EDITORIAL

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AI-ECG and the Prediction of Accelerated Aging

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The paper by Shelly et al[1] in this issue of *Mayo Clinic Proceedings* represents a next step in our understanding of artificial intelligence (AI)—interpreted electrocardiogram (ECG) changes as a potential marker of biological aging. In the case reported here, the authors provide early evidence for the relationship between *LMNA* mutations and biological age *in excess* of chronological age.

Life span in patients with *LMNA* mutations varies on the basis of phenotype, but average life span generally is very short—approximately 12 years in patients with congenital muscular dystrophy and 14.5 years in patients with progeria syndrome.[2,3] Other phenotypes carry risk of lethal ventricular arrhythmias and therefore also risk of shorter life span, albeit at variable and older ages. Also, not all patients with *LMNA* mutations display progeroid features. Most patients with progeria carry *LMNA* c.1824C>T or, less commonly, mutations in exon 11 or intron 11 resulting in production of progerin.[3] On occasion, progeroid features have been observed in patients carrying other *LMNA* mutations. Therefore, it cannot be certain if or how well the excess biological age seen in individuals with *LMNA* mutations correlates with expected life span owing to rarity and heterogeneity of the phenotypes.

Shelly et al use a so-called age gap to express the difference between predicted ECG age and chronological age. Previous work addressed the possibilities that the age gap could be due to AI bias or simply poor accuracy. Original evaluation of these possibilities attempted to predict chronological age using the ECG through convolutional neural networks, with actual (chronological) age as the standard for prediction. There was good but not extremely high prediction with *R* values approximately 0.75.[4] This imperfect prediction was subsequently shown to represent ECG information related to aging[5] rather than error (ie, the ECG could not predict age well). Furthermore, a positive ECG age gap was associated with increased mortality, and a negative age gap was associated with increased survival. This association persisted after risk factors and comorbidities were considered and held up even after exclusion of patients with cardiovascular disease. The overall validity and reliability of the age gap concept from AI-ECG has now been confirmed in multiple studies.[4-8]

Shelly et al show that *LMNA* mutation carriers, including asymptomatic individuals, had a predicted biological age significantly older than that of matched controls, the age gap about 16 years older by ECG criteria than that of non-*LMNA* carriers. This finding suggests that biological aging can be predicted in accelerated aging syndromes, perhaps before clear manifestations of disease. However, can the age gap relationship be exploited to translate this information into early medical intervention? Can the age gap also serve as a disease marker? The former question presupposes that AI-ECG interpretation can predict the specific cardiac, muscular, or neurologic complications that could be intervened on early and the latter question that AI-ECG interpretation can diagnose individuals with *LMNA* mutations.

Whereas an early diagnosis of laminopathy is crucial for early therapeutic strategies and interventions, the age gap does not permit the early diagnosis of laminopathy, only an association with accelerated aging, which potentially could be discerned with any precocious aging syndrome. There is also uncertainty that AI-enabled ECG age could be a disease marker specific for laminopathy because it could rather be a

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biomarker for cardiac disease risk in a genetic disorder or perhaps for other disease states that are manifested in biologically older individuals. Because increased age gap is not equivalent to the diagnosis of laminopathy and the advanced age gap is not specific to laminopathy, similar studies evaluating other genetic disorders potentially involving the cardiovascular system are needed. A positive age gap in a known laminopathy, however, could be leveraged to inform about clinical responsiveness to therapy, such as gene therapy, and also encourages similar future studies.

The authors compared the estimated age gap in 2 patients with an *LMNA* mutation previously reported in progeroid phenotypes (patients 4 and 21, Supplementary Table 1) vs other *LMNA* patients with cardiomyopathy and muscular dystrophy and found that the median age gap was not statistically significant between these 2 groups. Although the sample size is small in the progeroid group, the results suggest that the AI-ECG interpretation has perhaps captured something abnormal related to the laminopathy itself, rather than something specific to early detection of cardiomyopathy or muscular dystrophy. This is also supported by AI-ECG predictions that patients with *LMNA* mutations have a biological age older than chronological age even in the absence of cardiac abnormalities. Another possibility is that Shelly et al are identifying cardiovascular disease before its clinical discovery or that accelerated biological aging can be detected in progeroid syndromes with AI-ECG. Additional longitudinal studies and larger patient cohorts would be informative in this regard.

POTENTIAL COMPETING INTERESTS

The author reports no competing interests.

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