Designs to Address the Multifaceted Targets of Interventions to Promote Resilience in Older Adults

AGS/NIA R13 Bench-to-Bedside Conference Series

Optimizing Resilience

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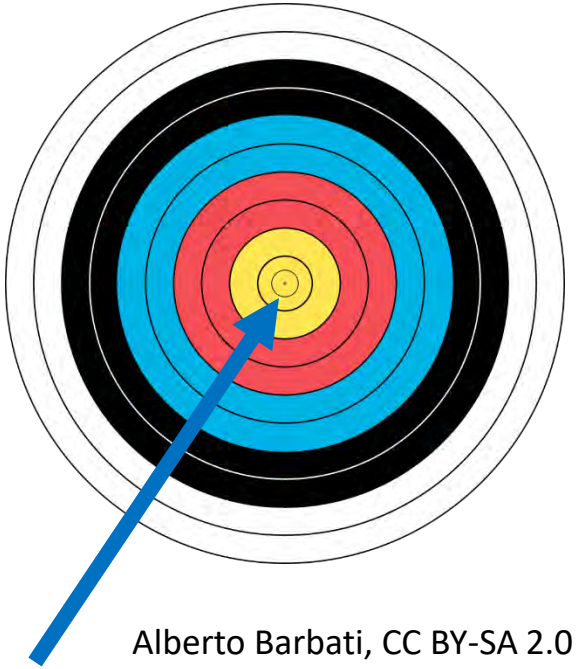
Disclosures

- I have no relevant financial disclosures

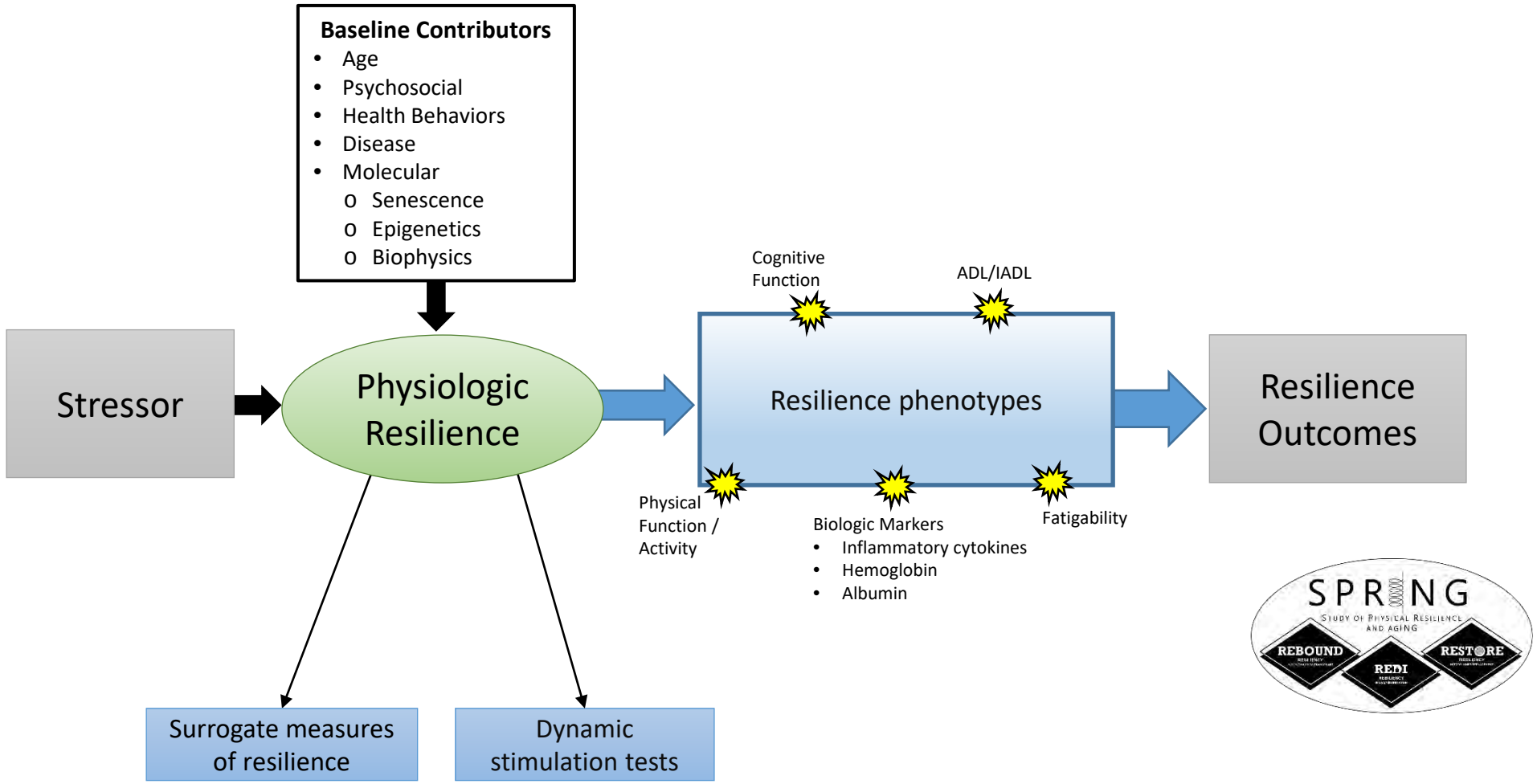
- I used Undermind AI to assist in literature review

What is Resilience?

- **Capacity to bounce back** from a [physical] challenge
  (Resnick et al., 2011)
- Ability to **resist functional decline / recover [physical] health** after a stressor
  (Whitson et al., 2016)
- **Ability of a [physiologic] system to recover** from a stressor … that [pushes] the system … far from its original equilibrium
  (Varadhan et al., 2019)
- Capacity to maintain… function **with aging and disease**
  (Stern et al., 2022)



1. At least two “resilience” targets



Walston et al., J Am Geriatr Soc, 2023

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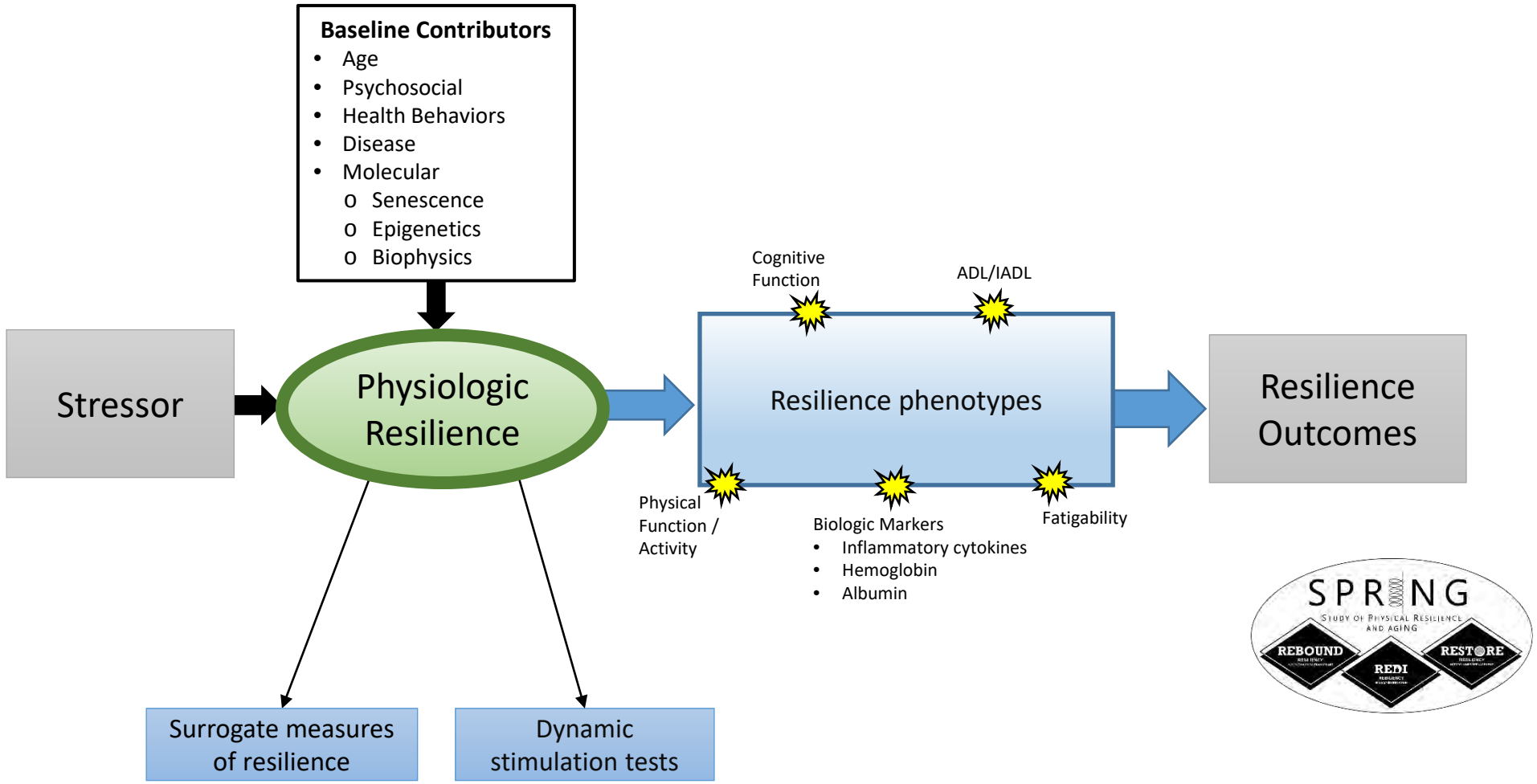

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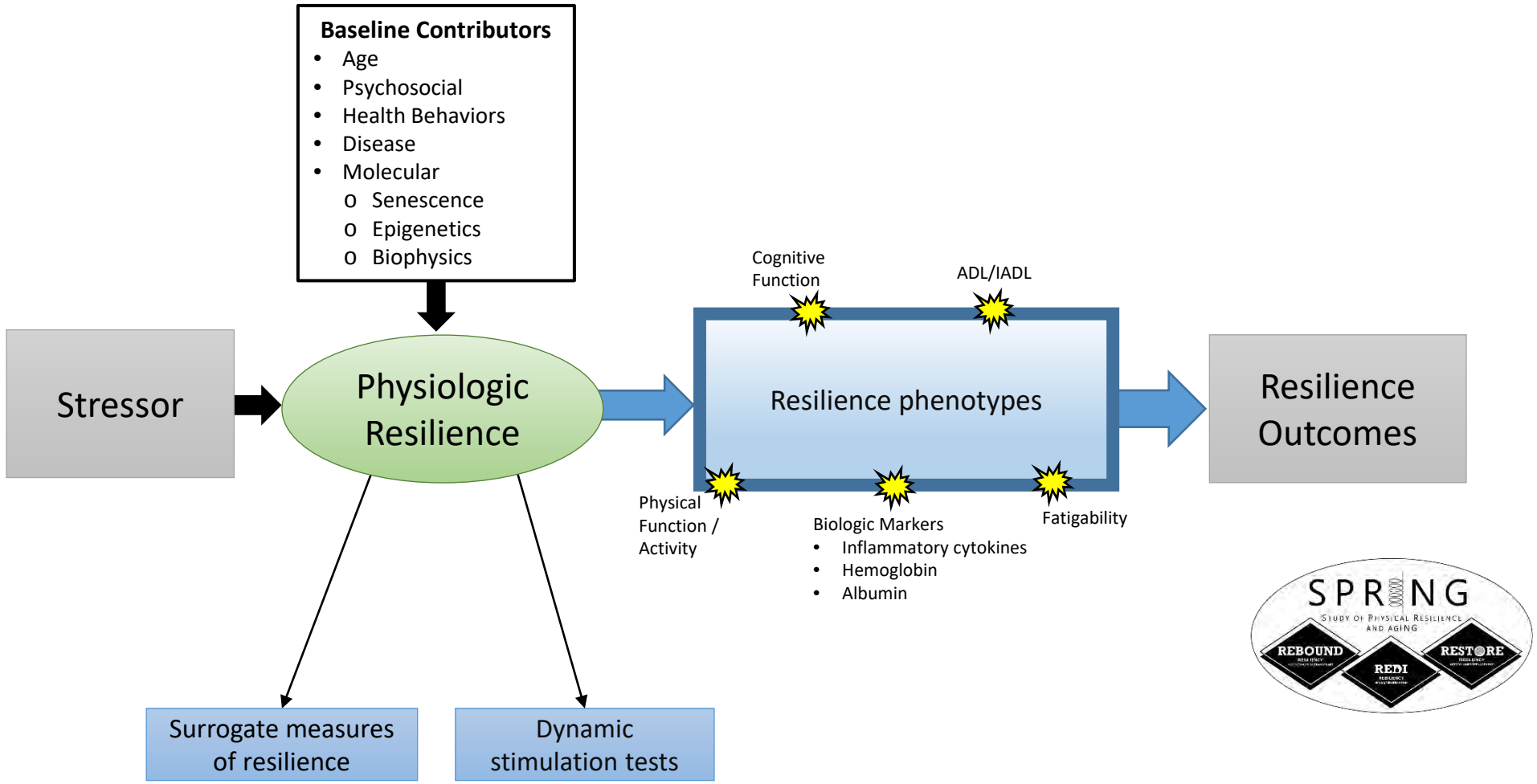

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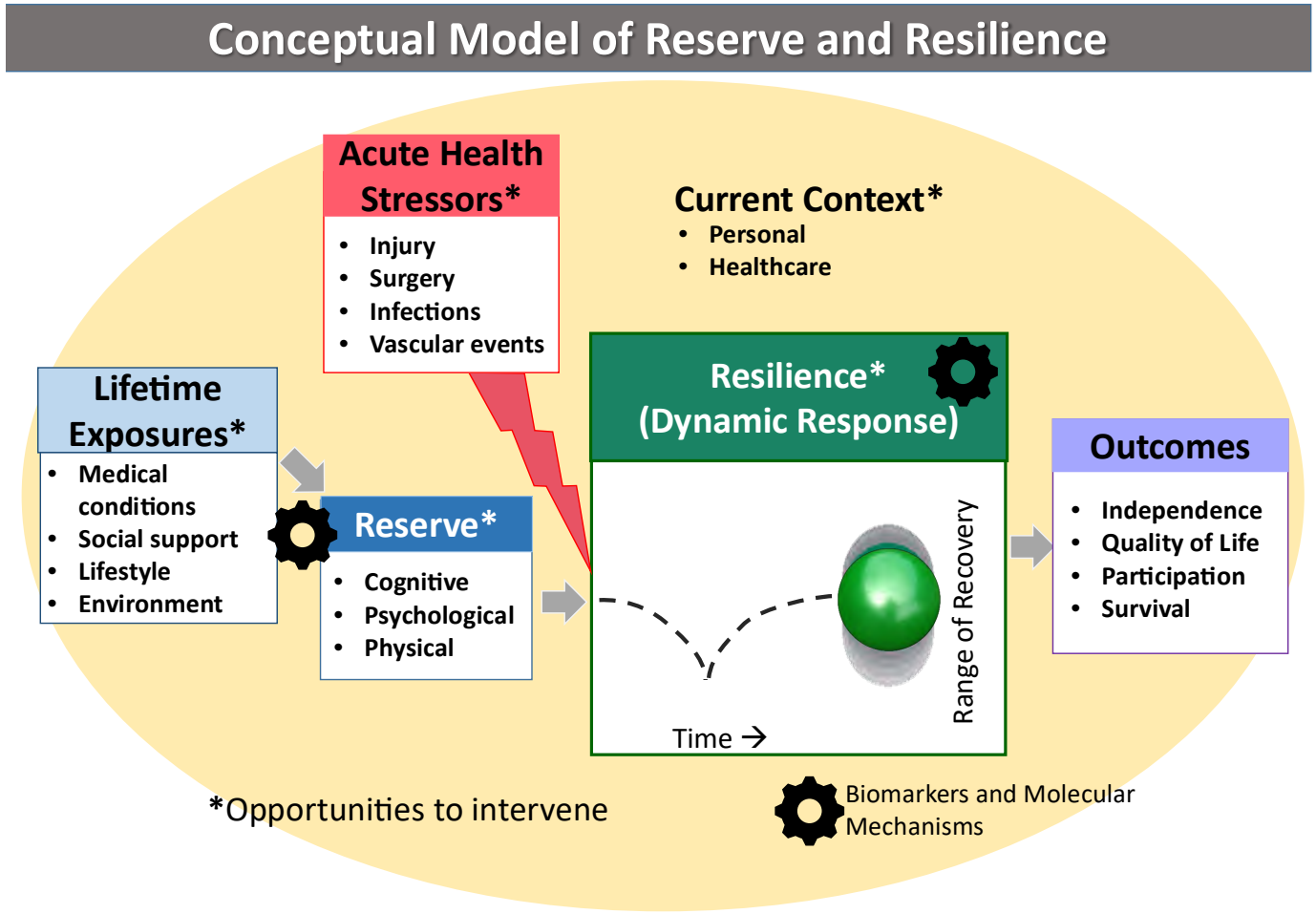
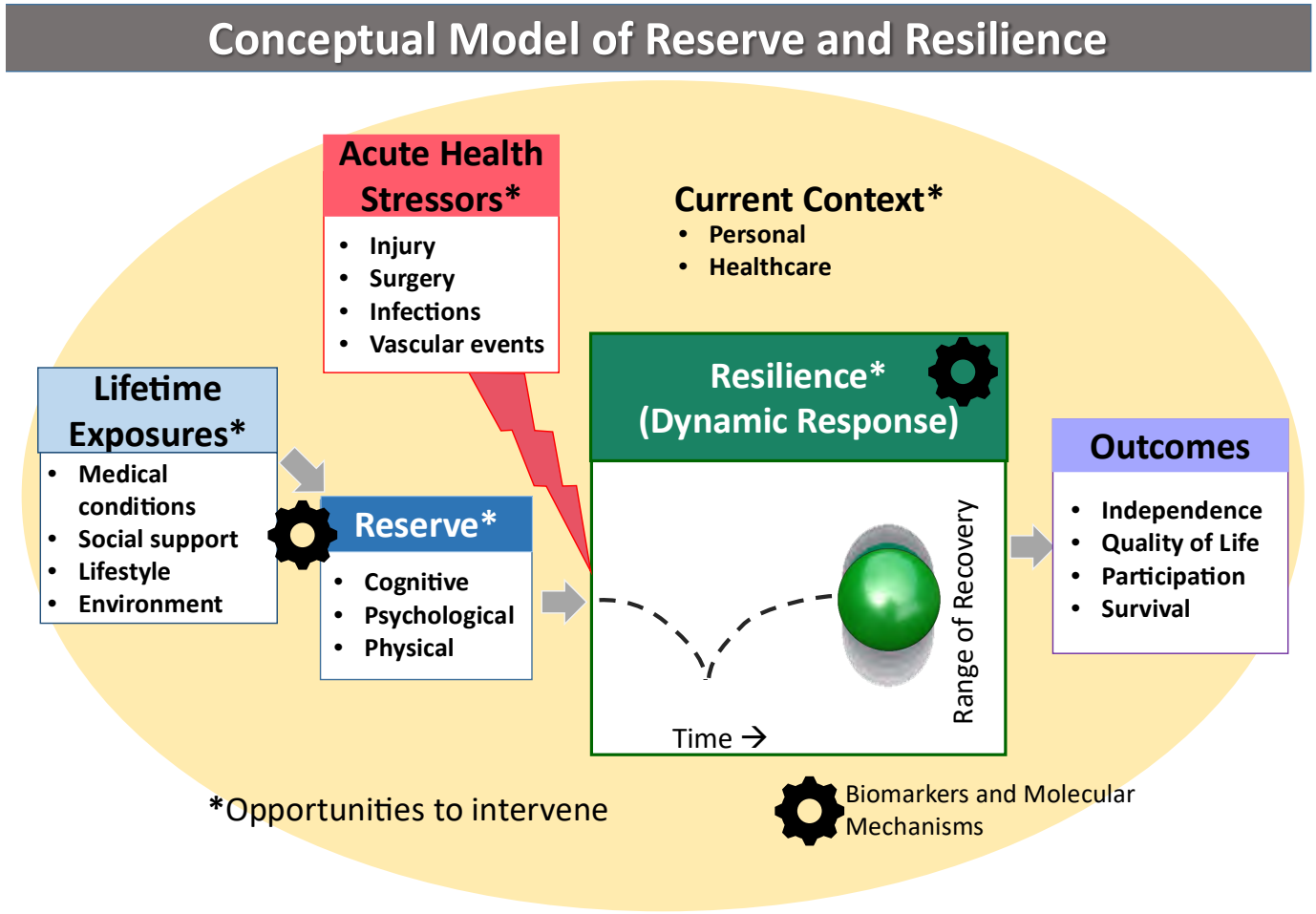
1. More resilience-related intervention targets



Whitson et al., J Am Geriatr Soc, 2021

2. Measuring the intervention targets



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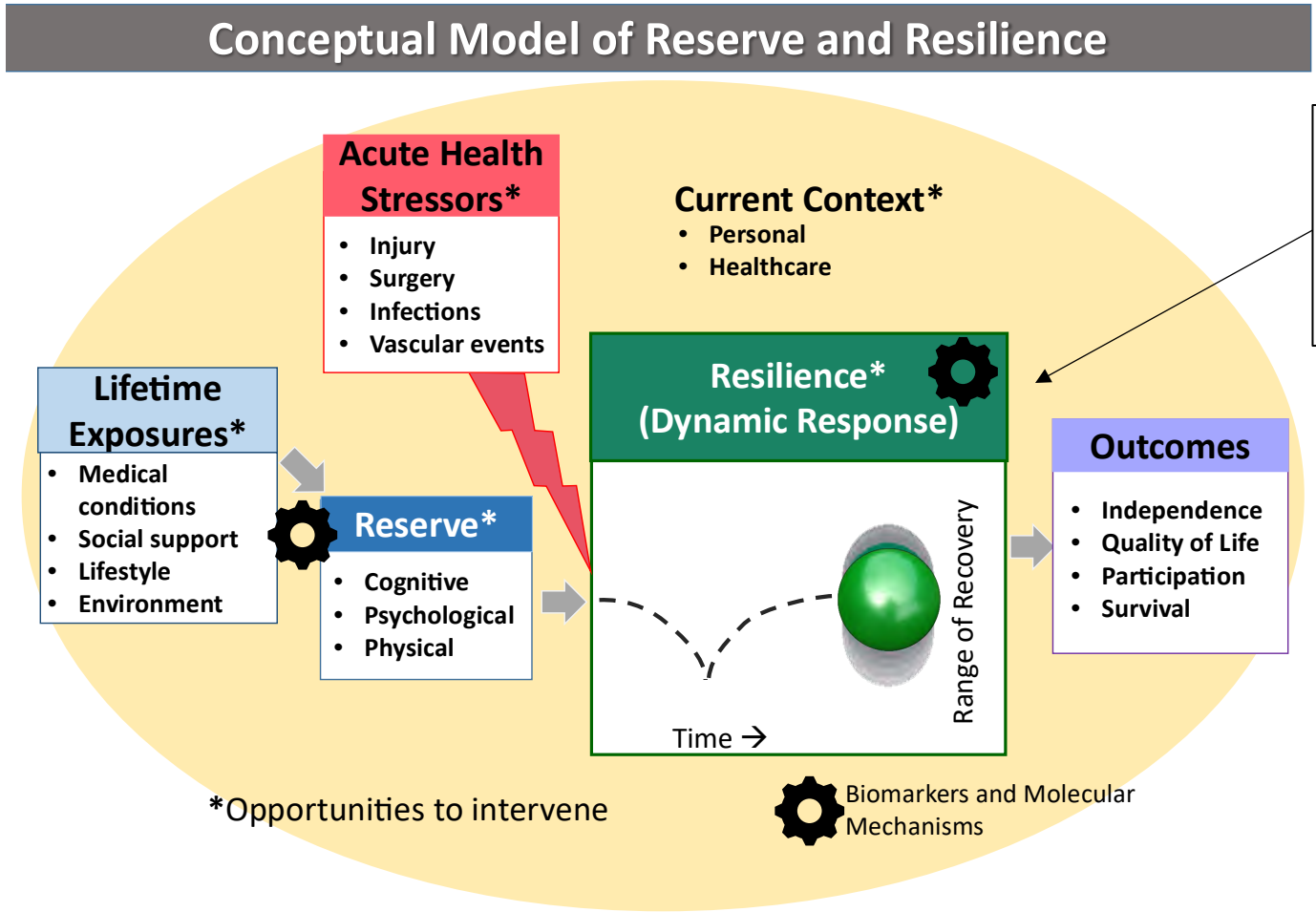

Great work here, but questions remain

Whitson et al., J Am Geriatr Soc, 2021

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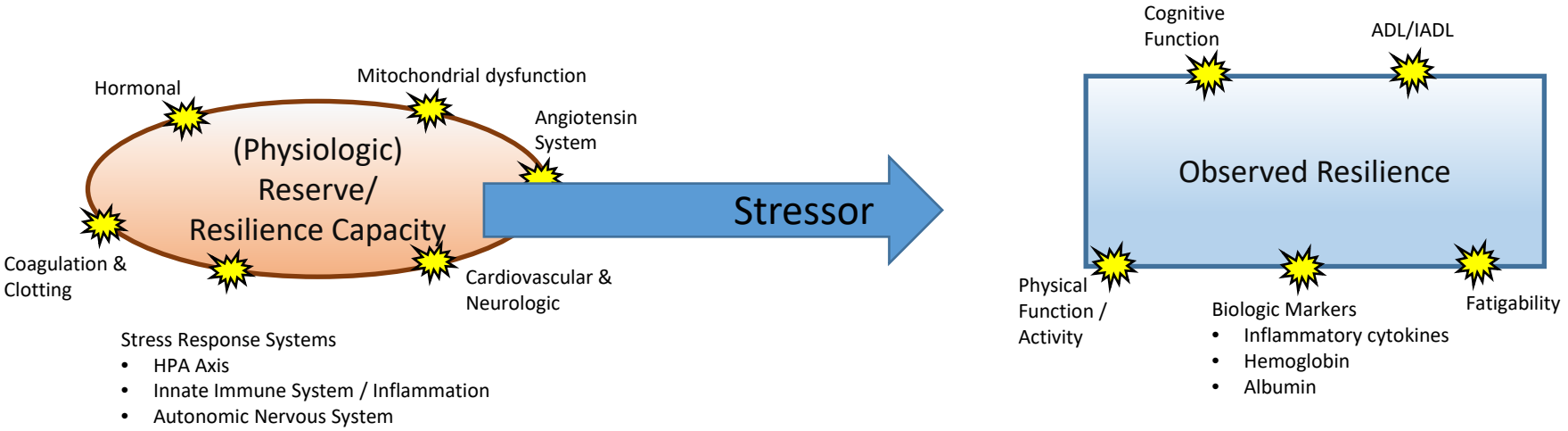

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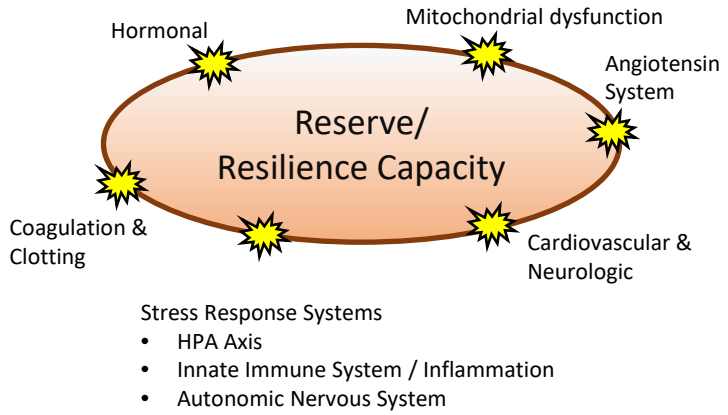

Csete, M. E. & Doyle, J. C. Reverse engineering of biological complexity. *Science*. **295**, 1664–1669 (2002).

Resilience capacity = function of health of all of the above: Dynamical system

Gold standard testing mechanism: Dynamic stimulation

Data: Pre-post time series of responses

PSYCH:

Bergeman, Blaxton, Joiner, 2021

Widowhood: Bisconti, Bergeman, Boker, 2004-6

PHYSICAL – POST-STRESSOR:

Rector et al., 2025

COVID-19 Daily respiratory function data

System equations?

PHYSICAL – PRE STRESSOR:

Bandeen-Roche et al., 2025

Physiologic adaptation: HRV, Cortisol

A challenge: Insufficient response "density"

PHYSICAL – "FREE-LIVING"

Arbeev et al., 2019

Biomarker profiles – Mahalanobis distance

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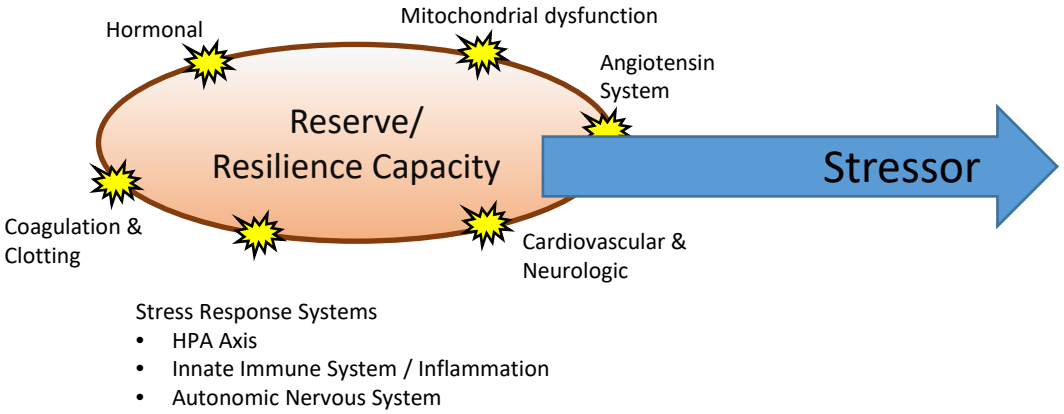


TOTAL KNEE REPLACEMENT:

Sieber et al, 2025

Challenges include:

"Exogenous" vs. "Endogenous" stressors

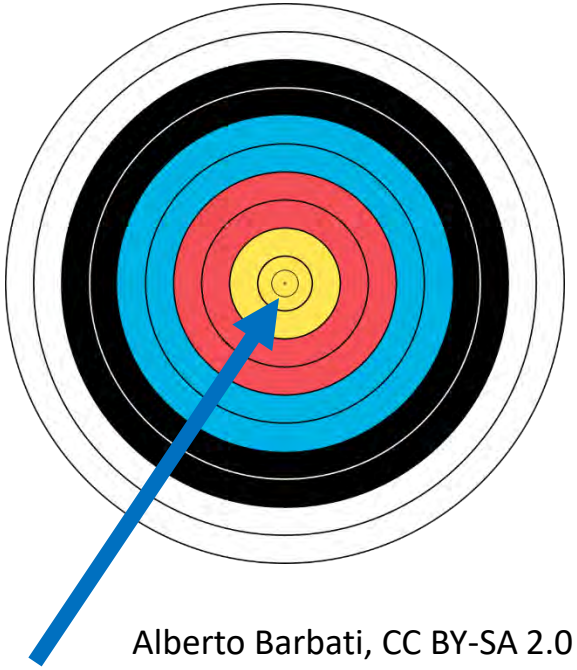
"Randomizable" vs. "Reflects reserve"

Within-institution homogeneity

Multi-center studies needed

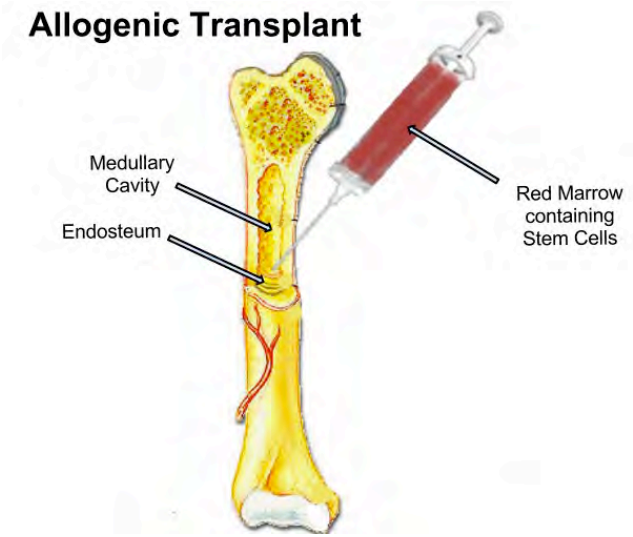
3. Cost-effectiveness

- **One intervention strategy**
  - Measure “resilience”
  - Target an intervention to improve the outcomes of the non-resilient
- **Three important considerations**
  - Diagnostic accuracy
  - Cost-effectiveness
  - Outperforms competing concepts?
    - Frailty (many flavor!), functional limitation, intrinsic capacity, multimorbidity, etc.
    - Undermind AI – **198 papers** on prospective interventional studies to improve physical/functional resilience (multiple targets) post-stressor even if not explicitly labeled as “resilience—vast majority employed frailty or functional limitation.



4. Addressing death and intercurrent events

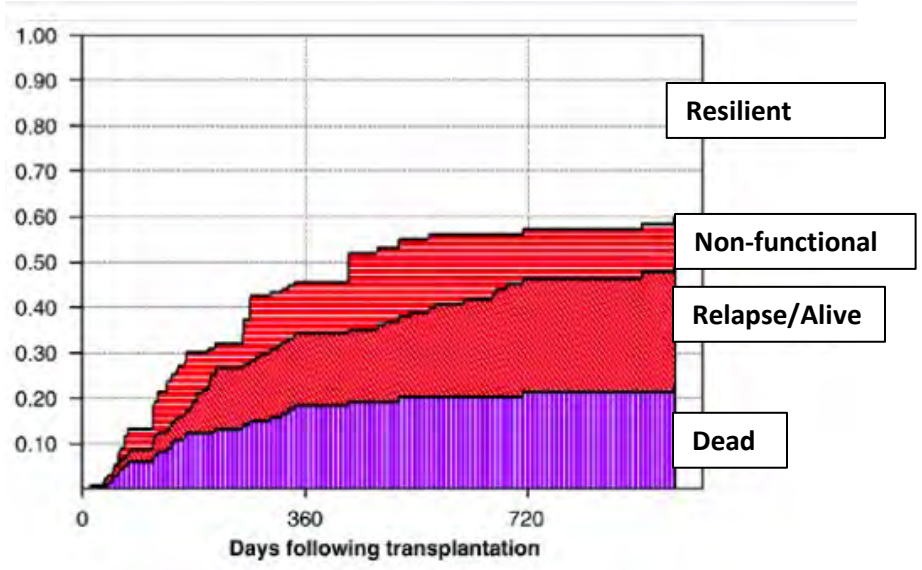
- **Example: Bone Marrow Transplant for Hematological Cancers**
  - Death is frequent
  - Relapse additionally occurs



- Analysis of typical resilience measures (e.g. “functional recovery”) may be biased
  - Incompletely informs patients
  - Kaplan-Meier invalid (unless ‘death’ is independent of ‘recovery’)

4. Addressing death and intercurrent events

- **Method 1: Composite outcome**
  - "Non-resilience" = "Failed recovery" or "death" (or "relapse", or….)
  - Strong when the multiple options reflect a shared underlying mechanism
- **Method 2: Competing-risks analyses**
  - **Cause-specific**
    - Recovery before death; Death before recovery
    - Implementable as a standard Cox model
  - **Cumulative incidence/subhazards/ "Fine & Gray"**
    - Not recommended as treatment efficacy outcome: Conflates effects on main v competing outcomes



Troendle, Leifer, Kunz, 2018

Figure: Modifies Lim et al., 2007

4. Addressing death and intercurrent events

- **Method 3: Joint longitudinal/survival models**
  - Imagines a shared “frailty” underlying functional trajectory and (say) mortality risk

Hickey et al., 2018

Bone Marrow Transplant: Composite Outcome Example

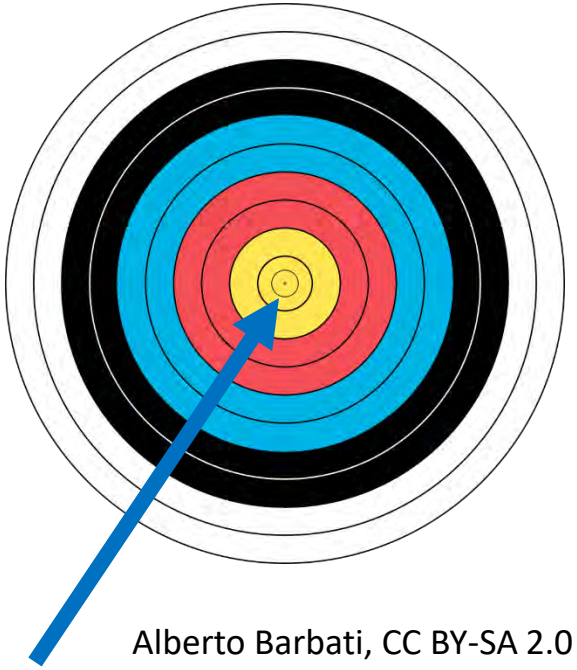
+1 Positive Change	0 No Significant Change	−1 Adverse Change	−5 Relapse / Mortality

Sub-Domain	Score +1 (Positive)	Score 0 (No Change)	Score −1 (Adverse)	Notes
Weight	N/A	<10% loss or weight gain	≥10% weight loss	Gain excluded — may reflect fluid retention
SPPB	Any positive change	No change or top quartile at baseline & 6 months	Any negative change	Short Physical Performance Battery
PFS Score	Decrease of ≥5 (improvement)	Change between −5 and +5	Increase of ≥5 (worsening)	Patient-reported fatigue; imputation if ≥7/10 answered
Grip Strength	Increase ≥5 kg	Change between −5 and +5 kg	Decrease ≥5 kg	Clinically meaningful threshold
Relapse	N/A	No relapse (0)	−5 penalty	Score of −5 to prevent resilient classification
Mortality	N/A	No mortality (0)	−5 penalty	Score of −5 to prevent resilient classification

Final Score: Sum of all sub-domains | Resilient = score ≥ 0 | Non-Resilient = score < 0

5. Assuring study strength

- **Accounting for competing risks**
- **Recruiting the full-range target population**
  - Attracting the non-resilient to participate
- **Study “size”, informativeness to achieve aims**
  - Interactions (effect modification) may be of primary interest
  - Modifiers include: Stressor magnitude, baseline status, targeted/non-targeted, between-domain



Knowledge gaps

- **Dynamical mechanisms** underlying "physiologic" resilience
  - **Methods** by which to measure these using feasible data, and then target these
  - How do biological, physiological, cognitive, psychological reserve modify each other?
- **What are the interventions** for each resilience target?
  - Reserve, Stressor, Phenotypes, Outcomes
- **How cost-effective** is the resilience concept for targeting interventions?
- Key **intervention design** questions
  - How to include the full range of reserve? Full range of (competing) outcomes?
  - How to study, account for varying stressor magnitude and types?

Research opportunities

- Improved **data**
  - Finer grain time scale for measuring a priori dynamical systems data
    - Wearables, implantables, sensors….
  - Larger, multisite cohorts – to evaluate key interactions

- **Hybrid observational / intervention studies**
  - Jointly obtaining **richer data** needed while **piloting** low-risk interventions and evaluating their cost-effectiveness, implementation challenges
  - **Multimodal** intervention strategies

- **Older adult priorities**

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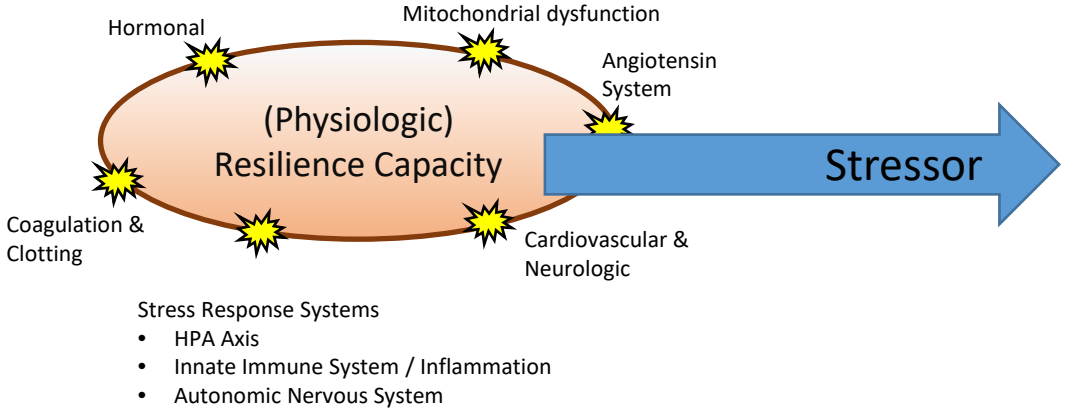
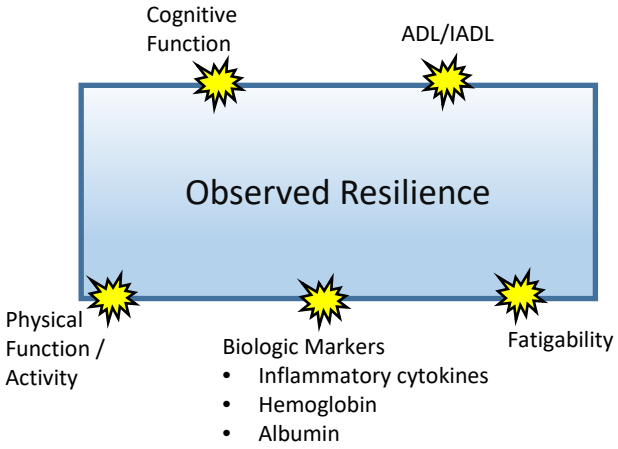
EXTRAS

Physical resilience: Before and After the Fact





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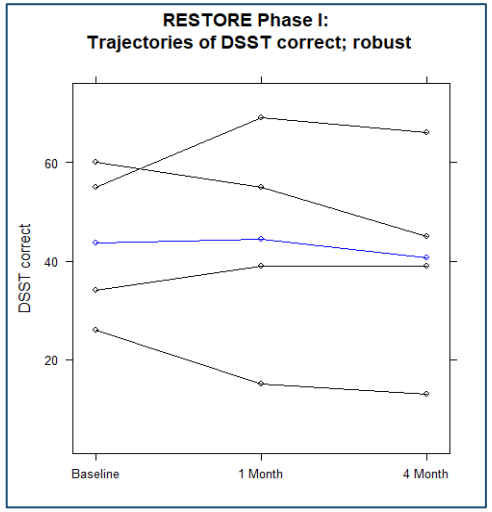
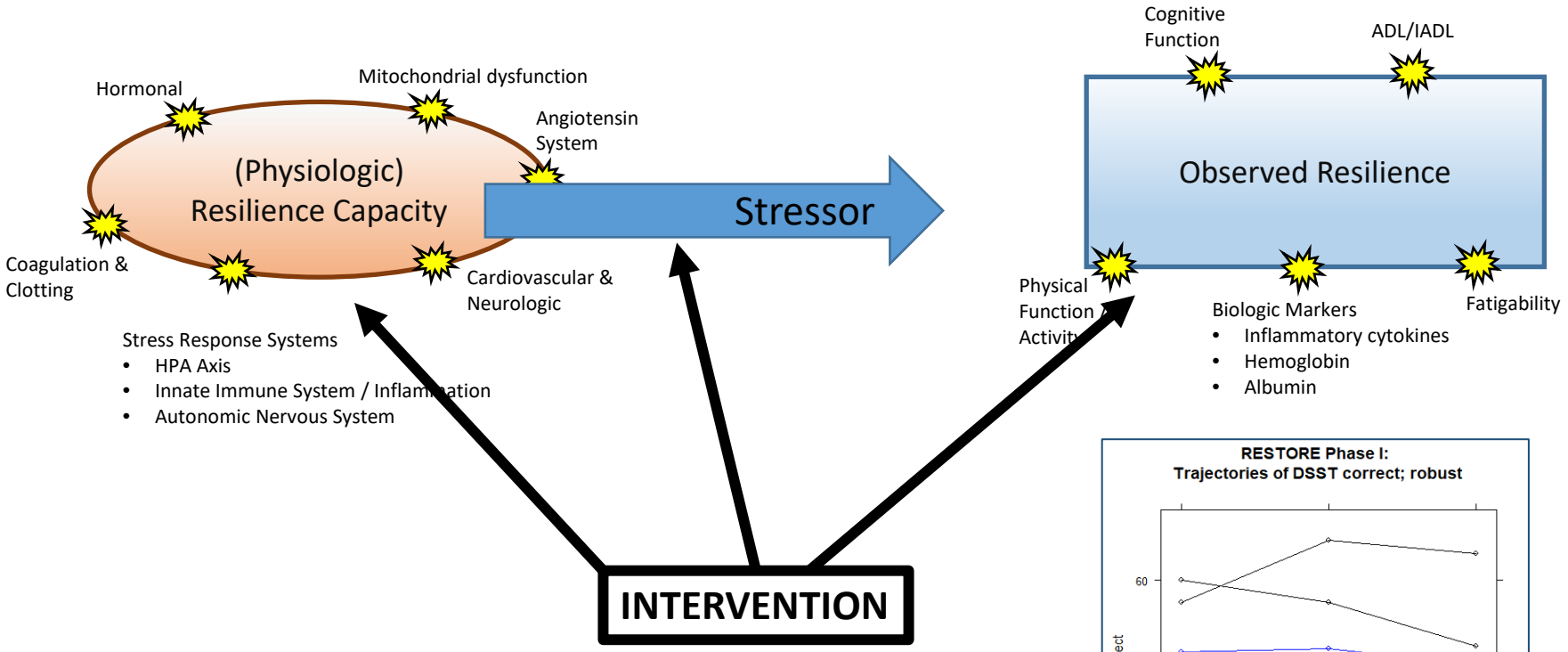
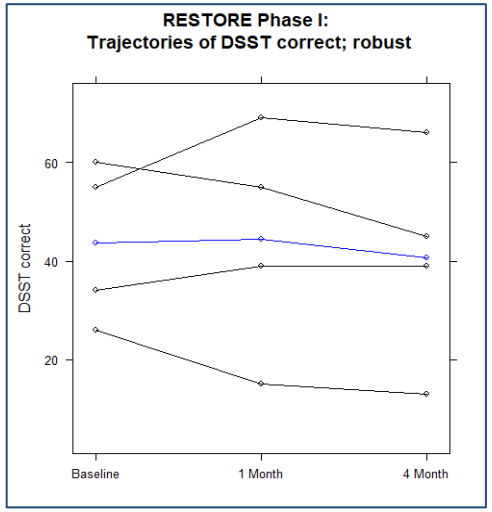


Physical resilience: Before and After the Fact





Defining the Resilience Phenotype

Resilient Outcome: Alive, relapse-free, and no aggregate adverse change across key sub-domains at 6 months post-transplant vs. baseline.

Six Sub-Domains

⚖	🚶	📋	✊	⚕	♡
Weight	**SPPB**	**PFS Score**	**Grip Strength**	**Relapse**	**Mortality**
Avoid ≥10% loss	Physical performance	Fatigue symptoms	Muscle function	Disease status	Survival

Combined Resilience Score = sum of all sub-domains **Resilient: score ≥ 0** | **Non-Resilient: score < 0**

Relapse and mortality each carry a −5 penalty score to ensure these outcomes always classify as non-resilient.