Living Longer, Living Better — Executive Summary

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Project Summary / Abstract

Aging is increasingly understood as a dynamic, modifiable process rather than an inevitable decline. Behavioral, environmental, and socioeconomic forces shape *how long* and *how well* we live at least as powerfully as the genetic blueprint we inherit. Yet today's longevity landscape is saturated with expensive, unproven, and often outrageous "cures'' for aging — influencer protocols, supplement stacks, and biological reductionism dressed up as science. Distinguishing real scientific signal from this hype demands rigorous, evidence-based analytical tools, grounded in mechanism and validated in human cohorts.

This proposal extends the pharmacogenomics paradigm into "**aging-genomics**.'' Where pharmacogenomics asks *which drug is right for which person, given their genome?*, aging-genomics asks *which way of living and which interventions are right for which person, given their genome, epigenome, mitochondrial state, and real-time physiology?* The mechanistic premise is the mitochondrial-inflammaging vicious cycle: dysfunctional mitochondria release damage-associated molecular patterns (mtDNA, oxidized cardiolipin) and reactive oxygen species that activate the NLRP3 inflammasome, NF-κB, and chronic inflammatory cascades, which in turn drive cellular senescence, tissue damage, and accelerated biological aging. Conversely, beneficial behaviors — physical activity, optimal nutrition, restorative sleep, social engagement — drive a virtuous cycle of mitochondrial biogenesis, enhanced mtDNA repair, and dampened inflammation. A largely-overlooked dimension is the *maternal* inheritance of mtDNA, layered with *numts* (nuclear mitochondrial insertions, a process led by Ryan Mills) which are bi-parentally transmitted and may modulate cellular regeneration.

We propose a three-aim program to translate this mechanism into a clinically deployable readout. **Aim 1** develops the *Longevity & Cardiovascular Health Index (LCI)* integrating nuclear and mitochondrial whole-genome sequencing, cardiorespiratory fitness (CRF, METs — one of the strongest predictors of all-cause mortality), standard clinical risk factors, and continuous real-time physiology from the FDA-cleared BioIntelliSense BioButton wearable. The model trains on the

Michigan Genomics Institute (MGI, ∼90{,}000 recontactable patients) and the Multicenter Perioperative Outcomes Group (MPOG, millions of records across 85+ hospitals; founded by Sachin Kheterpal at UM), validates against military exercise-stress-test biorepositories (DoDSR, USAFSAM, Cooper Institute, VETS) and at scale against the Oracle Health 150-million-patient EHR via the Ellison Institute partnership. **Aim 2** develops the *Epigenetic & Mitochondrial Health Panel (EMHP)* — a clinically-practical blood-based panel of inflammatory and mitochondrial biomarkers (DNA methylation at key CpGs, targeted expression, circulating metabolites) calibrated against BioButton-captured behavioral and physiologic states. Phase 2 expands via genome-wide methylation and CRISPR Perturb-seq for causal-flow discovery in patient-derived iPSCs. **Aim 3** translates the platform into therapeutic targets and Precision Longevity Programs — individualized prioritization of lifestyle levers and candidate therapeutics with the same rigor that pharmacogenomics has brought to oncology and cardiology.

The deliverables are a CLIA/IVD diagnostic, an Oracle Cloud Infrastructure-hosted decision-support layer, and a pre-clinical drug target pipeline. The work is built on three decades of foundational mtDNA-atherosclerosis collaboration between the Ballinger and Runge laboratories, leverages UM's unique cohort assets, and is designed for clinical and commercial deployment through Oracle Health and Ellison Institute of Technology channels.

References