

Testing time for telomeres

Telomere length can tell us something about disease susceptibility and ageing, but are commercial tests ready for prime time?

Howard Wolinsky

After 30 years of research, the analysis of telomere length is emerging as a commercial biomarker for ageing and disease, as well as a tool in the search for new medications. Several companies offer tests for telomere length, and more are due to launch their products shortly. Even so, and despite the commercial enthusiasm, interpreting precisely what an individual's telomeres mean for their health and longevity remains challenging. As a result, there is some division within the research community between those who are pushing ahead with ventures to offer tests to the public, and those who feel that telomere testing is not yet ready for prime time.

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Peter Lansdorp, a scientist at the British Columbia Cancer Agency and a professor at the University of British Columbia (Vancouver, Canada), founded his company, Repeat Diagnostics, in response to the number of questions and requests he received from physicians for tests for telomere length. The company became the first to offer commercial telomere testing in 2005 and now mainly serves medical researchers, although it makes its test available to the public through their physicians for C \$400. Nevertheless, Lansdorp thinks that testing is of limited use for the public. “Testing [...] outside the context of research studies is in my view premature. Unfortunately I think some scientists are exploiting it,” he said. “At this point, I would discourage people from getting their telomeres tested unless there are symptoms in the family that may point to a telomere problem, or a disease related to a telomere problem. I don't see why on Earth you would want to do that for normal individuals.”

Others are more convinced of the general utility of telomere tests, when used in combination with other diagnostic tools. Elizabeth Blackburn, Professor of Biology and Physiology at the University of California (San Francisco, USA), was a co-recipient of the Nobel Prize for Physiology or Medicine in 2009 for her part in the discovery of telomerase, the enzyme that replenishes telomeres (Sidebar A). She stressed that the point of telomere testing is to obtain an overall picture “using a marker that integrates many inputs, and produces a robust statistical association with [...] disease risks. It is not a specific diagnostic.” Telome Health, Inc. (Menlo Park, California, USA)—the company that Blackburn helped found and that she now advises in a scientific capacity—plans to begin selling its own US \$200 telomere test later this year. “The science has been emerging at a rapid pace recently [...] for those who are familiar with the wealth of the evidence and the accumulated data, the overwhelming pattern is that there are clear associations with telomere maintenance, including longitudinal patterns, and health measures that have had well-tested clinical relevance,” she explained.

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María Blasco, Director of the Centro Nacional de Investigaciones Oncológicas (CNIO; Spanish National Cancer Research Centre; Madrid, Spain), is similarly optimistic about the prospect of telomere testing becoming a routine health test. “As an analogy, telomere length testing could be similar to what has occurred with cholesterol tests, which went in [the] early 80s from being an expensive test for which

no direct drug treatment was available to being a routine test in general health check-ups,” she said.

Carol Greider, Professor and Director of Molecular Biology and Genetics at Johns Hopkins University (Baltimore, Maryland, USA) and co-recipient of the 2009 Nobel Prize with Blackburn, however, does not believe that testing is ready for widespread use, although she agreed that telomere length can reveal a lot about disease and is an important subject for research. “Certainly, right now, I think it's very premature to be offering this kind of testing to the public. I don't think that the research has yet told us about the risks, what we can actually say statistically with high confidence, so it's unclear to me if there is any real value to the general public to testing telomeres,” she said.

...two things will drive demand for telomere testing: the growing number of clinical studies [...] and [...] interest in lifestyle changes and interventions that help maintain telomeres

Blasco is Chief Scientific Advisor to Life Length, a CNIO spin-off company that launched its test last year to a storm of media attention. “For some scientists, there is always a question that needs to be solved or has not been sufficiently evaluated,” she said. “We have lots of information showing that telomere length is important for understanding ageing and certain diseases [...] New technologies have been developed that allow us now to measure telomere length in a large scale using a simple blood sample or a spit sample. The fact that the technology is here and the science is here makes this a good moment to market this testing.”

Apart from discussion of the science, companies that offer telomere testing are also encountering scepticism from ethicists and other scientists about the value of telomere-length testing for normal healthy people.

Lansdorp, who is a medical doctor by training, thinks that practitioners are not yet ready to use and interpret the tests. “It's a new field and there are good clinical papers out there, but the irony is that our work [that] has highlighted the value of these tests for specific clinical conditions [is] now being

Sidebar A | Telomeres and telomerase

Telomeres are regions of repetitive DNA sequence that prevent the DNA replication process or damage from degrading the ends of chromosomes, essentially acting as buffers and protecting the genes closest to the chromosome ends. Russian biologist Alexei Olovnikov first hypothesized in the early 1970s that chromosomes could not completely replicate their ends, and that such losses could ultimately lead to the end of cell division (Olovnikov, 1973). Some years later, Elizabeth Blackburn, then a postdoctoral fellow in Joseph Gall's lab at Yale University (New Haven, Connecticut, USA), and her colleagues published work suggesting that telomere shortening was linked with ageing at the cellular level, affected lifespan and could lead to cancer (Blackburn & Gall, 1978; Szostak & Blackburn, 1982). In 1984, Carol Greider, working as a postdoc in Blackburn's lab at the University of California (Berkeley, USA), discovered telomerase, the enzyme that replenishes telomeres. Blackburn and Greider, together with Jack Szostak, were awarded the 2009 Nobel Prize in Physiology or Medicine for "the discovery of how chromosomes are protected by telomeres and the enzyme telomerase" (http://nobelprize.org/nobel_prizes/medicine/laureates/2009/).

used [...] to make the point that it's really important to have your telomeres tested, but the dots are not connected by a straight line," he said.

Jonathan Stein, Director of Science and Research at SpectraCell Laboratories (Houston, Texas, USA)—which offers its US \$250 telomere test as an extension of its nutritional product line that is sold to family physicians, chiropractors and naturopaths—said that there has only really been demand for the telomere test from his company among physicians and their spouses, but not for use in the clinic. "Doctors are incredibly curious about [the test] and then when we do follow-ups in general, they tell us it's interesting and they know it's valuable, but they're not entirely sure what it means to people. Where we go from the bench to bedside, there seems to be a real sticking point," he said, adding that he thinks demand will increase as the public becomes increasingly educated about telomeres and health.

Arthur Caplan, Professor of Bioethics and Director of the Center for Bioethics at the University of Pennsylvania (Philadelphia, USA), is not clear that even an educated public will be interested in what the test can tell them. "We don't have any great reason to

think that people will be interested in knowing facts about themselves [...] if they can't do anything about it. I think most people would say 'I'm not going to spend money on this until you tell me if there's something I can do to slow this process or expand my life.'" As such, he thinks that companies that are getting in early to 'cash in' on the novelty of telomere testing are unlikely to see huge success, partly because the science is not yet settled.

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Calvin Harley, President and Chief Science Officer at Telome Health, disagrees. He thinks that two things will drive demand for telomere testing: the growing number of clinical studies validating the utility of the test, and the growing interest in lifestyle changes and interventions that help to maintain telomeres.

But these are early days. Jerry Shay, Professor of Cell Biology and Neuroscience at the University of Texas Southwestern Medical Center (Dallas, USA) and an adviser to the company Life Length, said that early adopters are likely to be the health conscious and the curious. "Some people will say, 'Well, look, I had my telomeres measured: I'm a 60 year old with 50-year-old telomeres'," he explained. "It will have 'My telomeres are longer than your telomeres' type of cocktail talk appeal. That's fine. I have no problem with that as long as we can follow this sort of population and individuals over decades."

Shay's last point is the key—research and data collection. Even those commercializing telomere-length tests agree that our understanding of telomere biology, although extensive, is incomplete and that we have yet to unpick fully the links between telomeres and disease. Stefan Kiechl, a telomere researcher in the Department of Neurology at Innsbruck Medical University (Austria), published an article last year on telomere length and cancer (Willeit *et al.*, 2010). "The appealing thing with telomere length measurements

is that they allow the estimation of the biological—in contrast to the chronological—age of an organism. This was previously not possible. Moreover, long telomere length has been linked with a low risk of advanced atherosclerosis, cardiovascular disease and cancer, and, vice versa, short telomere length is associated with a higher risk of these diseases."

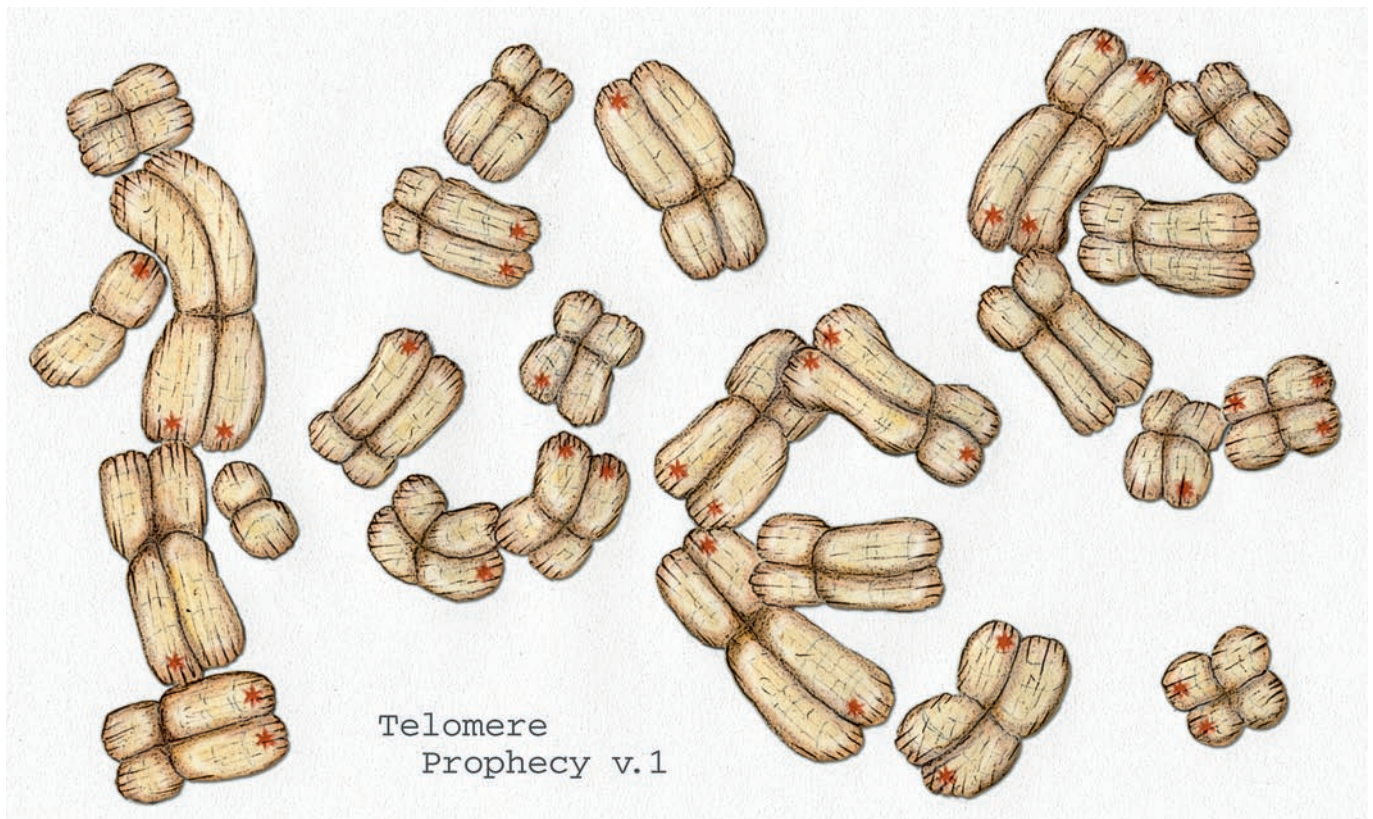
But, he said that problems remain to be resolved, such as whether telomere length can only be measured in cells that are readily available, such as leukocytes, and whether telomere length in leukocytes varies substantially from telomere length in other tissues and cells. "Moreover, there is still insufficient knowledge on which lifestyle behaviours and other factors affect telomere length," he concluded.

This might be a bumpy road. When Life Length announced its launch in May, newspapers carried headlines such as 'The £400 test that tells you how long you'll live', reporting: "A blood test that can show how fast someone is ageing—and offers the tantalizing possibility of estimating how long they have left to live—is to go on sale to the general public in Britain later this year" (Connor, 2011).

The story was catchy, but Life Length officials are determined to explain that, despite the name of the company, its tests do not predict longevity for individuals. Blasco said that the word 'life' in the name is meant as an analogy between telomeres and life. "A British newspaper chose to use this headline, but the company name has no intention to predict longevity," she said. Instead, the name refers to extensive research correlating the shortened chromosome tips with the risk for certain diseases and personal habits, such as smoking, obesity, lack of exercise and stress, Blasco explained.

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Life Length's test measures the abundance of short telomeres, as they claim that there is genetic evidence that short telomeres are the ones that are relevant to disease. "The preliminary results are exciting: we are observing that the percent of short telomeres with increasing age is more



divergent between individuals than average telomere length for the same group of individuals," Blasco explained. "This is exactly what you would expect from a parameter [abundance of short telomeres] that reflects the effects of environmental factors and lifestyle on people's telomeres." She noted that being in a lower quartile of average telomere length and the higher quartile of abundance of short telomeres would indicate that telomeres are shorter than normal for a given age, which has been correlated with a higher risk of developing certain diseases.

So, what can be done about an abundance of short telomeres? Lansdorp said that, as a physician, he would be hard pressed to know what to tell patients to do about it. "The best measure of someone's age and life expectancy is the date on their birth certificate. Telomere length, as a biomarker, shows a clear correlation with age at the population level. For an individual the value of telomere length is very limited," he said. "I suspect there's going to be a lot of false alarms based on biological variation as well as measurement errors using these less accurate tests."

Harley, however, said that if telomere length were perfectly correlated with age, it would be a useless biomarker, except for in forensic work. "The differences in telomere length between individuals at any given age is where the utility lies [...] people with shorter telomeres are at higher risk for morbidity and mortality. In addition, there is emerging data suggesting that people with shorter telomeres respond differently to certain drugs than people with longer telomeres. This fits into the paradigm of personalized medicine," he said.

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While he was at Geron Corporation, Harley was the lead discoverer of telomerase activators purified from the root of *Astragalus membranaceus*. Harley, Blasco and colleagues have published two peer-reviewed papers on one of those molecules, TA-65—one in humans and the other in mice (de Jesus *et al*, 2011; Harley *et al*, 2011). Both showed positive effects on certain health

measures, and Blasco's lab found that mice treated with TA-65 had improved health status compared with those given a placebo. "However, we did not see significant effects on longevity," Blasco said.

In the meantime, researchers are squabbling about the techniques used by the testing companies. Greider maintains that Flow-FISH (fluorescence *in situ* hybridization), which was developed by Lansdorp, is the gold standard used by clinical researchers and that it is the most reliable technique. Harley argues that the quantitative real-time (qRT)-PCR assay developed by the Blackburn lab is just as reliable, and easier to scale-up for commercial use. Blasco pointed out that, similarly to its rivals, the qFISH used by Life Length offers measurements of average telomere length, but that it is the only company to report the percentage of short telomeres in individual cells. In the end, Lansdorp suggested that the errors inherent in the tests, along with biological variations and cost, should give healthy people pause for thought about being tested.

Ultimately, whichever test for telomere length is used and whatever the results

can tell us about longevity and health, it is unlikely that manipulating telomere length will unlock the fountain of youth, à la Spanish explorer Juan Ponce de León y Figueroa (1474–1521). Nevertheless, telomere testing could become a key diagnostic tool for getting a few more years out of life, and it could motivate people to follow healthier lifestyles. As Kiechl pointed out, “[t]here is convincing evidence that calculation of an individual’s risk of cardiovascular disease [...] substantially enhances compliance for taking medicines and the willingness to change lifestyle. Knowing one’s biological age may well have similar favourable effects.”

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

REFERENCES

- Blackburn EH, Gall JG (1978) A tandemly repeated sequence at the termini of the extrachromosomal ribosomal RNA genes in *Tetrahymena*. *J Mol Biol* **120**: 33–53
- Connor S (2011) The £400 test that tells you how long you’ll live. *The Independent* 16 May
- de Jesus B *et al* (2011) The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging Cell* **10**: 604–621
- Harley CB, Liu W, Blasco M, Vera E, Andrews WH, Briggs LA, Raffaele JM (2011) A natural product telomerase activator as part of a health

maintenance program. *Rejuvenation Res* **14**: 45–56

Olovnikov AM (1973) A theory of marginotomy. The incomplete copying of template margin in enzymic synthesis of polynucleotides and biological significance of the phenomenon. *J Theor Biol* **41**: 181–190

Szostak JW, Blackburn EH (1982) Cloning yeast telomeres on linear plasmid vectors. *Cell* **29**: 245–255

Willeit P *et al* (2010) Telomere length and risk of incident cancer and cancer mortality. *JAMA* **304**: 69–75

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EMBO reports (2011) **12**, 897–900.
doi:10.1038/embor.2011.166