Greetings, I am Dr Karl Nath, the Editor-in-Chief of *Mayo Clinic Proceedings*, and I am pleased to welcome you to the multimedia summary for the journal’s July 2018 issue. There are 4 articles this month that have been selected as our Editor’s Choice or Highlights articles.

Our Editor's Choice is an Original Article that utilized voice signal analysis, an emerging noninvasive diagnostic tool, to determine whether patient voice signal characteristics are associated with the presence of coronary artery disease. It is authored by Dr Elad Maor and colleagues from Mayo Clinic in Rochester, Minnesota.

The study population included 166 patients who were enrolled between January 2015 and February 2017, and which included 129 patients who underwent coronary angiography. Patients who underwent coronary angiography were referred to the chest pain clinic and were not known to have preexisting coronary artery disease. Control groups were included to improve overall quality of voice features normalization, and to exclude the possibility of bias associated with preprocedural anxiety; these control groups included subjects undergoing no procedures and those who underwent noncardiac procedures.

Each subject spoke aloud a predetermined amount of text into a recording device with no prior coaching. A total of three 30-second separate baseline voice recordings were analyzed for each participant: first, a prespecified text; second, a description of a positive emotional experience; and, third, a description of a negative emotional experience. Voices were analyzed for multiple features of voice intensity and frequency using the “Beyond Verbal Communications” clinical trial application, which was downloaded to the patients’ smartphone. The voice analysis was done in a semiautomated fashion, and all voice files were examined by a voice analytics expert. A defined set of acoustic features was extracted from each voice file.

The primary end point was coronary artery disease, with the study population divided into those with or without coronary artery disease. A univariate model was applied separately for all 81 voice features of the 3 baseline recordings. The analysis revealed 5 voice features that were associated with coronary artery disease in at least 1 of the 3 baseline recordings. There were no differences between healthy subjects and patients with coronary artery disease as regards the remaining 76 features. The strongest association between voice and coronary artery disease was observed when patients were requested to record their voice while describing an emotional experience; this association was independent of age, sex, and other cardiovascular risk factors.
This study is the first to describe an association between voice characteristics and coronary artery disease. The authors conclude that this holds the potential to assist physicians in estimating the pretest probability of coronary artery disease among patients presenting with chest pain, especially in the setting of telemedicine, the latter providing clinical health care at a distance.

The article is accompanied by an Editorial by Dr Sugrue and colleagues from Mayo Clinic in Rochester, Minnesota. These authors begin their editorial by envisioning a virtual house-call scenario using the emerging technologies of telemedicine and artificial intelligence to diagnose patients from a distance. They emphasize that telemedicine is thriving because it enables health care delivery to relatively inaccessible and under-resourced areas; and it provides health care with less day-to-day interruption for patients. Additionally, the potential of these technologies is just being realized; for example, in those vulnerable populations, such as babies or the elderly, where voice analysis and other detection systems may monitor their current condition at a distance. Sugrue et al underscore that voice analysis could be easily integrated into current technological platforms such as a smartphone, thereby enabling its transmission to processing areas; and, along with the emerging tools of telemedicine and artificial intelligence, voice analysis may offer remarkable and expanding opportunities for diagnosing cardiac and other human diseases.

Our first Highlight is an Original Article that examined whether persistent bilateral global nephrograms are associated with acute kidney injury (AKI), dialysis, and mortality. It is authored by Dr Jennifer McDonald and colleagues from Mayo Clinic in Rochester, Minnesota, and Jacksonville, Florida, and the University of South Carolina, in Charleston.

Prior studies report a correlation between persistent global nephrograms and the development of acute kidney injury. However, the poor correlation of changes in serum creatinine levels as a biomarker for acute kidney injury may cloud the potential relationship between nephrograms and renal injury. Moreover, prior studies examined very small numbers of patients and none addressed whether there is an association between nephrograms and other outcomes besides AKI.

The authors identified all patients who received: First, a contrast-enhanced computed tomography (CT) exam or cardiac catheterization with iohexol between January 2000 and December 2014 and; Second, a noncontrast abdominal CT exam in the subsequent 24 hours. Nephrograms were identified by radiologist review and CT attenuation measurements. Univariate and multivariate analyses were performed to determine nephrogram risk factors. AKI (defined by an increase in serum creatinine of
0.5 mg/dL or greater), or AKI (Stages 1 through 3), dialysis, and mortality proportions were compared between patients with and without bilateral global nephrograms. A total of 123 patients met all inclusion criteria. The proportion of patients with a nephrogram was 37%, with a higher proportion following interventional versus diagnostic catheterization or contrast enhanced CT. Age, chronic kidney disease, and acute hypotension or shock were significant risk factors for nephrogram development. Nephrogram patients had significantly and markedly higher rates of AKI, dialysis, and mortality compared to non-nephrogram patients. The presence of persistent bilateral global nephrograms thus associates with an increased risk of AKI, dialysis, and mortality when compared to patients whose kidneys fully eliminated the contrast material. These findings indicate that the presence of a persistent bilateral global nephrogram may be a good marker of renal injury after exposure to intravenous contrast material.

The second Highlight is an Original Article which examined the relationship between estimated cardiorespiratory fitness using nonexercise equations and all-cancer mortality in a representative sample of the US population. It is authored by MsDr Ying Wang, from the University of South Carolina, Columbia, and colleagues from national and international institutions.

Cardiorespiratory fitness is an indicator of general health. Epidemiologic studies have found that cardiorespiratory fitness is inversely correlated with all-cancer and cancer-specific mortality. There are limitations, however, in such studies: the first involves the generalizability of these findings to other patient populations; the second stems from the fact that cardiorespiratory fitness is mainly quantified in these studies as metabolic equivalents, the latter requiring exercise by treadmill or cycle ergometer. To avoid the need for exercise testing, these investigators used nonexercise models.

A total of 8506 study participants were derived from the Third National Health and Nutrition Examination Survey, conducted from October 1988 to October 1994. These participants were followed for all-cancer mortality. Cardiorespiratory fitness was estimated from nonexercise models based on age, BMI, waist circumference, heart rate, physical activity, and smoking status; estimated cardiorespiratory fitness was further grouped into quintiles. Hazard ratios were calculated from Cox proportional hazards models for the relationship between cardiorespiratory fitness and all-cancer mortality. During approximately 20 years of follow-up, 455 cancer deaths were registered. After adjustment for race/ethnicity, age, educational level, current smoking, hypertension, diabetes mellitus, and hypercholesterolemia, each 1-metabolic equivalent increase in cardiorespiratory fitness was associated with 30% and 27% risk reduction for all-cancer mortality in men and women, respectively. When estimated
cardiorespiratory fitness was categorized into quintiles, hazard ratios were reduced across incremental quintiles in women. The estimated cardiorespiratory ratio was inversely associated with all-cancer mortality in quintiles 2 and 4 in women. However, none of the hazard ratios reached statistical significance in men.

Thus, at least for women, cardiorespiratory fitness associates with less all-cancer mortality. As concluded by the authors, more research is needed to evaluate the association between cardiorespiratory fitness estimated from nonexercise equations and all-cancer mortality in men, as well as the dose-response relationship between estimated cardiorespiratory fitness and cancer mortality.

The third Highlight is a Review article which describes short telomere syndromes caused by inheritable gene mutations resulting in decreased telomere lengths and accelerated aging syndromes. In this syndrome, organ systems with increased cell turnover, such as the skin, bone marrow, lungs, and gastrointestinal tract, are commonly affected. It is authored by Drs Mangaonkar and Patnaik, from Mayo Clinic in Rochester, Minnesota.

Telomeres are hexanucleotide tandem repeats at the ends of chromosomes that protect them from degradation during aging. Telomere losses occur over time and contribute to the process of aging. Telomere attrition occurs at an estimated rate of 50 to 150 base pairs per cell division. Once telomeres become critically short, the ends of chromosomes are exposed as double-stranded DNA breaks, resulting in the DNA damage response, p53 activation, senescence, and apoptosis. This forms the basis for telomere lengths representing the molecular clock in human beings.

Shortened telomeres are commonly associated with bone marrow failure syndromes, including aplastic anemia. Among these, the classical telomere disorder that presents in early childhood is dyskeratosis congenita. Associated features may include pulmonary fibrosis, emphysema, liver cirrhosis, lacrimal ductal, esophageal, and urethral stenosis, premature graying of hair, avascular necrosis, periodontal disease, and a risk for epithelial and hematologic malignancies.

Telomere length can be measured by several methods. Flow cytometry-fluorescence in situ hybridization provides the initial screening test. Mutational analysis for genes that cause the syndrome can then be performed using next-generation sequencing assays. Several mutant genes have been identified affecting the telomere protein complex or telomerase, resulting in a dyskeratosis congenita phenotype. These genes include *DKC1, TERT, TERC*, among others. In 40% of cases with this syndrome, gene mutations cannot be identified.
Treatment requires a multidisciplinary approach. Organ transplant remains the mainstay for treatment of organ failure associated with short telomere syndromes, for example, allogeneic hematopoietic stem cell transplant for bone marrow failure syndromes, and lung and liver transplant for respective organ failure. Androgens are used with success in patients with aplastic anemia with reported hematologic response rates of approximately 50%. A recent clinical trial reported that in patients with short telomere syndromes, danazol administered for 12 months reduced telomere length attrition and stabilized pulmonary function.

Mayo Clinic has established an Inherited Bone Marrow Failure Precision Genomics Clinic to aid with the diagnosis and management of inherited bone marrow failure syndromes, including short telomere syndromes. Short telomere syndromes are suspected when patients present with, or have a strong family history of, premature graying of hair, idiopathic pulmonary fibrosis, premature emphysema or idiopathic interstitial pneumonia, unexplained cytopenias or bone marrow failure, nodular regenerative hyperplasia or cryptogenic cirrhosis of the liver, along with other stigmata of short telomere syndromes. Patients with telomere lengths greater than the 10th percentile are unlikely to have a short telomere syndrome, and those with telomere lengths in the 1st to 10th percentile range may have a short telomere syndrome.

Advances in understanding telomere biology and the use of gene therapy to augment impaired telomere functioning are exciting future prospects.

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