# Biomarkers of Human Aging
# Symposium Report
# from the
# 21st IAGG World Congress of Gerontology and Geriatrics
# San Francisco, CA
# Sunday, July 23, 11:00 a.m.-12:30 p.m.

Session Chair: Ronald A. Kohanski, National Institute on Aging, Division of Aging Biology
Session Report by Rozalyn Anderson, University of Wisconsin Madison

## Symposium Abstract:

The Geroscience hypothesis states that slowing the rate of aging will delay the onset and/or reduce severity of aging-related diseases and frailties without necessarily altering life span, thus improving health at older ages. This is based on the observation that the prevalence of adult-onset diseases and losses of function increase with age, suggesting that aging is a major risk factor for development of chronic diseases and degenerative conditions. In geroscience, we distinguish between age and aging: age is marked linearly by the passage of time, but aging encompasses the biological (molecular and cellular) changes from reproductive maturity onward and it is not necessarily linear nor is it uniform in all tissues. The rate of aging can be understood in two ways: the biological changes in adults, and the clinical changes in health in adults. It is often represented as physiological or biological age versus chronological age or years. From this simple picture three questions emerge: What are the metrics used to measure physiological aging? Do these metrics – or biomarkers of aging – explain the "risk factor" aspect of aging that underlies the geroscience hypothesis? Do these biomarkers of aging account for the variation in health for each age group in a population? Fundamentally, these constitute the challenge for identifying biomarkers of aging: Finding the molecular characteristics that identify – and predict – aging as it is seen in the clinic.

## Presentations:

**Daniel Belsky, Duke University School of Medicine**
***Quantification Of Biological Aging For Testing Geroprotective Interventions.***

An emerging concept in human aging studies is that early exposures contribute to future negative health outcomes, leading to the concept that preventative intervention in middle age might be a key strategy to "rectangularize" the mortality curve. A consensus view on how best to quantify of biological aging has yet to be reached however. Concepts include broad measures of disability or deterioration in physiological integrity, whereas others focus on cellular or molecular level indices. Although there are several methods in contention, a comparative investigation of their utility has not been conducted within a single cohort of humans. Belsky's group has undertaken just such as study using data from the Dunedin longitudinal study based in New Zealand, a 1972–3 birth cohort (N=1,037) followed prospectively through midlife. The team conducted comparative analysis of 7 measures of biological aging including cellular models based on telomere length or epigenetic marks, and clinical biomarker algorithms based on cross-sectional or longitudinal modeling. The team was able to show each of the indices behaved in the predicted manner, with a distribution around the mean, and each measure captured advancing biological age. Clinical measures transitioned to greater risk groups and deteriorating health, telomere length became shorter as a function of age and epigenetic clocks ticked forward. What was less clear, however, was if each were reflective of the same biology. Correlation analysis was conducted among biological ages estimated via different methods, tested against within-person change over time, and the models were compared to extant healthspan-related characteristics (physical functioning, cognitive decline, subjective signs of aging). The epigenetic-based biological clocks were related to each other and the clinical clocks were related to each other, however, the two classes of aging biomarkers appeared to be distinct. One possibility is that the clinical and cellular markers reflect different aspects of physiological and biological aging. Furthermore, none of the biological aging models effectively captured extant clinical status. Belsky suggests that a composite of cellular and patient data might ultimately be the best way to

usefully quantify biological age. Identification of a higher resolution index of biological age for human studies would be a major advance in Geroscience research.

**Rozalyn Anderson, University of Wisconsin Madison**
***Aging and Health Biomarker Discovery—Translational Insights From Nonhuman Primates***

Aging itself is the most significant risk factor for a range of diseases including cancer, neurodegenerative disease, cardiovascular disease, and diabetes. Recent studies in rhesus monkeys have confirmed the efficacy of caloric restriction (CR) as a means to delay aging as evidenced by enhanced survival and lowered incidence of diseases and disorders of aging. These findings place renewed emphasis on discovering the mechanisms of CR; insights that would have great potential to reveal the underlying biology of age-associated disease vulnerability. In the course of their investigation of CR's mechanisms, the Anderson lab has identified several biomarkers of delayed aging. The clinical and biomedical value of any biomarker is likely a balance of utility and complexity. Anderson proposes that classes of biomarker might be stratified on this basis and provides examples of each. Individual Parameters Biomarkers include measures such as body-composition or adiposity, indices of glucoregulatory function, circulating levels of inflammatory factors, or clinical lipoprotein profiling. These measures track well with what is known about disease vulnerability and likely have clinical utility but may not be highly informative about underlying biology. Circulating microRNAs also feature in this class of biomarkers and comprise a novel area of investigation in aging research. A second class is the Multi-Parameter Model-based Biomarkers that have potential for clinical application and may also inform about disease etiology. Examples include the tissue-type independent transcriptional network of CR that aligns not only with longevity but also with effective treatments to reverse metabolic dysfunction, and the lipid based predictive models that align with metabolic status, identifying insulin resistance in advance of impaired fasting glucose. The third class is the Signature Biomarkers of healthy aging. These high-density parameter models are generated using advanced computational approaches and reflect differences in the underlying biology. Although it would be sometime before such sophisticated analyses could be employed in a clinical setting, these high-resolution health signatures are nonetheless extremely valuable in biomedical research as they are founded on the underlying biology of disease vulnerability and are likely to reveal novel targets for anti-aging interventions.

**Nathan LeBrasseur, Mayo Clinic**
***Growth Differentiation Factors and Senescence-Related Proteins as Modifiers of Aging***

There is considerable heterogeneity in how aging manifests among individuals within any given population. This is reflected in the comment heard among geriatricians: "Once you have met one 70-year old, you've met one 70-year old". The identification of biomarkers of aging could prove transformative in clinical practice. Among these we might consider Indicators of disease and Surrogate Endpoints that inform of health status, both of which would likely contribute to the identification of Drugable Targets. Members of the TGFbeta superfamily of growth factors have garnered considerable attention in recent years as candidates in all three biomarker categories, namely GDF11 and GDF8. Myostatin (GDF8) is a negative regulator of muscle mass that has been considered as a target for treatment of muscle wasting. Although both proteins are highly homologous, circulate as latent and active forms, and to some extent share receptors and downstream effectors, there are key differences. Deletion of GDF8 produces a hypermusclular phenotype while deletion of GDF11 is embryonic lethal and associated with broad scale developmental defects. There have been conflicting reports about age-related declines in GDF11 and its potential rejuvenating effects. LeBrasseur's group undertook a study in humans and showed limited effects of aging on GDF11 levels in circulation. Analysis of GDF11 in the context of cardiovascular disease revealed no predicative capabilities of GDF11 as a biomarker of risk; however, higher GDF11 was associated with greater comorbidity prevalence and morality risk, and even performed well as a biomarker of frailty in being additive with age and sex. Preliminary investigations conducted by LeBrasseur and colleagues point to GDF11 as a potential biomarker of neurodegeneration in the context of Alzheimer's disease and cognitive decline. Together these studies suggest that rather than being an anti-geronic factor as was previously thought, GDF11 may be a biomarker of age-related compromised health status. A causative role for cellular senescence in creating age-related disease vulnerability is an emerging paradigm in aging research. Indeed, Le Brasseur's groupd has shown that biomarkers of senescence such as $p16^{INK4a}$ and the Senescence Associated Secretory Phenotype have utility

as biomarkers of human aging. LeBrassuer calls for interdisciplinary strategic partnerships invested in forward and reverse translation including biological and clinical perspectives to advance this important area.

**Eline Slagboom, Leiden University Medical Centre**
***Generic Biomarkers in Ageing: Tools to Study Metabolic Health and Response to Interventions*.**

Although we all recognize that age is the more significant risk factor for a range of diseases, there is enormous diversity in health span with age, ranging from unhealthy 60- to vital 90-year-olds. This diversity is poorly understood and likely obscures the effect of interventions, many of which are validated only in younger persons. A standardization of baseline measures specifically in older populations will be necessary to fully optimize treatments and efficacy tracking. Clinical data from the Leiden Longitudinal Study points to a metabolic basis for intrinsic health variation. In contrast, several molecular based biomarkers, including telomere length and DNA methylation, fail to capture enhanced longevity. Biomarkers based on metabolic indices could improve evidence-based medicine among the elderly, but will require coordinated efforts in longitudinal and intervention studies. The concept here is that biomarkers to classify individuals are not the same as efficacy of treatment biomakers, which are not the same as biomarkers that inform of disease etiology. Complex multi-parameter models may have even greater predictive power than traditional metrics of metabolic health, especially in the fastest growing population of elderly humans. In their ongoing research on omics as biomarker in ageing, Slagboom and colleagues report signatures of early development in addition to age-related dys-differentiation, revealing both generic and disease-specific signatures. Specifically they have identified a group of 22 lipid-associated panel that constitutes a biomarker that connects to disease constellation risk. Data from the Northern Finland Cohorts study shows a positive relationship between VLDV diameter and mortality; however, age has an impact on this relationship. An NMR based panel has been developed using stepwise regression of health outcome and metabolite measures. Hazard ratio calculations identify parameters, such as triacylglyceride burden or prevalence of branched chain amino acids, that are associated with individual health outcomes. Here again the score is not equivalent across age. Slagboom have recently embarked on a longevity study similar to the CALERIE framework but in older adults that may serve as the “go-to” study for biomarker development. Here considerations will be given to individual heterogeneity, taking into consideration that fact that biomarkers showing negative risk may not be the same as those that reflect health improvement. Slagboom proposes that the strongest leads will likely be obtained by linking intervention and epidemiological studies.

**Summary:**

The consensus view from all four speakers points to the tremendous utility of biomarkers of aging in biological, pre-clinical, and clinical research. The ability to accurately assign health status in older populations would be a substantial advance in designing treatments and interventions, with the expectation of significant improvements in the quality of health care that might be delivered. All four speakers called for a more nuanced approach to identifying candidate factors, drawing the distinction between causation and correlation, and proposing that new biomarkers may include representative parameters from a range of biological processes.