translational research that have the potential to delay or conceivably prevent most such disorders. However, there is a caveat that requires more thorough investigation: the degree to which interventions that retard aging and delay the onset of age-related disorders will be accompanied by a compression of morbidity. In other words, will such interventions regularly lead to an increase in the ratio of health span to life span? Will our medicated centenarians lead fulfilling lives with eventual sudden collapse, or will they suffer from proportionally protracted durations of chronic disease? Although some research on centenarians suggests a compression of morbidity (*14*)—and rapamycin, in particular, appears to disproportionately enhance many measures of health span in mice (*15*)—future progress in geroscience interventions will need to be carefully monitored.

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ACKNOWLEDGMENTS

Geroscience in our laboratories and the labs of others at the University of Washington is supported by the Nathan Shock Center of Excellence in the Basic Biology of Aging, NIA grant P30AG013280.

10.1126/science.aad3267

REVIEW

Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection

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Telomeres are the protective end-complexes at the termini of eukaryotic chromosomes. Telomere attrition can lead to potentially maladaptive cellular changes, block cell division, and interfere with tissue replenishment. Recent advances in the understanding of human disease processes have clarified the roles of telomere biology, especially in diseases of human aging and in some aging-related processes. Greater overall telomere attrition predicts mortality and aging-related diseases in inherited telomere syndrome patients, and also in general human cohorts. However, genetically caused variations in telomere maintenance either raise or lower risks and progression of cancers, in a highly cancer type–specific fashion. Telomere maintenance is determined by genetic factors and is also cumulatively shaped by nongenetic influences throughout human life; both can interact. These and other recent findings highlight both causal and potentiating roles for telomere attrition in human diseases.

The telomere is a highly regulated and dynamic complex at chromosome ends, consisting of a tract of tandemly repeated short DNA repeats and associated protective proteins (Fig. 1) (*1*).

The telomere protects the genomic DNA through various mechanisms. One function is to prevent the end of the linear chromosomal DNA from being recognized as a broken end. This prevents processes—such as DNA end-joining, DNA recombination, or DNA repair—that would lead to unstable chromosomes. The general chromosomal DNA replication machinery cannot completely copy the DNA out to the extreme ends of the linear chromosomes. Over the course of cell divisions, this leads to attrition of chromosome ends. This deficiency can be resolved in eukaryotes by the cellular ribonucleoprotein enzyme telomerase, which can add telomeric repeat sequences to the ends of chromosomes, hence elongating them to compensate for their attrition (*2*).

Other damage-causing mechanisms can also contribute to telomere-shortening processes; these include nuclease action, chemical (such as oxidative) damage, and DNA replication stress. To offset these various processes, telomerase, as well as recombination between telomeric repeats, can act to replenish telomere length (*3*).

In many human cell types, the levels of telomerase (or of its action on telomeres) are limiting, and in humans, telomeres shorten throughout the life span. The degree of shortening is roughly proportionate to risks of common, often comorbid, diseases of aging as well as mortality risk. Inherited telomere syndromes (*4*, *5*) have been highly informative for dissecting the roles and interactions of telomere maintenance defects in the general population's human aging and age-related diseases. Declining telomere maintenance has pathophysiological effects on cells that can lie upstream of, as well as interact with, a number of the cellular hallmarks of aging (*6*). Because the effects of compromised telomere maintenance in humans play out in cell- and tissue-specific ways, they consequently differ between

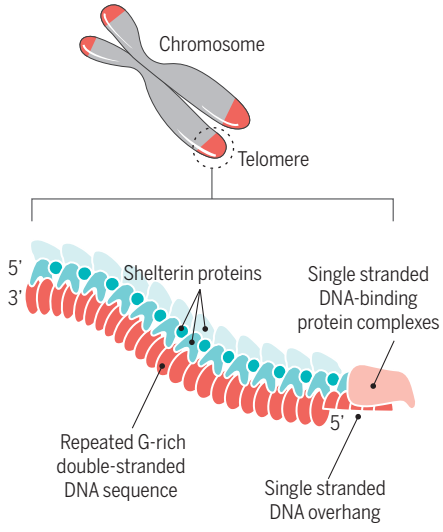

Fig. 1. Telomere structure. The human telomere complex consists of a chromosomal-terminal tract of a tandemly repeated DNA sequence bound by protective shelterin component proteins, with additional protective proteins on the overhanging single-stranded end region of the telomeric DNA repeat. This simplified schematic does not indicate details of the protein structures or of the architecture of the telomeric complex.

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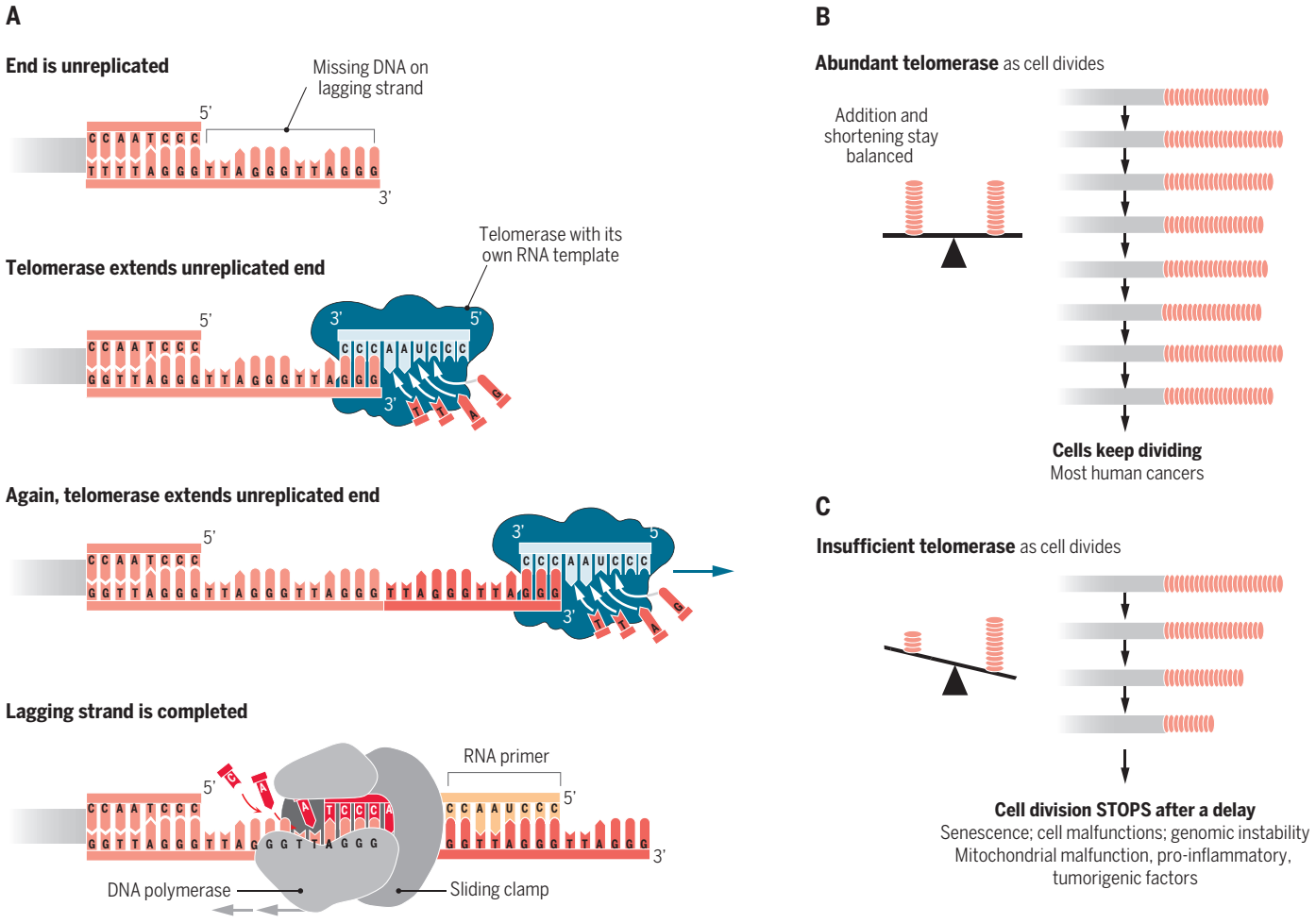

Fig. 2. Long-term maintenance of telomeric DNA length requires telomerase. (**A**) Replication of telomeric DNA. Elongation of one DNA strand, via the reverse transcriptase mechanism of telomeric DNA synthesis by telomerase, is followed by synthesis of the other telomere DNA strand by DNA polymerase. (**B**) As cells divide, shortening of telomeres through incomplete DNA replication and other processes causing attrition can be balanced by compensatory telomere-elongating action by telomerase. (**C**) Net telomere shortening when telomerase is insufficient leads to critically short telomeres. Telomere damage signaling leads to cession of cell division and other cellular responses.

the various diseases of aging. Particularly among cancers, genetic determinants for longer telomeres raise risks in cancer type–specific ways. Recent advances in understanding the links of mortality and aging-related diseases to telomere maintenance, driven by genetic and nongenetic inputs, highlight the roles of telomere maintenance in diseases of aging, and their subtleties, in humans. Telomere biology in model systems has been extensively reviewed (*1*–*4*, *7*–*11*).

Here, we will focus on human genetic and clinical findings as to whether telomere shortness in humans is a bystander or a cause of diseases and syndromes of aging. The best current understanding is that telomere shortening can both promote and be a result of disease etiology and progression and may in some situations set up a vicious cycle that interacts with other disease processes.

Telomere loss and replenishment

Many adult human cells, such as fibroblasts, have very low or no detectable telomerase. Such cells, in tissue culture, undergo progressive telomere shortening. When the telomeres become critically short or sufficiently damaged, the deprotected telomeres set up a sustained form of DNA damage signaling. This causes altered transcriptional profiles, and cells to become senescent. Depending on cell type, the senescent cell characteristics have various consequences (Fig. 2) (*11*).

In humans and model organisms (including mammalian), telomeric DNA is often particularly susceptible to damage and abnormalities that occur genome-wide. First, the G-cluster–rich telomeric DNA is chemically more prone to oxidative damage reactions than is the general genome (*12*). Second, the telomere-bound protective proteins block or deflect DNA repair processes (*10*). Third, as a result, the sustained DNA signaling elicited by telomeric DNA damage is not resolved (*7*), and often cannot be unless by telomerase action, which, as described above, is often limiting in human cells.

It may seem paradoxical that telomeres, which are a part of the genome dedicated to genomic protection, are so susceptible to damage. However, telomeres may be "first responders" to threats to genomic stability and problems with DNA maintenance, by which telomeric DNA acts as the "canary in the coal mine," altering the cells' responses before damage to informational genetic coding sequences occurs.

In general, although in cells of most human tissues telomeres shorten throughout human life, the idea of a constantly ticking mitotic clock is also over-simplistic. It is heavily confounded by, among other factors, the variable levels of telomerase activity—and hence variable capacities for telomere length replenishment—in stem cells. These can constantly renew somatic tissue cells. For example, telomerase is enriched in hemopoietic and intestinal villus stem cells and their transit amplifying cells in growth phase hair follicle cells, and in other stem cells including germline lineage cells and embryonic stem cells. Furthermore, it is not known how much of the normal senescence or death observed in many human cells in vivo can be attributed to causes other than

telomere-initiated DNA damage signaling resulting from loss of telomere protection (*11*).

Telomere regulation is highly interactive

Human telomeric DNA forms a scaffold for a hierarchy of proteins ranging from nucleosomal histones to shelterin components to conditionally associating DNA repair factors (Fig. 1) (*1*). Telomere replenishment and its regulation are part of extensive networks of cellular interactions. These include tight regulation of telomerase expression and action and of a complex of telomere-protective proteins called shelterin. In addition to protecting telomeres from deleterious DNA damage response processes (*1*), shelterin components have dual roles: They both recruit telomerase to telomeres and prevent it from acting on them in highly regulated fashions. Other factors, including DNA repair proteins, also pay transient visits to telomeres, some via shelterin component-specific interactions. Shelterin components have other functions besides telomere maintenance (Box 1). Thus, they have exquisitely balanced roles, and a dynamically regulated balance of shelterin component actions is important, rather than simply having larger amounts of them.

Aging in humans versus model organisms

Apart from overt signs of aging in humans—such as hair graying, skin wrinkling and spotting, muscle wasting, and altered adiposity—susceptibility to diseases dramatically increases as we enter the last decades of life. Such aging-related diseases prominently include, but are not restricted to, insufficient immune function, cardiovascular diseases, cancers, diabetes, depression, and cognitive decline. Some of these seemingly unrelated age-related diseases occur together in the same person more often than expected by chance (comorbid diseases).

Life spans vary by over 5 orders of magnitude across eukaryotes. Extrapolating findings from laboratory model systems may present problems because of the long, multidecades time frame of human aging, as well as differences such as body mass and other evolutionary differences. Telomeres shorten throughout the human life span, including during the aging portion of life. In marked contrast, critical telomere shortening appears to be negligible during the normal aging of the mostly much more short-lived animal models used for laboratory studies of aging. Thus (unless telomere maintenance is experimentally deleted genetically), laboratory mice and rats normally die of old age with intact and relatively long telomeres (*13*), as do other commonly studied short-lived nonmammalian models, such as the worm *Caenorhabditis elegans* (*9*), zebrafish (*14*), and the African turquoise killifish (*8*). During evolution, the telomerase-mediated system of telomere maintenance was completely lost from the fruit fly *Drosophila* (*15*). Determining which mechanistic underpinnings of aging are applicable to humans requires consideration of the steps or mechanism (or mechanisms) that are rate-limiting on the human aging time frame. These are not necessarily the same ones that are rate-limiting in a shorter-lived mammal.

Genetics: Telomere compromise can cause diseases

That inadequate telomere maintenance can cause several eukaryotic aging phenotypes in laboratory model organisms is demonstrated only by experimentally deleting telomere maintenance genes (*4*, *8*, *9*, *13*, *16*, *17*). For example, in mice a complete null genotype for a telomerase component or a telomere protective protein causes, after telomeres have shortened sufficiently to become deprotected, characteristic accelerated aging phenotypes (*4*, *13*). The challenge has been to determine the degree to which, in humans, telomere maintenance deficiency causes these same disease processes during normal aging.

Monogenetic inherited disorders of telomere maintenance clearly demonstrate, at the simplest conceptual level, that unprotected telomeres can play causal roles in aging and diseases of aging of humans. Such diseases are caused by Mendelian mutations that compromise telomere function. They usually (but not always) manifest as very short telomeres in vivo. This results from excessive telomere shortening, with consequent loss of telomere capping and protection. As described above, the resultant signaling from the damaged telomeres causes phenotypes that lead to diseases.

Such single-gene inactivating mutations are known in 11 human genes to date. Each mutated gene has a known, molecularly defined, direct function in telomere maintenance: It encodes either a telomerase component (TERC, TERT, DKC1, NOP10, NHP2, or WRAP53) or a telomere-binding protein, found on telomeres in vivo and shown experimentally to have an essential telomere protection function (TINF2, RTEL1, POT1, CTC1, and TPP1) (*4*, *5*).

These inherited diseases comprise a seeming plethora of tissue- and organ-specific pathologies and disease classifications. All are united by one common causal molecular mechanism: the response to unprotected (usually drastically shortened) telomeres. They parallel many phenotypes of experimental mouse models that are null for a telomere maintenance gene (*18*–*20*). We refer to this clinically diverse collection of monogenetic mutation diseases as "inherited telomere syndromes." These diseases are frequently autosomal-dominant. In humans, functional haploinsufficiency often underlies the pathology and gene dose, and hence the level of the relevant telomere maintenance pathway gene product is important for protection against an organism-wide range of diseases and syndromes.

In patients, clinical variability, incomplete penetrance, and variable expressivity of the mutation occur (*5*). Yet inherited telomere syndromes are increasingly understood to fall into characteristic patterns. They can include one or more of the following: loss of immune function through loss of bone marrow stem cell reserves, certain cancers (hematological such as leukemias and myelodysplastic syndrome, or squamous-cell skin and gastrointestinal cancers), pulmonary fibrosis (accounting for the most frequent single-gene mutational cause of this disease), gastrointestinal disorders, liver cirrhosis, and neuropsychiatric conditions. Patients often have additional phenotypes of accelerated aging, including diabetes, myocardial infarction, hair graying, and skin pigmentation (*20*).

Mouse models of telomerase deficiency usually require several generations before their progressive telomere shortness reaches the point when phenotypes manifest (*4*, *8*, *9*, *13*, *16*). Similarly, a hallmark of monogenetic human telomere syndromes is genetic anticipation, with succeeding generations of mutation carriers in a family pedigree having successively earlier disease onsets,

BOX 1. Recently emerged off-telomere functions of shelterin components.

Various shelterin components are found throughout the nucleus as well as on telomeres; some of these are transcription factors that act genome-wide. Multiple shelterin components, from budding yeast to mammals (and thus presumably in humans), show highly regulated binding to a plethora of genomic nontelomeric sites, where they control transcription of several cell and developmental stage–specific gene networks. For example, the evolutionarily conserved shelterin RAP1 has transcriptional roles. Genetic manipulations of RAP1 in mice cause gender-specific obesity even though the telomeres are not damaged. Hence, other gene networks, in addition to DNA damage and stress responses, are controlled by shelterin components acting as transcription factors and can be affected by their balance at telomeres versus other genomic locations (*61*).

Shelterin components, in turn, are themselves regulated by gene expression and modification pathways that are cell type– and developmental stage–specific. For example, a well-studied longevity-promoting transcription factor, FOXO3, increases the expression of the essential telomere-protective POT1a in mouse neuronal stem cells. Such regulation may be especially important for these recently recognized off-telomeric roles of shelterin components. Thus, the influence of telomere complexes extends from transcriptional responses caused by DNA damage responses to uncapped telomeres, to the multifunctional shelterin components that act as transcription factors to reprogram networks that include metabolic genes (*61*).

These multiple layers reveal nuanced, two-way conversations between telomere integrity and cellular and organism functions. How they interplay throughout multiple tissues and stages of human life is likely to be complex.

and the types of diseases are also characteristically different down the generations. Particularly in later generations of families, early death results. Together with the mouse models, these observations provided a crucial insight: proof that short telomeres themselves are the major mechanistic cause of the disease phenotypes. Strikingly, disease even manifests in noncarrier offspring when they inherit short telomeres from an affected carrier parent (*4*, *5*, *21*).

Telomeres also exert context-dependent impacts on diseases. As well as telomere syndrome symptoms, human carriers of monogenetic telomerase mutations develop emphysema and chronic obstructive pulmonary disease, specifically if they are smokers (*22*). The interactive nature of telomere compromise is elegantly demonstrated by combining telomerase deletion with a mutation for a disease gene. In diverse genetically defined mouse transgenic models of human monogenetic diseases, even at early generations after telomerase loss in the double-mutant mice, telomere shortness and dysfunction synergize with the genetic lesion to cause the full organism-wide range of human symptoms and pathology, which in the single-mutant animals is often incomplete (Box 2) (*23*–*25*). Thus, telomere dysfunction can interact with other disease etiologies and could contribute aspects to human diseases that originate from other primary causes. Furthermore, in addition to attrition from lack of telomerase-mediated replenishment, other forms of telomere damage, such as oxidative damage accumulating with age, could also underlie contributions of telomere dysfunction to diseases of aging.

BOX 2. Additive/synergistic effects of telomere attrition and specific disease genes.

In mouse models with $Wrn^{-/-}$ $Terc^{-/-}$ double (*62*) or $Wrn^{-/-}$ BlmM3/M3 $Terc^{-/-}$ triple mutations (*23*), the telomerase deletion phenotypes appear in earlier generations after deletion of TERC, as opposed to the sixth generation in a $Terc^{-/-}$ but otherwise wild-type background (*23*, *62*).

Additional phenotypes specific to human Werner and Blooms are also observed and are more severe than are $Wrn^{-/-}$ or $Wrn^{-/-}$ BlmM3/M3 mice with wild-type TERC. Recent in vitro work showed that added telomerase protects Werner syndrome lineage-specific human stem cells from premature aging (*24*), which reinforces a previous finding that indicated that telomere dysfunction contributes to premature aging phenotype in Werner syndrome (*63*).

In the diabetic Akita mouse that carries a mutation in the insulin gene, Ins2C96Y/WT, misfolded insulin causes endoplasmic reticulum stress and leads to β-islet cell apoptosis (*25*). TERC deletion in the Akita background leads to increased β-islet cell apoptosis and greater loss of glucose tolerance compared with that from the Ins2C96Y/WT mutation alone, suggesting that the assault of telomere dysfunction and ER stress are additive.

Duchenne muscular dystrophy is a muscle-wasting disease caused by a mutation in dystrophin, which results in muscle degeneration and premature death. The mouse model with the same human mutation has surprisingly mild phenotypes. However, double-mutant mice that lack dystrophin and have shortened telomeres (*mdx/mTRKO*) develop phenotypes that mirror those seen in humans, including severe functional cardiac deficits such as ventricular dilation, contractile and conductance dysfunction, and accelerated mortality (*64*). These cardiac defects are accompanied by telomere erosion. Telomere length in cardiomyocytes of the *mdx/mTRKO* G2 mouse is shorter than that of the G2 mouse in which mTR was knocked out, demonstrating that the dystrophin mutation exacerbates telomere attrition. Again, a synergistic effect is seen for both the telomere and Duchenne muscular dystrophy phenotypes.

These findings broaden the scope of possible consequences of shortened telomeres for aging and disease and highlight that often, "the action is in the interaction."

Disease potentiator and mortality predictor

Although the inherited telomere syndromes often manifest earlier and with greater severity, their phenotypes are those of diseases that increase dramatically with aging in the general human population. Many of the common diseases of human aging—including poor immune function (*26*), cancers (*27*, *28*), diabetes (*29*), and cardiovascular disease (*30*)—are predicted by and/or associated with shortness of telomeres in total leukocytes or peripheral blood mononuclear cells (PBMCs).

Mean leukocyte telomere length (LTL) or PBMC TL reflects systemic influences on telomere maintenance in other tissues and, importantly, the senescent status of circulating cells of the immune system. A role for inflammation has been extensively documented for the pathological progression of such diseases as cardiovascular disease, diabetes, and possibly dementias. Because of the pro-inflammatory processes engendered by immune cell senescence, telomere attrition in immune cells has relevance for the etiology of these conditions.

Most human diseases of aging are influenced by complex genetic as well as nongenetic inputs. The mouse model examples (Box 2) show that causality inferred for a disease could be incomplete if telomere shortness is not taken into account. Unbiased genome-wide association studies (GWASs) on loci that affect white blood cell (leukocyte) human telomere length have consistently uncovered loci containing known telomerase and telomere-protective protein genes. Mendelian randomization established a causal relationship for LTL shortness and increased coronary artery disease (CAD) risk in one such large European study (*31*). This identified seven top common-gene variant alleles that together explain ~1% of the total LTL variation. The top-scoring five (TERC, TERT, NAF1, OBFC1, and RTEL1) of these seven genes encode components with molecularly defined, direct actions on telomeres. The allele scores for these same seven common genes linked to shorter telomeres were predictive in additive fashion of risk of CAD. The risk for CAD was ~20% higher than usual in those individuals with the highest allele score for six out of these seven top-scored shorter-telomere gene common variants (*31*). Common single-nucleotide polymorphisms (SNPs) of NAF1 and OBF1C have also been shown to associate with coronary heart diseases (CHD) (*32*, *33*). Cardiovascular and other diseases of general population aging are also seen in monogenetic inherited telomere syndromes. Hence, at least some common diseases, such as CAD and CHD, may be considered as partial "telomere syndromes." A recent paper also reported that the short telomere length allele of two of the SNPs described in (*31*) (TERT and OBFC1) is associated with higher risks for Alzheimer's disease (*34*), thus establishing a causal relationship between short TL and a higher risk for AD.

The minimum telomere length needed to ensure human telomere protective stability in white blood cells is 3.81 kb (*35*). Thus, a small change in human white blood cell telomeres has a bigger functional impact than its absolute magnitude might suggest. For example, the GWAS LTL gene (*31*) with the largest effect, the telomerase RNA component TERC, causes a mean telomere length decrease of 117 base pairs (bp) per TERC telomere-shortening allele. In a typical middle-aged adult's ~5-kb repeat leukocyte telomeric DNA tract length, this allele effect represents an ~10% drop in the effective 1.19 (that is, 5 – 3.81) kb functional telomere reserve. Mean LTL is usually the measure performed for feasibility and cost reasons, and it is unknown to what extent the more resource-intensive measurement of the shortest telomeres will add information useful for many clinical studies.

As humans age, average telomere length declines, and mortality increases. Chronological age accounts for less than 10% of human telomere length variation. Recent large cohort studies have clarified that independent of age and other previously known mortality risk factors, the degree of telomere shortness is also a clear statistical predictor of human all-cause mortality (*36*, *37*). But telomere length maintenance is highly interactive, and as described below, telomere measures show much greater predictive power when combined with other factors.

A recent California 100,000-adult study, in which 75 years is the age of maximum mortality risk, showed that in humans aged above 75 years, the trend of telomere shortness with age is reversed (*38*). This V-shaped relationship and trend

to longer cross-sectional telomeres in the oldest subjects suggests that increased telomere length with increasing exceptional longevity is associated with selection for survival. This interpretation is reinforced by previous findings: LTL in the Nicoya Peninsula Exceptional Longevity population in Costa Rica was consistently longer for the Nicoya Peninsula population compared with the control Costa Rica population across ages, but only until the age defined as extreme longevity —95 years and above—at which age the two groups' telomere length curves converged (*39*). This selection bias can help explain some previous mixed findings on telomere length and mortality.

Most mortality in the large cohorts studied to date for LTL results from common diseases of aging, prominently cardiovascular diseases, cancers, and diabetes. Therefore, predictions of future incidences of such diseases and of future mortality are expected to be consistent. Indeed, in a graded fashion, white blood cell telomere shortness prospectively predicted higher future incidences (new diagnoses) of both cardiovascular diseases and all cancers combined, across the following 10 years (*40*). In a large cohort, it predicted both cardiovascular and all-cancers mortality in a 7-year average follow-up (*36*). Short telomeres predicting future disease onset is consistent with telomere attrition having a causal role but is not proof. The proof for a partial contributory role for telomere shortness came from the GWASs on CAD described above. It is biologically consistent with the disease and mortality phenotypes of inherited telomere syndrome patients and mice null for a telomere maintenance gene.

Cancers: Telomerase teetering on the brink

In tumor cells, which often behave as though effectively immortalized, telomere maintenance becomes ensured by various routes. In 80 to 90% of fully malignant human tumors, cancer cell telomerase activity is up-regulated compared with normal tissue counterparts. Yet the more than 200 types of cancers in humans result from a wide range of cancer etiologies and series of events. As expected from this diversity, cancers vary regarding how telomere maintenance up-regulation—or its compromise—promotes the complex processes of cancer etiology and progression. On the one hand, the inherited telomere syndromes show that organism-wide inadequate telomerase action causes high frequencies of hematological, squamous cell, and gastrointestinal tumors. These all involve tissues whose high demands for stem cell replenishment become compromised by the lack of telomere maintenance. Mutations in the gene encoding shelterin component POT1 cause a specific human glioma type (brain tumor), and the molecular nature of these mutations indicates that they may cause improperly capped telomeres or possibly alter telomerase action (*41*). On the other hand, a germline activating mutation in the promoter of the telomerase component TERT, identified in a family pedigree, that increased TERT expression only ~1.4-fold was sufficient to cause fully penetrant melanoma (*42*). Also, in multiple population-based cohorts, common germline longer-LTL variants in known telomere maintenance genes, especially telomerase genes, raised risks of melanomas, nonsmokers' lung cancer, and many gliomas (*43*). Thus, even mildly over-activating telomere maintenance promotes risks of subsets of cancers. Telomere maintenance–promoting alleles potentially prolong survival of certain cancer-prone or precancerous cells, increasing their chances of undergoing the multiple steps that generate tumors.

Nongenetic factors: Life stressors and lifestyle

Heritability estimates of human telomere length range from 30 to 80%. Very short telomeres are inherited in telomere syndrome mutation families (*21*). Similarly, it has been suggested that in the general population, in addition to conventional heritable genetic factors, the direct inheritance of telomeres through the parental gametes could account for a considerable proportion of the estimated heritability of telomere length (*44*).

However, telomere length heritability declines with age (*45*), and substantial nongenetic influences, especially shared environmental influences, have been demonstrated (*46*). Epigenetic influences on telomere length may help mediate the large number of now-recognized nongenetic environmental and other factors that affect telomere maintenance. When just the telomere-lengthening alleles of three telomere maintenance genes were considered alone, they increased all-cancers mortality risk (*36*). Yet with longer observed telomeres, all-cancers mortality was lower. Hence, the impacts of genetic versus nongenetic causes of longer telomeres differ on cancers (Fig. 3). Nongenetic, including epigenetic, influences on telomere maintenance therefore are of considerable interest for their roles in disease etiologies.

In humans, associations between stress and telomeres can be seen early in life. Newborn human telomere length was shorter in proportion to the stress levels experienced by the mother during her pregnancy (*47*). Degrees of exposure to violence or neglect in childhood and to various categories of adverse childhood events (ACEs) were associated with substantially shorter telomere lengths, as measured either in children or retrospectively in adults (*48*). "Dose-dependent" effects of exposure to stressors on telomere shortness have also been observed in adults. Examples include durations of exposures to domestic violence, unmedicated depression, or caregiving for a family member with chronic illness (*49*). Experimental studies exposing young birds to stress demonstrate that chronic psychological stress is a causal factor in telomere shortening (*50*).

Mechanisms of the stress-telomere relationship are starting to be examined and are likely multifold. The transmission of maternal stress to offspring may be mediated through direct effects, parental shorter gamete telomere length, epigenetics, or indirect effects, such as by alterations in the intrauterine environment due to elevated stress hormones or poor nutrition (*50*, *51*). Several studies in birds have shown maternal transmission of stress is in part through glucocorticoid exposure in either mother or egg (*50*). In humans, shorter telomeres are associated with greater cortisol reactivity (*52*), and in vitro work suggests that high glucocorticoids may dampen down telomerase activity (*53*).

Such studies provide suggestive evidence that chronic psychological stress may be one causal factor in telomere shortness in humans. Adults with major depressive disease tend to have shorter telomere length (*54*), especially with greater severity and duration of depression (*55*). Telomere shortness is thus likely a result of the disease, although shortening may also precede onset of depression in children at high risk (*52*).

Other factors reported to be associated with telomere length range from social and environmental factors to lifestyle factors, such as smoking or exercise (*49*, *56*). Although observed telomere length, or a telomere-related allele, may alone have a small effect on disease, the effect can be magnified by, for example, depression (*57*) or smoking (*58*, *59*). Thus, interactive effects of nongenetic and genetic telomere determinants are potentially powerful and are relatively unexplored.

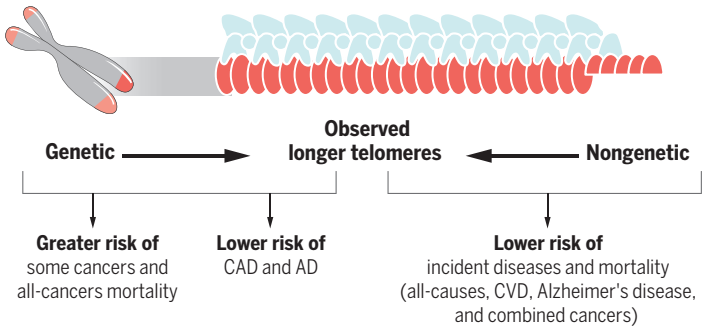

Fig. 3. Different inputs to telomere maintenance have disease-specific consequences. Observed telomere length results from combined genetic and nongenetic inputs. Longer observed telomeres are associated with lower overall risks for mortality and diseases. The variants of telomere maintenance genes that promote longer telomeres decrease CAD and Alzheimer's disease risks yet raise risks of specific cancer types and for combined all-cancers mortality. Nongenetic influences that lead to better telomere length maintenance are protective.

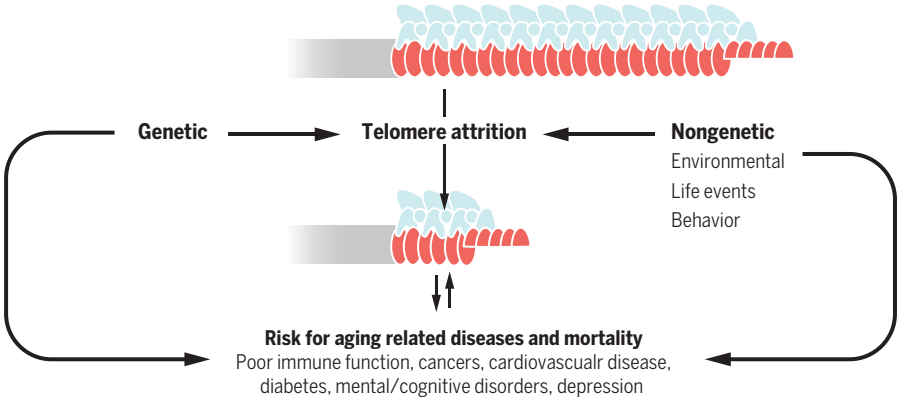

Fig. 4. Relationship of telomere attrition to human aging-related diseases. Telomere attrition is depicted as an underlying, shared, interactive contributor to the etiologies of aging and aging-related diseases. Because both nongenetic and genetic influences affect it, telomere maintenance is a malleable and integrative indicator of overall health.

Clinical ramifications and conclusions

A single mechanism—loss of telomere protective function—causes the inherited telomere syndromes that result in aging-like disease pathologies. Their organism-wide nature provides a strong hint that in the often comorbid diseases of aging (such as diabetes and cardiovascular disease), telomere shortness could similarly be a shared underlying contributing factor (Fig. 4).

Except for rare telomere syndromes, telomere measures only produce statistical estimates of probability and alone are not specifically diagnostic for an individual. Because telomere length is affected by so many nongenetic factors, measures of telomere length maintenance may be a proxy for assessing the "exposome"—that is, all of the exposures promoting disease. Research on interactions between independent and overlapping pathways influencing human telomere length is in its earliest stages. It will be important, in the new era of precision medicine studies, to determine whether combining other predictors—genomic associations, clinical, behavioral, and disease data—with telomere length measures can increase the precision of predicting disease progression and outcomes. A striking example of synergism comes from a study of a cohort of bladder cancer patients. Shorter mean LTL measured at the time of diagnosis in bladder cancer was not alone significantly associated with future mortality. However, when combined with a depression diagnosis, median survival time was reduced from 200 months (all other groups) to 31 months in multivariate analyses that adjusted for demographic and clinical variables (*57*).

Telomere maintenance in humans encompasses a surprisingly delicate trade-off between reducing risks of many aging-related diseases while raising risks of certain less common but often lethal cancers. Clinically unproven unregulated nostrums purporting to boost telomerase action thus could plausibly engender long-term cancer risks. Telomere biology is best viewed in context: It shows promise as a powerful interactive factor that could be helpful in precision medicine for clinical health monitoring and assessing disease. How genetic and nongenetic determinants of telomere length maintenance may interact—with each other and with other disease etiologies—to become rate-limiting for disease risks requires future research. Early observational evidence from human studies indicates that health behaviors may buffer effects of stress or depression on telomere length (*56*) and that behavioral interventions may improve telomere maintenance in certain settings (*60*). Continued mechanistic research will increase understanding of the plasticity of telomere maintenance and identify when and how intervention can be effective for affecting disease and health.

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ACKNOWLEDGMENTS

We thank our many colleagues and apologize to those whose work we were unable to cite owing to article length constraints. E.H.B acknowledges support from NIH (grants GM026259 and CA096840) and from the Barbro and Bernard Osher Foundation. E.H.B. and E.E. report no conflicts of interest; E.H.B. and E.E. were former cofounders of a company, Telome Health (now Telomere Diagnostics), but donated all their shares to a nonprofit organization. J.L. owns stock in Telomere Diagnostics.

10.1126/science.aab3389

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Science **350** (6265), 1193-1198.
DOI: 10.1126/science.aab3389