress. Fear of missing out on treatments might lead to societal stigmatization of untreated individuals.	Foster societal acceptance of aging as a natural process, even with rejuvenation options available. Provide psychological support and counselling for individuals undergoing treatments.
Cultural and societal norms	Challenges to cultural beliefs about aging and mortality.	May disrupt traditional views on aging as a natural life process. Could exacerbate ageism if older individuals are pressured to ‘rejuvenate’ to stay relevant.	Engage cultural and religious leaders in discussions to promote ethical use of therapies. Need to advocate for inclusive narratives about aging and societal value.
Economic consequences	High costs associated with developing and administering advanced genetic therapies.	Risk of creating ‘longevity elites’ who can afford therapies.	Implementation tiered pricing models to make treatments affordable.

Table IV. Continued.

Ethical Issues	Description	Potential impacts on individuals	Solutions
Potential for misuse	Risk of therapies being used for non-therapeutic or enhancement purposes.	Could lead to the pursuit of cosmetic or performance enhancements rather than addressing legitimate health concerns.	Enforce regulations restricting therapies to medically necessary applications. Monitor and penalize unethical marketing or unauthorized applications.
Long-term safety	Lack of data on the long-term effects of genetic interventions.	Unknown health consequences might emerge decades after treatment. Individuals may experience unforeseen complications as they age.	Requires ongoing longitudinal studies to track the effects of therapies over time. Establish transparent reporting systems for adverse effects.
Personal identity	Concerns about how altering aging trajectories could affect an individual's sense of self.	Reprogramming cellular age might alter how individuals perceive themselves in terms of their life stage and societal roles.	Counselling to help individuals adjust to the psychological and social impacts of therapy.

The integration of these advances into healthcare systems represents a paradigm shift from reactive disease management to proactive health preservation. Age-reprogramming therapies could form the backbone of preventive medicine, focusing on mitigating age-related decline before clinical symptoms emerge. Early intervention programs that screen for biological aging markers during routine health check-ups could enable timely therapeutic applications, such as senolytics or epigenetic reprogramming, to delay the onset of age-related diseases (79). Personalized medicine, driven by genetic, epigenetic, and lifestyle data, could ensure that therapies are tailored to individual patients for maximum efficacy (80). Additionally, longitudinal care models, incorporating periodic interventions to maintain cellular and tissue health over decades, could become standard practice.

AI will play a pivotal role in this transformation by customizing therapies, predicting patient responses, and managing treatment schedules. AI integration could make age-reprogramming therapies more accessible and efficient, streamlining their adoption into mainstream healthcare. By bridging these innovative approaches with preventive and personalized care, age-reprogramming therapies have the potential to redefine healthcare, shifting aging from an inevitable decline to a manageable and reversible process. With interdisciplinary collaboration and continued technological advancements, these therapies could become a cornerstone of 21st-century medicine, enhancing both lifespan and health span while fundamentally reshaping our approach to aging.

7. Conclusions

Age reprogramming and cellular rejuvenation therapies represent a transformative frontier in medicine, aiming to extend health spans by addressing the biological roots of aging. These therapies promise to reduce age-related diseases and redefine societal views on aging, enabling longer, healthier lives. However, realizing their potential requires overcoming key challenges. International collaboration is essential to harmonize regulatory frameworks, streamline clinical trials, and establish universal safety standards to build public trust. High costs remain a barrier, necessitating investments in scalable manufacturing, standardized gene-editing platforms, and cost-effective delivery systems to ensure affordability.

Equity must be prioritized to prevent widening global health disparities. Public-private partnerships, tiered pricing, and subsidized funding can improve accessibility, particularly in low- and middle-income countries. At the same time, interdisciplinary research is crucial to enhance the safety, efficacy, and precision of these therapies, focusing on advancements in targeted delivery, biomarkers, and personalized treatments. By combining scientific innovation, ethical governance, and equitable access, age reprogramming therapies can redefine healthcare, transforming aging from an inevitable decline into a manageable and reversible process.

Acknowledgements

Not applicable.

Funding

The study was supported by program-targeted funding from the Ministry of Science and Higher Education of the Republic of Kazakhstan 'Prolonging healthy longevity: using new technologies and machine learning to control reversal of aging in old cells' (grant no. BR24992900).

Availability of data and materials

Not applicable.

Authors' contribution

TS conceived the study and contributed to the writing of the original draft, as well as the methodology and formal analysis. PBS wrote, reviewed, edited and supervised the study, and contributed to project administration. Both authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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