On Bridging the Theory and Measurement of Frailty

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Introduction
Whither “frailty measurement”?

• “Geronmetrics”
  – a.k.a.: econometrics, psychometrics, biometrics
  – Goal: Accurate and precise measurement of complex health states or spectra

• Rigorous measurement is essential to
  – Sensitivity, specificity for genetic, other discovery
  – Theory operationalization, testing
  – Correctly targeted, evaluated interventions

• Worth measuring as stand-alone construct?
  – If not, pursuing items under the last bullet makes little sense
Geronmetric Measurement

- Proposition: Most effective when attacked “from both ends”
  - Mechanisms / basic science
  - Phenotype / validity
    - Face: Sensible?
    - Content: Captures all aspects? Excludes extraneous aspects?
    - Criterion: Predicts relevant outcomes?
    - Construct: Captures assessment target?
This poster aims to...

- Present theory identifying frailty
- Propose a frailty validation methodology
- Present measurement validation findings
- Highlight areas of promise for future work
Theory: Frailty...

- Is recognizable to (some?) geriatricians
- Has adverse geriatric consequences
- An *outcome of dysregulation* in multiple physiological systems
  - Inflammatory? Hormonal? Nutritional? Etc.?
- Is a *syndrome* of decreased resiliency and reserves manifesting in multiple domains
  - e.g., see next slide
- Is *distinct* from disease or disability

*References 1-8*
One Theory
The Frailty Construct

Fried et al., J Gerontol 56:M146-56; Bandeen-Roche et al., J Gerontol, in press
Frailty Measurement Validation Methodology

- **Criterion validity:** “Frailty” = combination of aspects which well predicts adverse outcomes, or is well predicted by hypothesized risk factors.

- **Methods:** Standard regression models; also neural nets, regression trees, logic regression, etc.

Goal: “Leaves” that are homogeneous re frailty status.
Frailty Measurement Validation Methodology

- **Content validity**: Science — Clarity in construct definition
  - Arguably: Key source of current debate

- **Construct validity**: Theory testing
  - Proposal: Latent ("underlying") variable modeling — panels to follow

- Not a focus of this poster, but worth keeping in mind: reliability of measures
Frailty Construct Validation
Latent Variable Modeling

• Views frailty as underlying; inferred through surrogates

• Then interest is in
  – Measurement: How does underlying frailty relate to measured criteria?
  – Structure: Relation of frailty to putative etiology or consequences
Frailty Construct Validation
Latent Variable Modeling

Discriminant validity

Theory informs relations (arrows)

Frailty

Determinants

Adverse outcomes

$Y_1$

$Y_p$

$e_1$

$e_p$
Frailty Construct Validation Philosophy

• Role of latent variable modeling?
  – Reveal underlying truth?
  – Operationalize and test theory
    • Convergent and discriminant
  – Sensitivity analyses
    • Do minor changes to theory greatly affect conclusions?
Validation Findings
Fried et al, 2001, Phenotype

• Measures: 5 criteria
  - Robust = none; Intermediate=1-2; Frail=3 or more

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss</td>
<td>Either of: i) Weight at age 60–weight at exam &gt;= 10% of age 60 weight; ii) BMI at exam &lt; 18.5.</td>
<td>12.7</td>
</tr>
<tr>
<td>2. Exhaustion</td>
<td>Self report of any of: i) low usual energy level (&lt;=3, range 0-10); felt unusually (ii) tired (iii) weak in last month</td>
<td>14.1</td>
</tr>
<tr>
<td>3. Low Energy Expenditure</td>
<td>90 on activity scale (6 items)</td>
<td>19.8</td>
</tr>
<tr>
<td>4. Slowness</td>
<td>walking 4m: speed &lt;= 4.57/7 for height &lt;= 159 cm; speed &lt;= 4.57/6 for height &gt; 159 cm</td>
<td>31.3</td>
</tr>
<tr>
<td>5. Weakness</td>
<td>Grip strength: &lt;= 17 for BMI &lt;= 23; &lt;=17.3 for BMI 23.1 - 26; &lt;= 18 for BMI 26.1 – 29; &lt;= 21 for BMI &gt; 29 As for CHS.</td>
<td>20.8</td>
</tr>
<tr>
<td>OVERALL FRAILTY STATUS</td>
<td>Robust</td>
<td>44.9</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>43.8</td>
</tr>
<tr>
<td></td>
<td>Frail</td>
<td>11.3</td>
</tr>
</tbody>
</table>
Validation Findings
Strengths

• Face validity
  – Criteria reflect geriatric impression
  – WHAS I:  prevalence increases with age
  – WHAS:  prevalence higher among more disabled (25.4%) than overall (11.3%)

• Cross validity
  – Prevalence similar across cohorts (11.3% in WHAS; 11.6% in age-matched CHS women)
Validation Findings
Strengths: Criterion Validity

Association of Baseline Frailty Status and Risk of Incident Adverse Events,
Combined WHAS I (rounds 1, 4, 7) and WHAS II (rounds 1, 2, 3) Cohorts (n=784)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted Hazard Ratios (95% Confidence Intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td>Fall (n=560)</td>
<td>0.92 (0.63, 1.34)</td>
</tr>
<tr>
<td>Severe ADL Disability (n=612)</td>
<td>5.68 (2.41, 13.42)</td>
</tr>
<tr>
<td>Severe IADL Disability (n=698)</td>
<td>3.53 (1.20, 10.35)</td>
</tr>
<tr>
<td>Hospitalization (n=715)</td>
<td>0.99 (0.67, 1.47)</td>
</tr>
<tr>
<td>Permanent Nursing Home Entry (n=750)</td>
<td>5.16 (0.81, 32.79)</td>
</tr>
<tr>
<td>Death (n=766)</td>
<td>3.50 (1.91, 6.39)</td>
</tr>
</tbody>
</table>

- Phenotype strongly predicts adverse outcomes
- Phenotype predicted by signs of systemic dysregulation: inflammatory, immunological, hormonal, nutritional
Validation Findings
Strengths

• Internal convergent validity

• Criteria manifestation is syndromic

  “a group of signs and symptoms that occur together and characterize a particular abnormality”

- Method: Latent class analysis
Syndrome validation
Latent class analysis

• Seeks clinically homogeneous subgroups
• Features that characterize latent groups
  – Prevalence in overall population
  – Percentage manifesting each criterion
• If criteria characterize syndrome:
  – At least two groups (otherwise, no co-occurrence)
  – No subgrouping of symptoms (otherwise, more than one abnormality characterized)
### Table 3
Conditional Probabilities of Meeting Criteria in Latent Frailty Classes
WHAS

<table>
<thead>
<tr>
<th>Criterion</th>
<th>2-Class Model</th>
<th>3-Class Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CL. 1 NON-FRAIL</td>
<td>CL. 2 FRAIL</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>.073</td>
<td>.26</td>
</tr>
<tr>
<td>Weakness</td>
<td>.088</td>
<td>.51</td>
</tr>
<tr>
<td>Slowness</td>
<td>.15</td>
<td>.70</td>
</tr>
<tr>
<td>Low Physical Activity</td>
<td>.078</td>
<td>.51</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>.061</td>
<td>.34</td>
</tr>
<tr>
<td>Class Prevalence (%)</td>
<td>73.3</td>
<td>26.7</td>
</tr>
</tbody>
</table>

Bandeen-Roche et al., 2006
Syndrome Validation
Summary

- Two class model fit is good
  - Pearson $\chi^2$ p-value = .22; minimized Akaike & Bayesian Information Criteria

- In three-class model: mean # of criteria in “intermediate,” “frail” groups = 1.26, 3.42—in line with defined cutoffs

- Frailty criteria prevalence stepwise across classes—no subclustering

- Syndromic manifestation well indicated
Measurement of Frailty
Areas of Promise

• Content validity: All aspects covered?
  – Cognitive decline?
  – Depression / anxiety?
  – Physiotype rather than phenotype?

• Construct validity
  – Discriminant: What is frailty not?
  – External validity
    • Link to multisystemic dysregulation
    • Specificity re vulnerability to stressors
Measurement of Frailty
Areas of Promise

• Criterion validity
  
  - ...i.e. utility for screening, diagnosing & targeting adverse geriatric outcomes

  - Needed
    • Delineation of predictive accuracy
    • Comparison among competitors
    • Threshold relationships?
Acknowledgments

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• References: Please take handout

• Basis: Forthcoming paper

PHENOTYPE OF FRAILTY:
CHARACTERIZATION IN THE WOMEN’S
HEALTH AND AGING STUDIES