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Telomeres in the Clinic, Not on TV

See also pages 834 and 904

Recent discoveries have extended the reach of telomere biology from the basic sciences into the heart of clinical medicine.[1] Telomeres were discovered in a pond protozoan; their basic biology has been dissected in model systems like maize, yeast, and mice.[2] In cultured human cells, telomere length predicts the onset of the Hayflick limit, the finite replicative potential of cells before they senesce, and the exogeneous expression of the telomerase catalytic component, *TERT*, can bypass senescence.[3,4] These early discoveries have led to a hypothesized role for telomeres in processes related to aging and cancer, but the exact clinical contexts in which telomere biology matters for patient care have not until recently been elucidated.

The strongest evidence supporting that telomeres play a causal role in human disease comes from observations that mutations in genes that encode telomerase components and other telomere maintenance genes cause disease. Because these diseases have systemic features that matter for clinical management, we have referred to them as the telomere syndromes.[1] Mutations in 13 telomerase and telomere maintenance genes cause the *short* telomere syndrome phenotype; the most common of these are mutations in *TERT*.[1] Gain-of-function *TERT* mutation, in contrast, up-regulates telomerase expression and manifests as familial melanoma,[5] likely related to excessively long telomere length. The latter has been hypothesized to be a manifestation of *long* telomere syndromes.[1]

Lessons from recent work highlight that short telomeres, at clinically relevant thresholds, cause recognizable disease patterns and not generic forms of premature aging.[6] In children and young adults, a severe form of short telomere syndromes manifests as bone marrow failure, immunodeficiency, and abnormalities in the skin and gastrointestinal tract.[1,6] This form primarily affects high turnover tissues. Adult-onset disease is estimated to account for more than 90% of short telomere syndrome presentations and represents an attenuated form of the short telomere syndrome phenotype. Its common presentation is lung disease, predominantly as idiopathic pulmonary fibrosis (IPF) and related interstitial diseases as well as emphysema.[7-9] Pulmonary fibrosis shows autosomal dominant inheritance, and approximately one-third of patients with familial clustering carry mutations in telomerase and telomere-maintenance genes.[1,10] In sporadic forms of IPF, approximately half the patients have short telomeres, often in the range of patients with germline mutations in telomerase.[11] Telomere genetics thus explain a sizeable subset of susceptibility of familial and sporadic IPF.

Beyond understanding the basis of genetic susceptibility, recognizing patients with short telomere—related disease is now established to be critical for patient care decisions. Affected patients are prone to increased toxicities from otherwise routine therapies, especially immunosuppression. Mutant telomerase and telomere genes are the most common cause of inherited bone marrow failure, and recognizing these patients in the hematopoietic stem cell transplant evaluation alters decisions about donor and ablative regimens.[6] Similarly, there is growing evidence that identifying patients with telomere-mediated lung disease could aid in the management of lung transplant, both for anticipating and averting complications.[12] These examples, and others, support the measurement of telomere length, using clinically validated methods, as a precision medicine tool.[6] The retrospective

experience presented by Mangaonkar et al[13] and a review from the same group[14] published in this issue of the *Proceedings* represent Mayo Clinic's efforts to ensure meeting the clinical demands in this new area of medicine. The case series presented reflects the opportunities and challenges of integrating molecular testing and of identifying patients who have such heterogeneous clinical presentations of the same molecular pathology.

Several challenges still remain in the full implementation of telomere molecular medicine and efforts such as the one described by Mangaonkar et al.[13] One is that the care of patients with short telomere syndromes requires input from clinical disciplines that have not traditionally worked together. At our center, patients with short telomere IPF often require evaluation by clinicians from medical genetics, hematology, pulmonary medicine and hepatology. Integrating these opinions into consensus requires appreciation for a unique and only recently defined natural history (example in[15]). There is also the gap between the primary literature in rapidly evolving areas and existing clinical guidelines. Clinicians may therefore find themselves with data that are critical for patient care but that have not yet been acknowledged or incorporated into consensus statements. Importantly, as patients are identified earlier in their course with growing awareness and access to testing, there is a risk of excessive procedures that could cause harm. There are currently no known therapies that lengthen telomeres, and the mainstay of treatment remains supportive and in the case of organ failure, stem cell or organ transplant where feasible. Careful observation without causing harm thus becomes critical for this group of patients who often have a protracted course. The full impact of telomere medicine to patient care settings will require new ways of educating, evaluating, and treating patients who have disease phenotypes we have long seen now that we appreciate their molecular etiology.

While the importance of telomere biology in clinical settings has grown, in parallel there has been a recent direct-to-consumer campaign advertising telomere length measurement and "telomere products" to the public. These products present an oversimplified view of telomere length health: "short telomeres are bad" equitable with aging, while "long telomeres are good" and signify youthfulness. This premise presents several problems that warrant caution for clinicians and the public alike. The first is that the assays used to measure telomere length in direct-to-consumer testing have been extensively documented to be highly variable and have problems with reproducibility and robustness.[16] The second is a problem of interpretation. Many direct-to-consumer tests consider only the median value as normal, and any shorter value is interpreted as "aged" and longer as "youth." Telomere length shows a wide and definable distribution in the human population with upper and lower boundaries.[6] This flawed interpretation is analogous to the absurdity of reporting any value that is below the median for a white blood cell count, for example, as abnormal. The direct-to-consumer telomere testing thus risks causing unnecessary anxiety, with some believing they are "biologically aged" and further leading them to pursue untested products. Adding to the argument against the use and interpretation of telomere length data in nonclinical settings is the large and growing body of evidence linking long telomere length not to youthfulness but to a measurable risk of several cancers, including melanoma, glioma, and others.[17] The thresholds for both short and long telomeres that present a risk of disease in healthy individuals are unknown because longitudinal studies have not been done. For these reasons, caution is warranted against telomere length testing in commercial settings. Telomere length is predominantly genetically determined, and there is biological rationale to believe that only extremes of shortening are sufficient to provoke cellular phenotypes and thus a risk for disease.

In summary, recognizing the clinical indications in which telomere length testing matters for patient care decisions exemplifies molecular medicine at its best. Distinguishing these indications from commercial testing is critical. While the former may be lifesaving, the latter may be considered a form of molecular palm reading.

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