and application of the methodology presented in this symposium will highlight the importance of using longitudinal data to improve understanding of physical and cognitive trajectories with aging.

SYSTEMS-LEVEL MODELING OF BIOLOGICAL AND MOLECULAR AGING CHANGES OVER TIME

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Aging is associated with numerous changes at all levels of biological organization. Harnessing this information to develop measures that accurately and reliably quantify the biological aging process will require longitudinal modeling and incorporation of systems level approaches. We will describe applications of network modeling for longitudinal multi-system biomarker data. Using data from the Baltimore Longitudinal Study of Aging (BLSA) we are able to generate systems level models of biological and physiological function, and then demonstrate how these networks change with age. We will also link systems-level aging changes to hallmarks of aging, including epigenetic alterations, senescence, mitochondrial dysfunction, and proteostasis. Given the complexity of the biological aging process, modeling of systems dynamics over time will both lead to the development of better biomarkers of aging, and also inform our conceptualization of how alterations at the molecular level propagate up levels of organization to eventually influence morbidity and mortality risk.

TRAJECTORIES OF PHENOTYPIC MARKERS OF AGING AS PRECURSORS TO FUNCTIONAL CHANGE

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Delineating trajectories of aging phenotypes is essential to understanding mechanisms of clinical disease and disability. We investigated longitudinal changes in measures of body composition, energy expenditure, and brain volumes in >900 participants (age 67.0 (IQR: 57-77) years, 48.1% male) of the Baltimore Longitudinal Study of Aging using mixed effects regression models. Computed tomography-derived thigh muscle cross-sectional area declined 754.2 cm2 per decade at age 60 years (p<0.001) and 1294.3 cm2 at 75 years (p<0.001). Energy reserves, defined as a ratio of energy-cost-to-energy-capacity measured using indirect calorimetry, decreased 11.2% per decade at 60 years (p<0.001), and 16.8% at 75 years (p<0.001). MRI-derived measures of total brain volumes declined 41.6 cm3 per decade at 60 years (p<0.001) and 44.9 cm3 at 75 years (p<0.001). Linking these findings to biological and clinical measures of aging may contribute to more accurate assessment of phenotypic age.

LONGITUDINAL CHANGE OF PHYSICAL AND COGNITIVE FUNCTIONS IN BLSA

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Optimally integrating metrics of aging requires evaluating the metrics' change with aging. We investigated longitudinal changes of physical and cognitive functions in the Baltimore Longitudinal Study of Aging. Usual gait speed declined -0.08 m/s (p<0.001) per decade at age 60 years, -0.10 m/s (p<0.001) per decade at 65 years, and -0.13 m/s (p<0.001) per decade at 70 years, after adjusting for sex and height. No sex difference of gait speed decline was observed after adjustment for height. Time to finish Trails B, an indicator of executive function, increased 11.3 seconds per decade at 60 years, 17.7 seconds (p<0.001) per decade at 65 years, and 24.1 seconds (p<0.001) per decade at 70 years, after adjusting for sex, education, and race. No sex difference of longitudinal decline in executive function was observed. Linking these findings to physiological measures may unveil an important mechanism of aging.

ANALYTICAL CONSIDERATIONS OF DEVELOPING A PHENOTYPIC AGING MEASURE: THE CONCEPTUAL FRAMEWORK MUST COME FIRST!

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We propose a latent structural model framework where phenotypic aging is a latent variable influenced by chronological age, genes and environment. Within this framework, phenotypic age influences aging-related outcomes and is reflected by latent domains of aging (body composition, energetics, homeostasis, and neural functioning) reflected by biomarkers. First, we validate the framework by selecting age-associated domain-specific biomarkers and assessing internal consistency and convergent construct validity (Cronbach's alpha). Using data from the Baltimore Longitudinal Study of Aging, within-domain Cronbach's alphas ranged from 0.80 to 0.92, supporting convergent construct validity. Second, we evaluate two broad methods for combining biomarkers into one phenotypic age measure customized to different objectives: 1) confirmatory factor analysis of chronological