Living Longer, Living Better: An Aging-Genomics Platform

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May 12, 2026

Project Summary / Abstract

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

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

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

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

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

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 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.

2 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.

3 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.

4 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