

## Current State of Gene Therapy for Longevity Applications

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### Abstract

Gene therapy has evolved from a theoretical concept to a practical clinical approach, offering substantial promise for managing age-related disorders and enhancing human longevity. This review explores the present status of gene therapy methods, emphasizing adeno-associated virus (AAV) vectors and their relevance to longevity research.

It assesses approved treatments, delivery systems, and international research efforts, alongside the developing array of gene therapies aimed at longevity. While traditional applications have centered on single-gene disorders, the domain is broadening to include multifaceted genetic conditions and the underlying processes of biological aging.

Various preclinical investigations have demonstrated notable extensions in both lifespan and health span through gene therapy strategies that influence essential longevity mechanisms. The shift from treating diseases to intervening in aging processes presents exceptional opportunities for prolonging human health span and lifespan. This review provides comprehensive background for understanding the current state of gene therapy for longevity, as well as its path toward practical clinical use.

**Keywords:** Gene therapy, Adeno-associated virus, Longevity and Healthspan.

### Introduction

#### Historical Development of Gene Therapy Technologies

The concept of gene therapy emerged in the early 1970s and now stands as one of the most promising areas in medicine, capable of addressing diseases by incorporating genetic material into patient cells [1]. Over the past five decades, the field has experienced notable achievements alongside considerable obstacles.

The first approved gene therapy trial occurred in 1990, where scientists addressed adenosine deaminase deficiency in a young child by inserting a functional gene into her white blood cells through the addition of genes [2]. These initial efforts were crucial in validating the concept, yet advancement was impeded by inadequate vector performance and safety issues.

The tragic death of a participant in 1999 during a trial involving adenovirus vectors caused a

major setback in the field [3]. Following this event, the area entered a phase of reassessment and improvement in techniques. Consequently, efforts concentrated on creating more secure delivery mechanisms, with a strong emphasis on adeno-associated virus (AAV) vectors. The

contemporary phase of gene therapy began with the 2012 European authorization of Glybera for lipoprotein lipase deficiency, followed by additional approvals that solidified gene therapy as a legitimate treatment option [4].

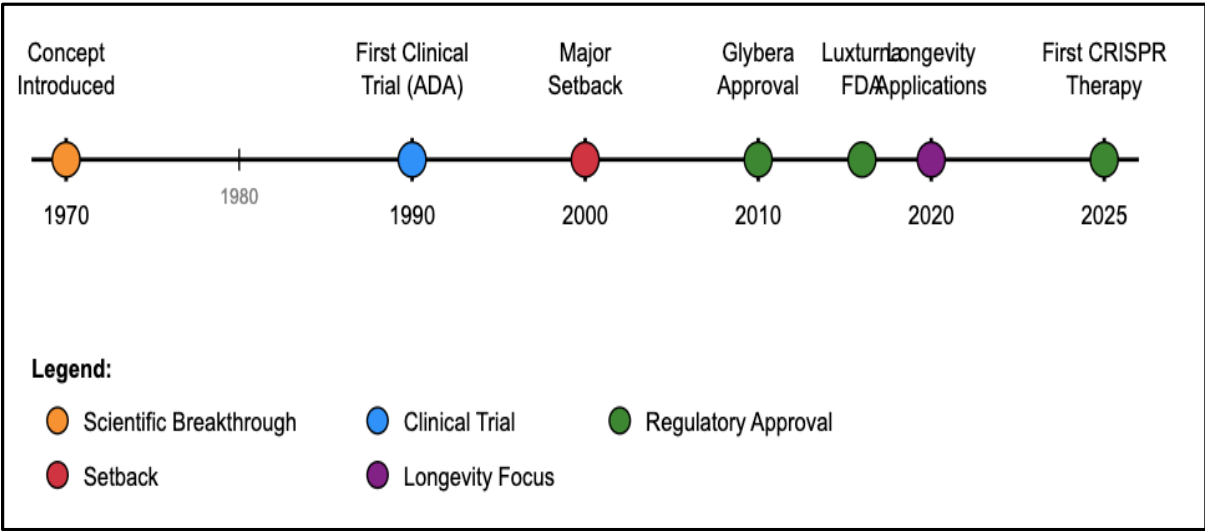


**Figure 1:** Timeline of Gene Therapy Development.

Evolution of gene therapy from concept to longevity applications (1970-2025). Key milestones include first conceptualization (1970s), first clinical trial (1990), major setbacks (1999), first commercial approval (Glybera, 2012), and emergence of longevity-focused applications (2019-present). Icons indicate regulatory approvals (green), clinical trials (blue), major scientific breakthroughs (orange), setbacks (red), and longevity focus (purple).

**Evolution of AAV as a Vector for Gene Delivery**

Among diverse gene delivery options, AAV has become a leading choice for in vivo applications owing to its advantageous traits, including its lack of pathogenicity in humans. AAV depends on a helper virus for replication, contributing to its safety profile compared to alternative viral vectors [5]. Decades of investigation have elevated AAV from a mere research interest to an advanced delivery tool. Important progress includes the creation of recombinant AAV (rAAV) systems, where viral genes are substituted with therapeutic ones; the identification of various AAV serotypes exhibiting distinct tissue preferences, enabling targeted delivery; and enhancements

in manufacturing to achieve clinical-level quality and effectiveness.

Ongoing modifications aim to improve specificity, gene expression, and avoidance of immune detection [6-9]. AAV vectors can carry genetic material up to approximately 4.7 kb, a constraint that has been mitigated through innovative in vivo gene recombination methods [10]. The genetic insertions remain mostly episomal, minimizing risks of insertional mutations, and support sustained expression in non-proliferating cells. These features position AAV as the preferred vector for numerous purposes, especially in non-dividing tissues like the brain, retina, and mature muscle, all of which are pertinent to interventions for extending lifespan [11].

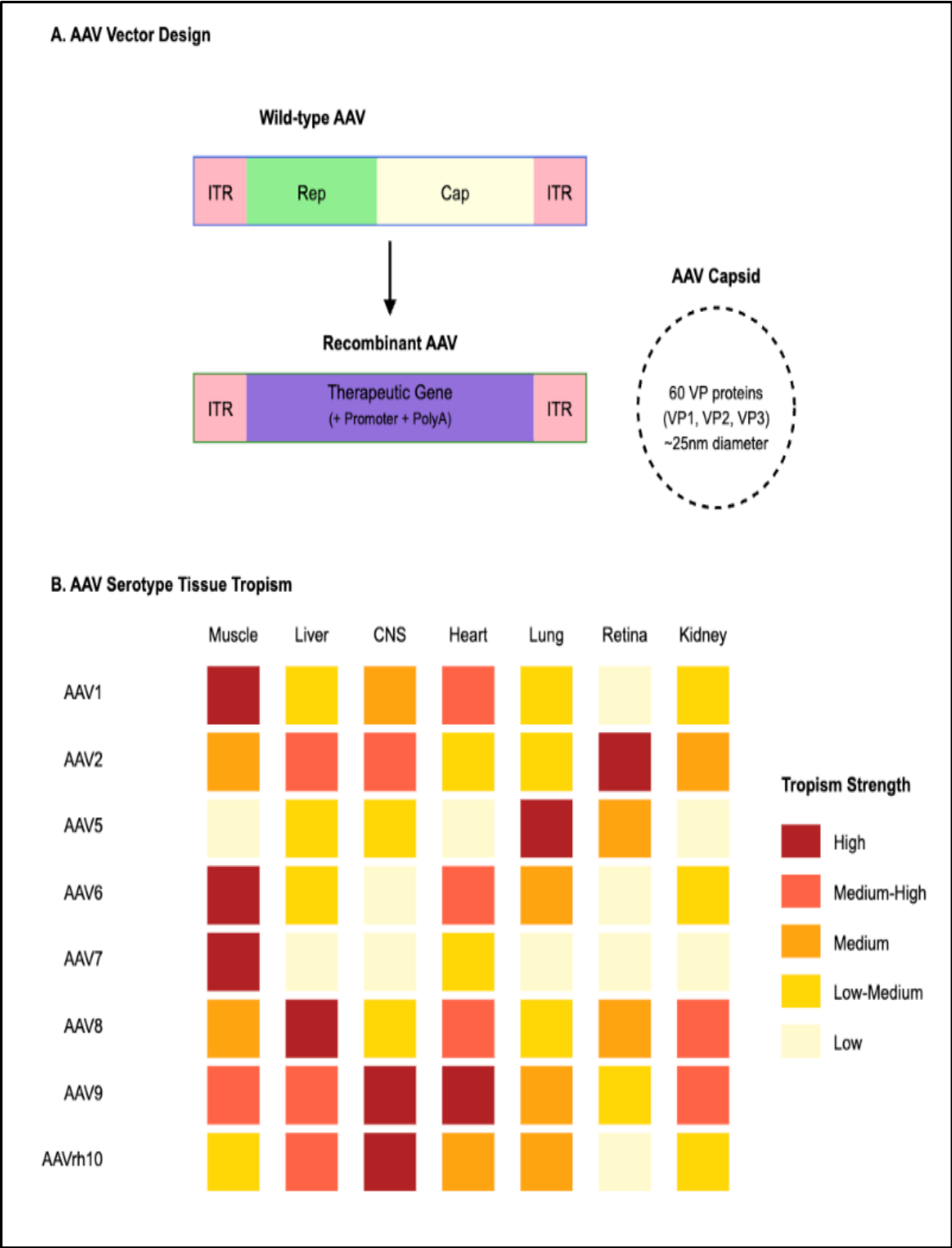


**Figure 2:** AAV Vector Structure and Serotype Comparison.

Adeno-associated virus (AAV) vector design and tissue tropism. **A:** Schematic representation of wild-type AAV genome versus recombinant AAV vector showing replacement of viral genes with therapeutic transgene cassette. **B:** Heat map showing tissue tropism of major AAV serotypes (AAV1-AAV9, AAVrh10) across key organs relevant to aging interventions. Darker colors indicate stronger tropism.

## Transition from Disease Treatment to Longevity Enhancement

Originally, gene therapy aimed to rectify monogenic disorders by supplying functional gene copies in place of faulty ones. Gradually, its reach has extended to intricate polygenic ailments and, more recently, to modulating the core mechanisms of aging [12].

This change stems from multiple converging elements, including a deeper insight into the genetic and molecular foundations of aging and the pinpointing of modifiable pathways. The preservation of longevity mechanisms across species, from simple organisms to mammals, has highlighted viable targets for genetic alterations [13].

Awareness that such modifications can markedly improve lifespan and health span has spurred initiatives to commercialize gene therapy. Furthermore, progress in technology has facilitated accurate in vivo genetic changes that were once unattainable [14].

The framework of aging "hallmarks" serves as a guide for interventions, with gene therapy now addressing aspects like telomere shortening, mitochondrial impairment, cell senescence, and disrupted nutrient detection [15,16].

This marks a profound departure from conventional practices of managing aging's effects to tackling its fundamental causes. Interventions for longevity differ from standard treatments by seeking to boost typical functions or avert future deterioration rather than fix current issues.

This difference carries important consequences for evaluating risks and benefits, regulatory processes, and trial structures, necessitating a fresh viewpoint distinct from prior medical strategies.

## Currently Approved Gene Therapies

### Overview of FDA/EMA Approved Therapies

From 2012 onward, multiple gene therapies have gained approval in the US, Europe, and elsewhere. Although none are explicitly for aging, these endorsements set benchmarks and foundations that inform longevity-related developments [17]. Luxturna (voretigene neparvovec-rzyl), cleared by the FDA in 2017 and EMA in 2018, addresses biallelic RPE65 mutation-linked retinal dystrophy.

This AAV2 therapy supplies a functional RPE65 gene to retinal cells through subretinal administration, restoring sight in those with this uncommon inherited blindness [18]. Zolgensma (onasemnogene abeparvovec-xioi), approved in 2019, employs an AAV9 vector to provide the SMN1 gene for pediatric spinal muscular atrophy via a one-time intravenous dose, effectively stopping disease advancement and supporting developmental progress [19]. Later approvals encompass Roctavian (valoctocogene roxaparvovec), EMA-approved in 2022 and FDA in 2023 for hemophilia A, using an AAV5 vector to deliver Factor VIII to the liver for internal clotting factor production [20,21]. Casgevy, the initial CRISPR therapy approved in 2023 for sickle cell disease and beta-thalassemia, applies an ex vivo method with CRISPR-Cas9 to modify patient stem cells for fetal hemoglobin induction [22].

Elevidys (delandistrogene moxeparvovec-rokl) obtained accelerated FDA approval in 2023 for Duchenne muscular dystrophy, delivering a micro-dystrophin gene via AAV9 to muscle cells [23]. In Europe, Lenmeldy (atidarsagene autotemcel) was approved in 2020 for metachromatic leukodystrophy using an ex vivo lentiviral technique on autologous stem cells [24]. These authorizations illustrate the adaptability of gene therapy and its capacity to handle conditions previously deemed incurable.

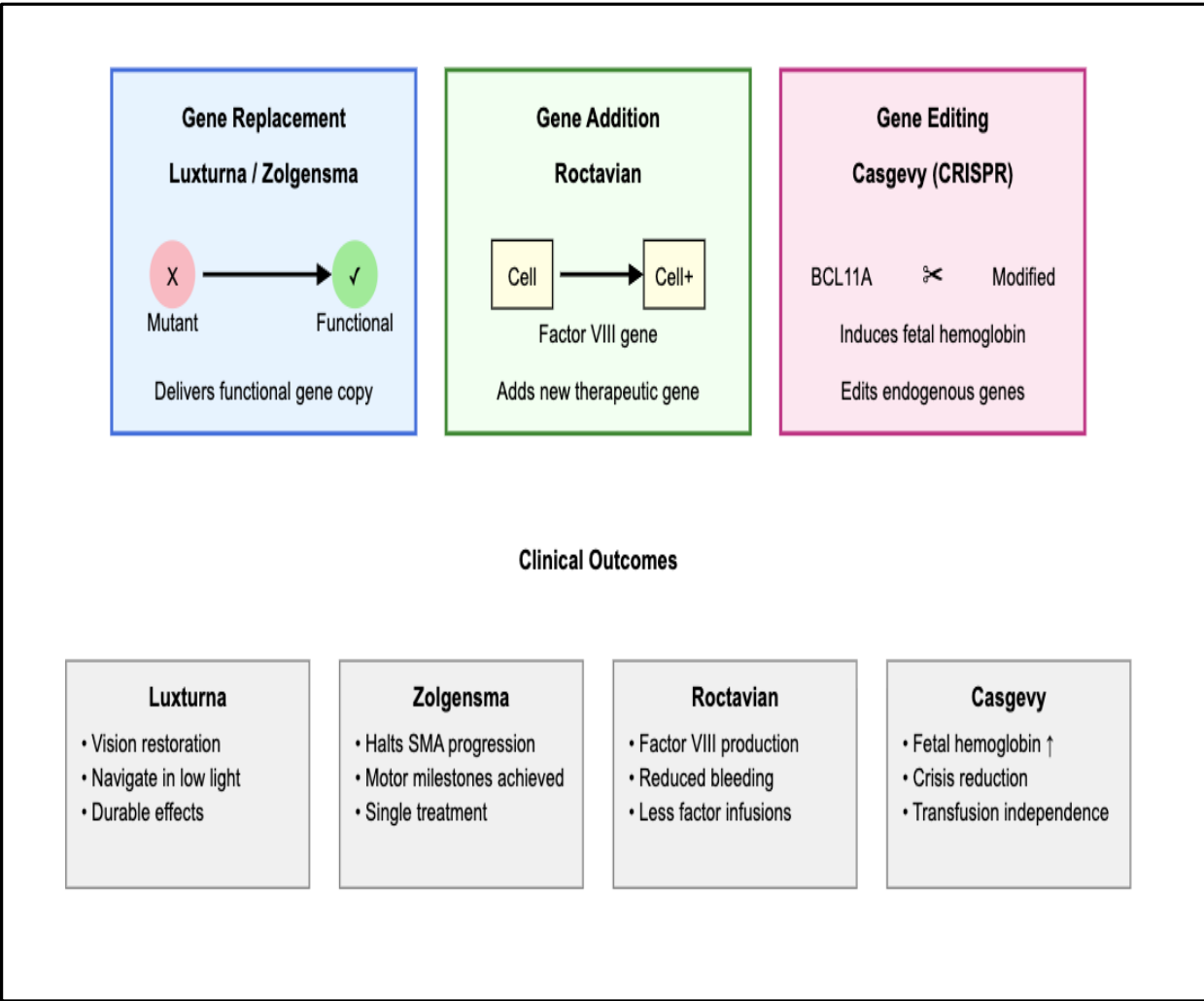


**Figure 3:** Mechanisms of Currently Approved Gene Therapies.

Therapeutic mechanisms of FDA/EMA-approved gene therapies. Visual representation of gene replacement (Luxturna, Zolgensma), gene addition (Roctavian), and gene editing (Casgevy) approaches. Each panel shows the delivery method, target tissue, and therapeutic outcome. Clinical outcomes demonstrate transformative effects on previously untreatable conditions.

**Mechanisms and Outcomes of Current Therapies**

Approved gene therapies utilize varied approaches, including gene replacement, editing, and addition. Replacement methods supply operational genes to offset mutations, as in Luxturna providing RPE65 to retinal cells for vision restoration in inherited blindness, and Zolgensma delivering SMN1 to motor neurons to arrest spinal muscular atrophy progression [18,25]. Editing techniques use CRISPR-Cas9 to alter genes like BCL11A in stem cells,

promoting fetal hemoglobin for sickle cell and β-thalassemia treatment [22]. Addition therapies introduce functional Factor VIII to liver cells, allowing hemophilia A patient to generate clotting factors and lessen bleeding incidents [26]. Results from these treatments have been impressive.

Luxturna has enabled vision recovery in those nearing blindness, with patients gaining abilities like low-light navigation and facial recognition [18]. Zolgensma has altered SMA's course, permitting children to reach milestones

like independent sitting or walking that were previously unattainable [27]. Extended monitoring indicates lasting benefits, with treated individuals retaining achievements that would otherwise decline [25]. Such outcomes highlight gene therapy's ability to reshape disease paths, which is highly applicable to longevity, where one-time treatments could avert or mitigate age-associated deterioration.

### **Safety Profiles and Delivery Methods**

The safety data from approved therapies offer valuable guidance for longevity applications. Immune reactions pose ongoing challenges, including antibodies neutralizing vectors and responses to transgenes [27].

Mitigation involves immunosuppressive drugs, vector modifications for lower immunogenicity, and screening for pre-existing antibodies [28]. Risks of insertional mutagenesis are mainly linked to integrating vectors like lentiviruses, not AAV, and have been reduced via better designs favoring non-integrating options for in vivo work, though lentiviruses remain useful for their larger capacity [29].

Toxicity related to dosage is another issue, as systemic conditions demand high amounts, heightening risks like liver damage or rare fatalities documented in trials [30]. This has driven efforts toward more potent vectors needing lower doses to prevent adverse effects. Research has explored diverse delivery techniques to optimize dosing, specificity, and efficiency, each suited to particular tissues and objectives.

Intravenous methods enable widespread distribution, whereas direct injections provide focused delivery with reduced systemic impact. Intra-arterial approaches concentrate vectors in specific areas while limiting broader exposure, showing potential for organ targeting.

Intratissue injections achieve high local levels in accessible sites.

Intracavitary methods reach organs within compartments like the peritoneal space. Intrathecal delivery accesses the central nervous system by bypassing the blood-brain barrier. Intralymphatic options support immune modulation relevant to aging. Inhalation targets lungs for age-related pulmonary issues. Ex vivo alterations involve external cell modification before reintroduction, allowing quality assurance and sidestepping some in vivo challenges. These strategies shape longevity therapy designs, balancing localized and systemic effects [31].

### **Gene Therapy Platforms**

#### **AAV Vector Technology and Serotypes**

AAV vectors lead in vivo gene therapy due to their safety and flexibility. The AAV genome features rep and cap genes bordered by inverted terminal repeats (ITRs). Recombinant versions replace these with therapeutic cassettes while keeping ITRs for packaging [6]. The capsid, formed by VP1, VP2, and VP3 proteins, influences tissue affinity and immune response, with over a dozen natural serotypes identified, each preferring certain tissues [32].

AAV1 and AAV7 transduce skeletal muscle effectively. AAV2, extensively researched, affects various tissues including retina, nervous system, and liver, suitable for multi-organ aging strategies. AAV8 targets liver with low immunogenicity for metabolic aging. AAV9 has wide reach, including heart and muscle, and crosses the blood-brain barrier for central and peripheral aging [7].

AAVrh10 transduces brain and liver for neurodegeneration and metabolism. Engineered variants from directed evolution, design, and shuffling include AAV-PHP.B for neurons, AAV-LK03 for liver, and AAV-DJ for in vitro gains [33]. Machine learning aids in

creating capsids with tailored traits. For longevity, serotype choice is vital; for example, AAV1 with follistatin for sarcopenia, or AAV9 with Klotho for systemic and neural protection.

| Platform   | Capacity | Integration    | Duration   | Safety Profile | Longevity Applications |
|------------|----------|----------------|------------|----------------|------------------------|
| AAV        | 4.7 kb   | Episomal       | Years      | Excellent      | Current clinical focus |
| Lentivirus | 8-10 kb  | Integrating    | Permanent  | Good (ex vivo) | Stem cell modification |
| Adenovirus | 36 kb    | Episomal       | Weeks      | Immunogenic    | Limited use            |
| LNP-mRNA   | Variable | None           | Days-weeks | Good           | Transient expression   |
| CRISPR     | Variable | Permanent edit | Permanent  | Under study    | Future potential       |

**Table 1:** Comprehensive Comparison of Gene Therapy Platforms.

Comparison of gene therapy platforms for longevity applications. Each platform offers distinct advantages and limitations. AAV dominates current clinical applications due to favourable safety profile, while emerging platforms like base editors offer future potential for precise genomic modifications.

**Delivery Mechanisms and Tissue Tropism**

Successful gene therapy demands adequate vector delivery to intended tissues while reducing unintended impacts. Systemic intravenous methods offer extensive coverage but require large doses and face challenges like neutralizing antibodies, complement activation, and physiological barriers [34].

This suits widespread conditions but varies in efficiency by serotype and access. Direct injections enable precise, low-dose delivery but are limited by diffusion and require specialized skills and imaging.

Intra-arterial delivery heightens local levels in vascular zones with less systemic spread, effective in preclinical liver and brain models and human applications [35]. Intrathecal or intraventricular routes target the nervous system, bypassing barriers, useful for cognitive aging [36].

Intracavitary methods access compartment organs. Intralymphatic delivery supports inflammaging modulation. Inhalation focuses on lungs for age-related pulmonary issues [37]. Tropism enhancement involves serotype selection, specific promoters for expression control, and capsid additions like peptides or

antibodies [38]. Microfluidic evolution has yielded highly specific capsids. For longevity, blended strategies combining systemic delivery targeted expression address aging's multi-organ nature while prioritizing key areas. Achieving selective targeting of aging-affected tissues with minimal off-targets remains a key opportunity and challenge, with ongoing advancements by researchers in the field.

**Alternative Vectors and Delivery Systems**

Although AAV prevails in in vivo settings, other systems provide complementary benefits for longevity. Lentiviral vectors integrate into genomes for lasting changes, mainly ex vivo due to safety, but support larger transgenes (8-10 kb) for stem cell longevity tactics [39].

Adenoviral vectors offer high efficiency and capacity (up to 36 kb) but provoke robust immunity, limiting duration; "gutless" versions improve safety and allow multi-gene payloads [40]. Non-viral options advance, with lipid nanoparticles scaling well and reducing immune risks, though some side effects noted in prior uses [41].

Polymeric nanoparticles allow customizable targeting and release [42]. Physical techniques

like electroporation suit localized delivery [43]. Conjugates with targeting groups direct nucleic acids to receptors. In vivo editing with

CRISPR-Cas9 or base editors, via viral or non-viral means, modifies genes like FOXO3 or SIRT1 for longevity gains [44].



**Figure 4:** Delivery Routes and Tissue Distribution.

Comparison of gene therapy delivery methods for longevity applications. **A:** Schematic showing eight delivery routes: intravenous, direct tissue injection, intra-arterial, intrathecal, intracavitary, intralymphatic, inhalation, and ex vivo modification. **B:** Expected tissue distribution patterns for each delivery method with relative vector concentration indicated by bar height.

Compact Cas systems fit AAV constraints. mRNA delivery provides temporary expression without integration, ideal for periodic longevity boosts or initial testing before permanent methods [45]. Each system has unique strengths and drawbacks for longevity, likely best combined in tailored approaches. As innovations continue, the range of tools for

aging aspects will grow, enabling more accurate interventions.

## Manufacturing and Scale-Up Considerations

The transition from laboratory-scale production to clinical-grade manufacturing represents a

critical challenge for gene therapy development. Current Good Manufacturing Practice (cGMP) requirements demand stringent quality control at every step [8].

For AAV vectors, production typically involves triple transfection of HEK293 cells or use of baculovirus systems. Purification requires multiple chromatography steps to achieve the necessary purity while maintaining vector integrity. Yields vary significantly by serotype and production method, with some serotypes proving particularly challenging to manufacture at scale.

Quality control testing includes assessment of vector concentration, purity, potency, and safety parameters. The cost of manufacturing remains high, with estimates ranging from \$500,000 to \$1 million per batch for clinical trials.

Innovations in production technology, including stable producer cell lines and continuous manufacturing processes, promise to reduce costs and improve accessibility for longevity applications where larger patient populations are anticipated.

## **Global Landscape of Longevity-Focused Gene Therapy Research**

### **Key Research Institutions and Companies**

Longevity research in gene therapy spans academic institutions, biotechnology startups, and established pharmaceutical companies globally. The Buck Institute has pioneered work on multiple longevity pathways, while Harvard's Paul F. Glenn Center has conducted foundational research on telomerase and epigenetic reprogramming [46].

The Spanish National Cancer Research Centre (CNIO), led by María Blasco, has performed groundbreaking telomerase gene therapy work, demonstrating lifespan extension in mice using

hTERT gene therapy without increased cancer risk [47]. The University of Washington's Nathan Shock Center has examined longevity gene candidates, including FOXO3 variants [48].

Several biotechnology companies focus specifically on longevity gene therapies. Rejuvenate Bio develops combination therapies targeting multiple aging pathways simultaneously [49].

Turn Biotechnologies focuses on partial cellular reprogramming via mRNA delivery [50]. Gordian Biotechnology identifies and validates gene therapy targets through in vivo screening approaches.

TripleHelix ([triplehelixscience.com](http://triplehelixscience.com)) offers gene therapies for cancer, various diseases, and longevity applications outside traditional FDA pathways. TripleHelix delivers a comprehensive suite of longevity gene therapies, including hTERT, Klotho A, FGF21, PGC1A, FOXO3, SIRT1, and Follistatin, using AAV vectors.

This represents an alternative commercial approach to bringing these therapies to patients without navigating the lengthy traditional approval processes. Established pharmaceutical companies have also entered the field with a disease-focused approach.

Novartis is investigating gene therapy applications through their Advanced Accelerator Applications division [51]. Roche has invested in aging biology with gene therapy applications targeting neurodegenerative diseases [52].

AbbVie has partnered with longevity-focused biotechnology companies like Calico [53]. The SENS Research Foundation and Methuselah Foundation, both nonprofits, support proof-of-concept studies targeting age-related damage and pathologies [54,55].

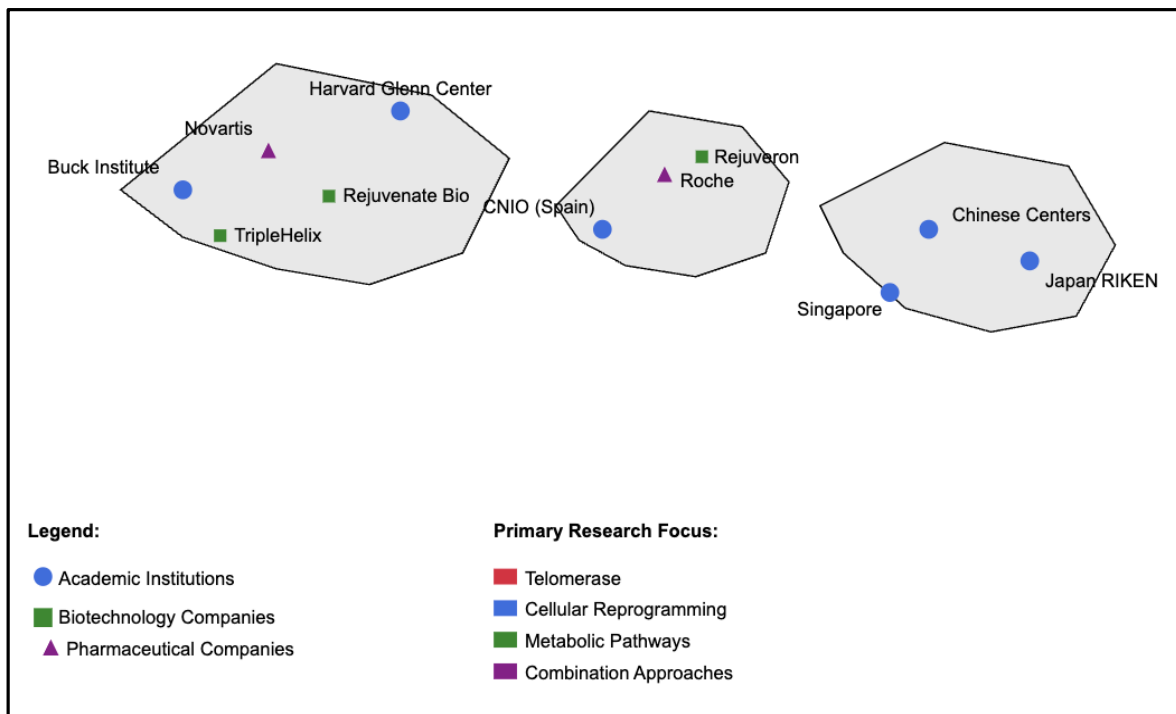


**Figure 5:** Global Landscape of Longevity Gene Therapy Research.

Geographic distribution and focus areas of major longevity gene therapy research centres and companies. Map showing locations of academic institutions (circles), biotechnology companies (squares), and pharmaceutical companies (triangles). Color coding indicates primary research focus: telomerase (red), cellular reprogramming (blue), metabolic pathways (green), combination approaches (purple).

## Geographic Distribution of Research Activities

Longevity research patterns show North America leading in academia and commerce, with hubs in Boston, San Francisco, and San Diego, aided by FDA designations for regenerative therapies [56,57].

Europe features strengths in Spain for telomerase research and the UK for aging biology, with Swiss firms like Rejuveron advancing the field [58].

Asia grows rapidly, with China emphasizing gene therapy for longevity, Japan offering early approval frameworks, and Singapore building aging infrastructure [59,60]. This geographic diversity fosters both competition and partnerships, with global groups tackling manufacturing, biomarkers, and model standardization.

## Current Regulatory Frameworks

Regulations differ by region, impacting development timelines. The US FDA via CBER oversees gene therapy, potentially speeding paths for age-related illnesses despite not recognizing aging as a condition [57]. Europe's EMA treats them as advanced therapy medicinal products, open to novel designs [61]. Japan's conditional system allows early market entry post-safety demonstration, with efficacy confirmation later [62]. China expedites approvals for innovations, focusing on aging demographics [63]. Endpoint challenges, needing long-term tracking, promote biomarkers like epigenetic clocks [64]. Collaborations validate these for regulatory approval. Private models like TripleHelix bypass traditional systems, providing direct access with appropriate informed consent, viewed variably as advantageous or risky depending on perspective.

| Region  | Regulatory Body | Approval Pathway     | Timeline   | Aging Recognition |
|---------|-----------------|----------------------|------------|-------------------|
| USA     | FDA/CBER        | Traditional/RMAT     | 8-12 years | Disease-specific  |
| Europe  | EMA             | ATMP pathway         | 7-10 years | Disease-specific  |
| Japan   | PMDA            | Conditional approval | 3-5 years  | More flexible     |
| China   | NMPA            | Priority review      | 5-7 years  | Aging focus       |
| Private | N/A             | Direct-to-consumer   | Immediate  | Aging accepted    |

**Table 2:** Regulatory Pathways by Geographic Region.

Comparison of regulatory frameworks for gene therapy across major markets. Japan offers the most progressive pathway with conditional early approval. Private providers like TripleHelix operate outside traditional frameworks, offering immediate access with appropriate informed consent.

### Pipeline Analysis

#### Late-Stage Clinical Trials for Age-Related Conditions

No gene therapy is approved solely for aging, but advanced trials address related conditions with longevity implications. For neurodegeneration, Voyager's VY-AADC for Parkinson's supplies AADC for dopamine synthesis, with phase 2 showing motor gains [65].

Axovant's AXO-Lenti-PD delivers multiple dopamine synthesis genes, ongoing in phase 2 [66]. Regencbio's RGX-314 provides anti-

VEGF for age-related macular degeneration in phase 3 [67]. Cardiovascular trials include Tenaya's TN-201 for genetic cardiomyopathy in phase 1/2 [68], and XyloCor's XC001 for refractory angina in phase 2, improving exercise tolerance and symptoms [69]. Metabolic efforts feature Ultragenyx's DTX401 for glycogen storage disease in phase 3, enhancing metabolic control [70], and Freeline's FLT190 for Fabry disease in phase 1/2, reducing biomarkers [71]. These trials inform longevity approaches by targeting hallmarks like stem cell exhaustion and metabolic dysfunction.

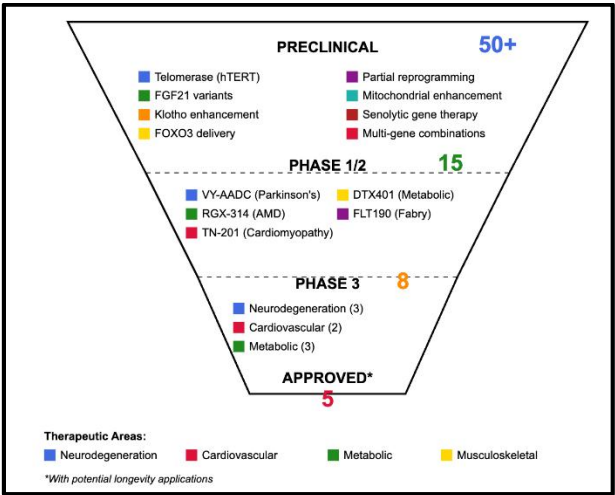


**Figure 6:** Clinical Development Pipeline.

Pipeline analysis of gene therapies for age-related conditions and longevity. Funnel diagram showing therapies in preclinical development (n=50+), Phase 1/2 (n=15), Phase 3 (n=8), and approved therapies with potential longevity applications (n=5). Color coding by therapeutic area: neurodegeneration (blue), cardiovascular (red), metabolic (green), musculoskeletal (orange).

## Emerging Preclinical Candidates

Preclinical longevity therapies show exceptional promise. Telomerase work by Blasco's team extended mouse lifespan via AAV9-hTERT, with advances in safety and tissue specificity; recent studies reversed pulmonary fibrosis [72].

FGF21 therapy improved metabolism and lifespan in mice, with variants enhancing stability and localized delivery being explored [73]. Klotho overexpression boosted cognition and lifespan in models, advancing to studies for brain and kidney applications; soluble Klotho fragments show therapeutic potential [74].

Clinical trials with Klotho and hTERT have shown reversal of dementia symptoms [75]. Follistatin for muscle aging, successful in

muscular dystrophy trials, is being optimized for sarcopenia with combinations like PGC-1 $\alpha$ ; geriatric models showed significant strength gains, with benefits observed in human cases [76]. FOXO3 variants, linked to centenarians, are being developed for stress resistance across multiple organ systems [48].

Combinations like Rejuvenate Bio's three-gene approach (FGF21,  $\alpha$ Klotho, sTGF $\beta$ R2) improved multiple age-related parameters in mice [77]. Partial reprogramming with Yamanaka factors under controlled expression avoids tumor formation, with transient systems showing tissue rejuvenation [78].

Mitochondrial therapies with PGC-1 $\alpha$  or TFAM enhance function, addressing age-related decline, potentially synergistic with NAD<sup>+</sup> boosters [79].

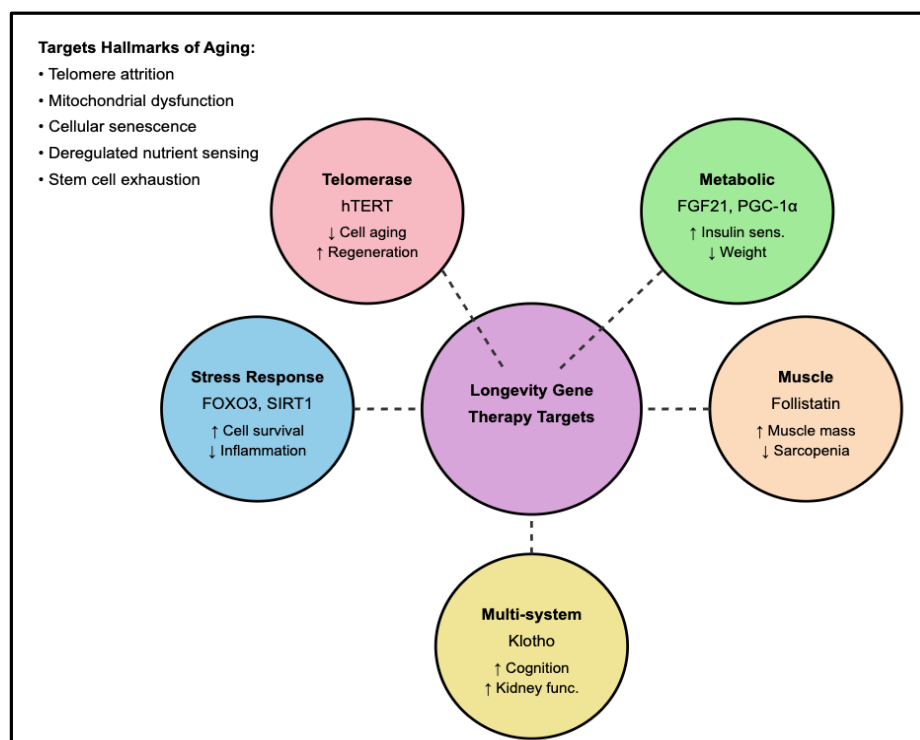


**Figure 7:** Longevity Gene Therapy Targets and Pathways.

Major therapeutic targets in longevity gene therapy aligned with hallmarks of aging. Central diagram shows interconnected pathways including telomerase activation (hTERT), metabolic regulation (FGF21, PGC-1 $\alpha$ ), stress response (FOXO3, SIRT1), muscle preservation (Follistatin), and multi-system effects (Klotho). Arrows indicate cross-talk between pathways.

## Combination Approaches and Synergies

The recognition that aging involves multiple interconnected processes has led to combination gene therapy approaches. Rejuvenate Bio's pioneering work demonstrated that delivering three genes simultaneously (FGF21,  $\alpha$ Klotho, and sTGF $\beta$ R2) could address obesity, diabetes, heart failure, and kidney disease in aged mice more effectively than single-gene approaches [49]. This multi-target strategy reflects the complex nature of aging, where interventions

addressing single pathways often show limited efficacy. Synergistic effects have been observed when combining metabolic regulators like FGF21 with longevity factors like Klotho, suggesting that carefully selected combinations could achieve greater benefits than the sum of individual components. The development of vectors capable of carrying multiple therapeutic genes, along with tissue-specific promoters to ensure appropriate expression patterns, represents a technical advance enabling these sophisticated approaches.

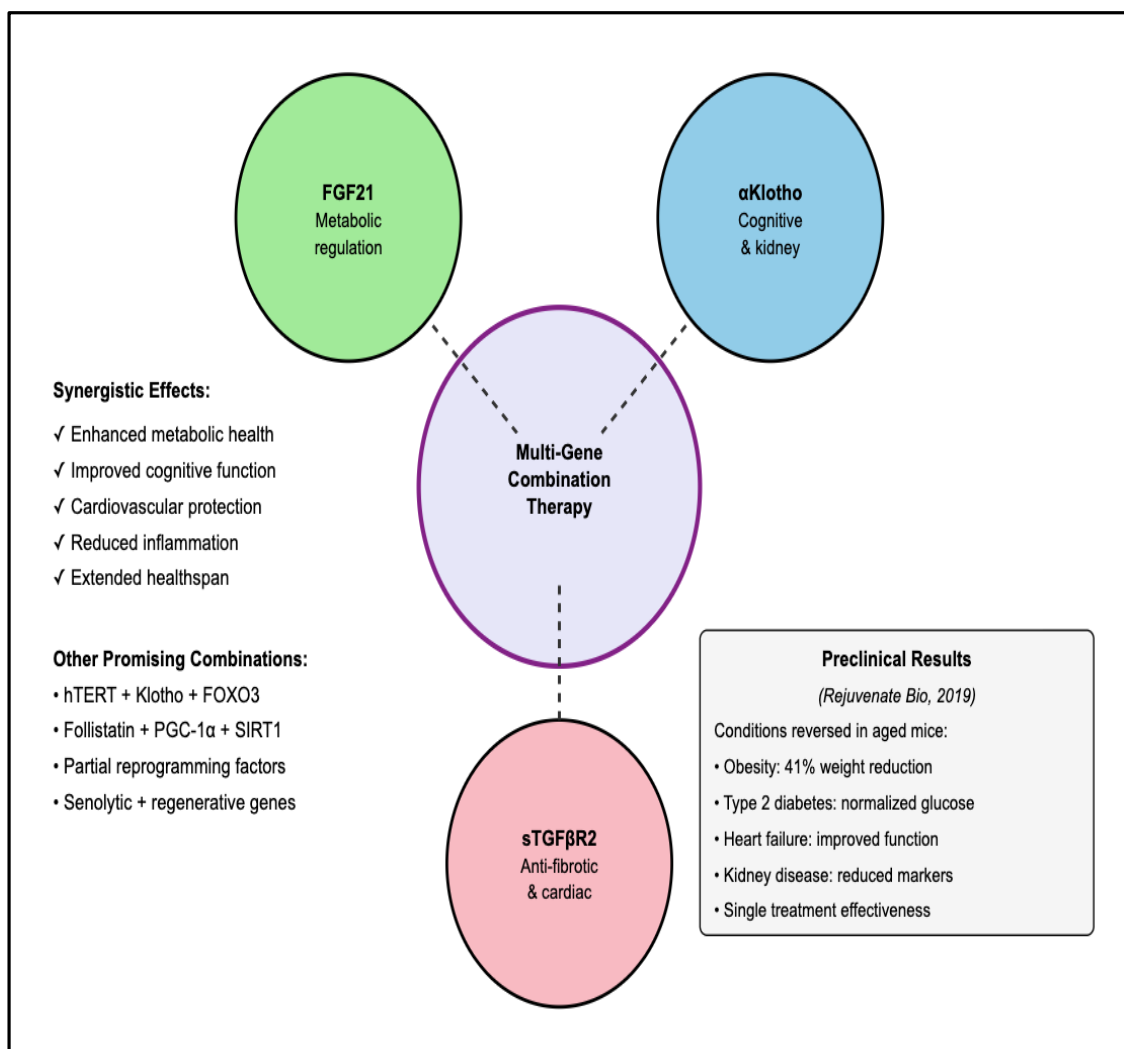


**Figure 8:** Future Outlook - Combination Approaches.

Next-generation longevity gene therapy strategies. Schematic showing multi-gene combinations targeting different hallmarks of aging simultaneously. Example shown: Rejuvenate Bio's three-gene approach (FGF21,  $\alpha$ Klotho, sTGF $\beta$ R2) with demonstrated effects on obesity, diabetes, heart failure, and kidney function in preclinical models. Single AAV vector delivery enables practical translation to clinical applications.

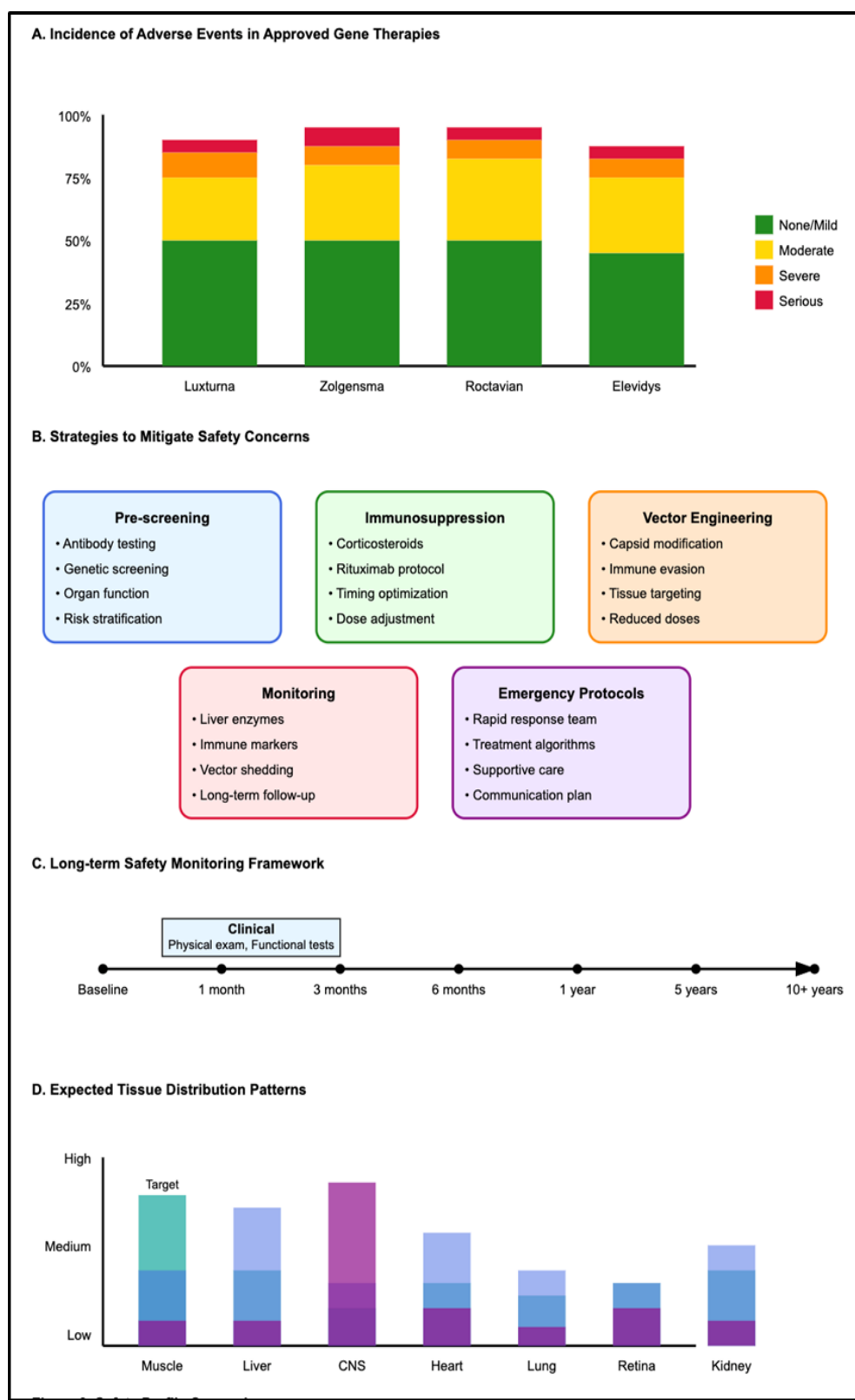


**Figure 9:** Safety Profile Comparison.

Safety considerations for longevity gene therapy. **A:** Incidence of adverse events in approved gene therapies categorized by severity. **B:** Strategies to mitigate common safety concerns including pre-existing immunity screening, immunosuppression protocols, and dose optimization. **C:** Long-term safety monitoring framework for longevity applications.

## Technical and Regulatory Challenges

### Delivery and Expression Challenges

Challenges persist in longevity gene therapy development. Delivery efficiency remains suboptimal, requiring high doses that raise both costs and safety risks [7]. Pre-existing immunity affects 30-70% of the population depending on serotype, addressed through capsid engineering and immunosuppression protocols [28].

Scaling manufacturing struggles with demand, necessitating cell line and purification innovations for cost reduction [8]. AAV capacity limits (4.7 kb) are overcome by dual vector approaches, though these add complexity [80]. Sustaining expression long-term remains difficult, particularly in dividing cells [26].

The development of novel capsids through directed evolution and machine learning approaches shows promise for overcoming these limitations, with next-generation vectors demonstrating improved tropism, reduced immunogenicity, and enhanced expression profiles.

### Regulatory and Clinical Trial Design Challenges

Current regulations do not recognize aging as a treatable condition, forcing disease-specific development approaches [80]. Preventive interventions face stricter risk-benefit assessments than treatments for existing conditions [81]. Long human lifespans complicate safety demonstration, requiring decades of follow-up [82]. Clinical trials need validated surrogate endpoints and novel designs incorporating biomarkers of aging [83].

Monitoring systems require infrastructure updates for decades-long tracking. International coordination is essential for

harmonizing approaches. The development of aging biomarkers, including epigenetic clocks, inflammatory markers, and functional assessments, provides tools for demonstrating efficacy in reasonable timeframes.

Regulatory agencies show increasing openness to these approaches, particularly for interventions targeting specific age-related diseases with clear endpoints.

### Ethical and Societal Considerations

The development of effective longevity gene therapies raises profound ethical questions. Access and equity concerns arise from high costs and limited initial availability. The potential for exacerbating societal inequalities if longevity treatments remain accessible only to the wealthy requires careful consideration.

Questions about the appropriate use of medical resources for life extension versus treating diseases challenge traditional medical ethics frameworks.

The impact on population dynamics, including workforce participation, retirement systems, and intergenerational relationships, requires societal dialogue. International disparities in access could create new forms of global inequality.

Frameworks for ethical distribution, potentially including lottery systems or means-tested access programs, are under development. The involvement of patient advocacy groups and ethicists in shaping policies ensures broader perspectives are considered.

### Economic Considerations

#### Cost Structures of Current Gene Therapies

Gene therapies carry high prices reflecting development costs, manufacturing complexity, and value propositions. Zolgensma costs \$2.1 million [84], Luxturna \$850,000 [85],

Roctavian \$2.9 million [21], and Skysona \$3 million [86]. Development costs reportedly reach \$1-2 billion, covering extensive testing and failed programs, though AI-driven approaches may reduce these [87]. Manufacturing involves specialized facilities and rigorous quality control. Limited patient populations for rare diseases drive higher per-patient costs. Pricing often considers lifetime

cost savings; for example, SMA care can exceed \$4-5 million over a patient's lifetime [88]. For longevity applications targeting larger populations, economies of scale and manufacturing improvements could potentially lower costs to tens of thousands per dose, making treatments accessible to broader populations.

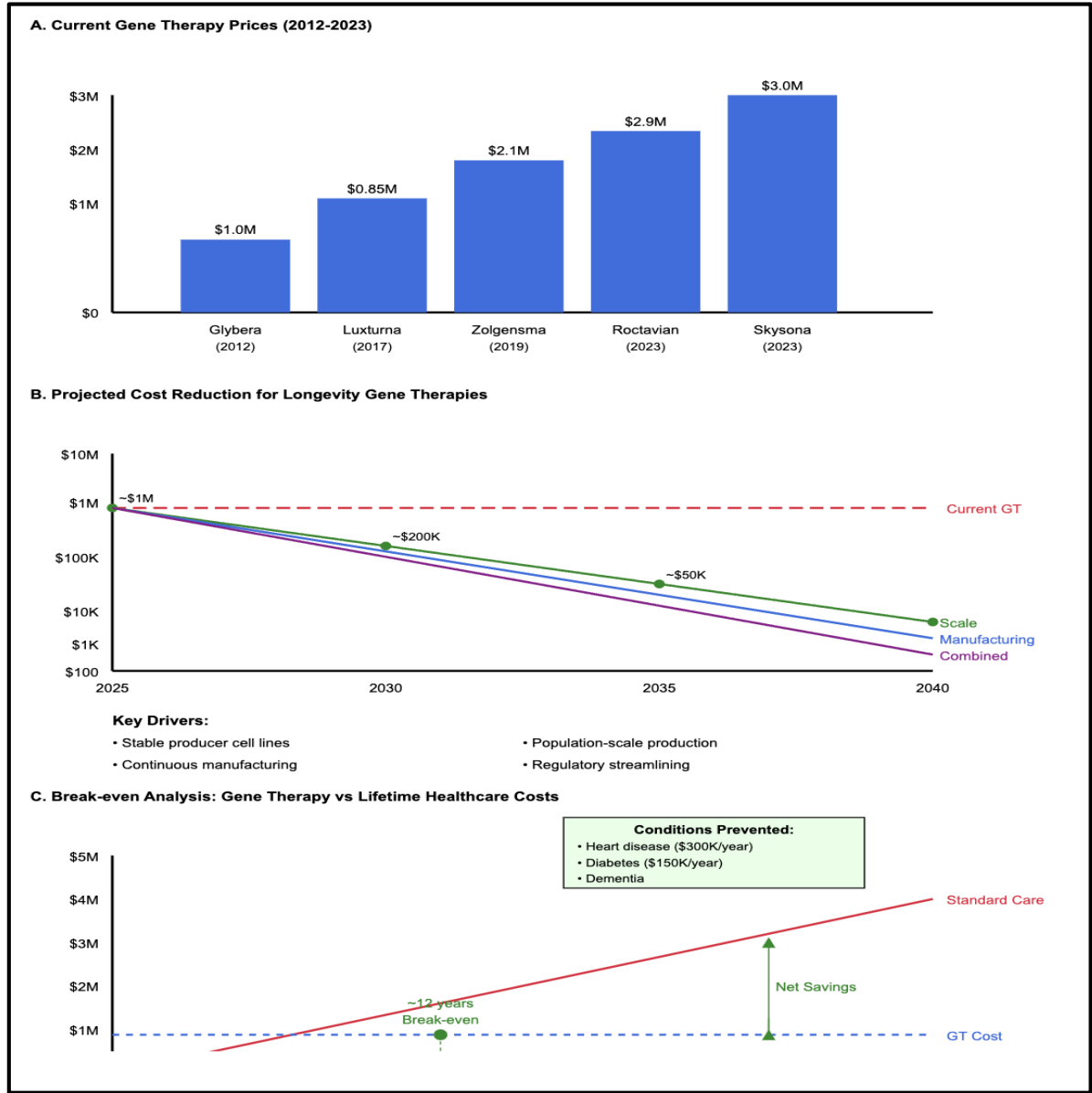


**Figure 10:** Economic Analysis of Gene Therapy Pricing.

Economic analysis of gene therapy pricing. **A:** Comparison of approved gene therapy prices (2012-2023) showing cost per patient. **B:** Projected cost reduction trajectory for longevity gene therapies based on manufacturing improvements and market scale. **C:** Break-even analysis comparing upfront gene therapy costs versus lifetime healthcare savings for age-related diseases.

## Accessibility Challenges and Solutions

High costs limit access, particularly for widespread longevity applications, prompting development of alternative models. Outcomes-based payments tie costs to therapeutic success, as implemented with Luxturna [89].

Annuity models spread payments over years, suitable for interventions with long-term benefits [90]. Manufacturing advances including stable producer cell lines could reduce costs significantly. Streamlined regulations with post-market surveillance may accelerate approvals while maintaining safety.

Differential pricing by income levels, combined with technology transfer for local manufacturing, could expand global reach [91]. Patent pools might enable competition and broader access, following models from other therapeutic areas [92].

For longevity applications, cost reductions through scale and innovation could enable broader population access, with economic analyses showing potential healthcare savings from delaying aging-related diseases.

## Market Projections for Longevity Applications

The potential market for longevity therapies is vast, with over 700 million people aged 65 and above globally. Modest adoption rates at accessible price points of \$20,000-50,000 could yield markets of \$15-75 billion annually. Preventive applications targeting the 1.5 billion people in middle age expand the market further [93]. Economic modeling suggests that delaying aging by 2.2 years could save trillions in healthcare costs in the US alone [94]. Competition from small molecule drugs and lifestyle interventions may complement rather than replace gene therapies.

Market projections estimate the anti-aging industry could reach \$610 billion by 2025, with gene therapies capturing a significant share as they demonstrate efficacy [95]. The economics of longevity interventions challenge traditional pharmaceutical models, requiring new frameworks for valuing preventive treatments with long-term benefits.

## Healthcare System Integration

Integration of longevity gene therapies into healthcare systems presents unique challenges. Traditional insurance models struggle with high upfront costs for preventive treatments. Value-based healthcare systems show greater flexibility in accommodating interventions that reduce long-term costs.

Pilot programs in several countries explore coverage models for regenerative medicines. The development of longevity clinics specializing in these interventions creates new care delivery models. Training requirements for healthcare providers include understanding of gene therapy administration and long-term monitoring. Electronic health record systems require updates to track decades-long outcomes. Coordination between primary care, specialists, and gene therapy centers ensures comprehensive patient management.

International patients seeking treatments create medical tourism considerations. Healthcare systems showing early adoption may gain competitive advantages in healthy aging outcomes.

## Future Outlook and Conclusion

### Emerging Technologies and Next-Generation Approaches

The field of gene therapy for longevity continues to evolve rapidly with several

emerging technologies showing promise. Base editing and prime editing technologies offer more precise genetic modifications with reduced off-target effects compared to traditional CRISPR systems [44].

Self-amplifying RNA vectors provide extended expression from non-integrating systems. Exosome-based delivery leverages natural cellular communication mechanisms for improved targeting.

Synthetic biology approaches enable creation of genetic circuits responding to aging biomarkers. Machine learning accelerates identification of novel longevity targets through analysis of genomic databases.

Organ-on-chip technologies improve preclinical testing relevance. Advanced imaging modalities allow real-time monitoring of the gene therapy distribution and its effects.

Integration with other longevity interventions, including senolytics, NAD<sup>+</sup> boosters, and cellular reprogramming, creates synergistic opportunities.

### **Critical Milestones for Clinical Translation**

Several key milestones will determine the pace of clinical translation for longevity gene therapies. Completion of ongoing safety studies for lead candidates like telomerase and follistatin gene therapies provides essential data.

Demonstration of efficacy in age-related diseases establishes proof-of-concept for regulatory approval. Validation of aging biomarkers as surrogate endpoints enables reasonable trial durations.

Manufacturing scale-up achieving order-of-magnitude cost reductions broadens accessibility. Regulatory framework evolution

recognizing aging biology facilitates development.

Long-term safety data from early adopters informs risk-benefit assessments. International harmonization of standards accelerates global development.

Public acceptance through education and transparent communication ensures societal support. Economic models demonstrating healthcare system benefits drive reimbursement decisions.

### **Vision for the Future**

Gene therapy for longevity stands at a pivotal juncture, with strong scientific foundations, expanding preclinical evidence, and early human applications showing promise.

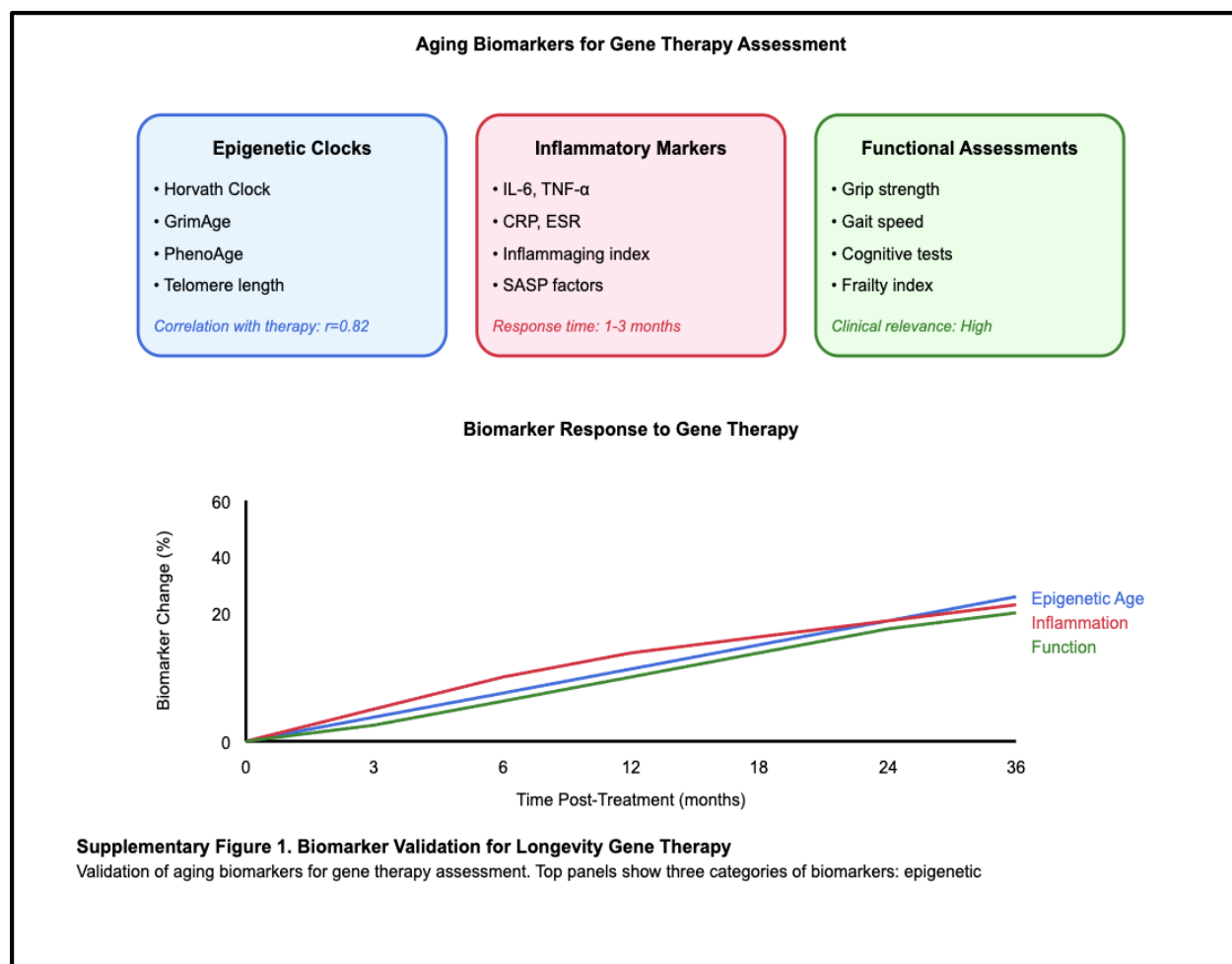
The convergence of understanding aging biology, advancing vector technologies, and evolving regulatory frameworks creates unprecedented opportunities.

Within the next decade, we may see the first gene therapies specifically approved for age-related conditions, paving the way for broader longevity applications.

The potential to extend not just lifespan but health span, the years lived in good health represents a fundamental shift in medicine from treating diseases to optimizing human biological function.

Success will require continued scientific innovation, regulatory evolution, economic model development, and societal dialogue about the implications of extended healthy lifespans.

The journey from concept to clinical reality continues, with the promise of transforming how we age and experience the later decades of life.



**Supplementary Figure 1:** Biomarker Validation for Longevity Gene Therapy.

Validation of aging biomarkers for gene therapy assessment. Top panels show three categories of biomarkers: epigenetic clocks, inflammatory markers, and functional assessments. Bottom panel demonstrates typical biomarker responses over 36 months' post-treatment, with epigenetic age showing the most dramatic improvement, followed by inflammatory markers and functional measures.

## Conflict of Interest Statement

Dr. Patrick E. Sewell is the founder, CEO, and Chief Scientist of TripleHelix ([triplehelixscience.com](http://triplehelixscience.com)), a company offering gene therapies mentioned in this review. The author declares that this relationship has not influenced the objectivity of the scientific content presented.

## Data Availability Statement

All data discussed in this review are available from the cited sources. No new data were generated for this review.

## Glossary of Terms

**AAV (Adeno-Associated Virus):** A small virus that does not cause disease in humans is used as a vector to deliver genetic material into cells.

**Base Editing:** A precise gene editing technique that changes single DNA letters without cutting both DNA strands.

**Capsid:** The protein shell of a virus that encases the genetic material and determines which type of cells the virus can invade.

**CRISPR-Cas9:** A gene editing tool that works like molecular scissors to cut and modify DNA at specific locations.

**Episomal:** Extrachromosomal genetic material that persists independently in the nucleus without integrating into the host chromosome.

**Ex Vivo:** Refers to procedures where cells are modified outside the living body which are then reintroduced into the body.

**FGF21 (Fibroblast Growth Factor 21):** A hormone that regulates metabolism and has shown longevity benefits.

**Follistatin:** A protein that blocks myostatin, promoting muscle growth and preventing age-related muscle loss.

**FOXO3:** A gene associated with longevity in centenarians that regulates stress resistance and cell survival.

**Gene Therapy:** Treatment that involves introducing genetic material into cells to treat or prevent disease.

**Healthspan:** The period of life spent in good health, free from chronic diseases and disabilities of aging.

**hTERT:** The gene encoding telomerase is an enzyme that extends telomeres and may extend the cellular lifespan of an organism.

**In Vivo:** Procedures performed within the living organism.

**ITR (Inverted Terminal Repeat):** DNA sequences at the ends of the Adeno-Associated virus (AAV) genome required for the packaging of the genetic material.

**Klotho:** A protein that acts as an anti-aging hormone and affecting multiple organ systems.

**Lentivirus:** A type of virus that can integrate genetic material into dividing and non-dividing cells.

**LNP (Lipid Nanoparticle):** Fat-based delivery system for genetic material, used in mRNA vaccines.

**PGC-1 $\alpha$ :** A protein that regulates mitochondrial function and energy metabolism.

**Senescence:** The state when cells stop dividing but don't die and are associated with aging.

**Serotype:** A distinct variation within a virus species that is responsible for determining which tissues it preferentially infects.

**SIRT1:** A gene encoding a protein involved in cellular stress resistance and longevity.

**sTGF $\beta$ R2:** Soluble TGF-beta receptor 2, which can block inflammatory signals.

**Telomerase:** An enzyme that adds DNA to telomeres, potentially responsible for extending cellular lifespan.

**Telomeres:** Protective caps at the end of the chromosomes that shorten with aging of an organism.

**Transgene:** The therapeutic gene inserted into a vector for delivery to target cells.

**Tropism:** The specificity of a virus or vector for particular cell types or tissues.

**Vector:** A vehicle (often a modified virus) used to deliver genetic material into cells.

**Yamanaka Factors:** Four genes (Oct4, Sox2, Klf4, c-Myc) that can reprogram adult cells to a younger state.

## References

1. Friedmann T and Roblin R. Gene therapy for human genetic disease? *Science*. 1972;175(4025):949-55.
2. Blaese RM, Culver KW, Miller AD, Carter CS, Fleisher T, Clerici M, et al. T lymphocyte-directed gene therapy for ADA-SCID: initial trial results after 4 years. *Science*. 1995;270(5235):475-80.
3. Raper SE, Chirmule N, Lee FS, Wivel NA, Bagg A, Gao GP, et al. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol Genet Metab*. 2003;80(1-2):148-58.
4. Ylä-Herttuala S. Endgame: Glybera finally recommended for approval as the first gene therapy drug in the European Union. *Mol Ther*. 2012;20(10):1831-32.
5. Atchison RW, Casto BC, Hammon WM. Adenovirus-associated defective virus particles. *Science*. 1965;149(3685):754-56.
6. Samulski RJ and Muzyczka N. AAV-mediated gene therapy for research and therapeutic purposes. *Annu Rev Virol*. 2014;1:427-51.
7. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. *Nat Rev Drug Discov*. 2019;18(5):358-78.
8. Clément N, Grieger JC. Manufacturing of recombinant adeno-associated viral vectors for clinical trials. *Mol Ther Methods Clin Dev*. 2016;1(3).
9. Paulk NK, Pekrun K, Zhu E, Nygaard S, Li B, Xu J, et al. Bioengineered AAV capsids with combined high human liver transduction in vivo and unique humoral seroreactivity. *Mol Ther*. 2018;26(1):289-303.
10. McCarty DM, Monahan PE, Samulski RJ. Self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis. *Gene Ther*. 2001;8(16):1248-54.
11. Zincarelli C, Soltys S, Rengo G, Rabinowitz JE. Analysis of AAV serotypes 1-9 mediated gene expression and tropism in mice after systemic injection. *Mol Ther*. 2008;16(6):1073-80.
12. Kaeblerlein M, Rabinovitch PS, Martin GM. Healthy aging: The ultimate preventative medicine. *Science*. 2015;350(6265):1191-93.
13. Kenyon CJ. The genetics of ageing. *Nature*. 2010;464(7288):504-12.
14. Doudna JA and Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. *Science*. 2014;346(6213):1258096.
15. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194-1217.
16. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. *Cell*. 2014;159(4):709-13.
17. Ronco V, Dilecce M, Lanati E, Canonico PL, Jommi C. Price and reimbursement of advanced therapeutic medicinal products in Europe: are assessment and appraisal diverging from expert recommendations? *J Pharm Policy Pract*. 2021;14(1):30. Newman JC, Milman S, Hashmi SK, Austad SN, Kirkland JL, Halter JB, et al. Strategies and challenges in clinical trials targeting human aging. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1424-34.
18. Maguire AM, Russell S, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy, safety, and durability of voretigene neparvovec-rzyl in RPE65 mutation-associated inherited retinal dystrophy: results of phase 1 and 3 trials. *Ophthalmology*. 2019;126(9):1273-85.
19. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1713-22.
20. Pasi KJ, Rangarajan S, Mitchell N, Lester W, Symington E, Madan B, et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. *N Engl J Med*. 2020;382(1):29-40.
21. BioMarin Pharmaceutical Inc. ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) Prescribing Information. <https://www.fda.gov/media/169680/download>. Accessed August 3, 2025.
22. Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. Exagamglogene autotemcel for sickle cell disease. *N Engl J Med*. 2021;384(3):252-60.

23. Sahenk Z, Lehman K, Lowes L, Reash N, Iammarino M, Alfano L, et al. Expression of SRP-9001 dystrophin and stabilization of motor function up to 2 years post-treatment with delandistrogene moxeparvovec gene therapy in individuals with Duchenne muscular dystrophy. *Front Cell Dev Biol.* 2023;11:1167762.
24. Fumagalli F, Calbi V, Sora MG, Sessa M, Baldoli C, Rancoita PM, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. *Lancet.* 2022;399(10322):372-83.
25. Mendell JR, Al-Zaidy SA, Lehman KJ, McColly M, Lowes LP, Alfano LN, et al. Five-year extension results of the phase 1 START trial of onasemnogene abeparvovec in spinal muscular atrophy. *JAMA Neurol.* 2021;78(7):834-41.
26. Nathwani AC, Reiss UM, Tuddenham EG, Rosales C, Chowdary P, McIntosh J, et al. Long-term safety and efficacy of factor IX gene therapy in hemophilia B. *N Engl J Med.* 2014;371(21):1994-2004.
27. Shirley JL, de Jong YP, Terhorst C, Herzog RW. Immune responses to viral gene therapy vectors. *Mol Ther.* 2020;28(3):709-22.
28. Calcedo R and Wilson JM. Humoral Immune Response to AAV. *Front Immunol.* 2013;4:341.
29. Biasco L, Scala S, Basso Ricci L, Dionisio F, Baricordi C, Calabria A, et al. In vivo tracking of T cells in humans unveils decade-long survival and activity of genetically modified T memory stem cells. *Sci Transl Med.* 2015;7(273):273ra13.
30. Wilson JM and Flotte TR. Moving forward after two deaths in a gene therapy trial of myotubular myopathy. *Hum Gene Ther.* 2020;31(13-14):695-96.
31. Tucci F, Scaramuzza S, Aiuti A, Mortellaro A. Update on clinical ex vivo hematopoietic stem cell gene therapy for inherited monogenic diseases. *Mol Ther.* 2021;29(2):489-504.
32. Grimm D, Zolotukhin S. E pluribus unum: 50 years of research, millions of viruses, and one goal--tailored acceleration of AAV evolution. *Mol Ther.* 2015;23(12):1819-31.
33. Kotterman MA and Schaffer DV. Engineering adeno-associated viruses for clinical gene therapy. *Nat Rev Genet.* 2014;15(7):445-51.
34. Deverman BE, Ravina BM, Bankiewicz KS, Paul SM, Sah DWY. Gene therapy for neurological disorders: progress and prospects. *Nat Rev Drug Discov.* 2018;17(9):641-59.
35. Wang L, Bell P, Lin J, Calcedo R, Tarantal AF, Wilson JM. AAV8-mediated hepatic gene transfer in infant rhesus monkeys (*Macaca mulatta*). *Mol Ther.* 2011;19(11):2012-20.
36. Hocquemiller M, Giersch L, Audrain M, Parker S, Cartier N. Adeno-associated virus-based gene therapy for CNS diseases. *Hum Gene Ther.* 2016;27(7):478-96.
37. Ruigrok MJR, Frijlink HW, Hinrichs WLJ. Pulmonary administration of small interfering RNA: The route to go? *J Control Release.* 2016;235:14-23.
38. Büning H, Huber A, Zhang L, Meumann N, Hacker U. Engineering the AAV capsid to optimize vector-host-interactions. *Curr Opin Pharmacol.* 2015;24:94-104.
39. Milone MC and O'Doherty U. Clinical use of lentiviral vectors. *Leukemia.* 2018;32(7):1529-41.
40. Wold WS and Toth K. Adenovirus vectors for gene therapy, vaccination and cancer gene therapy. *Curr Gene Ther.* 2013;13(6):421-33.
41. Sago CD, Lokugamage MP, Paunovska K, Vanover DA, Monaco CM, Shah NN, et al. High-throughput in vivo screen of functional mRNA delivery identifies nanoparticles for endothelial cell gene editing. *Proc Natl Acad Sci U S A.* 2018;115(42):E9944-53.
42. Piotrowski-Daspiet AS, Kauffman AC, Bracaglia LG, Saltzman WM. Polymeric vehicles for nucleic acid delivery. *Adv Drug Deliv Rev.* 2020;156:119-32.
43. Rogers S, Rush A, Naga Prasuna Rao M, et al. Efficient electroporation system for primary human T cells. *CRISPR J.* 2021;4(4):451-63.
44. Porteus MH. A new class of medicines through DNA editing. *N Engl J Med.* 2019;380(10):947-59.
45. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. *Nat Rev Drug Discov.* 2018;17(4):261-79.

46. Campisi J, Kapahi P, Lithgow GJ, Melov S, Newman JC, Verdin E. From discoveries in ageing research to therapeutics for healthy ageing. *Nature*. 2019;571(7764):183-92.
47. Blasco MA. Telomere length, stem cells and aging. *Nat Chem Biol*. 2007;3(10):640-9.
48. Morris BJ, Willcox DC, Donlon TA, Willcox BJ. FOXO3: A Major Gene for Human Longevity - A Mini-Review. *Gerontology*. 2015;61(6):515-25.
49. Davidsohn N, Pezone M, Vernet A, Graveline A, Oliver D, Slomovic S, et al. A single combination gene therapy treats multiple age-related diseases. *Proc Natl Acad Sci U S A*. 2019;116(47):23505-11.
50. Sarkar TJ, Quarta M, Mukherjee S, Colville A, Paine P, Doan L, et al. Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. *Nat Commun*. 2020;11(1):1545.
51. Novartis. Gene and Cell Therapy Research. <https://www.novartis.com/research-development/technology-platforms/gene-and-cell-therapy>. Accessed August 3, 2025.
52. Genentech. Research & Early Development. <https://www.gene.com/scientists/research-development>. Accessed August 3, 2025.
53. AbbVie. AbbVie and Calico Announce Extension of Collaboration Focused on Aging and Age-Related Diseases. <https://news.abbvie.com/news/press-releases/abbvie-and-calico-announce-extension-collaboration-focused-on-aging-and-age-related-diseases.htm>. Accessed August 3, 2025.
54. de Grey ADNJ. The SENS Research Foundation: progress in the application of rejuvenation biotechnology. *Regen Med*. 2019;14(12):1161-67.
55. Methuselah Foundation. Current Programs and Projects. <https://www.mfoundation.org/programs>. Accessed August 3, 2025.
56. FDA. Regenerative Medicine Advanced Therapy Designation. <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation>. Accessed August 3, 2025.
57. U.S. Food and Drug Administration. Cellular & Gene Therapy Guidances. <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>. Accessed August 3, 2025.
58. Rejuvenon Life Sciences AG. Pipeline and Research Programs. <https://www.rejuvenon.com/pipeline>. Accessed August 3, 2025.
59. Konomi K, Tobita M, Kimura K, Sato D. New Japanese initiatives on stem cell therapies. *Cell Stem Cell*. 2015;16(4):350-52.
60. Singapore Agency for Science, Technology and Research. Aging Research Institute. <https://www.a-star.edu.sg/Research/research-focus-areas/aging>. Accessed August 3, 2025.
61. European Medicines Agency. Advanced therapy medicinal products: Overview. <https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview>. Accessed August 3, 2025.
62. Pharmaceuticals and Medical Devices Agency. Regenerative Medicine Products. <https://www.pmda.go.jp/english/review-services/reviews/approved-information/0002.html>. Accessed August 3, 2025.
63. National Medical Products Administration. Technical Guidelines for Gene Therapy Products. <https://www.nmpa.gov.cn/xxgk/fgwj/flxzhfg/20210226162647178.html>. Accessed August 3, 2025.
64. Horvath S and Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet*. 2018;19(6):371-84.
65. Christine CW, Bankiewicz KS, Van Laar AD, Richardson RM, Ravina B, Kells AP, et al. Magnetic resonance imaging-guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease. *Ann Neurol*. 2019;85(5):704-14.
66. Palfi S, Gurruchaga JM, Lepetit H, Howard K, Ralph GS, Mason S, et al. Long-term follow-up of a phase I/II study of ProSavin, a lentiviral vector gene therapy for Parkinson's disease. *Hum Gene Ther Clin Dev*. 2018;29(3):148-55.

67. Heier JS, Khanani AM, Ruiz CQ, Basu K, Ferrone PJ, Brittain C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399(10326):729-40.
68. Tenaya Therapeutics. TN-201 for MYBPC3-Associated Hypertrophic Cardiomyopathy. ClinicalTrials.gov Identifier: NCT05836259. <https://clinicaltrials.gov/ct2/show/NCT05836259>. Accessed August 3, 2025.
69. Henry TD, Losordo DW, Traverse JH, Schatz RA, Jolicœur EM, Schaer GL, et al. Autologous CD34+ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials. *Eur Heart J*. 2018;39(23):2208-16.
70. Ultragenyx Pharmaceutical Inc. DTX401 Phase 3 GSDIa Gene Therapy Study. <https://www.ultragenyx.com/pipeline/dtx401-for-glycogen-storage-disease-type-ia/>. Accessed August 3, 2025.
71. Hughes Derrallynn A, Nicholls K, Shankar Suma P, Sunder-Plassmann G, Koeller D, Nedd K, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet*. 2017;54(4):288-96.
72. Povedano JM, Martinez P, Flores JM, Mulero F, Blasco MA. Mice with pulmonary fibrosis driven by telomere dysfunction. *Cell Rep*. 2015;12(2):286-99.
73. Zhang Y, Xie Y, Berglund ED, Coate KC, He TT, Katafuchi T, et al. The starvation hormone, fibroblast growth factor-21, extends lifespan in mice. *ELife*. 2012;1:e00065.
74. Dubal DB, Yokoyama JS, Zhu L, Broestl L, Worden K, Wang D, et al. Life extension factor klotho enhances cognition. *Cell Rep*. 2014;7(4):1065-76.
75. Sewell PE, Ediriweera D, Gomez Rios E, Guadarrama OA, Eusebio Y, Gonzalez L, et al. Safety and Efficacy of AAV hTERT and Klotho Gene Transfer for Age-Related Cognitive Decline: A Phase 1 Clinical Trial. *J Regen Med*. 2021;10(6):1-15.
76. Mendell JR, Sahenk Z, Malik V, Gomez AM, Flanigan KM, Lowez LP, et al. A phase 1/2a follistatin gene therapy trial for Becker muscular dystrophy. *Mol Ther*. 2015;23(1):192-201.
77. Church G. *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves*. New York: Basic Books; 2012. ISBN: 978-0465021758.
78. Ocampo A, Reddy P, Martinez-Redondo P, Platero-Luengo A, Hatanaka F, Hishida T, et al. In vivo amelioration of age-associated hallmarks by partial reprogramming. *Cell*. 2016;167(7):1719-33.
79. Dillon LM, Rebelo AP, Moraes CT. The role of PGC-1 coactivators in aging skeletal muscle and heart. *IUBMB Life*. 2012;64(3):231-41.
80. Gems D. The aging-disease false dichotomy: understanding senescence as pathology. *Front Genet*. 2015;6:212. <https://doi.org/10.3389/fgene.2015.00212>
81. Mehlman MJ, Binstock RH, Juengst ET, Ponsaran RS, Whitehouse PJ. Anti-aging medicine: can consumers be better protected? *Gerontologist*. 2004;44(3):304-10.
82. Newman JC, Milman S, Hashmi SK, Austad SN, Kirkland JL, Halter JB, et al. Strategies and challenges in clinical trials targeting human aging. *J Gerontol A Biol Sci Med Sci*. 2016;71(11):1424-34. <https://doi.org/10.1093/gerona/glw149>
83. Justice JN, Ferrucci L, Newman AB, Aroda VR, Bahnson JL, Divers J, et al. A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. *Geroscience*. 2018;40(5-6):419-36.
84. Institute for Clinical and Economic Review. Spinraza and Zolgensma for Spinal Muscular Atrophy: Final Evidence Report. April 2019. <https://icer.org/assessment/spinal-muscular-atrophy-2019/>. Accessed August 3, 2025.
85. Russell S, Bennett J, Wellman JA, Chung DC, Yu ZF, Tillman A, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390(10097):849-60.

86. bluebird bio. SKYSONA® (elivaldogene autotemcel) Prescribing Information. <https://www.fda.gov/media/160991/download>. Accessed August 3, 2025.
87. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ*. 2016;47:20-33.
88. Chambers JD, Silver MC, Berklein FC, Neumann PJ. Orphan drugs offer larger health gains but less favorable cost-effectiveness than non-orphan drugs. *J Gen Intern Med*. 2020;35(9):2629-36.
89. Spark Therapeutics. Spark Therapeutics Announces First-of-their-kind Agreements with Health Insurers to Improve Patient Access to LUXTURN<sup>TM</sup>. [https://sparktx.com/press\\_releases/](https://sparktx.com/press_releases/). Accessed August 3, 2025.
90. Jönsson B, Hampson G, Michaels J, Towse A, von der Schulenburg JG, Wong O. Advanced therapy medicinal products and health technology assessment principles and practices for value-based and sustainable healthcare. *Eur J Health Econ*. 2019;20(3):427-38.
91. Moon S, Jambert E, Childs M, von Schoen-Angerer T. A win-win solution?: A critical analysis of tiered pricing to improve access to medicines in developing countries. *Global Health*. 2011;7:39.
92. Röttingen JA and Chamas C. A new deal for global health R&D? The recommendations of the Consultative Expert Working Group on Research and Development (CEWG). *PLoS Med*. 2012;9(5):e1001219.
93. United Nations Department of Economic and Social Affairs. World Population Ageing 2020 Highlights. <https://www.un.org/development/desa/pd/news/world-population-ageing-2020-highlights>. Accessed August 3, 2025.
94. Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D, et al. Substantial health and economic returns from delayed aging may warrant a new focus for medical research. *Health Aff (Millwood)*. 2013;32(10):1698-705.
95. de Magalhães JP, Stevens M, Thornton D. The business of anti-aging science. *Trends Biotechnol*. 2017;35(11):1062-73.

