National Institute on Aging Workshop

Research on Determinants of Species Differences in Human and Nonhuman Primate Life Spans and Health Spans

Role in Developing Interventions to Extend Human Longevity and Health Span

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I. Introduction and Workshop Rationale

In August 2021, the National Institute on Aging convened a workshop on determinants of species differences in primate life spans and the role of research on this topic in developing interventions to extend human longevity and health span. Participants' expertise spanned a wide range, including epidemiology, human genetics and omics, cheminformatics and drug development, evolutionary biology, primatology, biological anthropology, biodemography, neuroscience, and comparative biology of aging.

A central premise of the workshop was that cross-species analysis of primates can reveal factors that contribute to their large differences in life span. Such associations can lead to identification of mechanisms whose modulation could strongly influence human longevity, but which would not be readily detectable by comparisons confined to humans, particularly if variability in such factors among individual humans is limited or absent.

Such species comparisons can complement ongoing human translational longevity studies based on comparisons of individuals or families (Slagboom et al. 2018) and are being applied in integrative studies combining the two approaches (Raghavachari et al. 2022). Human studies can identify factors that increase individuals' likelihood of survival to exceptional ages and identify potential targets for interventions. However, the relative differences between ages of exceptional human survival and median survival are only moderate. US life tables indicate that only approximately 1% of the cohort born in 1920 survive to ages that exceed their median life expectancy by 35% or more (Social Security Administration 2020 Trustees Report: Cohort Life Tables). This degree of variability, though important from clinical and public health perspectives, provides limited signal strength for identifying factors that could have substantial positive effects on human life span. In contrast, life span variation across mammalian species is far greater, potentially providing a stronger signal from factors that contribute to large effects.

Comparative species studies also enhance opportunities to gain insights into factors that may extend longevity which operate well before old age. Human studies on such factors, based on variation of individual life spans, are limited by a scarcity of long-term longitudinal and retrospective data, and the inability to predict the length of a young individual's future survival with confidence. Thus, most current human data on phenotypes predicting survival to advanced age are confined to the interval beginning in early old age or later. However, comparisons of young individuals from species with substantial known life span differences can clarify the relationship of such factors to species longevity.

Primates present several particularly valuable features for comparative life span analyses. They have a very wide range of life spans. Maximum life spans of the 154 primate species listed in the AnAge database range from 17 years (giant mouse lemur) to 122 years (humans) (Tacutu et al. 2018). Numerous primate species survive beyond 40 years, thus providing an opportunity to identify factors contributing to these long

life spans that might not be found in shorter-lived species, and to assess the effects of factors that affect longevity of shorter-lived species on survival at older ages. In addition, the phylogenetic proximity of humans and nonhuman primates facilitates comparisons of phenotypes and assessments of orthologous relationships among proteins and genes that may be sources of species variation in longevity.

The close phylogenetic relationship between humans and other primates is also valuable for examining the complex basis of sex differences in aging and mortality. Contributory factors could be found through comparisons of humans and other primates who share their female longevity advantage (e.g., gorillas and gibbons) with others in whom males survive longer (e.g., titi monkeys, owl monkeys) and other species with only small sex differences in mortality (e.g., muriquis). Sex differences in mortality risk could be related to social and mating systems as well as to genetic factors (including differences in X and Y chromosomes) and hormonal differences between the sexes.

In addition, unique factors in primate evolution have likely influenced longevity. Various brain regions have expanded or changed. New forms of family and social organization and behavior have appeared, accompanied by changes in the timing of reproductive and maturational schedules. Primates have developed varying feeding and foraging strategies, accompanied by changes in mobility and systemic energy throughput. Hominins, in particular, expanded into very diverse environments posing diverse physiologic and behavioral challenges. Numerous genetic changes that may be related to these exposures also occurred in primate evolution. Understanding the interactions between such factors and the determinants of species life span could reveal novel mechanisms influencing longevity. Some factors may be distinct to differences between specific primate taxa, e.g., hominids versus short-lived primates, or humans versus other hominids.

The workshop addressed a variety of topics related to the above considerations, and opportunities and needs for further research and resources.

- Human translational longevity studies
- Comparative biology of longevity across multiple phyla
- Biodemography of primate species longevity and life histories
- Biological and evolutionary factors related to primate species longevity
- Evolutionary differences in primate brain aging and susceptibility to neurodegenerative disorders
- Resources for human and nonhuman primate comparisons.

II: Human studies of determinants of longevity and health span, and approaches for identifying targets for human interventions.

Contribution of Longitudinal Studies to Insights about Determinants of Aging-Related Outcomes. In addition to their crucial role in determining the relationships of biomarkers or risk factors at differing ages to subsequent survival, longitudinal studies are essential for identifying and characterizing aging-related changes that influence survival. Both of these roles can contribute to the identification of potential therapeutic targets for interventions to extend longevity.

Cross-sectional studies comparing individuals of differing ages pose several limitations for characterizing such changes: Because they were born at different times, their current phenotypes may reflect birth-cohort effects and differing environmental exposures, including nutrition and medical interventions. This poses challenges for distinguishing between effects of such factors and those of aging-related factors.

In addition, differences (or lack thereof) in risk factors among individuals of differing ages in cross-sectional studies may not reflect changes within individuals as they age, due to survivorship bias. Individuals whose risk factor levels place them at higher mortality risk are less likely to be present in older age groups. For example, circulating IL-6 levels increase more rapidly with age in individuals compared to differences found in cross-sectional comparison of age groups, reflecting IL-6's association with higher mortality (Fabbri et al. 2015). Similarly, individual longitudinal declines in aerobic capacity exceed cross-sectional age differences (Fleg et al. 2005).

Survivorship bias can also influence the selection of components of composite aging measures based on cross-sectional correlations of levels of multiple markers with chronologic age. These composite measures can be used to estimate an individual's "predicted age", which is the age at which one's observed value of the measure is expected, based on its correlation with age in the population (Horvath 2013). The difference between an individual's predicted and chronologic age has been used as an indicator of the magnitude of age-related changes compared to age-matched peers. Simulation studies have demonstrated that the selection of markers based on cross-sectional chronologic age differences is biased against selecting factors that adversely affect survival, compared to factors that do not influence survival (Nelson et al. 2020). These analyses also show that this bias can be mitigated by training the model on markers that incorporate information from longitudinal studies on the correlation of specific phenotypic factors to the duration of survival. In addition, an analysis of longitudinal NHANES data on such markers and their relationship to survival showed that adding this information increased the proportion of variation in survival time above than explained by age alone.

These studies have also shown, using Gompertz parameters characterizing mortality risk as a function of age, that differences between chronologic age and predicted age based on cross-sectional data correlate with the rate of mortality rise with age (the function's slope), but not with its y-intercept. This has implications for assessing potential effects of interventions on survival based on their effects on such measures. Since an intervention could affect either or both Gompertz parameters, the effects of an intervention on predicted age would give only a partial view of its potential favorable or unfavorable impact.

Longitudinal rates of changes with age in composite markers whose levels correlate with age in cross-sectional comparisons can also differ in degree from cross-sectional findings. In longitudinal studies of DNA-methylation-based markers of "predicted age," developed from cross-sectional studies, the values changed more slowly with increasing age compared to cross-sectional age differences (Marioni et al. 2019), suggesting that their relationship to mortality risks and other outcomes may be at least in part related to differences established early in life. Longitudinal data are also essential for assessing differences in the degree of change with age among components of composite markers and the temporal relationships among such changes, which could illuminate sequential causal mechanisms.

More broadly, longitudinal data are essential for distinguishing between two alternative causes of interindividual differences found in old age: differences in their rate of change with age vs. differences present in earlier life that remain over the life course. These two patterns could reflect differing biologic mechanisms. Longitudinal data can also identify more complex relationships, such as differing ages of flexion points when individuals transition from stable values to changes with age, and relationships between baseline risk factors and subsequent rates of change, as was reported in a study on IL-6 (Fabbri et al. 2015).

Genetics and Omics Approaches in Studies of Exceptional Human Longevity. Human studies have identified genetic and phenotypic factors associated with extreme longevity that could provide clues to potential targets for interventions to increase life span and health span. These studies have utilized various strategies, including genetic and genomic analyses, to identify single and composite biomarkers associated with longevity.

While a wide variety of morbidities (Evert et al.2003), including dementia (Leung et al. 2022) are found in a high proportion of exceptionally long-lived persons, several studies indicate that a substantial number of centenarians delay or escape aging-related diseases and disabilities, particularly "supercentenarians" who survive the age of 110 (Evert et al. 2003, Terry et al. 2008, Andersen et al. 2012). The genetic, molecular, and environmental determinants of exceptional longevity and its association with extended

health span remain elusive, and the identification of the modifiable factors that allow centenarians to live long and healthy lives is still an open question (Pignolo 2019).

The heritability of human longevity is limited (Kaplanis et al. 2018). However, extreme longevity clusters in families (Perls et al. 2000), and siblings of centenarians have a much better chance of living to extreme old ages compared to their birth cohort's expectations (Perls et al. 2002, Sebastiani et al. 2016, van den Berg et al. 2019). Notably, siblings of centenarians have a sustained mortality advantage at almost all ages (Perls et al. 2002), suggesting the presence of protective familial factors that exert their effects across the life span.

Genome-wide association studies (GWAS) of human longevity have mainly focused on common genetic variants that can be measured using single nucleotide polymorphism arrays. Such studies have identified variants associated with exceptional human longevity (Deelen et al. 2011, Sebastiani et al. 2012, Broer et al. 2015, Sebastiani et al. 2017, Deelen et al. 2019, Melzer et al. 2020), including replicated associations of variants of *APOE* (Sebastiani et al. 2019), *FOXO3* (Bae et al. 2018), and *CDKN2A/CDKN2B* (Pilling et al. 2016, Joshi et al. 2017). GWAS have also identified multigenic profiles associated with exceptional longevity (Sebastiani et al. 2012). In addition, pooling data sets from multiple exceptional longevity studies has provided sufficient power to allow GWAS detection of the association of rare variants with exceptional survival (Sebastiani et al. 2017). Notably, there are differing effects of several variants on survival during extreme old age vs. survival at earlier ages (Sebastiani et al. 2017). Whole-genome sequencing results from several large longevity studies are expected in the next few years and will provide enhanced opportunities for power and precision in association studies. Ongoing pedigree studies in multigenerational families provide additional opportunities to identify very rare variants contributing to longevity that would not be detected in population association studies. Such studies in long-lived families have identified linkage of genetic regions to traits associated with exceptionally healthy aging (Province et al. 2020).

Most traits, including major diseases and physiologic phenotypes, are highly polygenic, reflecting combined small effects of multiple individual genes. This can be characterized by calculating polygenic risk scores (PRSs), which aggregate effects of the variants known to be associated with a trait to compute a probability that that individual will manifest the trait. PRSs based on variants related to longevity ("polygenic longevity scores") predict life span (Timmers et al. 2019), discriminate between centenarians and aged non-centenarians, and predict survival probability in old age (Tesi et al. 2021).

PRSs have been shown to correlate with risk for various chronic diseases (Khera et al. 2018). There have been divergent findings on the relationship of disease PRSs to longevity: Some studies found a lack of significant relationships to exceptional

longevity (Beekman et al. 2010, Stevenson et al. 2015), while another found significantly lower PRSs for coronary artery disease and Alzheimer's disease in the exceptionally long-lived compared to controls (Gunn et al. 2022). PRSs for several physiological disease risk factors are correlated with longevity (Sakaue et al. 2020).

In parallel to genetics, proteomic and other biomarker studies have found that healthy agers and centenarians carry specific molecular profiles (Sebastiani et al. 2017, Tanaka et al. 2018, Lehallier et al. 2019, Tanaka et al. 2020, Sebastiani et al. 2021), some of which have been associated with diminished mortality risk. Proteomic profiles have also been identified for genetic variants associated with extreme longevity, such as *APOE* alleles (Sebastiani et al. 2019) and *CDKN2B* (Gurinovich et al. 2021) which indicate that some genotypes may be associated with slowing of age-related changes in circulating levels of specific proteins.

Insights from the relationships of such biomarker profiles to genetic longevity variants could increase understanding of the mechanism of action of these variants and their interaction with the environment at ages before substantial mortality has occurred. This knowledge could provide the basis to develop both preventive and treatment interventions. Further development of computational tools to integrate these data and connections is also needed.

Multicomponent processes influencing aging and survival. Aging changes are influenced by complex regulatory processes involving numerous components interacting with each other in multiple pathways and feedback loops. These web-like interactions limit the ability to interpret analyses of regulatory factors based on levels of a single component or the interaction of two or more. To capture the properties of multicomponent systems that may influence aging changes, integrative analytic dimensionality reduction strategies are needed to characterize their behavior (Cohen et al. 2012). Such strategies will be particularly important in analyses of dense multi-omics data to identify processes influencing longevity.

Two strategies have identified multicomponent physiologic system properties related to aging. One is a measure of physiologic dysregulation based on the concept of Mahalanobis distance (D_M) (Mahalanobis 1936). This approach combines measures of the extent to which the level of each of a group of factors in an individual differs from its mean level in a reference population into a single measure that reflects the rarity of that individual's combination of values for these factors. Higher values of D_M are used as an indicator of the degree of dysregulation of the system (Cohen et al. 2013). Within a wide range of potential biological markers, levels of D_M increase with the number of markers selected but, if a sufficient number of markers are selected, are relatively insensitive to the choice of individual markers (Cohen et al. 2015).

In a longitudinal human cohort analysis using panels of blood chemistry and hematologic laboratory measures, D_M increased with age in older women and predicted mortality over follow-up intervals averaging 8 years (Cohen et al. 2013). Subsequent analyses in other, primarily older, populations also found that D_M predicted mortality risk (Li et al. 2015, Arbeev et al. 2020) and found associations with diabetes and other age-related outcomes, but a lack of association with cancer (Li et al. 2015). Mahalanobis distances also increase with age in a traditional forager-horticulturalist population (Kraft et al. 2020). In a cohort of persons 38 years old, D_M was inversely related to measures of physical and cognitive functions (Belsky et al. 2018).

A second strategy to identify multicomponent system effects that influence aging changes used principal components analysis (PCA) of a set of 43 common clinical laboratory and hematologic measures in a study of three, primarily older, human cohorts (Cohen et al. 2015). The first principal component axis explained approximately 10% of the total variance of the measures in the data sets, and was driven by indicators of anemia, inflammation, and levels of calcium and albumin. The properties of this axis were termed "integrated albunemia". The relative contributions of the individual measures driving this axis were consistent across the three populations, suggesting that it reflects a multisystem physiologic process that is widely shared in humans. Integrated albunemia increased at an accelerating rate with age in these populations, and predicted mortality over intervals of up to 10 years, and frailty (using the Cardiovascular Health Study-based definition in (Fried et al. 2001), but was not related to presence or risk of chronic disease onset. The second principal component explained 8% of the variance in the data set. It included factors found in metabolic syndrome, predicted mortality, and was associated with presence of frailty, cardiovascular disease, and diabetes.

Integrative approaches to identify candidate targets and drugs using human and nonhuman genetic data. Evidence indicating human genotypic relationships to potential targetable mechanisms influencing traits is associated with an increased likelihood of success in the drug development and testing pipeline and in securing regulatory approval (Nelson et al. 2015). The multigenic basis of longevity suggests that there may be numerous potential drug targets for further consideration. However, the degree and context to which these genes contribute to longevity and hence provide evidence of their candidacy and consideration as drug targets needs exploration.

Identification of potential targets for interventions to increase human longevity can benefit from integrative approaches using human and nonhuman data. The contribution of such approaches is illustrated by a recent study comparing protein-coding genes in long- and short-lived mammals. The study identified amino acid changes in 996 genes associated with species longevity. Notably, there is little or no

variation within human populations at the specific amino acid sites of these changes, and the variants found at these sites generally have allele frequencies of less than 1%. However, human variants in these genes contribute to their enriched heritability for longevity as assessed in a UK Biobank GWAS analyses of parental life span (Farre et al. 2021). These results indicate the potential contributions of comparative studies, both in identifying factors that may influence human longevity that would not be found through human comparisons, and in identifying genes of interest for comparisons among humans. Integrating biologic insights from findings on longevity-related variants in cross-species comparisons of a given gene and comparisons among human variants of that gene could enhance the ability to identify potential targets.

However, a review of existing data from human and laboratory animal studies, combined with genetic and cheminformatics databases, did not find evidence that human variants in genes targeted by interventions that extend life span in mice influence human longevity. It also found that existing data on human SNPs associated with exceptional longevity do not provide strong evidence for their potential value in target identification and drug development, based on criteria such as their presence in coding regions or the presence of longevity-related variants in linkage disequilibrium with them (McCorrison et al. 2019). However, variants in linkage disequilibrium with longevity SNPs are associated with various age-related conditions and functional effects (McCorrison et al. 2019). The study authors note that the paucity of evidence for translatability of human longevity genetic findings to drug target identification may result in part from gaps in chemoinformatic and gene expression databases on the effects of pertinent drugs and gene expression pathways, particularly related to human longevity. These limitations could be addressed by further studies on functional effects of pertinent genetic variants.

Integrating findings from human and comparative species studies will require an appreciation of the fact that evolutionary differences in gene structure and content are more pronounced across species than within species. For example, in mammalian speciation, there has been extensive gene gain and loss through changes in copy number, with particularly high rates of appearance of fixed duplication variants in humans and chimpanzees (Thomas et al. 2021).

The presence of large structural genetic differences across species can complicate direct comparisons of factors such as effects of specific nucleotide substitutions on longevity. For example, while most human variants of the APOE and FOXO3 genes are single-nucleotide substitutions, many species differences in APOE and FOXO3 reflect alterations in large nucleotide sequences (Ensembl Comparative Genomics). In addition, the functional elements and processes involved in the regulation of gene expression have likely undergone substantial 'rewiring' as species diverged over an evolutionary timescale. For example, cross-species comparisons of the mTOR pathway

in *H. sapiens, M. musculus, D. melanogaster,* and *C. elegans* identified species differences in the presence or absence of regulatory elements found in humans (Podder et al. 2021). Research addressing the challenges of generalizing findings of genetic longevity studies from one species to another, and how studies of one species can inform the interpretation of observations in another species, must consider such phenomena.

Thus, there is a need to better characterize both regulatory networks within species, as well as the potential 'rewiring' of those networks across species that has occurred over evolution. This will help put into context the potential that a gene has as a target for longevity-enhancing drug development. Within species, genetic variation impacting a phenotype can reveal pathway-specific genes that may not be detected in cross-species comparisons because of species differences in regulatory networks. Across species, gain or loss of genes or gene components during evolution could influence species life spans and reveal targets for inhibitors that may enhance longevity. In addition, there is a need for more information on differences in gene splicing variants across species, and corresponding comparisons of their expression and gene products.

III. Identifying factors influencing longevity through comparisons of species with differing life spans.

Comparative strategies to probe mechanisms influencing species life span. Comparative studies of species with differing life spans have been extensively used to search for factors and biological pathways that may influence longevity (Ma and Gladyshev 2017, Tian et al. 2017). Whether there are a small number of universal mechanisms of longevity common throughout evolution, or numerous genes and genetic variants that contribute to variations in species' longevity is still unknown. In addition to genetic comparisons, phenotypic comparisons may be made on *in vivo* traits, tissue samples, and cell lines *in vitro.*

A common strategy to probe the relationship of a factor to species longevity is to determine its correlation with species life spans. These correlational studies have spanned differing taxonomic ranges (e.g., vertebrates, mammals, individual mammalian orders). This approach has identified correlations of numerous traits with species life spans, including epigenetic factors (Mayne et al. 2019), somatic mutation rates (Cagan et al. 2022), transcriptional regulation of various pathways (Ma et al. 2016, Lu et al. 2022), cellular metabolite concentrations (Ma et al. 2016), and resistance to certain cytotoxic agents (Harper et al. 2007). Such analyses require consideration of phylogenetic proximity between species, since closely related species may have inherited genes that modulate both longevity and the trait of interest even if these outcomes are not related to one another through any causal pathway (Garland et al. 2005).

Other studies have found mammalian species' longevity to be strongly correlated with

life-history traits such as time to maturity, gestation period, weaning time, and body weight. Studies on organ samples from various species identified relationships of transcriptional differences in pathways including tissue repair and energy metabolism to both life span and the timing of these earlier life history events (Fushan et al. 2015). It has been suggested that these correlations may reflect factors that contribute both to development and to adverse post-developmental changes (de Magalhaes 2012).

Studies in multiple clades. A key issue for assessing factors associated with species longevity is whether the association is found among multiple clades or is distinct to a clade. If association of a trait with longevity in one clade (e.g., primates) is also found in diverse independent branches of the evolutionary tree, it may be more likely to reflect a shared causal mechanism influencing longevity rather than coincidence. Traits that are correlated with species life span in multiple clades including primates are of particular interest.
In vitro studies of skin-derived fibroblasts from species with a wide range of life spans found correlations of longer life span with several traits within several clades, including primates. The finding of such correlations *in vitro* suggests that they may be related to species cellular differences that are retained even in the presence of identical environmental milieus. Such studies showed that resistance to induction of protein damage by oxidative stress *in vitro* is correlated with species life span (Pickering et al. 2015). Related *in vitro* studies have identified correlations of activity and abundance of the mitochondrial form of the antioxidant protein thioredoxin reductase with species life span in both rodents and primates (Pickering et al. 2017). These studies also found correlations of thioredoxin mRNA levels in a variety of primate tissues with species lifespan. Notably, however, values of these traits in human cells in the above studies do not closely fit the life span correlations found among other primate species. Another study found correlation, within multiple clades, of the timing of phosphorylation of stress-activated protein kinases (Elbourkadi et al. 2014).

Studies on exceptional taxa. Another comparative strategy to identify factors contributing to species longevity is to characterize differences between "outlier" taxa (e.g., species or orders) whose life spans, given their values of traits with known correlations to longevity (e.g., body mass), substantially exceed the duration predicted by these correlations, vs. taxa whose life spans fit these correlations (Ma and Gladyshev 2017). Examples include naked mole rats compared to other rodents, bats compared to other mammalian orders, and humans compared to other primates.
These studies have found that species longevity is associated both with lineage-specific adaptations and common mechanisms across species. They have identified unique traits associated with longevity within an individual clade, e.g., high translational fidelity in the naked mole rat, as well as traits shared across multiple clades, e.g., enhanced DNA repair. Notably, differing longevous species

sharing a common feature, e.g., increased cancer resistance, have in many cases evolutionarily acquired that feature by differing molecular mechanisms, e.g., higher propensity to cell cycle arrest in naked mole rats, greater propensity to apoptosis in elephants.

Evolutionary genetics of species longevity. Evolutionary approaches have been used to characterize genetic factors affecting species longevity across a variety of taxa and mechanisms mediating them. A study in 20 mammalian species with life spans ranging from 4 to 122 years, including humans and six other primates, examined the relationships of gene duplication to evolutionary changes in longevity. Using a database of species transcripts and protein family assignments (Tacutu et al. 2018), gene families were characterized as "longevity associated" if a protein within them was coded by a gene included in a database of genes related to longevity or aging. Five gene families with longevity-associated genes had a significant evolutionary expansion by duplication in long-lived species within their clades, but no increase in short-lived species. These gene families are enriched for factors involved in 3-UTR-mediated translational regulation, metabolism, and gene expression (Doherty and de Magalhaes 2016). The potential mechanisms by which these pathways or the emergence of new genes in them by duplication could influence species longevity are not yet clear.

Another genomics study compared protein differences within pairs of closely related primates and other mammalian species having similar life spans versus differences within pairs in which one species had evolved greater longevity than the other. These comparisons found associations of increases in longevity with accelerated changes in proteins involved in lipid metabolism, DNA damage responses, and the proteasome-ubiquitin system, suggesting that these systems were under positive selection in the evolution of longevity (Li and de Magalhaes 2013).

The above studies illustrate challenges and opportunities for genome-wide analyses to identify factors influencing species longevity. Direct demonstration of statistical significance for individual genes in interspecies comparisons may be hindered by the large number of comparisons involved, and possibly also by differing mechanisms in differing species to achieve longevity. However, such studies can identify candidate genes and variants that can be examined more closely in follow-up genetic and biological studies.

IV. Biodemographic and life history considerations in primate species comparisons.

Trajectories of mortality over the life course. In characterizing species differences in survival over the life course, it is important to consider both the pace of mortality (e.g., life expectancy from birth or maturity) and the shape of mortality. The shape of mortality can be characterized as the trajectory of age-specific mortality relative to

average adult mortality and can be expressed numerically as a measure of the inequality of ages at death. The combination of both types of metrics is important for understanding the impact of factors influencing survival and longevity (Baudisch 2011). Pace and shape measures can also be applied to life history stages such as the pattern of fertility (Baudisch and Stott 2019). Use of such metrics could be useful in exploring the relationships between the temporal distributions of reproduction and mortality over the life span.

Use of combined pace and shape measures in comparisons of human populations, spanning traditional and industrial societies, has shown that life expectancy is positively correlated with life span equality and follows a tight linear relationship (Colchero et al. 2016). However, in some human populations, recent increases in life expectancy that have been principally driven by decreases in mortality in old age have been accompanied by decreased equality in ages of death (Aburto et al. 2020).

The trajectory of mortality over the life span has also been characterized by functional relationships between age and mortality rate. The widely used Gompertz-Makeham model defines mortality rate as the sum of an age-independent component and a single exponential age-dependent component (Finch et al. 1990). Another model creates separate functions for three life stages: an early life component in which mortality probability decreases from birth to maturation, a component between later childhood and young adulthood that reflects age-independent mortality risk, and a later-life component in which mortality risk increases with age (Siler 1979). A study of multiple populations in seven primate genera found that, within genera, life span equality and life expectancy were linearly correlated. Use of this model indicates that the within-genus relationship is principally determined by variation among populations in early-life and age-independent mortality risk, rather than by differences in the rate of mortality rise in old age. However, there are substantial differences across primate genera in the late-life exponential rate of mortality increase (Colchero et al. 2021). Across and within primate species (including humans) there is a need for more comparative demographic data on the relationships among survival parameters at differing phases of the life span.

Relationships of reproductive strategies to life history traits. Species differences in survival risk during development and early adulthood in humans and larger primates are related to differing strategies of maternal investment in reproduction and health. These strategies entail variation in the timing of births and maternal support for offspring that may be also related to subsequent life history and life span.

An evolutionary theory of aging has postulated a tradeoff between fertility and longevity due to the competing energy demands of reproduction and somatic maintenance (Kirkwood and Holliday 1979). However, this relationship is not consistently found across species comparisons (Maklakov and Chapman 2019, Cohen et al. 2020). Among non-hominid primates, the interbirth interval is correlated with both body mass and adult life expectancy, consistent with the concept of trade-offs between

early reproduction and life span, but interbirth intervals in great apes and humans do not fit these correlations well (Emery Thompson 2022 in press, (Alberts et al. 2013, Bronikowski et al. 2016, Conde et al. 2019). In apes, although life expectancy is predicted by the relationship of primate body mass to species life span, interbirth intervals are longer than that that predicted based either on species life span or body mass. In contrast, human life span is greater than predicted by body mass, but interbirth interval is shorter than predicted by either body mass or adult life expectancy.

These differences are at least partly related to differences between smaller primates and the hominids in the timing of conception (Thompson 2013, Van Noordwijk et al. 2013). Most smaller primates breed annually, triggered by external seasonal cues, in a cycle that allows lactation to occur when food is usually abundant, but risks high mortality if food is scarce during infancy. In hominids, conception is dependent on internal cues, with conception conditional on good health and energy balance. This strategy can entail prolonged durations of non-conceptive cycling, but it lessens the risk to infants and mothers in times of scarcity. The duration of lactation and its relationship to resumption of cycling differ correspondingly between smaller primates and hominids: In smaller primates, infants are weaned when their nutritional needs exceed the mother's ability to meet them (usually within months) and cycling resumes. In humans and other hominids, lactation can extend for several years, and resumption of cycling is driven by restoration of positive energy balance after parturition, when the mother's energy intake exceeds the level she needs for herself and provision to offspring, which also may not occur for several years (Valeggia and Ellison 2004, Thompson et al. 2012). Differences in maternal energy availability can be related to social factors: Whereas chimpanzee mothers are largely self-reliant in obtaining food for themselves and their offspring, human mothers have both technology and cooperative care systems to provide food and can regain positive energy balance more quickly.

Maternal energy surpluses are used in differing strategies for reproductive fitness, which can affect both maternal reproductive life spans and offspring growth rates, as well as interbirth intervals: Shorter-lived primates use energy surpluses to support higher reproductive rates or faster infant growth. Longer-lived primate species can use surpluses to decrease interbirth intervals, but also to improve maternal health, which may contribute to longer reproductive life span by diminishing maternal mortality. There is evidence that hominids invest in a long reproductive life span to produce greater reproductive fitness in the face of relatively higher reproductive costs than would direct investment in fertility. For example, female mortality is higher in birth seasons than mating seasons in rhesus macaques (Hoffman et al. 2008), while lactating mothers did not experience elevated mortality risk in a chimpanzee population.

Primate species also differ in strategies for distribution of energy surpluses between mothers and offspring. These energy distributions can affect offspring growth rates as well as maternal health. In baboons, greater maternal energy availability is associated with both higher reproductive rates and improved infant growth (Garcia et al. 2009), whereas chimpanzee mothers with greater energy availability have faster reproductive

rates, but slower growth of their offspring (Thompson et al. 2016). In a human Ethiopian population, interventions that provide energetic benefits to mothers under conditions of limited energy availability were associated with higher fertility but also with increased risk of child malnutrition (Gibson and Mace 2006).

Human's longer post-reproductive lifespan compared to apes is likely to have influenced other life history stages. Multi-generational caregiving and resource sharing, documented in the Bolivian Tsimane (Hooper et al. 2015) enable earlier weaning, more frequent pregnancies, and lower overall mortality. These benefits provided by older family and community members suggest that unique social interactions enabled evolution of our longer lifespans compared with apes, who have minimal participation by older members of their community in childcare.

For both humans and nonhuman primates, more understanding is needed on relationships between reproductive schedules, social environments, and health and longevity of mothers and offspring over their life courses. Both field studies and captive populations provide opportunities for longitudinal studies on these topics.

In addition, there is a need for understanding how biologic factors that regulate the reproductive cycle and its timing, and variability across species in such factors, e.g., factors that affect the age of sexual maturation, the likelihood of conception in differing conditions of short- and long-term energy balance, and protective physiology between successive reproductive bouts that evolved in long-lived primate mothers, may influence both reproductive and organismal life span.

V. Evolutionary factors in primate species longevity

Evolution of primate-specific, hominoid-specific, and human-specific genes and relationships to phenotypes. New genes originating within the evolution of primates, hominoids, and humans may contribute to differences in primate species life spans and the evolution of human longevity. At least three general mechanisms can drive emergence of new genes: DNA-level gene duplication, RNA-level gene duplication mediated by retrotransposon capture of mRNA followed by re-incorporation into the genome by reverse transcriptase, and *de novo* gene origination in which functional genes emerge from pre-existing noncoding regions (Chen et al. 2013). Duplication events of gene fragments, including introns or sections of them, can contribute to the appearance of functionally new chimeric proteins. There is evidence of these processes in human DNA (Tan et al. 2021).

Notably, genes originating in mammalian evolution before the divergence of primates may be converted to pseudogenes in some species (including primate species) yet regain activity in subsequent evolution of new species. (This occurred for the HBBP1 gene, which regulates human erythropoiesis) (Ma et al. 2021). One implication of this phenomenon is that a longevity-influencing gene found in some but not all primate

species may be a reactivated ancestral gene, not originating in primate evolution, and may also be active in non-primate taxa.

Duplication and *de novo* mechanisms have resulted in the addition of more than 300 human-specific genes and 1,000 primate-specific genes to the human genome (Zhang and Long 2014). One example is the duplication of GLUD2 from GLUD1 in a hominoid ancestor. GLUD1 and GLUD2 encode glutamate dehydrogenase (GDH). Sequence changes in GLUD2 occurred through positive selection after the duplication, yielding amino acid changes that produce a GDH isotype allowing high neurotransmitter flux in the brain. This may have contributed to enhanced brain function in humans and apes (Burki and Kaessmann 2004).

During evolution, new genes can undergo selection pressure to support biological processes of an evolving organ function. Thus, in addition to the products of new genes, it is important to learn the distributions of tissues in which they are expressed, and the functional pathways in which they participate. In a study that assigned human genes appearing in primate evolution (primate-specific genes, PSGs) to tissue co-expression modules based on adult gene expression databases, PSGs were particularly likely to be expressed in testis and placenta, suggesting selection pressure and rapidly evolving changes in sexual reproduction and mother-fetus interactions (Shao et al. 2019). In this study based on adult gene expression patterns, expressed PSGs were found less frequently in the brain than organism wide. In human fetal brain, PSG expression is enriched compared to other genes, particularly during middle-fetal development (Zhang et al. 2011, Ma et al. 2022). Interestingly, PSGs upregulated in the embryonic brain also tend to be upregulated in tumors and contribute to elevated tumor risk (Ma et al. 2022). This pattern is consistent with the antagonistic pleiotropy hypothesis whereby natural selection could maximize fitness in youth at the cost of diseases of aging (Williams 1957).

Evolutionary longevity-related genetic, epigenetic, and gene expression differences in primates. A whole-genome analysis in multiple primate species examined the relationship of changes in genes for orthologous proteins to evolution of longevity using two strategies (Muntane et al. 2018): In one approach, species within each primate family were divided into two groups, one with life spans more than one standard deviation above the family mean ("increased life span species") *versus* the remaining species in the family. "Increased life span" species included *Homo sapiens, Macaca mulata,* and *Macaca fascicularis*. Twenty-five amino acid substitutions in 25 proteins were found in all of the "increased life span" species. Though this number of parallel changes was not greater than expected by chance, the set of 25 was significantly increased in the proportion of genes related to wound healing, hemostasis, and cardiovascular disorders. Notably, 20 of the 25 variants were fixed (i.e., without polymorphisms) in human populations, indicating that they would not have been identified by genetic comparisons in human populations.

The second approach was a genome-wide analyses of correlations between changes in longevity (and other life history traits correlated with longevity) with selection of changes in genes coding for orthologous proteins, based on the rates of nonsynonymous vs. synonymous amino acid coding changes during branching of the primate evolutionary tree. This approach found no significant correlations of such coding changes with life span or other life history traits after correction for multiple comparisons. However, a secondary analysis of proteins with nominally significant correlations for at least one of four life history traits (maximum life span, age of female maturity, gestation length and weaning time), found that that evolutionary genetic changes in 19 were related to all four traits, a degree of clustering significantly greater than expected by chance. The genes included GDF15, whose circulating levels are correlated with mortality and health span in humans (Tanaka et al. 2018, Tanaka et al. 2020). This set of genes was enriched in factors related to heart disorders. Genes related to all four life history traits may be of particular interest in exploring potential mechanisms that underlie the correlations of durations of earlier life history stages to species life span.

A more recent study comparing humans, chimpanzees, rhesus macaque, marmosets, bush babies, and mouse lemurs identified 276 protein coding genes whose rate of evolution, as measured by rate of nonsynonymous to synonymous mutation correlates with species life span, consistent with positive selection for these genes in the evolution of longevity differences. These included genes related to cancer, cell senescence, immune function, and development. Five of these genes were found exclusively in hominid evolution (Tejada-Martinez et al. 2022).

Increased CpG density in promoters is also associated with longer species life span within primates (McLain and Faulk 2018). It has been suggested that higher CpG density may provide greater buffering capacity against age-related dysregulation of DNA methylation. A genome-wide study characterized evolutionary changes in CpG methylation patterns in hominid evolution. It found accelerated methylation changes in humans compared to other hominids in genes in pathways influencing telomere regulation, development, neuron differentiation, and other functions (Sahm et al. 2021).

The above studies illustrate challenges and opportunities for genome-wide analyses to identify factors influencing primate species longevity. Demonstration of statistical significance for individual genes in interspecies comparisons is limited by the large number of comparisons involved. However, such studies can identify candidate genes and variants that can be examined more closely in follow-up genetic and biological studies. In addition, comparative genome wide studies need to address the challenges posed by possible differences among taxa in mechanisms that affect life span, and by differences in function of putative orthologs, related to evolutionary rearrangements of genetic architecture, discussed in a previous section.

Non-coding genetic regions of accelerated human evolutionary change. A variety of evolutionary genetic changes may have contributed to differences in primate species phenotypes including life spans (Table 1). Differences between humans and chimpanzees include 35 million single nucleotide substitutions, five million deletions/insertions, 10 large chromosome inversions, chromosome fusion, human chromosome 2, duplications comprising 5% of the genome, human-specific constitutive heterochromatin bands on at least four chromosomes, and human-specific pericentric inversions on at least two chromosomes (Franchini and Pollard 2015).

Table 1: Evolutionary Genetic Changes

- Single nucleotide substitutions
- Nucleotide insertions and deletions
- Gene duplications
- Gain or loss of genes
- Heterochromatin changes
- Rearrangements of topologically associating domains
- Chromosome inversions and fusions

Evolutionary selection for nucleotide substitutions in gene coding regions can be assessed by differential rates of synonymous and nonsynonymous changes. However, this approach does not apply to non-coding regions. A strategy to identify differences in non-coding regions between humans and other primates that are associated with their phenotypic divergence is to identify such regions with conserved identity in other primates, but which have accumulated multiple changes in humans (Franchini and Pollard 2017). Researchers have identified more than 2500 of these "human accelerated elements" (HARs), which cluster near regulatory genes, including transcription factors expressed in development (Franchini 2021).

Functional differences related to HARs have been found in several studies. An investigation of the human genome for HAR clustering found that the largest cluster, 14 HARs, was in the gene for the transcription factor NPAS3 (which regulates brain neurogenesis). Human NPAS3 variants are associated with neurologic diseases. Transgenic zebrafish studies indicate that 11 of these HARs function as transcriptional enhancers. Kamm et al. 2013 studies in developing mice found that the human sequence of an HAR in NPAS3 produced NPAS2 expression in more constituents of the nervous

system, compared to the chimpanzee (2xHAR142) sequence (Kamm et al. 2013). Analogous studies found numerous HARs in a topologically associating domain that includes the FOXP2 locus (which is associated with speech function). These studies found that the human forms of two of these HARs result in gain of FOXP2 function, compared to the chimpanzee form (Caporale et al. 2019).

HAR-based methods could be applied to other phenotypes and functions beyond the brain and could potentially illuminate human evolutionary factors influencing life span. Identification of such HARs could be broadened and accelerated by using higher-throughput alternatives to the methods described above, including massively parallel reporter assays that screen thousands of sequences for regulatory activity (Ernst et al. 2016, Klein et al. 2020). Such methods could be further enhanced by combination with CRISPR gene editing (Franchini and Pollard 2017).

Comparative studies of platyrrhine primates: Value in longevity studies. Platyrrhine primate species exhibit a wide range of life spans, body sizes, brain sizes, ages of first reproduction, litter sizes, and living environments. This variation makes them valuable for comparative studies of aging and biological processes. Marmosets, a short-lived platyrrhine species, are widely used in aging studies. Capuchin monkeys are exceptionally long-lived - the only non-hominid species with similar lifespans to nonhuman hominids. They also have other longevity-associated traits, including a long period of juvenescence before sexual maturity (the longest of any monkey species) and large brains. (Melin et al. 2020). These characteristics provide a unique opportunity to study factors contributing to evolution of primate longevity in a separate taxon, which could complement and illuminate studies on hominids. Moreover, like humans, they demonstrate a high degree of flexibility and adaptability to differing habitats (Melin et al. 2014).

A comparative genetics study of the long-lived white-faced capuchin *Cebus imitator* with 10 other primate species and 4 other mammalian species found evidence for positive selection for several hundred genes in the *Cebus* lineage (Orkin et al. 2021). Functional analyses found many of these genes to be associated with neurogenesis and brain development. There was also evidence for positive selection on 48 genes listed as related to longevity in the GenAge and CellAge databases (Tacutu et al. 2018), including genes influencing DNA damage responses, metabolism, insulin signaling, and cell cycling and proliferation. Some of these functions have been implicated as influencing species longevity in other studies (Grube 1992, Li and de Magalhaes 2013). This study did not compare selection in regulatory regions and differences in gene copy number, which could also be related to capuchins' species life span. In addition, the functional properties in capuchins of the genes identified in this study remain to be fully explored.

Understanding factors affecting interactions of physiology, environment, behavior, reproductive life history, and genetic factors that influence aging in nonhuman primates can be greatly enhanced by a greater ability to collect and analyze specimens

from individuals in field studies, including isolation of DNA of sufficient quality for genotyping. Urine and feces provide opportunities for population sampling and longitudinal tracking of individuals in such studies. Such specimens provide opportunity to assess aging-related biological factors such as cellular senescence, telomere attrition, epigenetic alteration, as well as other indicators of host and microbiota status, and their interactions with other factors in influencing aging-related outcomes.

An example of how such approaches can identify environmental interactions contributing to genetic variability within a species is a study which sequenced DNA from epithelial cells isolated by flow cytometry from fecal samples of individuals in two *C. imitator* populations, comparing those from dry and rainforest environments. Findings revealed population divergence in genes affecting water balance, kidney function and metabolism (Orkin et al. 2021). Such genetic differences in species subpopulations could be related to their life history and survival characteristics and help to inform inferences based on species comparisons.

Interactions of the exposome with factors affecting longevity, immune function, and cognition in hominin evolution. Humans have a longer life span than apes, including a longer post-reproductive life span. They are at higher risk for several diseases principally found in the post-reproductive period, including atherosclerotic cardiovascular disease and Alzheimer's disease. The evolutionary increase in hominin life span was accompanied by several changes in the exposome: a shift from vegan to omnivorous diets, social and environmental changes associated with multigenerational caregiving, increases in exposures to human and domestic animal feces, changes in exposure to parasitic and microbial infections and a variety of inflammogens, including wood smoke and cooked meat and, more recently, industrial pollutants and adiposity (Trumble and Finch 2019).

These exposome changes have been accompanied by changes in genes affecting inflammation and defenses against infection, as well as genes affecting brain functions. These two functional categories interact, e.g., in immune defenses against brain infection. Some of the altered genes in human evolution affect both brain and immune/inflammatory functions: Human-specific alleles have evolved in both APOE and CD33 (Siglec-3), which influence risk of both Alzheimer's disease and infection (Siddiqui et al. 2017, Trumble and Finch 2019). More information about interactions of these genes could illuminate the pathogenesis of Alzheimer's disease.

The phenotypic effects of genes interacting with the exposome can change with alterations in the exposome: For example, the human APOE4 allele variant, which diverged from the ancestral primate form early in human evolution, appears to provide resistance to pathogens to which early humans became increasingly exposed, thereby providing survival benefits. APOE4 allele frequency was associated with increased

female fertility and survival in a rural Ghanaian population with high pathogen burden (van Exel et al. 2017). In other rural, non-industrialized populations where parasite infections are common, cognitive function is maintained or improved in older adults with high levels of eosinophilia related to parasite burden who carried the APOE4 allele, but not in non-carriers (Trumble et al. 2017).

However, the transition to industrialized societies was accompanied by exposome changes, in which the burden of many infections found in traditional societies decreased. The decrease in pathogen-driven inflammatory factors associated with these infections was accompanied by an increase in 'sterile" inflammatory factors including adiposity and pollutants (Trumble and Finch 2019). In this environment, APOE4 has pro-inflammatory effects and is associated with a higher risk of both mortality and inflammation-related late-life conditions, such as cardiovascular disease and Alzheimer's disease, compared to the later-evolving APOE2 and APOE3 alleles. APOE4 has been found to aggravate the increases in risk for cognitive decline and dementia posed by air pollutants, compared with other APOE alleles (Cacciottolo et al. 2017).

Notably, APOE is part of a gene cluster whose order on the DNA strand is highly conserved across mammalian species, including more than 20 genes affecting lipoproteins, inflammation, brain function, reproduction, and longevity. In humans, genetic variation within this cluster has been associated with differences in longevity and risk for several conditions including Alzheimer's disease, atherosclerosis, and obesity. These genes interact and have conserved co-expression in several tissues, including the brain. Transcription factor binding motifs in this cluster are highly conserved across species (Haghani et al. 2021). Other gene clusters, such as the major histocompatibility complex, also have analogous coordinated multi-gene responses. It has been suggested that such clusters producing pleiotropic effects on multiple aging-related factors, may play a role in the regulation of species longevity (Finch and Rose 1995).

VI. Biological factors related to primate species life spans and health spans

Primate species bioenergetic differences in relation to brain and life history. There has been long-standing interest in the relationship of metabolic rates to species life spans. "Rate-of-living" theories were based on the premise that cells have a fixed limit on energy expenditure over the life span, which is exhausted more quickly in species with faster metabolic rates, thus causing an inverse relationship between metabolic rate and life span. However, an analysis in mammals and bird species that accounted for the relationship of body mass to both life span and metabolic rates found that, after adjustment for body mass, species life span was only weakly correlated with daily energy expenditure (and not with basal metabolic rates) in mammals, and with neither

daily expenditure nor basal metabolic rates in birds (Speakman 2005). Another study which also added adjustment for phylogenetic distances between species found no relationship of mammalian or bird life spans to metabolic rates (de Magalhaes et al. 2007).

The relationship of metabolic rates to life span is also a feature of the "free radical theory of aging" proposed in the 1950s (Harman 1956). This theory predicts that life span is inversely related to the level of oxidative stress produced by aerobic respiration. Higher metabolic rates would be expected to produce greater amounts of oxyradicals and more oxidative stress. However, the level of oxidative stress produced by a given metabolic rate could be modulated by cellular processes to prevent, mitigate, or repair oxidative damage, which would modulate the relationships of metabolic rates to life span.

Caloric restriction studies, in which energy intake and expenditure are experimentally reduced, has found increases in longevity in most (but not all) rodent models, though results in nonhuman primates have been conflicting (Mattison et al. 2012, Colman et al. 2014, Pifferi et al. 2018). Evidence of effects on markers of oxidative stress in rodents has also been conflicting (Ward et al. 2005, Mitchell et al. 2015). A study of 2-year human caloric restriction found a significant treatment-related decrease in one marker of oxidative stress but not in others (Redman et al. 2018). The decrease was correlated with the degree of reduction in daily energy expenditure.

There are important differences between primates and non-primates, and between humans and other hominids, in relationships between metabolic rates and life span. Primates have low levels of daily energy expenditure based on their body size compared to other placental mammals (Pontzer et al. 2014), despite their large, metabolically expensive brains. In addition, primates have longer life spans in relation to their body size than other placental mammals. The combination of these two findings is consistent with an inverse relationship between metabolic rates and primate life span. However, as with non-primate species, differences among primates in life span from levels predicted by body size are not well correlated with differences in daily energy expenditure from predicted values (Pontzer et al. 2014). This suggests that other factors, possibly differences in protection against oxidative damage from metabolic processes, contribute to variation in primate species lifespan.

Notably, humans have higher daily energy expenditure and basal metabolic rates in relation to fat-free body mass than other hominoids, while having a longer life span, shorter interbirth intervals, more prolonged childhood growth, and larger brains. This was demonstrated in a comparison of adult chimpanzees, bonobos, gorillas, orangutans, and humans (Pontzer et al. 2016), which also found that the difference persisted after adjustment for physical activity. The higher basal metabolic rates in humans are consistent with higher mass-specific organ metabolic rates. The higher

human rates are sufficient to allow the energy needed for human faster reproductive schedules and larger brain size. They could also allow greater allocation for somatic maintenance, which could influence longevity.

Anatomical and behavioral adaptations in human evolution may also have contributed to the ability to provide sufficient energy intake to allow humans' higher energy expenditure and its allocation to processes contributing to increased longevity, increased fertility, and slower life history traits. This includes a reduction in gut size accompanied by a shift to a more digestible energy-dense diet (Aiello and Wheeler 1995), food sharing to minimize risks of periodic shortfalls in energy intake below levels needed to maintain a high energy expenditure, and increased walking efficiency to allow increased energy obtained from foraging (Pontzer et al. 2014).

Thus, primates present two differing relationships between metabolic rates and longevity: 1) primates' combination of slower metabolic rates and increased longevity compared to other placental mammals of similar size, and 2) humans' combination of faster metabolic rates and increased longevity compared to other hominoids. Greater understanding of the mechanistic bases for each of these relationships could yield valuable insights for translational efforts to develop interventions affecting human longevity.

One possible factor related to both relationships could be the role of metabolically related oxidative damage. Slower metabolic rates in nonhuman primates could be associated with lower rates of oxidative damage accumulation, resulting in slower age-related declines in function and health. Humans may have developed better protective mechanisms than other hominoids against metabolically-related oxidative damage, allowing them to survive longer with high rates of energy expenditure, some of which may have been used to protect against oxidative damage itself. These possibilities could be tested in primate species comparisons of differing measures of oxidative stress, oxidative damage, and repair of oxidative damage, in relation to the level of energy expenditure. Although some measures of oxidative stress products such as urinary isoprostanes or urinary 8-hydroxydeoxyguanosine (8-OHdG), are available, additional measures of the rate of generation of reactive oxygen species and of damage accumulation and removal are needed.

Age-related physiologic dysregulation across primate species. Increases in physiologic dysregulation with age have been found in multiple primate species, as measured by the Mahalanobis distance measure of dysregulation and the PCA-based measure of integrative albunemia discussed in the section on human studies. These studies used nonhuman longitudinal data available through the Primate Aging Database from routine laboratory blood chemistry and hematology measures collected approximately every three months on multiple primate species, as well as age and mortality metrics. In

humans, other hominids, Old and New World monkeys, and lemurs, dysregulation increased with age in males and females in all species, significantly so in almost all (Dansereau et al. 2019). In an analysis of four nonhuman primate species in this study (chimpanzees, rhesus macaques, pigtailed macaques, and common marmosets) higher D_M distances predicted significantly increased mortality risk independent of age in all except rhesus macaques.

Notably, for most species in the study, including humans, Mahalanobis distances calculated using the species' own physiologic data as a reference point correlated positively with distances using another primate species' physiologic data as a reference point. Correlations tended to be stronger for phylogenetically closer pairs, particularly chimpanzees and humans. Such correlations suggest shared physiologic dysregulation processes across the paired species.

In comparisons of integrative albunemia (IA) among humans and nonhuman primate species, IA was positively correlated with age in all species except rhesus macaques, in whom it was negatively correlated (Wey et al. 2019). This study also found positive correlations between IA and mortality risk in species except macaques. However, individual nonhuman species correlations fell short of statistical significance but were significant for species combined. Many of the individual drivers of integrative albunemia had similar contributions across species, suggesting a shared pathophysiology.

As with Mahalanobis distance, a species' IA based on using its own physiologic data to calculate its PC axis was correlated with its IA based on using another species' physiologic data to calculate the axis, suggesting a shared physiologic process. Correlations were generally stronger than those for D_M and were less related to phylogenetic distance. Notably, however, chimpanzees' species-specific IA scores were poorly predicted by their scores based on loadings from several other species including humans, while humans' IA scores were well predicted by their IA scores using chimpanzee loadings.

These types of studies illustrate the value of data routinely collected at primate centers which are often available for studies without substantial additional costs. These data provide the opportunity for numerous additional integrative physiologic comparative studies to identify similarities and differences among primate species in factors influencing aging, with potential translatability to humans.

Age-related pathologies in differing primate species: Examples from chimpanzee studies. Comparisons of age-related pathologies in humans and non-human primates can reveal both similarities and differences related to their phylogenetic proximity, differing environmental influences during evolution, and husbandry-related effects. Studies on age-related pathologic and pathophysiologic outcomes in chimpanzees illustrate the insights from such studies and the research issues they face.

In an analysis of clinical and necropsy data on 36 adult captive chimpanzees (most of whom were carriers of hepatitis B or C, or HIV1), sudden cardiac arrest was the leading cause of death in 42% of all deaths and in 11 of 15 male deaths. Renal disease and septicemia accounted for the majority of remaining deaths (Lammey et al. 2008). The cardiovascular pathologies found in this population differ markedly from the atherosclerotic vascular pathologies that most prominently contribute to cardiovascular deaths in older humans. Interstitial myocardial fibrosis and ventricular ectopy were found in a high proportion of animals and were associated with risk of sudden death. Other studies also found high prevalence of interstitial myocardial fibrosis and its relationship to sudden cardiac death in chimpanzees, as well as other great apes (Varki et al. 2009).

Data collection over the life span of differing primate species is crucial for understanding pathophysiology-pathology relationships, and their differences across species. A key need is to establish reference ranges for each species to clarify relationships between healthy and pathologic conditions. A study in chimpanzees established reference ranges for normotension, pre-hypertension, and hypertension, and found a relative mortality risk of 2.6 associated with hypertension (Ely et al. 2011). Another study established normal values for echocardiographic parameters in chimpanzees (Sleeper et al. 2014).

In addition to data from regular health exams and specimen collection at primate centers, additional continuous monitoring data can be valuable. For example, implantable loop recorders have been valuable in assessing relationships of cardiac arrhythmias to clinical outcomes in chimpanzees (Lammey et al. 2011).

It is also important to clarify and compare the relationships of *in vivo* biomarkers to conditions and pathophysiology in differing nonhuman primate species. For example, a case control study of chimpanzees with and without cardiovascular disease (CVD) found that circulating levels of the human CVD marker brain-type natriuretic protein were also associated with CVD in chimpanzees, whereas other human CVD markers, e.g., C-reactive protein and lipid panel components were not (Ely et al. 2011).

Findings such as the above raise implications for further studies. In many cases, the mechanisms underlying major age-related conditions in nonhuman primates (e.g., myocardial fibrosis and the electrophysiologic events in sudden cardiac deaths in chimpanzees) are not well understood. It will also be useful to identify similarities as well as shared pathologies across primate species. It will be important to consider the implications of better clinical care and husbandry of captive nonhuman primates that could result from greater understanding of these pathologies. Improvements in husbandry and care could result both in longer survival and differences in the spectra of prevalent age-related pathologies from those currently found.

VII. Primate species differences in brain anatomy, metabolism, and neuropathology

Differences in brain anatomy and their relationship to life history traits. In multiple mammalian taxa, including haplorrhine primates, large brains are associated with slow development, late maturation, low reproductive turnover, and a long life span (Allman et al. 1993, Isler and van Schaik 2009, Gonzalez-Lagos et al. 2010). Evolutionary hypotheses have been proposed to account for positive correlations between brain size and life span. The "cognitive buffer" hypothesis attributes the relationship to cognitive benefits of large brains, which increase flexibility in behavioral responses to environmental challenge, thereby enhancing survival and achieving longer life span. The "developmental costs" hypothesis attributes the correlation of brain size and life span to the longer interval during development required to produce larger brains (Powell et al. 2019).

Phylogenetic comparative analyses of correlations in 128 eutherian mammal species between brain size and various life history traits lend support to the developmental costs hypothesis, particular in relation to early development. These analyses found a strong relationship between maternal investment (duration of gestation plus lactation) and species life span, consistent with the developmental costs hypothesis. Further, when duration of maternal investment was included in a multivariate analysis of the relationship of life history traits to brain size, brain size was significantly related to duration of maternal investment, but not to life span or other life history traits (Barton and Capellini 2011).

Recent primate studies indicate differing relationships of the development of specific brain regions to life history traits, including life span. A comparison of 48 primate species found cerebellar size to be significantly related to the duration of the juvenile period from weaning to age at first birth, and to adult life span, whereas neocortical size is related to gestation length and not to adult life span (Powell et al. 2019). Compared to non-apes, apes have greater cerebellar volumes in relation to neocortex volumes (Barton and Venditti 2014), and longer lactation and juvenile periods than expected based on their body mass (Powell et al. 2019). Notably, in primates the cerebellum reaches its maximum size much later in post-natal development than does the neocortex. Together these findings suggest the possibility that apes' prolonged juvenile cerebellar development provides extended opportunities for environmental inputs that contribute to the development of cerebellar functions that might influence survival and life span.

This work, and the previously-noted studies on social factors in primate reproductive life histories, indicate the importance of looking at relationships of evolutionary changes in individual brain regions and their development to social and life history traits, and their potential pleiotropic effects that could affect survival in adulthood. Further insights into evolutionary relationship between brain size and slow life history

in humans could come from species comparisons of more specific regions (e.g., various neocortical regions) and other brain phenotypes, e.g., extent of myelination, or number of neurons and other types of brain cells in particular regions. The complexity of neurodevelopment and the extended period of growth and wiring of the human brain suggest that comparative measures of neurodevelopment and neurodegeneration may require refinement to better identify changes in the primate lineage.

In addition to differences among brain regions, there is a need for attention to species differences in the number and phenotypic properties of differing brain cell types. For example, single-cell transcriptomic studies from samples taken from differing brain regions of six primate species, including humans and chimpanzees, found greater species transcriptomic divergence in oligodendrocytes and astrocytes than in neurons (Berto et al. 2019, Khrameeva et al. 2020).

Relationships of brain bioenergetic differences to primate species life histories. Comparisons of humans and chimpanzees have identified additional brain differences related to differences in life history traits. Humans' larger brains and highly metabolically active brains place high energetic demands. Humans allocate a very high proportion of total energy expenditure to the brain: over 20% in adulthood compared with approximately 10% in chimpanzees (Hofman 1983, Bauernfeind and Babbitt 2020). In human childhood, when cortical synaptogenesis is highly active, this proportion is even higher. Human PET and MRI studies have found an inverse relationship between brain glucose metabolism and growth rate from birth to adulthood in humans, consistent with the concept that energetic costs of brain development are related to slowing and protracted duration of body growth (Kuzawa et al. 2014). Humans and chimpanzees also differ in life history stages in which aspects of brain development are completed: Chimpanzees and other primates complete cortical myelination around the time of sexual maturity. In humans, cortical myelination is slower during childhood and extends well beyond sexual maturity, past adolescence, and into early adulthood, and may contribute to enhancement in emotional control and decision-making (Miller et al. 2012).

It has been proposed that the energetic demands of developing and maintaining large metabolically active brains limit energy available for offspring growth, limit growth rates, extend the duration of development, and increase selection for extended adult life span to support juvenile growth (Charnov and Berrigan 1993). To care for needy, culture-bearing, human infants over long dependent periods of development, it has been hypothesized that there was selection for an elongated life span, so that multiple caregivers, including perhaps grandparents, could contribute to the care of these needy infants (Hawkes and Finlay 2018).

Neuroanatomic species differences. Increases in human brain plasticity during evolutionary divergence of humans and other primates correspond to development of social and cognitive abilities to provide these functions (Sherwood and Gomez-Robles 2017). Studies of brain architecture have shown increased and strengthened connections in cortical association areas of the human brain compared to the chimpanzee brain (Rilling and van den Heuvel 2018, Ardesch et al. 2019). Prolonged neurogenesis in primate species appears to allow for an expanded number of upper layer neurons, promoting more connectivity among cortical areas (Charvet et al. 2017). Comparative studies of humans and chimpanzees have also shown that human pyramidal neurons are larger, more integrative, and have longer and more branched dendritic branching (Bianchi et al. 2013). These findings show evidence for enhanced connectivity and signaling integration within the human brain.

Additional changes may reflect shifts in humans' brain's processing of social reward signals. Compared to chimpanzees and other primates, humans have increased expression of tyrosine hydroxylase TH and DOPA decarboxylase in the striatum, higher numbers of TH+ interneurons in the dorsal caudate nucleus and putamen (Sousa et al. 2017), and greater dopaminergic innervation in the ventral pallidum and nucleus accumbens, which have been linked to evolutionary changes in social behavior and language (Hirter et al. 2021). These changes may have contributed to humans' unique social behavior profile which provided for extended support of offspring.

Neotenic features of human brain evolution. In its divergence from chimpanzees, the human brain shows features of neoteny - the expansion and prolongation of developmental traits in the brain. Its large size in relation to body size is itself a juvenile trait. There has been a dramatic increase in the ratio of human brain size relative to body size over human evolution (Smaers et al. 2021). Humans' longer maintenance of high juvenile brain metabolic rates and later age of peak metabolism during development is also a neotenic feature (Bauernfeind and Babbitt 2020). In contrast to chimpanzees, human brain metabolism continues to rise well into childhood and remains high into adolescence and young adulthood, paralleling extended synaptic growth and myelination patterns (Goyal et al. 2018).

Neoteny also is found in human brain gene expression patterns, with prolonged expression of many genes related to brain development, compared to chimpanzees. The dorsolateral prefrontal cortex and the superior frontal gyrus of human brains demonstrate prolonged developmental gene expression profiles resembling that of juvenile chimpanzees. These human neotenic genes tend to be genes expressed in gray matter regions and involved in growth and development (Somel et al. 2009).

Metabolic and transcriptional neoteny are linked: Human brain regions with the most transcriptional neoteny (medial cortical regions and large portions of the frontal lobes) also have elevated levels of aerobic glycolysis, which peaks during early development, and is maintained at high levels in adulthood. Genes enriched in these areas include those involved in neuronal differentiation and projections, regulation of axon and dendrite development, and synaptic transmission (Goyal et al. 2014).

In adulthood, humans differ in the degree to which neotenic brain metabolic traits are maintained. Using a composite measure of four brain metabolic functions, individuals' "metabolic brain ages" were calculated by comparing their observed values with age-specific values predicted by a regression of measured values in 205 persons 20 to 82 years old. Women had significantly lower metabolic brain ages in relation to their chronologic age than did men. An analysis of the components of the metabolic brain age measure in women and men indicates that differences in glucose metabolism are important contributors to the gender difference (Goyal et al. 2019).

Human brain neoteny interacts with life history and social factors: Because neoteny contributes to proportionately higher body metabolic rates in childhood than in adulthood, it increases families' daily requirements for the calories they need to provide to children while they are dependent. In families with multiple children, this also extends the interval from first birth over which families' caloric needs to support offspring are elevated. A variety of adaptions at the family, physiologic, technologic, and societal level likely facilitated meeting this increased requirement, and correspondingly influenced brain evolution (Goyal et al. 2018).

The degree of human neoteny in youth and persistence of neotenic traits in later life may have both positive and negative effects. On one hand, there is evidence that the more youthful pattern of brain metabolism in women contributes to greater cognitive resilience to amyloid pathology (Sundermann et al. 2020). On the other hand, amyloid accumulates primarily in regions with high metabolic rates and high aerobic glycolysis during early adulthood (Vlassenko et al. 2010, Goyal et al. 2020). These findings imply that there may be fundamental metabolic trade-offs in energy allocation among three crucial brain functions: neuronal activity vs. synaptic homeostasis and plasticity vs. housekeeping functions such as proteostasis and mitostasis.

To clarify such possibilities, there is a need for further development of signatures of human brain neoteny and youthful physiology that can be related to other factors such as cognition. Understanding the sources of a persistent youthful neotenous human brain might help us to identify potential treatments that improve brain resilience and function. Efforts to characterize and assess the effects of neotenous changes in humans can be aided by studies in nonhuman primates, such as macaques and marmosets, that can integrate MRI measures of brain architecture and functional tract imaging in non-

sedated animals with immunocytochemical identification of cell types (Hayashi et al. 2021).

If such studies are coupled with interventions that influence brain development and neoteny, it would be possible to test causal hypotheses about how neoteny and various features of human brain development influence brain aging and life span. This approach could be taken using transgenic models, e.g., marmosets with the human-specific ARHGAP11B gene, which was shown to drive fetal expansion of the neocortex reflecting evolutionary changes in human neocortical development (Heide et al. 2020).

Relationships of evolutionary brain changes to risk for Alzheimer's disease and other neurodegenerative diseases. There have been considerable efforts to understand the causes of the absence of Alzheimer's disease in nonhuman primates. Insights into these factors, and to evolutionary changes contributing to them, could inform strategies for Alzheimer's disease prevention.

Humans and non-human primates, including hominids (Perez et al. 2016, Edler et al. 2017) share many Alzheimer's disease (AD) features, including microglial activation (Edler et al. 2018) and myloid beta peptide (Aβ) deposition, Aβ amino acid sequence, and similar Aβ cleavage patterns (Rosen et al. 2016, Freire-Cobo et al. 2021). All studied primate species display abundant Aβ brain pathology, yet only humans seem to undergo extensive neuronal loss and associated neurodegenerative disease (Edler et al. 2020).

Aβ may aggregate into differing structural forms with differing functional effects in humans and nonhuman primates. This possibility is suggested by reduced binding to the imaging agent Pittsburgh Compound B (PIB) in nonhuman primates compared to humans (Rosen et al. 2011). The basis for the presence of substantial tauopathy in Alzheimer's disease but not nonhuman primates, despite great similarities of tau proteins across species, is also unclear. The role of expression of tau exon 8, found in macaques, but not humans (Nelson et al. 1996) is presently unknown.

There is a need to know more about primate species' similarities and differences in interactions between Aβ and tau and how these may contribute to protein misfolding and aggregation. Comparing the differences between tau accumulation in the brains of NHPs and humans and the effect of Aβ isoforms, as well as possible species-specific structural differences and their effects on tau assembly into filaments may help identify mechanisms to defer or prevent cognitive decline. PIB binding studies and cryo-electron microscopy analyses (Kollmer et al. 2019) could assess Aβ structural forms for differences in folding and three-dimensional structure modifications distinct to humans. This may allow for the classification of structures that are more closely associated with cognitive decline and neuronal loss.

Evolutionary selection factors that may have contributed to differences in sequence or structure of Aβ and tau have not been identified. However, there is evidence suggesting evolutionary influences on biological processes influencing neuropathology which affect risk for AD and other neurodegenerative conditions. One factor is humans' longer life span. Most cases of AD occur at ages beyond the longest nonhuman primate life spans. Development of tauopathy may simply require a longer chronologic interval than nonhuman primate life spans, except in rare human forms of early-onset AD.

In addition, evolutionary brain changes that enabled extended life histories and longer human life spans by increasing behavioral plasticity and social functioning may also contribute to neurogenerative diseases. Brain regions with high metabolic rates, lengthened connective neurons, increased dendritic branching and synaptic homeostasis, and high neuronal activity may have higher needs for proteostasis and other maintenance processes. Accordingly, these regions might be prone to proteostasis failure, amyloid deposition, and metabolic failure seen in AD, and to other degenerative brain pathologies resulting from inadequate proteostasis. These possibilities and their implications could be explored in comparative studies of metabolically active brain regions and neotenous gene signatures to decipher associations with AD pathology and cognitive decline.

Variations in APOE genotypes may also contribute to species differences in AD susceptibility. Nonhuman primates, including chimpanzees, share human APOE4-defining residues in positions 112 and 158, but differ from humans at residue 61, conferring properties more similar to APOE3 (Morelli et al. 1996, McIntosh et al. 2012). The role of this difference in accounting for differential risk of AD needs more clarification. One factor, noted earlier, may be pro-inflammatory properties of APOE4 which may have enhanced survival early in human evolution because of its protective effects against parasitic infection (Trumble and Finch 2019) but whose inflammatory effects may contribute to AD in later life.

Notably, nonhuman primates are also resistant to other human age-related neurodegenerative conditions, such as Lewy Body Dementia and Parkinson's disease. It is possible there are common factors explaining these differences in risks for multiple neurodegenerative conditions. Comparative omics analysis could be very informative in searching for such factors, which could potentially provide a basis for interventions that could extend human cognitive health span.

Generation of data sets on brain-specific, and possibly even brain-region-specific comparative gene expression, regulation, and associated brain architecture throughout development and lifespan from a wide range of primate species would likely help further narrow the contributing factors involved in human cognition and the process of degenerative diseases. These datasets would aid researchers in developing new models

to study these processes and species differences in stem cell models and organoids. Essential to these future studies are methodological standardization and centralized or easily accessible banked samples from closely related primate species, such as the chimpanzees and great apes.

VIII. Resources for comparative studies of factors that influence life span in humans and nonhuman primates

A variety of informational, animal, tissue, and computational resources are valuable for comparative studies to identify factors affecting human and nonhuman primate species life spans and life histories. Current and potential new resources of particular interest include:

Databases on species life spans, survival trajectories, and life histories. Valid biodemographic information is crucial for comparisons of species with differing life spans and survival characteristics. Such comparisons require data resources using shared definitions of survival characteristics or providing sufficient information to allow users to harmonize data across multiple species. To allow appropriate comparisons across species using such data, it is also crucial to provide information on demographic and environmental factors such as gender differences in survival, captive vs. wild birth status, location of free-living and captive environments, and husbandry status of captive animals, including nutrition and medical care.

The AnAge curated database of multiple taxa contains data on maximum life spans for 176 primate species (Tacutu et al. 2018). For a limited number of species, data on survival functions, ages of weaning and sexual maturity, interbirth intervals and other reproductive life history characteristics are also provided. Other databases also include primate species biodemographic information (Conde et al. 2019). Primary data on primates in zoos in multiple countries is available through the Species 360 Zoological Information Management Software.

However, for many species in these biodemographic databases, information has been based on small populations and/or confined to captive populations. Careful integration and curation from a range of databases and resources, including primate centers, field studies, historical records, and human cohort data from current and historic populations, may aid in providing reliable metrics of species life span (and intraspecies variability) that could be utilized across studies.

A primary consideration in comparative data on species with differing life spans is the method of characterizing life span. The age at death of the longest-lived individual in the species is the most widely used in biodemographic databases but has important limitations. It can be strongly influenced by sample size. Even in the absence of differences in the distributions of ages at death, larger samples will tend to yield a higher maximum age at death than will smaller samples. Further, in small samples, one

exceptionally long-lived individual can survive substantially longer than the next-longest survivor, thus creating potential problems in assessing the longevity of the population. This is exemplified by reports of individual chimpanzees surviving far longer than their counterparts (Havercamp et al. 2019, Che-Castaldo et al. 2021). These problems could be mitigated by alternative definitions of species longevity, e.g., the age at which the surviving proportion of the population has dropped to 10%. Such metrics are less affected by sample size and more robust against effects of sampling errors (Moorad et al. 2012). Life span information can be enhanced by additional characterization of survival over the life course, such as Gompertz (Finch et al. 1990) and Siler (Siler 1979) functions.

Animal, biospecimen, and histologic resources. US nonhuman primate (NHP) colonies support populations with a wide range of species life spans, providing potential opportunities for comparative longevity studies. The seven National Primate Research Centers (NPRCs), supported by NIH's Office of Research Infrastructure (ORIP), provide a valuable resource for such studies. Specifically, the NPRC's house twelve primate species, on which they collect life history data and tissue resources. NPRC Research Support Capabilities and Resources are available for collaborations across NPRCs and with non-NPRC researchers. Other ORIP-supported centers maintain additional species, including, for example, owl monkeys and squirrel monkeys (Keeling Center for Comparative Medicine and Research), tufted capuchins (New Iberia Research Center and vervet monkeys (Wake Forest Vervet Research Colony). ORIP also supports populations of free-ranging rhesus macaques at the Caribbean Primate Research Center. The Duke Lemur Center maintains populations of 13 lemur species. There are also opportunities for collaborations with primate research centers, sanctuaries, and field projects in other countries, which include additional species, e.g., the Tchimpounga Chimpanzee Sanctuary in the Republic of the Congo, the Amboseli Baboon Research Project and the Institute of Primate Research in Kenya, which supports research on baboons and other primates, and the Santa Rosa Primate Project in Costa Rica, which studies capuchins, howler monkeys, and spider monkeys. Though most centers and sanctuaries have not engaged extensively in aging research, they constitute a valuable potential resource for comparative studies.

Notably, colonies that maintain breeding populations have detailed knowledge of their lineages, facilitating genetic studies. Primate centers provide important opportunities for longitudinal studies on the relationship among differing life history stages. Such studies require maintenance of sufficient numbers of healthy young animals through old age.

Captive chimpanzees are supported in the United States at the Keeling Center, the Alamogordo Primate Facility, and primarily at Chimp Haven, though breeding programs have been ended. Although invasive chimpanzee studies are not allowed,

these facilities allow some noninvasive studies and requests for specimens collected as part of the chimpanzees' health care. Necropsy specimens are also collected. The National Chimpanzee Brain Resource contains specimens from over 350 individuals. Since these aging chimpanzee populations will not be replaced, there is special value in obtaining specimens while it remains possible. Chimpanzee specimens could be made more widely available for research, given sufficient resources.

The potential for primate field studies to provide biospecimens for comparative studies far exceeds their current use. Many collect specimens noninvasively, and some conduct periodic blood draws and obtain telemetric data. Increasing field study investigators' appreciation of the value in comparative studies using data from these specimens could expand and enhance their use, given sufficient resources.

Research on a broader range of NHP species can be facilitated by zoos accredited by the Association of Zoos and Aquariums (AZA). Many of these zoos have internal processes for reviewing research requests, including requests for biospecimens collected during animals' physical exams. The AZA Biobanking Scientific Advisory Group provides oversight and information on policies and procedures for requesting specimens. The AZA's associated Taxon Advisory Groups, including groups on apes, new world primates, and prosimians, can provide advice regarding resources from these taxa.

Other resources, in addition to those noted above, provide primate biospecimens. The National Institute on Aging's Nonhuman Primate Tissue Bank provides tissues from young and old NHPs, primarily rhesus and marmosets, and is currently expanding the range of species to be included. Cells cultured from multiple primate species are available from the Coriell Institute's NIA-sponsored Aging Cell Repository. The contribution of primate cell resources to elucidating relationships of evolutionary genetic changes to effects in specific tissues and cell types would be enhanced by the availability of induced pluripotent stem cells from multiple primate species.

Valuable human specimen resources for comparisons with NHPs include the NIH-supported Human Tissue and Organ Research Resource (HTORR) which provides normal and diseased human tissue biospecimens and organs. Notably, HTORR is available for prospective studies, in which it collaborates with investigators on selecting the methods it will use for obtaining requested specimens. Human post-mortem brain tissue and associated biospecimens are available for research studies through the NIH-funded NeuroBioBank. Human specimens for comparisons of early life history traits with NHPs are available from the National Institute of Child Health and Human Development's Brain and Tissue Bank for Developmental Disorders which stores tissues from healthy and diseased individuals.

In addition to biospecimens, neuroanatomical tissue slide collections of NHP and human tissues are available, including the National Museum of Health and Medicine's

extensive Neuroanatomical Collections. Although many histological collections are available throughout various institutions, the vast majority of these collections would need to be digitized to be accessible to the broader scientific community.

Data, imaging, and informatics resources. A variety of databases and informatics resources provide information on NHP biological variables and social/behavioral characteristics, colony genotypes and phenotypes resources, and transcriptome data. The Primate Aging Database contains data for more than 20 species on body weight, blood chemistries and hematology at differing ages. In addition to data and samples collected from captive colonies, there are many under-utilized datasets from studies of wild primate populations (primarily of baboons, chimpanzees, gorillas, and capuchins). Most of these are short-term behavioral studies but, with additional support, could provide rich sources of demographic data for species with restricted research availability. Some field studies collect telemetric behavioral data which, with appropriate analytical resources could be useful for comparative studies.

The Nonhuman Primate Reference Transcriptome Resource provides deep-sequenced transcriptomes from multiple tissues of 11 NHP species and subspecies. The Evo-Devo resource is a searchable database of gene expression profiles across a dozen developmental stages of seven organs in humans and rhesus macaques, as well as other non-primate species (Cardoso-Moreira et al. 2019) which could be valuable in studies on the relationships of early life history traits to subsequent survival. Information on genomic variability in macaques and its relationships to phenotypic differences is available from the Macaque Genotype and Phenotype Resource of the Oregon NPRC. Information on intraspecies genetic variation is critical for interpreting inter-species genetic comparisons. Readily available information on genetic variation within additional NHP species would be very valuable, particularly because many NHP species exhibit greater genetic variability than do humans.

Evolutionary genomics resources for studies on the relationships of genetic changes during primate evolution to life span, life history, and age-related degenerative conditions include GenTree, an integrated resource for analyzing the evolution and function of new coding regions in the human genome (Shao et al. 2019). The RhesusBase resource (Zhang et al. 2013) of annotated rhesus macaque sequence data also provides software to support functional genomic comparisons with humans (Zhang et al. 2014). Reference genome assembly data for humans and many nonhuman primate species is available on the University of California Santa Cruz Genome Browser. The National Center for Biotechnology Information's Sequence Read Archive provides raw sequence and alignment data on multiple species.

The availability of both NHP and human brain imaging and atlas resources provides opportunities for comparative species studies. NHP resources include the NIH Non-

Human Primate Atlas, which provides gene expression and neuroanatomic data on the cellular and molecular architecture of the developing rhesus macaque brain. The Primate Data Exchange (PRIME-DE) has compiled functional, diffusion, and morphometric magnetic resonance imaging data from multiple studies on macaques for the purpose of mapping the nonhuman primate connectome. The National Chimpanzee Brain Resource provides brain atlas tools and a data repository in addition to its specimen collection. Corresponding human resources include the Allen Institute's Human Brain Atlas, which integrates anatomic and genomic data, and its BrainSpan Atlas which combines transcriptome and image data spanning ages from prenatal development to adulthood. Elucidating the bases of human neurodegenerative disease would be aided by development of combined data sets and tissue banks from multiple primate species, including apes. Such resources would allow multi-species comparisons of brain-specific, and possibly brain-region-specific, gene expression, regulation, and associated brain architecture throughout development and lifespan. These data would also aid researchers in developing new models to study these processes and species differences in stem cell models and organoids.

Comparisons to identify relationships of species differences in genes and their expression to life span and other life history traits depend on correct identification of orthologs. Numerous Orthology Databases are based on differing methods to identify orthologs, many of which are based on sequence similarities (Altenhoff et al. 2019). The quality of evidence supporting the presumption of orthology based on similar sequences depends critically on the assembly of the genomes in which the sequences are found. Without information on the regulatory architecture associated with sequences in the species being compared, interpretation of the functional significance of cross-species sequence differences (or lack thereof) will be subject to uncertainties. Several projects, including Zoonomia, DNA Zoo, and the Vertebrate Genomes Project, are providing annotated assembled reference genomes from multiple species, including many primates, using a variety of assembly methods. In addition to their value in ortholog identification, high quality reference genomes are crucial for identifying changes in gene copy number, paralogs, and other new genes arising in primate evolution that may influence longevity, and for functional genomic species comparisons. Given the considerable genetic variation within NHP species, it would be desirable to assemble reference genomes from more than one individual per species.

A range of databases is available to support searches for small molecules that might influence longevity by modulating mechanisms whose cross-species variation is associated with life span. Such molecules can be used in experimental therapeutic studies in laboratory animals and, given evidence of safety and potential benefit, could also be administered in human physiologic studies. The largest such database, PubChem (Kim et al. 2021) is not limited to compounds whose bioactivity has been

demonstrated, while ChEMBL (Gaulton et al. 2017) combines chemical, bioactivity, and genomic data related to bioactive molecules with drug-like properties. DrugBank (Wishart et al. 2018) contains clinical, chemical, and mechanistic information on currently approved, formerly approved, and investigational drugs, including tools for assessing potential repurposing.

Additional small molecule databases provide more specialized and/or integrated information. The Library of Integrated Network-based Cellular Signatures (LINCS) catalogs changes in gene expression in response to drugs and other perturbing agents (Subramanian et al. 2017), thus allowing potential identification of drugs that influence pathways related to species longevity. The ZINC database lists commercially available compounds and provides links (using information from databases such as PubChem and ChEMBL) to support virtual screening based on factors such as their ligands (with gene annotation) and chemical structures, and facilitates identification of metabolite and natural product analogs (Sterling and Irwin 2015). DrugAge is a curated database of compounds that extend life span in model organisms, principally nematodes, flies, yeast, and rodents. It also provides data on functional enrichment of pathways by these compounds (Barardo et al. 2017).

Two informatics tools enhance use of small molecule databases. ChemMine Tools supports analyses and clustering of novel compounds in PubChem based on structure and chemical properties (Backman et al. 2011). The signatureSearch software provides links to multiple gene expression signature databases to accommodate searches for compounds that act by similar mechanisms or have similar cellular responses (Duan et al. 2020).

IX. Conclusion

The preceding sections have presented data and research issues from a range of fields, including evolutionary biology and genetics, biological anthropology, primatology, neuroscience, epidemiology, human genomics, and cheminformatics, that are pertinent to understanding the bases of differences in primate life spans and their potential contribution to developing interventions to extend human longevity and health span. The previous sections identify many specific needs and opportunities for research and resources. This concluding section is focused on broader considerations reflecting the range of workshop presentations and discussions.

Most fundamentally, the information and concepts presented at the workshop illustrate the substantial variation among primate species in multiple factors that may influence species life spans. They also indicate the need for understanding interactions among these factors that may be crucial for their effects on longevity and health span. For example, evolutionary changes affecting primate species life spans may be mediated by

interactions among reproductive schedules, duration and nature of development, multigenerational social behavior, and biological mechanisms which both mediate the above factors and influence the trajectory of morbidity and mortality over the life span.

The need for integrating multiple research fields in comparative life span studies on multiple primate species has intellectual and practical implications. Collaborations in planning such research among the fields represented at the workshop could generate novel testable hypotheses and allow development of harmonized measures to allow comparability across research fields and primate species. In particular, participants noted the value of continued interactions among nonhuman primate researchers, researchers on comparative aging biology, and researchers on determinants of human longevity and their translational implications. Such ongoing interactions could be supported by infrastructure for information exchange and research planning. Integrating multiple research fields in comparative primate studies also poses needs for resources to enhance comparability and crosstalk across data of different types (e.g., genetic, life history, neuroanatomic) for a given primate species and across multiple primate species, including humans.

The workshop highlighted the substantial and increasing potential contribution of nonhuman primate field studies to comparative species longevity research. Such studies provide unique opportunities to assess interactions between environmental factors, behavior, and life histories. They also have generated substantial biodemographic and phenotype data on a range of NHP species extending beyond captive populations. Their increasing use of new technology for noninvasive monitoring and specimen collection and analyses will expand their contribution to research on biologic factors related to longevity.

The workshop also illustrated the complementarity between comparative studies to elucidate the causes of differing primate species life spans and primate aging studies assessing aging changes within a species. Comparisons of young animals from species with differing life spans are an important aspect of the former approach, particularly because they provide the opportunity to identify species differences in determinants of the rates of progression of aging pathologies before the causal factors become obscured by secondary changes. Comparisons of aging changes within differing species, particularly those with longitudinal data on individuals, also provide insights into mechanisms affecting species longevity. These may reveal differences in rates of progression of similar conditions across species, or species-specific aging pathologies, as illustrated by chimpanzee-human differences in myocardial disease and differences between humans and apes in development of Alzheimer's disease pathology. Such differences may reveal possible trade-offs in which mechanisms that enhance species longevity nonetheless increase the risk of some aging-related pathologies.

The importance of research on genomic changes in primate evolution and their effects on factors that may influence longevity was noted in several contexts during the workshop. Evolutionary genomics methods will be particularly important for assessing structural changes and emergence of new genes, both for their direct effects and in assessing effects of putative orthologs or paralogs. Exploration of the relationship of genetic changes to differences in gene expression and intermediary physiology could clarify their functional significance. Integrating evolutionary genomic information with data on human polymorphisms could help in identifying targetable pathways for human interventions. The need for well-assembled functionally annotated reference genomes from multiple primate species in this research was also noted. Given the substantial genetic heterogeneity within primate species, it is important to generate reference genomes from more than one individual per species, in order to clarify interpretation of the significance of inter-species genetic differences.

Finally, the workshop presentations illustrated the wide variation among primate species in traits that are unique to primates, including extended reproductive and developmental life history stages, primate-specific social factors, and unique neuroanatomy and cognition, as well as the appearance of new genes in primate evolution, including human-specific genes. Thus, comparisons of humans and nonhuman primate species are essential for understanding the relationships of such factors to species longevity, may be crucial for revealing factors that contribute to humans' longer life span than that of any other primate (or any terrestrial mammal), and could identify targets for interventions to extend human longevity and health span.

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