Quantification of Biological Aging

Implications for Clinical Trials of Therapies to Extend Healthy Lifespan

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Outline

Introduction
Biological aging is a treatment target for healthspan extension

Part 1. Human trials of geroprotectors
Challenges & opportunities

Part 2. Quantification of biological aging in young adults

Part 3. Testing biological aging in a geroprotector trial

Conclusion
The global population is aging and strategies are needed to extend healthy lifespan.
Aging itself is a leading risk factor for many diseases

Aging is a biological process a gradual and progressive decline in system integrity.

Kennedy et al. 2014 Cell

Lopez-Otin et al. 2013 Cell
Geroprotective Intervention?
Evolving theoretical models of aging

Evolving theoretical models of aging

Disease → Disability/Frailty → Death

Belsky et al. 2015 PNAS
Moffitt et al. 2016 J Geron A Med Sci
Evolving theoretical models of aging

Disease $\rightarrow$ Disability/Frailty $\rightarrow$ Death

Early-life Adversity

Belsky et al. 2015 PNAS
Moffitt et al. 2016 J Geron A Med Sci
Evolving theoretical models of aging

Disease → Disability/Frailty → Death

Early-life Adversity

Accelerated Aging

Belsky et al. 2015 PNAS
• Exposures accumulate from early life
• Changes to physiology precede disease onset
• Preventive intervention must begin early

Belsky 2017
Exposures accumulate from early life
Changes to physiology precede disease onset
Preventive intervention must begin early
• Exposures accumulate from early life
• Changes to physiology precede disease onset
• Preventive intervention must begin early
Outline

**Introduction**
Biological aging is a treatment target for healthspan extension

**Part 1. Human trials of geroprotectors**
Challenges & opportunities

**Part 2. Quantification of biological aging in young adults**

**Part 3. Testing biological aging in a geroprotector trial**

**Conclusion**
Ideal Geroprotector Trial Design

Belsky 2017
Ideal Geroprotector Trial Design

Belsky 2017
Ideal Geroprotector Trial Design

Belsky 2017
Ideal Geroprotector Trial Design

Months

Healthspan Extension

Decades

Healthspan Extension

Belsky 2017
**Problem:** Healthspan follow-up from midlife prevention takes too long

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**Decades of the Human Life Course**

<table>
<thead>
<tr>
<th>1\textsuperscript{st}</th>
<th>2\textsuperscript{nd}</th>
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</thead>
</table>

- **Early-life Adversity**
- **Accelerated Aging**
- **Disease \rightarrow Disability/Frailty \rightarrow Death**

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Belsky 2017
Solution: Measure aging processes as healthspan surrogate endpoint for trial.
Alternative Geroprotector Trial Design

Years

Control

Normal Pace of Aging

Rx

Slower Pace of Aging

Belsky 2017
Alternative Geroprotector Trial Design

- Years

- Control
- Normal Pace of Aging
- Normal Pace of Aging
- Slower Pace of Aging
- Treatment

- Biological Age
- Y1
- Y2
- Y3

- Control
- Slowed Pace of Aging
Alternative Geroprotector Trial Design

---

Belsky 2017
Part 1 Summary

- Biological aging may be a modifiable risk factor for age-related disease and disability
- New (and old) therapies to slow biological aging now have proof-of-concept in animal models, and more are on the way
- Translation of midlife geroprotective interventions to humans faces a barrier – follow-up takes too long
- Translation to humans can be accelerated using study designs that measure biological aging as a surrogate endpoint for healthspan extension
Introduction
Biological aging is a treatment target for healthspan extension

Part 1. Human trials of geroprotectors
Challenges & opportunities

Part 2. Quantification of biological aging in young adults

Part 3. Testing biological aging in a geroprotector trial

Conclusion
Dunedin, New Zealand
## The Dunedin Longitudinal Study

*Percent assessed, of those who were alive at each age.*

<table>
<thead>
<tr>
<th>Age</th>
<th>Year</th>
<th>Number</th>
<th>Percent*</th>
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</table>
Can we measure the rate of aging in young, healthy humans?

<table>
<thead>
<tr>
<th>Decades of the Human Life Course</th>
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<tbody>
<tr>
<td>1\text{st}</td>
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<tr>
<td>Early-life Adversity</td>
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</table>

\textit{Accelerated Aging}
The Pace of Aging

Aging is characterized by a gradual and progressive decline in system integrity

The rate of aging can be inferred from the rate of decline in integrity across multiple organ systems

Belsky et al. 2015 PNAS
The Pace of Aging

Belsky et al. 2015 PNAS
The Pace of Aging

Belsky et al. 2015 PNAS
The Pace of Aging

Belsky et al. 2015 PNAS
The Pace of Aging

Belsky et al. 2015 PNAS
The Pace of Aging

Belsky et al. 2015 PNAS
Cross-sectional measurement of biological age

Belsky et al. 2015 PNAS

Klemera-Doubal Method Biological Age

\[ B_{EC} = \frac{\sum_{j=1}^{m} (x_j - q_j) \frac{k_j}{s_j} + \frac{C}{s_B}}{\sum_{j=1}^{m} \left( \frac{k_j}{s_j} \right)^2 + \frac{1}{s_B}} \]

Albumin
Alkaline Phosphatase
BUN
Creatinine
CRP
HbA1c
SBP
Total cholesterol
CMV
FEV1

Klemera & Doubal 2006 Mech Ag Dev

Levine 2013 J Geron A
Cross-sectional measurement reflects recent rate of change

Klemera-Doubl Method Biological Age

\[ B_{EC} = \frac{\sum_{j=1}^{m} (x_j - q_j) \frac{k_j}{s_j} + \frac{C}{s_B}}{\sum_{j=1}^{m} \left( \frac{k_j}{s_j} \right)^2 + \frac{1}{s_B}} \]

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Belsky et al. 2015 PNAS

Klemera & Doubal 2006 Mech Ag Dev

Levine 2013 J Geron A
Does variation in rate of aging predict signs of aging?

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**Early-life Adversity**

**Accelerated Aging**

Disease → Disability/Frailty → Death
Faster aging predicts poor physical function

Belsky et al. 2015 PNAS
Faster aging predicts declining brain health

Belsky et al. 2015 PNAS
Faster aging predicts subjective signs

1. In general, would you say your health is:

<table>
<thead>
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<th>Health Rating</th>
<th>Value</th>
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<tbody>
<tr>
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<tr>
<td>Very good</td>
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<tr>
<td>Fair</td>
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<tr>
<td>Poor</td>
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Belsky et al. 2015 PNAS
Part 2 Interim Summary

- The rate of aging can be measured in healthy young adults.
  Repeated-measures clinical-exam and blood-test data can track aging-related changes decades in advance of disease onset.
- The aging rate in healthy young adults is already variable.
- A faster rate of aging correlates with deficits in physical and cognitive function and subjective signs of aging.
Do early-life risks accelerate the page of aging?

Belsky et al. 2017
Aging Cell
Decades of the Human Life Course

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Early-life Adversity  Accelerated Aging  Disease → Disability/Frailty → Death

Belsky et al. 2017
Aging Cell
## Life-Course Design

### Decades of the Human Life Course

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**Belsky et al. 2017**

**Aging Cell**
Belsky et al. 2017
Aging Cell
Midlife pace of aging has origins in childhood

Belsky et al. 2017
Aging Cell
## Retrospective Personal-History Risk Assessment for Screening Geroprotector Trial Participants

<15min battery
5-point scale

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measurement</th>
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<tbody>
<tr>
<td>Familial Longevity</td>
<td>Grandparent &gt; 80y (life expectancy)</td>
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<tr>
<td>Childhood Social Class</td>
<td>Low (e.g. low-skill occupation)</td>
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<tr>
<td>ACEs</td>
<td>CDC ACE Inventory</td>
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<tr>
<td>Childhood IQ</td>
<td>Low education</td>
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<tr>
<td>Childhood Self-Control</td>
<td>5-item Nurse rating</td>
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</table>

Belsky et al. 2017
Aging Cell
### Personal-history risk assessment identifies fast-aging group

<table>
<thead>
<tr>
<th>Pace of Aging</th>
<th>Cohort (N=686)</th>
<th>Prescription Register (N=686)</th>
<th>Hospital Admission (N=183)</th>
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<tbody>
<tr>
<td></td>
<td>No Risks</td>
<td>1 Risk</td>
<td>2+ Risks</td>
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<td>Fast</td>
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<td>Normal</td>
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<tr>
<td>Slow</td>
<td>53</td>
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Belsky et al. 2017
Aging Cell
Part 2 Summary

- The rate of aging can be measured in healthy young adults
  Repeated-measures clinical-exam and blood-test data can track aging-related changes decades in advance of disease onset
- The aging rate in healthy young adults is already variable
- A faster rate of aging correlates with deficits in physical and cognitive function and subjective signs of aging
- Midlife aging rate has origins in childhood
  Possible to screen participants to balance enrollment in geroprotector trials
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Conclusion
Alternative Geroprotector Trial Design

Control

Normal Pace of Aging

Slower Pace of Aging

Y1

Y2

Y3

Years

Biological Age

Control

Treatment

Normal Pace of Aging

Slowed Pace of Aging
N=145 Randomized to 25% CR (12% achieved)
N=75 Randomized to AL (2% CR on average)
Baseline 12mo 24mo

T1 T2 T3

Belsky et al. 2017 JGBS
Repeated measures of biological age

- Klemera-Doubal method Biological Age
- Homeostatic Dysregulation

Belsky et al. 2017 *JGBS*

Repeated measures of biological age:

- Albumin
- Alkaline Phosphatase
- BUN
- Creatinine
- CRP
- HbA1c (glucose)
- SBP
- Total cholesterol
- Uric Acid
- WBC

\[
B_{EC} = \frac{\sum_{j=1}^{m} (x_j - q_j)^2 + \frac{C}{n}}{\sum_{j=1}^{m} (k_j / s_j)^2 + \frac{1}{n}}
\]

\[
D_M(\bar{x}) = \sqrt{(\bar{x} - \bar{\mu})^T S^{-1} (\bar{x} - \bar{\mu})}
\]

Klemera & Doubal 2006 *Mech Ag Dev*
Levine 2013 *JGBS*
Cohen et al. 2013 *Mech Ag Dev*
Li et al. 2015 *Aging Cell*
Belsky et al. 2017 JGBS

Klemera-Doubal method Biological Age at baseline

Baseline

12mo

24mo

T1

T2

T3

Baseline 12mo 24mo
Baseline 12mo 24mo

T1 T2 T3

Change in KDM Biological Age (years)

Baseline 12-months 24-months

CALERIE Assessment

Belsky et al. 2017 JGBS
Part 3 Summary

• Moderate (~10%) CR slows the rate of biological aging as measured from physiology

• Implementation of biological aging measures within already-collected data from RCTs can advance validation efforts

• Long-term follow-up will be needed (and should be planned for)
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Conclusion
Conclusions

• Aging is a lifelong process with effects already manifest by midlife
• The midlife rate of aging is variable in apparently healthy adults

*Interventions to slow aging should begin early*

• The midlife rate of aging can be measured
• The midlife rate of aging can be modified (e.g. by CR)

*Geroprotector trials should consider the rate of change in biological age as a surrogate endpoint for healthspan extension*
Not all measures of aging measure the same thing

Belsky et al. AJE 2017
Not all measures of aging measure the same thing

<table>
<thead>
<tr>
<th>Telomere Shortness</th>
<th>353-CpG Clock</th>
<th>99-CpG Clock</th>
<th>71-CpG Clock</th>
<th>KDM Biological Age</th>
<th>Age-related Homeostatic Dysregulation</th>
<th>Pace of Aging 26-38</th>
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<tbody>
<tr>
<td>Effect-Size (Pearson r)</td>
<td>-0.3</td>
<td>-0.2</td>
<td>-0.1</td>
<td>0.0</td>
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Belsky et al. AJE 2017
Next Steps

• Refine measures to quantify biological aging
  *Critical validation is that rate of change predicts healthspan*

• Expand scope of intervention testing
  *Exercise trials and other lifestyle interventions are low hanging fruit*
  *But Rx is the frontier*
Thank You!