

Topic 3: What biomarkers and stress tests predict resilience and what clues do they give us about resilience biology?

AGS/NIA R13 Bench-to-Bedside Conference Series

Aging-Related Molecular Changes, Related Biomarkers, and their Utility in Resilience Detection

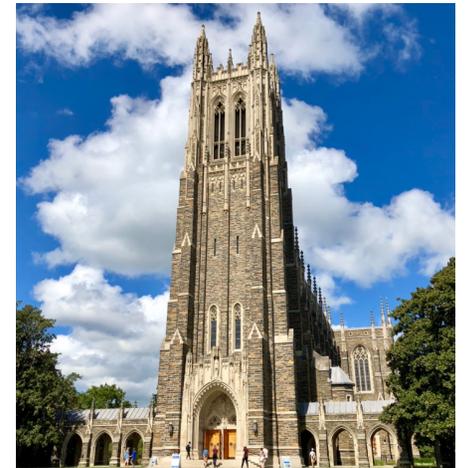


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Disclosures: None related to this talk

WHY IDENTIFY MOLECULAR FACTORS OF RESILIENCE CAPACITY?

“Molecular origins of resilience are complicated and not yet well understood”

(Ryan 2022, PMID:35599764)

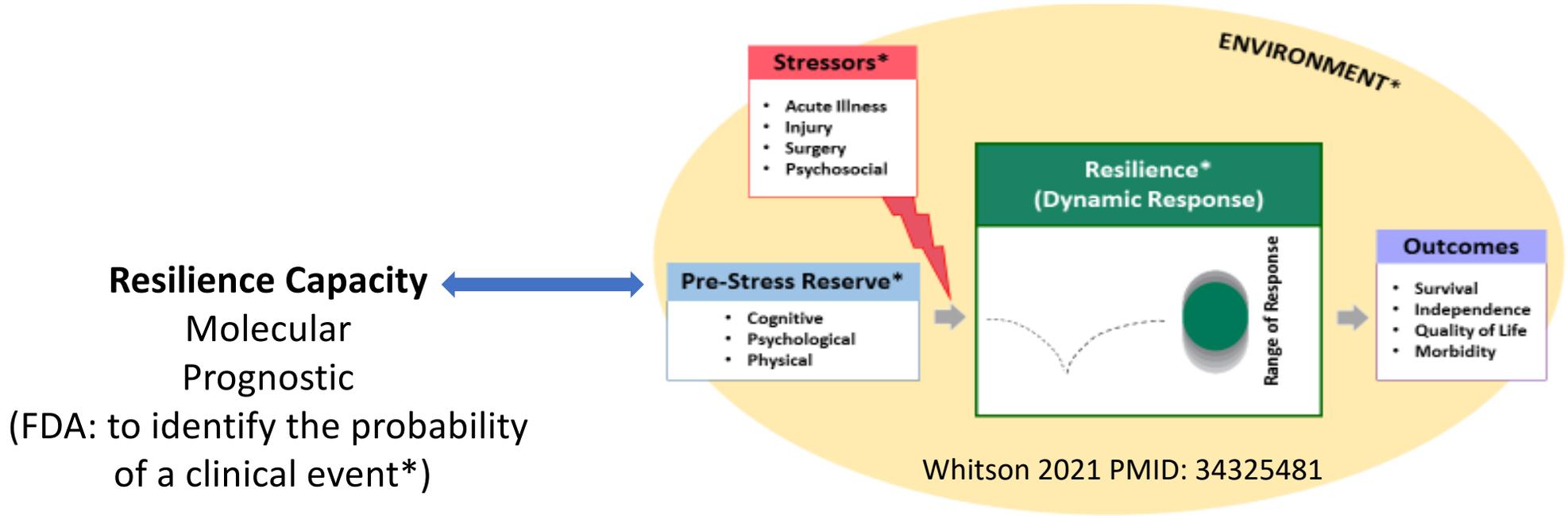


Graphic adapted from: <https://fastercapital.com/content/Stress-Testing-and-RAROC--Strengthening-Resilience-in-Turbulent-Times.html>

RESILIENCE CAPACITY

The capacity of a physiologic system to recover to, or improve upon, a baseline level of health and function after experiencing a significant clinical stressor (Walston 2023, PMID:37386913)

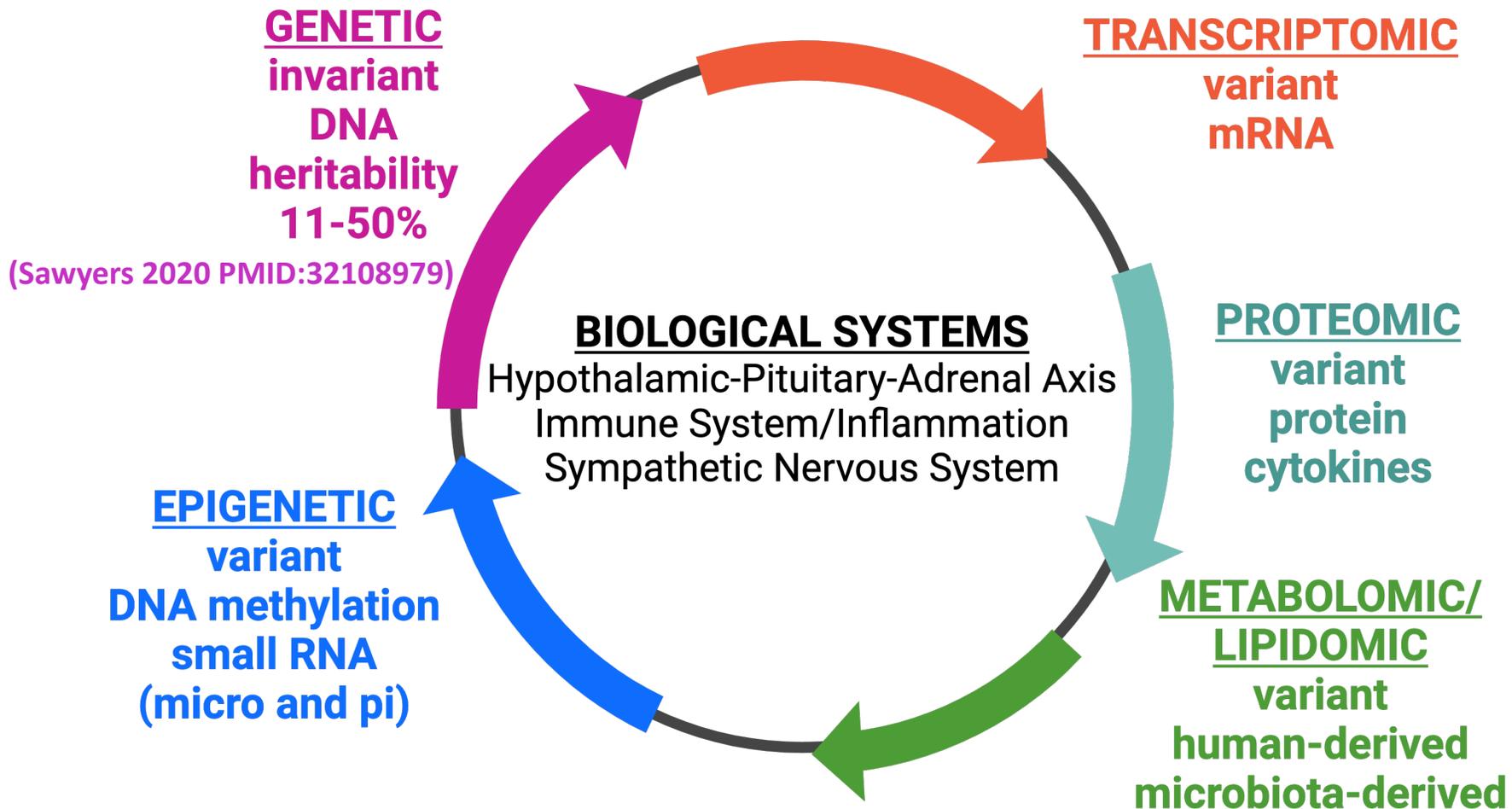
Conceptual model of reserve and resilience.



*Opportunities to intervene

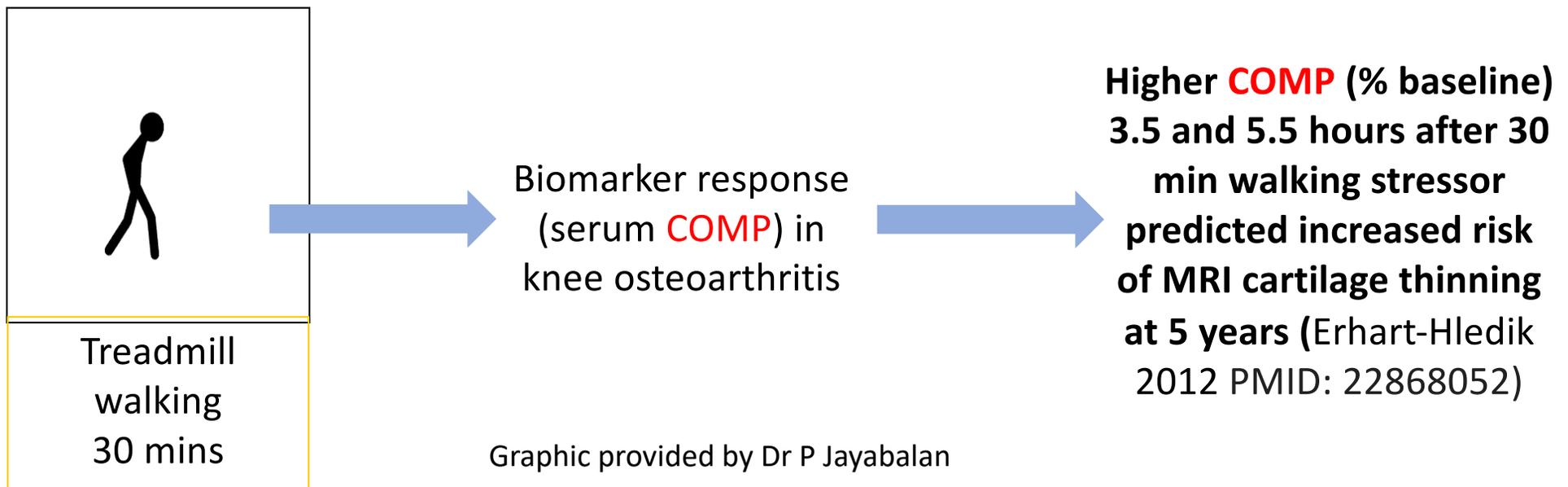
*Food and Drug Administration-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. In. Silver Spring, MD: FDA; 2016.

MOLECULAR BIOMARKERS OF 'RESILIENCE CAPACITY'



BIOMARKER “STRESS TESTS”

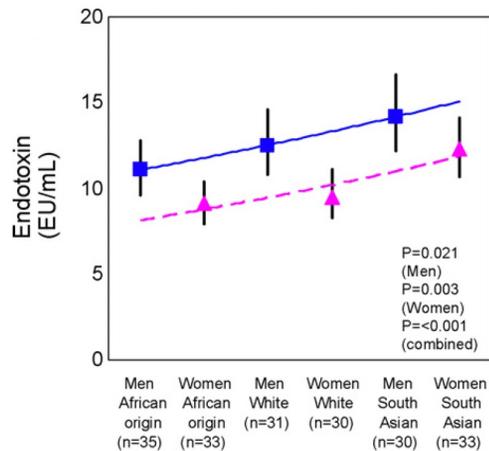
- Stimulus response framework analogous to a cardiac stress test
- Measured before, during and/or after a controlled stressor
- Can unmask abnormalities and endotypes: mechanistic pathways
- Examples of molecular stress tests: ACTH stimulation test; 24hr salivary cortisol profile; glucose tolerance tests; **Cartilage oligomeric matrix protein (serum COMP) mechanosensitivity**



Graphic provided by Dr P Jayabalan

BIOMARKER “STRESS TESTS” *ex vivo* response to lipopolysaccharide

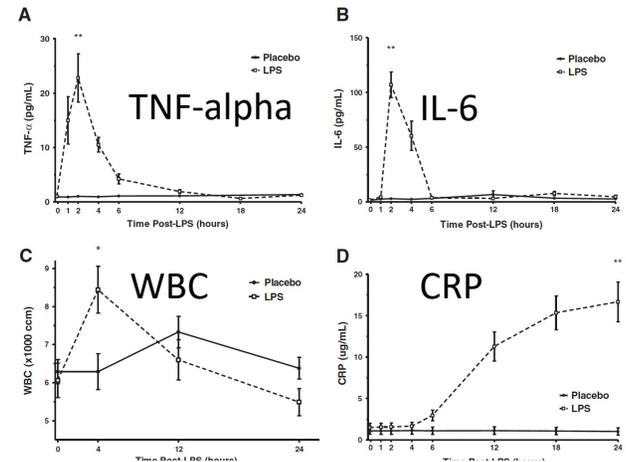
LPS/endotoxin is not just a “model system” it is a physiological stressor



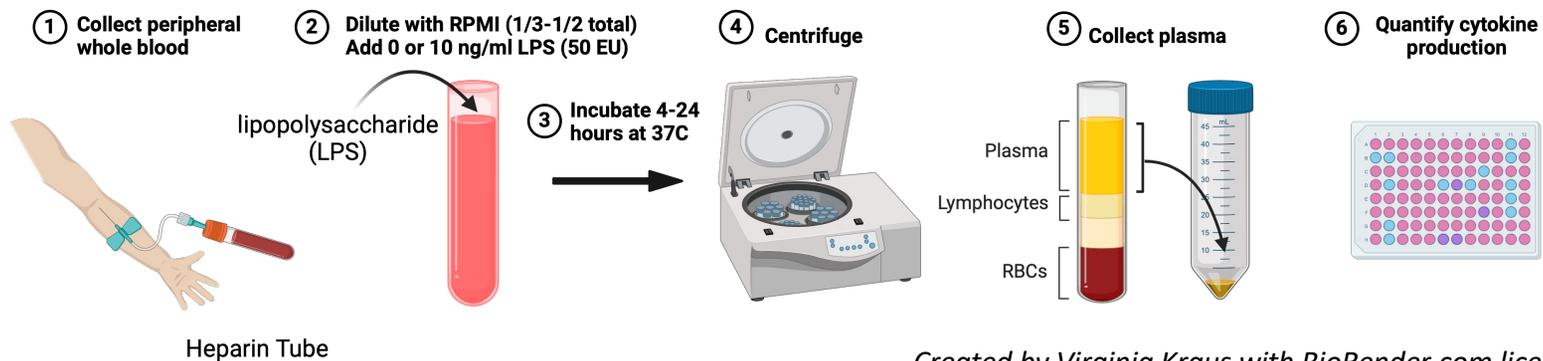
In vivo

Natural plasma levels
(Miller 2009 PMID:18672240)

Pro-inflammatory effect
of 0.6 ng/kg LPS IV
(Mehta 2012 PMID:22709547)



LPS used as an *ex vivo* measure of immune response to a metabolic stressor

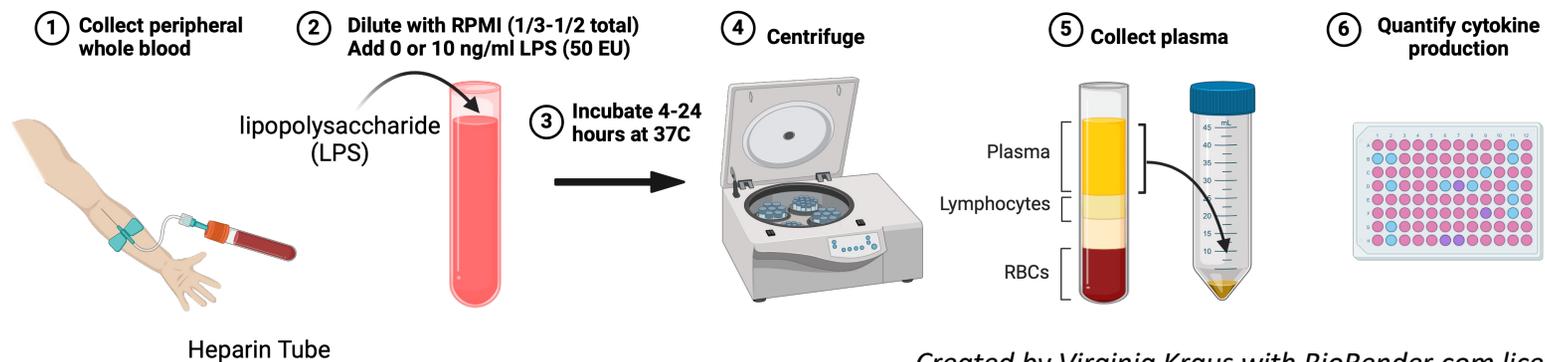


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BIOMARKER “STRESS TESTS” Significance of LPS in resilience

- Physiological stressor in sepsis and dysregulated metabolism/obesity/fatty liver/low level of small **HDL** particles (innate countermeasure of LPS) (Kraus 2022 PMID:36182774)
- Cytokine production (IL-1 β , IL-1Ra, IL-10, IL-6, TNF- α) by LPS stimulation is under tight **genetic** control (>50% heritability) (De Craen, 2005 PMID:15674372)
- Low *ex vivo* LPS responsiveness (low IL-1 β and IL-6) associated with the absence of **Osteoarthritis** (OA) in 90 year olds (Goekoop 2010 PMID:20417290)
- High responsiveness (high IL-1 β and IL-1Ra, low IL-10) is associated with increased **OA risk** (Riyazi 2005 PMID:15880595)
- Exaggerated responses of immune system cells to LPS in **frail** compared to non-frail older adults (Walston 2023 PMID:37386913)
- Under chronic stress conditions, resistance develops to **cortisol**, another innate countermeasure of LPS (van Looveren 2020 PMID:32383538)

LPS *ex vivo* test system preserves physiological cellular interactions



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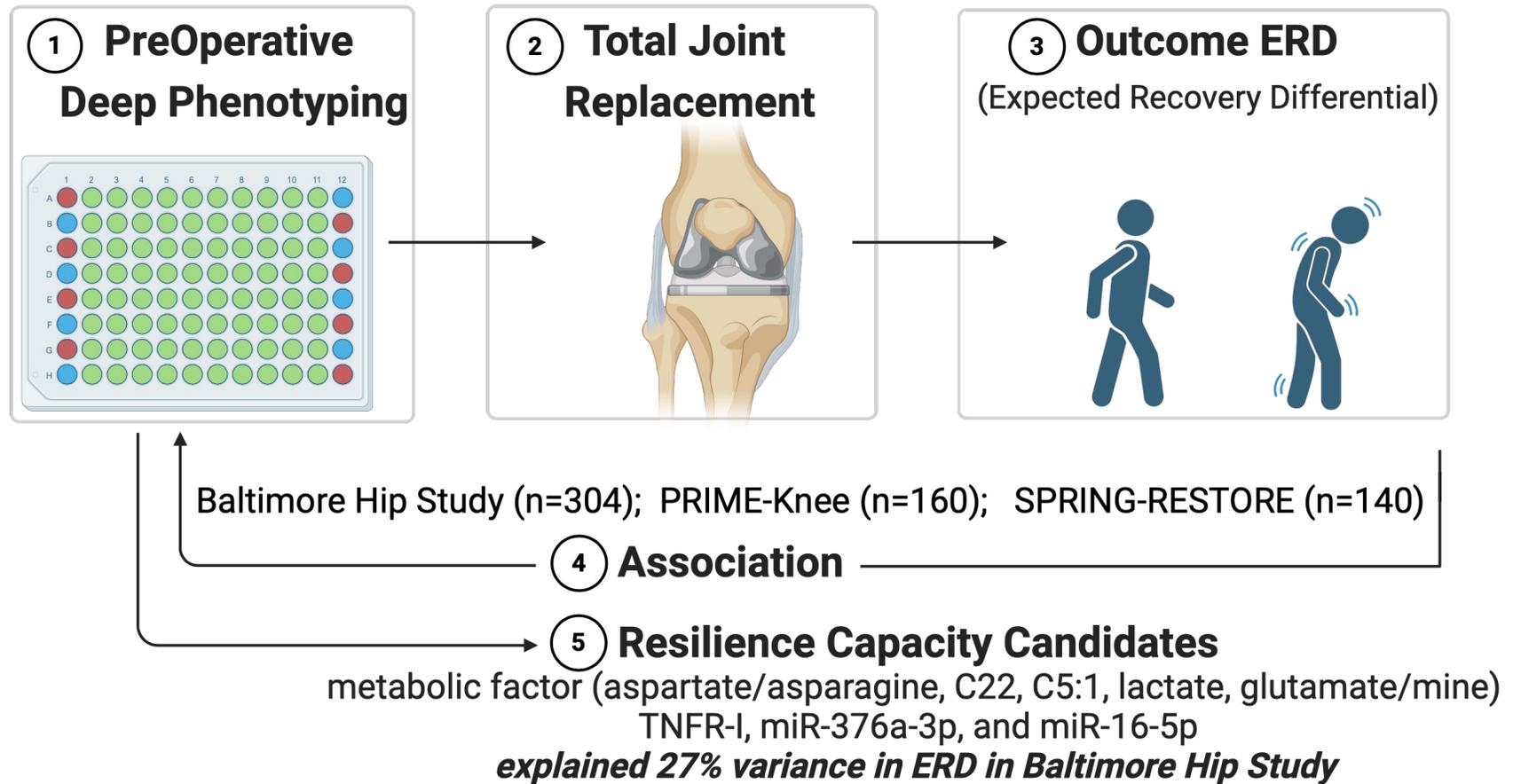
Examples of “Less is More” Resilience Biomarkers

- JAK inhibitors (immunomodulators) consistently reduce covid-19 mortality (Sweeney 2024 PMID:38182048)
- NOD/RIPK2 inflammatory signalling and OA susceptibility (Juryneć 2022 PMID:35732460)
- FKBP5 (stress response gene modulates intracellular glucocorticoid signaling) higher methylation (lower expression) in Holocaust and World Trade Center survivors (Ryan and Ryznar 2022 PMID:35599764)



Photo by [Etienne Girardet](#) on [Unsplash](#)

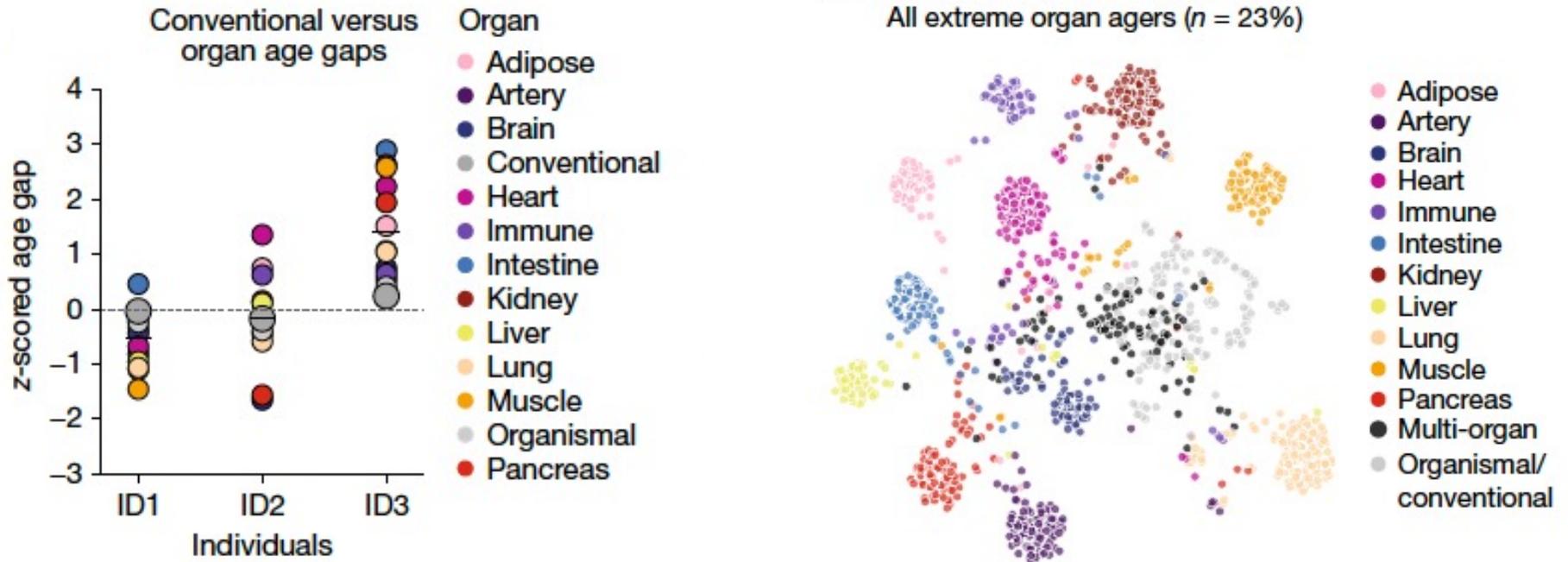
Study Paradigm for Resilience Capacity Analyses



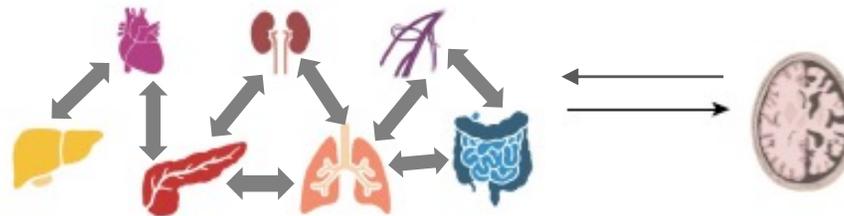
Parker 2020 PMID:32386291; Whitson 2021 PMID:34325481; Walston 2023 PMID:37386913

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Tissues Age at Different Rates (Oh 2023 PMID: 38057571)



Choice of appropriate testing approach must consider risks to be assessed, the related tissue and biological systems under study

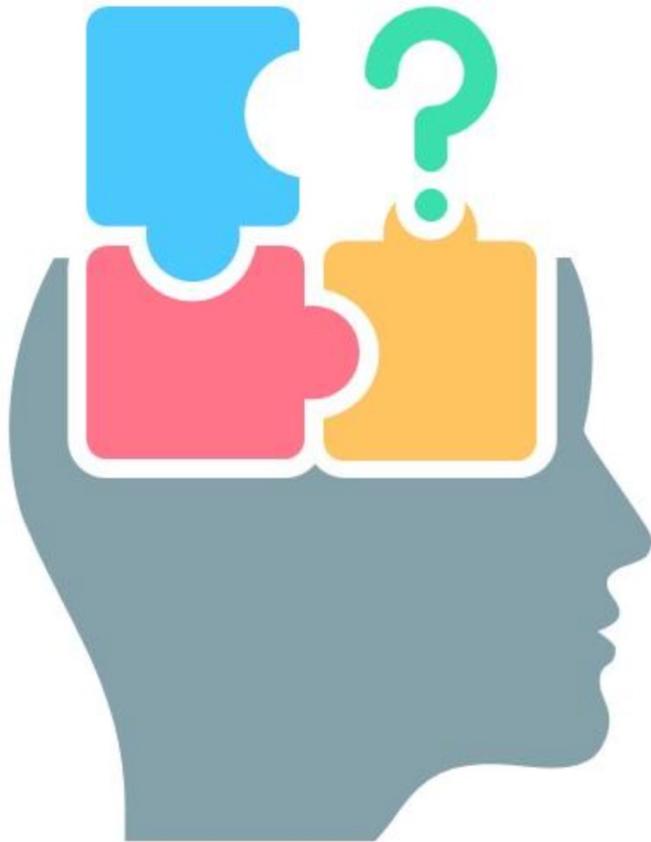


What clues do molecular biomarkers give us about resilience biology?



- Resilience is a dynamic process
- Many factors underly resilience capacity
- Resilience is genetically differentiable from psychopathology
- In some cases dampened and in some cases heightened responses to a stressor are protective
- Organ-specific plasma proteins capture disease-relevant heterogeneity of aging within and across individuals that can be applied to understanding organ and organismal resilience
- New insights into aging can come from understanding molecular components of resilience capacity

Knowledge Gaps



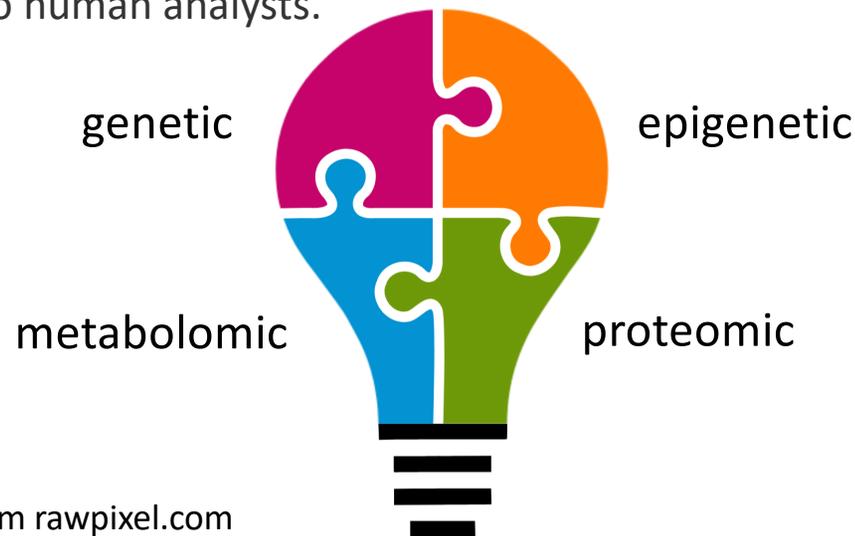
- Does “ONE SIZE FIT ALL” or do prognostic molecular biomarkers differ by stressor, body system stressed and/or resilience outcome used?
- Can resilience capacity be strengthened?
- What treatments mitigate risk and enhance resilience capacity?
- What molecular markers mediate resilience?
- What are the limitations of the models used to identify and validate molecular biomarkers of resilience?

Adapted by Virginia Kraus from SlideTeam

Research Opportunities

What are the molecular determinants of resilience?

- Establish cohorts with baseline and longitudinal biospecimens and resilience outcomes in which to discover & validate high level candidate prognostic resilience capacity biomarkers.
- Examine biomarkers in many biological systems and their roles in resilience.
- Test new resilience interventions taking into account molecular endotypes of resilience capacity.
- Examine molecular determinants of resilience capacity to different stressors.
- Adopt machine learning and artificial intelligence techniques to identify patterns and relationships that may not be apparent to human analysts.



Graphic: adapted by Virginia Kraus from rawpixel.com