Frailty Risk Adjustment-
A Role in the Development of Neurological Tx?

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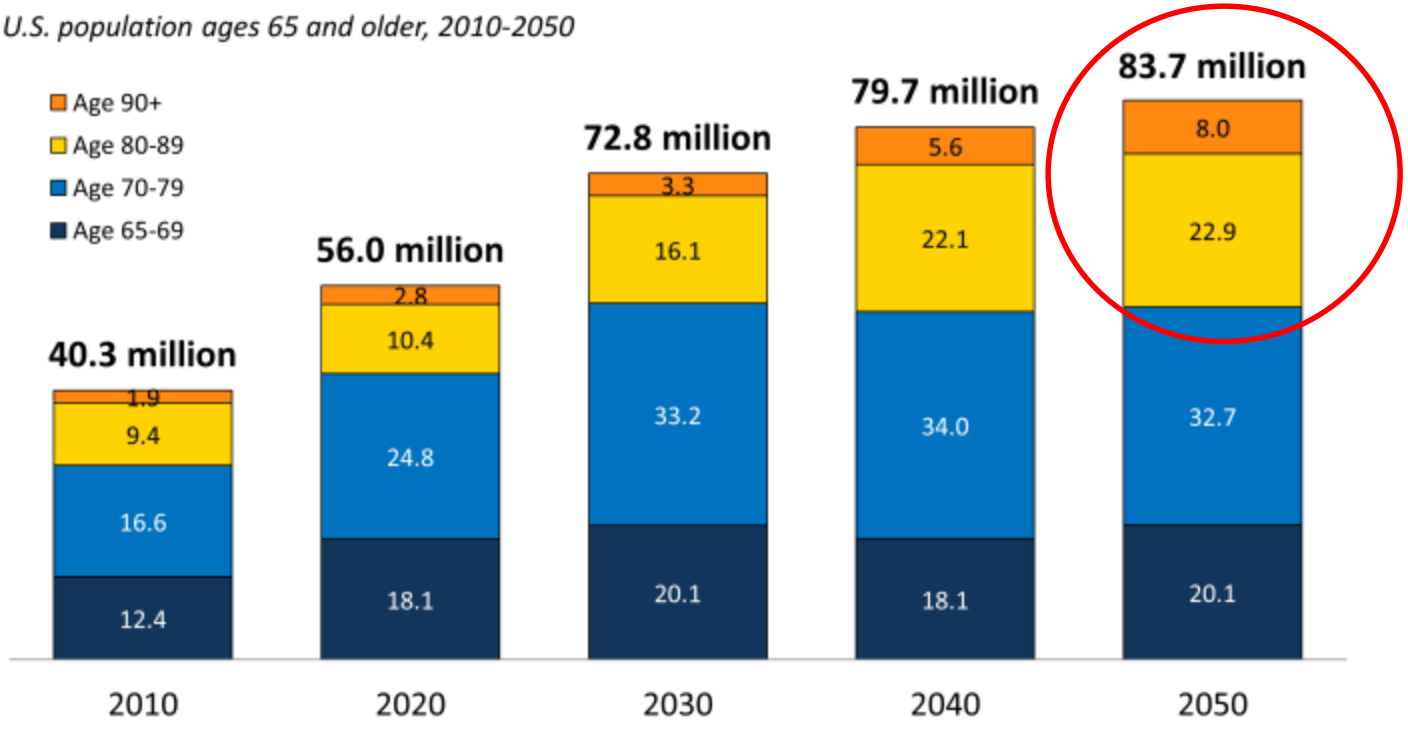
Exhibit 1.1

The U.S. population ages 80 and older will nearly triple between 2010 and 2050; the number of people ages 90 and older will quadruple

U.S. population ages 65 and older, 2010-2050



SOURCE: Kaiser Family Foundation analysis of 2010 population estimates from U.S. Census Bureau. Population Division. Vintage 2011: National Tables. Table 1. Annual Estimates of the Resident Population by Sex and Five-Year Age Group for the United States: April 1, 2010 to July 1, 2011 (NC-EST2011-01), May 2012; and 2020-2050 population projections from U.S. Census Bureau, Population Division. 2012 National Population Projections: Summary Tables. Projections of the Population by Age and Sex for the United States: 2015 to 2060 (NP2012-T12); December 2012.

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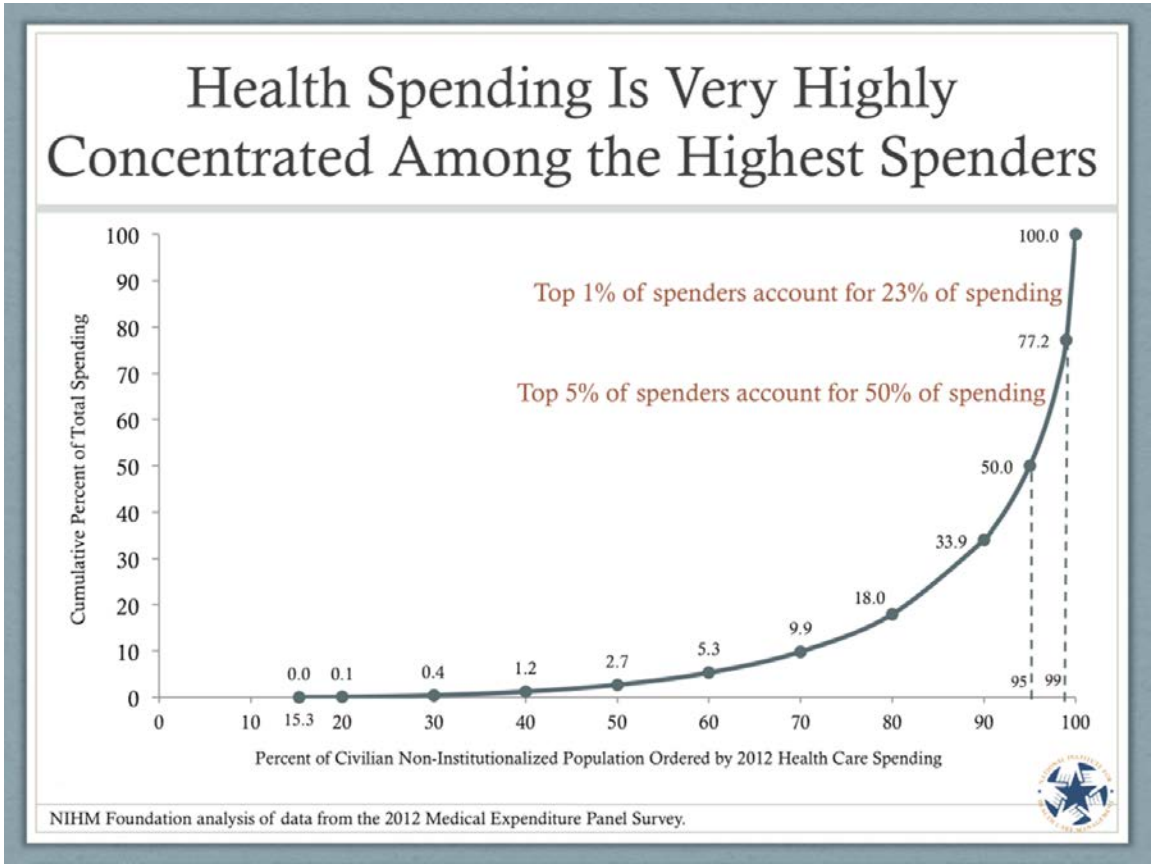
More, Growing Older, Especially 80+

Those 65+

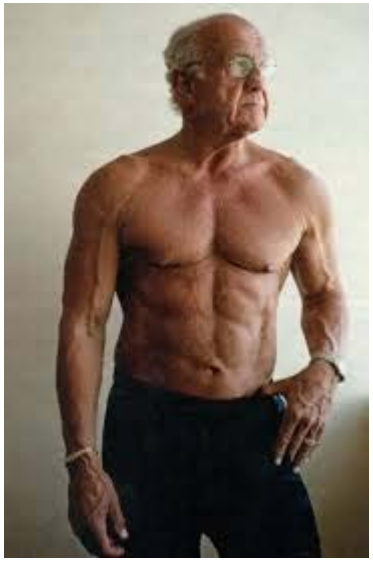


- 35.3% of all IP procedures
- 32.2% of all OP procedures
- 25% of Medicare $$ for last year of life
- Only 14% of population

Top 5% Account for 50% of Health Care Spending- Many are Frail Elders

Heterogeneity of Aging

- Overall, chronological age is a very imprecise predictor of health status, future care needs or health care costs.



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Copeland et al 1991; Yancik et al 1998; Ogle et al 2000,

Risk Stratification

- We need an approach to help us understand who is at increased risk for poor outcomes
- How to risk stratify treatment & management strategies
- How to more precisely estimate outcomes (adjusting for functional capacity/frailty)
- Optimization of therapies in the elderly with the availability of validated tools capable of predicting outcomes.

Frailty = Biologic Aging

- Frailty is a hyperinflammatory geriatric syndrome resulting from age-related cumulative declines across multiple physiologic systems, with impaired homeostatic reserve and a reduced capacity of the organism to resist stress.

Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol a-Biol 2001;56:M146-M56.

Frailty Prevalence: Community

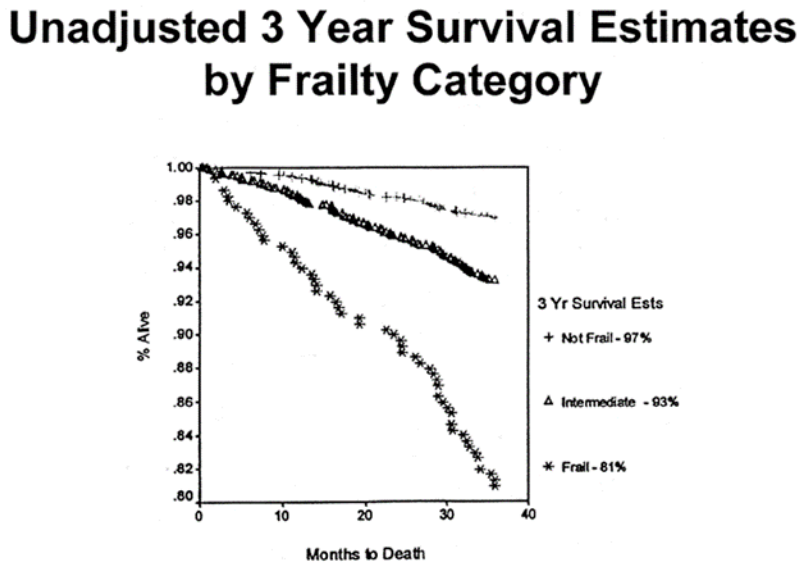
- ~Equal to Alzheimer's Disease in prevalence
- 10.7% (95% CI = 10.5 -10.9) in community dwelling elders 65+ in 21 studies; 61,500 participants
  - Much higher in hospitalized & institutionalized elders
- 20-30% in those ages 75+
- 40% in those aged 90

Collard RM, Boter H, Schoevers RA, Voshaar RCO. Prevalence of Frailty in Community-Dwelling Older Persons: A Systematic Review. J Am Geriatr Soc 2012;60:1487-92.

Poor Outcomes

- Poor quality of life
- Hospitalization, LOS, never events
- Tx complications and adverse events
- Disability
- institutionalization
- Death

(Heuberger, 2011)



(Fried, 2001)

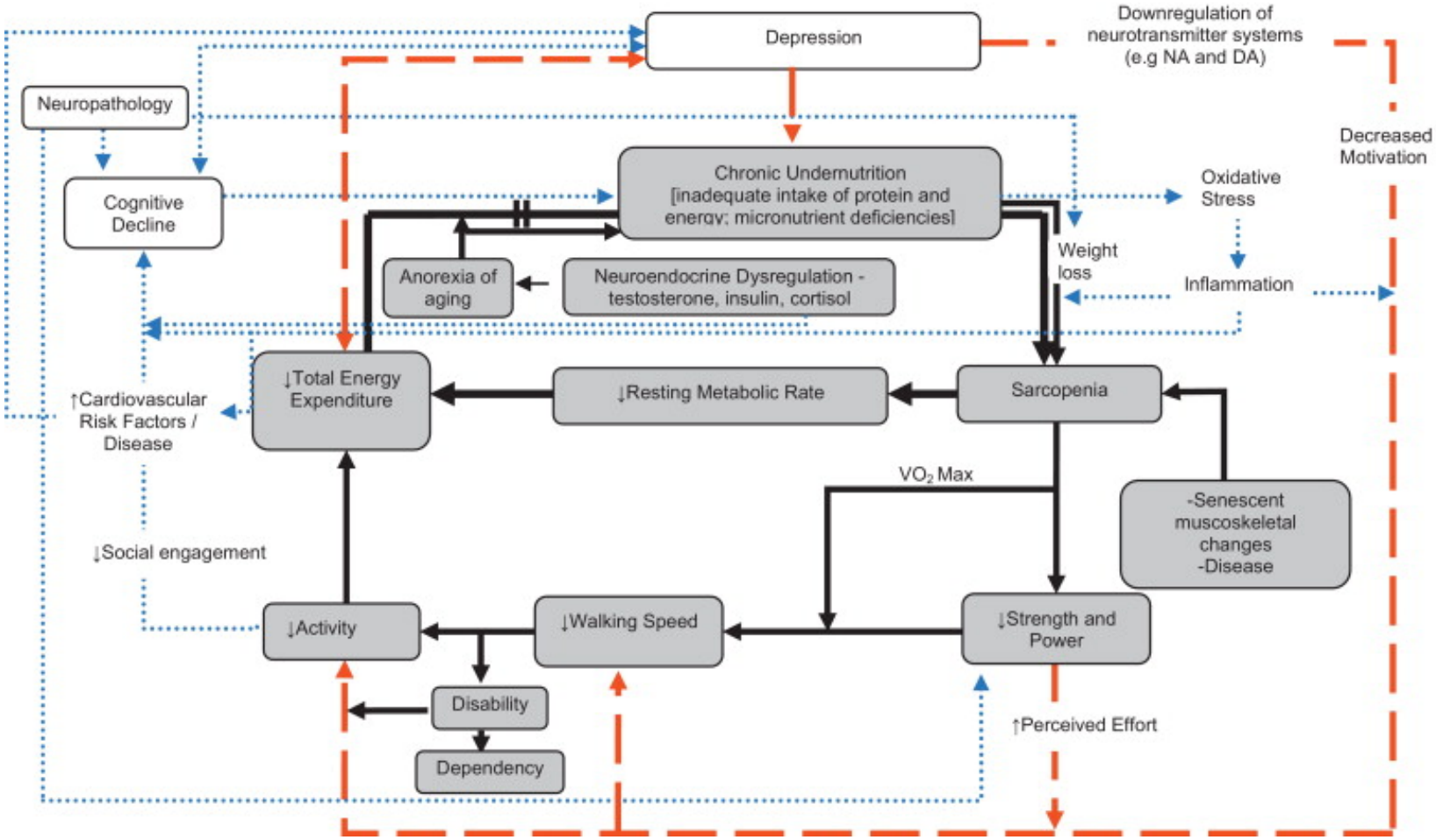
Importance of Frailty Assessment

- More sensitive predictor of outcomes than is age [1,2]
- Frail patients are **2.5 times** longer length of stay, and **20 times** as likely to be discharged to a nursing home [2]
- American College of Surgeons guidelines: "frailty score" for optimal perioperative decision-making, management, and discharge strategy [3]
- Elders underrepresented in clinical trials (esp. those >70. We can't assume they are equal to younger patients[4]

1: Winograd CH, et al. (1991); 2: Makary MA, et al. (2010); 3: Chow WB et al., (2012); 4:JCO November 15, 2004 vol. 22 no. 22 4626-4631

Frailty & Cognitive Impairment

Fig. 1. The cycle of frailty and cognitive impairment. Fried et al.'s (2001) model is outlined in the grey shaded boxes. Our additions to this model are the mental health cycle outlined in red (dashed) and the cognitive decline cycle outlined in blue (dotted) lines



Robertson, DA Frailty and cognitive impairment—A review of the evidence and causal mechanisms, Aging Research Review 2013

How Do We Measure Frailty?

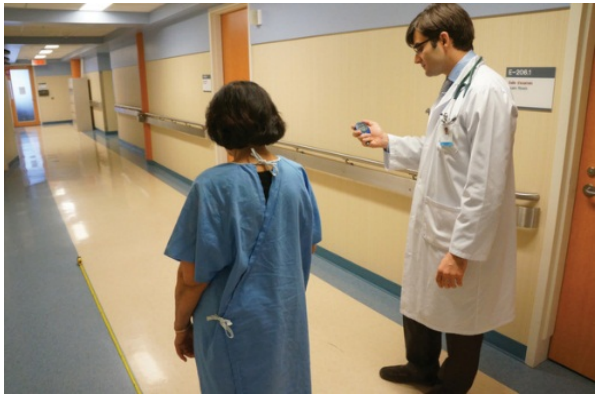
- Few practical, objective instruments can categorize age-related functional status

- Perfect Tool:
- Measures overall function (dynopenia and sarcopenia)
- Low cost, fast, easy to perform (not gait reliant)
- Provides categorical (frail/pre-frail/non-frail) and numerical score
- Sensitive to change over time
- Objective and EHR compatible

Frailty Assessment Methods

- Single Markers
  - Grip strength
  - Walking speed
- Phenotypic Frailty Indices
  - CHS (Fried) index
  - SOF index
  - FRAIL index
- Multi-dimensional Indices
  - Rockwood
  - FI-CGA-10
  - MPI
  - SHERPA
  - HARP

- Functional Decline Instruments
  - ADL
  - CCI

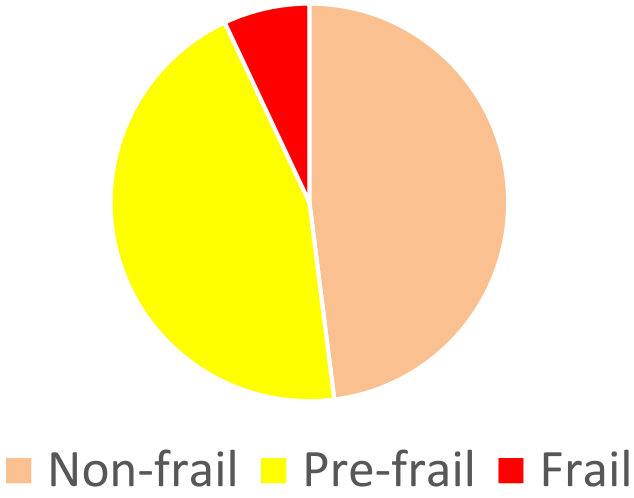


CHS – Fried Frailty Index

- Frailty was defined as a clinical syndrome in which three or more of the following criteria were present:
  1. unintentional weight loss (10 lbs in past year)
  2. self-reported exhaustion
  3. low physical activity
  4. weakness (grip strength)
  5. slow walking speed

- 5,317 men and women 65 years and older

Not Frail (0 criteria):	48%
Intermediate (1-2):	45%
Frail (3-5):	07%



1: Fried LP, et al., (2001)

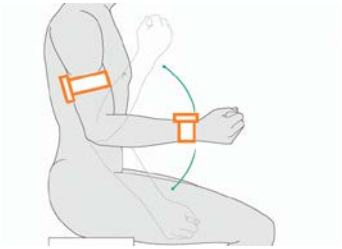
Examples of Sensor-Based Frailty Measures

Inertial Sensors (gyroscopes & accelerometers) Gait-based	Greene, BR, 2014	TUG
	Schwenk, M. 2014	Gait speed Walking bout duration variability
	Merchant, R.A., 2016	Trunk posture
	Najafi,B, 2014	Stand and Flop
	Bahureksa, L, 2017	Gait speed Stride length Stride time
Inertial Sensors (gyroscopes & accelerometers) Upper Extremity Based	Toosizadeh,N.	Upper extremity function
Dynamometer	Schwenk, M. 2014; Greene, BR, 2014	Grip strength
ECG	Parvaneh, 2017	Heart rate variability

A Novel Test using Upper-extremity Motion

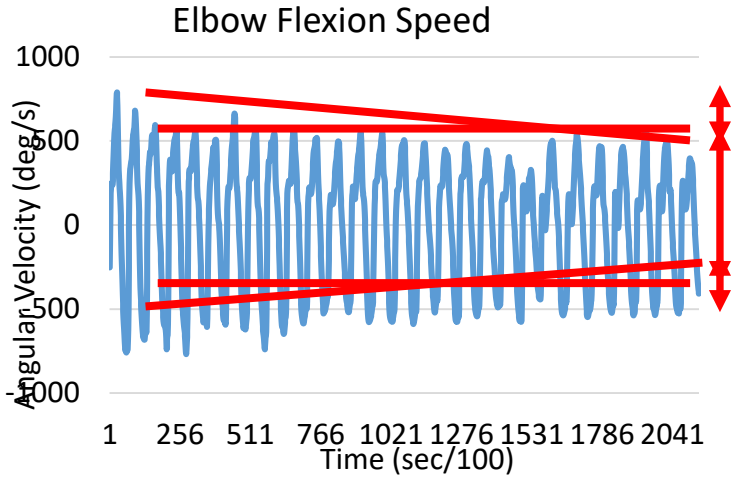
Toosizadeh, N., Mohler, J., Najafi, B., (2015) Assessing Upper Extremity Motion: An Innovative Method to Identify Frailty. Journal of the American Geriatrics Society, 63 (6), 1181-1186.

UEF Kinematics



- UFM allows measuring various kinematic parameters associated with:

  - Slowness as measured by speed of movement
  - Weakness as measured by power and moment on arm
  - Exhaustion as measured by reduction in speed of movement and speed variability
  - Flexibility as measured by elbow range of motion
  - Variability



CDISC Mission, Development of Neurological Treatments & "Frailty"

- CDISC- *Support the approvals of safe and efficacious medicines for patients*

Measuring Aging Function— "Frailty" Status

1. Adjust for aging heterogeneity "biologic age
2. Predict who will benefit
3. Identify who will have poor outcomes