Biomarkers & Translational Geroscience: I’ve collected blood... now what?

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Assistant Professor, Internal Medicine, Gerontology and Geriatrics
Sticht Center on Healthy Aging and Alzheimer’s Prevention (CHAAP)
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
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

Treatment
Prevention

Aged, ‘At-Risk’

Aging Outcome

FDA Indication:
• Functions
• Feels
• Survives

Respiratory Illness
Knee OA
Alzheimer's Disease
Cancer
COPD
Hip / Knee Surgery
Met.S.
MCI / Dementias
Discharge/Readmission
CVD
IPF
HSCT

Murielle Vanhove
Biomarkers create a common currency across studies
Example Case at Wake Forest: I-CARE
Infrastructure for Cancer and Aging Research Engagement

Heidi Diana Klepin, MD
Professor, Hematology and Oncology
Research Interests
Geriatric Oncology

2013 Beeson Scholar!
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.
No biomarker is perfect, but some are useful.

Embrace feasible biomarker plans that include:

• Targeted biomarker panels and multivariable composites
• Data-intensive platforms: “omics”
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Geroscience: Biomarkers and Evaluation Continuum
From Biologic Mechanisms to Age-Related Disease

Biomarkers

- Molecular-Level Changes
- Changes in Mortality & Disease Assoc. Biomarkers
- Retard Emergence Of Age-Related Disease
- Lower Mortality Rate

- Change in Cellular Physiology
- Slow Age-Related Physiologic Degeneration
- Delay Frailty & Geriatric Syndromes
- Extend Life Span

Time
Expense
Salience

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

Measuring biological aging in humans: A quest

Luigi Ferrucci¹ | Marta Gonzalez-Freire¹ | Elisa Fabbri¹,² | Eleanor Simonsick¹ |
Toshiko Tanaka¹ | Zenobia Moore¹ | Shabnam Salimi² | Felipe Sierra⁴ | Rafael de Cabo¹

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

N.K. LEBRASSEUR¹, R. DE CABO², R. FIELDING³, L. FERRUCCI⁴, L. RODRIGUEZ-MANAS⁵,
J. VIÑA⁶, B. VELLAS⁷
# Biomarkers of biological pillars or hallmarks of aging

What can be measured using sample from blood draw?

<table>
<thead>
<tr>
<th>Biological Pillars or Hallmarks of Aging</th>
<th>Measured using blood draw samples?</th>
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</thead>
<tbody>
<tr>
<td>Genomic Instability</td>
<td></td>
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<tr>
<td>Telomere Attrition</td>
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<tr>
<td>Epigenetic</td>
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<td>Proteostasis</td>
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<td>Nutrient Sensing</td>
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<td>Mitochondrial</td>
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<td>Cellular Senescence</td>
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<td>Stem Cell Exhaustion</td>
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<td>Cell Communication</td>
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<td>Immune Aging</td>
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<tr>
<td>Others: damage accum., transcriptome, etc.</td>
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</tbody>
</table>

*ready to be overwhelmed?*
<table>
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<tr>
<th>Biological Aging</th>
<th>Measured using blood draw?</th>
<th>Stored or Fresh?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomic Instability</td>
<td><strong>Whole Blood</strong>: Single-cell/NGS, SNP analysis&lt;br&gt;<strong>PBMC</strong>: DNA repair</td>
<td>Stored: DNA, WB, PBMC</td>
</tr>
<tr>
<td>Telomere Attrition</td>
<td><strong>Whole Blood</strong>: telomere length&lt;br&gt;<strong>PBMC</strong>: DNA damage response</td>
<td>Stored: DNA, WB, PBMC</td>
</tr>
<tr>
<td>Epigenetic</td>
<td><strong>Whole Blood</strong>: DNA methylation&lt;br&gt;<strong>PBMC</strong>: Histone acetylation</td>
<td>Stored: DNA, WB, PBMC</td>
</tr>
<tr>
<td>Proteostasis</td>
<td><strong>Blood</strong>: autophagy markers, proteomics&lt;br&gt;<strong>PBMC</strong>: autophagic flux (e.g. protein LC3B-II)</td>
<td>Stored: plasma, serum, cells</td>
</tr>
<tr>
<td>Nutrient Sensing</td>
<td><strong>Blood</strong>: insulin, IGF-1 signaling&lt;br&gt;<strong>PBMC</strong>: AMPK activation (phospho-Thr172), mTOR signaling</td>
<td>Stored: plasma, serum, cells&lt;br&gt;Live Cells: AMPK activation</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td><strong>Blood</strong>: NAD+ metabolites, sirtuins, oxidative stress&lt;br&gt;<strong>PBMC</strong>: mitochondrial respiration, mtDNA</td>
<td>Stored: WB, plasma, serum&lt;br&gt;Fresh: mito resp.</td>
</tr>
<tr>
<td>Cellular Senescence</td>
<td><strong>Blood</strong>: senescence associated secretory proteins&lt;br&gt;<strong>PBMC</strong> subpops: expression of p16INK4a, p21, p53</td>
<td>Stored: plasma, serum, and isolated cell subpops</td>
</tr>
<tr>
<td>Stem Cell Exhaustion</td>
<td><strong>PBMC</strong>: proliferative capacity</td>
<td>Fresh: Live cells <em>(in vitro)</em></td>
</tr>
<tr>
<td>Cell Communication</td>
<td><strong>Blood</strong>: chemokines, growth factors (shared with SASP)?, endocrine / hormone, etc. (catch-all?)</td>
<td>Stored: plasma, serum, cells</td>
</tr>
<tr>
<td>Immune Aging</td>
<td><strong>Blood</strong>: cytokines, chemokines – (CXCL9)&lt;br&gt;<strong>PBMC</strong>: immune age, iAge (see Sayed et al Nat Aging 2021)</td>
<td>Stored: plasma, serum, and isolated cell subpops&lt;br&gt;Fresh: cells</td>
</tr>
<tr>
<td>Others: Damage, transcriptome, etc.</td>
<td><strong>Blood</strong>: cell free DNA (cfDNA), exosomes, noncoding RNA&lt;br&gt;<strong>PBMC</strong>: transcriptome (bulk, single-cell /nuc. RNAseq)</td>
<td>Stored: blood, cells (with RNA stabilizers)</td>
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*NOTE: technology always improving!*
No biomarker is perfect, but some are useful.
Biomarkers & Translational Geroscience: I’ve collected blood… now what?

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

**Identification**

**Biomarkers Workgroup** → **Comprehensive Reviews**

258 Candidate Biomarkers Identified

**Candidate Biomarkers Ranked**
- Feasibility, Frequency of use, Expert knowledge

**Prioritization**

**Highest Ranked, Meet Biomarker Framework**

1. Represent biologic aging processes?
2. Robust across datasets and populations?
3. Robust & consistent association with risk of clinical or functional trial endpoints and death?
4. Responsive to intervention?

**Selection**

**Pre-Specified Biomarkers**

Justice et al. GeroScience 2018
**Primary Finding:** Paucity of blood-based biomarkers meet basic criteria in literature

<table>
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<tr>
<th>Biomarker</th>
<th>Underlying Biological Process &amp; Role</th>
</tr>
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<tbody>
<tr>
<td>IL-6, TNFR-I / II</td>
<td>Inflammation &amp; Intercellular Signaling</td>
</tr>
<tr>
<td>GDF15</td>
<td>Stress Response &amp; Mitochondria</td>
</tr>
<tr>
<td>Cystatin-C</td>
<td>Kidney Aging</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Cardiovascular Health</td>
</tr>
</tbody>
</table>


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

Exercise
Caloric Restriction
5-Months
EX + CR
Control

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

Caloric Restriction
Treatment Group
- CR
- Not CR

Ex 14.06 ± 0.58
Not EX 13.95 ± 0.58

Exercise
Treatment Group
- EX
- Not EX

CR 14.17 ± 0.58
Not CR 13.79 ± 0.58

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

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Targeted Biomarkers: Common Use or Hallmarks / Pillars

Molecular-Level Biomarkers

Deficit Accumulation Index (or KDM Biological Age, or Pace of Aging)
A PROTEOMIC ATLAS OF SENESCEENCE-ASSOCIATED SECRETOMES FOR AGING BIOMARKER DEVELOPMENT

Nathan Basisty¹, Abhijit Kale¹, Ok Hee Jeon¹, Chisaka Kuehnemann¹, Therese Payne¹, Chirag Rao¹, Anja Holtz¹, Samah Shah¹, Vagisha Sharma², Luigi Ferrucci³, Judith Campisi¹,⁴, Birgit Schilling**¹

SASP Atlas

http://www.saspatlas.com/
651 of 1301 proteins associated with chronological age in InCHIANTI

Biomarker discovery

Tanaka et al eLife (2020)
Wandering along the epigenetic timeline

- **2013**: Horvath's pan tissue clock
  - 353 CpGs
  - Tissue independent
  - Measures aging rate

- **2018**: Horvath's skin and blood clock
  - 391 CpGs
  - Tissue independent
  - Measures EAA in ex-vivo studies

- **2019**: PhenoAge by Levine
  - 513 CpGs
  - Tissue independent
  - Predicts phenotypic age: mortality risks

- **2019**: GrimAge by Horvath
  - 1030 CpGs
  - Tissue independent
  - Predicts lifespan and healthspan

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

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?

- Biological Age
- Targeted Biomarkers: Common Use or Hallmarks / Pillars
- Molecular-Level Biomarkers
- Deficit Accumulation Index (or KDM Biological Age, or Pace of Aging)
- Other: Imaging, AI-Based Approaches, Resilience, etc

Multidimension / Aggregate

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

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