# Living Longer, Living Better: An Aging-Genomics Platform

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May 12, 2026

## Platform Pitch — Foundation & Philanthropic Funders

### What we are asking you to fund

A 7-year program to operationalize *aging-genomics* — the natural extension of pharmacogenomics into healthspan — as a clinically-deployable platform: a predictive index that integrates genetics, epigenetics, real-time wearable physiology, and cardiorespiratory fitness into a single score; a blood-based diagnostic that tracks biological age over time; and a decision- support layer that translates each person's score into specific lifestyle and therapeutic recommendations.

### Theory of change

The longevity / healthspan field is not technology-limited. The mechanistic biology (mitochondrial-inflammaging axis; epigenetic regulation by lifestyle; maternal mtDNA inheritance and numts) has been mature for two decades. Long-read sequencing, FDA-cleared continuous wearables, and CRISPR Perturb-seq for causal-flow discovery have converged in the last five years. The decision-support infrastructure exists in working clinical deployment via pharmacogenomics. **What's missing is not invention; it is disciplined translation.**

The field is also not capital-limited at the marketing end. The contemporary longevity marketplace generates substantial revenue from under-validated influencer-driven products. What is severely capital- constrained is the rigorously-validated infrastructure — the multicenter cohort design, the FDA-pathway IVD development, the decision-support deployment — that converts mature mechanism into deployed clinical impact. Foundation philanthropy, with its tolerance for long-horizon validation and its alignment with public-health- benefit rather than direct-to-consumer wellness, fills the gap that neither NIH (mechanism-fragmented) nor venture capital (short-horizon, consumer-marketing-driven) covers.

## Why this team is uniquely positioned

**Mechanism.** Three decades of Ballinger-Runge collaboration established the mtDNA-atherogenesis foundation that anchors the mitochondrial-inflammaging axis at the heart of the proposal.

**Infrastructure.** Michigan Genomics Initiative (∼90{,}000 deeply-phenotyped recontactable patients), Multicenter Perioperative Outcomes Group (Kheterpal; 85+ hospitals; multicenter prospective trials at scale), federal exercise-stress-test cohorts (DoDSR, USAFSAM, Cooper, VETS), and the Ellison Institute / Oracle Health partnership giving access to the 150-million-patient EHR for external validation. No other academic institution combines these assets.

**Translation.** Athey's pharmacogenomics decision-support work demonstrates the ability to take methodology to clinical-deployment impact. The team's combined wet-lab + computational + multicenter- clinical-trial fluency is what aging-genomics demands at scale.

## What you would get

A measurable program with explicit phase deliverables:

- **Phase 1 (Years 1–3).** Discovery + biomarker prioritization + initial patents on diagnostic algorithms.
- **Phase 2 (Years 4–6).** EMHP IVD development; FDA / CE- Mark dossiers; LCI external validation against Oracle Health 150M EHR; pre-clinical drug-lead optimization.
- **Phase 3 (Years 7+).** EMHP IVD commercial launch via Oracle Health channels; personalized longevity programs licensed to longevity clinics and employer/payer wellness programs; therapeutic candidates advancing through Phase 1–3 trials.

The platform also produces public-health-relevant outputs along the way: open-source analytical pipelines (6-month-delayed release), publicly-available summary statistics with each peer-reviewed publication, and an explicit refusal to participate in direct-to- consumer wellness marketing of unvalidated products.

## What we are asking

A platform-level commitment that extends across the discovery → product → launch arc, not a single-aim short-horizon grant. The exact form (research grant, partnership, equity-aligned commitment, sponsored-research agreement) is appropriate to the funder's mechanism; we are open to structuring discussions accordingly. The through-line is the same: foundation capital fills the gap between mature mechanism and deployed clinical infrastructure that other funding sources do not cover.

## Where to read more

Dashboard: `single-molecule-sequencing.github.io/longevity-platform-grant`. Both source documents (authored by Marschall S. Runge), all 26 atom- generated funding-mechanism PDFs, the slide deck, the A0 conference poster, the cabinet-briefing format, and a status grid showing what's authored vs. what needs PI input vs. what's blocked on partnership- governance terms.

## 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 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.

## References