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Precision Medicine and Progress in the Treatment of Hutchinson-Gilford Progeria Syndrome

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Hutchinson-Gilford progeria syndrome (HGPS) is an ultrarare autosomal dominant genetic disorder, with an incidence of 1 in 4 million live births, for which there is no known cure.

Children with HGPS appear normal at birth but present in infancy with severe failure to thrive, accompanied by a prematurely aged appearance, alopecia, and progressive lipodystrophy, joint contractures, skeletal dysplasia, and atherosclerosis, although intellectual development is normal.¹ Accelerated cardiovascular disease results in death due to myocardial infarction or stroke at an average age of 14.6 years.²

It took 117 years after the initial description of the phenotype in the 1880s^{3,4} to identify the cause of classic HGPS as a recurrent, single base substitution, c.1824C>T in the *LMNA* gene.⁵ Lamin A is a structural protein of the inner membrane of the cell nucleus, and a wide range of inherited human diseases, including muscular dystrophy, dilated cardiomyopathy, peripheral neuropathy, and lipodystrophy, which have collectively been termed *laminopathies*, are caused by heterogeneous pathogenic variants in the *LMNA* gene.⁶ The c.1824C>T variant that causes nearly all cases of HGPS has been shown to activate an alternative splice site, resulting in accumulation of an abnormal lamin A derived protein named progerin. Normal production of lamin A depends on posttranslational enzymatic cleavage of the intermediate protein's 15 C terminal amino acids, including a cysteine residue modified by farnesylation. The progerin isoform of lamin A lacks this crucial cleavage site, resulting in a permanently farnesylated protein that accumulates in and causes thickening of the nuclear membrane. This understanding led to the question of whether existing cancer drugs that inhibit farnesyltransferase enzymes could be repurposed to treat HGPS.

In this issue of *JAMA*, Gordon et al⁷ report the results of treatment with the farnesyltransferase inhibitor lonafarnib on mortality in 63 patients enrolled in 2 clinical trials. The ProLon 1 trial enrolled 27 patients with HGPS with genetically confirmed

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pathogenic *LMNA* variants who were treated with oral lonafarnib every 12 hours at 115 mg/m² for 4 months, increased to 150 mg/m² for a minimum of 2 years.⁸ The ProLon2 trial included 36 patients treated with oral lonafarnib monotherapy at 150 mg/m² and is ongoing. In this observational study, treated patients from the trials were compared with untreated controls matched in a 1:1 ratio for age, sex, and home continent. The primary outcome was comparison of mortality rates in untreated vs lonafarnib-treated patients in ProLon 1.

Administration of lonafarnib was associated with a reduction in mortality in the treated cohort (1/27 deaths [3.7%]) compared with the matched untreated cohort (9/27 deaths [33.3%]) in ProLon1 as well as in a secondary analysis of mortality in the larger group of 63 patients in ProLon1 and ProLon2 (4/63 deaths [6.3%] in the treated group vs 17/63 deaths [27.0%] in the matched untreated group). Among 73 patients with an identified cause of death, 58 deaths (79%) were due to heart failure.

The limitations of the study are due to the observational design. Conducting a placebo-controlled, randomized trial is difficult because of the rarity of HGPS and the ethical issues involved in recruiting fragile children and their families. The investigators matched each treated patient with an untreated control and performed a sensitivity analysis to assess the contribution of confounding factors, further validating the results.

These results are the first of their kind for HGPS and can be traced directly back to identification of the underlying genetic basis of the disease and the cell biology and mouse model studies that supported the use of farnesyl transferase inhibitors as a potential therapeutic modality.⁹ At the same time, enthusiasm is tempered by recognizing that lonafarnib is not a cure for HGPS because several aspects of the phenotype, including alopecia, joint contractures, insulin resistance, and conductive hearing loss, do not improve with treatment.⁸ It remains an open question whether earlier treatment would prevent these or other disease manifestations. The clinical trials have each lasted approximately 2 years, and longer-term follow up data are not yet available.

Preclinical studies of additional drugs that target farnesylation as well as alternative therapeutic targets are also in progress.¹⁰ In vitro studies of mammalian target of rapamycin (mTOR) inhibitors and the diabetes drug metformin have demonstrated a reduction of progerin accompanied by the restoration of cellular HGPS phenotypes.^{11,12} Reactivation of the antioxidant NRF2 has also been shown to reverse the cellular defect of HGPS in an animal model.¹³

It is unclear whether these results have implications for normal aging. Hutchinson-Gilford progeria syndrome is a segmental progeroid syndrome, like Werner syndrome (adult onset progeria).¹⁴ No one progeroid syndrome faithfully recapitulates all of the features of normal aging in terms of declines in physiologic function and increased risk of common age-related diseases, from cataracts to cancer and osteoporosis. In particular, patients with HGPS do not generally develop cancers or neurodegenerative diseases of old age, but the vasculopathy of HGPS, like that of normal aging, includes vascular stiffening, hypertension, vascular calcification, cardiomegaly, and congestive heart failure. Furthermore, progerin is expressed at very low levels in healthy individuals, and progerin expression in coronary arteries is

reported to increase by approximately 3% per year with aging.¹⁵ Investigations into the mechanism and treatment of HGPS may yield new insights into the treatment of age-related cardiovascular disease.¹⁶

The results of the study by Gordon et al have implications for other rare diseases. A rare disease was defined in the OrphanDrugAct of 1983 as one that affects fewer than 200 000 people.¹⁷ Because there are more than 7000 individual rare diseases, most of which are genetic, rare diseases are estimated to affect 25 million to 30 million people in the United States.¹⁸ The rate of rare disease gene discovery is accelerating with the introduction of rapid exome and genome sequencing technologies. Hutchinson-Gilford progeria syndrome illustrates that a drug developed for one disease may be repurposed to treat another in this case, using a drug developed for advanced cancer to treat a disease with growth insufficiency, premature aging, skeletal abnormalities, and cardiovascular disease but only rarely cancer. In 2007, when the first clinical treatment trial for HGPS began, this was a novel approach.⁹ Precision medicine, by leveraging rational pathway based repurposing of drugs based on genetic variation, is becoming increasingly common in diseases from cancer to epilepsy. Poly(adenosine diphosphate) polymerase inhibitors were first used in the treatment of ovarian adenocarcinoma but recently have been shown to be effective in metastatic prostate cancer.¹⁹ Some children with epileptic encephalopathies refractory to conventional treatments are found to have disease-causing gain-of-function variants in GRIN2A or GRIN2D, which encode subunits of the *N*-methyl-D-aspartate (NMDA) receptor; early case reports suggest that improvements in seizure control and development are possible with drugs that block the NMDA receptor channel, including memantine.²⁰

For numerous other rare diseases, the example of HGPS highlights the importance of a solid basic research foundation in understanding the disease, the vital role of patient registries and engagement of patients and families, the need to foster close, ongoing, multidisciplinary collaboration between scientists and clinicians, and support from governmental agencies.

REFERENCES

1. Merideth MA, Gordon LB, Clauss S, et al. Phenotype and course of Hutchinson-Gilford progeria syndrome. *N Engl J Med*. 2008;358(6): 592–604. [PubMed: 18256394]
2. Gordon LB, Massaro J, D'Agostino RBSr, et al.; Progeria Clinical Trials Collaborative. Impact of farnesylation inhibitors on survival in Hutchinson-Gilford progeria syndrome. *Circulation*. 2014;130(1):27–34. [PubMed: 24795390]
3. Hutchinson J Congenital absence of hair and mammary glands with atrophic condition of the skin and its appendages, in a boy whose mother had been almost wholly bald from alopecia areata from the age of six. *Med Chir Trans*. 1886;69:473–477.
4. Gilford H Ateleiosis and progeria: continuous youth and premature old age. *BMJ*. 1904;1904:914–918.
5. Eriksson M, Brown WT, Gordon LB, et al. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature*. 2003;423(6937):293–298. [PubMed: 12714972]
6. Worman HJ. Nuclear lamins and laminopathies. *J Pathol*. 2012;226(2):316–325. [PubMed: 21953297]
7. Gordon LB, Shappell H, Massaro J, et al. Association of lonafarnib treatment vs no treatment with mortality rate in patients with Hutchinson-Gilford progeria syndrome [published online April 24, 2018]. *JAMA*. doi:10.1001/jama.2018.3264

8. Gordon LB, Kleinman ME, Miller DT, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. *Proc Natl Acad Sci USA*. 2012;109(41):16666–16671. [PubMed: 23012407]
9. Kieran MW, Gordon L, Kleinman M. New approaches to progeria. *Pediatrics*. 2007;120(4): 834–841. [PubMed: 17908771]
10. Blondel S, Egesipe AL, Picardi P, et al. Drug screening on Hutchinson Gilford progeria pluripotent stem cells reveals aminopyrimidines as new modulators of farnesylation. *Cell Death Dis*. 2016;7:e2105. [PubMed: 26890144]
11. Cao K, Graziotto JJ, Blair CD, et al. Rapamycin reverses cellular phenotypes and enhances mutant protein clearance in Hutchinson-Gilford progeria syndrome cells. *Sci Transl Med*. 2011;3(89):89ra58.
12. Egesipe AL, Blondel S, Cicero AL, et al. Metformin decreases progerin expression and alleviates pathological defects of Hutchinson-Gilford progeria syndrome cells. *NPJ Aging Mech Dis*. 2016;2:16026.
13. Kubben N, Zhang W, Wang L, et al. Repression of the antioxidant NRF2 pathway in premature aging. *Cell*. 2016;165(6):1361–1374. [PubMed: 27259148]
14. Hisama FM, Oshima J, Martin GM. How research on human progeroid and antigeroid syndromes can contribute to the longevity dividend initiative. *Cold Spring Harb Perspect Med*. 2016;6(4):a025882.
15. Olive M, Harten I, Mitchell R, et al. Cardiovascular pathology in Hutchinson-Gilford progeria: correlation with the vascular pathology of aging. *Arterioscler Thromb Vasc Biol*. 2010;30(11):2301–2309. [PubMed: 20798379]
16. Gordon LB, Kleinman ME, Massaro J, et al. Clinical trial of the protein farnesylation inhibitors lonafarnib, pravastatin, and zoledronic acid in children with Hutchinson-Gilford progeria syndrome. *Circulation*. 2016;134(2):114–125. [PubMed: 27400896]
17. Gahl WA. The battlefield of rare diseases: where uncommon insights are common. *Sci Transl Med*. 2012;4(154):154ed7.
18. National Center for Advancing Translational Sciences Genetic and Rare Diseases Information Center. FAQs about rare diseases. <https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases>. Accessed March 19, 2018.
19. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373(18):1697–1708. [PubMed: 26510020]
20. Li D, Yuan H, Ortiz-Gonzalez XR, et al. *GRIN2D* recurrent de novo dominant mutation causes a severe epileptic encephalopathy treatable with NMDA receptor channel blockers. *Am J Hum Genet*. 2016;99(4):802–816. [PubMed: 27616483]