A Comprehensive Review on Hutchinson–Gilford Progeria Syndrome: Pathogenesis, Clinical Spectrum, Diagnosis and Emerging Therapeutic Approaches

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***Abstract*—Hutchinson–Gilford progeria syndrome (HGPS) is an exceptionally rare genetic disorder in which children develop a distinctive combination of features resembling selected aspects of accelerated ageing. Severe postnatal growth failure, loss of subcutaneous adipose tissue, characteristic craniofacial and skeletal changes, and progressive vascular disease define the clinical phenotype. In most affected individuals, a de novo heterozygous LMNA c.1824C>T (p.Gly608Gly) variant activates a cryptic splice donor in exon 11. The resulting transcript encodes progerin, an abnormal lamin A isoform that retains its farnesylated carboxy-terminal region and accumulates at the nuclear envelope. Progerin disrupts nuclear architecture, chromatin organization, DNA-damage responses, mechano transduction and cellular homeostasis. Vascular smooth-muscle-cell depletion and progressive arterial pathology are major contributors to premature morbidity and mortality. Diagnosis is based on clinical recognition followed by molecular confirmation. Lonafarnib, a farnesyltransferase inhibitor, remains the established disease-modifying pharmacological treatment and has been associated with improved survival; however, it does not correct the underlying LMNA variant or eliminate cardiovascular risk. This review examines the epidemiology, inheritance, clinical course, molecular mechanisms, diagnostic pathway and multidisciplinary management of HGPS. It also evaluates emerging therapeutic concepts, including progerinin, autophagy and mTOR modulation, antisense and RNA-interference approaches, and genome/base editing. A 2026 preclinical study of mutation-agnostic base editing directed at the LMNA farnesylation motif represents an important proof of concept, but remains far from clinical application. Future progress will depend on safe delivery to disease-relevant tissues, preservation of normal lamin function, long-term safety assessment and validated molecular, vascular and functional outcome measures.**

***Index Terms*—Hutchinson–Gilford progeria syndrome; LMNA; lamin A; progerin; nuclear lamina; premature ageing; lonafarnib; farnesyltransferase inhibitor; RNA therapeutics; base editing.**

I. INTRODUCTION

Biological ageing is a multifactorial process involving progressive changes in genome integrity, epigenetic regulation, protein quality control, mitochondrial function, cellular senescence and communication between tissues. Rare progeroid disorders provide valuable opportunities to investigate selected components of these processes in humans. Hutchinson–Gilford progeria syndrome is among the best-characterized examples. It is a segmental progeroid condition: affected children show accelerated manifestations in several tissues, particularly the cardiovascular and musculoskeletal systems, but do not experience a uniform acceleration of every feature of normal ageing.

The syndrome was first described by Jonathan Hutchinson in 1886 and was subsequently characterized by Hastings Gilford, whose work contributed to the eponym now in use. Identification of pathogenic LMNA variants established the molecular basis of classic HGPS and transformed understanding of the disease from a primarily clinical observation into a defined laminopathy. The discovery that aberrant RNA splicing produces progerin provided a mechanistic explanation for the

characteristic nuclear abnormalities and created a rationale for targeted therapeutic development. Despite major advances, HGPS remains life-limiting, and cardiovascular disease continues to dominate its clinical burden. [1–3]

This review integrates current knowledge of the relationship between the LMNA defect, progerin associated cellular injury and tissue-specific disease. It also distinguishes established clinical practice from investigational strategies so that experimental findings are not mistaken for proven treatments.

II. EPIDEMIOLOGY, INHERITANCE AND GENETIC COUNSELLING

HGPS is an ultra-rare disorder. Frequently cited estimates suggest an occurrence of approximately one affected individual per four to eight million births, although estimates vary with case ascertainment, diagnostic access and registry coverage. Historical case totals in older publications should not be interpreted as current prevalence figures because additional cases may be recognized over time and reporting is not uniform across regions. [1]

Classic HGPS is generally inherited as an autosomal dominant condition, but the pathogenic variant arises de novo in the great majority of affected children. Approximately 98% of cases are reported to result from a new variant rather than inheritance from an affected parent. A small residual recurrence risk remains because parental gonadal or low-level somatic mosaicism may not be detected by routine testing. Thus, recurrence risk for siblings is low but should not be described as zero. [1,3]

The most frequent molecular finding is LMNA c.1824C>T, which is synonymous at the protein-coding level but alters pre-mRNA splicing. Less common LMNA variants can produce atypical progeroid phenotypes, while disorders involving defective prelamin A processing, including selected ZMPSTE24-associated conditions, require distinction from classic HGPS. Reports of recessive progeroid laminopathies should not be used to characterize the inheritance pattern of classic c.1824C>T-associated HGPS.

Genetic counselling should explain the usual de novo dominant mechanism, the limits of recurrence-risk estimation and the implications of identifying a pathogenic variant in the affected child. Once the familial variant is established, targeted testing may be discussed for relevant family members and reproductive planning. Advanced paternal age has been associated with some de novo mutations, but it is not a deterministic predictor and should not be used to estimate an individual family's risk.

III. CLINICAL MANIFESTATIONS AND NATURAL HISTORY

3.1 Early presentation and growth

Infants with HGPS may appear unremarkable at birth. Clinical features usually become apparent during the first or second year of life, when growth velocity declines and weight gain becomes increasingly difficult. Progressive loss of subcutaneous fat, reduced muscle mass and characteristic skin changes contribute to the distinctive appearance. Common findings include severe postnatal growth deficiency, low body weight, alopecia, prominent scalp veins, tight or sclerodermatous skin, a relatively small face and jaw, a narrow nasal ridge and tip, prominent eyes, thin lips and protruding ears. Dental development is frequently abnormal, with delayed eruption, crowding and irregular shedding. [1]

3.2 Musculoskeletal, dental and sensory features

Skeletal involvement may include short or tapered clavicles, distal phalangeal osteolysis, coxa valga, hip abnormalities, joint contractures and restricted range of movement. These changes can affect gait, posture and functional mobility. Bone mineral density requires cautious interpretation because short stature and reduced body size influence measurements; the skeletal phenotype should not automatically be equated with conventional osteoporosis. Dental care is important because crowding, delayed eruption and abnormal tooth shedding may complicate feeding, oral hygiene and quality of life.

Ophthalmic complications may include dry eye and exposure keratopathy, particularly where incomplete eyelid closure is present. Conductive hearing impairment has also been reported. Regular assessment allows supportive interventions to be introduced before complications substantially affect daily function. Intellectual development is generally preserved, although physical limitations and repeated medical care may influence educational and social experiences.

3.3 Cardiovascular and cerebrovascular disease

Progressive vascular disease is the principal determinant of premature mortality in HGPS. Arterial stiffness, calcification, atherosclerotic change, fibrosis and loss of vascular smooth muscle cells can compromise arterial integrity and function. Clinical consequences include myocardial infarction, heart failure, transient is chaemic attack and stroke. Cerebrovascular disease may progress with few warning symptoms, making planned surveillance important even when the child appears clinically stable.

Conventional lipid concentrations do not fully capture the vascular pathology of HGPS. Cardiovascular risk assessment should therefore not depend on a lipid profile or electrocardiogram in isolation. The natural history is variable, but untreated cohorts have reported an average age at death of approximately 14.5 years. GeneReviews reports a longer average lifespan among individuals treated with lonafarnib; cohort-level estimates describe groups and cannot be used as an individualized prognosis. [1,4]

IV. GENETIC AND MOLECULAR BASIS

4.1 LMNA and the nuclear lamina

The LMNA gene, located at chromosome 1q22, encodes the A-type nuclear lamins, principally lamin A and lamin C. These intermediate-filament proteins form a major structural component of the nuclear lamina beneath the inner nuclear membrane. In addition to maintaining nuclear shape and mechanical stability, lamin A/C participates in chromatin organization, regulation of gene expression, DNA replication and repair, and cellular responses to mechanical stress. Disruption of these functions can therefore affect both nuclear structure and the regulation of cellular activity. [1,5]

4.2 Aberrant splicing and progerin formation

In classic HGPS, the recurrent c.1824C>T substitution in exon 11 of LMNA does not change the encoded amino acid (p.Gly608Gly). Nevertheless, the nucleotide substitution alters pre-mRNA processing by activating a cryptic splice donor site. The resulting transcript lacks 150 nucleotides, corresponding to 50 amino acids in the carboxy-terminal region of prelamin A. The abnormal truncated protein is known as progerin. [1,3,5]

Normal prelamin A undergoes several post-translational modifications. The cysteine within its carboxy-terminal CAAX motif is farnesylated; the terminal –AAX residues are removed, the exposed carboxyl group is methylated, and the farnesylated tail is finally cleaved by ZMPSTE24. This final processing step releases the farnesylated segment and produces mature lamin A. Progerin lacks the region required for the final cleavage and consequently remains persistently farnesylated. Its abnormal association with the nuclear envelope is central to HGPS pathogenesis.

4.3 Cellular and tissue-level consequences

Progerin accumulation alters nuclear shape and mechanical properties, often producing nuclear blebbing and irregularity. It also disturbs lamina-associated domains, heterochromatin organization and epigenetic marks, with downstream changes in the expression of genes involved in cell-cycle control, extracellular-matrix remodelling, inflammation and tissue maintenance. Increased DNA-damage signalling and impaired repair of double-strand breaks have been described alongside telomere dysfunction, mitochondrial abnormalities, oxidative stress, altered autophagy and premature cellular senescence. These processes are interconnected and should be understood as components of a broader disturbance in cellular homeostasis rather than independent mechanisms.

Telomere attrition may contribute to cellular dysfunction, but HGPS is not primarily a telomere-shortening disorder. The initiating molecular event in classic HGPS is aberrant LMNA splicing and progerin production. This distinction is important because it directs therapeutic strategies toward reducing progerin production, limiting its toxicity or preventing its abnormal processing and localization.

Vascular tissues are particularly vulnerable. Progerin expression in vascular smooth muscle cells and other mesenchymal-lineage cells is associated with cellular depletion, arterial stiffening, fibrosis and calcification. Endothelial dysfunction, inflammatory signalling and altered extracellular-matrix composition may further compromise vessel integrity. HGPS is therefore better conceptualized as a tissue-selective disease driven by progerin toxicity than as a uniform acceleration of all ageing processes.

V. DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical suspicion is raised by the combination of postnatal growth failure, progressive lipodystrophy, alopecia, characteristic skin changes and skeletal abnormalities, particularly when intellectual development is relatively preserved. Because individual features may overlap with other progeroid disorders, molecular confirmation is essential. Targeted analysis of LMNA exon 11 and the adjacent intronic splice region can detect the classic c.1824C>T variant and many other progerin-producing variants. If targeted testing is negative despite strong clinical suspicion, comprehensive LMNA sequencing and consideration of ZMPSTE24 analysis or a broader progeroid-disorder gene panel may be appropriate. [1]
Radiographic evaluation can demonstrate clavicular changes, distal phalangeal osteolysis, coxa valga and other skeletal abnormalities. Cardiovascular assessment may include blood-pressure measurement, electrocardiography, echocardiography and carotid duplex imaging. MRI or magnetic resonance angiography of the head and neck may be considered according to clinical findings and specialist recommendations. The choice and frequency of investigations should be individualized.
No routine blood test independently establishes the diagnosis. Laboratory investigations may assist general clinical assessment but cannot replace molecular testing. Urinary hyaluronan has been discussed in historical literature; it is not a validated diagnostic criterion and should not be used to confirm or exclude HGPS. [1]
The differential diagnosis includes mandibuloacral dysplasia, restrictive dermopathy, Werner syndrome, Rothmund–Thomson syndrome, Cockayne syndrome, Wiedemann–Rautenstrauch syndrome and other laminopathies or progeroid conditions. Because clinical overlap can be substantial, interpretation of the phenotype alongside molecular findings is central to accurate classification.

VI. ESTABLISHED TREATMENT AND SUPPORTIVE MANAGEMENT

6.1 Lonafarnib

Lonafarnib (Zokinvy) is an oral farnesyltransferase inhibitor and the first pharmacological treatment approved by the US Food and Drug Administration for HGPS. By inhibiting farnesylation, the drug reduces the abnormal membrane association of progerin and has been associated with improvements in selected clinical and cellular measures. The FDA indication includes patients with HGPS aged 12 months and older who meet the labelled body-surface-area requirement; the label also covers specified processing-deficient progeroid laminopathies. [6]
Evidence supporting lonafarnib was generated through open-label clinical studies and comparison with an untreated natural-history cohort, with extended follow-up. These studies demonstrated a survival benefit, commonly summarized as approximately 2.5 years in the relevant analyses. The evidence is important given the rarity of HGPS, although the non-randomized design and small patient population should be considered when interpreting effect estimates. Lonafarnib has altered the therapeutic landscape, but it is not curative: it does not remove the pathogenic LMNA variant, completely eliminate progerin or abolish the risk of cardiovascular events. [4,6]
Treatment requires specialist supervision, individualized dose adjustment according to body surface area and tolerability, and careful review of concomitant medicines. Gastrointestinal adverse effects—including vomiting, diarrhoea, nausea and reduced appetite—may affect nutrition and weight gain. The current prescribing information also identifies clinically important drug interactions and monitoring requirements. The November 2026 FDA label should be consulted for current contraindications, precautions, dose modifications and monitoring; dosing details in older reviews should not be used as prescribing instructions. [6]

6.2 Other pharmacological approaches

A combination of lonafarnib, pravastatin and zoledronic acid was previously investigated to influence different points in the isoprenoid pathway and address skeletal abnormalities. Although selected bone-density measures improved, the combination did not establish an additional overall clinical benefit over lonafarnib alone and subsequent analyses raised concern about increased extraskeletal calcification. It should therefore not be presented as a preferred or routine HGPS regimen. [1,4]

Antiplatelet agents, anticoagulants, lipid-lowering medicines, antihypertensive drugs and other cardiovascular interventions may be considered when clinically indicated. Such decisions require individual assessment by the treating team. Low-dose aspirin has been considered in selected patients, but it is not a universal self-directed intervention and must be weighed against bleeding risk, age, intercurrent illness and the overall clinical context. Calcium supplementation should likewise be guided by specialist assessment rather than prescribed routinely because of concern about extraskeletal calcification. Growth hormone is not an established disease-modifying treatment, and oxygen should be used for conventional clinical indications rather than as therapy for the underlying genetic disorder.

VII. EMERGING AND INVESTIGATIONAL THERAPEUTIC STRATEGIES

7.1 Progerinin

Progerinin is an investigational small molecule developed to interfere with progerin-associated protein interactions and cellular toxicity. Its proposed mechanism differs from simply inhibiting farnesylation and may therefore offer a complementary therapeutic approach. A Phase 2a randomized, open-label study (ClinicalTrials.gov identifier NCT06775041) is evaluating progerinin in combination with lonafarnib against lonafarnib alone, with assessment of safety, tolerability, pharmacokinetics and dose-related parameters. The trial record available for this review described a small study and did not provide posted efficacy results. Progerinin must therefore be regarded as experimental until adequate clinical data demonstrate benefit. [7]

7.2 Autophagy and mTOR-pathway modulation

Progerin accumulation can impair protein quality control and disrupt cellular homeostasis. Autophagy is responsible for degrading damaged or abnormal cellular components, while mechanistic target of rapamycin (mTOR) signaling regulates growth, metabolism and autophagic activity. In experimental models, rapamycin and related interventions have improved selected cellular phenotypes, potentially by enhancing clearance of abnormal proteins. Clinical investigation of lonafarnib in combination with everolimus has also been undertaken, but definitive published efficacy evidence was not identified in the literature considered here. These strategies remain investigational and require careful evaluation of immunosuppression, metabolic effects and long-term safety. [1]

7.3 RNA-based therapeutic approaches

Antisense oligonucleotides and RNA-interference strategies are being explored to reduce the abundance of the abnormal LMNA transcript or modify splicing in a way that decreases progerin production. A potential advantage of RNA-based treatment is that its effects may be reversible and do not necessarily require permanent alteration of genomic DNA. However, successful treatment will depend on efficient delivery to relevant tissues, including vascular smooth muscle, bone and skin. Additional challenges include durability, repeated administration, immune activation and preservation of normal lamin A and lamin C expression. Broad suppression of LMNA could itself be harmful; approaches that selectively target the pathogenic transcript or splice event are therefore particularly attractive.

7.4 Genome editing and base editing

Genome-editing approaches seek either to correct the pathogenic LMNA sequence or to prevent production and accumulation of toxic progerin. Earlier proof-of-concept studies in cells and animal models demonstrated that editing can reduce progerin expression and improve selected disease-associated features. Mutation-specific correction, however, may require a tailored strategy for each pathogenic variant and must address risks such as unintended sequence changes, large on-target deletions and chromosomal rearrangements.

A notable 2026 study reported Farnesylation Amino-acid Targeted Editing (FATE), a mutation-agnostic base-editing strategy directed at the LMNA farnesylation motif. In human pluripotent-stem-cell-derived neuromuscular organoids, FATE reduced perinuclear progerin accumulation and improved aspects of DNA-damage repair and nuclear architecture. The investigators also explored transient delivery of editor mRNA using lipid nanoparticles. These findings provide a compelling preclinical proof of concept, but do not establish clinical safety or efficacy in children with HGPS. [8]

A separate 2026 preclinical report described in vivo base editing in a mouse model and partial improvement in bone dysplasia. Such work broadens the potential scope of tissue-directed editing, but translation will require evidence of adequate delivery to relevant cell populations, reproducible editing efficiency, durable benefit and acceptable immune responses. Both intended and unintended on-target changes, off-target editing, mosaicism and long-term consequences must be assessed. These issues are particularly important when considering interventions in infants and young children. [9]

7.5 Additional molecular targets

Other proposed targets include isoprenylcysteine carboxyl methyltransferase, inflammatory and senescence-associated pathways, oxidative stress, mitochondrial dysfunction, extracellular-matrix remodeling and angiopoietin-related vascular signaling. Senolytic agents, which aim to eliminate selected senescent cells, and senomorphic agents, which modify their secretory phenotype, are also being explored in experimental systems. None of these approaches is currently established as standard HGPS care. The principal challenge is to demonstrate that mechanistic improvements translate into clinically meaningful outcomes, particularly preservation of vascular function and reduction of cardiovascular events. [10,11]

VIII. MONITORING AND MULTIDISCIPLINARY CARE

The complexity of HGPS requires coordinated care rather than management by a single specialty. Depending on individual needs, the clinical team may include clinical genetics, paediatric cardiology, neurology, endocrinology, nutrition, orthopaedics, dentistry, ophthalmology, audiology, physiotherapy, occupational therapy, psychology and palliative or supportive-care professionals. Care coordination should be continuous and responsive to changes in function, symptoms and family priorities. [1]

Longitudinal monitoring commonly includes assessment of growth, weight, caloric intake and hydration at each clinical review. Cardiovascular surveillance may incorporate blood pressure, electrocardiography, echocardiography and carotid imaging at intervals determined by specialist guidance and the patient's condition. Neurological assessment and head-and-neck MRI/MRA may be recommended according to clinical circumstances. Dental, orthopaedic, ophthalmic and audiological evaluations should occur regularly, often at least annually, with frequency adjusted to identified problems. [1]

Nutritional care should aim to maintain adequate energy intake and hydration, with dietetic input where poor weight gain, feeding difficulty or gastrointestinal adverse effects are present. Physiotherapy and occupational therapy can help maintain joint mobility, functional independence and participation in daily activities. Exercise and activity recommendations should account for joint limitations and the risk of falls, hip injury or trauma without imposing unnecessary restrictions. Families should have access to psychosocial support, genetic counselling and age-appropriate information. Fever, dehydration and anaemia warrant timely assessment, particularly in individuals with advanced vascular disease.

Supportive care should address not only clinical complications but also comfort, autonomy, education and social participation. A person-centred approach helps ensure that surveillance and treatment do not unnecessarily diminish quality of life.

IX. BIOMARKERS AND CLINICAL OUTCOME ASSESSMENT

The small number of individuals living with HGPS creates substantial challenges for clinical research. Trials may be limited by small enrolment, variable disease progression and difficulty measuring meaningful change over relatively short periods. Biomarkers and standardized outcome measures are therefore important for identifying biological activity, monitoring disease progression and interpreting treatment response.

Candidate molecular biomarkers include LMNA genotype, progerin abundance, markers of DNA damage such as γH2AX, telomere dysfunction and epigenetic alterations. Cellular and systemic candidates include senescence-associated secretory factors, inflammatory mediators, oxidative-stress measures and indicators of mitochondrial function. Vascular assessment may include arterial stiffness, pulse-wave velocity, carotid structure and function, and vascular calcification. These measures vary in

maturity and validation; none should be assumed to be a fully established surrogate for clinical benefit.

Clinical endpoints should combine survival and major cardiovascular events with functional measures such as growth trajectory, mobility, joint range of motion, six-minute walk performance and patient- or caregiver-reported quality of life. A 2026 review emphasized the potential value of integrating molecular, cellular, inflammatory and vascular biomarkers, while highlighting the need for further validation. Biomarker panels should complement, not replace, outcomes that matter directly to patients and families. [10]

X. CRITICAL SYNTHESIS AND UPDATED INTERPRETATION

Several concepts in historical literature require careful interpretation in light of current molecular and clinical evidence. First, classic HGPS should be described as an autosomal dominant disorder that is usually caused by a de novo LMNA variant; recessive inheritance should not be generalized from other, distinct progeroid laminopathies. Second, telomere dysfunction may contribute to cellular pathology, but it is not the primary initiating event in classic HGPS. The central molecular defect is aberrant LMNA splicing and progerin production.

Third, molecular genetic testing is the diagnostic standard. Historical biochemical observations, including urinary hyaluronan measurements, do not substitute for confirmation of a pathogenic LMNA variant. Fourth, lonafarnib is the established disease-modifying pharmacological treatment, whereas aspirin, statin/bisphosphonate combinations, antioxidants and other medicines should not be portrayed as universal or proven HGPS therapies. Their use, where appropriate, depends on individual clinical indications and specialist judgement.

Finally, RNA therapeutics and genome editing have moved beyond purely theoretical proposals, with encouraging cell, organoid and animal-model findings reported through 2026. Nevertheless, preclinical efficacy must be distinguished from clinical effectiveness. The gap between molecular rescue in experimental systems and safe, durable benefit in children remains substantial. This distinction is essential for balanced scientific communication and responsible counselling.

XI. RESEARCH PRIORITIES AND FUTURE DIRECTIONS

The next phase of HGPS research should address several interconnected priorities. A major requirement is the development of delivery systems capable of reaching vascular smooth muscle cells and other disease-relevant tissues at therapeutically meaningful levels. A second priority is to reduce progerin abundance or toxicity while preserving the normal functions of lamin A and lamin C. Strategies that achieve molecular specificity without broader disruption of nuclear-lamina biology may offer the most favorable therapeutic profile.

Clinical trials will need robust natural-history comparators, harmonized outcome definitions and sufficiently long follow-up to detect changes in disease progression. Given the very small patient population, international collaboration, patient registries and partnerships with affected families will remain essential for recruitment and longitudinal assessment. Combination therapies should be selected on the basis of complementary mechanisms and should demonstrate added clinical value rather than relying solely on improvements in cellular readouts.

Long-term safety is especially important for gene- and RNA-based interventions administered early in life. Research programmes should prospectively evaluate immunogenicity, off-target effects, editing durability, tissue distribution and the consequences of modifying lamin-related pathways over many years. The field is moving toward an integrated view of HGPS: progerin affects nuclear mechanics, chromatin regulation, DNA repair, stress responses and tissue-specific function. Future treatment may therefore require a combination of progerin-directed therapy, vascular protection and individualized supportive care.

XII. CONCLUSION

Hutchinson–Gilford progeria syndrome is a rare and severe laminopathy that has provided important insight into the relationship between nuclear-envelope biology, cellular homeostasis and selected features of premature ageing. In classic HGPS, aberrant LMNA splicing produces progerin, a persistently farnesylated lamin A variant that disrupts nuclear architecture and contributes to multisystem pathology. Molecular diagnosis has clarified the dominant, usually de novo

inheritance pattern, while multidisciplinary surveillance remains essential because progressive cardiovascular disease is the principal life-limiting complication.

Lonafarnib represents a major therapeutic advance and is associated with improved survival, but it does not eliminate progerin or fully prevent vascular disease. Investigational strategies—including progerinin, autophagy modulation, RNA-based treatment and genome/base editing—offer additional avenues for research. The 2026 FATE organoid findings and emerging in vivo editing data are promising experimental developments, not established clinical therapies. Progress will depend on safe tissue delivery, preservation of normal lamin function, rigorous clinical evaluation and sustained collaboration among researchers, clinicians and affected families.

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