Predicting Chemotherapy Toxicity in Older Adults

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CARG
CANCER & AGING RESEARCH GROUP

NATIONAL CANCER INSTITUTE

Muss et al., Journal of the American Medical Association 2005

Cassidy et al., Journal of Cancer Research and Clinical Oncology 2010

Rocha Lima et al., Cancer 2002

Argiris et al., Journal of Clinical Oncology 2004

Hurria et al., Journal of Clinical Oncology 2011

Hudes et al., New England Journal of Medicine 2007

Folprecht et al., Annals of Oncology 2011

Older adults are at risk for cancer therapy toxicity

Goldstone et al., Blood 2001

Muss et al., Journal of Clinical Oncology 2007

Zauderer et al., Journal of Geriatric Oncology 2013

Quoix et al., Lancet 2011

Schild et al., Journal of Clinical Oncology 2003

Machtay et al., Journal of Clinical Oncology 2008

Zhu et al., Journal of the American Medical Association 2012

Pinder et al., Journal of Clinical Oncology 2007

Crivellari et al., Journal of Clinical Oncology 2000

Rather than putting out fires…
Can we anticipate and prevent them?

Chronological Age ≠ Functional Age

To weigh the risks and benefits → Functional Age vs. Chronological Age

The Extra Challenge:
The Ultimately Efficient Clinic

➢ Vitals Taken

➢ Patient in Gown

➢ Sitting on Exam Table

What is old?

65

Understanding the Grey

Factors other than chronological age that predict morbidity & mortality in older adults

- ➤ Functional status
- ➤ Comorbid medical conditions
- ➤ Cognition
- ➤ Nutritional status
- ➤ Psychological state
- ➤ Social support
- ➤ Medications (polypharmacy)

Geriatric Assessment

Benefits of Geriatric Assessment in Older Patients with Cancer

➢ Predict toxicity to cancer treatment

➢ Predict survival of older patients with cancer

➢ Uncover problems not detected by routine H&P

➢ Leads to interventions to:

  ▪ Improve mental health and well-being

  ▪ Improve pain control

Hurria et al. JCO 2011, Maione et al. JCO 2005, Repetto et al. JCO 2002, Poon et al. JCO 2011, Rao et al. J Gerontol A Biol Sci 2005, Extermann et al. Cancer 2012

Developing a Geriatric Assessment for Oncologists

- **Functional Status:**
  Activities of Daily Living (subscale of MOS Physical Health)
  Instrumental Activities of Daily Living (subscale of the OARS)
  Karnofsky Performance Rating Scale
  Timed Up & Go
  Number of Falls in Last 6 Months

- **Comorbidity:** Physical Health Section (subscale of the OARS)

- **Cognition:** Blessed Orientation-Memory-Concentration Test

- **Psychological:** Hospital Anxiety and Depression Scale

- **Social Functioning:** MOS Social Activity Limitations Measure

- **Social Support:**
  MOS Social Support Survey: Emotional and Tangible Subscales
  Seeman and Berkman Social Ties

- **Nutrition:**
  Body Mass Index
  % Unintentional Weight Loss in the Last 6 Months

-Validity

-Reliability

- Length

- Time to complete

- Ability to self-administer

- Multidisciplinary input

- Alliance Cancer in Elderly Committee

Determining the Utility of an Assessment Tool for Older Patients with Cancer

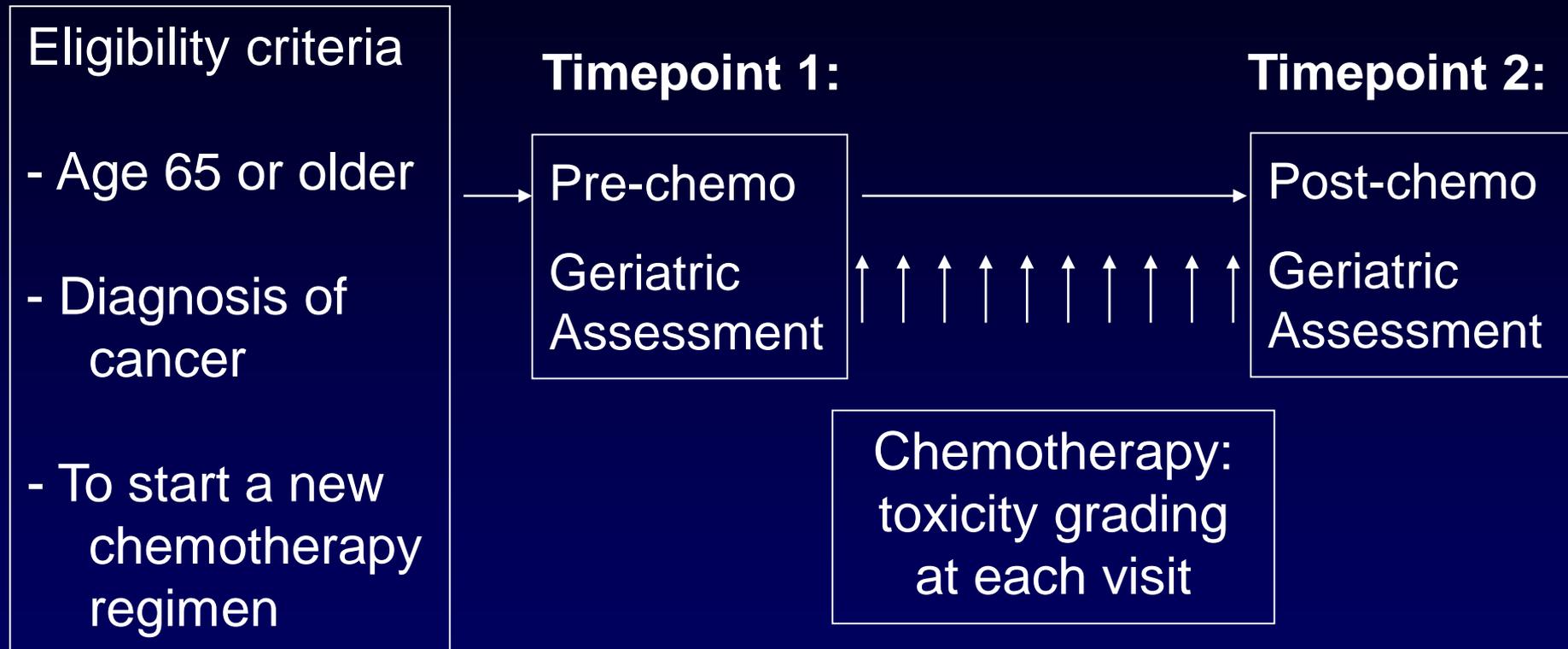## Cancer and Aging Research Group (PI: Hurria)

Primary Objective:

To determine the geriatric assessment's ability to predict risk of toxicity to chemotherapy

Secondary Objective:

To evaluate the longitudinal effect of the cancer and chemotherapy treatment on geriatric assessment parameters

Hurria et al, JCO 2011
Hurria et al, JCO 2016

Can Geriatric Assessment Predict Chemo Toxicity? (PI: Hurria)

Eligibility criteria

- Age 65 or older

- Diagnosis of cancer

- To start a new chemotherapy regimen

Timepoint 1:

Pre-chemo

Geriatric Assessment

Timepoint 2:

Post-chemo

Geriatric Assessment

Chemotherapy: toxicity grading at each visit

- Sample size: 750 patients (Chemo alone)
- 10 participating institutions (Cancer and Aging Research Group)

Hurria et al, JCO 2011
Hurria et al, JCO 2016

Predictors of Toxicity

- Age ≥ 72 years → **Age**

- GI/GU Cancer
- Standard Dose
- Polychemotherapy → **Tumor/ Treatment Variables**

- Hemoglobin (male: <11, female: <10)
- Creatinine Clearance (Jelliffe-ideal wt <34) → **Labs**

- Fall(s) in last 6 months
- Hearing impairment (fair or worse)
- Limited in walking 1 block (MOS)
- Assistance required in medication intake (IADL)
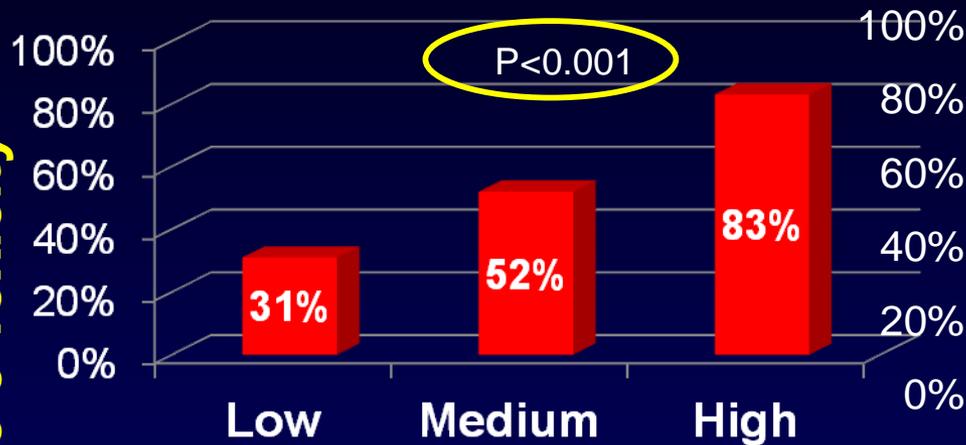- Decreased social activity (MOS) → **Geriatric Assessment Variables**

MD-rated KPS vs. Predictive Model

Chemotherapy Toxicity Predictive Model

% with Grade 3-5 Toxicity

Development Cohort (N=500)
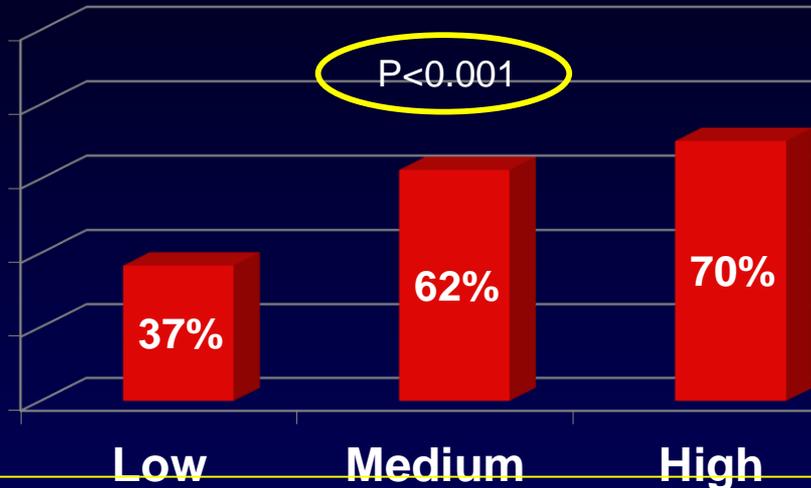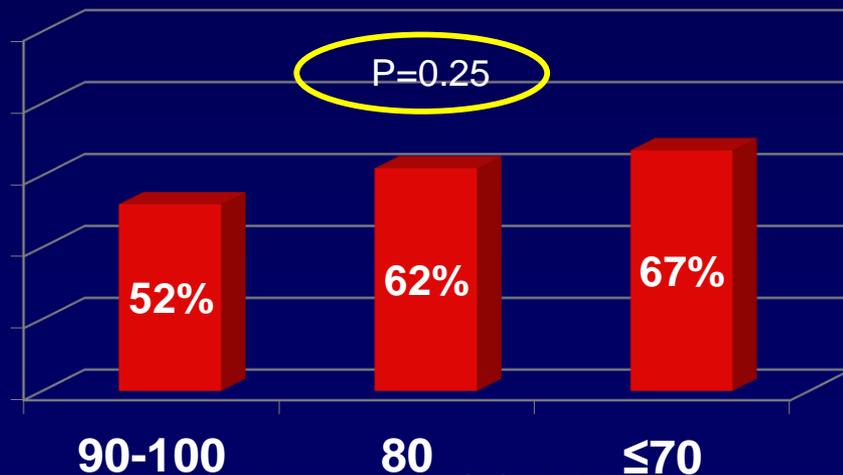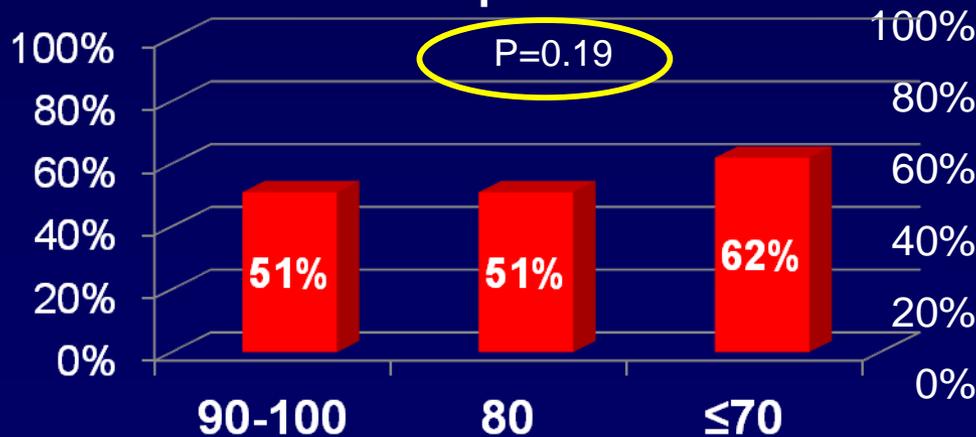
P<0.001

- Low: 31%
- Medium: 52%
- High: 83%

Validation Cohort (N=250)

P<0.001

- Low: 37%
- Medium: 62%
- High: 70%

MD KPS

Development Cohort

P=0.19

- 90-100: 51%
- 80: 51%
- ≤70: 62%

Hurria et al. JCO 2011

Validation Cohort

P=0.25

- 90-100: 52%
- 80: 62%
- ≤70: 67%

Hurria et al. JCO 2016

Geriatric Assessment for Older Adults with Cancer on Cooperative Group Trials

CALGB 360401 (PI: Hurria)
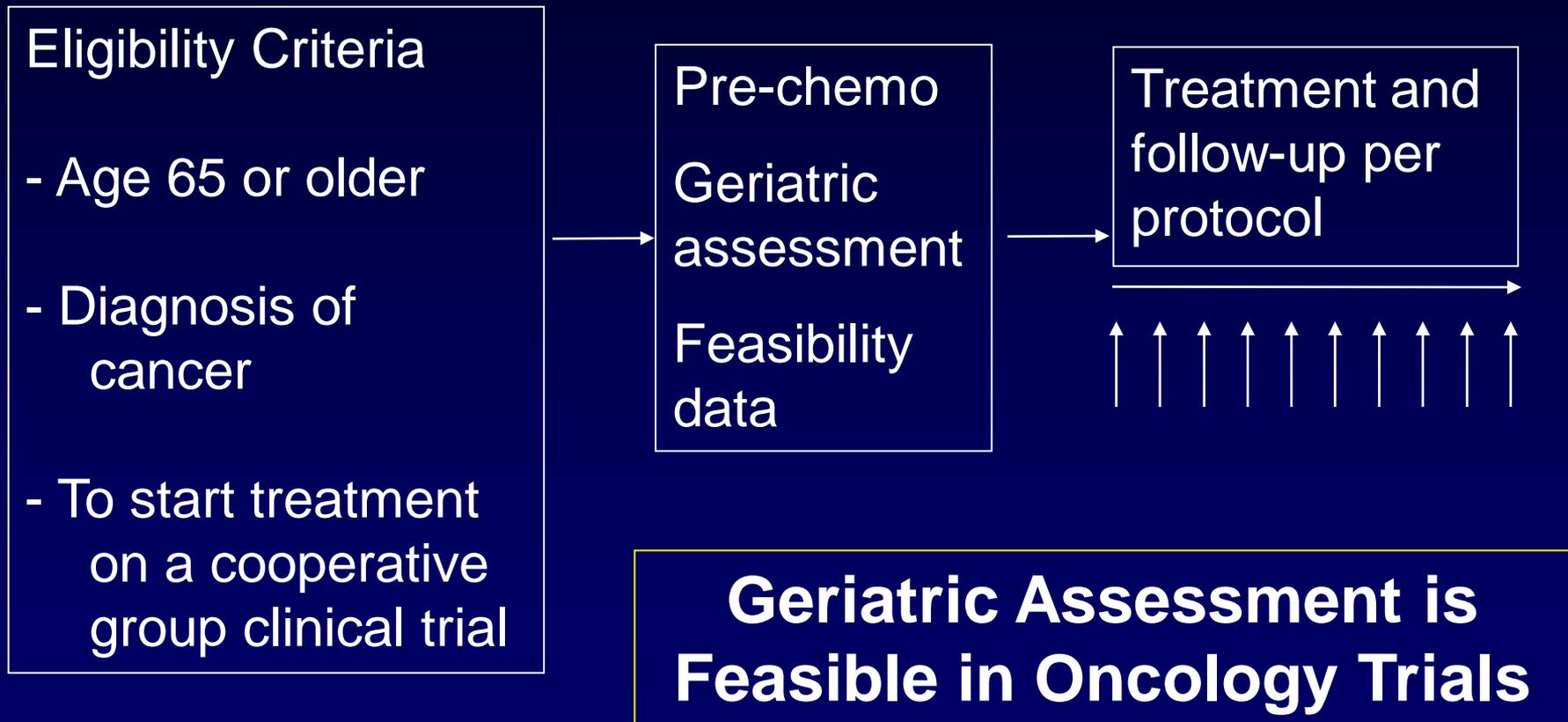
Eligibility Criteria
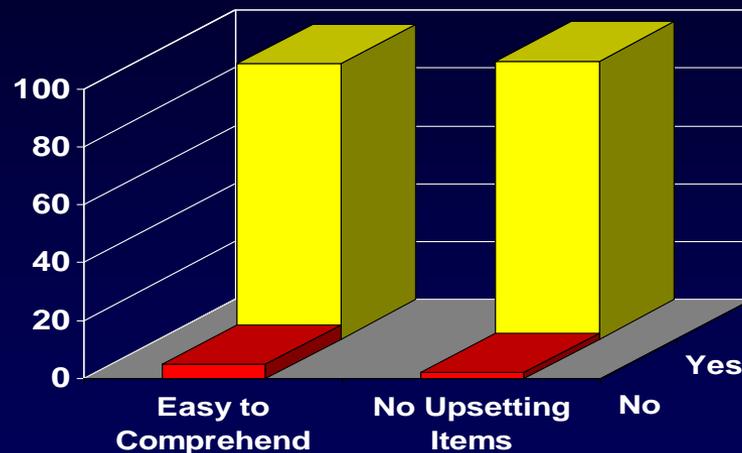
- Age 65 or older

- Diagnosis of cancer

- To start treatment on a cooperative group clinical trial

Pre-chemo

Geriatric assessment

Feasibility data

Treatment and follow-up per protocol

Geriatric Assessment is Feasible in Oncology Trials

Hurria et al, JCO 2011

Geriatric Assessment is Feasible in Oncology Trials
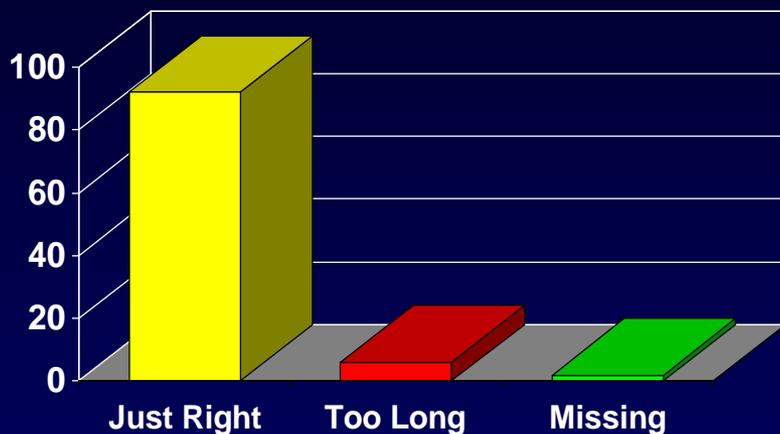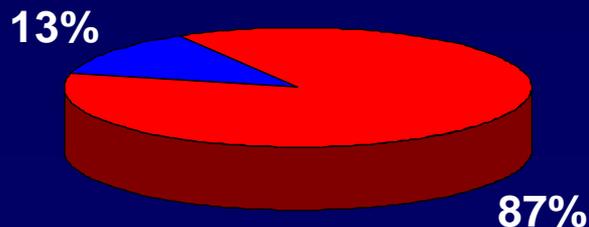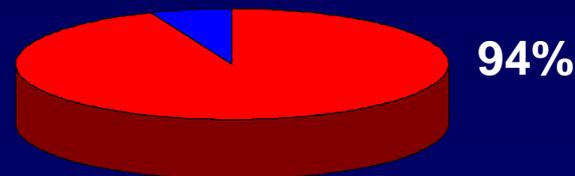
Validation in Breast Cancer
(R01 & BCRF Grant, PI: Hurria)

Objective: To identify clinical and biological predictors of severe chemotherapy side effects in older patients with breast cancer

Breast Cancer Cases (starting chemo)	Breast Cancer Control (no chemo)	Healthy Controls
419 enrolled	**97 enrolled**	**100 enrolled**

Timepoint 1:

Geriatric Assessment

Blood Draw (biomarkers of aging)

Chemotherapy: toxicity grading at each visit

Timepoint 2:

Geriatric Assessment

Blood Draw (biomarkers of aging)

2+ yrs

Timepoint 3:

Geriatric Assessment

Blood Draw (biomarkers of aging)

Across 15 institutions　　　　　　　　**COH Only**
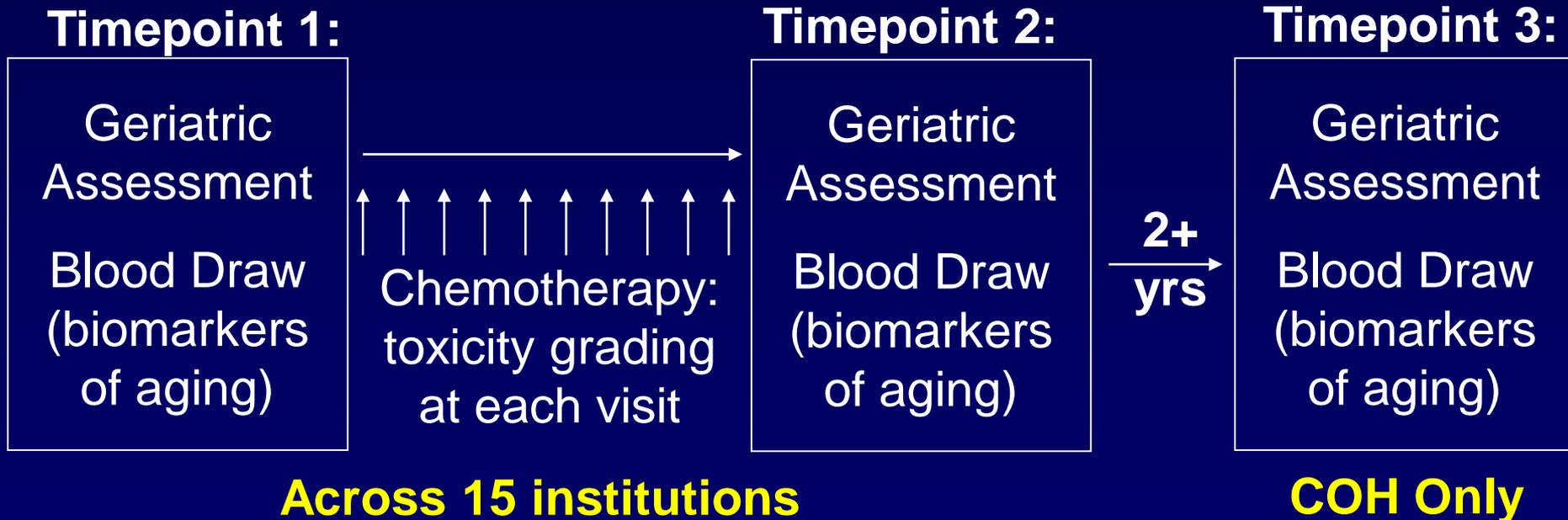
Validation in Other Disease Types: Ongoing Cooperative Group Trials

➢ Ovarian: First Line Age $\geq$ 70 (Dr. VonGreunigan)

➢ Breast: Endocrine Therapy +/- Bevacuzimab (Dr. Dickler)

➢ Breast: Taxanes in Metastatic Breast Cancer (Dr. Rugo)

➢ AML: First Line Age $\geq$ 60 (Dr. Klepin/Dr. Ritchie)

➢ CLL: First Line Age $\geq$ 65 (Dr. Woyach)

➢ GI: First Line Age $\geq$ 75 (Dr. McCleary)

Development of a Touchscreen Geriatric Assessment

COH IRB#08147 (PI: Hurria)

www.mycarg.org

GERIATRIC ASSESSMENT TOOLS

Geriatric Assessment Tool

A geriatric assessment is utilized to capture information about a patient's medical history as well as functional, cognitive, and psychosocial status, which can then be used by treating physicians to identify the most vulnerable patients (for example, those at high risk for chemotherapy toxicity). However, these assessments have not been routinely used in oncology practice because of the time and resources required for their administration. A geriatric assessment tool (that can be completed primarily by patients) was developed for incorporation into oncology clinical trials and routine care settings.[1,2] The domains that are assessed include functional status, comorbidities, medications, nutritional status, cognitive function, and psychosocial status.

Please click on the below for more information regarding the geriatric assessment tool:

[1]Hurria et al. Cancer 2005

[2]Hurria et al. JCO 2011

Geriatric Assessment (Patient) - English
Evaluación Geriátrica (Paciente) - Español
老人評估（患者）- 中文
Geriatric Assessment (Healthcare Team) - English

The Chemo-Toxicity Calculator

The Chemo-Toxicity Calculator is a pre-chemotherapy assessment that captures sociodemographics, tumor/treatment variables, laboratory test results (hemoglobin, creatinine clearance), and geriatric assessment variables (function, comorbidity, cognition, psychological state, social activity/support, and nutritional status). The Chemo-Toxicity Calculator is based on the results of a study which enrolled 500 patients across seven participating institutions, in order to identify factors that predict risk of severe chemotherapy-related side effects in older adults with cancer (Hurria et al. JCO 2011). The results from this study were identified by the American Society of Clinical Oncology's as one of the Clinical Cancer Advances in 2012. Having this predictive model that incorporates geriatric and oncologic correlates of vulnerability to chemotherapy toxicity in older adults could help both the healthcare provider and the patient weigh the benefits and risks of chemotherapy treatment. Our ultimate goal is to utilize this Chemo-Toxicity Calculator in clinical practice, where it can be used as a part of shared decision-making.

Chemo Toxicity Calculator

Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score

➢ Prospective multicentric study

➢ 518 patients age ≥ 70 yrs

  ▪ 2:1 split for derivation and validation cohorts

➢ Mean age: 76 (70-92)

➢ Separate models for heme and non-heme toxicity
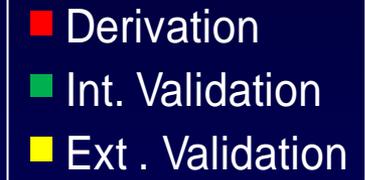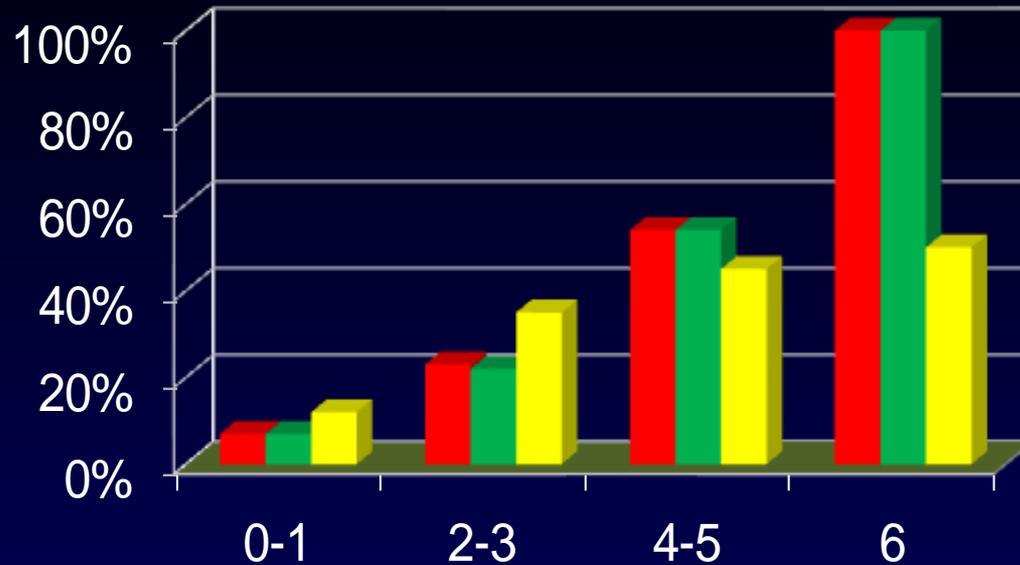
Heme Model

Predictors of Toxicity	Points		
	0	1	2
Diastolic Blood Pressure	≤ 72	> 72	
IADL	26-29	10-25	
Lactate Dehydrogenase	0-459		>459
Chemotherapy Toxicity	0-0.44	0.45-0.57	>0.57

Non-Heme Model

Predictors of Toxicity	Points		
	0	1	2
ECOG PS	0	1-2	3-4
Mini Mental Health Status	30		<30
Mini Nutritional Assessment	28-30		<28
Chemotherapy Toxicity	0-0.44	0.45-0.57	>0.57

Extermann et al, Cancer 2012

CRASH Model

Extermann et al. Cancer, 2012

CRASH Score

https://www.moffitt.org/eforms/crashscoreform/

Extermann et al. Cancer, 2012

The Past:
Risk Factors for Chemotherapy Toxicity

- ➢ Patient Factors
  - ▪ Age
  - ▪ ECOG PS/KPS
  - ▪ Labs
- ➢ Tumor and Treatment Factors
  - ▪ Cancer Type
  - ▪ Chemotherapy

The Present:
Geriatric Assessment Items Predictive of Chemotherapy Toxicity

Risk Factors	Aaldriks	Aparicio	Extermann	Freyer	Hurria	Kanesvaran	Soubeyran	Puts
Daily Activities (ADL & IADLs)		X	X	X	X	X	X	X
Hearing (Fair or Deaf)					X			X
Nutrition	X		X			X	X	X
Cognition	X	X	X			X	X	X
Psychological Status	X	X		X		X	X	X
Social Activities					X			X

Aaldriks et al, Crit Rev Oncol Hematol 2011
Aparicio et al, J Clin Oncol 2013
Extermann et al, Cancer 2012
Freyer et al, Annals of Oncology 2005
Hurria et al, J Clin Oncol 2011
Kanesvaran et al, J Clin Oncol 2011

Soubeyran et al, J Clin Oncol 2012
Puts et al, Ann Oncol 2014

Case Example

- 76 yo with stage IV NSCLC (mets to the bones)

- Lives with wife, ambulatory with cane

- Comorbidities: COPD, HTN, CAD, s/p
  CABG, osteoporosis, hard of hearing

- 5' 10", 160 lbs, BMI 20, BP 136/72, 124/68, HR 96

- Albumin 3.5, Hgb 10.8, Creatinine 1.2

Case Example

➢ ADLs: independent

➢ IADLS: wife does shopping, cooking, cleaning & meds, he drives & pays the bills

➢ Less socially active than before due to health

➢ Timed up & go test: 10 s

➢ Fell 6 months ago (tripped outside on the curb)

➢ MMSE 29/30

Predictive Model Applied to Our Case

	Toxicity Factor/Question	Value/Response	Score
☑	Patient's Age	Age >= 72	2
☐	Cancer Type	Other	0
☑	Dosage	Standard dose	2
☐	Number of chemotherapy agents	Mono-chemo therapy	0
☑	Hemoglobin	<11 g/dL	3
☑	How is your hearing (with a hearing aid, if needed)?	Poor	2
☑	Number of falls in the past 6 months?	1 or more	3
☑	Can you take your own medicines?	With some help (able to take medicine if someone prepares it for you and/or reminds you to take it)	1
☑	Does your health limit you in walking one block?	Limited a little	2
☑	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	Some of the time	1
☐	Creatinine Clearance	49	0

Patient Total Risk Score: 16

Risk of Toxicity by Score
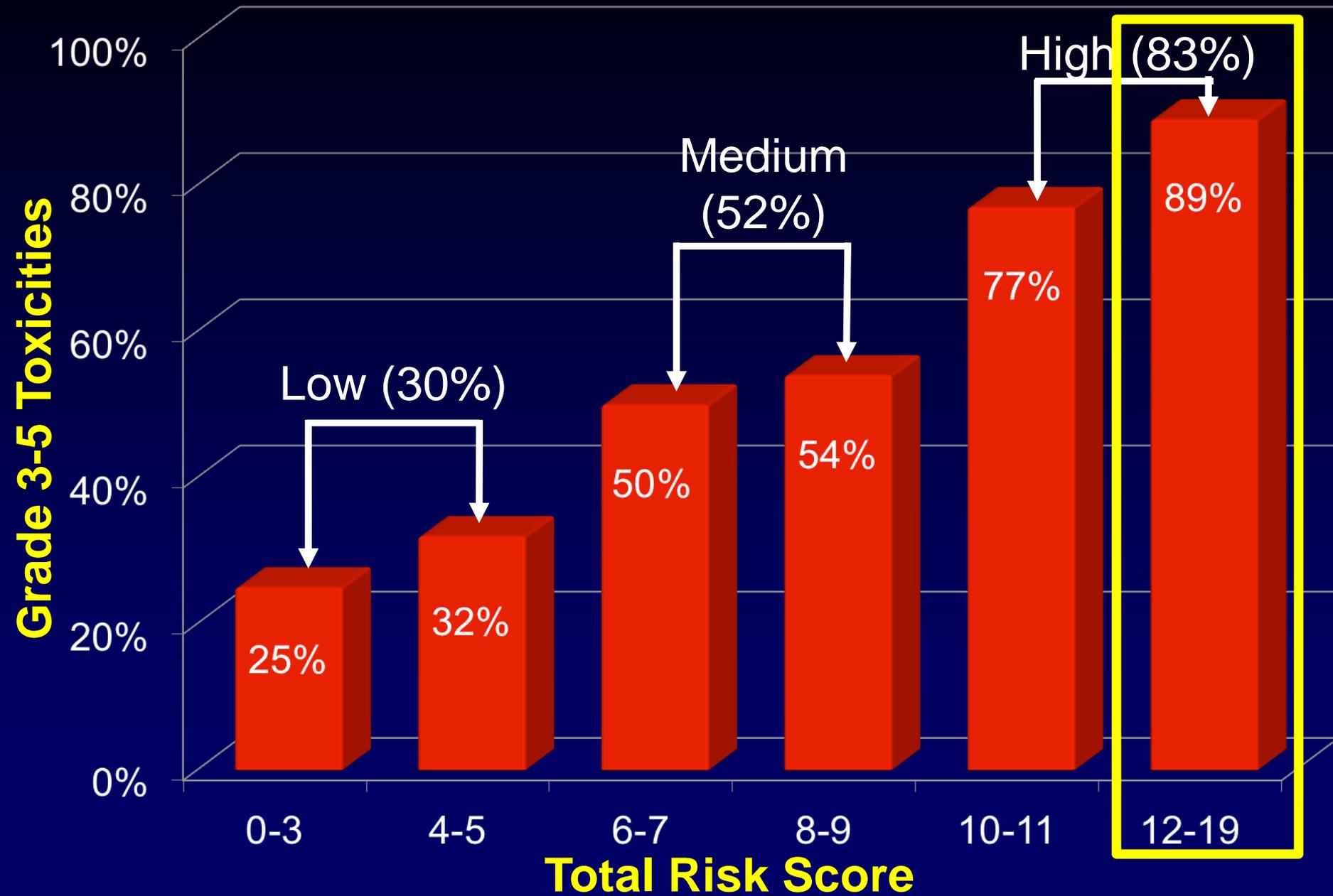
CRASH Score

CRASH Score Calculator

This score stratifies patients in 4 risk categories of severe toxicity. Reference for derivation and validation results: Extermann et al. Cancer, Epub Nov 9,2011 http://www.ncbi.nlm.nih.gov/pubmed/22072065. Formal clinical applications of the score still need to be studied.

* **Please click on each link to view/close help on assigning scores**

Chemotherapy risk

Chemotherapy risk	0

Hematologic Risk Factors

Diastolic blood pressure	0
IADL	0
LDH	0

Non-Hematologic Risk Factors

ECOG PS	0
MMS	0
MNA	0

Submit

Description	Score	Risk
Heme Score	3	Low
Non Heme Score	6	Med High
Combined Score	**9**	**Med High**

Extermann et al. Cancer, Epub Nov 9,2011 http://www.ncbi.nlm.nih.gov/pubmed/22072065.

We Can Anticipate Toxicity?

<u>Moving Beyond Prediction:</u>

Using Geriatric Assessment in Oncology Practice to Guide Practical Interventions

Geriatric Assessment-Guided Care Processes for Older Adults: A Delphi Consensus of Geriatric Oncology Experts

Supriya Gupta Mohile, MD, MS[a]; Carla Velarde, MPH[a]; Arti Hurria, MD[b]; Allison Magnuson, DO[a]; Lisa Lowenstein, PhD[a]; Chintan Pandya, MD[a]; Anita O'Donovan[c]; Rita Gorawara-Bhat, PhD[d]; and William Dale, MD, PhD[d]
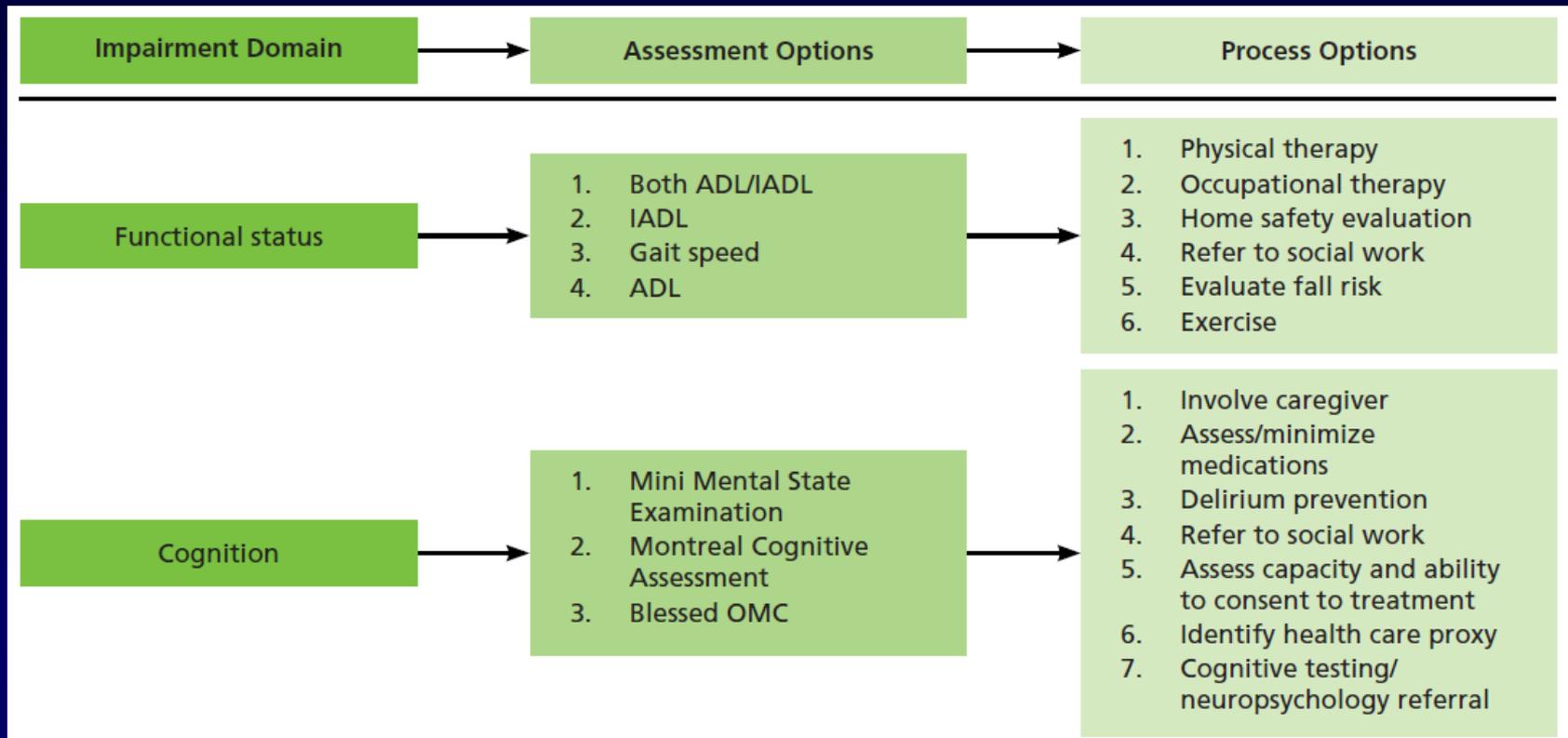
Impact of Geriatric Assessment on Management of Cancer Care

➤ <u>Objective</u>: Evaluate impact of geriatrician-led comprehensive geriatric assessment (CGA) interventions on chemotherapy toxicity in older patients with cancer

➤ Patients age 70+ receiving chemotherapy

- Standard Oncology Care: 70 patients

- CGA Interventions: 65 patients

➤ Results:

- No significant different in toxicity among both groups

- Intervention patients were more likely to:

  • Complete treatment as planned

  • Required fewer treatment modifications

Kalsi et al, BJC 2015

The effect of a geriatric evaluation on treatment decisions for older cancer patients – a systematic review

Marije E. Hamaker, Anandi H. Schiphorst, Daan ten Bokkel Huinink, Cees Schaar & Barbara C. van Munster

➢ Only 26% of patients received intervention recommendations in trials which relied on the cancer specialist for implementation

➢ Implementation of interventions highest in trials with:

- Standardized intervention protocol
- Geriatric consultation

Can We Intervene to Decrease the Risk? (UniHealth Grant, PI: Hurria)

Objective: To determine whether the geriatric assessment driven interventions will lead to improvement patient outcomes

Pre-Chemotherapy (Baseline)
- Geriatric Assessment
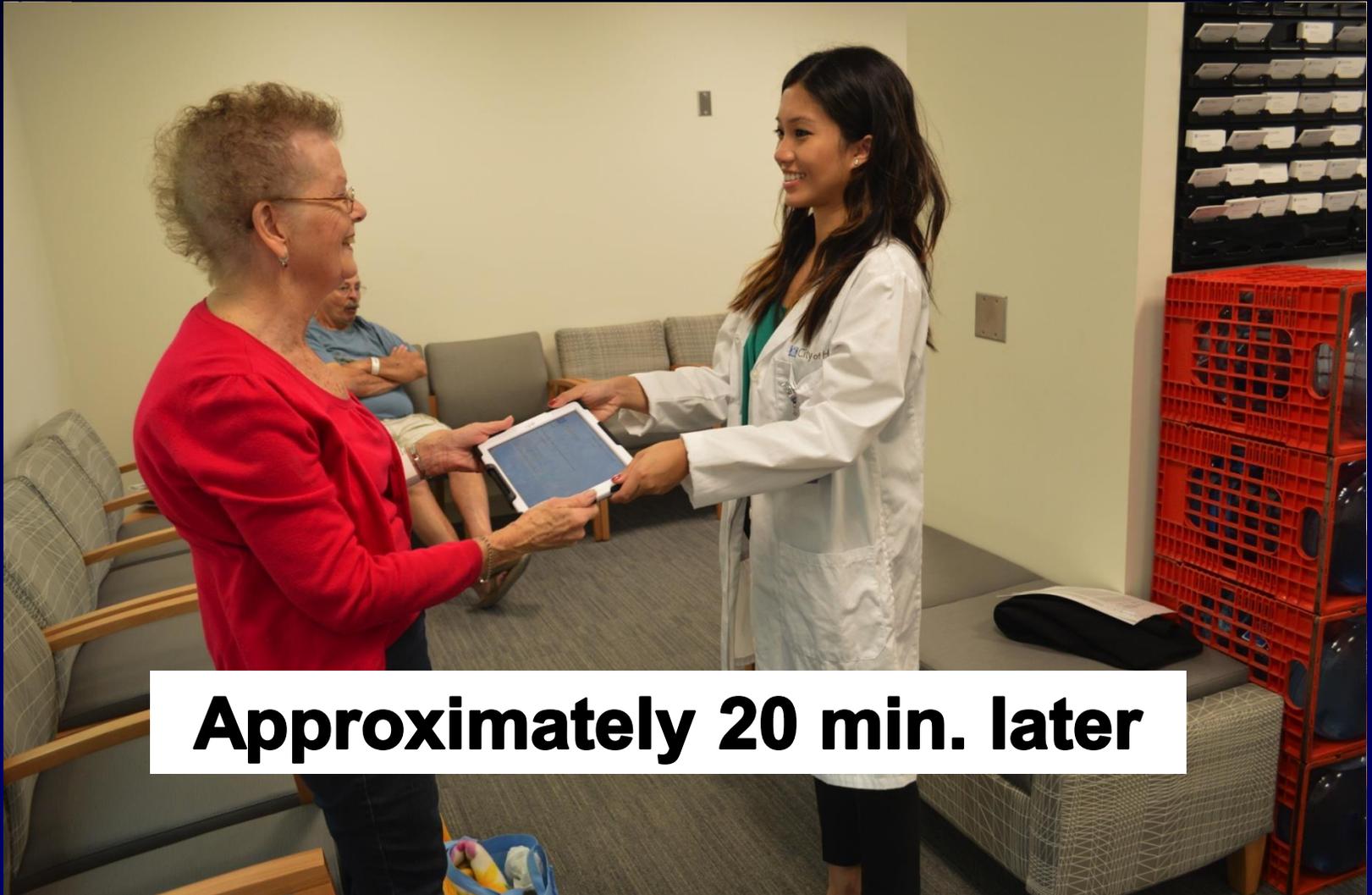- Calculation of Chemotherapy Toxicity Risk Score

↓

RANDOMIZATION (2:1)

Usual Care

Usual Care + Geriatric Assessment Intervention
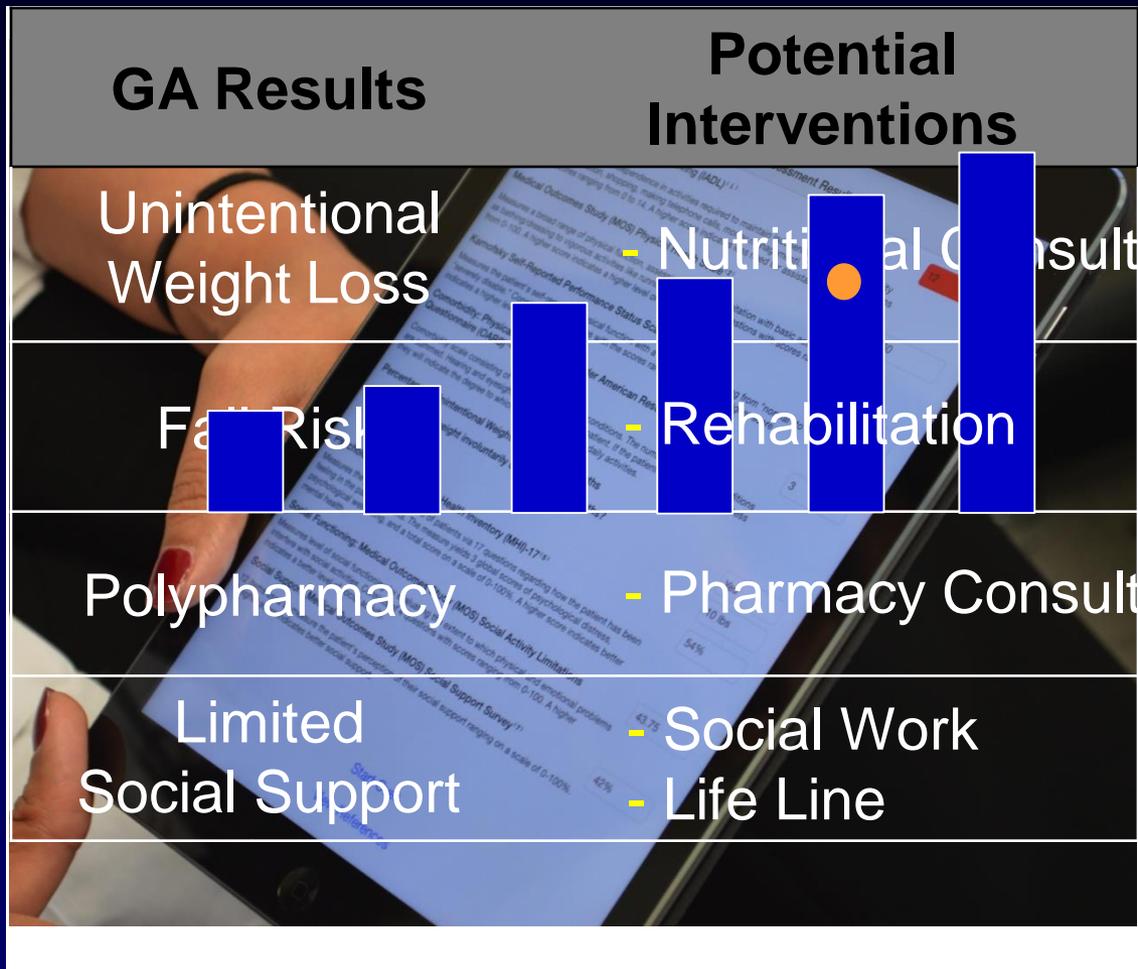
Facilitating Quality Cancer Care

Approximately 20 min. later

Facilitating Quality Cancer Care

Information Provided to the Healthcare Team

- Geriatric Assessment Results
- List of Potential Interventions
- Chemotherapy Toxicity Risk Score is Generated

GA Results	Potential Interventions
Unintentional Weight Loss	- Nutritional Consult
Fall Risk	- Rehabilitation
Polypharmacy	- Pharmacy Consult
Limited Social Support	- Social Work - Life Line

Facilitating Quality Cancer Care

Facilitates Communication and Decision-Making Between the Oncologist and Patient
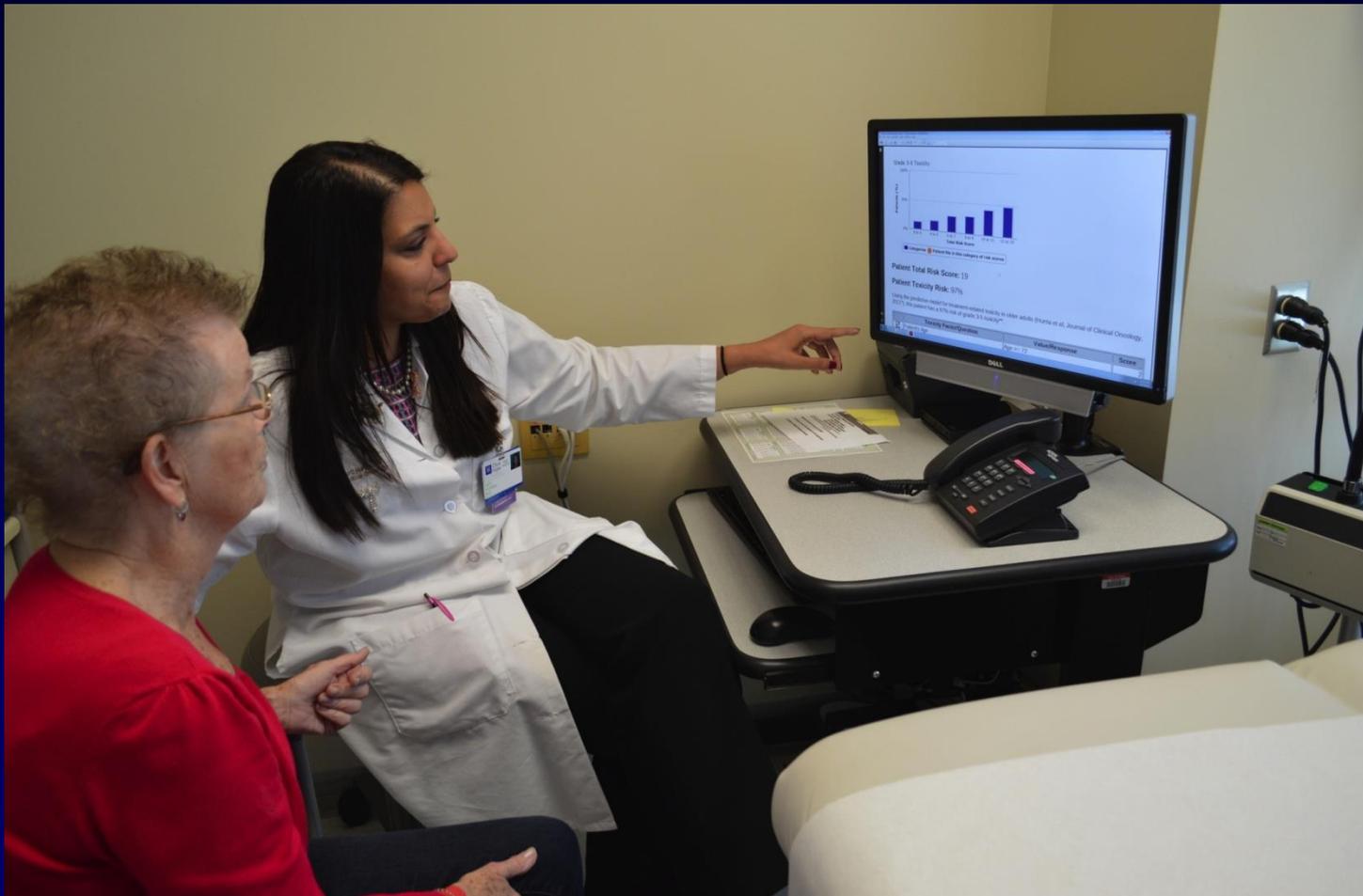
http://www.mycarg.org/mctc

Cancer and Aging Research Group

Mentoring Junior Faculty in Geriatric Oncology: Report From the Cancer and Aging Research Group

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Cary Gross, *Yale University, New Haven, CT*
Supriya Mohile, *University of Rochester, Rochester, NY*
Heidi Klepin, *Wake Forest University, Winston-Salem, NC*
William Tew, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Leona Downey, *University of Arizona, Tucson, AZ*
Ajeet Gajra, *University of New York Upstate Medical University, Syracuse, NY*
Cynthia Owusu, *Case Western Reserve University, Cleveland, OH*
Homayoon Sanati, *University of California at Irvine, Irvine, CA*
Theodore Suh, *The Cleveland Clinic, Cleveland, OH*
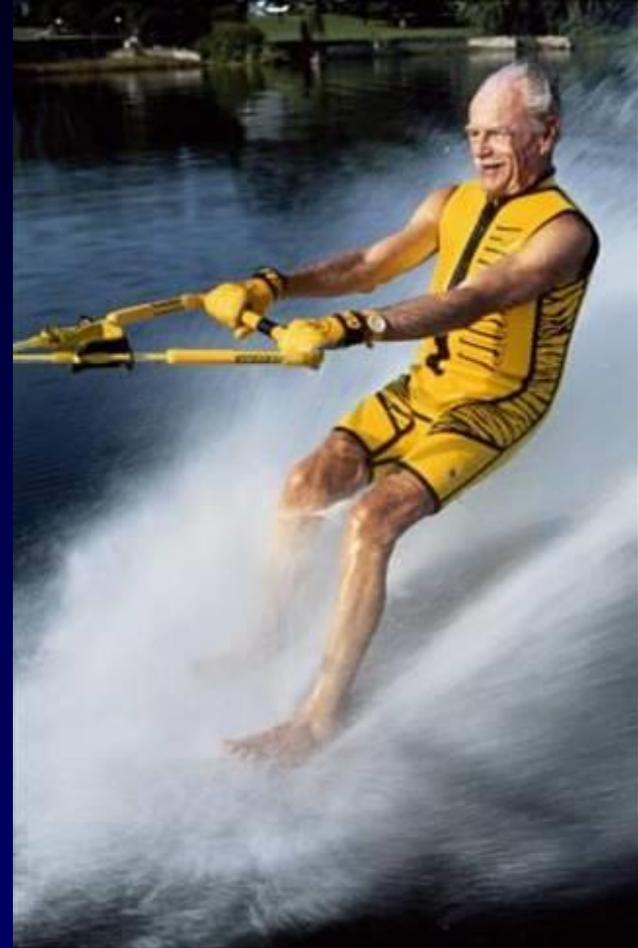Robert Figlin, *City of Hope, Duarte, CA*

Conclusions

➢ The population is aging

➢ Cancer is a disease associated with aging

➢ "Chronological age" ≠ "functional age"

➢ We need better tools to understand the risks and benefits of chemotherapy in older adults

➢ A melding of geriatric and oncology principles
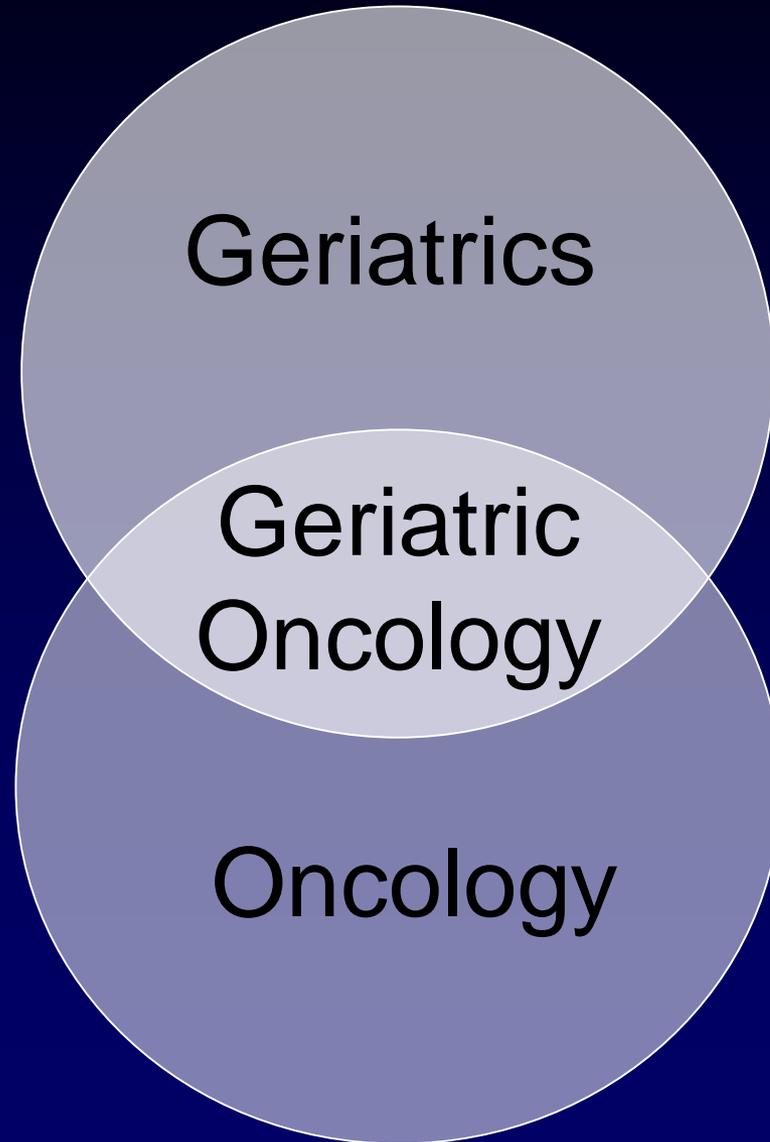
Chronological Age 80

Functional Age 90

Functional Age 70

Chronological Age ≠ Functional Age

100 Year Old Completes Marathon