WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advancing Therapeutic Insights into Hutchinson-Gilford Progeria Syndrome: Current Challenges and Future Directions

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ABSTRACT :

Hutchinson-Gilford Progeria Syndrome (HGPS) is an ultra-rare, usually sporadic genetic disorder characterized by severe growth failure, loss of subcutaneous fat, distinctive craniofacial and skeletal features, and progressive vascular disease that leads to premature death, most often from myocardial infarction or stroke. Classic HGPS is primarily caused by the heterozygous LMNA c.1824C>T variant, which activates a cryptic splice site and generates progerin, a truncated and permanently farnesylated form of prelamin A. Progerin accumulates at the inner nuclear membrane and disrupts nuclear architecture, chromatin organization, DNA repair, mechanotransduction, cellular homeostasis, and vascular function. Although HGPS remains without a definitive cure, therapeutic development has progressed from symptom-directed care to mechanism-based interventions. Farnesyltransferase inhibition with lonafarnib is the established targeted therapy and has demonstrated vascular benefits and an extension of average lifespan. Experimental approaches include antisense oligonucleotides and peptide-conjugated morpholinos that suppress pathogenic LMNA splicing, agents that enhance progerin clearance or autophagy, and genome-editing strategies designed to correct or silence the pathogenic allele. Recent preclinical work also illustrates the potential of precision RNA therapeutics and emerging computational approaches for designing optimized antisense molecules. This review summarizes the molecular basis, clinical phenotype, pharmacological management, investigational therapies, and future research priorities in HGPS, with particular emphasis on translating molecular insights into durable, safe, and accessible treatments.

Keywords: Hutchinson-Gilford Progeria Syndrome; HGPS; LMNA; Progerin; Farnesyltransferase inhibitors; Lonafarnib; Antisense oligonucleotides; Gene editing; CRISPR-Cas; Rare disease; Pharmacology.

1. Introduction

Hutchinson-Gilford Progeria Syndrome is one of the most informative human models of premature cellular and vascular aging. The disorder is extraordinarily rare and is usually caused by a de novo pathogenic variant in LMNA. Children are generally developmentally normal at birth, while characteristic features become evident during infancy or early childhood. The disease is not simply an acceleration of every aspect of normal aging; instead, it represents a specific laminopathy in which abnormal processing of lamin A produces progerin and triggers a network of cellular defects. Nevertheless, HGPS provides important biological insights into nuclear-envelope integrity, mechanobiology, genome maintenance, cellular senescence, and vascular aging.

Modern understanding of HGPS has shifted the therapeutic paradigm. Earlier management focused mainly on nutrition, physical therapy, cardiovascular surveillance, and treatment of complications. The identification of progerin farnesylation as a druggable step led to the development of farnesyltransferase inhibitors, culminating in FDA approval of lonafarnib in 2020 for eligible patients with HGPS. Current clinical guidance reports that average lifespan is approximately 14.5 years without lonafarnib treatment and approximately 18.7 years with lonafarnib, highlighting both the benefit of targeted treatment and the continuing need for curative strategies.

2. Epidemiology and Clinical Characteristics

HGPS is an ultra-rare disorder. The classic phenotype usually begins during the first two years of life with postnatal growth failure, progressive loss of subcutaneous fat, alopecia, skin changes, characteristic facial appearance, delayed dentition, joint stiffness, and skeletal abnormalities. Intelligence and early motor development are generally preserved. With disease progression, cardiovascular and cerebrovascular complications become dominant clinical concerns. Premature and accelerated atherosclerotic disease, arterial stiffness, aortic-valve disease, myocardial ischemia, stroke, and heart failure are major causes of morbidity and mortality. Other important manifestations include low-frequency conductive hearing loss, ocular surface disease, dental abnormalities, hip pathology, and reduced joint mobility.

3. Genetic and Molecular Basis

The LMNA gene encodes lamin A and lamin C, structural proteins of the nuclear lamina. In classic HGPS, a heterozygous c.1824C>T substitution (p.Gly608Gly) is usually present. Although this is a synonymous coding change, it activates a cryptic splice donor site in exon 11. The resulting aberrant transcript lacks 150 nucleotides and encodes progerin, a lamin A variant lacking 50 amino acids. Approximately 90% of classic HGPS cases carry this variant, while nonclassic HGPS can result from other progerin-producing LMNA variants.

Normal prelamin A undergoes farnesylation followed by proteolytic processing, carboxymethylation, and final ZMPSTE24-dependent cleavage. In progerin, the deletion removes the region required for the final processing event. Consequently, progerin retains its farnesylated C-terminal structure and becomes abnormally tethered to the inner nuclear membrane. This persistent membrane association is central to the disease mechanism and explains why inhibition of farnesylation became an attractive therapeutic strategy.

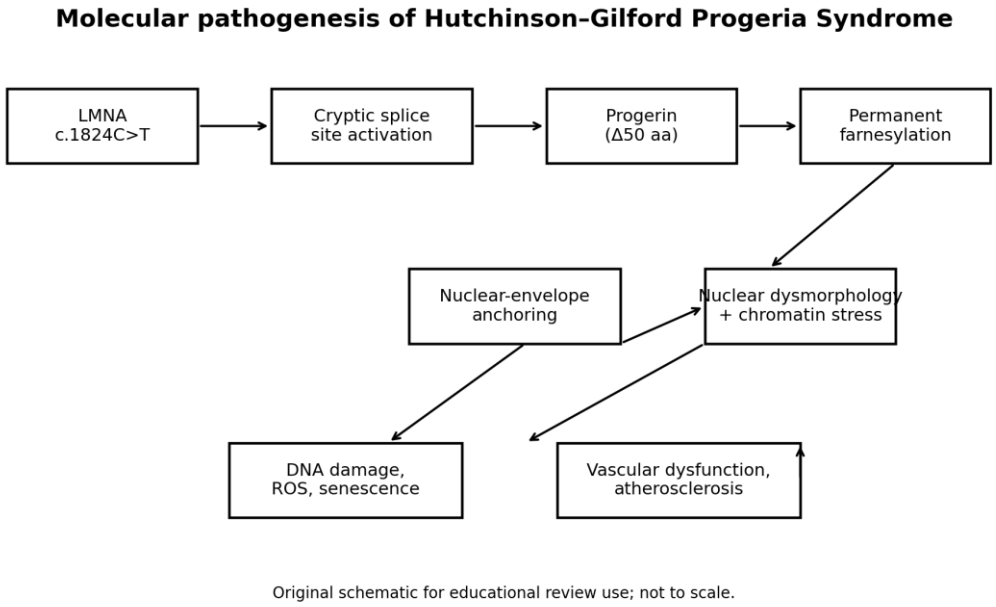


Figure 1. Molecular pathogenesis of HGPS from LMNA mutation to progerin accumulation and systemic disease.

4. Cellular Pathophysiology

4.1 Nuclear-envelope and chromatin abnormalities

Progerin accumulation produces nuclear blebbing, lobulation, abnormal nuclear shape, and altered organization of nuclear-envelope proteins. These changes are accompanied by disruption of peripheral heterochromatin and abnormal localization or expression of proteins involved in nuclear architecture. Nuclear-pore organization and mechanotransduction can also be altered. The resulting nuclear instability contributes to impaired transcriptional regulation and cellular stress.

4.2 DNA damage, replication stress and senescence

HGPS cells show increased baseline DNA damage, impaired DNA-damage responses, replication-associated stress, and telomere-related abnormalities. Persistent genomic stress can activate p53-dependent pathways and promote cellular senescence. Progerin therefore acts through interacting disturbances in nuclear mechanics, chromatin regulation, genome maintenance, and stress responses rather than through a single toxic pathway.

4.3 Vascular pathology

The cardiovascular system is the major determinant of survival in HGPS. Vascular smooth-muscle cell dysfunction, arterial stiffening, abnormal extracellular-matrix remodeling, calcification, and accelerated atherosclerotic changes contribute to progressive loss of vascular compliance. The clinical value of lonafarnib appears to be strongly linked to slowing this vascular deterioration.

5. Diagnosis and Clinical Evaluation

Diagnosis is suspected from the characteristic phenotype and should be confirmed by molecular genetic testing. Targeted LMNA analysis should include

exon 11 and the relevant intronic region; if a pathogenic variant is not identified, broader LMNA sequencing and consideration of ZMPSTE24 or a progeroid-syndrome gene panel may be appropriate. Molecular confirmation is particularly important because other progeroid laminopathies can produce overlapping phenotypes.

Domain	Typical findings	Assessment	Clinical importance
Growth/nutrition	Short stature, low weight, lipodystrophy	Serial growth and nutrition assessment	Optimize intake and hydration
Cardiovascular	Arterial stiffness, atherosclerosis, valve disease	BP, ECG, echocardiography, vascular imaging	Major determinant of survival
Neurologic	Stroke/headache risk	Neurologic review; MRI/MRA when indicated	Early recognition of cerebrovascular disease
Musculoskeletal	Joint stiffness, hip disease	PT/OT and orthopedic assessment	Maintain mobility and reduce injury
Dental/ocular/auditory	Delayed dentition, exposure keratopathy, hearing loss	Dental, ophthalmic and audiologic review	Prevents functional complications

Table 1. Major clinical domains in HGPS and practical evaluation priorities.

6. Current Pharmacological Therapy

6.1 Lonafarnib: the established targeted therapy

Lonafarnib is an oral farnesyltransferase inhibitor that reduces addition of the farnesyl group to progerin. By reducing membrane association of progerin, the drug partially improves cellular and vascular phenotypes. The U.S. FDA approved lonafarnib (Zokinvy) on November 20, 2020 for patients aged 12 months or older who meet the labeled criteria, including HGPS.

Clinical studies have demonstrated improvements in vascular stiffness and other disease measures, and long-term follow-up has been associated with clinically meaningful survival extension. Current GeneReviews guidance summarizes an average lifespan increase of approximately 4.2 years. Treatment is an important advance, but it does not eliminate progerin production or fully reverse established disease.

The main adverse effects are gastrointestinal, including diarrhea, nausea, vomiting, abdominal discomfort, and reduced appetite. Drug interactions and patient-specific tolerability require careful monitoring. Treatment should be coordinated through clinicians experienced in HGPS and according to current prescribing information and specialist guidance.

6.2 Other pharmacological approaches

Several investigational strategies have been evaluated to interfere with progerin processing, enhance clearance, or mitigate downstream injury. Earlier combination approaches involving lonafarnib, pravastatin, and zoledronate did not demonstrate broad superiority over lonafarnib monotherapy and raised concerns about extraskeletal calcification. Rapalog/mTOR-pathway approaches such as everolimus have been investigated because autophagy may help remove abnormal proteins. A clinical trial of lonafarnib plus everolimus has been completed, while the broader evidence base continues to evolve.

Therapy/strategy	Primary target	Evidence	Potential benefit	Key limitation
Lonafarnib	Farnesyltransferase	Clinical / approved	Vascular benefit; survival extension	Does not correct mutation; GI toxicity
ASO/PPMO	Aberrant LMNA splicing	Preclinical	Reduce progerin RNA; vascular rescue in mice	Delivery and durability
Everolimus/rapalog	mTOR/autophagy	Clinical investigation	Potential abnormal-protein clearance	Clinical benefit uncertain
Progerin-binding inhibitors	Progerin–lamin interactions	Early clinical investigation	May reduce toxic interactions	Long-term efficacy unknown
CRISPR/base editing	Mutant LMNA allele	Preclinical	Potential genetic correction/silencing	Delivery and off-target risk
Supportive cardiovascular care	Disease complications	Clinical standard	Reduces morbidity	Does not alter root cause

Table 2. Selected therapeutic strategies for HGPS. Evidence categories are not equivalent measures of clinical efficacy.

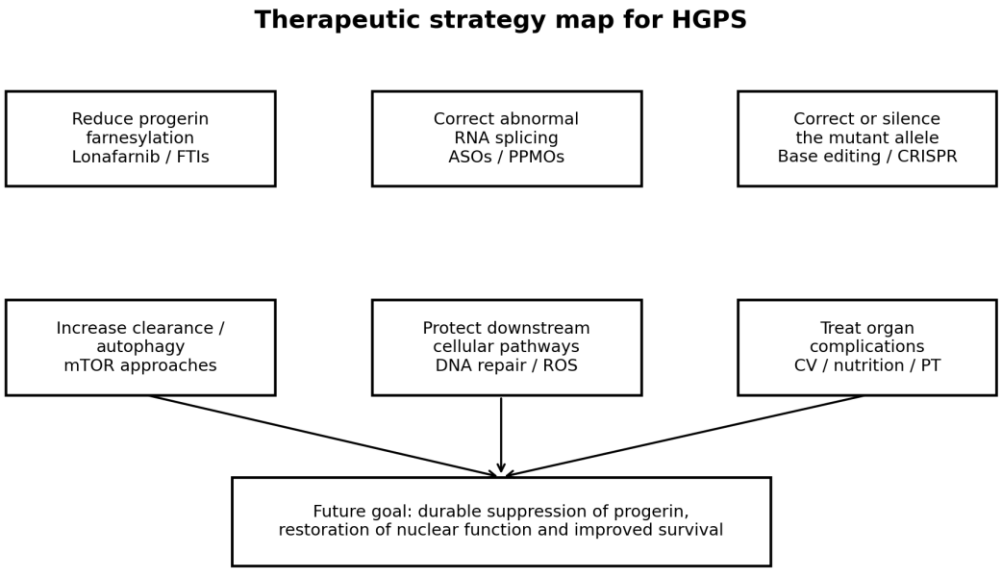


Figure 2. Therapeutic strategy map for HGPS.

7. RNA-Based Therapeutics

RNA-based therapy is attractive because the pathogenic event in classic HGPS is an abnormal splicing decision. Antisense oligonucleotides (ASOs) can bind LMNA pre-mRNA and redirect splice-site recognition, thereby decreasing production of progerin. Systematic screening published in 2021 identified optimized ASOs that reduced progerin expression in vivo and improved survival in a mouse model. A complementary study developed peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs); the candidate SRP-2001 reduced progerin transcripts and produced vascular and survival benefits in a mouse model.

Important translational challenges include tissue penetration, repeat dosing, pharmacokinetics, immune reactions, long-term toxicity, and preservation of normal lamin A/C expression. Because cardiovascular pathology is especially important, successful systemic RNA therapy will need adequate exposure in vascular tissues and durable target engagement.

8. Gene Editing and Genome Engineering

Genome editing offers the possibility of correcting or silencing the pathogenic LMNA allele rather than repeatedly suppressing downstream products. Preclinical CRISPR-Cas9 studies in HGPS models have demonstrated reduction of progerin expression and improvement of disease-related phenotypes in mice. Such studies establish proof of principle but do not yet constitute a human treatment.

Base editing and other precision-editing strategies are particularly interesting because the classic HGPS mutation is a single-nucleotide substitution. A future design could potentially correct the pathogenic nucleotide without a conventional double-strand DNA break. However, translation faces major barriers including delivery, editing efficiency, allele specificity, off-target effects, immune responses, mosaic correction, and the irreversible nature of genomic modification. These approaches therefore remain investigational.

9. Emerging and Repurposed Approaches

HGPS has been used as a platform for testing strategies that target downstream aging pathways. Autophagy-enhancing approaches may increase removal of abnormal proteins, while antioxidant, DNA-repair, senescence, and cytoskeletal pathways have been explored in cellular and animal models. Such findings are biologically informative but should not be equated with clinically established therapy. Rational combination therapy is particularly attractive if separate agents can suppress progerin production, reduce its membrane anchoring, and protect vulnerable vascular tissues without creating unacceptable toxicity.

10. Recent Research Directions

The therapeutic landscape continues to evolve. Current clinical resources describe investigation of progerin-targeting small molecules and combination approaches. Recent preclinical research has also explored computationally assisted design of antisense oligonucleotides. A 2026 report described an AI-driven pipeline that generated an optimized ASO candidate, LM2556, which reduced pathogenic lamin A isoforms and improved cardiovascular and progeroid phenotypes in experimental models. These results are promising but remain preclinical and require independent validation and eventual human

clinical testing.

CRISPR-based functional screens are also being used to identify regulators of LMNA aberrant splicing. Recent work identified ZNF207 as a regulator of the progeria-associated splicing event, illustrating how genetic screening can uncover therapeutic nodes upstream of progerin production.

11. Patient Management and Supportive Care

Targeted pharmacotherapy must be integrated with multidisciplinary supportive care. Current guidance recommends regular cardiovascular surveillance, including blood pressure, ECG, echocardiography and vascular assessment, together with periodic neurologic, dental, ophthalmologic and audiologic evaluation. Physical and occupational therapy help maintain joint mobility and function. Nutritional support should focus on frequent small meals and adequate hydration rather than unrealistic expectations that increased caloric intake will normalize genetically determined growth failure.

Anesthesia and surgery require particular caution because of cardiovascular and airway risks. Orthopedic interventions may be considered when symptoms are severe, but risks must be carefully weighed. Families also benefit from genetic counseling, social-work support, educational accommodations, and rare-disease networks. Most classic HGPS cases result from de novo variants, although parental gonadal mosaicism creates a small recurrence risk.

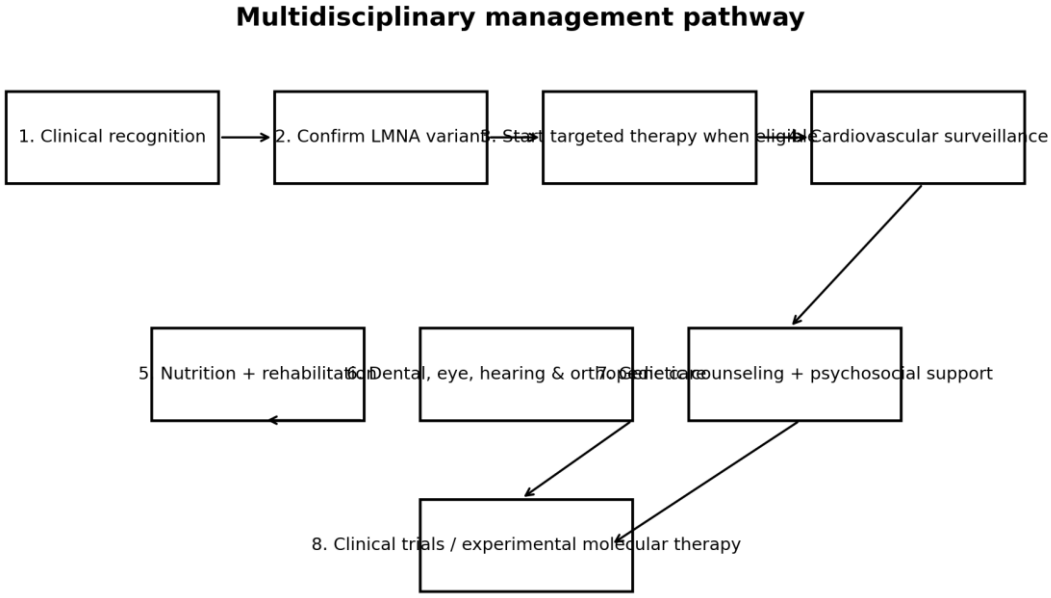


Figure 3. Suggested multidisciplinary management pathway for individuals with HGPS.

12. Challenges in Drug Development

Challenge	Why it matters	Potential solution
Ultra-rare population	Small patient numbers limit conventional trials	International registries, natural-history controls and validated endpoints
Disease heterogeneity	Nonclassic variants may differ biologically	Genotype-aware stratification
Target-tissue delivery	Disease is systemic, especially vascular	Optimized systemic and tissue-targeted delivery
Long-term safety	Children may need years of treatment	Long-term pharmacovigilance
Endpoint selection	Survival is meaningful but difficult to study quickly	Validated vascular, imaging and molecular biomarkers
Access and cost	Specialized therapy may be difficult to obtain	Rare-disease policy and equitable reimbursement

Table 3. Major translational challenges and potential solutions in HGPS therapeutic development.

13. Future Directions

Future research should prioritize interventions that act as close as possible to the genetic origin of disease while maintaining an acceptable pediatric safety profile. Three complementary directions are particularly compelling: next-generation RNA therapeutics for durable suppression of progerin, precision genome editing for correction or selective silencing of the pathogenic allele, and rational combination therapy that simultaneously suppresses progerin

and protects vascular tissues. Biomarker development is equally important. Quantification of progerin RNA and protein, vascular stiffness, arterial imaging, cardiac function, and molecular measures of cellular senescence may allow smaller and more informative trials.

Patient-derived induced pluripotent stem cells, vascular organoids and multi-omics approaches can complement animal models and help predict treatment response. Artificial intelligence may accelerate therapeutic design, but computational predictions must remain subordinate to rigorous biological validation and clinical safety testing.

14. Discussion

The history of HGPS therapy demonstrates the value of mechanism-based drug development in rare disease. Lonafarnib emerged because researchers understood that progerin remains farnesylated and membrane-associated. The drug does not repair the LMNA mutation, yet it changes the biochemical behavior of the disease-causing protein and provides measurable clinical benefit. This shows that meaningful progress can occur before a definitive cure is available.

At the same time, the remaining disease burden shows why downstream inhibition alone may be insufficient. Progerin continues to be produced in treated patients, and established nuclear, vascular and cellular damage may not be completely reversible. RNA therapeutics and genome editing therefore represent logical next steps because they target the disease closer to its source. The most realistic near-term strategy may be layered therapy rather than a single universal cure: targeted progerin suppression combined with rigorous cardiovascular care and, when supported by evidence, investigational molecular therapies.

The field must maintain a careful distinction between promising preclinical findings and proven clinical efficacy. Many compounds improve HGPS phenotypes in fibroblasts or mice, but translation to children requires demonstration of appropriate distribution, sustained target engagement, safety and clinically meaningful outcomes. Because HGPS is a pediatric disease with potentially irreversible treatment consequences, ethical and regulatory safeguards are particularly important.

15. Conclusion

HGPS is a devastating laminopathy caused predominantly by aberrant LMNA splicing and progerin accumulation. The disease links a single molecular defect to profound changes in nuclear architecture, chromatin, DNA repair, cellular senescence and cardiovascular function. Lonafarnib represents a major pharmacological advance and has improved survival and disease-related vascular measures, but it is not curative. The next generation of therapies is increasingly focused on RNA-level correction, progerin suppression, precision genome editing, enhanced clearance and rational combination therapy. Continued international collaboration, biomarker development, patient registries and carefully designed clinical trials will be essential. The long-term objective should be a therapy that safely prevents progerin production or restores normal LMNA function early enough to prevent the cascade of cellular and vascular injury.

16. Key Take-Home Points

- Classic HGPS is usually caused by LMNA c.1824C>T, which activates a cryptic splice site and produces progerin.
- Progerin remains farnesylated and accumulates at the nuclear envelope, disrupting nuclear structure and multiple cellular pathways.
- Cardiovascular disease is the dominant cause of morbidity and premature mortality.
- Lonafarnib is the established targeted therapy and has demonstrated vascular benefits and meaningful survival extension.
- Antisense oligonucleotides and PPMOs can reduce pathogenic LMNA splicing in preclinical models.
- CRISPR-based and other precision-editing approaches are promising but remain investigational.
- Multidisciplinary supportive care remains essential even when targeted therapy is available.

REFERENCES

1. Gordon LB, Brown WT, Collins FS. Hutchinson-Gilford Progeria Syndrome. GeneReviews®. University of Washington, Seattle. Updated March 13, 2025.
2. Gordon LB, et al. Long-term clinical and survival outcomes in Hutchinson-Gilford progeria syndrome; summarized in current GeneReviews® guidance.
3. Gonzalo S, Kreienkamp R, Askjaer P. Hutchinson-Gilford Progeria Syndrome: a premature aging disease caused by LMNA gene mutations. Ageing Res Rev. 2017;33:18–29.
4. Evangelisti C, et al. Hutchinson-Gilford Progeria Syndrome: Cellular Mechanisms and Therapeutic Perspectives. 2023.
5. Mekala S, et al. The Molecular and Cellular Basis of Hutchinson-Gilford Progeria Syndrome and Potential Treatments. Genes. 2023;14:602.
6. Gordon LB, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford Progeria Syndrome. Proc Natl Acad Sci USA. 2012.
7. U.S. Food and Drug Administration. Lonafarnib (ZOKINVY): orphan drug designation and marketing approval record. Approval dated November 20, 2020.
8. Puttaraju M, Jackson M, Klein S, et al. Systematic screening identifies therapeutic antisense oligonucleotides for Hutchinson-Gilford progeria syndrome. Nat Med. 2021;27:526–535. doi:10.1038/s41591-021-01262-4.
9. Erdos MR, Cabral WA, Tavarez UL, et al. A targeted antisense therapeutic approach for Hutchinson-Gilford progeria syndrome. Nat Med.

2021;27:536–545. doi:10.1038/s41591-021-01274-0.

10. Santiago-Fernández O, et al. Single-dose CRISPR-Cas9 therapy extends lifespan of mice with Hutchinson-Gilford progeria syndrome. Nat Med. 2019.

11. Cardiovascular Progerin Suppression and Lamin A Restoration Rescue Hutchinson-Gilford Progeria Syndrome. Preclinical CRISPR-based disease-reversal study.

12. An overview of treatment strategies for Hutchinson-Gilford Progeria syndrome. 2018.

13. Benedicto I, Chen X, Bergo MO, Andrés V. Progeria: a perspective on potential drug targets and treatment strategies. Expert Opin Ther Targets. 2022;26.

14. AI-driven therapeutic antisense oligonucleotide for processing-deficient progeroid laminopathies. MedJ. 2026; preclinical AI-assisted ASO development.

15. RNA-coupled CRISPR screens reveal ZNF207 as a regulator of LMNA aberrant splicing in progeria. PubMed-indexed research, 2026.