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Innovations

Taking Stock of Telomere Length at Telome Health

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Over the decades, scientists have discovered several biomarkers suggestive of disease risk; examples include lipid profiles or the presence of certain proteins. Telome Health, a new company based in Menlo Park, CA, is looking to market another biomarker measurement based on the science of telomeres.

Telomeres are long stretches of repetitive DNA sequences found at the end of chromosomes. Over the past several years, epidemiological studies have shown that telomeres shorten over time; this finding by itself is akin to the fact that hair grays as people age. Most compelling is that these studies also suggest that although telomere shortening is not diagnostic of a specific disease, individuals with shorter telomeres are more likely to experience loss of health, disease progression or more rapid disease progression, or mortality. "Many of these studies show that for individuals who are in the twenty-fifth or even the lower fiftieth percentile for telomere length are at a higher risk for disease, a future clinical event, or death, compared to people in the upper half or upper quartile of telomere length measurements," explains Calvin B. Harley, pioneering telomere researcher and now chief scientific officer at Telome Health. The team at Telome Health is building on these and other research findings to offer a telomere length measurement product.

Telomeres shorten each time chromosomes replicate as part of cell division, and therefore they naturally shorten over a lifetime. Large cross-sectional studies show an average decline in telomere length in populations of individuals from newborns to centenarians. "But when you look at the individual data there is a lot of scatter," says Harley. "That variation between the norm and the individual helps account for or predict the difference in disease risk between individuals."

Nobel Prize Foundational Medicine

In the 1980s, Elizabeth Blackburn of the University of California, San Francisco (UCSF), copresented findings showing that the repetitive telomere sequences protect the ends of chromosomes from degradation. In 2009, she was corecipient of the Nobel Prize in Physiology and Medicine for her contributions to this science. Teaming with Calvin Harley and two other UCSF researchers, Drs. Elissa Epel and Jue Lin, Dr. Blackburn cofounded Telome Health to pursue commercial applications of this work.

"At some point, we expect that telomere length will be incorporated into cardiovascular risk scores or cancer risk scores." — Daniel Hunt, Telome Health

Telomerase is the enzyme that adds telomeric DNA onto chromosome ends. Some people who have extremely short telomeres may have a disease condition caused by a mutation in telomerase or one of the telomere-associated proteins, which are critical for telomere maintenance. Individuals with a telomerase mutation, however, are a rare population, and this abnormality does not explain all of the individuals with shortened telomere lengths as compared to the cohort norms established thus far.

Some individuals with short telomeres may have inherited short telomeres, but Drs. Blackburn, Epel, and Lin's work at UCSF has at least partially offered another explanation: stress. In 2004, the team published a paper in the *Proceedings of the National Academy of Sciences* which indicated that women experiencing the chronic stress of providing care for disabled children and those with long-term illness have higher oxidative stress, shorter telomeres, and lower telomerase activity (Epel et al., 2004). Again, genetics alone did not explain the findings, and the study pointed to stress as a verifiable factor contributing to telomere shortening. In subsequent papers, Blackburn and Epel confirmed similar findings in dementia caregivers (Epel et al., 2010).

Adding to the knowledge of the biological mechanisms underlying telomere shortening, Epel and Blackburn and colleagues recently published a paper linking high levels of the proinflammatory molecules IL-6 and TNFα with short telomeres (O'Donovan et al., 2011).

Establishing the Norms

Just as lipid tests provide an absolute number that must be compared with established reference ranges to provide meaningful results, telomere length measurement in isolation does not provide enough information. Well-researched, large norms populations first need to be rigorously created. "We are in the process of defining the attributes to create the best norms database for telomere length in a US population," says Daniel Hunt, CEO of Telome Health. Other epidemiological surveys have been done, with fairly consistent findings.

Just this month, Dr. Blackburn's laboratory completed the largest telomere measurement epidemiological study ever conducted. The study was sponsored by the National Institutes of Health and was participated in by over 100,000 patients enrolled in the California-based Kaiser Permanente healthcare system. The average age of study participants was 65 years old.

Telome Health aims to develop a norms database of telomere length consisting of a normal, healthy population, purposely excluding as much as possible those with disease, on multiple medications, or otherwise in poor health. "We want to establish norms that focus on a healthy disease-free population, especially in the 30-80 year old age groups," says Hunt, who adds that the most meaningful information will come when a measurement is

compared with a normal, healthy population, not just the average population.

Autumn 2011 Commercial Entry

Currently, Telome Health offers a telomere measurement test for research purposes. They receive samples from companies interested in knowing whether their product (such as dietary supplements) helps maintain or increase telomere length. Others are hoping to prove that lifestyle changes, stress reduction, or a specific exercise program will be causally linked to increased telomere length and are using the test for their own corporate research purposes.

Telome Health hopes to achieve CLIA certification by October or November 2011 to market the assay to physicians. "A growing number of individuals…are very health-conscience and [are] taking charge of their own health monitoring using new technologies, like the personal genome test," says Harley. The company will not claim that the assay will be diagnostic of current or pending disease; however, it will provide an absolute measurement of telomere length and a percentile based on the Telome Health norms. Results will be provided to the physician, not direct to the consumer, and the results will not be part of a medical diagnosis or interpretation. To educate physicians who are ordering the assay about telomere biology, Telome Health further plans to have an active physician education campaign and materials available for physicians and customers.

Telome Health is also in discussion with pharmaceutical companies to design studies that would validate the use of telomere length as a potential diagnostic and as a product that may be used in drug development to stratify patients, to validate certain theories about disease, or to determine whether specific drugs' effects (positive or negative) are related to an individual patient's telomere biology.

The company obtained a worldwide exclusive license to the University of Utah's quantitative PCR (qPCR) measurement as the basis for its product. "We did that because it is the dominant and most scalable test available," explains Harley, "and the vast majority of the large epidemiological studies that established the clinical relationships between telomere length and health have used qPCR, which is a robust platform in itself."

Looking Forward

Telomere length can shorten dramatically, but it can get longer as well. What has not been established yet is a direct causal relationship between longer telomere length and people who exercise, eat a good diet, and have low stress and whether an unhealthy lifestyle drives telomere shortening. To determine this, large interventional studies need to be done to establish causation.

"In a fair number of the studies done, telomere length tells us something different [from] conventional biomarkers," says Harley. "The studies show that short telomeres are an independent risk factor and in some cases are more predictive than conventional markers." He cites two large cardiovascular disease (CVD) studies that included measurements of lipids, C-reactive protein, blood pressure, glucose, body mass index, and other markers for CVD risk (Brouilette et al., 2007; Bekaert et al., 2007).

In a 2010 article in the *Journal of the American Medical Association*, UCSF researchers and colleagues showed that individuals with CVD who take omega-3 fish oils had longer telomeres than those with CVD who did not take the supplement (Farzaneh-Far et al., 2010). This data may indicate, in part, a mechanism that explains why individuals with heart disease who have increased dietary intake of fish oils demonstrate longer survival.

Taken together, these results do not yet mean telomere length will replace established markers, but Telome Health hopes that it becomes one of several validated biomarkers used in combination with others. "There are upwards of 160 million cholesterol tests done each year in the United States," says Harley. "At some point, we expect that telomere length will be incorporated into risk scores for cardiovascular disease, cancer, and other conditions."

"But we first need to do the interventional studies in the cardiovascular disease space stratifying patients based on their telomere length," explains Hunt of the company's interest in developing a test that could be used as a diagnostic. "This information might be used to assess inclusion in clinical trials or whether those patients are eligible for a certain type of intervention that otherwise might not be cost-effective." It might inform interventional strategies for physicians either in combination with drug regimens or even without them.

Telome Health is not alone in its pursuit of a commercial telomere measurement test. Several other companies are providing telomere length testing: Repeat Diagnostics of Vancouver, Canada; SpectraCell Laboratories based in Texas; and the Spanish company Life Length. At least one company, T.A. Sciences, offers a telomerase activating dietary supplement licensed from Geron Corporation to aid in telomere maintenance.

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