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Supertitle: Progeria

Reaching for the cure as progeria research comes of age at 12th international scientific workshop

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Standfirst

In October 2025, the Progeria Research Foundation (PRF) convened its 12th International Scientific Workshop to review recent scientific advances in Hutchinson–Gilford progeria syndrome (HGPS, Progeria) and to identify priorities for therapeutic development. Topics discussed included gene editing, RNA-based therapeutics, longitudinal clinical outcomes, multi-omics profiling, emerging cellular and animal

models and disease mechanisms, and patient-engaged research. This Meeting Report highlights key considerations for advancing Progeria research and its broader relevance to cardiovascular disease (CVD) and biological aging.

Disease overview

HGPS is a fatal, ultrarare pediatric monogenic disorder characterized by features of accelerated aging, with an estimated prevalence of approximately 1 in 20 million living individuals¹. The disease manifests as a multisystem disorder, including growth failure, alopecia, lipodystrophy, joint contracture, bone dysplasia, neurovascular and cardiovascular disease with complications of progressive premature atherosclerosis leading to early death, typically in the teenage years . Progeria is caused by a heterozygous synonymous mutation in the *LMNA* gene (most commonly c.1824C>T; p.Gly608Gly) that activates an internal splice site, resulting in the production and accumulation of the abnormal, truncated form of the lamin A protein called progerin^{2,3}. By binding to lamin A and its lamin-associated proteins, progerin disrupts nuclear structure and myriad cellular processes.

Currently, only one FDA-approved therapy is available: the farnesyltransferase inhibitor lonafarnib (Zokinvy®)⁴, which extends lifespan by several years by reducing progerin accumulation¹. Although this represents a major clinical advance, lonafarnib does not correct the underlying mutation, and disease progression continues. As survival improves, new clinical challenges and therapeutic opportunities are emerging, which underscores the need for continued efforts to develop more effective treatments and ultimately achieve a cure for Progeria.

History of the meeting

Since 2001, PRF has convened a biennial scientific workshop to advance the search for a cure (<https://www.progeriaresearch.org/scientific-meetings/>). Speakers are required to present primarily unpublished data in an environment protected from publication risk, to maximize open scientific exchange and accelerate progress within the field. The 2025 meeting, the twelfth in the series, brought together patients and their families, clinicians, and researchers from both basic and clinical disciplines who would otherwise have limited opportunities to engage as a unified community focused on such an ultrarare disease.

Over the past 25 years, the field has undergone a transformation from a largely uncharacterized condition with virtually no active research to one defined by gene discovery, the identification of molecular mechanisms of progerin accumulation, the

development of animal models, the characterization of cellular processes downstream of progerin, natural history studies, clinical trials, and the approval of its first life-extending therapy. Despite these advances, substantial biological and therapeutic questions remain, particularly regarding mutation-corrective strategies and long-term disease modification.

Fostering global collaboration in Progeria research

The 2025 workshop featured oral and poster presentations from established investigators and early-career basic and clinical research scientists. More than 120 researchers from 16 countries participated, reflecting the international scope of both the research community and the patient population (Fig. 1A). Over 2.5 days of intensive interaction, participants shared their unpublished data from ongoing clinical trials, emerging preclinical models, and mechanistic studies, reinforcing global collaboration as a fundamental driver of progress.

Patient partnership and the evolving clinical phenotype

Engagement of the patient community remains central to progress in HGPS research. Based on its estimated prevalence, approximately 450 children and young adults are thought to be living with Progeria worldwide. PRF has identified and maintains longitudinal communication with 150 of these patients and their families, living in 32 countries, through enrollment in The PRF International Progeria Patient Registry (www.progeriaresearch.org/international-registry-2/). Many participate in clinical trials and contribute to the Progeria Cell and Tissue Bank, providing critical resources for basic and translational research.

A central theme of the 2025 workshop was the emergence of a growing cohort of young adults with HGPS — a development made possible in part by long-term lonafarnib therapy. The session entitled *Coming of Age* featured a roundtable discussion led entirely by young adults living with Progeria, all of whom were long-term participants in Progeria clinical trials. The session was moderated by a young woman who had been the first patient enrolled in the first-ever Progeria clinical trial, in 2007 (Fig. 1B).

The discussion provided investigators with direct insight into the lived experiences of Progeria in early adulthood. Panelists described the hope afforded to them and their families by prior, ongoing, and potential future clinical trials. They stressed the importance of global Progeria community connections to their quality of life. They also discussed persistent challenges, including chronic pain, mobility limitations, social stigma, and uncertainty surrounding romantic relationships and family planning. In

addition, they highlighted structural barriers to accessing appropriately scaled medical interventions such as transcatheter aortic valve implantation (TAVI) or hip joint replacement procedures given their markedly small body size. The discussion underscored the urgency of developing bespoke therapies that improve both survival and quality of life.

Clinical research to define natural history and therapeutic endpoints

Since 2007, PRF has funded and coordinated a series of clinical trials centralized at Boston Children's Hospital. These trials have collectively enrolled over 100 participants with HGPS from 42 countries, establishing an experienced multidisciplinary team dedicated to defining the natural history of HGPS, identifying measurable endpoints to optimize detection of therapeutic benefit, and evaluating the safety and efficacy of investigational agents.

Longitudinal trial data presented at the workshop demonstrated advances in cardiovascular imaging, including echocardiographic measures, and in surrogate biomarkers such as plasma progerin levels. These approaches are being integrated with quantitative assessments of bone, adipose tissue, joint integrity, cardiac function, and skin pathology to develop robust composite clinical endpoints.

Although HGPS is a multisystem disorder, heart failure consequent to premature atherosclerosis remains the leading cause of mortality, accounting for approximately 80% of deaths¹. Presentations highlighted the expanding experience with cardiovascular interventions, including apicoaortic conduit placement and aortic valve replacement. While such procedures remain high risk for patients with Progeria, selected cases have demonstrated meaningful improvements in both functional status and survival⁵.

A particularly informative presentation described unpublished autopsy findings from a young man who lived into his mid-twenties on long-term lonafarnib therapy through Progeria clinical trials. Having developed aortic stenosis, an increasingly prevalent consequence of progeria as patients live longer with treatment, he underwent the first known transcatheter aortic valve replacement (TAVR) for HGPS at age 23 years. His decision to donate his body for Progeria research is critical to the field, as there is no published autopsy data from either lonafarnib-treated or TAVR-treated individuals with classic HGPS⁵. The presentation focused on macroscopic analysis of the heart and aorta, revealing the physical effects of long-term atherosclerosis and surgical intervention that have not previously been demonstrated. Continued analysis of these findings, in combination with microscopic studies, will provide important insights into the pathophysiology of Progeria in the context of modern treatment and extended survival.

Treatments targeting the underlying genetic defect

Considerable attention focused on upstream therapeutic strategies aimed at addressing the underlying genetic defect by targeting progerin directly, blocking its transcription, or correcting the causative mutation.

Initial data were presented from the only currently active clinical trial evaluating progerinin, an investigational small molecule designed to disrupt the interaction between progerin and lamin A, which has demonstrated preclinical efficacy by improving cardiovascular abnormalities including stroke volume, ejection fraction, and fractional shortening; and extending lifespan in progeroid mice⁶. Full enrollment has been completed in this novel trial design testing two dose levels where 8 children received the experimental treatment and are being compared to 2 control untreated children. Data collection is ongoing before full analysis of the results can be reported.

Gene-targeted approaches that can far exceed the improved vascular phenotypes and extended lifespans of humanized HGPS mice treated with any small molecule treatment candidates to date, were discussed extensively. A single dose AAV-based adenine base editor designed to correct the most common Progeria-causing mutation (*LMNA* c.1824C>T) reported progression from a dual-vector proof of concept study⁷ to a single-vector AAV delivery system for improved editing efficiency and decreased risk of drug toxicity. Importantly, new preclinical studies demonstrated these approaches were more effective for HGPS bone dysplasia when implemented earlier in life. This aligns with a growing body of evidence in skin, vasculature and lifespan in HGPS mice that supports intervention earlier in life may increase the extent of therapeutic efficacy^{7,8}. RNA therapy presentations highlighted progress with two distinct yet highly contemporary areas of ultrarare disease drug discovery. The first focused on the use of emerging technologies and treatment designs to maximize patient inclusion. An innovative AI-driven antisense oligonucleotide (ASO) designed to block aberrant *LMNA* splicing was introduced as a potentially lower-risk therapeutic strategy. The use of AI to rapidly and efficiently prioritize ASO candidates yielded promising proof-of-concept data, demonstrating improvements in hallmark progeroid phenotypes in both human progeroid cardiomyocytes and a humanized HGPS mouse model. The second body of work focused on maximizing patient eligibility through more broadly applicable, disease-oriented approaches to RNA therapy target selection. As in many rare and ultrarare diseases, certain fatal progeroid genetic variants have a much lower incidence than the predominant HGPS genotype and are therefore even less commercially attractive to pharmaceutical companies than classic HGPS. As academic efforts to develop genetic therapies continue, children with these ultrarare variants must not be left behind. With

178 this in mind, a broadly applicable targeted knockdown strategy using miRNA was
179 presented, aimed at elements shared by both lamin A and progerin.

180 Despite encouraging advances in gene targeting, significant translational challenges
181 remain. These include achieving efficient systemic delivery across affected tissues,
182 ensuring durable and controlled expression, improving tissue specificity, and minimizing
183 off-target effects. Participants emphasized that continued mechanistic research will be
184 essential to identify complementary targets and to develop combinatorial strategies
185 integrating small molecules, RNA-based therapies, and gene editing approaches.

187 **Expanding mechanistic understanding across tissues and downstream drug** 188 **targets**

189 Extensive research has identified numerous downstream consequences of progerin
190 expression. Progerin accumulation is associated with genomic instability, telomere
191 dysfunction, mitochondrial impairment, oxidative stress, altered nuclear architecture,
192 disrupted proteostasis, and epigenetic changes^{9,10}. However, the temporal sequence
193 linking progerin-induced molecular alterations to tissue degeneration remains
194 incompletely defined, limiting our understanding of not only the pathobiology underlying
195 disease phenotype in Progeria, but also the corresponding biology of health.

196 To share insights into this broad knowledge gap, a wide array of emerging studies were
197 presented in both oral and poster forms. Investigators presented emerging studies
198 examining nuclear–cytoskeletal interactions and their relevance to vascular
199 development, RNA interference–based screening strategies to identify modifiers of
200 proteostatic defects, and new murine models enabling tissue-specific analysis of DNA
201 methylation patterns. Additional work described analyses of somatic mutations in HGPS
202 models to better understand tissue-specific consequences of progerin-generated
203 genomic instability.

204 Although CVD is the primary cause of mortality, new data highlighted endocrine,
205 gastrointestinal, and adipose tissue involvement, suggesting broader metabolic
206 contributions to HGPS progression. Emerging findings also demonstrated
207 downregulation of angiopoietin-2 in progerin-expressing endothelial cells; experimental
208 angiopoietin-2 supplementation partially restored endothelial function in preclinical
209 systems¹¹, illustrating the therapeutic potential of targeting downstream pathways.

210 Workshop participants emphasized the importance of both traditional HGPS patient-
211 derived fibroblasts, induced pluripotent stem cell–derived vascular cells and mouse
212 models, and introduced state-of-the-art complementary model systems — including,
213 organoids, and advanced two- and three-dimensional culture systems. These platforms

enable systematic evaluation of therapeutic strategies, including RNA interference approaches, novel ASO chemistries, and proteolysis-targeting chimeras.

Single-cell and multi-omic technologies were highlighted as critical tools to refine molecular hallmarks of HGPS, identify stage-specific dysregulated pathways, and establish new markers of therapeutic response.

Progeria and physiological aging: convergence and divergence

HGPS recapitulates key features associated with physiological aging that emerge in childhood and proceed at an accelerated rate, including atherosclerosis, stroke, lipodystrophy, alopecia, and chronic vascular dysfunction^{1,10}. Previous studies have found evidence supporting common mechanisms implicated in HGPS vascular disease and age-associated vascular pathology in the general population. This was mentioned at the meeting and informally discussed. These included vascular stiffening with accompanying medial fibrosis, smooth muscle cell defects and calcifications, and augmented YAP/TAZ pathway activation and endoplasmic reticulum stress¹².

Low-level progerin expression has been detected in non-HGPS individuals^{10,13,14,15}, and somatic acquisition of the 1824C>T *LMNA* mutation has been reported in aging tissues in physiological vascular aging and chronic kidney disease¹⁵. These observations suggest that insights from HGPS, where progerin is an unconfounded pathologic stimulus, may inform broader mechanisms of vascular aging.

At the same time, participants emphasized the importance of distinguishing accelerated monogenic aging from physiological aging processes. Carefully designed comparative studies will be necessary to delineate shared versus disease-specific pathways and to define the extent to which therapeutic insights from HGPS can be translated to common age-related disorders.

Defining strategic priorities for the field

Progeria is a rapidly evolving field. This workshop served as a vital forum for aligning on the **immediate priorities** essential for long-term clinical and scientific success. The closing session, structured as a large-scale roundtable forum (Figure 1C), culminated in the strategic pillars illustrated in Figure 2

Conclusions

The 2025 PRF scientific workshop reflected a field transitioning from proof-of-principle preclinical lifespan extension toward mutation-corrective and combinatorial strategies aimed at durable disease modification. As patient survival improves and therapeutic strategies mature, similarly immersive forums that unite patients, basic scientists, and clinical researchers will be critical accelerators for not only new mechanistic insight into the biology of Progeria and diseases of aging, but also for translating these insights into cures at the bedside.

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Competing interests

None to declare.

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Figure 1. Photos from The PRF 12th International Scientific Workshop: Coming of Age

A. The International progeria research community leads the way to tomorrow's advancements.
 B. Adults with Progeria self-lead an intimate patient session C. Final session all-attendee round table discussion to define research pillars inspired by the meeting – see Figure 2.

Figure 2. Strategic pillars to accelerate the development of novel therapies for Hutchinson-Gilford Progeria Syndrome (HGPS)

Pillar 1



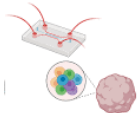
Advance Promising Therapies to the Clinic. Advance the clinical development of high-potential therapies by integrating basic and translational science to optimize the risk-benefit profile for patients. Strategic focus areas include upstream genetic modulation (DNA and RNA-based therapies to prevent progerin production), post-translational progerin reduction, and downstream interventions that meaningfully improve established disease pathology.

Pillar 2



Decode Disease Mechanisms. Champion basic research on the cell and molecular underpinnings of Progeria, adding omics approaches to better identify and understand the interplay between dysregulated pathways, targetable mechanisms, and disease biomarkers.

Pillar 3



Validate Predictive Models. Test new treatments as monotherapies and in combination with the standard-of-care treatment, lonafarnib, in relevant preclinical models that accurately recapitulate HGPS, including cells, organoids, and animals, thereby enabling effective preclinical evaluation of biological responses to treatment.

Pillar 4



Optimize Clinical Trial Design. Support initiatives to improve clinical trial design by leveraging data from longitudinal cohorts that monitor the natural history of progeria, both on and off lonafarnib, to assess disease progression, define efficacy outcomes, and provide a robust foundation for future combination therapy trials.

Pillar 5



Bridge to Physiological Aging. Expand the study of progerin in physiological aging and in age-related diseases that exhibit progeria-like phenotypes. Cross-disciplinary collaboration will accelerate the development of transformative therapies for both progeria and the broader population.

Pillar 6



Sustain global collaboration. Organize frequent, longitudinal communication among patients, basic scientists, and clinical researchers, recognizing each group as a vital partner for success.