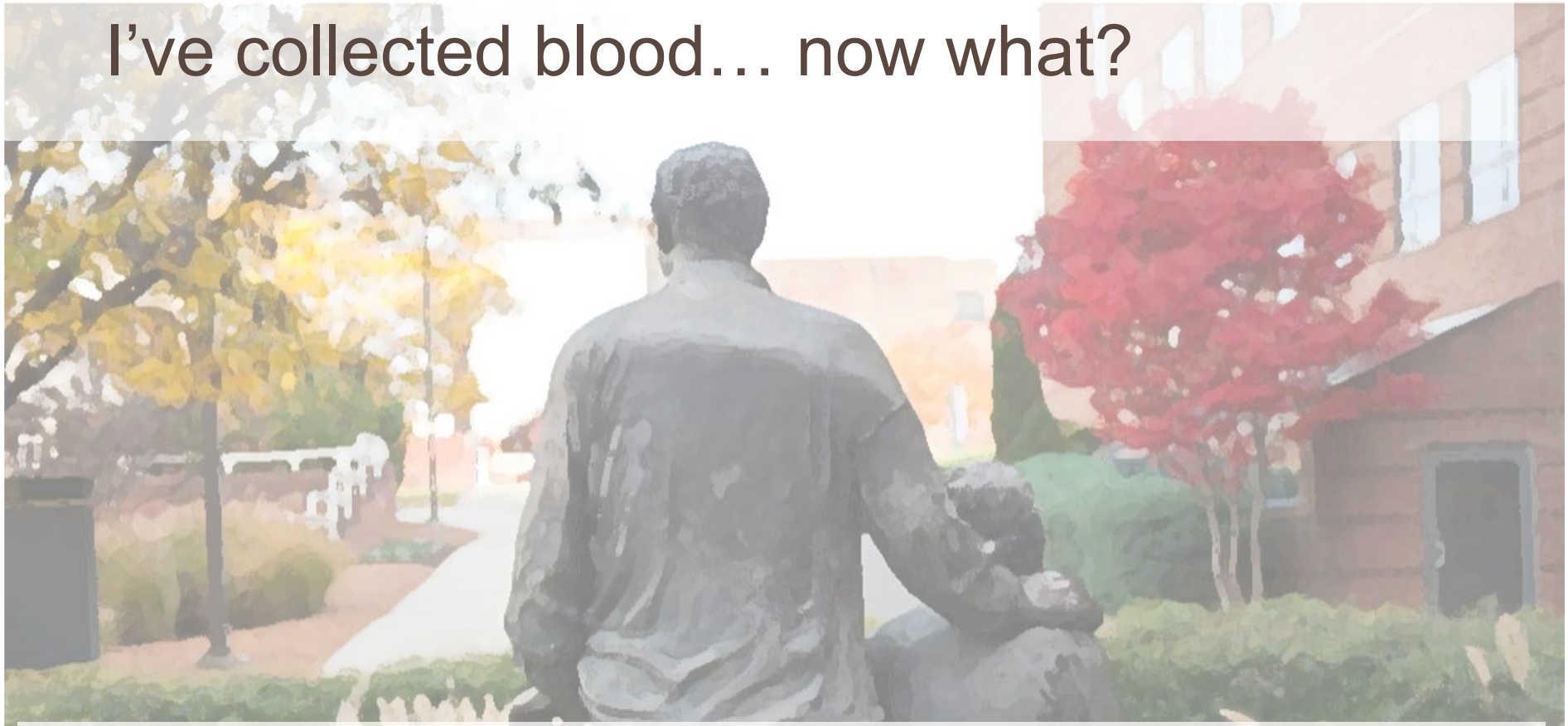
Biomarkers & Translational Geroscience: I've collected blood… now what?



Jamie N. Justice, Ph.D.
Assistant Professor, Internal Medicine, Gerontology and Geriatrics
Sticht Center on Healthy Aging and Alzheimer's Prevention (CHAAP)
Wake Forest School of Medicine

Wake Forest™ School of Medicine

AFAR's Beeson Meeting
Nov 19, 2021

Conflicts to Disclose:
None

Funding sources:

- American Federation of Aging Research & Glenn Foundation (TAME)
- National Institutes of Health

Eudes Correia

Biomarkers & Translational Geroscience: I've collected blood… now what?

Measuring Biological Age

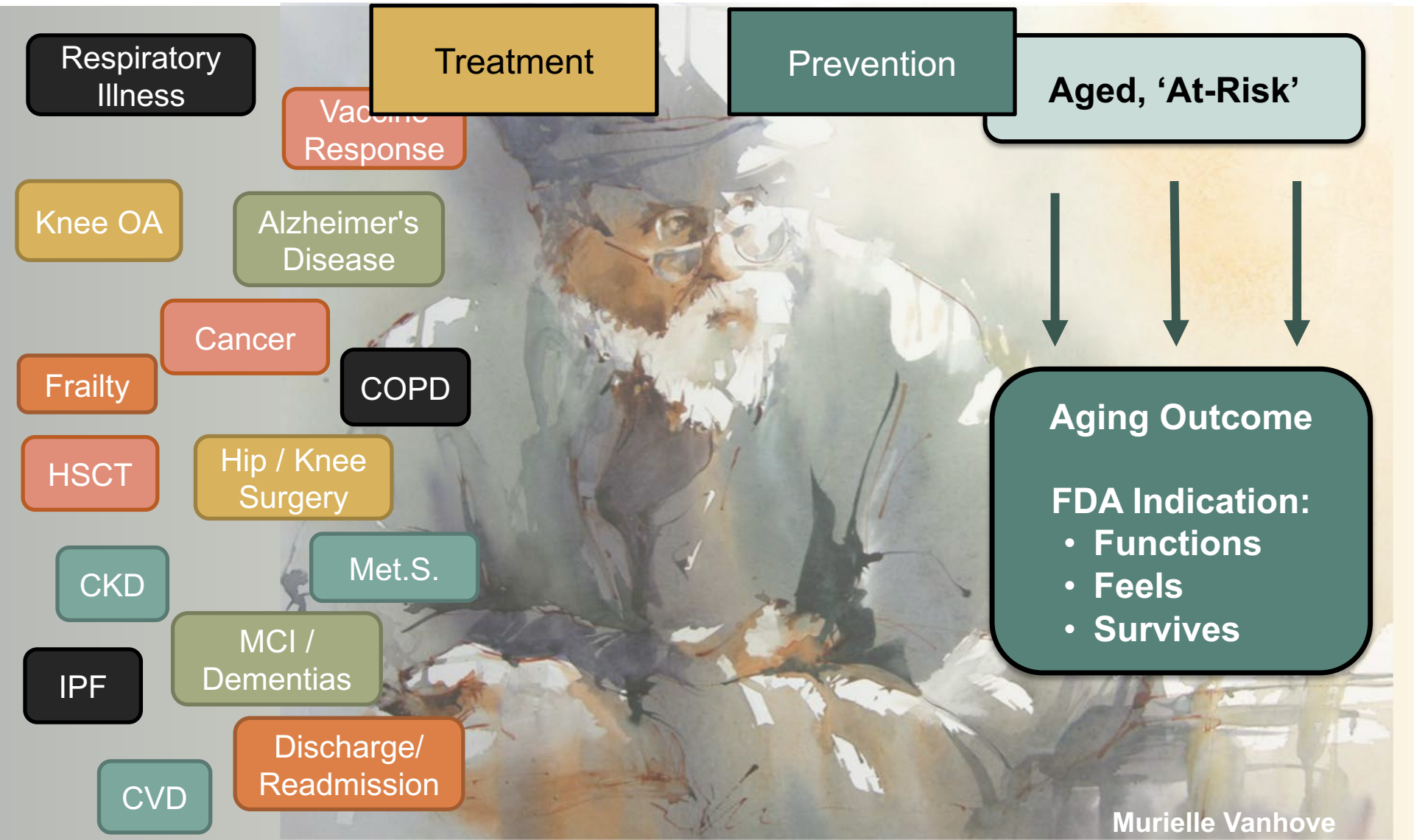
No biomarker is perfect, but some are useful.

Embrace feasible biomarker plans that include:

- Targeted biomarker panels and multivariable composites
- Data-intensive platforms: "omics"
- Biobanking: longitudinal collections

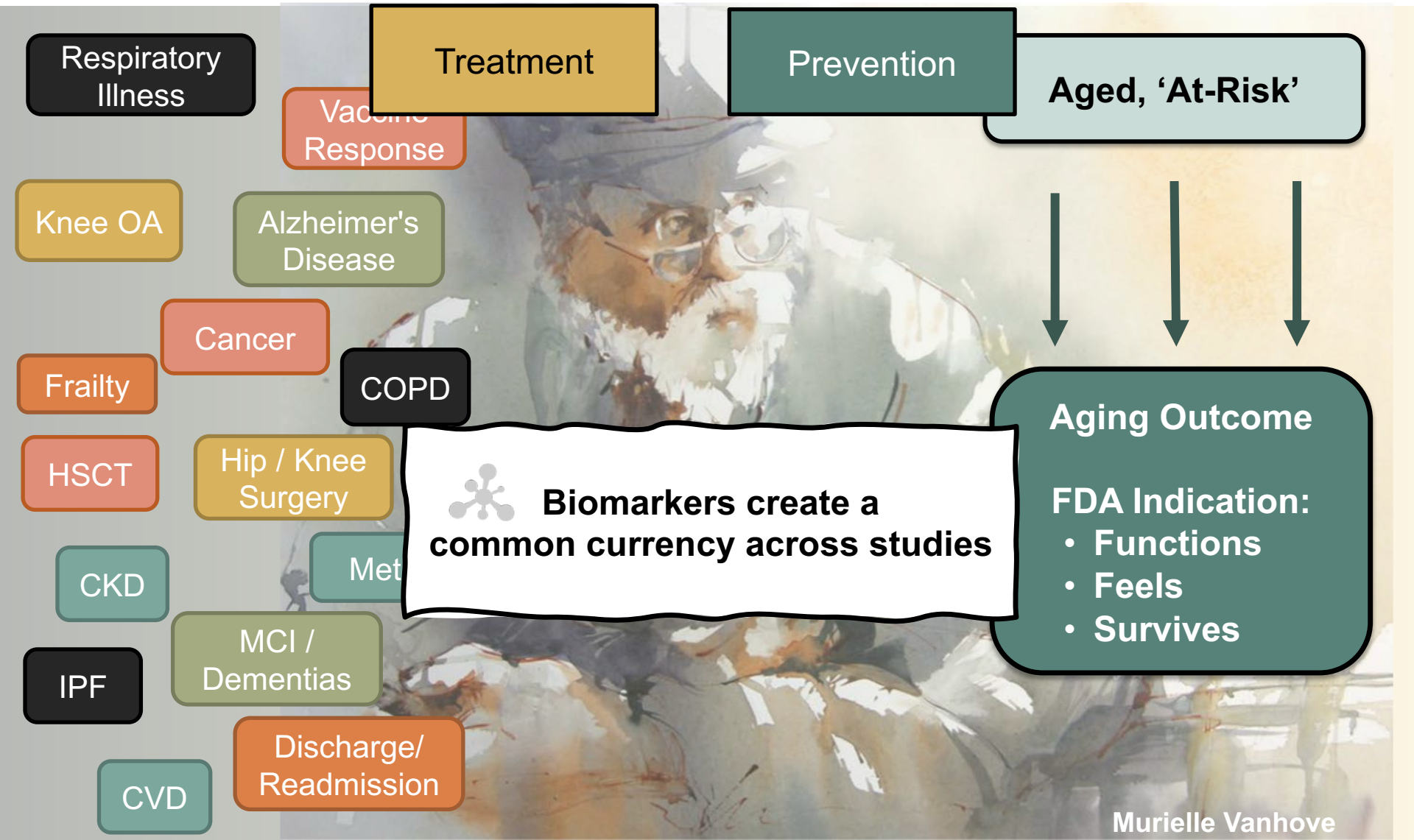
Geroscience and Interventions

Age-Related Disease Trials & Prevention Trials



Geroscience and Interventions

Age-Related Disease Trials & Prevention Trials



Example Case at Wake Forest: I-CARE

Infrastructure for Cancer and Aging Research Engagement

Example Case at Wake Forest: I-CARE

Infrastructure for Cancer and Aging Research Engagement

Newly funded grant at our WF Comprehensive Cancer Center (PI, Klepin)

A key gap: lack of characterization of the phenotypic and biologic heterogeneity of older adults with cancer.

Innovation: A new tool, an electronic record frailty index (eFI), can capture routine measures in EHR that is predictive of hospitalization and survival in an older adult primary care population.

Overall Goals:

1) Develop and evaluate a novel cancer-adapted eFI (eFI-cancer), and
2) Correlate with geriatric assessment measures, patient reported outcomes, and biomarkers of aging.

Example Case at Wake Forest: I-CARE

Infrastructure for Cancer and Aging Research Engagement

Overall Goals: (PI, Klepin)

1) Develop and evaluate a novel cancer-adapted eFI, and
2) Correlate with geriatric assessment measures, patient reported outcomes, and biomarkers of aging.

Heidi: "Jamie – What biomarker should we use to make it 'geroscience-y'?"

- **Unstated #1)** use only blood or biofluids collected during clinical visit.
- **Unstated #2)** we have almost no budget for special processing, live cells, or data-intensive measures. So biomarkers must be cheap or use stored blood so that we can apply for get a second grant to pay for more measurements.
- **Unstated #3)** Collaborate! Team science approach is essential.

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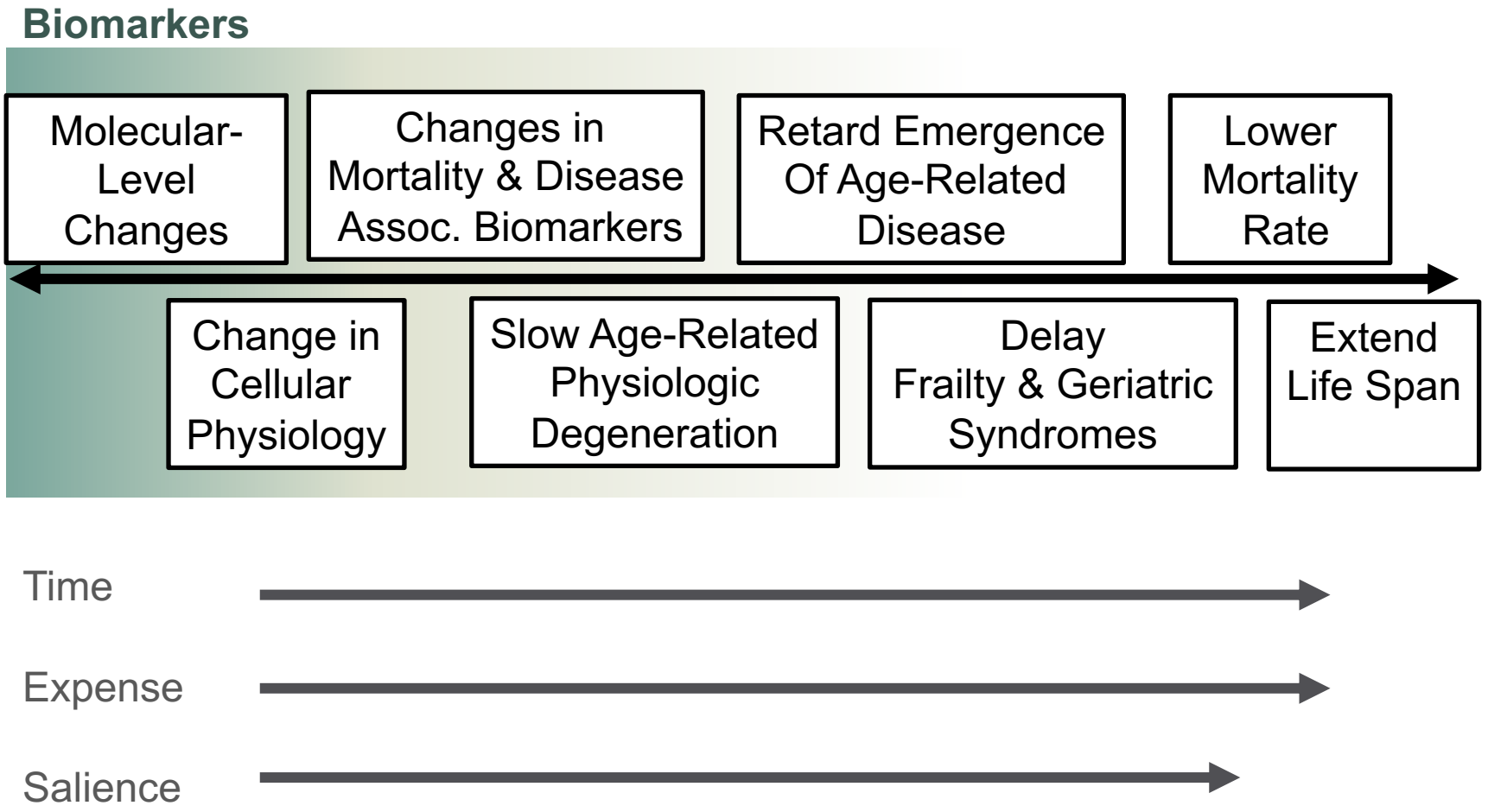
Geroscience: Biomarkers and Evaluation Continuum

From Biologic Mechanisms to Age-Related Disease



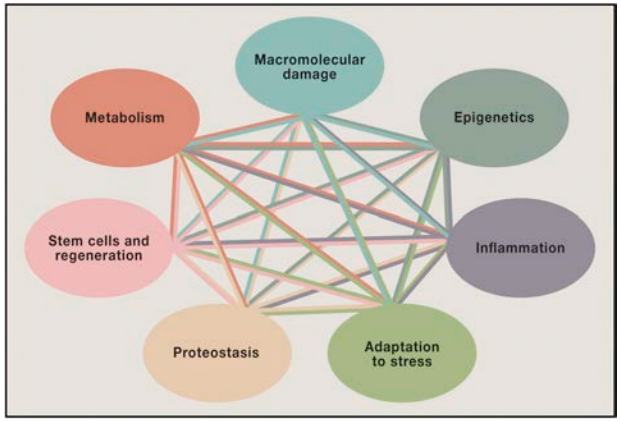
Kritchevsky, Justice. *JGMS* (2020) 75(1): 99–101.

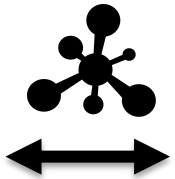
What is a Biomarker?

Objective measurement that reflects an interaction between a biologic system and a potential hazard.

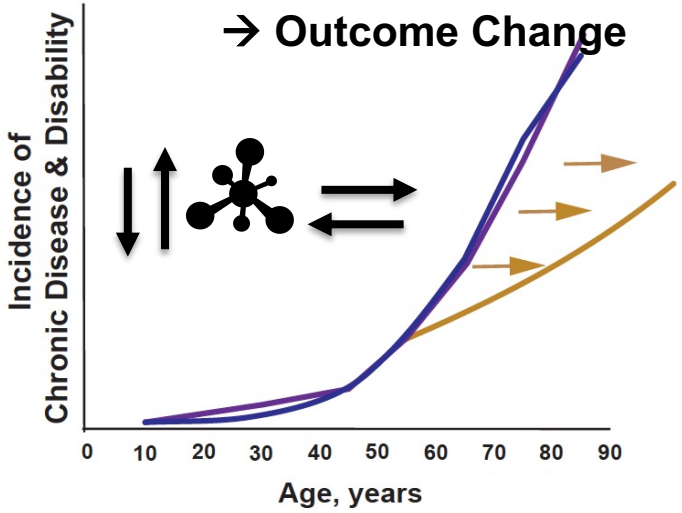
1) Indicator of normal or pathogenic process
2) Measure response to an intervention

Reflects Underlying Biology





Biomarker Change → Outcome Change



Biomarkers of biological pillars or hallmarks of aging

Challenges: validation, access to tissues, instruments for measurement

Received: 9 July 2019 | Revised: 22 October 2019 | Accepted: 27 October 2019

DOI: 10.1111/acel.13080

REVIEW

Aging Cell WILEY

Measuring biological aging in humans: A quest

Luigi Ferrucci[1] | Marta Gonzalez-Freire[1] | Elisa Fabbri[1,2] | Eleanor Simonsick[1] | Toshiko Tanaka[1] | Zenobia Moore[1] | Shabnam Salimi[3] | Felipe Sierra[4] | Rafael de Cabo[1]

The Journal of Frailty & Aging
Volume 10, Number 3, 2021

SPECIAL ARTICLE

IDENTIFYING BIOMARKERS FOR BIOLOGICAL AGE: GEROSCIENCE AND THE ICFSR TASK FORCE

N.K. LEBRASSEUR[1], R. DE CABO[2], R. FIELDING[3], L. FERRUCCI[4], L. RODRIGUEZ-MANAS[5], J. VIÑA[6], B. VELLAS[7]

Biomarkers of biological pillars or hallmarks of aging

What can be measured using sample from blood draw?

Biological Aging	Measured using blood draw samples?
Genomic Instability	
Telomere Attrition	
Epigenetic	
Proteostasis	
Nutrient Sensing	
Mitochondrial	
Cellular Senescence	
Stem Cell Exhaustion	
Cell Communication	
Immune Aging	
Others: damage accum., transcriptome, etc.	

ready to be overwhelmed?

Biomarkers of biological pillars or hallmarks of aging

What can be measured using sample from blood draw?

Biological Aging	Measured using blood draw?	Stored or Fresh?
Genomic Instability	**Whole Blood**: Single-cell/ NGS, SNP analysis **PBMC**: DNA repair	Stored: DNA, WB, PBMC
Telomere Attrition	**Whole Blood**: telomere length **PBMC**: DNA damage response	Stored: DNA, WB, PBMC
Epigenetic	**Whole Blood**: DNA methylation **PBMC**: Histone acetylation	Stored: DNA, WB, PBMC
Proteostasis	**Blood**: autophagy markers, proteomics **PBMC**: autophagic flux (e.g. protein LC3B-II)	Stored: plasma, serum, cells
Nutrient Sensing	**Blood**: insulin, IGF-1 signaling **PBMC**: AMPK activation (phospho-Thr172), mTOR signaling	Stored: plasma, serum, cells Live Cells: AMPK activation
Mitochondrial	**Blood**: NAD+ metabolites, sirtuins, oxidative stress **PBMC**: mitochondrial respiration, mtDNA	Stored: WB, plasma, serum Fresh: mito resp.
Cellular Senescence	**Blood**: senescence associated secretory proteins **PBMC** subpops: expression of p16INK4a, p21, p53	Stored: plasma, serum, and isolated cell subpops
Stem Cell Exhaustion	**PBMC**: proliferative capacity	Fresh: Live cells (*in vitro*)
Cell Communication	**Blood**: chemokines, growth factors (shared with SASP)?, endocrine / hormone, etc. (catch-all?)	Stored: plasma, serum, cells
Immune Aging	**Blood:** cytokines, chemokines – (CXCL9) **PBMC:** immune age, iAge (see Sayed et al Nat Aging 2021)	Stored: plasma, serum, and isolated cell subpops Fresh: cells
Others: Damage, transcriptome, etc.	**Blood:** cell free DNA (cfDNA), exosomes, noncoding RNA **PBMC**: transcriptome (bulk, single-cell /nuc. RNAseq)	Stored: blood, cells (with RNA stabilizers)

NOTE: technology always improving!

Biomarkers & Translational Geroscience: I've collected blood… now what?

Measuring Biological Age

No biomarker is perfect, but some are useful.

Biomarkers & Translational Geroscience:
I've collected blood… now what?

Biological Age

Targeted Biomarkers:
Common Use or
Hallmarks / Pillars

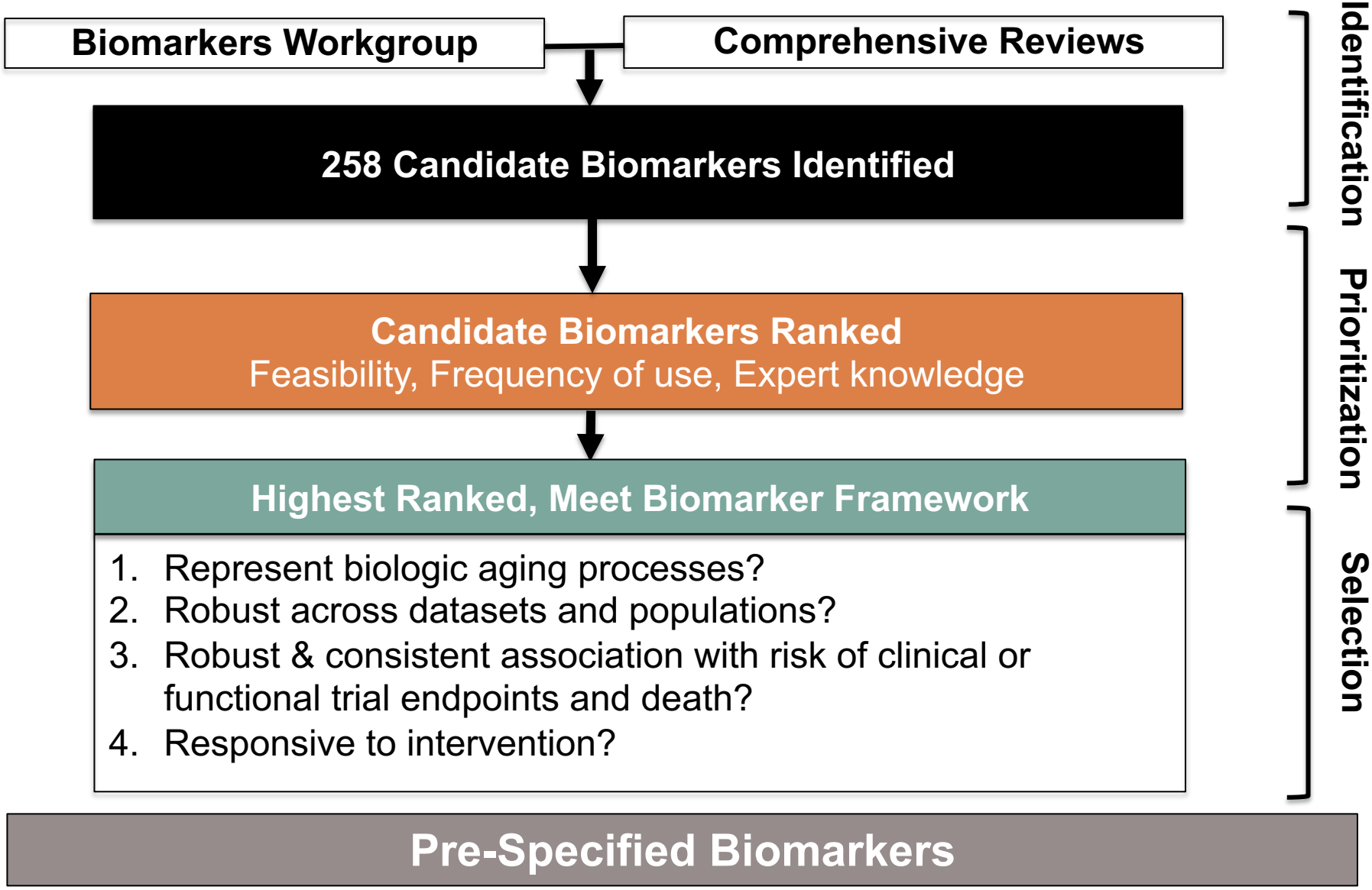
Molecular-Level Biomarkers

Deficit Accumulation Index
(or KDM Biological Age,
or Pace of Aging)

AI-Based Clocks

Resiliency Markers

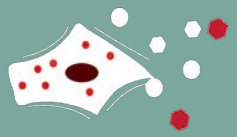
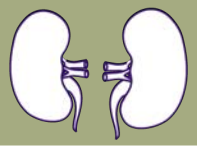
A priori literature-justified blood-based biomarkers:
expert opinion, experimental evidence, and epidemiologic literature



Justice *et al*. GeroScience 2018

Primary Finding: Paucity of blood-based biomarkers meet basic criteria in literature

Blood-based markers of biological & physiological aging processes

Biomarker	Underlying Biological Process & Role
IL-6, TNFR-I / II	 Inflammation & Intercellular Signaling
GDF15	 Stress Response & Mitochondria
Cystatin-C	 Kidney Aging
NT-proBNP	 Cardiovascular Health

Index

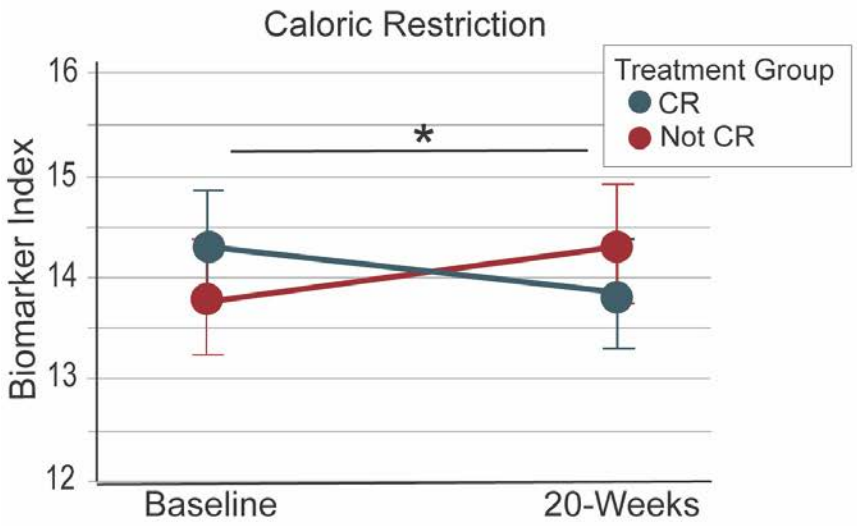
Exciting? No.
Useful? Yes.

Justice *et al*. GeroScience 2018

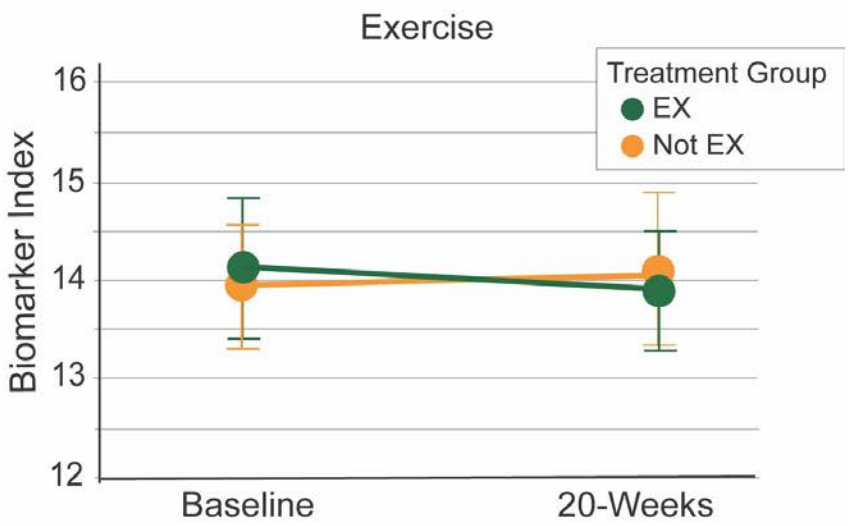
Blood-based markers of biological & physiological aging processes

Ancillary to SECRET Trial (2x2 Factorial Trial)
Aged 60+ yrs, Obese, HFpEF

Biomarker Levels → **Scored by Quintile Cutpoints** → **Sum Quintiles** → **Biomarker Index**



	Baseline	20-Weeks	p-value
CR	14.17± 0.58	13.80 ± 0.58	
Not CR	13.79 ± 0.58	14.23 ± 0.58	0.05



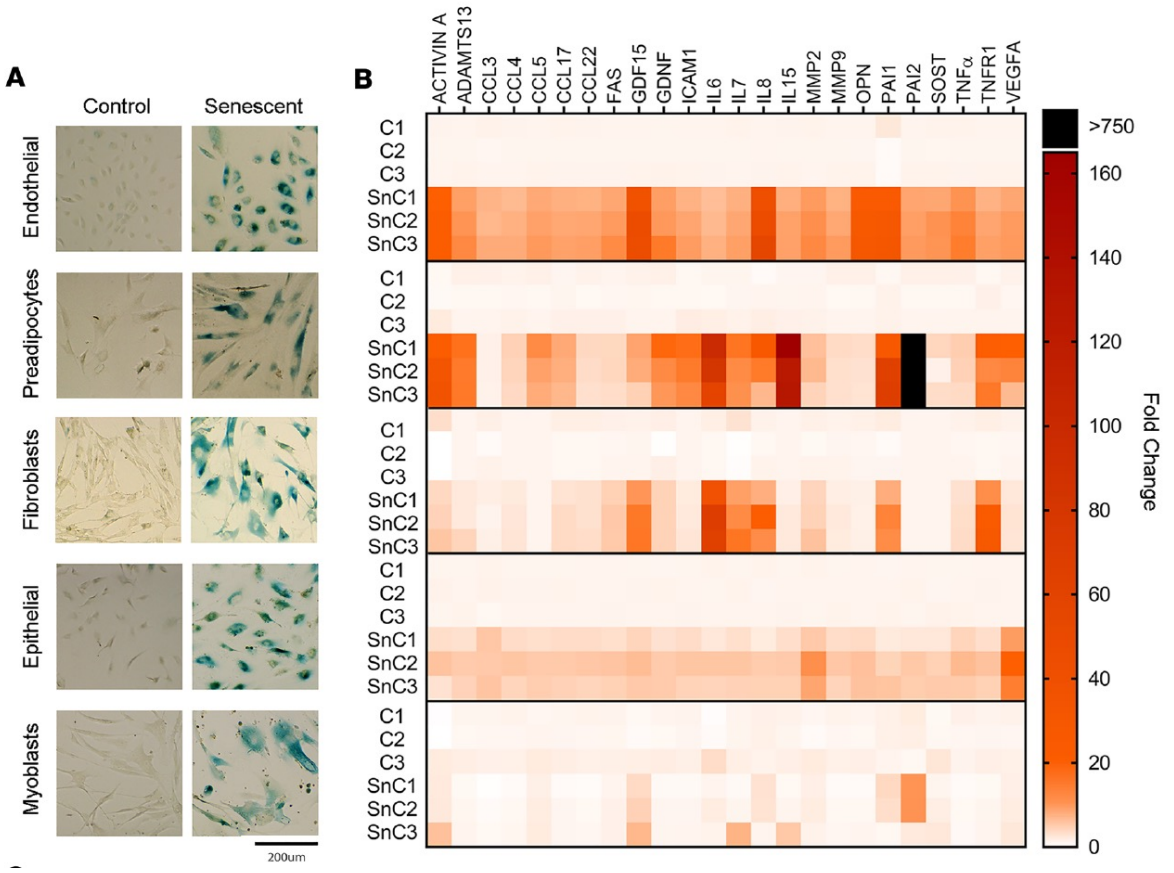
	Baseline	20-Weeks	p-value
EX	14.06 ± 0.58	13.95 ± 0.58	
Not EX	13.90 ± 0.59	14.07 ± 0.59	0.49

Justice *et al. Geroscience.* In Review

Markers of Hallmarks / Pillars: cell senescence

Example: identifying circulating markers

Induce senescence → **Measure secreted factors** → **Test associations with clinical data across:**



- Chronologic age
- Severe aortic stenosis
- Ovarian cancer

↓

Panel of 'SASP' Factors:

- GDF15
- TNFR superfamily 6 (FAS)
- TNF receptor 1 (TNFR1)
- Osteopontin (OPN)
- ACTIVIN A
- Chemokine (C-C motif) ligand 3 (CCL3)
- IL-15

Schafer *et al*. J Clin Invest. 5(12):e133668 (2020)

Biomarkers & Translational Geroscience:
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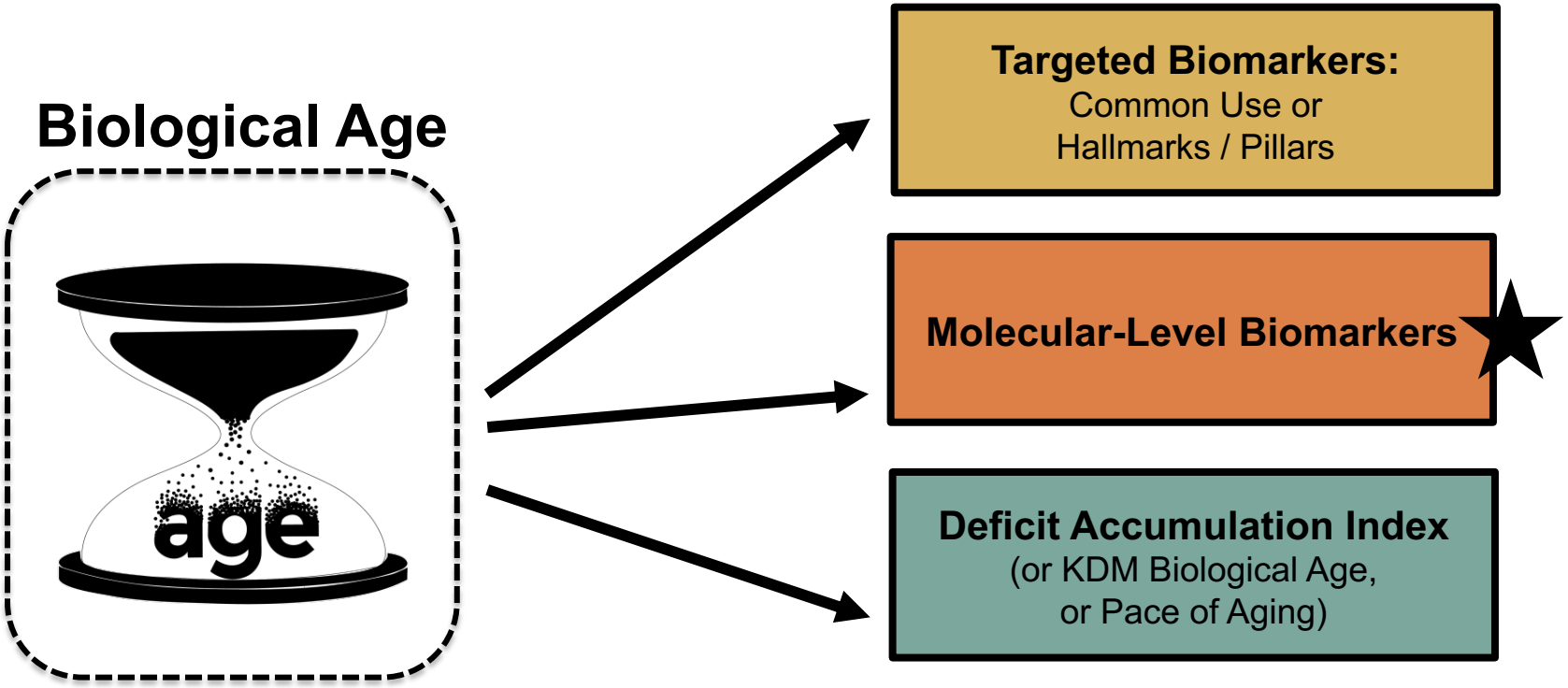


SASP ATLAS

Senescence Associated Secretory Phenotype.

A PROTEOMIC ATLAS OF SENESCENCE-ASSOCIATED SECRETOMES FOR AGING BIOMARKER DEVELOPMENT

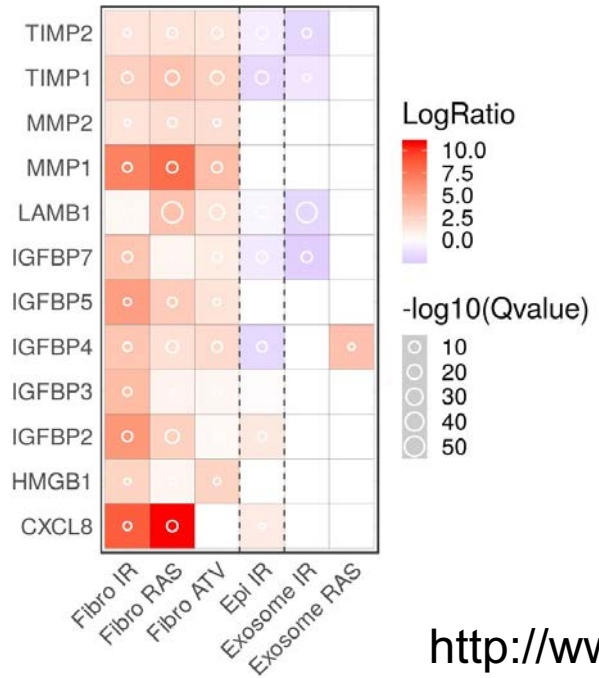
Nathan Basisty [1], Abhijit Kale [1], Ok Hee Jeon [1], Chisaka Kuehnemann [1], Therese Payne [1], Chirag Rao [1], Anja Holtz [1], Samah Shah [1], Vagisha Sharma [2], Luigi Ferrucci [3], Judith Campisi [1, 4], Birgit Schilling [**1]

SASP Atlas

Genes

IGFBP5
IGFBP7
IGFBP2
IGFBP3
IGFBP4
CXCL1
CXCL8
HMGB1
MMP1
MMP2
LAMB1
TIMP1
TIMP2

Download CSV

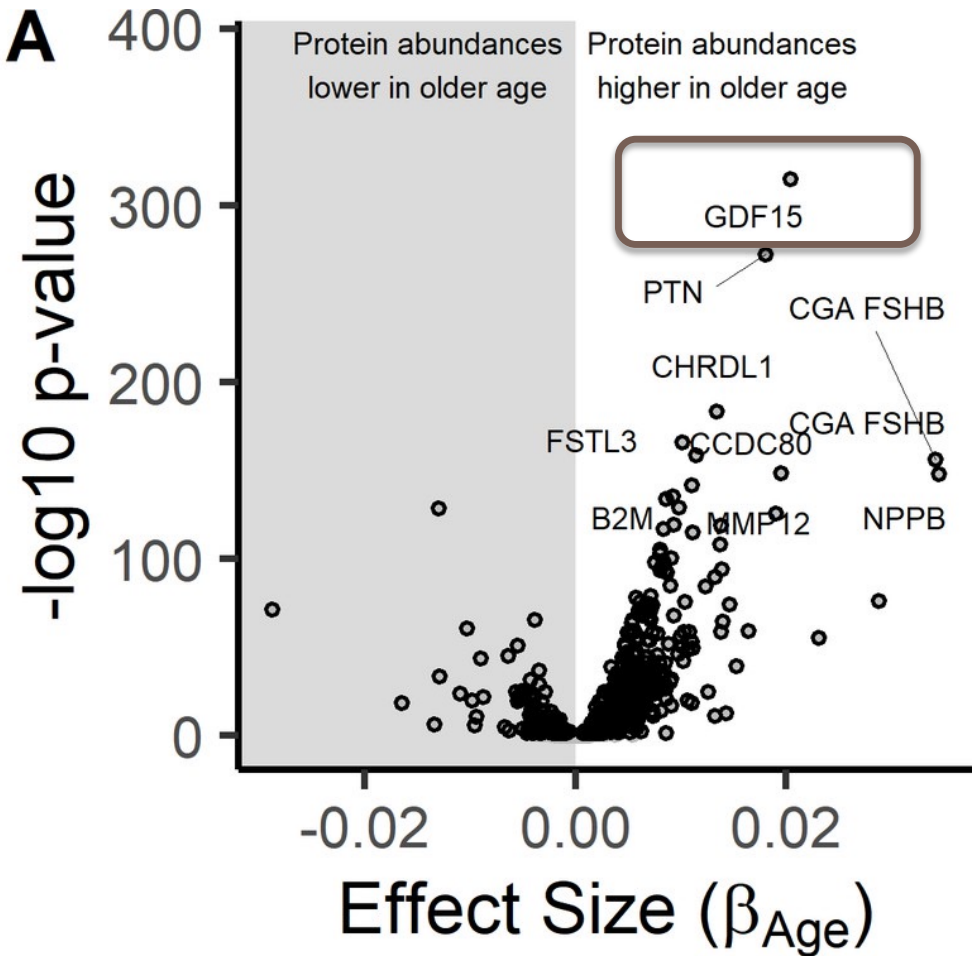


http://www.saspatlas.com/

Biomarkers & Translational Geroscience

Biomarker discovery

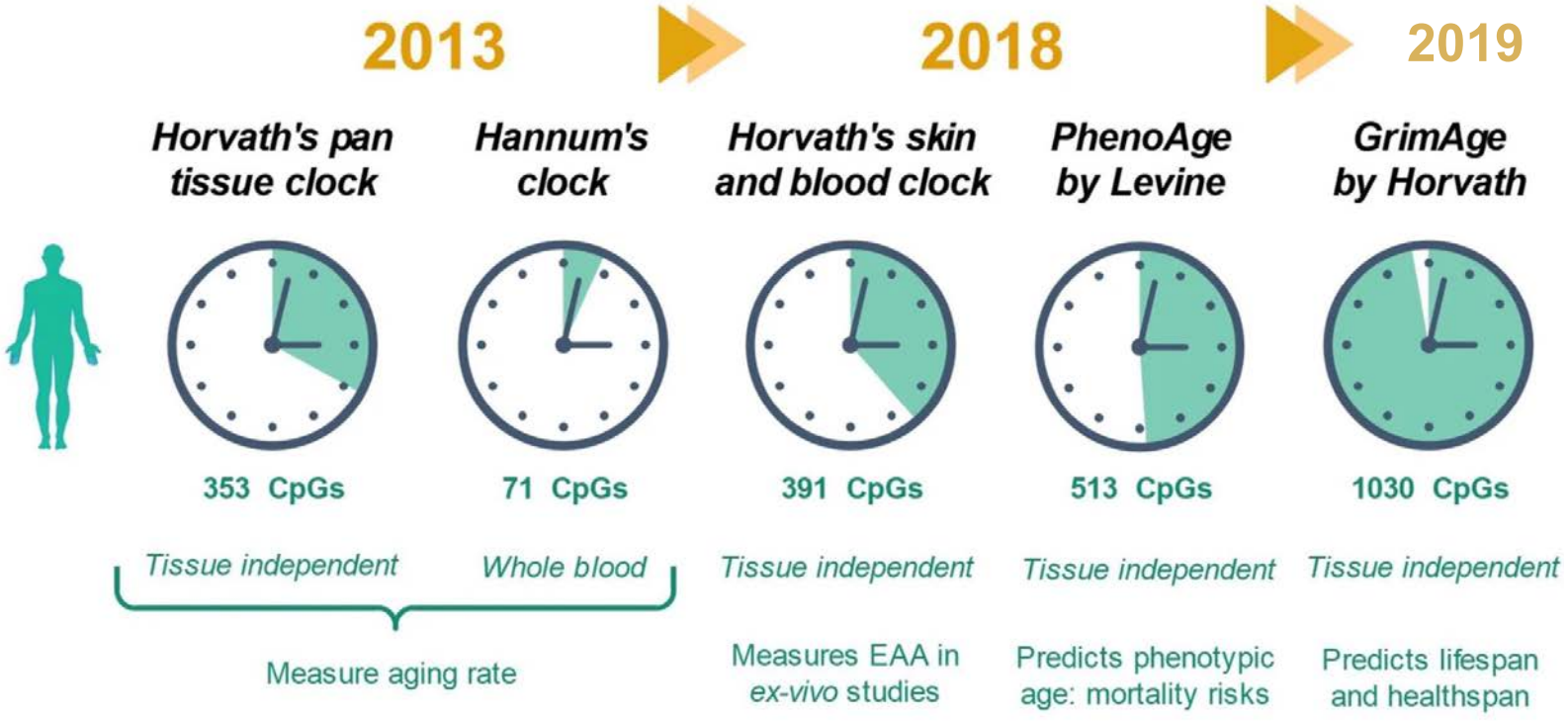
651 of 1301 proteins associated with chronological age in InCHIANTI



Tanaka *et al* eLife (2020)

REVIEW Open Access

Wandering along the epigenetic timeline



Epigenetic clocks discussed in this review. EAA: epigenetic age acceleration

adapted from Topart, Werner, Arimondo. *Clin Epigenet* **12,** 97 (2020).

Biomarkers & Translational Geroscience:
I've collected blood… now what?

Biological Age

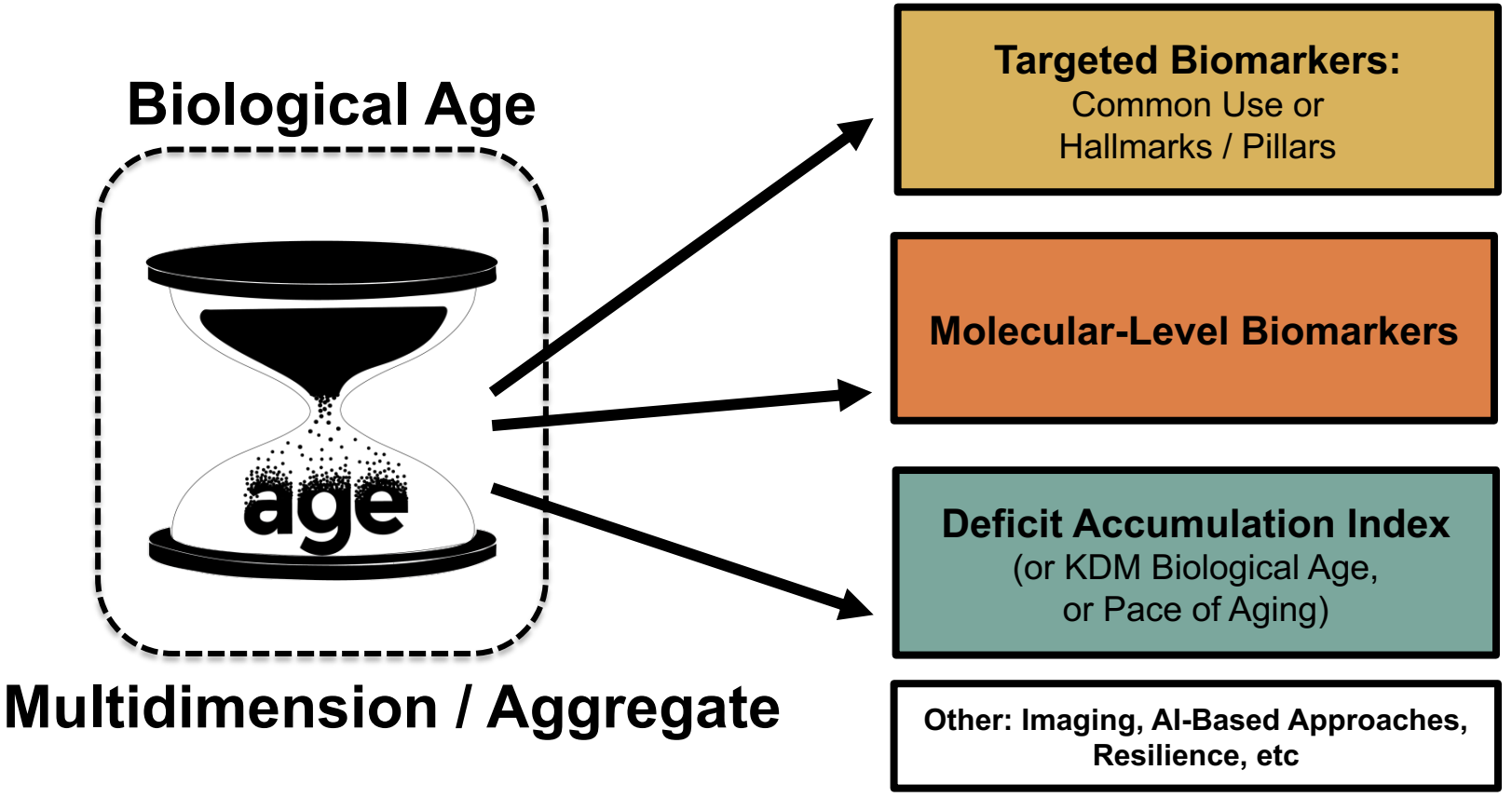
Targeted Biomarkers:
Common Use or
Hallmarks / Pillars

Molecular-Level Biomarkers

Deficit Accumulation Index
(or KDM Biological Age,
or Pace of Aging)

- Use clinical labs and routine measures.
- Newest - most exciting models - include longitudinal assessments.

Biomarkers & Translational Geroscience:
I've collected blood… now what?



Specimen and Data Repository:
Include other samples, longitudinal assessment!

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Thank you!

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