I Don’t Bounce Back Like I Used To:

Age-related Changes in Resilience

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Disclosures

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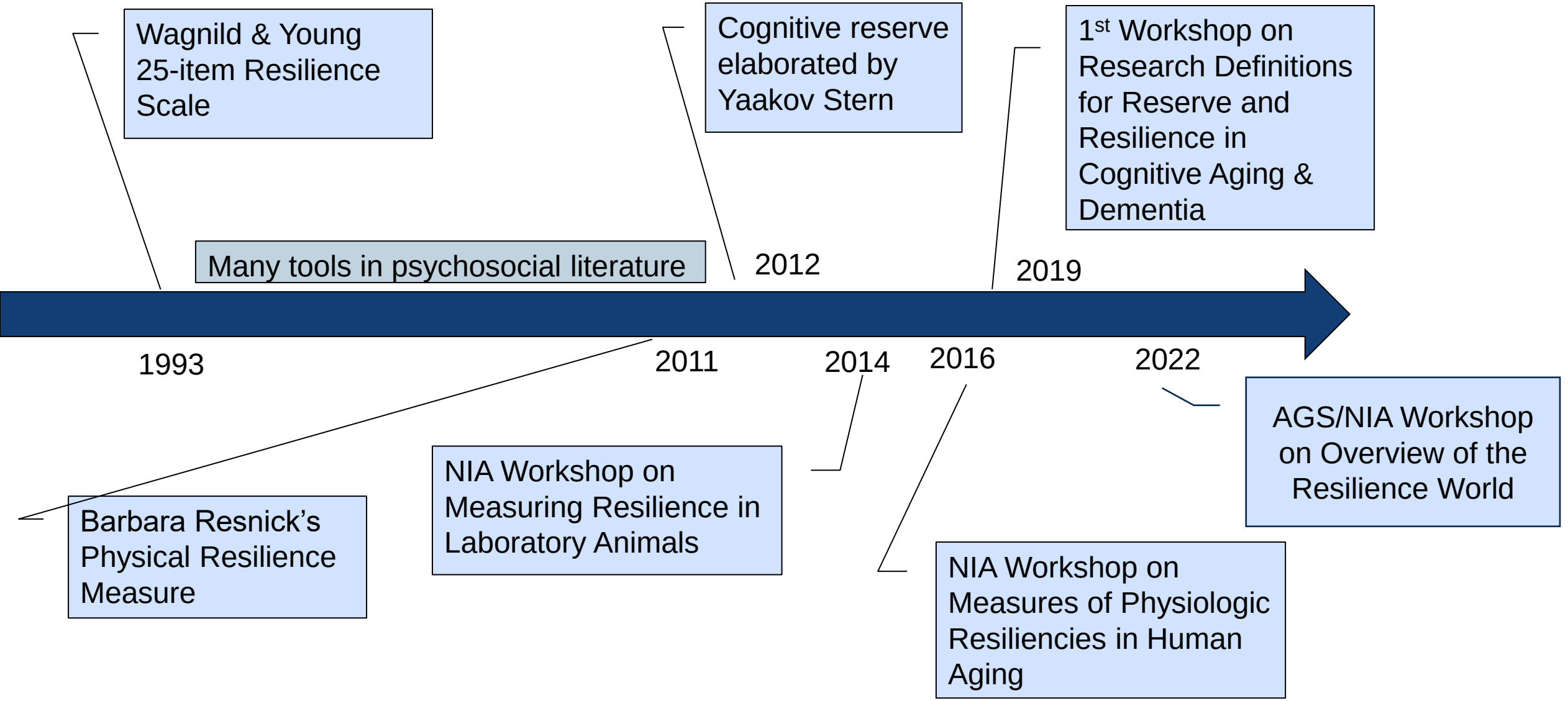
Objectives

1) The importance of **resilience to stressors** in overall human health
2) The role of aging in resilience
3) How do we measure “resilience” after a stressor?
4) Can we get better at predicting and promoting resilience to health stressors?

“I don’t bounce back like I used to”

DukeHealth

A Brief (and surely incomplete) History of Resilience in Aging Research

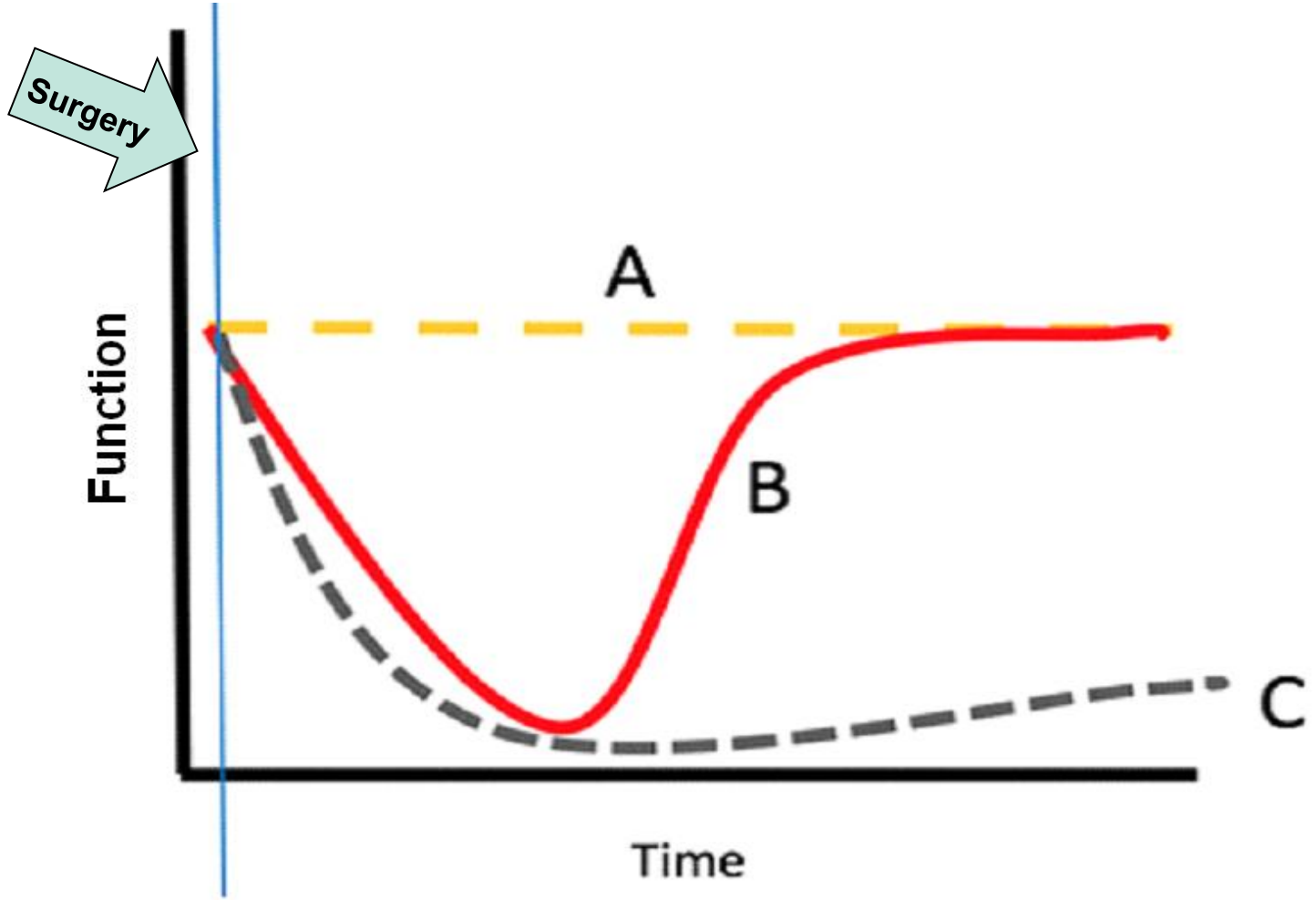


Consider two patients being evaluated as candidates for total knee replacement.

76 year old woman who is a caregiver for her husband. She has obesity, depression, sedentary life style, and history of coronary artery disease treated with a stent in 2015. She had gall bladder surgery and a hysterectomy, each more than 10 years ago.

75 year old man with well-controlled hypertension and glaucoma who plays golf and tennis weekly and has a supportive wife and two daughters nearby. He has never had a surgery.

Much of Successful Aging Depends on “Bouncing Back” After Stressors



Every person is a complex dynamic system

Interconnected Systems and Sub-systems constantly moving, transitioning, and adapting to changing environments and new stressors

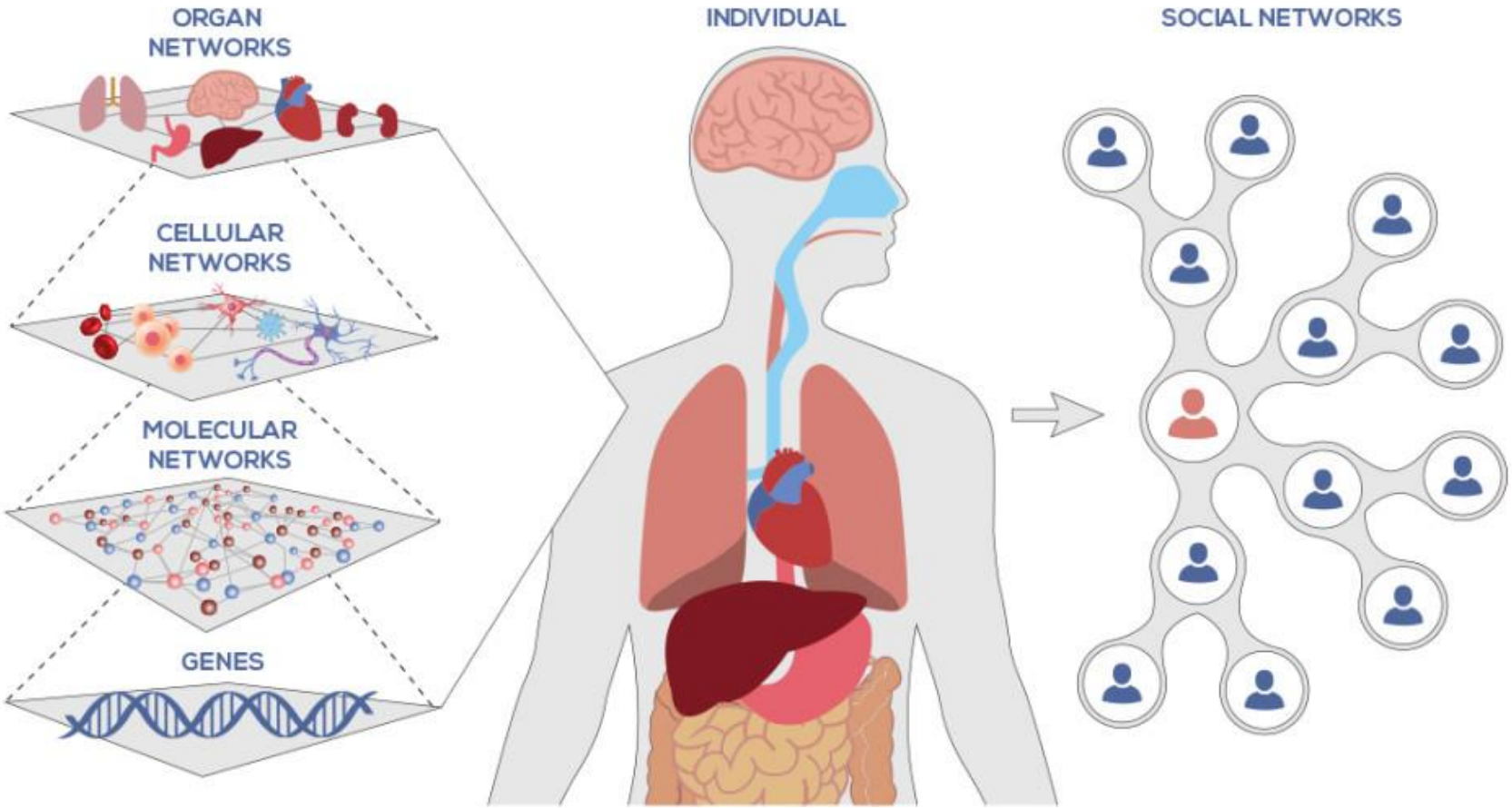
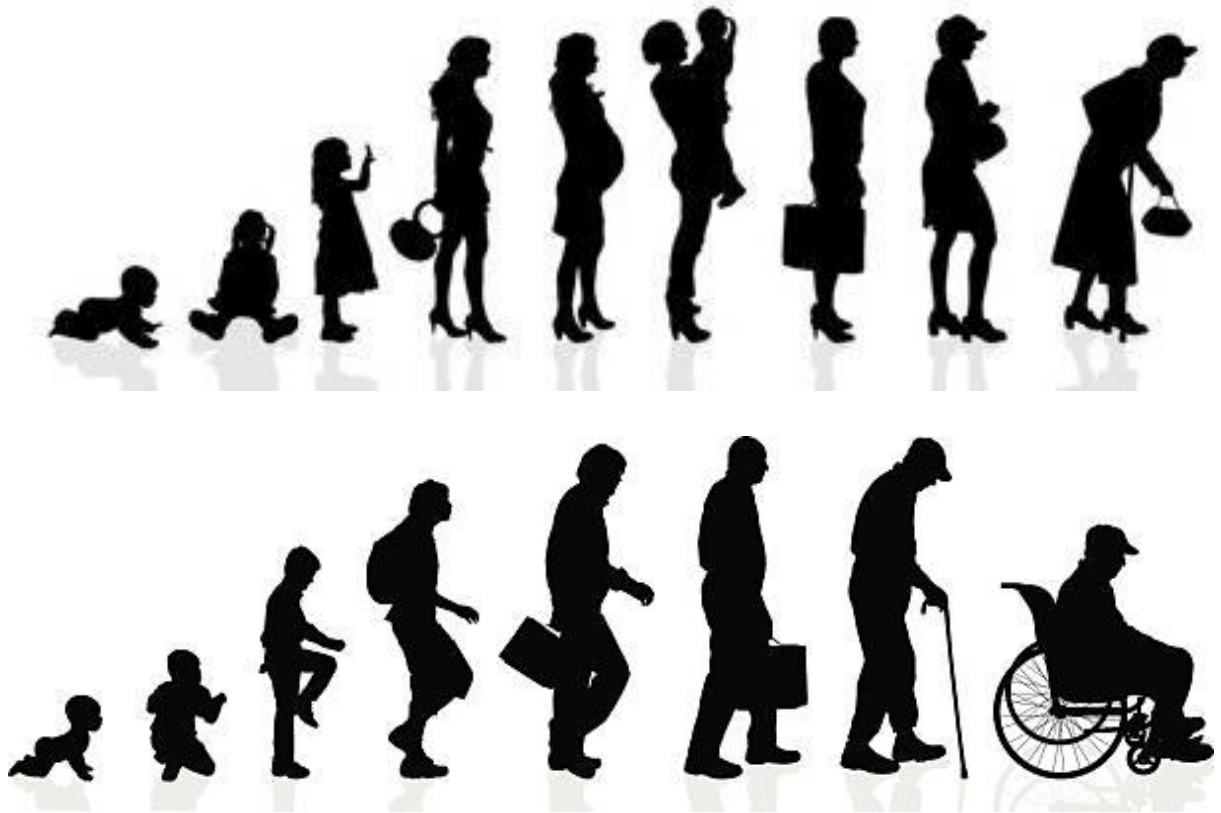


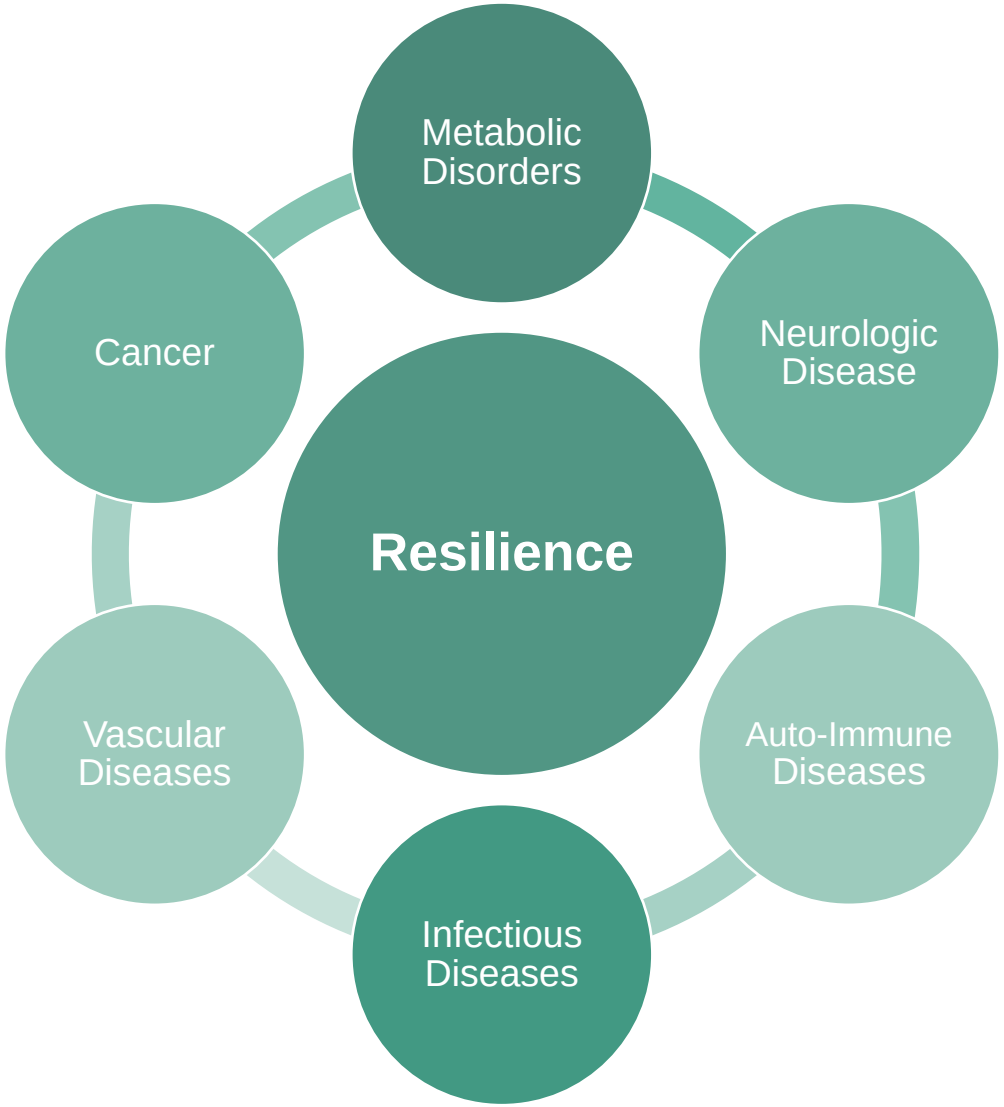
Image by: Institute for Systems Biology, Seattle, WA

With age, our ability to respond briskly and adaptively to perturbation declines.



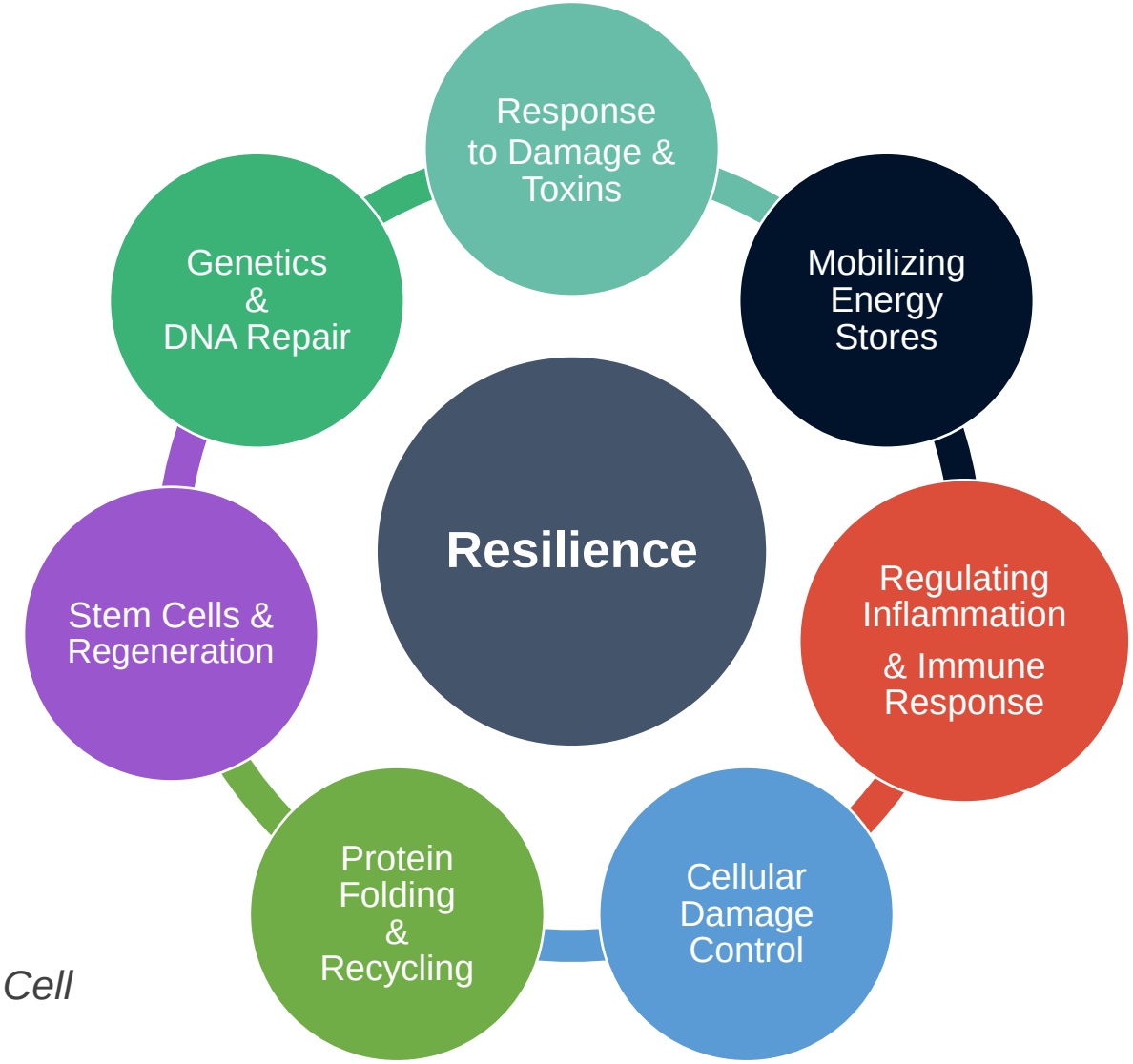
A vicious cycle

Diseases can diminish biologic resilience…



and lower resilience makes us vulnerable to the next disease…

Geroscience: Biological resilience has a molecular basis



…and all of these molecular pathways exhibit decline with age (over time), even in the absence of serious disease.

Adapted from Kennedy et al. *Cell* 159; 2014

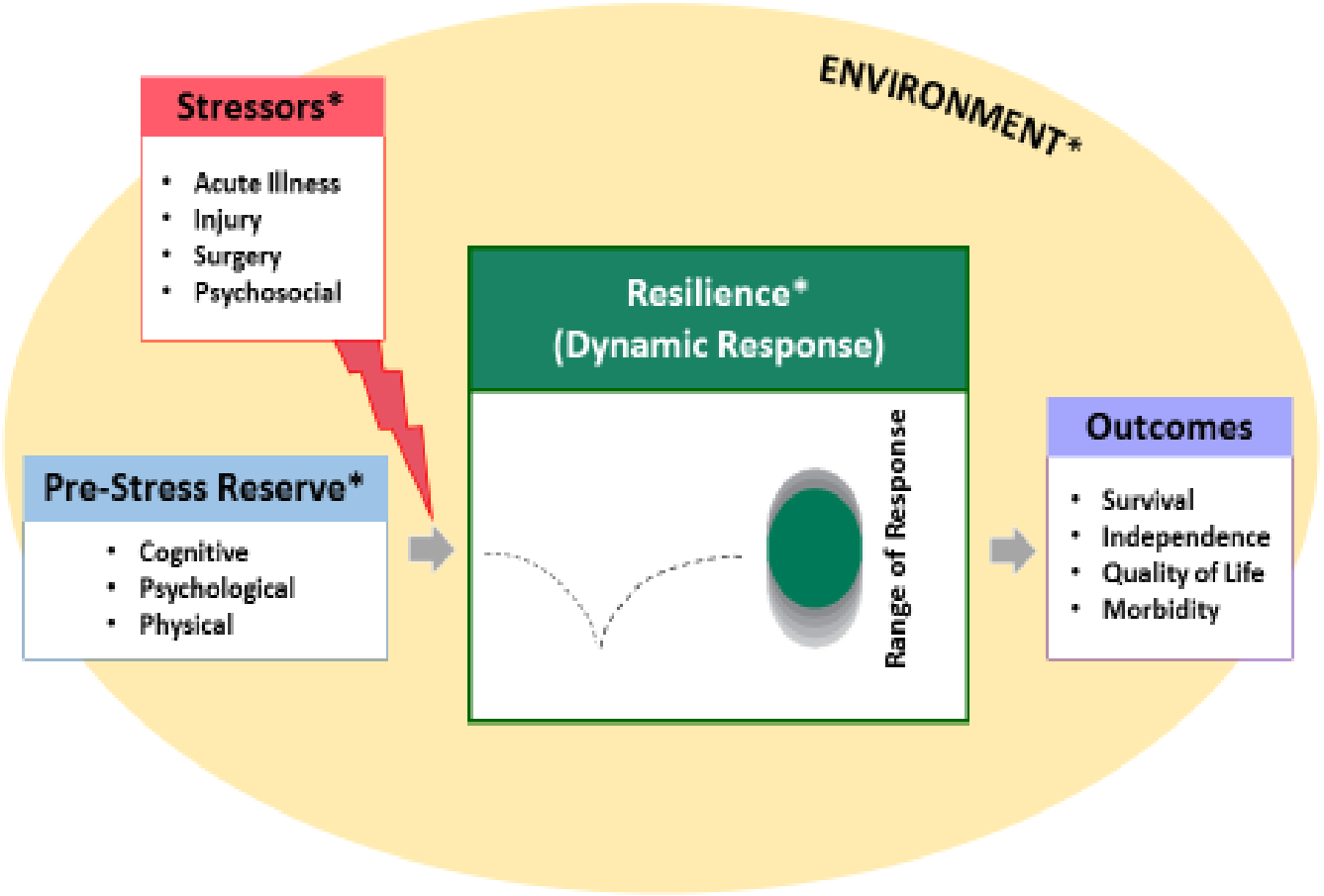
But the rate of decline is not the same for everyone. Why?

And sometimes our patients really surprise us…

Can we get better at predicting and promoting physical resilience to health stressors?

Step 1: We have to decide what to measure

Duke Pepper Center Conceptual Model of Physical Resilience

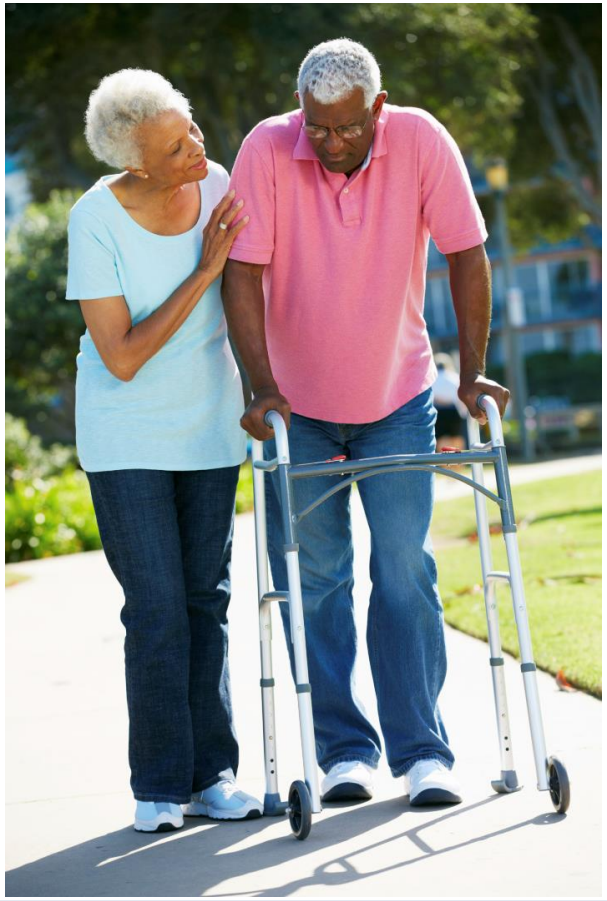


*Opportunities to intervene

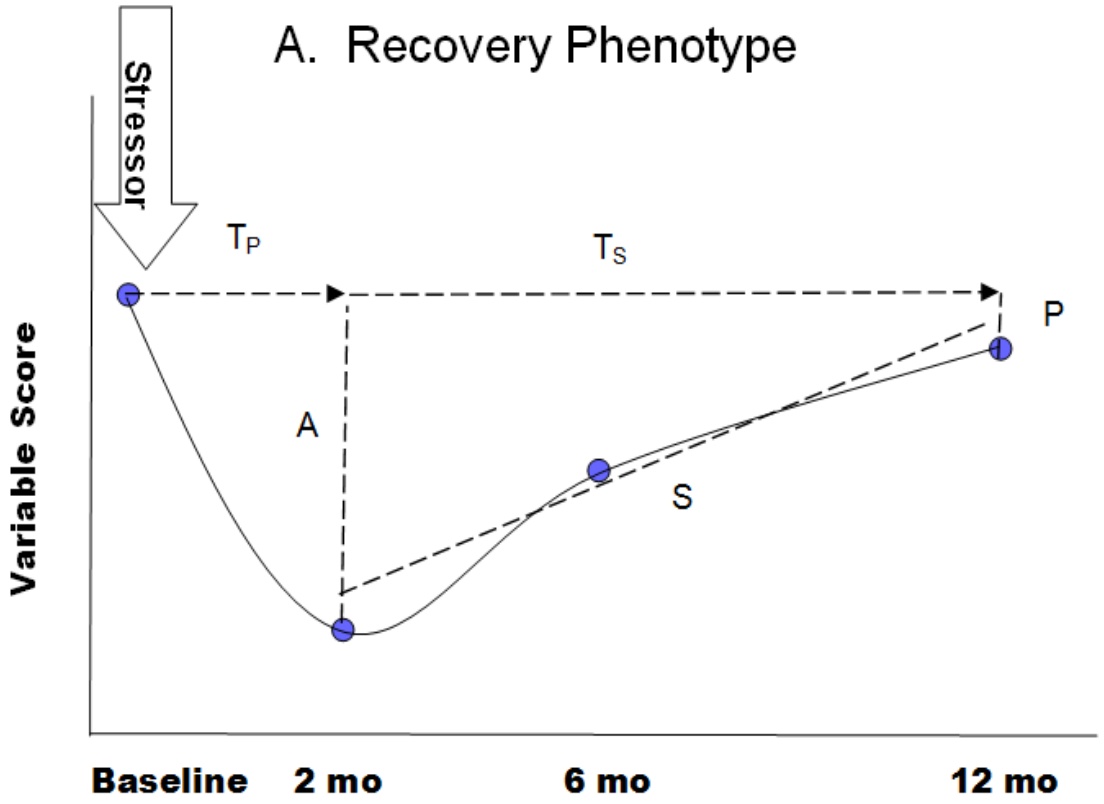
How might we quantify “resilience” after a stressor?

Two Key Clinical Questions

1. What is the pattern of recovery my patient will experience across health measures that matter?
2. How much better/worse will my patient do than expected, given their age and pre-stressor status?



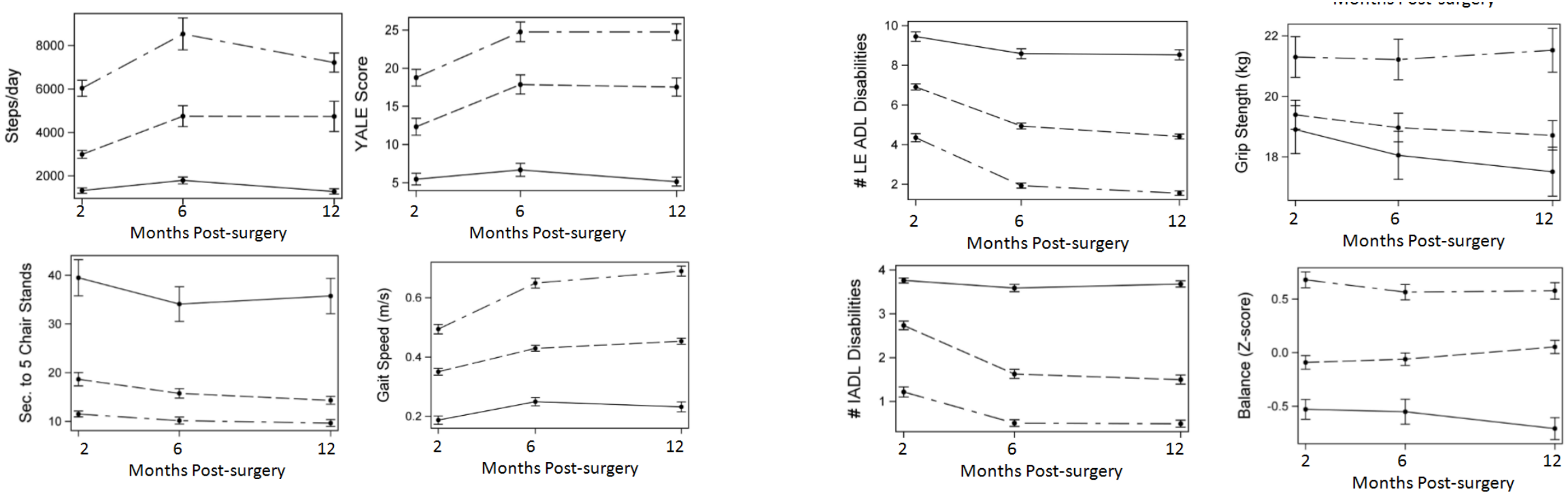
Recovery Phenotype Approach



- Descriptive
- Can quantify multiple parameters (slope, % recovery, etc)
- Can summarize multiple outcomes simultaneously
  - ❖Latent Class Trajectory Analysis
  - ❖Factor Analysis
  - ❖Principle Components Analysis
- Driven by age, comorbidities, pre-stressor function

J Gerontol A Biol Sci Med Sci. 2020 Mar 9;75(4):731-738.

Example: Recovery phenotype approach after hip fracture

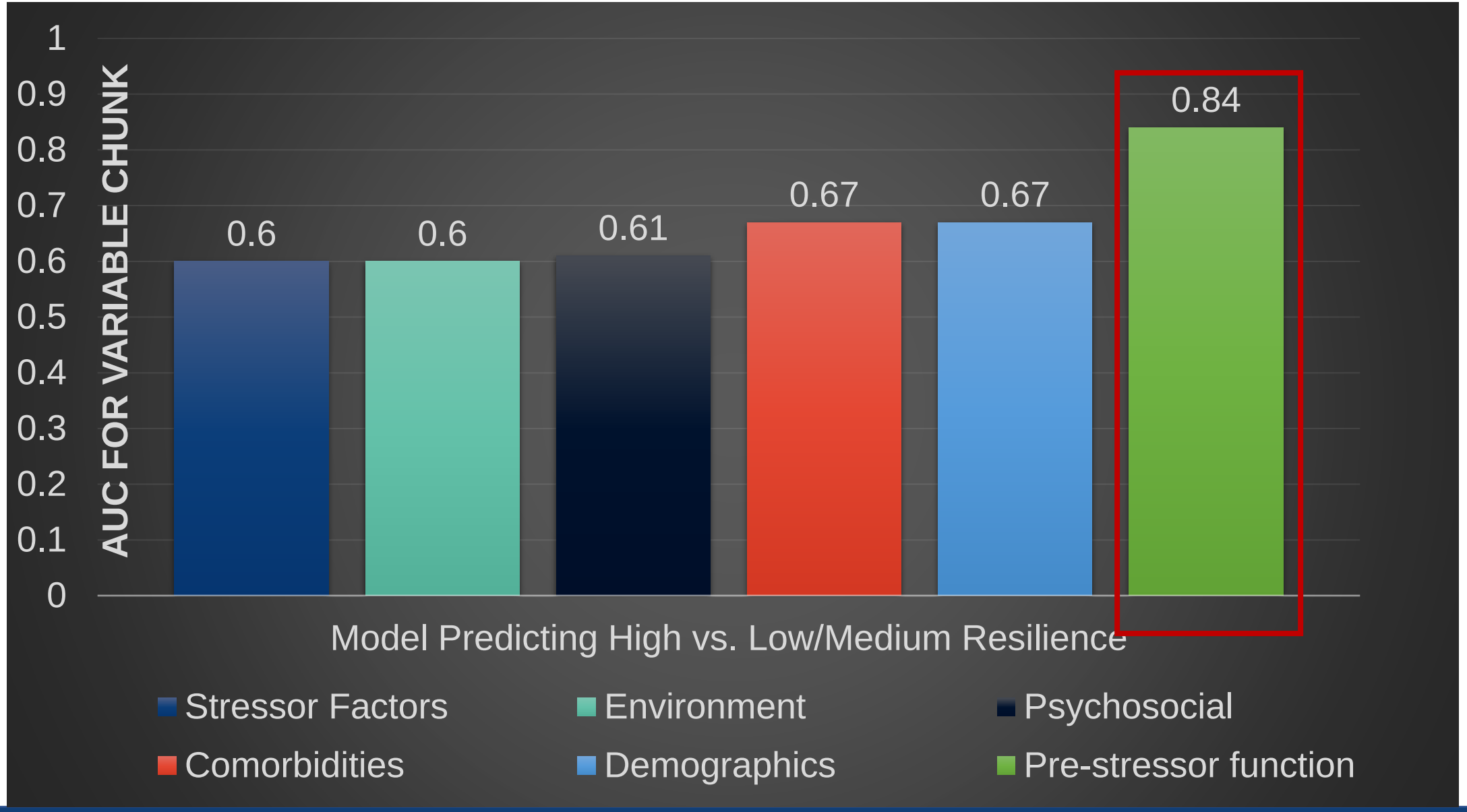


Latent Profile Analysis trajectory group

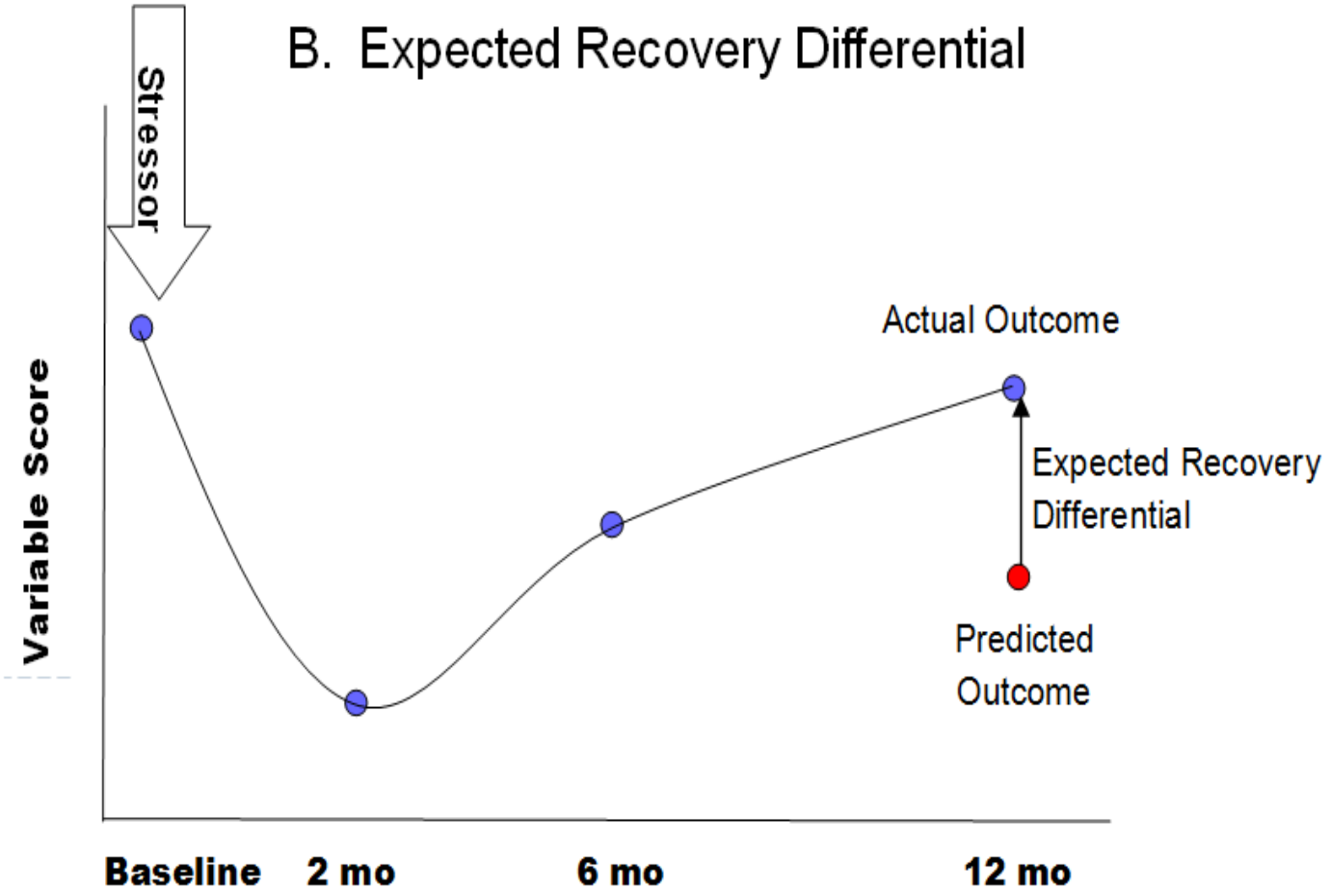
——— Lowest resilience — — — Medium resilience —— - — Highest resilience

J Am Geriatr Soc. 2019 Dec;67(12):2519-2527

What Factors Were Associated with the Phenotype of High Resilience after Hip Fracture?



Expected Recovery Differential (ERD) Approach

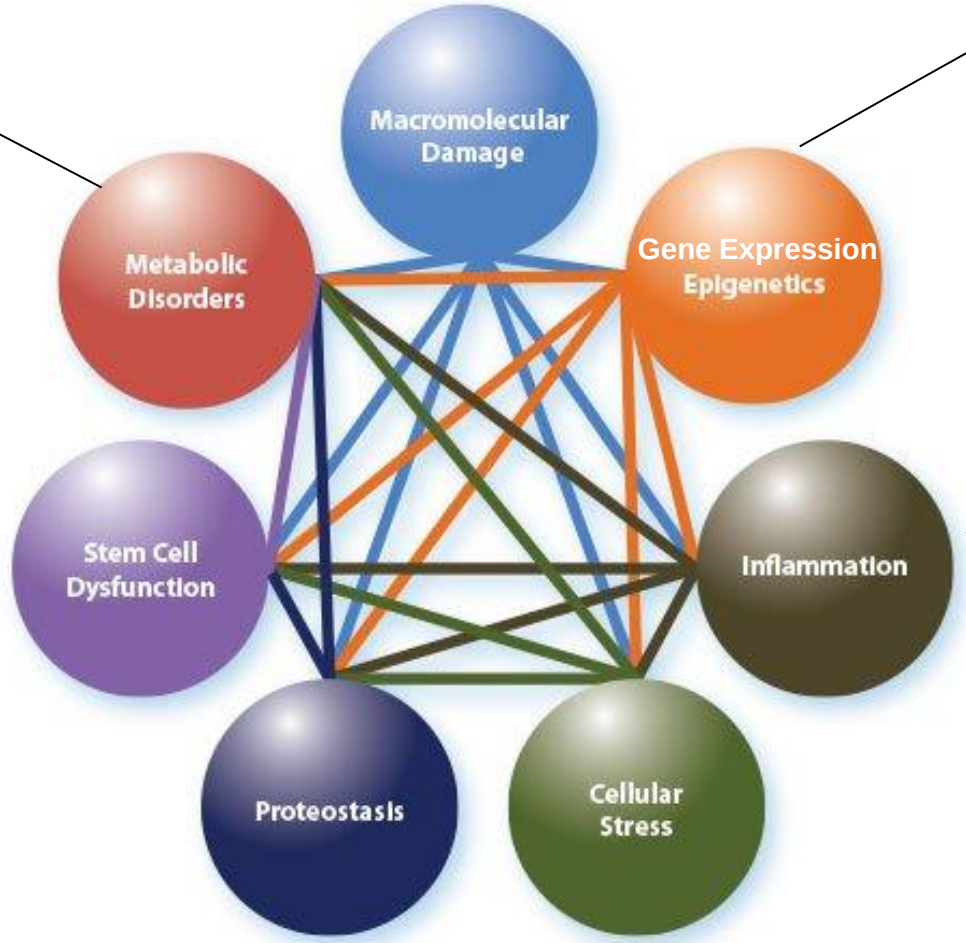


- Quantifies how observed outcomes differed from expected
- Requires predictive model from large cohort
- Accounts for baseline status, stressor factors, environment etc.

J Gerontol A Biol Sci Med Sci. 2020 Mar 9;75(4):731-738.

Proof of Concept Study: Are “Pillars of Aging” markers linked to Resilience after Hip Fracture?

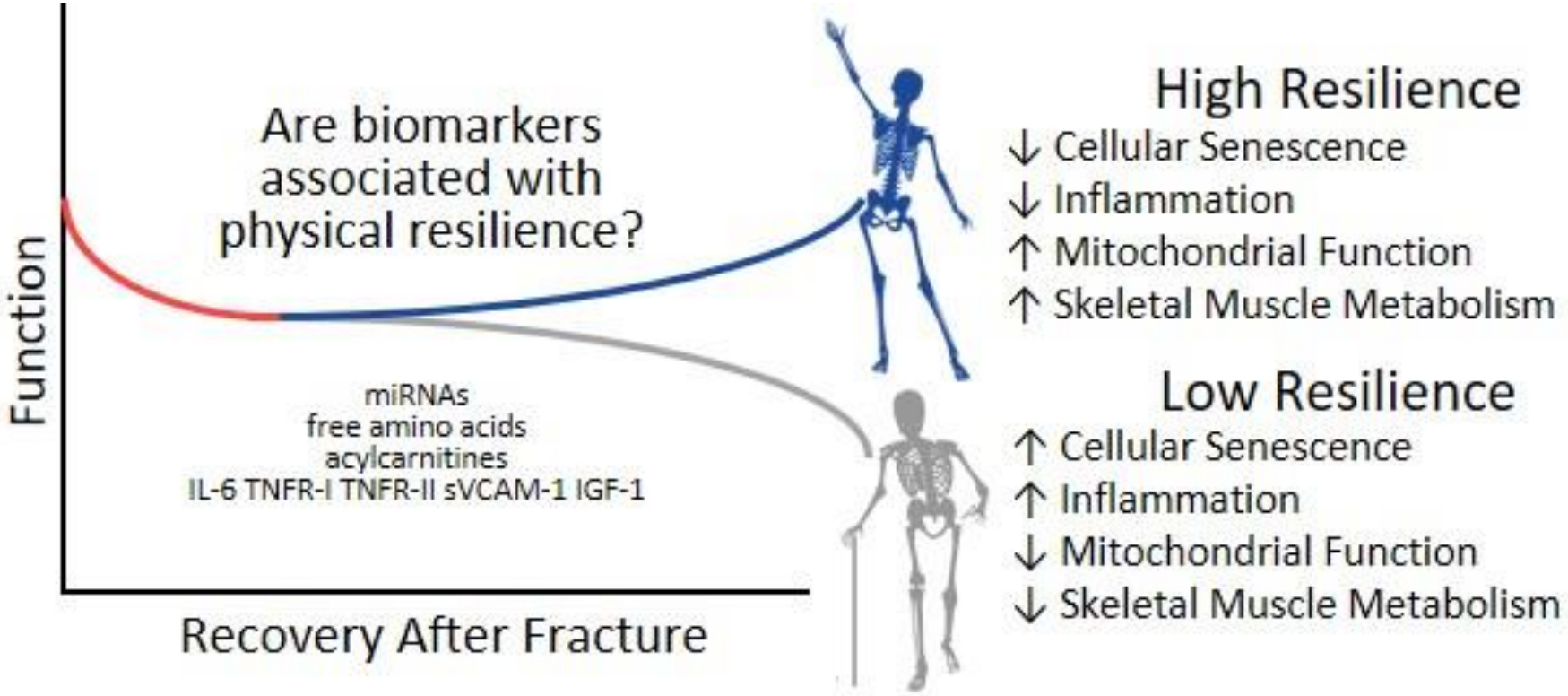
Metabolism
Acylcarnitine, branched chain amino acids, IGF-1

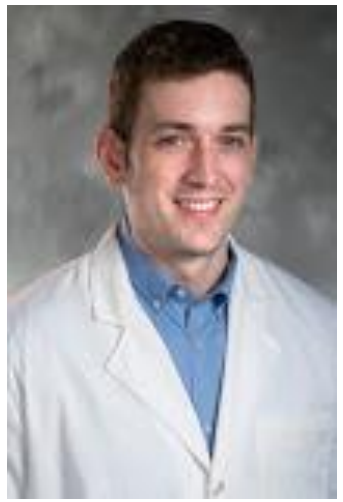


Gene expression
miRNA Panel associated with stress response

Inflammation
Senescence associated secretory phenotype (SASP) panel, IL6, IL10, V-CAM, TNF R1&2

This panel of biomarkers explained 38% of the observed variability in recovery differential after hip fracture.





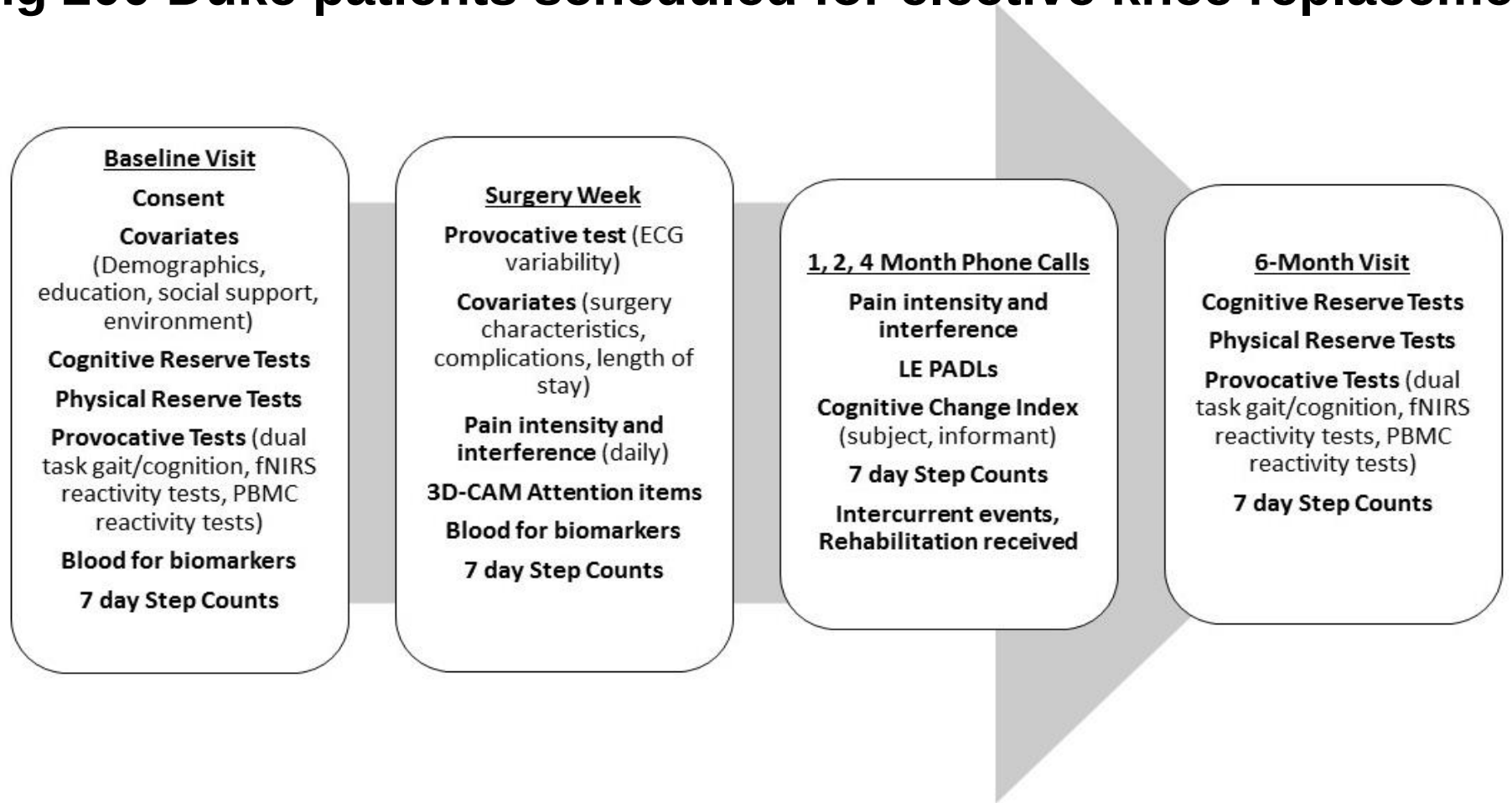
Daniel Parker, MD

J Gerontol A Biol Sci Med Sci. 2020 Sep 25;75(10):e166-e172.

Are there feasible, safe tests that can predict physical recovery after big health stressors?

PRIME-KNEE Study

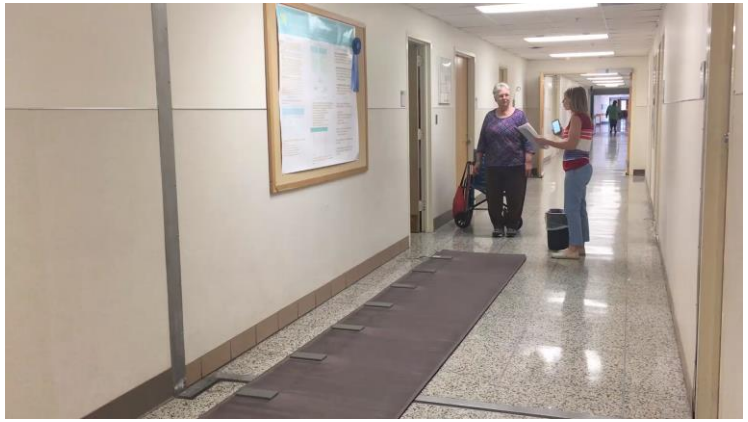
Enrolling 200 Duke patients scheduled for elective knee replacement surgery



Whitson et al. A template for physical resilience research in older adults: Methods of the PRIME-KNEE study. *J Am Geriatr Soc*. 2021 Nov;69(11):3232-3241

Provocative Tests: Baseline and 6 months

- **Gait Speed Dual Task Test** walking while performing a speech generation task
- **Near-Infrared Spectroscopy** (**NIRS**)cerebrovascular reactivity before and after cognitive task, orthostatic challenge
- **In vitro PBMC response** influenza vaccine/virus and LPS stimulation



A sneak peak at PRIME-KNEE data

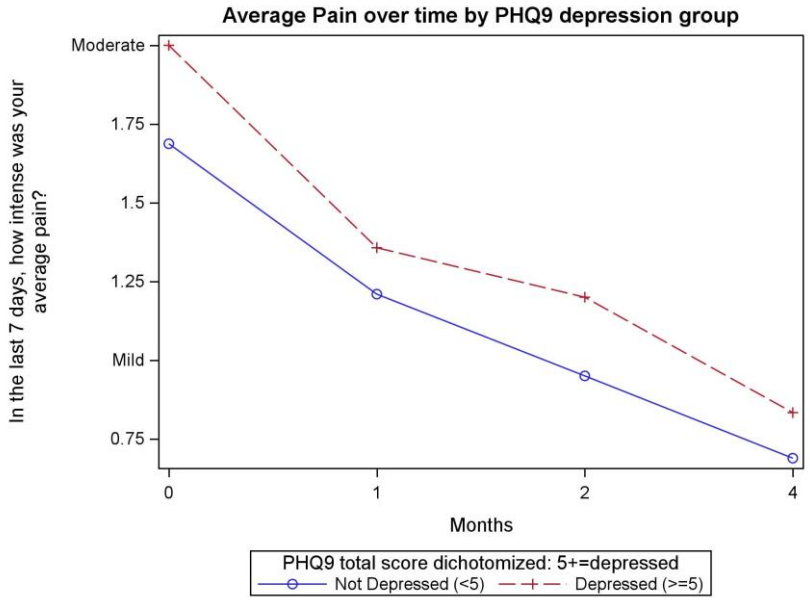
Do self-reported psychosocial measures collected before elective total knee arthroplasty predict pain trajectories in older adults?

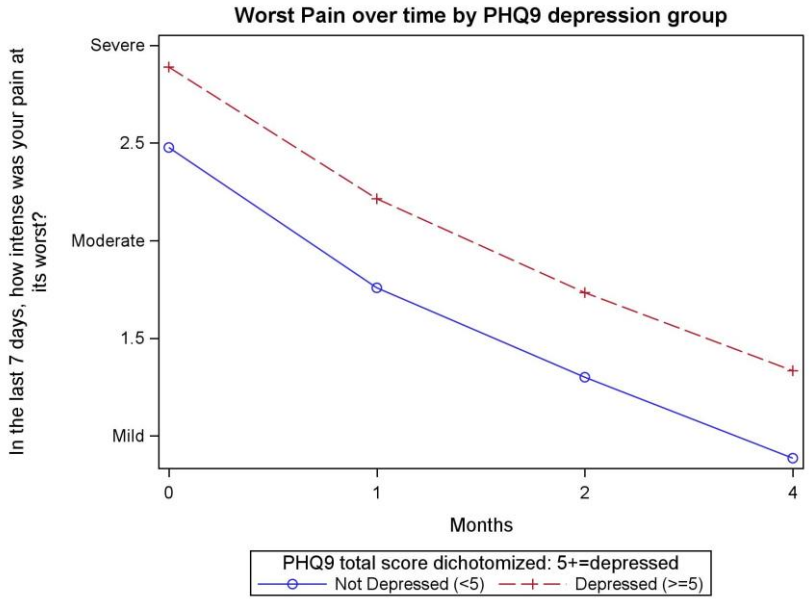
- PHQ9 Depression Scale
- Brief psychosocial resilience scale
- Emotional support questionnaire

Samantha Karle
Duke SoM MS3

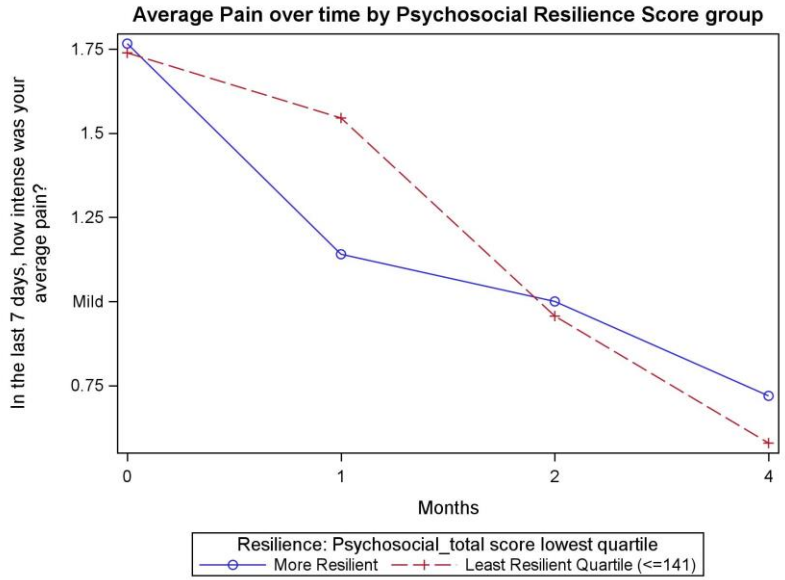
Predicting Pain Trajectories in PRIME-KNEE

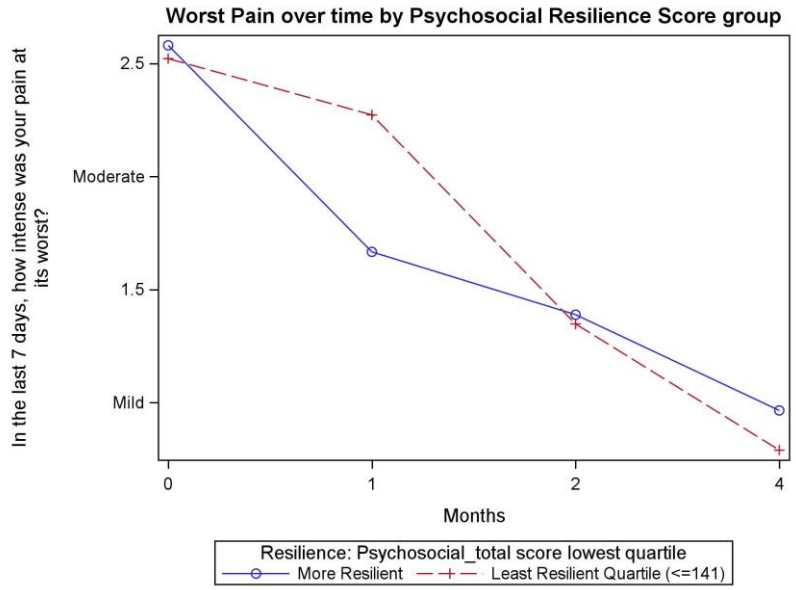
How is pain recovery different for people with depressive symptoms?





How is pain recovery different for people with low psychosocial resilience?





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Sheng Luo
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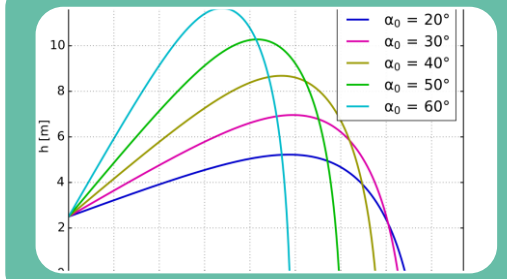
What populations are we studying?

- Sickle cell anemia
- Hemodialysis
- Glomerulosclerosis
- Rheumatoid arthritis
- Bone marrow transplant
- ECMO
- Osteoarthritis
- Fracture

- Dementia
- Urinary tract infections
- Vaccination
- Elective abdominal surgery
- Anesthesia/POCD
- Lemurs!

Goal: Promoting Resilience Before and During Health Stressors



Predict Recovery Trajectory

- Clinically feasible provocative tests
- Biomarkers

Current Interventions

- “Prehabilitation”
- Decision support tools

Nutrition
Psychosocial support

Future Interventions

- Resilience in a pill?

The Era of Resilience Medicine

Thank you and Questions

Duke Collaborators:
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U. Maryland Collaborators:
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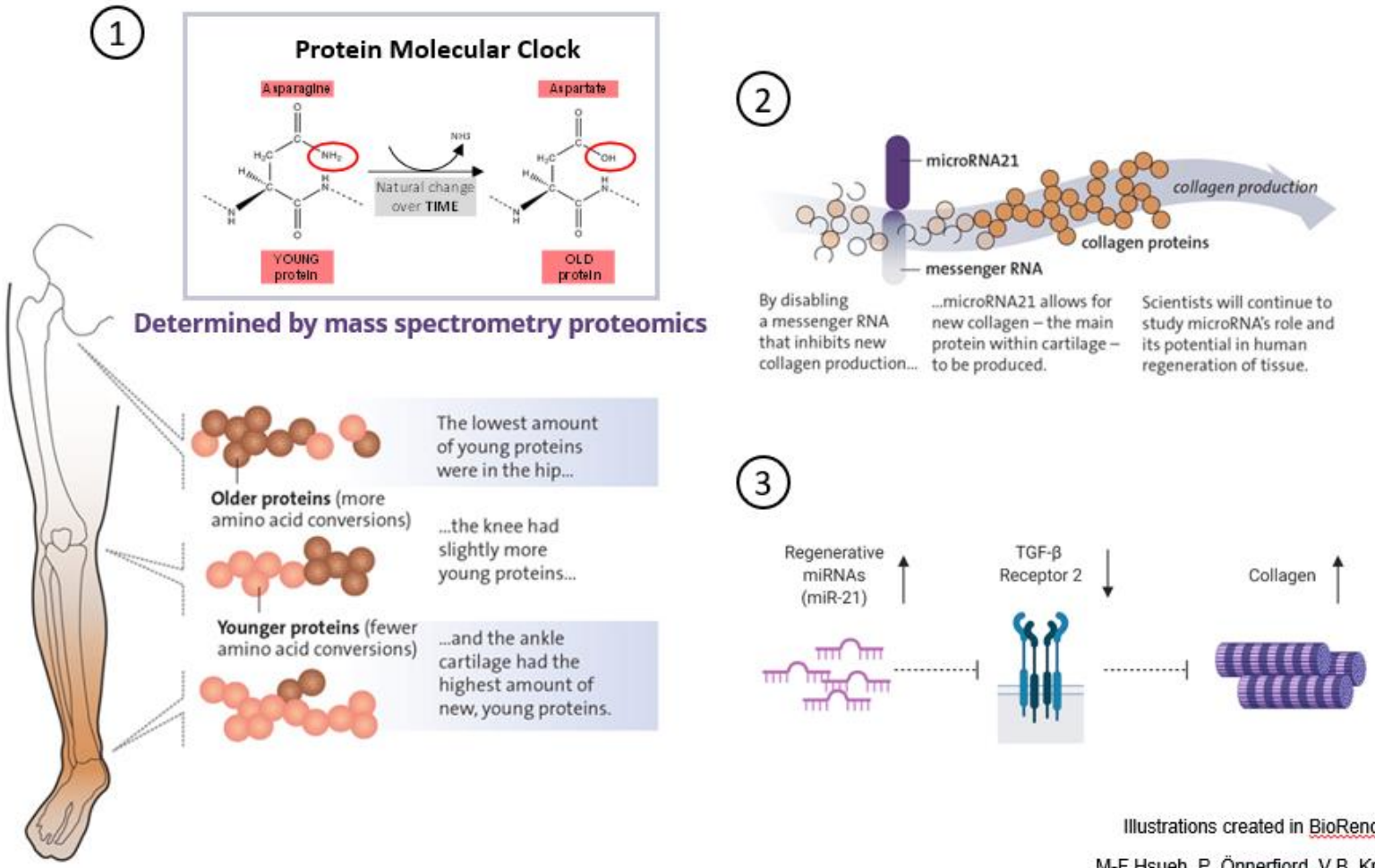
U. Connecticut Collaborators:
George Kuchel, Jacques Banchereau, Janet McElhaney
Harvard Collaborators:
Lew Lipsitz, Junhong Zhou
NIA Collaborators: Giovanna Zappala, Basil Eldadah, Chhanda Dutta

Molecular Measures of Resilience – Cartilage Regeneration

Humans may have innate cartilage regeneration ability

"Analysis of "old" proteins unmasks dynamic gradient of cartilage turnover in human limbs"



Ming-Feng Hsueh,
REC Scholar

Illustrations created in BioRender and in part by Alisa Weigandt

M-F Hsueh, P. Önnerfjord, V.B. Kraus et al. Science Advance, 2019