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EDITORIAL

From Waveforms to Wisdom: Gleaning More From the ECG About Biological Aging

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The age gap, also known as the difference between biological age and chronological age, has long served as a conceptual framework for understanding age-related disease processes. There have been numerous applications in cardiovascular research,[1] offering not only avenues for discerning accelerated versus delayed cardiovascular aging phenotypes but also opportunities for communicating with patients about age-related cardiovascular risks. One such example used coronary artery calcification measures to represent arterial age, which was based on estimating an equivalency ratio in relation to hazards for incident coronary heart disease.[2] The result was a linear equation that allowed for performing a simple calculation of a coronary artery calcification-age score to support a statement such as, you are 55-years-old, but your arteries appear more consistent with an arterial age of 65 years.[2] This particular age gap was specific to accelerated atherosclerosis pathways and most relevant to the outcome of coronary heart disease, by design. Now, with the advent of deep learning methods, even broader measures of the age gap can be derived from even more accessible diagnostic tests.

See Article by Brant et al

In this issue of *Circulation: Cardiovascular Quality and Outcomes*, Brant et al[3] have sought to determine how generalizable as well as informative a measure of biological age could be if derived from the standard 12-lead ECG (ECG). Specifically, they applied a model developed by investigators who previously used a deep neural network to predict age across over 1.5 million participants of 3 separate Brazilian cohort studies to produce a model-based variable termed ECG-age that correlated with all-cause mortality risk over up to a decade of follow-up.[4] In parallel work, an ECG-age variable was similarly derived using a convolutional neural network in a cohort of over 25 000 participants of the Rochester Epidemiology Project in Olmstead County, wherein it was shown to predict cardiovascular and all-cause mortality over almost 2 decades.[5] Similarly, this time in a cohort of over 70 000 adult patients of a health care system in Taiwan, yet another deep learning model was used to develop an ECG-age variable which was found to predict all-cause and particularly cardiovascular mortality in addition to several cardiovascular risk factor and disease diagnoses.[6] In the current study, Brant et al took on the important task of investigating whether the Brazilian cohort derived ECG-age could be predictive of outcomes in another community cohort and, in particular, cardiovascular disease specific outcomes. They found that this ECG-age variable, generated from applying the model to tracings from over 9000 participants of the Framingham Heart Study, was associated with adjudicated atrial fibrillation, myocardial infarction, heart failure, and all-cause mortality over a follow-up period of up to 3 decades. They also found that accelerated ECG-age (calculated as a positive difference from chronologic age) was related to higher risk of atrial fibrillation, heart failure, death whereas decelerated ECG-age (calculated as a negative difference from chronologic age) was related to lower risk of heart failure and death. These study findings

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are important for a few reasons. Importantly, the study provides further validation of ECG-age as a variable construct of biological significance given that the investigators used a separately developed ECG-age model and applied it de novo to a completely new cohort. Thus, the investigation extends from prior studies' development of their own ECG-age variable, a process that can introduce some cohort or region specific bias. Further, given the location and nature of prior studies of ECG-age, the current investigation adds to the totality of evidence indicating that ECG-age is measure that is not only feasible in multiple settings but carries prognostic significance across racial and ethnic groups, geographic regions, and diverse patient as well as community-based populations.

Notwithstanding these compelling findings, there is still more work to be done. ECG-age may well represent a globally accessible measure offering previously unrecognized prognostic information relevant to diverse settings. As with many deep learning developed tools, its utility will be augmented by its interpretability and, specifically, an improved understanding of the factors driving its predictive capacity. The next phase of discovery can now focus on what further knowledge can be gleaned from the recently completed and now repeatedly successful studies linking ECG-age to various outcomes. For instance, given the ability of the ECG-age to predict atrial fibrillation, it remains to be determined how much of the predictive signal relates to previously reported PR or QRS interval prolongation and underlying conduction disease.[7,8] The ability of ECG-age to predict myocardial infarction could be related to aggregate subtle alterations that tend towards but do not meet classic ECG criteria for ischemia or infarct while still representing unrecognized preexisting or subclinical coronary disease—which could be targeted for preventive therapies.[9] Similarly, the association of ECG-age with incident HF could be related to relative voltage alterations on the ECG that reflect change in cardiac chamber size, morphology, or filling pressures—all of which could also be targeted and potentially responsive to therapies.[10] Furthermore, the now well-validated signal for all-cause mortality may be driven by cardiovascular death but there could yet be noncardiovascular contributors that would be important to identify.[11,12] If we recall the often cited benchmarks for appraisal of new biomarkers,[13] we can consider that the ECG-age measure has high potential for meeting all 3 criteria: (1) can the clinician measure the biomarker? (2) does the biomarker add new information? (3) will the biomarker help the clinician to manage patients? For the final criterion, it is worth noting that for the ECG-age measure to either serve as a therapeutic target or facilitate patient engagement around disease risk modification—as with the coronary artery calcification-age score—further work is needed to refine and possibly redefine models that are outcome specific, as well as determine how such models may be implemented into clinical practice. Although recognizing the need for more work in the field, the current study serves to broaden our appreciation for the value of deep learning algorithms to discern new or additional information from readily available data sources. For the ECG, in particular, the emerging evidence of its ability to convey information relevant to biological aging is reassuring to thoughtful clinicians who have long understood that presumed normal variations or nonspecific findings on ECG tracings tend to increase in prevalence with aging and likely represent underlying subclinical disease processes even while not meeting existing specific criteria for any single discrete diagnosis. Now, deep learning algorithms can systematically and efficiently discern and quantify such alterations on an ECG in ways that are not easily measured and tallied by even the most diligent human calipers. Nonetheless, as these sophisticated algorithms continue to advance, ongoing clinician engagement in their development will be needed to ensure that applications in practice will be best positioned and incorporated into clinical workflows and efforts to improve outcomes for all.

ARTICLE INFORMATION

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