Genes, Aging, and Public Health

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New Orleans, LA
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There has been a 2-fold reduction in mortality at ages >70 in the past 50 years.

Fries, The Milbank Quarterly 2005

Infectious disease $\rightarrow$ chronic disease era

Vaupel et al., Science 1998
The older you are the longer you’ll live

![Graph showing life expectancy by age and gender](image-url)

Source: Social Security Administration (2010)
Graying of the U.S. population

United States - 2050

Population (in millions)
The “cost” of aging

### Forecasting Dependency of the Elderly Population

<table>
<thead>
<tr>
<th></th>
<th>Old-age dependency ratios (OADR)</th>
<th>Prospective OADR (POADR)</th>
<th>Adult disability dependency ratios (ADDR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switzerland*</td>
<td>0.27</td>
<td>0.41</td>
<td>0.48</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>0.23</td>
<td>0.36</td>
<td>0.52</td>
</tr>
<tr>
<td>Germany</td>
<td>0.33</td>
<td>0.48</td>
<td>0.63</td>
</tr>
<tr>
<td>France</td>
<td>0.28</td>
<td>0.44</td>
<td>0.51</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>0.27</td>
<td>0.36</td>
<td>0.41</td>
</tr>
<tr>
<td>Hungary</td>
<td>0.26</td>
<td>0.34</td>
<td>0.48</td>
</tr>
<tr>
<td>Italy</td>
<td>0.33</td>
<td>0.45</td>
<td>0.68</td>
</tr>
<tr>
<td>Japan*</td>
<td>0.35</td>
<td>0.55</td>
<td>0.78</td>
</tr>
<tr>
<td>Sweden</td>
<td>0.30</td>
<td>0.40</td>
<td>0.44</td>
</tr>
<tr>
<td>United States*</td>
<td>0.21</td>
<td>0.34</td>
<td>0.38</td>
</tr>
<tr>
<td>Average</td>
<td>0.28</td>
<td>0.41</td>
<td>0.53</td>
</tr>
</tbody>
</table>

* A country not in the EU-SILC survey.

Sanderson & Scherbov, Science 2010
Physiologic aging

Transition from premature to natural death

Fries, The Milbank Quarterly 2005
Average trajectories of physiological indices during aging

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Arbeev et al., Mech. Ageing Dev. 2011
Decline in performance with age

Plasticity of aging

Fries, The Milbank Quarterly 2005
Postponing physiologic aging

Incremental model of chronic disease

Compression of morbidity

Fries, The Milbank Quarterly 2005
Major age-related diseases

Age-related macular degeneration

Arthritis

Diabetes (type 2)

Osteoporosis

Inflammation

Aging is a risk factor

Alzheimer’s

Atherosclerosis

Cancer

Pulmonary disease

Contributors: damaged molecules and organelles

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A 16th Century Solution to the Aging Problem

Lucas Cranach, the Elder
Calorie restriction increases life span and postpones aging

![Graph showing survival rate over age with and without calorie restriction.]

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Incidence (%)</th>
<th>Mean age of death (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Restricted</td>
</tr>
<tr>
<td></td>
<td>Mean age of death† (months)</td>
<td></td>
</tr>
<tr>
<td>Hepatoma</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>47†</td>
<td>31</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Multiple</td>
<td>16†</td>
<td>6</td>
</tr>
<tr>
<td>No tumor</td>
<td>13†</td>
<td>25</td>
</tr>
</tbody>
</table>

Weindruch & Walford, Science 1982
Resveratrol extends yeast life span

Howitz et al., Nature 2003
Resveratrol extends life span and postpones aging of obese mice

Baur et al., Nature 2006
This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.
TOR determines yeast life span

Kaeberlein et al., Science 2005
TOR determines murine life span

Harrison et al., Nature 2009
Autophagy is a downstream effector of TOR on longevity

Hansen et al., PLoS Genetics 2008
Retrograde response extends life span

- Mitochondrial dysfunction accumulates with age
- Retrograde response is progressively induced with age

Expression of genes encoding cytoplasmic, mitochondrial, and peroxisomal proteins

Compensatory mechanism

Human longevity has a genetic component

Christensen et al., Nat. Rev. Genet. 2006
Insulin/IGF-1 signaling and aging

Christensen et al., Nat. Rev. Genet. 2006

Central versus peripheral effects?
Mechanisms of aging and longevity

Nutrients
Stress

Metabolism & Stress responses
TOR pathway
IGF-1 pathway
Autophagy

Physiologic aging
Healthy aging
Frailty
Disability
Death

Primary responses
Compensatory responses
APOE is the most highly replicated human longevity/frailty gene

Circulating lipids → Clearance

Aging

HRAS

LASS

APOE

HDL

Jazwinski et al., Aging Cell 2010

Christensen et al., Nat. Rev. Genet. 2006

Clearance

Apoptosis

Lipotoxicity

Dysfunction and morbidity
Late-life superadvantage of the effect of $LASS1$ on the $APOE \times HRAS1$ interaction

![Graph showing the frequency of $APOE$, $APOE \times HRAS1$, and $APOE \times HRAS1 \times LASS1$ across different age groups.](image)

Jazwinski et al., Aging Cell 2010
Survival by Deficit Index in nonagenarians

Healthy aging haplotype

\[ \text{ATTTC CGCGCGT CGT} \]

\[ \text{OR} \quad 15.48 \quad \text{adj \, p=2.11x10}^{-9} \]

\[ \text{APOE} \quad \text{HRAS1} \quad \text{LASS1} \]

Jazwinski et al., Aging Cell 2010
Polymorphisms in *LASS1* impact gene expression

Jazwinski et al., Aging Cell 2010

A little bit of a good thing is good for you.
An individual path to exceptional longevity

APOE (ATTTC) frequency ~0.24

APOE HRAS1 LASS1
ATTTC CGCGCGT CCT
frequency ~0.01 ~0.07 in centenarians

HRAS1 (CGCGCGGT) frequency ~0.63

LASS1 (CCT)

Birthdays are good for you.
The more you have, the longer you live.

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Joint influence of small-genetic effect variants on human longevity

Yashin et al., Aging 2010
Epigenetic stratification

\[ P_{n+1} = A e^{-P_n} \quad n = 0, 1, 2 \ldots \]

Jazwinski et al., Exp. Gerontol. 1998
Mortality rate plateaus with age

Jazwinski et al., Exp. Gerontol. 1998
Postponed aging delays population stratification

Individual yeasts age differently due to chance events, even when genetically identical and in the same environment.

Jazwinski et al., unpublished
Epigenetic change in DNA methylation and gene expression during aging

Fraga et al., PNAS 2005
Trajectories of disability during the last year of life

Gill et al., NEJM 2010
Lack of predictability in the etiology of disability

Gill et al., NEJM 2010

Flip side: Multiple morbidities and co-morbidities are a fact of long life
Goals of Jazwinski Lab

Long life

Retention of function