Uncovering Genetic Determinants of Health in Older Adults

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Aging Genetics

• Is aging genetic?

• How do we measure ‘aging’ process?
  – Traditional vs non-traditional traits

• Has there been success with traditional aging phenotypes?
  – Candidate gene, GWAS, mtDNA

• What are the next steps in aging genetics?
Heritability Studies in Aging

• General aging processes
  – Life span: 20-50%
  – Frailty: 19-43%
  – Grip strength: 22-65%
  – Walking speed: 10-42%

• Age-related diseases
  – Alzheimer’s disease: 79%
  – Prostate cancer: 57%
  – Heart-rate variability: 13-23%
  – Blood pressure: 38-46%
  – Bone mineral density: 46-92%

McGue, Vaupel et al. 1993
Lee, Flaquer et al. 2004
Perls and Terry 2003
Page, Braun et al. 1997
Gatz, Reynolds et al. 2006
Singh, Larson et al. 1999
Brown, Beck et al. 2003
Pocock, Eisman et al. 1987
Fredricksen, et al 2002
Tiainen et al 2004
McGue et al 2001
Plomin et al 1994
Murabito, Yuan, Lunetta, 2013
Genetic Contributions to Aging

Oxidative Stress
- SOD genes

Inflammation
- TLR genes
- IL-6, IL-10, IL-1

Disease pathways
- Acute Phase Response
- DNA Repair Dysregulation

DNA Repair Dysregulation
- FOXO3A
- ApoE

Reduced Energy Metabolism
- IIS genes
- Sirtuin genes

mtDNA

PON1
TP53
ACE

Fallin & Matteini, JGMS, 2009
Brooks-Wilson, Hum Genet 2013
Phenotypes of Aging

- Age-based measures
- Longevity
- Survival to age 90
- Death by age 65
- Frailty

- Age-related syndromes

Studies
- Cardiovascular Health Study
- Women’s Health and Aging Study
- Long Life Family Study
- CHARGE Consortium
Genetics and Longevity Phenotypes

• CHARGE consortium GWAS findings
  – Trait: Survival to age 90
  – 2.3 million SNPs evaluated, 2 discovery phases

  Study-specific ORs and 95% CI for MINPP1 rs9664222

  • 24 independent signals < 0.001 in phase 1
  • Meta-analysis of phase 1 and 2 cohorts MINPP1 SNP remained significant (p-value = 6.8x10^{-7})

Genetics and Longevity Phenotypes

• CHARGE consortium GWAS findings
  - Traits: all-cause mortality, disease-free survival
  - 2.3 million SNPs evaluated, 8-9 cohorts used
  - No hits of GW significance (< 10^-8)
  - Many SNPs < 10^-5 were in or near genes related to neural development and function, and autophagy.

Walter S, Atzmon G, et al
Neurobiol Aging 2011
Frailty Syndrome

Cycle of Frailty

- Neuroendocrine Dysregulation
- Anorexia of aging
- Total Energy Expenditure
- Activity
- Walking Speed
- Disability
- Dependency
- Resting Metabolic Rate
- Strength & Power
- VO_{2}\text{max}
- Immobilization
- Falls and Injuries
- Weight Loss
- Negative Energy Balance
- Negative Nitrogen Balance
- Aging: Senescent musculoskeletal changes
- Loss of muscle mass
- Sarcopenia
- Insulin sensitivity
- Osteopenia
### Candidate Pathways Related to Frailty

**Women's Health and Aging Study (n=349)**  
Candidate gene association study  
- 1,536 SNPs from 134 genes related to muscle maintenance and inflammation  
  - Multinomial logistic regression (3-level frailty)

- Apoptotic and transcription-regulation pathways highlighted

Results consistent with prior gene expression studies in animal models

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<table>
<thead>
<tr>
<th>Gene (total SNPs genotyped)</th>
<th>SNP Marker</th>
<th>MAF</th>
<th>Odds Ratio (95% CI)</th>
<th>LRT, p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTR (19)</td>
<td>rs10925235*</td>
<td>0.36 (A)</td>
<td>1.78 (0.97–3.27)</td>
<td>.0011</td>
</tr>
<tr>
<td></td>
<td>rs2297967*</td>
<td>0.36 (A)</td>
<td>1.89 (1.03–3.49)</td>
<td>.0015</td>
</tr>
<tr>
<td></td>
<td>rs10802569*</td>
<td>0.37 (G)</td>
<td>0.56 (0.31–1.03)</td>
<td>.0024</td>
</tr>
<tr>
<td></td>
<td>rs4659725</td>
<td>0.36 (C)</td>
<td>1.89 (1.03–3.47)</td>
<td>.0014</td>
</tr>
<tr>
<td></td>
<td>rs1770449</td>
<td>0.36 (G)</td>
<td>0.52 (0.29–0.97)</td>
<td>.0015</td>
</tr>
<tr>
<td></td>
<td>rs1050993</td>
<td>0.36 (A)</td>
<td>1.73 (0.96–3.15)</td>
<td>.0027</td>
</tr>
<tr>
<td>CASP8 (14)</td>
<td>rs3769827*</td>
<td>0.46 (G)</td>
<td>1.63 (0.94–2.81)</td>
<td>.0014</td>
</tr>
<tr>
<td></td>
<td>rs6747918*</td>
<td>0.49 (G)</td>
<td>0.79 (0.46–1.36)</td>
<td>.0032</td>
</tr>
<tr>
<td></td>
<td>rs2037815</td>
<td>0.50 (G)</td>
<td>0.77 (0.45–1.33)</td>
<td>.0037</td>
</tr>
<tr>
<td></td>
<td>rs6745051*</td>
<td>0.50 (C)</td>
<td>1.31 (0.76–2.25)</td>
<td>.0058</td>
</tr>
<tr>
<td>FN1 (15)*</td>
<td>rs7567647</td>
<td>0.25 (A)</td>
<td>4.20 (1.69–10.39)</td>
<td>.0016</td>
</tr>
<tr>
<td>CREBBP (17)</td>
<td>rs129968</td>
<td>0.35 (A)</td>
<td>2.98 (1.48–5.99)</td>
<td>.0038</td>
</tr>
<tr>
<td>GSTZI (7)</td>
<td>rs2287396</td>
<td>0.18 (A)</td>
<td>0.49 (0.25–0.97)</td>
<td>.0046</td>
</tr>
<tr>
<td>KAT2B (22)</td>
<td>rs2929408</td>
<td>0.17 (A)</td>
<td>0.47 (0.23–0.93)</td>
<td>.0079</td>
</tr>
<tr>
<td>TIAM1 (107)</td>
<td>rs2833383</td>
<td>0.23 (A)</td>
<td>0.87 (0.47–1.60)</td>
<td>.0088</td>
</tr>
<tr>
<td>STAT1 (10)</td>
<td>rs1400657</td>
<td>0.11 (C)</td>
<td>3.01 (1.44–6.29)</td>
<td>.0089</td>
</tr>
<tr>
<td>TCN2 (10)</td>
<td>rs740234</td>
<td>0.20 (G)</td>
<td>0.36 (0.14–0.94)</td>
<td>.0100</td>
</tr>
<tr>
<td>BTRC (33)</td>
<td>rs10883642</td>
<td>0.46 (A)</td>
<td>0.48 (0.27–0.85)</td>
<td>.012</td>
</tr>
<tr>
<td>FNI (15)</td>
<td>rs10883631</td>
<td>0.46 (A)</td>
<td>0.49 (0.28–0.86)</td>
<td>.014</td>
</tr>
<tr>
<td>VTN (3)</td>
<td>rs2227729</td>
<td>0.07 (G)</td>
<td>2.38 (1.13–5.01)</td>
<td>.013</td>
</tr>
</tbody>
</table>

Ho YY, Matteini AM, et al JGMS 2011
Candidate Pathways and Frailty

- Cardiovascular Health Study (CHS)
  - N = 3,186 CA, 790 AA
- 1,360 tag SNPs from 100 candidate genes related to methylation and transcription regulation
- Time to frailty diagnosis (F/U = 9 years)

Matteini AM, Walston JD, In preparation
## Candidate Pathways and Frailty

### Caucasians (n=3,186)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX7</td>
<td>rs1048915</td>
<td>0.66 (0.50-0.88)</td>
<td>0.004</td>
</tr>
<tr>
<td>PAX3</td>
<td>rs1835432</td>
<td>0.87 (0.79-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>rs7590760</td>
<td>0.89 (0.81-0.98)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

### African Americans (n=790)

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT3A</td>
<td>rs1303624</td>
<td>1.45 (1.20-1.75)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PAX3</td>
<td>rs1978859</td>
<td>1.43 (1.11-1.86)</td>
<td>0.007</td>
</tr>
<tr>
<td>WNT5B</td>
<td>rs1242488</td>
<td>0.72 (0.58-0.91)</td>
<td>0.005</td>
</tr>
<tr>
<td>CREBBP</td>
<td>rs1333480</td>
<td>1.45 (1.11-1.89)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Candidate Pathways and Frailty

- Cardiovascular Health Study (CHS)
- Methylation and transcription-regulation pathways highlighted
- Consistent with Ho YY, 2011 results

Matteini AM, Walston JD, In preparation
Mitochondrial Variation & Frailty

- Cardiovascular Health Study data
- Complete scan of mtDNA polymorphisms in pilot group of frailty extremes (n=315)
- 3 polymorphisms significantly associated with frailty in pilot were then typed in entire cohort (n=4,278)
  - mt146, mt204, mt228
  - C allele at mt204 associated with increased likelihood of frailty phenotype in entire CHS cohort

<table>
<thead>
<tr>
<th>Group</th>
<th>Odds ratio (95% confidence interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goodness of fit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity strata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.75 (0.74, 3.61)</td>
<td>.164</td>
</tr>
<tr>
<td>Non-pilot</td>
<td>1.11 (0.15, 4.70)</td>
<td>.904</td>
</tr>
<tr>
<td>Black</td>
<td>2.33 (0.82, 5.74)</td>
<td>.082</td>
</tr>
<tr>
<td>Combined</td>
<td>2.04 (1.07, 3.60)</td>
<td>.020</td>
</tr>
<tr>
<td>Sex strata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.33 (0.53, 2.86)</td>
<td>.503</td>
</tr>
<tr>
<td>Male</td>
<td>3.83 (1.48, 8.77)</td>
<td>.003</td>
</tr>
</tbody>
</table>

doi:10.1371/journal.pone.0011069.t003

Moore AZ, Biggs ML, Matteini AM, et al PLOS One, 2010
**mtDNA204 Polymorphism & Grip Strength**

- **Table 4.** Mean difference in grip strength (kg) associated with the mt204 C allele estimated by stratified multivariate regression models adjusted for age, (age−70)⁺, BMI, BMI², sex, and race.

<table>
<thead>
<tr>
<th>Group</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% confidence interval) p</td>
<td>Coefficient (95% confidence interval) p</td>
</tr>
<tr>
<td>Race/ethnicity strata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (n = 3435)</td>
<td>-1.60 (−3.10, −0.11) .035</td>
<td>-1.63 (−3.12, −0.14) .032</td>
</tr>
<tr>
<td>Black (n=558)</td>
<td>-3.11 (−5.85, −0.37) .027</td>
<td>-3.26 (−5.99, −0.54) .019</td>
</tr>
<tr>
<td>Combined (n = 3993)</td>
<td><strong>-1.80 (−3.10, −0.50) .006</strong></td>
<td><strong>-2.04 (−3.33, −0.74) .002</strong></td>
</tr>
<tr>
<td>Sex strata</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (n = 2274)</td>
<td>-0.87 (−2.20, 0.51) .217</td>
<td>1.13 (−2.56, 0.24) .105</td>
</tr>
<tr>
<td>Male (n = 1719)</td>
<td>-3.31 (−5.77, −0.85) .008</td>
<td>-3.48 (−5.94, −1.02) .006</td>
</tr>
</tbody>
</table>

*Adjusted for age, (age−70)⁺, and sex.
†Adjusted for age, (age−70)⁺, BMI, BMI², male sex and/or black race.
doi:10.1371/journal.pone.0011069.t004

- mt204 C allele associated with decreased grip strength in entire CHS cohort
Challenges to using traditional aging phenotypes

- Traits based on chronological age not ideal
  - Longevity, mortality, disease-based traits

- Frailty better represents underlying biology of aging
  - Small sample sizes
  - Phenotype harmonization across cohorts difficult
Hypothesized conceptual model of frailty

Molecular/Disease
- Oxidative stress
- Mitochondrial dysfunction
- Cell senescence
- DNA methylation
- DNA damage

Genetic variation

Inflammatory diseases

Physiology
- Inflammation
- Sarcopenia
- Immune function
- Anorexia
- Clotting
- Glucose metabolism

Neuroendocrine dysregulation

Clinical Outcomes
- Frailty
  - Robust
  - Frail
  - Slowness
  - Weakness
  - Weight loss
  - Low activity
  - Fatigue

Morbidity
Mortality

Adapted from Walston JD, Hadley EC, et al JAGS 2006
Phenotypes of Aging

- Age-based measures
  - Longevity
  - Survival to age 90
  - Death by age 65

- Age-related syndromes
  - Frailty

- Measured quantitative endophenotypes
  - Muscle strength
  - Walking speed
  - PC-based Phenotypes

- Latent categorical/quantitative based on measured proxies
  - Inflammation (measured serum levels)
  - Healthy Aging Index
Alternative Phenotype I: Principle Component Endophenotypes

Genetic susceptibility loci

- Pulmonary
- Metabolic
- Cardiovascular
- Physical Function
- Cognition

Exceptional longevity

- Do these domains contribute equally, independently to longevity?
- Is any single domain critical to long and healthy life?
- Is there a set (or sets) of correlated clinical measures closely associated with longevity?
  - within a single domain?
  - across domains?

Matteini AM, Fallin MD et al, JGMS 2010
Alternative Phenotype I: Principle Component Endophenotypes

**PC1:** Physical Activity and Lung Function

<table>
<thead>
<tr>
<th>Variable</th>
<th>Loadings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference</td>
<td>0.17</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>Average grip strength</td>
<td>0.88</td>
</tr>
<tr>
<td>Maximum grip strength</td>
<td>0.88</td>
</tr>
<tr>
<td>Gait speed</td>
<td>0.42</td>
</tr>
<tr>
<td>Total physical activity</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Presence of lung disease</td>
<td>−0.15</td>
</tr>
<tr>
<td>FEV1</td>
<td>0.85</td>
</tr>
<tr>
<td>FEV6</td>
<td>0.86</td>
</tr>
<tr>
<td>FEV1/FEV6 ratio</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Note: Loading weights by PC are reported for each variable.

- **PC2:**
  - Metabolic and Cardiovascular Health (HDL, Triglycerides)

- **PC3:**
  - Cognitive health

- **PC4**
  - Blood pressure

Matteini AM, Fallin MD et al, JGMS 2010
Alternative Phenotype I: Principle Component Endophenotypes

PC1 = 0.39 (lung/phys fx)
PC2 = 0.27 (metab/CVD)
PC3 = 0.36 (cognition)
PC4 = 0.25 (blood pressure)
PC5 = 0.16 (cholesterol)

Heritability ($h^2$)

Total Physical Activity
Presence of Lung disease
Gait speed
Presence of diabets
Systolic BP
Presence of hypertension
Presence of cholesterol
Total Cholesterol
Component 5
Creatinine
Diastolic BP
Component 4
Immediate Memory
Component 3
Estimated BMI
Vegetable Recall
Glycosylated Haemoglobin
Component 1
FEV6
Average Grip Strength
Maximum Grip Strength
Glycemia
Component 2
FEV1
Waist circumference
Triglycerides
Animal Recall
Estimated BMI
FEV1
PC1 = 0.39
PC2 = 0.27
PC3 = 0.36
PC4 = 0.25
PC5 = 0.16
Alternative Phenotype II: Health Aging Index

• Intermediate phenotype for longevity based on underlying physiology of aging
  – Systolic BP
  – FVC
  – Creatinine
  – Fasting glucose
  – MMSE

• Developed in CHS and LLFS cohorts

SCORE: 0-10

Sanders JL, Minster RL, et al JGMS 2013
Alternative Phenotype II: Health Aging Index

HAI Heritability Estimates (LLFS)
- Equal weights model: 0.24-0.40
- Mortality-optimized weights model: 0.28-0.32

Table 2. Hazard Ratios for Mortality by Healthy Aging Index Scores in the Cardiovascular Health Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events per 1000 pyrs</th>
<th>HR (95% CI) Unadjusted</th>
<th>HR (95% CI) Age, Sex, and Race</th>
<th>HR (95% CI) Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR per unit of index</td>
<td>—</td>
<td>1.22 (1.19, 1.24)</td>
<td>1.20 (1.17, 1.23)</td>
<td>1.17 (1.14, 1.21)</td>
</tr>
<tr>
<td>HR per category of index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>34.5</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3-4</td>
<td>44.0</td>
<td>1.31 (1.15, 1.50)</td>
<td>1.28 (1.12, 1.46)</td>
<td>1.25 (1.09, 1.44)</td>
</tr>
<tr>
<td>5-6</td>
<td>61.4</td>
<td>1.94 (1.70, 2.20)</td>
<td>1.79 (1.57, 2.04)</td>
<td>1.66 (1.44, 1.91)</td>
</tr>
<tr>
<td>7-10</td>
<td>93.4</td>
<td>3.28 (2.84, 3.78)</td>
<td>2.98 (2.56, 3.48)</td>
<td>2.62 (2.22, 3.10)</td>
</tr>
</tbody>
</table>

Notes: CI = confidence interval; HR = hazards ratio; pyrs = person years.
*Adjusted for age, sex, race, smoking, body mass index, education, physical activity, baseline chronic conditions, incident coronary heart disease, and incident cerebrovascular disease.
Alternative Phenotype III: Inflammatory aggregate

• Low-grade chronic inflammation underlies most age-related functional decline

• IL-6 and CRP are traditionally associated with mortality and morbidity

• Is there a set of inflammatory mediators that are predictive of mortality?

Alternative Phenotype III: Inflammatory aggregate

- Measured 15 NFκB-related markers in InCHIANTI
  - 5 markers associated with 5-year mortality
    - (CRP, IL-18, IL-1RA, IL-6 and sTNFR1)

- Measured 5 markers in CHS
  - Aggregate of these measures significantly associated with 10-year mortality?

- Summary measures created via inflammatory index score: AGE, IL-6, sTNFR1

Alternative Phenotype III: Inflammatory aggregate

Table 2. Mortality Risk of Inflammatory Phenotype in 1-, 2-, and 10-Year Cardiovascular Health Study (CHS) Cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>10-Year CHS</th>
<th></th>
<th></th>
<th>1-Year CHS</th>
<th></th>
<th></th>
<th>2-Year CHS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Log(IL-6)</td>
<td>1.42</td>
<td>1.36</td>
<td>1.49</td>
<td>1.87</td>
<td>1.56</td>
<td>2.24</td>
<td>1.72</td>
<td>1.52</td>
</tr>
<tr>
<td>Log(sTNFR1)</td>
<td>1.46</td>
<td>1.39</td>
<td>1.53</td>
<td>1.98</td>
<td>1.69</td>
<td>2.32</td>
<td>1.72</td>
<td>1.52</td>
</tr>
<tr>
<td>Log(CRP)</td>
<td>1.25</td>
<td>1.19</td>
<td>1.31</td>
<td>1.63</td>
<td>1.33</td>
<td>1.98</td>
<td>1.59</td>
<td>1.39</td>
</tr>
<tr>
<td>Log(IL-18)</td>
<td>1.10</td>
<td>1.05</td>
<td>1.15</td>
<td>1.26</td>
<td>1.02</td>
<td>1.56</td>
<td>1.25</td>
<td>1.08</td>
</tr>
<tr>
<td>Log(IL-1RA)</td>
<td>1.21</td>
<td>1.15</td>
<td>1.26</td>
<td>1.44</td>
<td>1.19</td>
<td>1.73</td>
<td>1.29</td>
<td>1.13</td>
</tr>
<tr>
<td>Age</td>
<td>1.80</td>
<td>1.72</td>
<td>1.87</td>
<td>1.53</td>
<td>1.27</td>
<td>1.83</td>
<td>1.62</td>
<td>1.43</td>
</tr>
<tr>
<td>WSS</td>
<td>1.47</td>
<td>1.41</td>
<td>1.54</td>
<td>2.14</td>
<td>1.77</td>
<td>2.58</td>
<td>1.88</td>
<td>1.65</td>
</tr>
<tr>
<td>PCS</td>
<td>1.44</td>
<td>1.37</td>
<td>1.50</td>
<td>2.04</td>
<td>1.69</td>
<td>2.47</td>
<td>1.85</td>
<td>1.62</td>
</tr>
<tr>
<td>IIS</td>
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Summary

• Longevity/Mortality
  – consistency in literature (APOE and FOXO3A)
  – Many other candidates, uneven results

• Frailty
  – May highlight interconnected biologic mechanisms
    • Apoptosis, methylation, transcription regulation
  – Low statistical power

• Overall, traditional measures of aging may have increased phenotypic heterogeneity
Summary

• Alternative aging phenotypes are significant predictors of mortality/healthy aging
  – Healthy Aging Index
  – Principal Component Traits
  – Inflammatotary Index Score

• Decreased phenotypic heterogeneity
• May offer insight for interaction among biological pathways, or pleiotropic effects of potential candidate genes
Ongoing Research

• Healthy Aging Index GWAS
  – CHARGE Consortium Aging Subgroup

• Principal Component Traits
  – Validation of PCs in independent population
  – GWLS, GWAS across multiple populations

• Inflammatory Index Score
  – GWAS
Relevant to HIV Research?
Pathways of interest

• APOE ε4/ ε4 genotype
  – associated with accelerated disease course
  – unclear association with HIV-related dementia

• Apoptosis
  – FOXO3A

• Transcription regulation
  – CREB pathway

• Chronic inflammation
  – NFκB pathway

• Methylation
  – Epigenetic changes
Relevant to HIV Research?

Molecular/Disease
- Oxidative stress
- Mitochondrial dysfn
- Cell senescence
- DNA methylation
- DNA damage

Genetic variation

HIV

Physiology
- Inflammation
- Sarcopenia
- Immune function
- Anorexia
- Clotting
- Glucose metabolism
- Neuroendocrine Dysregulation

Clinical Outcomes
- Frailty
  - Robust
  - Frail
- Morbidity
- Mortality
- Disability
- Hospitalization
- Polypharmacy

Molecular/Disease Physiology Clinical
- Outcomes
- Genetic
- variation
- Morbidity
- Mortality
- Disability
- Hospitalization
- Polypharmacy
Thank you!

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