Frailty Ascertainment: 
*Beginning of the pathway to treatment*

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Introduction
Whither “frailty ascertainment”?

• “Geronometrics”
  – 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
Introduction
Geronometric 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 module aims to...

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

- Obsolete: frailty = disability; disease
- Rockwood et al: accumulation of deficits; proximity to death
- Lipsitz: Loss of dynamical complexity
- Studenski: Geriatrician consensus
- Deeg: Static versus dynamic frailty—aggregate markers vs. changes

References 6; 24-26
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 1-17*
The Syndromic Cycle Theory

3-Fried et al., J Gerontol 56:M146-56; Bandeen-Roche et al., J Gerontol, 2006
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 (here); also neural nets, regression trees, logic regression, etc.
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 module, but worth keeping in mind: reliability of measures
Frailty Construct Validation
Latent Variable Methodology

- 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 Methodology

Discriminant validity

Theory informs relations (arrows)

Frailty

Adverse outcomes

Determinants

$Y_1$

$Y_p$

$e_1$

$e_p$
Syndrome Validation
Methods

• Internal convergent validity

• Criteria manifestation is syndromic

\[ \text{“a group of signs and symptoms that occur together and characterize a particular abnormality”}^{18} \]

– Method: Latent class analysis\(^{19,27}\)
Syndrome validation
Method: Latent class analysis

POPULATION

$P_1$  $\cdots$  $P_J$

$\Pi_{11}$  $\Pi_{1M}$  $\Pi_{J1}$  $\Pi_{JM}$

$Y_1$  $\cdots$  $Y_M$

$C_i$

19-Goodman, 1974; 27-McCutcheon, 1987
Syndrome validation
Method:  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)
Frailty Construct Validation
Method 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?
**Methods**

**Data: Women’s Health & Aging Studies**

- Fried et al. (2001) 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 ≥ 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall Frailty Status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Robust</td>
<td></td>
<td>44.9</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>43.8</td>
</tr>
<tr>
<td>Frail</td>
<td></td>
<td>11.3</td>
</tr>
</tbody>
</table>
Results

Face Validity

- 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)
Results
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
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
Results
Syndrome Validation

- Two class model fit is good
  - Pearson $\chi^2$ p-value = .22; minimized Akaike$^{22}$ & Bayesian$^{23}$ 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
Discussion: Areas of Promise

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

• Construct validity
  – External validity
    • Link to multisystemic dysregulation
    • Specificity re vulnerability to stressors
  – Discriminant: What is frailty not?
Discriminant Validity
More than Component Parts

- WHAS: Disease-adjusted analysis, mobility disability vs. components
  - Slowness = strongest predictor
    - OR = 17, 95% CI [7.8, 38] vs.
    - 6.6, 95% CI [2.2, 20] for weakness
  - All but weight loss predict (multiply)
Discriminant Validity Data
More than disease, disability (WHAS)

- Frail, # diseases associated, not redundant
  - “Frail” rare if no (2%) or 1 (5%) disease
  - “Intermediate” not rare these cases (>29%)
  - Many with comorbid diseases robust (>28%)

- Frailty strongly predicts mobility disability, independently of age, # diseases
  - OR for severe disability = 29 (95% CI [9.3, 88])
  - Little interaction w disease: not severity marker
Discriminant Validity Data

More than disease (WHAS)

- Mortality analysis with propensity scoring

<table>
<thead>
<tr>
<th>ADJUSTMENT</th>
<th>FRAILTY OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.42 (1.81,3.24)</td>
</tr>
<tr>
<td>Disease count, age</td>
<td>1.81 (1.33,2.45)</td>
</tr>
<tr>
<td>Cluster-based C/D/S vars.</td>
<td>1.74 (1.28,2.36)</td>
</tr>
<tr>
<td>Elements of score</td>
<td>1.69 (1.23,2.30)</td>
</tr>
<tr>
<td>Propensity score</td>
<td>1.67 (1.22,2.28)</td>
</tr>
<tr>
<td>P. Score: Mid-90</td>
<td>1.51 (1.07,2.13)</td>
</tr>
</tbody>
</table>
Frailty Ascertainment
Discussion: Areas of Promise

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

  – Needed
    • Delineation of predictive accuracy
    • Reliability delineation and refinement
    • Comparison among competitors
    • Threshold relationships?
Frailty Ascertainment: Summary

- Rigorous frailty ascertainment is essential to treatment development!

- A key element of rigor: validity
  - Does ascertainment “hit the target”?
  - Target: involves theory

- Working theory:

  *Frailty is a free-standing syndrome of decreased resiliency and reserves that results from dysregulation in multiple physiological systems and has adverse geriatric consequences*

- Evidence presented re Fried et al. (2001) phenotype:

  *Face, criterion, and construct validity for syndrome with adverse consequences*
Acknowledgments

• Funding / Institutional Support
  Johns Hopkins Older Americans Independence Center,
  National Institute on Aging, Brookdale National
  Foundation

• References:  See attached

• Basis:

  PHENOTYPE OF FRAILTY:
  CHARACTERIZATION IN THE WOMEN’S
  HEALTH AND AGING STUDIES
  *J Gerontol Med Sci, 2006*