From Pharmacogenomics to Aging-Genomics: A Path Forward

Marschall S. Runge, M.D., Ph.D. — Proposal architect / originating author[1], Steven L. Kunkel, Ph.D. (proposed Principal Investigator)[2], Brian D. Athey, Ph.D. (proposed co-Principal Investigator)[3], Sachin Kheterpal, M.D., MBA[4], Scott W. Ballinger, Ph.D.[5], Ryan E. Mills, Ph.D.[6], and Greg Farnum[7]

[1]Michigan Medicine, University of Michigan, Ann Arbor, MI
[2]Department of Pathology, University of Michigan
[3]Department of Computational Medicine and Bioinformatics, University of Michigan
[4]Multicenter Perioperative Outcomes Group (MPOG), University of Michigan
[5]Ellison Institute of Technology / Oracle Health (partnership)

May 12, 2026

From Pharmacogenomics to Aging-Genomics: A Path Forward

The longevity question is no longer hypothetical

The longevity question has crossed from the realm of speculation into the realm of clinical and commercial action. As reported by the BBC on 3 September 2025, a hot-mic exchange between Chinese President Xi Jinping and Russian President Vladimir Putin captured them discussing the prospect of living to 150 years. That conversation, held by two of the most resourced individuals on Earth, is a marker for where the question now lives: not whether substantial healthspan extension is possible, but how to distinguish credible paths from incredible ones.

The challenge is acute. The contemporary longevity marketplace is saturated with influencer protocols, supplement stacks, and biological reductionism dressed up as science. Claims about senolytics, NAD+ precursors, and "epigenetic age reversal'' circulate in popular media with confidence levels that the underlying clinical evidence does not support. Three decades of aging research, summarized in the *hallmarks of aging* framework˜[López-Otín et al.(2013)López-Otín, Blasco, Partridge, Serrano, make clear that aging is not a single problem with a single fix; the silver-bullet rhetoric of the longevity-influencer marketplace is a categorical mismatch with the underlying biology.

What is needed is not new mechanisms — the mitochondrial-inflammaging axis˜[Franceschi and Campisi(2014), Franceschi et al.(2018)Franceschi, Garagnani, Parini, Giuliani, and Santoro, Sun et al.(2020)Sun, Youle, and Fink the role of mtDNA damage in age-related disease˜[Ballinger et al.(2002)Ballinger, Patterson, Knight-Lozano, Burov Ballinger et al.(2000)Ballinger, Patterson, Yan, Doan, Burow, Young, et al.], and the predictive power of cardiorespiratory fitness˜[Blair et al.(1989)Blair, Kohl, Paffenbarger, Clark, Cooper, and Gibbons, Kokkinos et al.(2010)Kokkinos, Myers, Kokkinos, Pittaras, Narayan, Manolis, et al.] have been mature for two decades. What is needed is a clinical-translation framework rigorous enough to separate signal from hype and operational enough to deliver healthspan extension at population scale. We argue here that such a framework exists, and that it is the natural extension of an infrastructure already established for prescribing decisions: pharmacogenomics.

Aging-genomics as a paradigm extension

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, regulatory pathways for IVD diagnostics — is mature and at scale. Where pharmacogenomics asks *which drug is right for which person, given their genome?*, aging-genomics asks the analogous question one level up:

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

This reframing matters. It transforms longevity from a domain characterized by single-molecule miracle claims into a domain structured like the precision-medicine workflows that have already gained clinical adoption. It identifies what new measurement infrastructure is required (continuous physiology; epigenome and mitochondrial state in addition to genome) and what existing infrastructure can be reused (decision support, IVD regulatory pathways, EHR integration).

What is technically tractable now

Three specific technical capabilities have come together within the last five years that make aging-genomics tractable in a way that it was not at the turn of the millennium.

First, long-read sequencing of nuclear and mitochondrial genomes at clinical scale. Whole-genome sequencing prices have fallen to $\sim$ \$500$\$ persample for clinical - grade short - read 30\times$ output, and long-read platforms are converging on the same cost trajectory. Critically, mtDNA copy number, heteroplasmy, and haplogroup — the genetic-architecture variables that follow maternal transmission and that Ballinger's conplastic-mouse work established as sufficient to alter metabolic phenotype on a controlled nuclear background — can now be quantified routinely from clinical sequence data. Mills's nuclear-mitochondrial-insertion (numt) methodology adds a bi-parental nuclear layer to the inheritance picture. Pangenomic alignment methods reduce reference-bias artifacts in non-European- ancestry genomes, addressing a long-standing limitation of population- scale genetics.

Second, continuous physiology from FDA-cleared wearables. The BioIntelliSense BioButton and devices like it provide continuous heart-rate variability, respiratory rate, skin temperature, activity, and sleep architecture. Until recently, "lifestyle'' variables in clinical and research settings were captured as static questionnaire items at annual intervals. Continuous wearables transform these into high-resolution time series, enabling paired-blood-draw study designs that quantify acute transcriptional and epigenetic responses to real-world physiologic states (sleep deprivation, exercise bouts, acute illness, stress weeks, restorative recovery). Individuals whose inflammatory and mitochondrial gene responses are exaggerated or blunted for a given stressor become tractable phenotypes — high-value resilience-vs-vulnerability stratification that static lifestyle variables cannot deliver.

Third, CRISPR Perturb-seq for causal-flow discovery. A recurring weakness of biomarker-discovery programs has been the markers-versus-targets ambiguity: an associated CpG site or expression signature may be a downstream reporter of biological aging rather than an upstream modulator that interventions could profitably target. Perturb-seq, applied in patient-derived induced pluripotent stem cells and primary immune / vascular cells, systematically perturbs candidate genes and profiles single-cell transcriptomic responses, mapping causal flow in inflammatory and mitochondrial gene networks. This distinguishes biomarkers from actionable therapeutic targets — the central question that limits most biomarker-only programs.

What remains hard

These capabilities do not solve the field's central operational challenges. Three remain.

Validation at population scale. The MGI biobank (∼90{,}000 University of Michigan patients with deep phenotyping and recontact- friendly consent) and MPOG (Multicenter Perioperative Outcomes Group; 85+ hospitals; millions of records) provide large but bounded training cohorts. Validation at the scale required for clinical deployment — demographic diversity across ancestry, disease state, and environmental exposure — demands access to real-world EHR data at a scale unavailable in any single academic environment. Partnerships with major EHR vendors (the Oracle Health 150-million- patient ecosystem accessible through the Ellison Institute of Technology partnership; comparable Epic and Cerner footprints) make this tractable, but only via formal partnership terms that extend beyond standard IRB / DUA frameworks.

Regulatory pathway for combined diagnostics. Existing IVD regulatory pathways (FDA 510(k), de novo, CE Mark) accommodate single- analyte and multi-analyte molecular diagnostics well. Combined diagnostics — a clinical risk score that integrates genotype, epigenotype, methylation panel, circulating proteins, continuous physiologic features, and prediction outputs from machine-learning models hosted on regulated cloud infrastructure — are a newer category. Software-as-a-medical-device guidance is converging, but prospective collaboration with regulators during development will be required to avoid the late-stage surprises that have derailed comparable programs.

Distinguishing rigorous claims from hype. The same evidence- quality challenge that motivates the program threatens to engulf it. Aging-clock methodology is rife with overfitting, batch effects, and inadequate external validation. Premature commercialization claims — "test your biological age and reverse it' ' — have already attracted regulatory attention. The path forward requires deliberate pre-registration of analytic plans, transparent reporting of validation performance across demographically diverse cohorts, and explicit refusal to participate in the marketing-of-uncertainty that characterizes the consumer end of the market.

A platform program for the next decade

A useful program in this space, we argue, has four structural features:

- A **mechanistic spine** grounded in literature with multi-decade depth: in our framing, the mitochondrial-inflammaging axis with maternal mtDNA inheritance and numts as the genetic-architecture story.
- Three **operational aims**, organized as a closed loop — measure (Longevity & Cardiovascular Health Index integrating WGS, cardiorespiratory fitness, BioButton, and clinical risk), model (Epigenetic & Mitochondrial Health Panel with Phase 1 small- panel discovery and Phase 2 omics-plus-Perturb-seq expansion), intervene (therapeutic targets, drug discovery, and pharmacogenomics-analogous personalized longevity decision support).
- A **cohort hierarchy** that spans recontactable academic biobanks, multicenter clinical-trial infrastructure (MPOG-class), decades-long federal exercise-stress-test biorepositories, and EHR-vendor partnerships at population scale.
- A **commercialization roadmap** structured around regulated IVD diagnostics, decision-support licensing, pre-clinical therapeutic discovery, and ultimately clinical-trial-grade therapeutics — with the deliverables, IP filings, and regulatory milestones for each phase made explicit at proposal time.

A multi-PI program at the University of Michigan instantiating this template has been articulated in detail elsewhere.[1] The point of articulating it here is not to advocate for that specific program but to argue for the more general claim: that aging-genomics is now a tractable extension of clinical infrastructure rather than a speculative aspiration, and that the next decade's worth of healthspan-extension work belongs squarely within the same evidence- quality framework that pharmacogenomics established for prescribing decisions.

Why the framing matters

It is tempting in a paradigm-extension argument to be modest: to claim only that aging-genomics is an analogy to pharmacogenomics. We claim more. Pharmacogenomics succeeded clinically because three things aligned: a tractable mechanistic biology (cytochrome P450 metabolism; HLA-mediated drug response; receptor-tyrosine-kinase oncology), clinical-decision-support infrastructure that turned genotype into prescribing recommendations, and regulatory frameworks (FDA companion-diagnostic and CPIC guideline) that institutionalized the practice. Aging-genomics is now at the same alignment point, with the same three pieces in place at clinical scale: the mechanism (mito- inflammaging plus epigenetic regulation by lifestyle), the decision- support infrastructure (extending the pharmacogenomics layer that already exists in major EHR systems), and the regulatory pathway (software-as-a-medical-device, combined diagnostics, IVD).

What remains is execution. The field's challenge is not invention but discipline — the discipline to validate at population scale, to reject hype with the same rigor we reject p-hacked oncology biomarkers, and to build the operational infrastructure (cohorts, partnerships, regulatory engagement) that makes aging-genomics deployable rather than aspirational. The mechanistic biology has been waiting for two decades. The technical infrastructure has converged in the last five years. The decision-support paradigm exists in working clinical deployment. What remains is to do the work.

Acknowledgements

This Perspective draws on conversations and source documents authored by Marschall S. Runge (EVP for Medical Affairs / CEO of Michigan Medicine / Dean of UMMS), and on three decades of foundational mtDNA- atherogenesis research conducted with Scott W. Ballinger that established the mechanistic spine of the aging-genomics framing proposed here.

References

[López-Otín et al.(2013)López-Otín, Blasco, Partridge, Serrano, and Kroemer] Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, and Guido Kroemer. The hallmarks of aging. *Cell*, 153(6):1194–1217, 2013. doi: 10.1016/j.cell.2013.05.039.

[Franceschi and Campisi(2014)] Claudio Franceschi and Judith Campisi. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 69(Suppl 1):S4–S9, 2014. doi: 10.1093/gerona/glu057.

[1] See https://single-molecule-sequencing.github.io/longevity-platform-grant/ for the program-level dashboard, two source documents, twenty-six funding-mechanism PDFs, eight figures, and four reference tables. The proposal is led architecturally by Marschall S. Runge with multi-PI delegation to Steven L. Kunkel (PI), Brian D. Athey (co-PI), Sachin Kheterpal, Scott W. Ballinger, Ryan E. Mills, and Greg Farnum.

[Franceschi et al.(2018)Franceschi, Garagnani, Parini, Giuliani, and Santoro] Claudio Franceschi, Paolo Garagnani, Paola Parini, Cristina Giuliani, and Aurelia Santoro. Inflammaging: a new immune-metabolic viewpoint for an old paradigm. *Nature Reviews Endocrinology*, 14(10):576–590, 2018. doi: 10.1038/s41574-018-0059-4.

[Sun et al.(2020)Sun, Youle, and Finkel] Nuo Sun, Richard J. Youle, and Toren Finkel. Mitochondrial dysfunction and inflammaging: From mechanism to disease. *Journal of Clinical Investigation*, 130(9):4500–4513, 2020. doi: 10.1172/JCI136183.

[Ballinger et al.(2002)Ballinger, Patterson, Knight-Lozano, Burow, Conklin, Hu, et al.] Scott W. Ballinger, Cam Patterson, Carlos A. Knight-Lozano, David L. Burow, Curtis A. Conklin, Zhe Hu, et al. Mitochondrial integrity and function in atherogenesis. *Circulation*, 106(5):544–549, 2002. doi: 10.1161/01.CIR.0000023921.93743.89.

[Ballinger et al.(2000)Ballinger, Patterson, Yan, Doan, Burow, Young, et al.] Scott W. Ballinger, Cam Patterson, Chu-Nu Yan, Robert Doan, David L. Burow, Christopher G. Young, et al. Hydrogen peroxide- and peroxynitrite-induced mitochondrial DNA damage and dysfunction in vascular endothelial and smooth muscle cells. *Circulation Research*, 86(9):960–966, 2000. doi: 10.1161/01.RES.86.9.960.

[Blair et al.(1989)Blair, Kohl, Paffenbarger, Clark, Cooper, and Gibbons] Steven N. Blair, Harold W. Kohl, Ralph S. Paffenbarger, Debra G. Clark, Kenneth H. Cooper, and Larry W. Gibbons. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*, 262(17):2395–2401, 1989. doi: 10.1001/jama.1989.03430170057028.

[Kokkinos et al.(2010)Kokkinos, Myers, Kokkinos, Pittaras, Narayan, Manolis, et al.] Peter Kokkinos, Jonathan Myers, John P. Kokkinos, Andreas Pittaras, Puneet Narayan, Athanasios Manolis, et al. Exercise capacity and mortality in older men: A 20-year follow-up study. *Circulation*, 122(8):790–797, 2010. doi: 10.1161/CIRCULATIONAHA.110.938852.