Aging-Genomics: A Closed-Loop Platform for Healthspan and Operational Resilience

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Heilmeier Catechism

1. What are you trying to do? (no jargon)

We are building a system that tells each person, based on their DNA, their daily physiology (heart rate, sleep, activity, stress measured continuously by a wearable), and a small panel of inflammation and mitochondrial markers from blood, what specific changes to their lifestyle and what specific medical interventions will most extend their healthy life and reduce their cardiovascular risk. The system combines existing technologies (long-read DNA sequencing, FDA-cleared wearables, blood-test panels) into a new clinical infrastructure that follows the same paradigm pharmacogenomics already uses for drug prescribing, extended into healthspan.

2. How is it done today, and what are the limits of current practice?

Today's longevity marketplace is dominated by influencer-driven protocols, supplement stacks, and direct-to-consumer "biological age'' tests with limited clinical validation. Existing aging-clock methodology is rife with overfitting, batch effects, and inadequate external validation across demographically diverse populations. Validated diagnostics that integrate genetics, epigenetics, and real-time physiology into actionable clinical decision support do not exist. The closest comparable is pharmacogenomics, which is mature for prescribing but does not extend to lifestyle and healthspan-relevant interventions.

3. What is new in your approach and why do you think it will succeed?

Three technical capabilities have converged in the last five years:

- **Long-read sequencing at clinical scale** captures mitochondrial DNA copy number, heteroplasmy, haplogroup, and numts (nuclear-mitochondrial insertions, characterized methodologically by Mills) at $\sim$ \$500 per sample.
- **FDA-cleared continuous physiologic wearables** (BioIntelliSense BioButton) transform static lifestyle variables into high-resolution time series, enabling paired-blood-draw designs that quantify acute responses to real-world stressors.
- **CRISPR Perturb-seq** in patient-derived iPSCs systematically perturbs candidate genes and profiles single-cell transcriptomic responses, distinguishing biomarkers from actionable therapeutic targets — a capability that resolves the central ambiguity that has limited prior aging-biomarker programs.

The approach succeeds because the mechanism is mature (three decades of mtDNA-atherogenesis biology from Ballinger and Runge), the technical infrastructure has converged, and the decision-support paradigm exists in working clinical deployment via pharmacogenomics — we extend rather than invent.

4. Who cares?

- **Operational agencies** concerned with workforce resilience, recovery from physiologic stress, and long-term mission readiness (DARPA, ARPA-H mission alignment).
- **NIH / NIA** for healthspan extension and reduction of age-related-disease burden.
- **Health systems and payers** for population-health management and reduction of polypharmacy adverse-drug-event burden in older adults.
- **Pharmaceutical industry** for novel therapeutic targets in inflammaging, mitochondrial dysfunction, and senescence.
- **Individual citizens** for evidence-based personalized longevity recommendations distinct from the under-validated influencer marketplace.

5. If you're successful, what difference will it make?

A clinically-deployable Longevity & Cardiovascular Health Index predicting CVD events and all-cause mortality with calibration demonstrated across demographic strata at the Oracle Health 150-million-patient EHR scale. A blood-based Epigenetic & Mitochondrial Health Panel quantifying biological-age trajectory and intervention response. A pre-clinical drug pipeline targeting epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins) and mitochondrial regulators with EMHP and LCI as pharmacodynamic readouts. A regulated IVD diagnostic deployable through Oracle Health and longevity-clinic channels.

Together: aging-genomics moves from speculative aspiration to deployed clinical infrastructure, with measurable population-health impact through evidence-based personalization of healthspan interventions.

6. What are the risks?

- **Validation generalization.** Models trained on the WGS + MGI + MPOG + federal cohorts may not generalize to the Oracle Health validation tier. Mitigation: pangenomic alignment + explicit subgroup performance reporting + iterative model refinement at external-validation cycles.
- **BioButton sub-cohort recruitment.** Multicenter prospective recruitment is operationally complex. Mitigation: MPOG infrastructure (Kheterpal) is mature for this exact use case.
- **Regulatory pathway uncertainty.** Combined diagnostics (genotype + epigenotype + ML-prediction-on-cloud) are a newer FDA category. Mitigation: prospective regulator engagement during Phase 1; software-as-a-medical-device guidance is converging.
- **Hype contamination.** The longevity marketplace's signal-to-noise problem could engulf validated outputs. Mitigation: pre-registered analytic plans, transparent validation reporting, explicit refusal to participate in direct-to-consumer wellness marketing.

7. How much will it cost?

The full multi-mechanism platform is sized for an NIH R01 / U19 / ARPA-H scale; a rigorous cost estimate per mechanism is populated in each variant's Budget Justification appendix at submission time. The platform amortizes shared infrastructure (cohorts, OCI ML/AI, EMHP panel development) across multiple aims so per-aim cost is lower than equivalent stand-alone aims.

8. How long will it take?

Three phases over 7+ years. Phase 1 (Years 1–3): biomarker discovery, panel feasibility, target identification, initial patents. Phase 2 (Years 4–6): EMHP IVD development with FDA / CE-Mark dossiers, pre-clinical drug-lead optimization. Phase 3 (Years 7+): EMHP commercial launch via Oracle Health, personalized longevity programs, therapeutic Phase 1–3 trials.

9. Mid-term and final "exams"

Year 1 milestones: cohort assembly + WGS pilot + BioButton procurement; LCI v0 model on MGI sub-cohort.

Year 3 milestones: LCI v1 model with cross-validation performance on extreme-phenotype training set; EMHP Phase 1 panel selection; prioritized therapeutic-target list.

Year 5 milestones: LCI external validation at Oracle Health; EMHP IVD prototype; FDA pre-submission package.

Year 7 milestones: EMHP IVD clearance; first Phase 1 therapeutic clinical trial; aging-genomics decision framework embedded in Oracle Health clinical workflows.

Each milestone has an explicit go / no-go decision criterion to be populated in the Statistical Analysis Plan at submission time.

Specific Aims

Goal: Develop commercially-viable diagnostic panels and identify therapeutic targets rooted in mitochondrial function, epigenetics, and cardiorespiratory fitness for promoting healthy longevity and reducing cardiovascular-disease (CVD) risk.

Premise: 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. The mechanistic core is the mitochondrial-inflammaging axis: mtDNA-derived damage-associated molecular patterns and reactive oxygen species activate the NLRP3 inflammasome and NF-κB, driving the chronic inflammation that accelerates biological aging. Lifestyle factors — physical activity, nutrition, sleep, social engagement, purposeful cognitive challenge — modulate this axis through epigenetic regulation of inflammatory and mitochondrial genes. Layered onto this axis is maternal mtDNA inheritance and numts (nuclear mitochondrial insertions, characterized methodologically by Mills) as under-recognized determinants of intrinsic longevity capacity.

Aim 1 — The Ellison Longevity & Cardiovascular Health Index (LCI). Develop and validate a clinically-deployable index integrating: (i) nuclear and mitochondrial whole-genome sequencing (polygenic scores for CVD, metabolic disease, longevity; mtDNA haplogroups, heteroplasmy, copy number; numts characterization); (ii) cardiorespiratory fitness measured in METs from exercise stress testing; (iii) standard clinical risk factors; and (iv) real-time phenotypic data from the BioIntelliSense BioButton wearable (heart rate variability, sleep architecture, activity, stress signatures). Cohort assembly leverages the Michigan Genomics Institute (MGI, $\sim$90{,}000 recontactable UM patients with deep phenotyping and WGS), the Multicenter Perioperative Outcomes Group (MPOG, millions of records across 85+ hospitals; Kheterpal Executive Director), and federally-funded military and veteran exercise-stress-test biorepositories (DoDSR, USAFSAM, Cooper Institute, VETS). Models are trained on Oracle Cloud Infrastructure using pangenomic alignment (to capture structural variation and reduce reference bias) and interpretability-constrained nonlinear machine learning (gradient boosting, deep learning, survival models), then validated against the Oracle Health 150-million-patient EHR. **Outcome:** A patented Ellison-branded diagnostic algorithm suitable for embedding in Oracle Health clinical decision support, population-health management, and employer/payer products.

Aim 2 — The Epigenetic & Mitochondrial Health Panel (EMHP). Discover and validate a clinically-practical blood-based panel quantifying epigenetic age and trajectory, inflammatory and mitochondrial status, and responsiveness to interventions. *Phase 1* starts from a small, carefully-selected set of inflammatory genes and closely-related mitochondrial regulators (IL-6, IL-1β, TNF-α, NLRP3 / ASC / caspase-1, VCAM-1 / ICAM-1, PGC-1α, TFAM, sirtuins, GDF-15, FGF-21). For each gene, assays capture DNA methylation at key CpGs, expression levels (targeted RNA-seq or qPCR), and where appropriate circulating protein/metabolite levels. In sub-cohorts wearing BioButtons, paired blood draws bracket defined behavioral/physiologic states (sleep deprivation, exercise bouts, acute illness, stress-heavy weeks, restorative vacations) to quantify acute transcriptional and epigenetic responses to real-world stressors — and to identify individuals whose responses are exaggerated or blunted (high-value resilience-vs-vulnerability phenotypes). *Phase 2* expands via genome-wide DNA methylation (EPIC arrays, RRBS, or WGBS where justified), selective chromatin profiling (ATAC-seq; histone-mark ChIP-seq), and CRISPR Perturb-seq in patient-derived iPSC and immune/vascular cell models to clarify causal flow in gene networks (upstream regulators vs. downstream reporters — distinguishing markers from actionable targets). **Outcome:** A clinically-deployable EMHP comprising a limited set of CpG sites and protein/metabolite markers with OCI-hosted interpretive software, output as epigenetic age, mitochondrial burden, and links to recommended intervention frameworks.

Aim 3 — Targets, Therapies, and Precision Longevity Programs. Move from measurement to modulation. Network and pathway analysis across LCI, EMHP, WGS, methylation, BioButton, and Perturb-seq data identifies key epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins), transcription factors, non-coding RNA regulators, and mitochondrial stress pathways whose pertur-

bation most strongly shifts aging/recovery phenotypes. The therapeutic pipeline screens existing drugs and nutraceuticals (repurposing) and novel small molecules and biologics, advancing leads through pre-clinical efficacy and safety with EMHP and LCI as pharmacodynamic readouts and BioButton as continuous responder-monitor. In parallel, an aging-genomics *decision framework* (architected by Athey) integrates genotype + epigenotype + LCI + BioButton phenotypes to output individualized prioritization of lifestyle levers (sleep, movement, stress, diet, social/purpose) and to identify candidates for emerging therapeutics. The framework is built for integration into Oracle Health clinical workflows, population-health and employer/payer offerings, and EIT-affiliated longevity clinics. **Outcome:** A closed-loop *measure* → *model* → *intervene* → *re-measure* system, with a pipeline of pre-clinical drug targets and an evidence-based personalized-longevity decision-support layer.

Impact. Aging-genomics, like pharmacogenomics before it, can move precision medicine from reactive disease management to proactive healthspan extension — but only if grounded in rigorously-validated biomarkers and longitudinal data, not the silver-bullet rhetoric of the longevity-influencer marketplace. This program delivers the biomarkers, the decision-support, and the therapeutic pipeline that make aging-genomics clinically meaningful and commercially deployable at the scale of Oracle Health.

1 Research Strategy

2 Significance

The longevity question — and the longevity-influencer problem

How long is long enough? As captured in a "hot mic'' moment reported by the BBC on September 3, 2025, Chinese President Xi Jinping and Russian President Vladimir Putin were overheard discussing the possibility of living to 150 years of age. The question is no longer hypothetical for individuals or for healthcare systems. Aging is increasingly understood as a dynamic, modifiable process rather than an inevitable decline, and behavioral, environmental, and socioeconomic forces shape healthspan at least as powerfully as the genetic blueprint.

This understanding compels a rigorous, evidence-based approach, especially in an era saturated with expensive, unproven, and often outrageous "cures'' for aging — influencer protocols, supplement stacks, and biological reductionism dressed up as science. Aging is not controlled by any one pathway; the silver-bullet rhetoric of the longevity marketplace is a categorical mismatch with the underlying biology, in which the drivers are *groups* of genes whose regulation is tuned epigenetically by the daily activities of life. Decades-long clinical trials of aging are infeasible: what is needed are scientifically-valid biomarkers for biological aging, and the analytical tools to translate the macro-level lifestyle and environmental factors known to extend healthspan (Blue Zones, Cooper Clinic exercise cohorts) into the micro-level cellular changes that either promote resilience or accelerate decline.

Mitochondrial dysfunction as a driver of inflammaging

The central role of mitochondria in cellular energy metabolism makes them a focal point for understanding aging. Beyond their canonical bioenergetic role, mitochondria are signaling hubs that continuously monitor cellular stress and metabolic status. When their function is compromised, they switch from guardians of homeostasis to potent drivers of inflammation through three interconnected mechanisms.

First, release of mitochondrial damage-associated molecular patterns (DAMPs). Dysfunctional mitochondria release or expose specific molecular components that act as "danger signals.'' Mitochondrial DNA (mtDNA), structurally similar to bacterial DNA, is recognized by innate-immune receptors — TLR9, the cGAS-STING pathway, and the NLRP3 inflammasome — when released into the cytosol or extracellular space. These activate pro-inflammatory transcription factors (NF-κB) and the production of IL-1β and IL-18. Other DAMPs, including oxidized cardiolipin and N-formyl peptides, trigger parallel cascades.

Second, excessive reactive oxygen species (ROS). Dysfunctional electron-transport-chain complexes generate excessive mitochondrial ROS (superoxide, hydrogen peroxide), which act as critical second messengers that directly activate NF-κB and the NLRP3 inflammasome.

Third, impaired mitochondrial quality control. Mitochondrial dynamics (fission/fusion balance) and mitophagy (selective degradation of damaged mitochondria) maintain organelle health. An imbalance toward excessive fission or impaired mitophagy allows "sick'' organelles to accumulate, continuously leaking DAMPs and generating ROS — a persistent inflammatory stimulus that perpetuates inflammaging.

The vicious cycle: inflammation and accelerated aging

Chronic inflammation fueled by mitochondrial dysfunction contributes to accelerated aging through cellular senescence and the senescence-associated secretory phenotype (SASP), progressive tissue damage (endothelial dysfunction, atherosclerosis, neuroinflammation, sarcopenia), immune dysregulation (immunosenescence, autoimmune phenomena), and detrimental epigenetic modifications that further dysregulate gene expression and amplify the cycle.

The virtuous cycle: lifestyle, mitochondrial resilience, and maternal mtDNA inheritance

Beneficial behaviors — regular physical activity, optimal nutrition, adequate sleep, social engagement — activate cellular pathways that promote mitochondrial biogenesis (increased mtDNA copy number), enhance mtDNA repair, and improve OXPHOS efficiency. The result is a virtuous cycle: reduced ROS, decreased oxidative damage to mtDNA, and suppressed chronic inflammation. Detrimental lifestyles (sedentary behavior, poor diet, smoking) and metabolic dysregulation (diabetes, obesity) exacerbate the vicious cycle.

A largely-overlooked dimension is the *maternal* inheritance of mtDNA. Unlike nuclear DNA, mtDNA is transmitted from mother to all offspring. A mother's mitochondrial legacy — the quality, integrity, and specific haplogroups of her mtDNA — provides the foundational mitochondrial template for her children. In individuals exhibiting exceptional longevity (centenarians), emerging data suggest a stronger maternal inheritance of this trait. Layered onto this is *numtogenesis*: the integration of mtDNA fragments into the nuclear genome (numts), characterized methodologically by Ryan Mills, which can be bi-parentally transmitted and may modulate cellular regeneration. Maternal advantageous mtDNA variants, higher mtDNA integrity, and optimal mtDNA copy number jointly equip offspring with healthier mitochondrial starting points and longer-term health trajectories.

Foundational research and the case for human translation

Three decades of mechanistic research from the Ballinger and Runge laboratories have established the link between mitochondrial health and cardiovascular risk. ROS-induced mtDNA damage correlates with and directly contributes to atherosclerosis progression in mouse models; cigarette

smoke and high-fat diets dramatically increase mtDNA damage; NADPH-oxidase-derived superoxide drives experimental diabetes-induced atherosclerosis; PAI-1 (subject of Runge's NIA-funded program) intertwines vascular aging, fibrosis, and hypertension with cellular stress and mitochondrial function. Ballinger's independent conplastic-mouse work definitively established that mtDNA variation alone influences metabolic phenotype, including susceptibility to metabolic syndrome.

This mechanistic bedrock motivates the human-translation strategy of the present proposal. The pathways that drive atherosclerosis are highly shared with general aging mechanisms; atherosclerosis research provides faster cycle times for blood-based biomarker validation (8-OHdG, GDF-15, FGF-21) than purely longevity studies allow. Validated biomarkers can then be deployed in exceptional-longevity cohorts (centenarian families), birth cohorts (longitudinal mitochondrial-health tracking from birth correlated with parental longevity), and intervention studies assessing the impact of specific lifestyle or pharmacological interventions on mitochondrial biomarkers.

3 Innovation

Aging-genomics as the natural extension of pharmacogenomics

Pharmacogenomics has reshaped oncology and cardiology by personalizing drug selection and dosing through patient genotype. The clinical infrastructure — decision-support layers, EHR-integrated alerts, CPIC-style guideline frameworks — is mature and at scale. We propose that the same paradigm extends naturally to the negotiation each person conducts with their genome *across the lifespan*:

> *Which way of living and which interventions are right for which person, given their* ***genome, epigenome, mitochondrial state,*** *and* ***real-time physiology****?*

This is the central innovation of the program. Brian Athey, an expert and leader in pharmacogenomics and computational medicine, will architect the analytic framework and decision-support systems so that *aging-genomics* becomes as clinically meaningful and actionable as pharmacogenomics has become for warfarin, clopidogrel, and tamoxifen.

Epigenetics as "the negotiating table"

DNA methylation, histone marks, chromatin structure, non-coding RNAs, and RNA modifications respond to sleep and circadian rhythm, nutritional state, physical activity, psychosocial stress and joy, and purposeful cognitive engagement. These mechanisms determine *which genes are read, when, and how strongly* — and therefore how cells handle damage, repair, inflammation, and metabolism. Epigenetic clocks (Horvath, Hannum, universal mammalian estimators) already predict chronological and biological age with striking accuracy, and recent dietary-intervention pilot trials have demonstrated that epigenetic age is *reversible*. The platform proposed here unifies static methylation arrays with dynamic real-world phenotyping to capture not just biological age but biological-age *trajectory*.

Real-time phenotype: the BioIntelliSense BioButton

Until recently, most epigenetic and mitochondrial data were static snapshots — a single blood draw, an annual physical. We add *real-time phenotype* via the FDA-cleared BioIntelliSense BioButton wearable, which continuously collects heart rate and variability, respiratory rate, skin temperature

trends, body position and activity, sleep quantity and quality, and early signals of physiologic stress or illness.

Deploying BioButtons in targeted sub-cohorts and interventional studies enables a fundamentally new study design: paired blood draws bracket defined behavioral/physiologic states (sleep-deprivation nights, exercise bouts, acute respiratory illness, stress-heavy weeks, restorative vacation periods), allowing direct measurement of *acute* transcriptional and epigenetic responses of inflammatory and mitochondrial gene panels to real-world stressors. Static "lifestyle'' variables become high-resolution time series, and individuals whose responses are exaggerated or blunted (high-value resilience-vs-vulnerability phenotypes) become tractable.

CRISPR Perturb-seq for causal-flow discovery

A recurring weakness of biomarker-discovery programs is the markers-vs-targets ambiguity: an associated CpG site may be a downstream reporter of biological aging rather than an upstream modulator. We address this with CRISPR Perturb-seq applied in patient-derived iPSCs and immune/vascular cell models. By systematically perturbing top-priority genes from the EMHP panel and profiling single-cell transcriptomic responses, we map causal flow in the inflammatory and mitochondrial gene networks — distinguishing markers from actionable therapeutic targets.

Pangenomic methods, Oracle Cloud Infrastructure, and the Ellison Institute partnership

Standard reference-based variant calling under-represents structural variation, especially in non-European-ancestry genomes. The platform adopts pangenomic methods to capture this variation faithfully. Models are trained, deployed, and validated on Oracle Cloud Infrastructure (OCI), with secure HIPAA-compliant access to the Oracle Health 150-million-patient EHR via the Ellison Institute of Technology partnership. This pairing combines the analytical sophistication required for nonlinear ML/AI (gradient boosting, deep learning, survival models, with interpretability constraints appropriate for clinical use) with population scale and demographic diversity unattainable in any single academic cohort.

Closed-loop measure → model → intervene → re-measure

The cumulative innovation is a closed-loop precision-longevity system. **Measure**: WGS + EMHP + CRF + BioButton. **Model**: LCI predictive index + EMHP biological-age trajectory, on OCI. **Intervene**: aging-genomics decision framework outputs individualized lifestyle prioritization (sleep vs. movement vs.
stress vs. diet vs. social/purpose) plus therapeutic-candidate identification. **Re-measure**: BioButton continuous monitoring, periodic EMHP, longitudinal LCI re-scoring. The same rigor and clinical practicality that pharmacogenomics has brought to precision oncology becomes available for healthspan extension.

Approach — Aim 1: The Ellison Longevity & Cardiovascular Health Index (LCI)

Goal: A clinically-deployable index that predicts cardiovascular and aging outcomes by integrating nuclear and mitochondrial genomics, cardiorespiratory fitness (CRF), standard clinical risk factors,

real-time BioButton physiology, and longitudinal outcomes from UM, military/veteran, and Oracle Health EHR cohorts.

Commercial outcome: A patented diagnostic algorithm and scoring system suitable for embedding in Oracle Health clinical decision-support, population-health management, and employer/payer products.

Step 1 — Cohort assembly and phenotyping

We use three complementary cohort tiers.

University of Michigan tier. The Michigan Genomics Institute (MGI) is a health-system-based biobank with deep phenotyping (full EMR) and multiomic data — including WGS on the majority of ∼90{,}000 enrolled patients. Critically, MGI consent allows recontact for follow-up sampling and for solicitation into specific sub-studies, supporting the BioButton-paired-blood-draw design in Aim 2. MPOG (Multicenter Perioperative Outcomes Group, founded and led by Sachin Kheterpal) spans 85+ hospitals across multiple countries and contains millions of records, with up to twenty concurrent prospective trials at any given time and UM as the central Data Coordinating Center. The illustrative THRIVE multicenter trial demonstrates the operational maturity of the MPOG infrastructure.

Federal exercise-stress-test tier. Whole-genome sequencing on a selected, diverse cohort ($N = 10{,}000 - 20{,}000$) drawn from the DoDSR / USAFSAM / Cooper Institute / VETS biorepositories, selected on extreme phenotypes — top 10% vs. bottom 10% of longevity within follow-up, and exceptional vs. poor baseline CRF in METs. These cohorts uniquely combine objective baseline physiology (exercise-stress-test METs at enrollment), decades of longitudinal follow-up, biobanked longitudinal blood samples, and statistical power and demographic diversity (the VETS and DoDSR cohorts cover hundreds of thousands of individuals with significant ethnic and racial diversity).

BioButton sub-cohort. In selected MGI and federal-cohort subgroups, we deploy BioButton wearables for weeks to months to capture heart rate / HRV, respiratory rate, temperature trends, sleep architecture, activity / posture (sedentary vs. active patterns), and physiologic responses to ordinary life stressors.

Step 2 — WGS and mitochondrial analysis

Whole-genome sequencing on the high-information $10{,}000 - 20{,}000$ individuals yields:

- Polygenic scores for CVD, metabolic disease, and longevity endpoints.
- mtDNA haplogroups, heteroplasmy levels, and mtDNA copy number.
- Presence and characteristics of *numts* (nuclear mitochondrial insertions; characterized methodologically by Mills), including bi-parental transmission patterns.
- Pangenomic alignment to capture structural variation under-represented by reference-based callers.

GWAS and rare-variant association testing identify nuclear genetic variants and mtDNA features associated with: (i) exceptional baseline CRF and its maintenance over time; (ii) longitudinal healthy aging (survival without major age-related diseases); and (iii) reduced incidence of CVD events.

Step 3 — Model development on Oracle Cloud Infrastructure

Models are built on OCI integrating genotypes (nuclear + mtDNA + numts), CRF metrics and standard risk factors, BioButton-derived features (HRV as a proxy for autonomic / stress balance; sleep metrics; activity signatures), and clinical outcomes (CVD events, mortality, incident multimorbidity). We use nonlinear ML/AI (gradient boosting, deep learning, survival models) with interpretability constraints suitable for clinical deployment, and pangenomic alignment to avoid reference-bias and better capture structural variation.

Step 4 — Validation in the Oracle Health ecosystem

The LCI model is applied to large de-identified Oracle Health EHR subsets to validate predictive performance in diverse populations, assess calibration and subgroup performance, and refine the model based on external validation and clinical-input on interpretability and usability. The model is then validated in independent geographically-diverse subsets of the federal cohorts for predicting 10-year, 20-year, and lifetime risk for CVD and exceptional longevity.

Outcome and downstream integration

A robust, Ellison-branded *Longevity & Cardiovascular Health Index* embedded in Oracle Health products: clinical decision support, population-health management, employer/payer solutions, and EIT-affiliated longevity-clinic offerings. The LCI also feeds Aim 2 (EMHP calibration target) and Aim 3 (decision-framework input).

Approach — Aim 2: The Epigenetic & Mitochondrial Health Panel (EMHP)

Goal: A clinically-practical blood-based panel that quantifies epigenetic age and trajectory, inflammatory and mitochondrial status, and responsiveness to interventions.

Commercial outcome: A blood-based epigenetic diagnostic panel for monitoring biological age, mitochondrial health, and intervention response, deployable as a CLIA/IVD test with OCI-hosted interpretive software.

Phase 1 — Focused small-gene panel

Step 1 — Marker selection. We start with a small, carefully selected set of inflammatory genes and closely-related mitochondrial regulators, finalized iteratively with literature and pilot data. Candidate panel:

- **Core inflammatory cytokines:** IL-6, IL-1β, TNF-α.
- **Inflammasome components:** NLRP3, ASC, caspase-1.
- **Vascular inflammation and remodeling:** VCAM-1, ICAM-1, selected chemokine ligand/receptor pairs.
- **Mitochondrial stress and biogenesis:** PGC-1α, TFAM, selected sirtuins, GDF-15, FGF-21.

For each gene, assays capture: (i) DNA methylation at key CpGs (promoters, enhancers, sites known to change with aging or inflammation); (ii) expression levels via targeted RNA-seq or qPCR; (iii) where appropriate, circulating protein levels or related metabolites (e.g., 8-OHdG as an mtDNA-damage marker).

Step 2 — BioButton-paired sampling design. In sub-cohorts wearing BioButtons, we schedule baseline blood draws followed by follow-up draws *during* or *immediately after* defined behavioral and physiologic states:

- Sleep-deprivation nights (continuous BioButton sleep-architecture data).
- Defined exercise bouts (BioButton activity + HRV signatures).
- Acute respiratory illness (BioButton temperature + respiratory-rate trends).
- Stress-heavy weeks (BioButton HRV + sleep-quality decline).
- Restorative vacation periods (BioButton recovery signatures).

This design quantifies *acute* transcriptional and epigenetic responses of the small gene panel to real-world stressors, and identifies individuals whose responses are exaggerated or blunted for a given stressor — high-value resilience-vs-vulnerability phenotypes that are the leading edge of the dataset.

Step 3 — Modeling. On OCI we fit ML models linking panel gene methylation/expression + BioButton features + clinical risk factors to: (i) intermediate outcomes (blood-pressure changes, glycemic variability, CRF evolution); and (ii) long-term outcomes where available. Results prune the panel to a minimal, high-signal set of markers.

Phase 2 — Expansion via genome-wide omics and Perturb-seq

Step 1 — Full-scale methylation and chromatin profiling. In a subset of participants, genome-wide DNA methylation (Illumina EPIC arrays as the workhorse, RRBS or WGBS where deeper resolution is justified) plus selective chromatin profiling (ATAC-seq; ChIP-seq for key histone marks where feasible in PBMCs). Outputs include domain-specific epigenetic clocks (CVD clock, mitochondrial- resilience clock, inflammaging clock) and patterns of regulatory epigenetic changes near the small-panel genes and their network neighbors.

Step 2 — Integration with WGS and BioButton data. We combine WGS (including rare variants and structural variation via pangenomic alignment), genome-wide methylation/chromatin data, the small panel markers, and BioButton time-series features. ML/AI identifies gene clusters and pathways whose coordinated epigenetic state most strongly predicts LCI, biological age, and outcomes — plus interactive effects between genotype and epigenotype (SNPs that magnify or blunt the impact of methylation changes).

Step 3 — CRISPR Perturb-seq for causal discovery. In patient-derived iPSCs and primary immune/vascular cell models, we use CRISPR-based Perturb-seq to perturb top-priority genes (small-panel + extended networks) and profile single-cell transcriptomic responses. This clarifies causal flow in inflammatory and mitochondrial gene networks — distinguishing markers from actionable therapeutic targets, the central question that limits most biomarker-only programs.

Outcome

A clinically-deployable EMHP comprising a limited set of CpG sites plus protein/metabolite markers, with OCI-hosted interpretive software outputting epigenetic age and trajectory, inflammatory and mitochondrial burden, and explicit links to recommended intervention frameworks. The EMHP is the molecular complement to the LCI predictive index — LCI predicts outcomes; EMHP measures the biological-aging trajectory and intervention response.

Approach — Aim 3: Targets, Therapies, and Precision Longevity Programs

Goal: Move from measurement to modulation, both with lifestyle programs and therapeutic candidates.

Commercial outcome: A pipeline of pre-clinical drug targets, plus an evidence-based personalized-longevity decision-support layer licensable to longevity clinics, employer/payer wellness programs, and EIT-affiliated centers.

Step 1 — Network and pathway analysis

From LCI, EMHP, WGS, methylation, BioButton, and Perturb-seq data we map: (i) key epigenetic enzymes (DNMTs, TETs, HDACs, sirtuins); (ii) transcription factors; (iii) non-coding RNA regulators; and (iv) mitochondrial stress pathways. Causal-inference and network analysis (informed by Aim 2's Perturb-seq results) prioritizes nodes that, when perturbed in models, most strongly shift aging/recovery phenotypes. This delivers a ranked target list with explicit causal-direction annotations — the gap that pure association studies cannot fill.

Step 2 — Therapeutic pipeline

We screen for: (i) existing drugs and nutraceuticals with known effects on the prioritized pathways (repurposing opportunities); and (ii) novel small molecules and biologics that modulate specific epigenetic enzymes or mitochondrial regulators. High-throughput screening uses iPSC-derived disease models and primary immune / vascular cells; medicinal chemistry refines hits.

Early-phase trials and proof-of-concept studies use:

- EMHP and LCI as **pharmacodynamic readouts** (does the intervention shift the molecular trajectory?).
- BioButton as a **continuous responder-monitor** (does the intervention shift the daily-life physiologic signature?).

This gives a study design with rapid mechanism-aware decision points, analogous to the way pharmacogenomics-guided trials are structured in oncology.

Step 3 — Precision longevity programs (pharmacogenomics- analogous decision support)

Under Athey's leadership in the analytic-framework architecture, we develop an *aging-genomics / epigenomics decision framework*:

- **Input:** Genotype (WGS), epigenotype (EMHP and clock outputs), LCI, BioButton phenotypes.
- **Output:** Individualized prioritization of lifestyle levers (sleep optimization vs. increased movement vs. stress reduction vs. dietary modulation vs. social/purpose-focused changes), and identification of individuals likely to benefit particularly from candidate therapeutics.

The framework is integrated into Oracle Health clinical workflows (EHR alerts, dashboards), population-health and employer/payer offerings, and high-touch longevity clinics including EIT-affiliated centers.

Closed-loop integration

The aim closes the loop: **measure** (LCI, EMHP, BioButton) → **model** (OCI ML/AI on pangenomic data) → **intervene** (lifestyle program or candidate therapeutic) → **re-measure** (BioButton continuous + EMHP periodic + LCI re-scoring). Iteration with the same rigor and clinical practicality that pharmacogenomics has brought to precision oncology and cardiology.

4 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.

5 Commercialization and Governance

The program is designed for translation from academic discovery into clinical and commercial deployment. The roadmap follows three phases spanning years 1-7+ with explicit IP, regulatory,

and partnership milestones at each stage.

Phase 1 — Discovery and Pre-Validation (Years 1-3 — covered by Aims 1-3)

Biomarker discovery (genetic and epigenetic). Execute Aims 1 and 2 to identify robust genetic variants, mtDNA signatures, and epigenetic marks predictive of exceptional longevity, high CRF, and low CVD risk — particularly those linked to mitochondrial health and modulated by lifestyle. *Deliverable:* Prioritized lists of genetic and epigenetic biomarkers, initial predictive algorithms (LCI v1, EMHP v1). *IP goal:* File initial patents on biomarker panels and algorithms.

Diagnostic panel feasibility. Translate discovered epigenetic markers into a practical, blood-based panel suitable for high- throughput screening (methylation array or targeted qPCR panel). Optimize for cost-effectiveness and reproducibility. *Deliverable:* Prototype Longevity & Mitochondrial Health Epigenetic Panel.

Therapeutic target identification. Execute Aim 3 to identify and functionally validate epigenetic enzymes, genes, and pathways whose modulation improves mitochondrial function and reverses aging hallmarks in iPSC and pre-clinical *in vivo* models. *Deliverable:* Prioritized list of pre-clinical therapeutic targets. *IP goal:* Patents on therapeutic targets and modulation methods.

Phase 2 — Product Development and Regulatory Pathway (Years 4-6)

Diagnostic product development and validation. Refine the Longevity & Mitochondrial Health Epigenetic Panel into a clinical- grade In-Vitro Diagnostic (IVD). Conduct robust analytical and clinical validation (sensitivity, specificity, reproducibility, clinical utility) in diverse independent cohorts. *Deliverable:* Fully-validated IVD diagnostic kit and interpretive software/report. *IP goal:* Strengthen diagnostic patents; develop trade secrets for interpretive algorithms.

Regulatory submission and approval. Prepare and submit regulatory dossiers (FDA 510(k) or de novo; CE Mark in Europe) for the diagnostic panel as a predictor of longevity potential and CVD risk. *Deliverable:* Regulatory clearance for market launch.

Pre-clinical drug lead optimization. Initiate drug discovery (high-throughput screening, medicinal chemistry) for small molecules and biologics modulating identified epigenetic therapeutic targets. Conduct pre-clinical *in vivo* efficacy and safety. *Deliverable:* Lead compound candidates for longevity-enhancing or CVD-reducing therapeutics.

Phase 3 — Commercial Launch and Therapeutic Translation (Years 7+)

Commercial launch of the diagnostic. Market the Longevity & Mitochondrial Health Epigenetic Panel to longevity clinics, preventative-medicine practices, corporate wellness programs, and eventually direct-to-consumer (with appropriate medical oversight). Embed in Oracle Health products via the Ellison Institute partnership. *Deliverable:* Revenue from diagnostic sales; expanded user base.

Personalized longevity programs. Develop and license programs based on diagnostic results: tailored lifestyle (diet, exercise, sleep, cognitive, social) and nutritional-supplement recommendations to optimize individual epigenetic profiles and mitochondrial health. *Deliverable:* Subscription-based wellness programs; strategic partnerships with longevity-clinic and employer/payer channels.

Therapeutic clinical development. Advance promising drug candidates through Phase 1, 2, and 3 trials targeting specific age-related conditions (sarcopenia, metabolic dysfunction) and broadly as longevity-enhancing interventions. *Deliverable:* New chemical entities and biologics for longevity therapeutics.

Governance: permissions, agreements, compliance

The program operates under a layered permissions and compliance framework: primary IRB approval at the lead institution plus reliance agreements with collaborating IRBs (DoD, VA, Cooper Institute); informed-consent review across all source cohorts (broad genetic / omic / commercial-research permissions; re-consent or documented-waiver pathways where needed); Data Use Agreements (DUAs) and Data Sharing Agreements (DSAs) with each custodian (AFHSD for DoDSR, VA Research Offices for VETS, Cooper Institute for CCLS), with explicit IP clauses; Material Transfer Agreements (MTAs) for biospecimen transfer; collaboration and commercialization agreements with revenue-sharing, licensing, and patent-ownership terms; HIPAA-compliant data storage on OCI or institutional HPC with stringent access controls; and DoD/VA-specific regulations governing research with military personnel and veterans, which include additional layers of review and oversight for commercial applications.

6 Appendix

Multiple-PD/PI Leadership Plan

This is a multiple-PD/PI submission with **Steven L. Kunkel, Ph.D. as Contact PI** and **Brian D. Athey, Ph.D. as co-PI**. The leadership plan distributes scientific authority across complementary expertise areas while maintaining unified decision-making through a quarterly steering-committee cadence.

Kunkel (Contact PI; 0.60 cal mo/yr). Inflammaging axis scientific lead — NLRP3 / inflammasome biology, cytokine networks, tissue-specific inflammation. Leads Aim 2 panel composition and Aim 3 therapeutic-target prioritization. Final authority on inflammation-axis study design and reporting.

Athey (co-PI; 0.60 cal mo/yr). Computational-medicine and analytic-framework lead. Architects the LCI model (Aim 1) and the aging-genomics decision framework (Aim 3). Leads pharmacogenomics- analogous decision-support architecture, Oracle Cloud Infrastructure integration, and validation against the Oracle Health 150-million- patient EHR via the Ellison Institute partnership.

Kheterpal (senior collaborator; 0.30 cal mo/yr). MPOG operational lead. Gates MPOG cohort access (85+ hospitals, millions of records, up to twenty concurrent prospective trials with UM as central Data Coordinating Center). Provides large-scale prospective-trial infrastructure for Aim 2's BioButton-paired-blood- draw sub-cohorts.

Runge (senior collaborator; 0.20 cal mo/yr). Senior scientific leadership for the cardiovascular-translation arm. Foundational mtDNA-atherogenesis collaboration with Ballinger underwrites the mechanistic premise; NIA-funded PAI-1 program underwrites the vascular-aging connection. Provides Michigan Medicine institutional sponsorship and the Ellison Institute / Oracle Health channel.

Ballinger (collaborator; 0.10 cal mo/yr). mtDNA-only genetic-contribution validation framework based on conplastic-mouse work (Ballinger *et al.*, *Circulation Research* 2010).

Mills (co-investigator; 0.30 cal mo/yr). Numts methodology lead for Aim 1's nuclear-mitochondrial-insertion characterization.

Conflict resolution. Scientific disagreements escalate first to the Kunkel-Athey leadership pair; if unresolved within two weeks, to the steering committee (all six PIs and Farnum) for majority decision; if still unresolved, to the Michigan Medicine Office of Research for institutional adjudication.

Human Subjects Research

Risks to subjects

Recruitment and study procedures. The platform draws on existing biorepository samples and prospectively-recruited sub-cohorts. The minimal-risk procedures include: peripheral venipuncture for blood draws (biospecimens for WGS, EMHP, and plasma metabolomics), wearing of the FDA-cleared BioIntelliSense BioButton (worn on the chest with adhesive; risks limited to skin irritation), and EHR-data linkage. No experimental therapeutics are administered as part of the discovery aims; therapeutic-screen work in Aim 3 is conducted in iPSC and primary-cell models, not in human subjects.

Genetic-information risk. WGS data carry standard incidental-finding risk. Per ACMG guidelines, incidental medically actionable findings (ACMG SF v3.x list) are returned to participants through Michigan Medicine genetic-counseling infrastructure on an opt-in basis specified at consent.

Adequacy of protection against risks

Recruitment and informed consent. Existing informed-consent documents for all source cohorts are reviewed for permissions covering broad genetic, omic, and commercial research and de-identified data sharing. Where existing consent is insufficient, we pursue re-consent (feasible for MGI given its recontact-friendly cohort design with patient-portal-based recontact tooling) or document a waiver justification (for de-identified residual samples, minimal risk, clear public/commercial health benefit) for explicit IRB approval. BioButton sub-cohorts operate under fresh prospective consent that explicitly addresses continuous-physiologic-data collection, behavioral-state inferences, and commercial-research intent.

IRB framework. Primary IRB approval is obtained at the Michigan Medicine IRB (IRBMED) for the entire study protocol — including genetic and multi-omic analysis and commercial-research intent. External IRB approvals or reliance agreements are secured with each cohort custodian: DoD (DoDSR and USAFSAM cohorts; via the Armed Forces Health Surveillance Division Research Review Group), VA (VETS cohort; via the local VA Research & Development Committee and CIRB as appropriate), Cooper Institute (institutional IRB), MGI and MPOG operating IRBs, and the Ellison Institute / Oracle Health partnership.

HIPAA compliance. All clinical data are handled in accordance with HIPAA regulations for Protected Health Information. Identifiable data flows are limited to the minimum necessary for recontact and follow-up; analytical work uses de-identified data sets to the maximum extent compatible with research and commercial-validation needs. Data storage and analysis operate on Oracle Cloud Infrastructure HIPAA-compliant tenancy and on Michigan Medicine institutional HPC, with stringent role-based access controls and audit logging.

Confidentiality and Certificate of Confidentiality. A Certificate of Confidentiality (CoC) is requested via the NIH-issued CoC pathway covering all research participants and all study data. CoC protections preempt court-ordered disclosure and strengthen privacy protections beyond HIPAA's baseline.

Potential benefits of the proposed research

Direct benefit to subjects. Optional return of medically actionable incidental findings; optional access to a personalized LCI / EMHP report at conclusion of the participant's involvement.

Importance of knowledge gained. The platform produces the biomarker, decision-support, and therapeutic-target deliverables that are needed for evidence-based personalization of healthspan interventions, replacing the current longevity-marketplace reliance on under-validated influencer protocols and supplements.

Inclusion of women, minorities, and children

The military and veteran cohorts (DoDSR, USAFSAM, Cooper, VETS) provide substantial ethnic and racial diversity, and the MGI cohort reflects the demographics of the University of Michigan health-system catchment. The proposed sample-size targets ($N = 10{,}000 - 20{,}000$ for the WGS training set) are powered to support subgroup analyses across ancestry, sex, and age strata. Children (under 18) are not enrolled. Pregnant women are not specifically recruited but are not excluded if otherwise eligible.

Vulnerable populations

Active-duty military personnel and veterans are recognized as populations potentially vulnerable to coercion in research; specific DoD and VA regulations governing research with these populations apply, including additional layers of review and oversight when commercial applications are contemplated. Our protocol incorporates these requirements prospectively. Recruitment for any prospective sub-cohort within the DoD or VA cohorts uses non- coercive recruitment strategies and is reviewed by the relevant research-protections offices.

Older adults with cognitive impairment. The aging-focused cohort design includes individuals into late life, some of whom may have cognitive impairment. Capacity-to-consent assessments are implemented per Michigan Medicine IRBMED guidance; legally authorized representative consent is permitted where appropriate.

Inclusion of individuals across the lifespan

The proposed cohorts span 25 to 110 years, deliberately weighted toward older adults to maximize statistical power for late-life phenotype detection. The age strata are specified in the Statistical Analysis Plan and are used for stratified analysis across all aims.

Data Management & Sharing Plan

This plan complies with the NIH Data Management and Sharing Policy (NOT-OD-21-013, effective 2023) and addresses each required element.

Data type and metadata

Genomic data: Whole-genome sequence data (FASTQ, BAM, VCF files) for the Aim 1 training cohort ($N = 10{,}000 - 20{,}000$). Includes called variants (SNVs, indels, structural variants, mtDNA haplogroup calls, heteroplasmy levels, copy-number, numt characterizations).

Methylation and chromatin data: Illumina EPIC-array beta- values, RRBS / WGBS reads where deeper resolution is justified, ATAC- seq and selected histone-mark ChIP-seq for Aim 2 Phase 2 sub-cohort.

Expression and protein data: Targeted RNA-seq and qPCR expression data for the EMHP small panel; multiplexed circulating inflammatory and mitochondrial-protein measurements.

BioButton time-series data: Continuous heart-rate, heart-rate variability, respiratory rate, skin temperature, activity, posture, and sleep-architecture data, with metadata on deployment windows and behavioral / physiologic state annotations.

Clinical phenotype and outcome data: EHR-derived clinical phenotypes, longitudinal health outcomes (CVD events, mortality, incident multimorbidity, ADE), CRF metrics from exercise-stress-test records.

Perturb-seq data (Aim 2 Phase 2): Single-cell RNA-seq from CRISPR-perturbation screens in patient-derived iPSCs and primary cell models.

Models and analytical artifacts: LCI predictive-model weights, EMHP scoring algorithm, decision-framework rule sets, Perturb-seq causal-network outputs.

Metadata standards: GA4GH-compliant phenopackets for phenotype data; PRIDE-compatible mass-spec metadata; minimum- information-for-clinical-genomics annotation for variant calls; GTM-generic for BioButton sensor streams. Documentation captured via Datasheets-for-Datasets-style summaries.

Related tools, software, and code

Open-source release: The LCI scoring pipeline, EMHP marker-derivation scripts, pangenomic-alignment configurations, and the OCI-hosted decision-framework prototype are released as open-source repositories (Apache 2.0 licence) on a 6-month delay following the clinical-validation manuscript on each system. The delay protects pre-publication review integrity and supports patent-filing windows where IP protection is required for the commercialization roadmap.

Patent-protected components: Core diagnostic algorithms embedded in the regulated IVD product are protected as part of the commercialization roadmap (see roadmap section). Patent filings precede each public release of code for these components. Public documentation describes algorithm structure and validation; the licensable runtime artifacts are protected by patents and / or trade-secret licensing.

Standards

GA4GH (variant calls, phenopackets), CDISC (clinical phenotypes), HL7 FHIR (EHR linkage), MIRIAM-style provenance for analytical pipelines.

Data preservation, access, and timelines

Genomic data: Deposited at NIH dbGaP under controlled access. Embargo: data are released to dbGaP no later than the publication date of the primary analysis manuscript.

BioButton time-series data: Deposited at the NHLBI BioData Catalyst or equivalent NIH-controlled-access repository, on the same timeline as the genomic data.

Methylation, chromatin, and expression data: Deposited at NCBI GEO / SRA on a publication-aligned timeline.

Perturb-seq data: Deposited at the Single Cell Portal (Broad) or NCBI GEO with full Perturb-seq guide-library annotation.

Summary-statistic data: Effect sizes, polygenic scores, EMHP marker weights, LCI scoring weights without person-identifying linkages accompany each peer-reviewed manuscript on its publication date.

Long-term retention: All deposited data are retained for at least 10 years post-publication, per institutional policy and the relevant repository terms.

Access, distribution, and reuse considerations

Source-cohort restrictions apply: DoDSR, VA / VETS, Cooper Institute, MGI, and MPOG terms govern access to subsets of the deposited data; these restrictions are documented in dbGaP study metadata. Access is gated through the existing NIH dbGaP Data Access Committee mechanism plus the cohort-specific custodian access processes.

Oracle Health 150-million-patient EHR: Validation analyses are conducted within the Oracle Health / OCI tenancy under the Ellison Institute partnership terms; results (model performance, calibration, fairness metrics) are publicly released, but the underlying EHR data remain inside the Oracle Health environment per the partnership data-governance terms.

Oversight

The Michigan Medicine Office of Research Compliance and the IRBMED oversee compliance with this plan. The Data Management and Sharing Plan is reviewed annually and updated to reflect new data types, new repositories, or new partnership terms.

Authentication of Key Biological and/or Chemical Resources

Cell lines and iPSCs. Patient-derived iPSCs used for Perturb-seq are authenticated via STR profiling and karyotyping at receipt and at quarterly intervals. Pluripotency markers are confirmed by qPCR (NANOG, OCT4, SOX2). All lines are tested for mycoplasma contamination at receipt and quarterly thereafter.

Antibodies. Antibodies for ChIP-seq histone marks and inflammatory-protein quantification are validated by Western blot positive/negative controls on each new lot, with vendor catalog numbers and lot numbers recorded in laboratory notebooks.

Reagents. CRISPR guide RNAs for Perturb-seq are sequence- verified by Sanger sequencing prior to lentiviral packaging.

Cohort biospecimens. DoDSR, USAFSAM, Cooper, VETS, and MGI biospecimens are tracked under chain-of-custody documentation maintained by each biorepository, with sample integrity validated on receipt by absorbance spectrometry (DNA / RNA quality) and electrophoresis.

Vertebrate Animals

This proposal does not involve research with vertebrate animals. The mechanistic biology underlying the proposal (mitochondrial dysfunction, inflammaging, NLRP3 inflammasome activation, mtDNA-atherogenesis link) was established in prior published work of the Ballinger and Runge laboratories using mouse models; that work is cited but not repeated here. The current proposal is entirely human-subjects research and *in vitro* work in patient-derived iPSCs and primary human immune/vascular cells.

Select Agents

This proposal does not involve work with Select Agents as defined by the HHS / USDA Select Agents and Toxins regulations.

Resource Sharing Plan

Data sharing

See the Data Management & Sharing Plan section for the full NIH-2023- Policy-compliant data-sharing plan, including data type, repositories (dbGaP, NCBI GEO, BioData Catalyst), embargo timelines, source-cohort restrictions, and oversight.

Model organisms

N/A — this proposal does not generate new vertebrate model organisms. Mouse-model work that motivated this proposal is in prior published Ballinger and Runge laboratory output and is cited rather than repeated here. *In vitro* work uses patient-derived iPSC lines (see below) and primary human immune / vascular cells.

Software and analytical tools

Open-source release timeline. The LCI scoring pipeline, EMHP marker-derivation scripts, pangenomic-alignment configurations, and the OCI-hosted decision-framework prototype are released as open-source repositories (Apache 2.0 licence) on a 6-month delay following clinical-validation publication. The delay protects pre-publication review integrity and supports patent-filing windows.

Patent-protected components. Core diagnostic algorithms embedded in the regulated CLIA / IVD product are protected as part of the commercialization roadmap. Patent filings precede each public release of code for these components. Public documentation describes algorithm structure and validation; the licensable runtime artifacts are protected by patents and / or trade-secret licensing.

Code repositories. Hosted at the `Single-Molecule-Sequencing` GitHub organization with full release versioning, semantic-version tagging, and reproducibility manifests (Snakemake / Nextflow workflows; Apache Beam pipelines for OCI; Docker / Singularity images for analytical environments).

Cell lines, reagents, and biological materials

Patient-derived iPSC lines. iPSC lines generated under the proposal are deposited at the Coriell Institute following completion of the Perturb-seq experiments. Deposition includes full quality-control documentation (STR profiles, karyotype, pluripotency-marker qPCR, mycoplasma-negative status). The accompanying CRISPR guide- library used in the Perturb-seq screens is deposited at Addgene with plasmid maps and target-gene annotations.

Antibodies and assay reagents. Where novel antibodies or multiplexed-assay reagents are validated under the proposal, the validation documentation (Western-blot images, dynamic-range curves, specificity controls) is deposited in figshare or equivalent open-data repository with a permanent DOI.

Biospecimens. Residual biospecimens from prospectively- recruited sub-cohorts are deposited at the Michigan Medicine biorepository under MTAs allowing internal-research re-use; access to other researchers requires a new IRB protocol and execution of the standard Michigan Medicine MTA.

Trained personnel and training infrastructure

The proposed Research Training Plan (see appendix) includes 4 post- doctoral fellow positions and 2 predoctoral student positions; all trainees are co-mentored across the inflammation and computational axes. Trainees graduating from the proposal carry forward the analytical and operational skill set — the most durable form of resource sharing.

Budget Justification

Personnel

Kunkel (Contact PI; 0.60 cal mo/yr, 5% effort). Scientific direction of Aim 2 panel composition and Aim 3 therapeutic- target prioritization; chair of the steering committee; co-mentorship of Aim 2 and Aim 3 post-doctoral fellows. Salary requested at the NIH cap.

Athey (co-PI; 0.60 cal mo/yr, 5% effort). Architecture of the Aim 1 LCI predictive model and the Aim 3 aging-genomics decision framework; scientific direction of OCI ML/AI integration; oversight of the Oracle Health 150-million-patient EHR validation. Salary requested at the NIH cap.

Kheterpal (Senior Collaborator; 0.30 cal mo/yr, 2.5% effort). Operational direction of the MPOG sub-cohort design and governance terms; oversight of the BioButton-paired-blood-draw study deployment in MPOG sites.

Runge (Senior Collaborator; 0.20 cal mo/yr, 1.7% effort). Senior scientific leadership of the cardiovascular-translation arm; institutional sponsorship and the Ellison Institute / Oracle Health partnership channel.

Ballinger (Collaborator; 0.10 cal mo/yr, 0.8% effort, sub-award to UAB). Mitochondrial-genetics analytical leadership; mtDNA haplogroup, heteroplasmy, and copy-number characterization.

Mills (co-Investigator; 0.30 cal mo/yr, 2.5% effort). Numts methodology and pangenomic-alignment leadership.

Farnum (Investigator; 1.20 cal mo/yr, 10% effort). Bioinformatics operations and ML pipeline implementation; OCI build-and-deploy maintenance.

Postdoctoral fellows (4 FTE, full effort). One per Aim 1 LCI training, Aim 2 panel discovery, Aim 2 Perturb-seq, and Aim 3 target nomination.

Predoctoral students (2 FTE). One in computational medicine (Athey lab) and one in pathology (Kunkel lab).

Project manager (1.0 FTE). Operationally coordinates MPOG sub-cohort recruitment, BioButton deployment logistics, and IRB amendments across the multicenter footprint.

Bioinformatics staff (2.0 FTE). OCI pipeline build, methylation/expression assay quality control, and cohort harmonization.

Direct costs — equipment and consumables

BioButton wearables and recurring service fees. Procurement of $\sim$ 1,000 BioButton units across the project lifetime to cover sub-cohort enrollment plus device replacement. Recurring per-deployed-device service fees.

Whole-genome sequencing. Cohort-scaled WGS for the LCI training set (N = 10,000 − 20,000). Per-sample cost negotiated through Michigan Medicine procurement; budget assumes near-term $\sim$ \$500/sample $30\times\$short - readWGS$.

Methylation arrays and chromatin profiling (Aim 2). Illumina EPIC array (or successor) on the Phase 2 sub-cohort; ATAC-seq and ChIP-seq on a smaller subset.

CRISPR Perturb-seq (Aim 2 Phase 2). Patient-derived iPSC maintenance, lentiviral guide-library production, single-cell RNA-seq for the Perturb-seq screens.

Targeted protein and metabolite assays. Multiplexed inflammatory and mitochondrial protein panels; targeted metabolomics for circulating mitochondrial-activity readouts.

Direct costs — compute and data

Oracle Cloud Infrastructure. OCI HIPAA-compliant tenancy for the Aim 1 LCI training stack, Aim 2 chromatin-profiling analyses, and Aim 3 decision-framework deployment. Includes secure de-identified Oracle Health EHR access fees per the Ellison Institute partnership terms.

Internal HPC. Michigan Medicine institutional HPC for sequence-data processing and pangenomic alignment; storage on Michigan Medicine secure-research-data infrastructure.

Travel and dissemination

Travel to scientific meetings (one PI per year per major venue); travel to MPOG site visits for BioButton sub-cohort kickoffs. Open-access publication fees.

Subawards

University of Alabama at Birmingham (Ballinger). Subaward covering 0.10 cal mo/yr Ballinger effort plus mtDNA- genetics consumables.

Indirect costs

Calculated at the negotiated Michigan Medicine F&A rate for on-campus research. UAB subaward indirects calculated per UAB rates.

Note on scaling

The R01 (12-page) and NIA R01 variants assume the NIH modular budget ceiling; the U19 multi-PI Center variant exceeds the modular budget and uses a detailed budget per the NIA U19 mechanism rules. The detailed cohort-tier and per-aim cost breakdowns are populated at submission time by the EVPMA office (Runge), the Department of Anesthesiology MPOG operational budget (Kheterpal), and the Department of Computational Medicine & Bioinformatics (Athey).

Research Training Plan

The program is intentionally structured to produce a generation of trainees fluent at the intersection of inflammation biology, computational genomics, mitochondrial biology, and clinical decision support — the multidisciplinary skill set that aging-genomics will demand at scale.

Trainee positions

Four post-doctoral fellows (full-effort across the project period):

1. *LCI fellow* (Athey + Mills co-mentorship). Develops the Aim 1 LCI predictive model on OCI; pangenomic alignment; interpretable nonlinear ML.

2. *EMHP small-panel fellow* (Kunkel + Athey co-mentorship). Develops the Aim 2 Phase 1 inflammatory + mitochondrial-regulator panel and the BioButton-paired-blood-draw experimental design.

3. *Perturb-seq fellow* (Mills + Kunkel co-mentorship). Runs the CRISPR Perturb-seq screens in patient-derived iPSCs; causal-flow analysis distinguishing markers from actionable therapeutic targets.

4. *Therapeutic-target fellow* (Kunkel + Athey co-mentorship). Aim 3 network analysis, target prioritization, and small-molecule / biologic screen feasibility.

Two predoctoral students: one in computational medicine (Athey lab) and one in pathology (Kunkel lab), recruited through the relevant UM PhD programs.

Mentorship structure

Each trainee is *co-mentored* across the inflammation and computational axes. This is by design — the proposal's intellectual contribution requires fluency in both, and the co-mentorship pair ensures the trainee develops in both. The senior collaborators (Kheterpal, Runge, Ballinger) provide additional disciplinary mentorship in their respective domains as the trainee's project requires.

Skill development

Computational and analytical. OCI / Oracle Cloud Infrastructure proficiency (data engineering, ML pipelines, model deployment); pangenomic alignment and structural-variation calling; single-cell RNA-seq and Perturb-seq analysis; survival-analysis methods and interpretability-constrained ML.

Wet-lab and clinical. Inflammasome and inflammatory-cytokine assay execution; iPSC culture and CRISPR perturbation; multiplexed protein assays; phlebotomy-coordinated study design with the BioButton-paired sub-cohorts.

Translational and operational. IRB protocol design and amendment; multicenter consortium coordination through MPOG; data-governance and HIPAA-compliant workflow design; commercial- research and IP awareness.

Career-development infrastructure

Career milestones are tracked via the Michigan Medicine Office of Research trainee dashboard with quarterly individual development plan (IDP) reviews. Trainees participate in the UM Postdoctoral Association programming, the Computational Medicine & Bioinformatics training-program seminars, and the Department of Pathology trainee-development cohort. Senior fellows are supported in preparing K99 / R00 transition awards or industry-research transitions.

Diversity and inclusion

Recruitment across the four post-doctoral and two predoctoral lines prioritizes diverse candidate pools through the UM Rackham PhD Diversity Recruitment program, the Center for Computational Medicine Diversity Pipeline, and active outreach to MSI / HBCU institutions through Michigan Medicine partnerships. Quarterly DEI metrics are reviewed by the Steering Committee.

7 Biosketches

Steven L. Kunkel, Ph.D. — Principal Investigator

Personal statement. I am a pathologist whose three-decade research program has established core mechanisms of acute and chronic inflammation, with particular emphasis on cytokine and chemokine networks in tissue injury, NLRP3-axis activation, and the cellular basis of inflammaging. The present proposal builds on this body of work to operationalize the inflammaging axis as a measurable, modulatable pillar of the aging-genomics platform. As Principal Investigator I will lead Aim 2's panel-composition strategy (inflammatory and mitochondrial-regulator gene selection, methylation-vs-expression-vs-circulating-protein assay design, BioButton-paired stressor-response sub-cohort design) and Aim 3's therapeutic-target prioritization (NLRP3-inflammasome modulators, sirtuin-axis interventions, age-attenuating epigenetic drugs).

Positions and Honors. Distinguished University Professor and Endowed Professor of Pathology, University of Michigan Medical School; Senior Associate Dean, Research; member of the National Academy of Medicine; Society for Leukocyte Biology Bonazinga Award; American Association of Immunologists Distinguished Service Award.

Contributions to Science.

1. *Chemokine biology in inflammation and tissue injury.* Established the role of CXC and CC chemokines in neutrophil and monocyte recruitment in lung injury, sepsis, and tissue fibrosis. Foundational characterization of IL-8/CXCL8 and CXCR2-axis signaling in acute inflammation.

2. *Inflammasome biology and chronic disease.* Characterized NLRP3-inflammasome activation in chronic kidney disease, vascular inflammation, and tissue-specific aging-related dysfunction.

3. *Inflammaging in age-related disease.* Defined cytokine- network signatures distinguishing physiologic immunosenescence from pathologic chronic inflammation; linked IL-1β, IL-6, and TNF-α trajectories to functional decline, frailty, and adverse-drug-event risk in older adults.

4. *Translational inflammation diagnostics.* Multi-marker inflammatory panels for stratification of age-related inflammatory disease, providing the methodological foundation for the EMHP Phase 1 panel proposed here.

Research Support. Multi-decade NIH portfolio in chronic inflammation, tissue injury, and chemokine biology. Specific awards to be inserted at eRA-Commons biosketch finalization.

Brian D. Athey, Ph.D. — co-Principal Investigator

Personal statement. I am a computational biologist whose career has focused on translating large-scale multi-omic and clinical data into actionable, decision-support-ready frameworks for precision medicine. My work has spanned chromatin biology, large-data infrastructure (NIH Big Data to Knowledge / BD2K), pharmacogenomics- guided clinical decision support, and the integration of structural genomics into prescribing pipelines. As co-Principal Investigator on the present proposal I will lead the analytical architecture of the *Longevity & Cardiovascular Health Index* (Aim 1) and the aging-genomics *decision framework* (Aim 3), so that aging-genomics — like the pharmacogenomics infrastructure I helped build — becomes clinically meaningful and actionable across genotype, epigenotype, and real-time phenotype.

Positions and Honors. Michael Savageau Collegiate Professor of Computational Medicine & Bioinformatics; Professor of Internal Medicine, Pharmacology, and Psychiatry, University of Michigan Medical School; founding Director of the UM Department of Computational Medicine and Bioinformatics; founding Director of the Michigan Center for Translational Pathology.

Contributions to Science.

1. *Pharmacogenomics decision support.* Multi-decade program building EHR-integrated pharmacogenomics decision-support systems, including the cytochrome P450 / CPIC-aligned alerting frameworks that have informed Michigan Medicine and broader-network adoption of pharmacogenomics-guided prescribing. This is the architectural template extended to aging-genomics in the present proposal.

2. *Big Data to Knowledge infrastructure (BD2K).* Co-leadership of NIH BD2K-funded centers integrating multi-omic and clinical data at scale; computational-medicine training programs producing the next generation of clinical-data scientists.

3. *Chromatin and 3D genome organization.* Foundational electron-microscopy and computational-imaging contributions to understanding nucleosome packing, higher-order chromatin organization, and 3D genome topology — the structural substrate for the methylation-and-chromatin work in Aim 2.

4. *Translational omics.* Computational frameworks for integrating WGS, transcriptomics, and EHR-derived phenotypes, applied to oncology and cardiovascular precision medicine — directly portable to the LCI Aim 1 modeling stack on Oracle Cloud Infrastructure.

Research Support. NIH-funded portfolio across computational medicine, BD2K-era big-data infrastructure, and pharmacogenomics decision support. Specific awards to be inserted at eRA-Commons biosketch finalization.

Sachin Kheterpal, M.D., MBA — Senior collaborator (MPOG operational lead)

Personal statement. I am an anesthesiologist and outcomes researcher who founded and now leads the Multicenter Perioperative Outcomes Group (MPOG) — one of the largest multi-institutional clinical-data consortia in the United States, encompassing 85+ hospitals across multiple countries with millions of patient records and up to twenty concurrent prospective trials at a time. UM serves as MPOG's central Data Coordinating Center. As Senior Collaborator on the present proposal I will gate MPOG cohort access for the LCI training set (Aim 1) and design and operationalize the BioButton-paired-blood-draw sub-cohort protocols inside MPOG sites that anchor the EMHP discovery design (Aim 2). My role makes the multicenter prospective infrastructure of the proposal feasible at scale beyond a single academic center.

Positions and Honors. Professor and Senior Associate Chair for Research and Quality, Department of Anesthesiology, University of Michigan; Executive Director and founding architect, Multicenter Perioperative Outcomes Group (MPOG); founding member of the Anesthesia Quality Institute. Multiple national leadership roles in perioperative outcomes research and learning health systems.

Contributions to Science.

1. *MPOG — multicenter outcomes infrastructure.* Founding architect of MPOG, which standardizes EHR-derived perioperative data across an 85+ hospital network, enables prospective multicenter trials, and produces the largest perioperative research dataset in the world. The

operational template directly underwrites the present proposal's multicenter sub-cohort design.

2. *Perioperative outcomes research.* Studies on intraoperative hypotension, anesthetic management, and postoperative delirium that have shaped guidelines and demonstrated the methodology of using large-scale standardized EHR data for causal inference in clinical care.

3. *Learning health systems.* Implementation and study of prospective real-world evidence generation through MPOG's THRIVE trial framework — the operational paradigm by which the BioButton- paired-blood-draw sub-cohorts of Aim 2 will be deployed.

4. *Clinical decision support and informatics.* Design and evaluation of EHR-integrated decision support, alerting, and closed-loop quality-improvement systems — the integration target for the Aim 3 aging-genomics decision framework into Oracle Health.

Research Support. MPOG operational and research portfolio funded through institutional, foundation, and federal mechanisms. Specific awards to be inserted at eRA-Commons biosketch finalization.

Marschall S. Runge, M.D., Ph.D. — Senior collaborator (Cardiovascular translation lead)

Personal statement. I am a physician-scientist whose laboratory-based career has been dedicated to understanding how mitochondrial dysfunction and oxidative stress contribute to vascular disease. The mechanistic spine of this proposal — mitochondrial DNA damage, ROS-driven inflammation, and the inflammaging vicious cycle — emerged directly from work my collaborators and I conducted across more than two decades. My current administrative role at Michigan Medicine provides the institutional infrastructure (Ellison Institute of Technology partnership; Oracle Health 150-million-patient EHR access; Michigan Genomics Initiative consent framework; clinical translational pathology infrastructure) that makes this proposal operationally feasible at the scale it requires. As senior collaborator I will provide scientific leadership for the cardiovascular-translation arm and the institutional sponsorship that unlocks the Ellison-Oracle channel.

Positions and Honors. Executive Vice President for Medical Affairs, University of Michigan; Chief Executive Officer, Michigan Medicine; Dean, University of Michigan Medical School; Professor of Internal Medicine (Cardiovascular Medicine), University of Michigan Medical School. Past Department of Medicine Chair, University of North Carolina at Chapel Hill. Author of *The Negotiation of a Lifetime* (2024), which provides the conceptual scaffolding for "epigenetics as the negotiating table'' framing in this proposal.

Contributions to Science.

1. *Mitochondrial DNA damage in atherosclerosis.* Foundational mechanistic work with S.W. Ballinger linking ROS-induced mitochondrial DNA damage to atherogenesis in mouse models, including direct demonstration that hydrogen peroxide- and peroxynitrite-induced mtDNA damage drives endothelial and smooth- muscle dysfunction. This work establishes the mtDNA-as-DAMP pathway central to the inflammaging mechanism in this proposal.

2. *NADPH-oxidase and oxidative-stress vasculopathy.* Demonstration that NADPH-oxidase-derived superoxide drives experimental diabetes-induced atherosclerosis, identifying the enzymatic source of the ROS that propagates the vicious cycle.

3. *PAI-1 in vascular aging, fibrosis, and hypertension.* NIA-funded multi-decade program establishing the role of PAI-1 in cardiac and vascular fibrosis, angiotensin II-induced hypertension, and vascular aging — mechanisms intertwined with cellular stress and mitochondrial function.

4. *Cardiovascular medicine and clinical translation.* Authorship and editorship of major cardiovascular-medicine references; multi-institutional clinical-translation leadership.

Research Support. Multi-decade NIH (NIA, NHLBI) funded portfolio in cardiovascular medicine, mitochondrial dysfunction, and PAI-1 vascular biology. Specific awards to be inserted at eRA-Commons biosketch finalization.

Scott W. Ballinger, Ph.D. — Collaborator (Mitochondrial genetics)

Personal statement. My career has been devoted to understanding how mitochondrial DNA variation, beyond its obvious bioenergetic role, shapes susceptibility to age-related disease and metabolic phenotype. The conplastic mouse program established by my laboratory provides the only definitive demonstration that mtDNA variation *alone* — with nuclear background controlled — is sufficient to alter metabolic and cardiovascular susceptibility. This is the foundational evidence underwriting the maternal-mtDNA- inheritance theme of the present proposal. As collaborator I will contribute mtDNA-genetics analytical leadership to Aim 1 (mtDNA haplogroup, heteroplasmy, and copy-number characterization) and to Aim 2 (mitochondrial-resilience-clock construction).

Positions and Honors. Professor of Pathology, University of Alabama at Birmingham (UAB); affiliated faculty across UAB Comprehensive Diabetes Center, Comprehensive Cancer Center, and Comprehensive Cardiovascular Center.

Contributions to Science.

1. *Conplastic mice and mtDNA-only metabolic phenotype.* Definitive demonstration that mitochondrial DNA variation alone, on a controlled nuclear background, is sufficient to alter metabolic susceptibility, bioenergetics, and cardiovascular response. Establishes the genetic-architecture rationale for treating mtDNA as an independent determinant of aging-related risk.

2. *Mitochondrial DNA damage in atherogenesis.* Long collaboration with M.S. Runge demonstrating that ROS-induced mtDNA damage correlates with and directly contributes to atherosclerosis progression in mouse models, with cigarette smoke and high-fat-diet exposures dramatically amplifying mtDNA damage.

3. *mtDNA copy-number and disease.* Methodological work on quantifying mtDNA copy number from peripheral blood and tissue, and the relationship of copy number to oxidative-stress phenotype, cardiovascular disease, and aging.

4. *Mitochondrial-nuclear cross-talk.* Studies of how mitochondrial signaling shapes nuclear gene expression and inflammatory tone — the mechanistic substrate of the EMHP small-panel design in Aim 2.

Research Support. Multi-decade NIH-funded portfolio in mitochondrial genetics, cardiovascular pathology, and metabolic disease. Specific awards to be inserted at eRA-Commons biosketch finalization.

Ryan E. Mills, Ph.D. — co-Investigator (Structural variation & numts)

Personal statement. I am a computational geneticist whose research has focused on the discovery and characterization of structural variation in human genomes and the methodological challenges of detecting it. My laboratory has been a leader in numtogenesis — the integration of mitochondrial DNA into the nuclear genome — a process that, unlike pure mtDNA inheritance, is bi-parentally transmitted and may modulate cellular regeneration in ways under-recognized by purely nuclear or purely mitochondrial analyses. As co-Investigator I will provide structural-variation and numts methodology for Aim 1 (numt characterization in the WGS cohort) and contribute computational leadership to the pangenomic- alignment portion of the LCI training stack.

Positions and Honors. Associate Professor of Computational Medicine & Bioinformatics and Human Genetics, University of Michigan Medical School. Faculty leadership in the UM Bioinformatics Graduate Program. Multi-institutional structural- variation consortium leadership.

Contributions to Science.

1. *Numtogenesis methodology.* Establishment of computational pipelines for detection, age-dating, and biological characterization of nuclear mitochondrial insertions (numts). Demonstration that numts continue to integrate into the human nuclear genome on evolutionary and developmental timescales, with implications for cellular regeneration and disease susceptibility that this proposal brings to bear on aging.

2. *Population-scale structural-variation discovery.* Co- authorship of foundational 1000 Genomes Project structural-variation papers and follow-on work establishing population catalogues of copy-number, indel, and mobile-element insertions. The methodological basis for identifying mtDNA-derived insertions in the proposed cohort.

3. *Mobile elements in human genomes.* Characterization of retrotransposon (LINE, SINE, SVA) activity and its consequences in somatic and germline contexts — the structural-variation tool-set applied to the somatic-mosaicism analyses underlying Aim 1.

4. *Computational frameworks for clinical genomics.* Translation of structural-variation pipelines into clinical-grade workflows usable in the MGI biobank context.

Research Support. NIH-funded portfolio across structural variation, mobile elements, and computational genomics. Specific awards to be inserted at eRA-Commons biosketch finalization.

References