Living Longer, Living Better: An Aging-Genomics Platform

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Project Summary

Overview

This proposal extends the pharmacogenomics paradigm into *aging-genomics*: where pharmacogenomics personalizes drug selection by genotype, aging-genomics personalizes the negotiation each individual conducts with their genes across genome, epigenome, mitochondrial state, and real-time physiology. The mechanistic spine is the mitochondrial-inflammaging axis: mtDNA-derived damage-associated molecular patterns and reactive oxygen species activate the NLRP3 inflammasome and chronic inflammation; lifestyle factors modulate this axis through epigenetic regulation. Maternal mtDNA inheritance and numts (Mills's methodology) layer a largely- overlooked genetic dimension on top of the canonical Ballinger-Runge mtDNA-atherogenesis foundation.

Intellectual Merit

The proposal advances aging-research methodology in three ways that together establish aging-genomics as a tractable extension of the pharmacogenomics paradigm rather than a speculative aspiration.

(1) Long-read sequencing at clinical scale captures mitochondrial DNA copy number, heteroplasmy, and haplogroup — genetic-architecture variables that follow maternal transmission and that Ballinger's conplastic-mouse work established as sufficient to alter metabolic phenotype on a controlled nuclear background. Mills's numt methodology adds the bi-parental nuclear layer. Pangenomic alignment reduces reference-bias artifacts in non-European-ancestry genomes.

(2) BioButton-paired-blood-draw study designs couple continuous physiologic monitoring with strategically-timed blood draws bracketing real-world states (sleep deprivation, exercise bouts, acute illness, stress weeks, restorative recovery), producing acute-response measurements of inflammatory and mitochondrial gene panels. This is methodologically distinct from the traditional single-blood-draw biomarker design because it captures the *response function* of each individual to

physiologic stressors — enabling resilience-vs-vulnerability stratification that static lifestyle variables cannot deliver.

(3) CRISPR Perturb-seq for causal-flow discovery addresses the markers-versus-targets ambiguity that has limited prior aging- biomarker programs. Systematic perturbation of candidate genes in patient-derived iPSCs and primary immune / vascular cells, profiled by single-cell RNA-seq, distinguishes upstream regulators (actionable therapeutic targets) from downstream reporters (biomarkers only). This is the methodological capability that lets aging-genomics graduate from association to intervention.

Broader Impacts

The proposal has substantial broader impacts in five dimensions.

Public health relevance. Aging-related disease — cardiovascular, metabolic, neurodegenerative, immunosenescence-driven — represents the leading driver of US healthcare costs and accounts for the majority of lost healthy life years. Validated aging-genomics diagnostics and decision support translate directly to improved healthspan and reduced healthcare burden.

Training and workforce development. The proposal supports predoctoral and postdoctoral trainees at the intersection of inflammation biology, computational genomics, mitochondrial biology, and clinical decision support — the multidisciplinary skill set the field demands at scale.

Diversity in research populations. The cohort tier is deliberately inclusive: military / veteran biorepositories (DoDSR, USAFSAM, Cooper, VETS) provide substantial ethnic and racial diversity; the Oracle Health 150-million-patient EHR validation covers the full demographic span; Michigan Medicine catchment includes underserved populations. The proposed sample-size targets are powered to support subgroup analyses across ancestry, sex, and age strata, addressing a long-standing limitation of the predominantly-European-ancestry aging-clock literature.

Open science and data sharing. The data-management plan follows the NIH 2023 Data Management and Sharing Policy and includes 6-month-delayed open-source release of analytical pipelines, summary statistics, and model artifacts. Genomic data is deposited at NIH dbGaP under controlled access; methylation, expression, and Perturb- seq data at NCBI GEO / SRA on publication-aligned timelines.

Distinguishing rigorous claims from longevity hype. The proposal explicitly addresses the field's central operational challenge: the contemporary longevity marketplace is saturated with under-validated influencer-driven products. By committing to pre-registered analytic plans, transparent reporting of validation performance across diverse cohorts, and explicit refusal to participate in the marketing-of-uncertainty that characterizes the consumer end of the market, the proposal establishes a methodological template that the broader field can adopt.

Commercialization with public health intent. The commercialization roadmap (IVD diagnostic via FDA / CE Mark, decision- support licensing, pre-clinical therapeutic discovery, eventual clinical-trial-grade therapeutics) is structured to deliver healthspan-extension benefits at scale through regulated channels, not as direct-to-consumer wellness marketing.

Specific Aims

Aging-genomics extends the pharmacogenomics paradigm: where pharmacogenomics personalizes therapy by genotype, aging-genomics personalizes the negotiation each individual conducts with their genes across genome, epigenome, mitochondrial state, and real-time physiology. Mechanistically, the mitochondrial-inflammaging axis (NLRP3 inflammasome activation by mtDNA damage and oxidized cardiolipin) drives accelerated aging, and lifestyle factors modulate this axis through

epigenetic regulation. Maternal mtDNA inheritance and numts (Mills) layer a largely-overlooked genetic dimension onto this story.

Aim 1 — Longevity & Cardiovascular Health Index (LCI). Integrate nuclear and mitochondrial WGS, cardiorespiratory fitness (METs), standard clinical risk factors, and real-time BioIntelliSense BioButton physiologic data into a clinically-deployable predictive index. Train across MGI (∼90{,}000 UM patients), MPOG (Kheterpal, millions of records), and federal exercise-stress-test cohorts (DoDSR, USAFSAM, Cooper, VETS); validate against Oracle Health 150 M EHR via Ellison Institute partnership.

Aim 2 — Epigenetic & Mitochondrial Health Panel (EMHP). Build a blood-based panel calibrated against BioButton-captured behavioral/physiologic states. Phase 1 = small inflammatory and mitochondrial-regulator gene set (NLRP3, sirtuins, GDF-15, FGF-21, etc.) with paired methylation + expression + circulating-protein assays. Phase 2 = genome-wide methylation (EPIC arrays → RRBS/WGBS where justified) and CRISPR Perturb-seq for causal-flow discovery in patient-derived iPSCs.

Aim 3 — Targets, Therapies, and Precision Longevity Programs. Pathway analysis across all data layers prioritizes epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins) and mitochondrial regulators for therapeutic modulation. An aging-genomics decision framework (Athey) outputs individualized lifestyle prioritization and therapeutic-candidate identification, designed for Oracle Health clinical workflows and EIT-affiliated longevity clinics.

Closed-loop deliverable: measure → model → intervene → re-measure, with the same rigor that pharmacogenomics has brought to oncology and cardiology.

1 Team and Environment

Originating author

Marschall S. Runge, M.D., Ph.D. (Proposal architect). The two source documents underlying this proposal were authored by Marschall Runge — EVP for Medical Affairs, CEO of Michigan Medicine, and Dean of the University of Michigan Medical School. Runge is the originating scientific author of the program and proposed the multi-PI delegation that follows. His role on this submission is senior collaborator (cardiovascular-translation arm; institutional sponsorship; Ellison Institute / Oracle Health partnership channel).

Proposed PI roster (per doc 1, §"Specific Aims")

Steven L. Kunkel, Ph.D. (proposed Principal Investigator). Distinguished pathologist whose laboratory established core mechanisms of inflammaging, NLRP3-axis activation, and downstream tissue dysfunction. Provides the inflammation-axis expertise that anchors Aim 2's panel composition (NLRP3, ASC, caspase-1, IL-1β) and Aim 3's therapeutic-target prioritization.

Brian D. Athey, Ph.D. (co-Principal Investigator). Expert and leader in pharmacogenomics and computational medicine. Architects the analytic framework and decision-support systems so that *aging-genomics* becomes as clinically meaningful and actionable as pharmacogenomics has become in oncology and cardiology. Leads the LCI model architecture (Aim 1) and the precision-longevity decision framework (Aim 3).

Sachin Kheterpal, M.D., MBA. Founder, Lead Architect, and Executive Director of MPOG (the Multicenter Perioperative Outcomes Group spanning 85+ hospitals across multiple countries with millions of records). PI of major MPOG multicenter trials including THRIVE. Provides MPOG cohort access and large-scale prospective-trial operational infrastructure.

Marschall S. Runge, M.D., Ph.D. EVP for Medical Affairs + CEO of Michigan Medicine + Dean of UMMS. Foundational mtDNA- atherosclerosis collaboration with Ballinger established the mechanistic link between mtDNA damage, ROS, and atherogenesis (Ballinger & Runge, *Circulation Research* 2000; Ballinger, Patterson, ..., Runge, *Circulation* 2002). NIA-funded PAI-1 program established PAI-1's role in vascular aging, fibrosis, and hypertension. Provides Michigan Medicine institutional sponsorship, the connection to Ellison Institute of Technology and Oracle Health, and senior scientific leadership of the cardiovascular-translation arm.

Scott W. Ballinger, Ph.D. (collaborator). Foundational mtDNA-atherogenesis collaborator with Runge. Independent conplastic- mouse work established that mtDNA variation alone influences metabolic phenotype, including susceptibility to metabolic syndrome (Ballinger *et al.*, *Circulation Research* 2010). Provides the mtDNA-only-genetic-contribution validation framework underlying Aim 1's mtDNA-haplogroup analysis.

Ryan E. Mills, Ph.D. (co-investigator). UM investigator who has led knowledge growth on numtogenesis — the incorporation of mitochondrial DNA into nuclear genomes. Numts integrate into the nuclear genome and are bi-parentally transmitted; once in the nuclear genome they may modulate cellular regeneration. Provides the numts methodology underlying Aim 1's numt-characterization component.

Greg Farnum (investigator). Bioinformatics operations and ML core. Manages the OCI build pipelines, atom-system content infrastructure, and pangenomic alignment workflows.

Cohorts and biorepositories accessed

Michigan Genomics Institute (MGI). UM health-system biobank. Deep phenotyping (full EMR), multi-omic data including WGS on the majority of ∼90{,}000 enrolled patients. MGI consent supports recontact for follow-up sampling — enabling the BioButton-paired-blood-draw design in Aim 2.

Multicenter Perioperative Outcomes Group (MPOG). 85+ hospitals across multiple countries; millions of records; up to twenty concurrent prospective trials with UM as the central Data Coordinating Center. THRIVE is an illustrative concurrent multicenter trial.

Federally-funded military and veteran exercise-stress-test biorepositories. Department of Defense Serum Repository (DoDSR); USAFSAM (US Air Force School of Aerospace Medicine); Cooper Institute Biobank; Veterans Exercise Testing Study (VETS). Combine objective baseline CRF in METs at enrollment, decades of longitudinal follow-up, biobanked longitudinal blood samples, and statistical power and demographic diversity.

Oracle Health 150-million-patient EHR. Accessed via the Ellison Institute of Technology partnership. Provides population- scale validation of LCI and EMHP across diverse populations, disease states, and environmental exposures. Oracle Cloud Infrastructure (OCI) hosts the analytical pipeline.

Institutional environment

University of Michigan provides world-class infrastructure across all required disciplines: Department of Pathology (Athey-affiliated; Kunkel-affiliated; access to UMHS post-mortem biorepository), the Department of Computational Medicine & Bioinformatics (Athey, Mills), Michigan Medicine clinical and EMR infrastructure (Runge, Kheterpal), and the Center for Computational Medicine & Bioinformatics for OCI workflows (Farnum). The Ellison Institute of Technology partnership and Oracle Health provide the population-scale data-and-compute layer unavailable to any single academic environment.

References