Understanding the Effects of Chronological and Functional Age on Dosage Selection in Older Adults

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Disclosure:

- I am an employee of AbbVie but the content that I will present today is based on my own thoughts and experiences in my professional capacity as a Board Certified Pharmacist and Professor.

- All viewpoints provided are my own personal opinions and are not intended to reflect those of my employer, AbbVie.

- I wanted to recognize the late, great geriatric oncologist, Dr. Arti Hurria, who inspired the content included in the presentation.

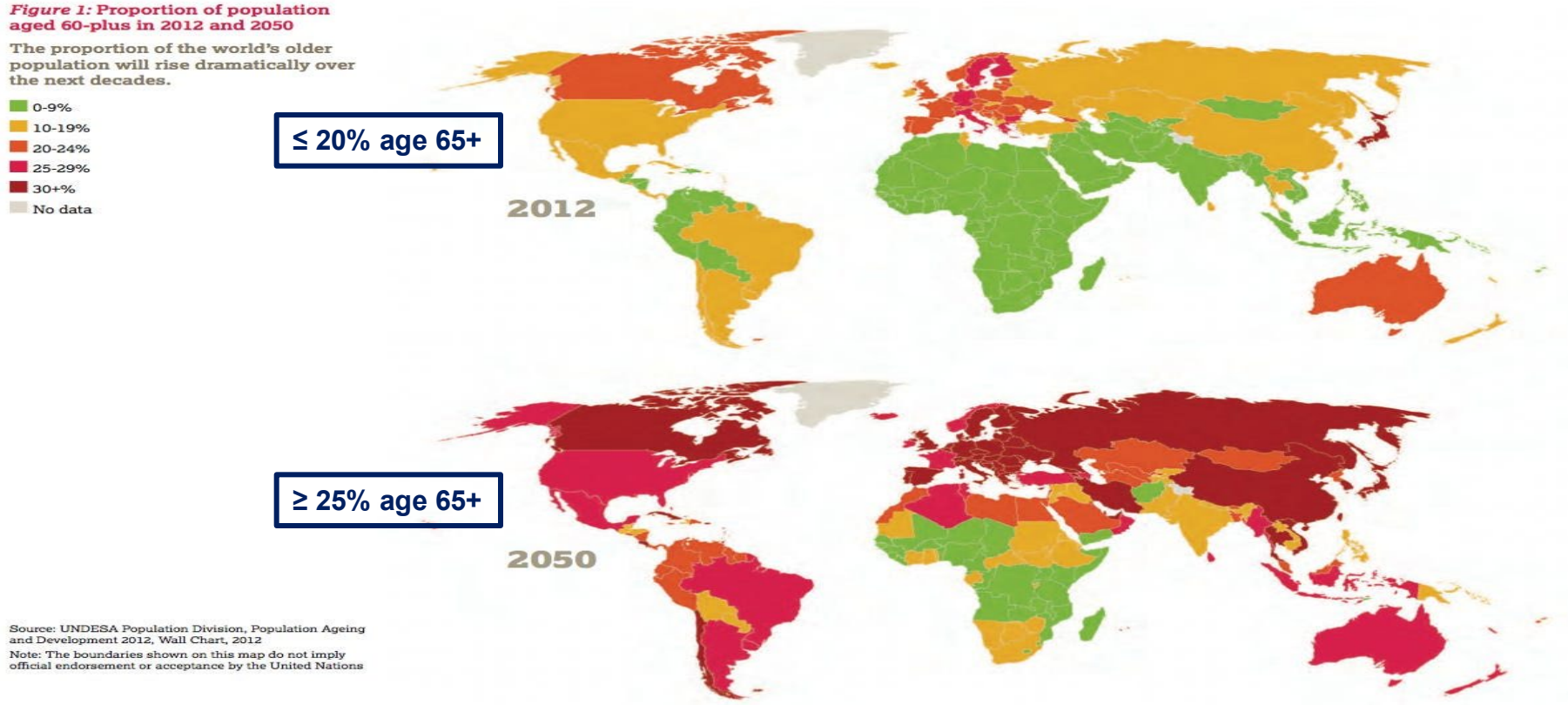
Objectives:

1. Compare and contrast chronological age and functional age

2. Identify physiologic changes and clinical pharmacology considerations for older adults when selecting treatments and dosing regimens

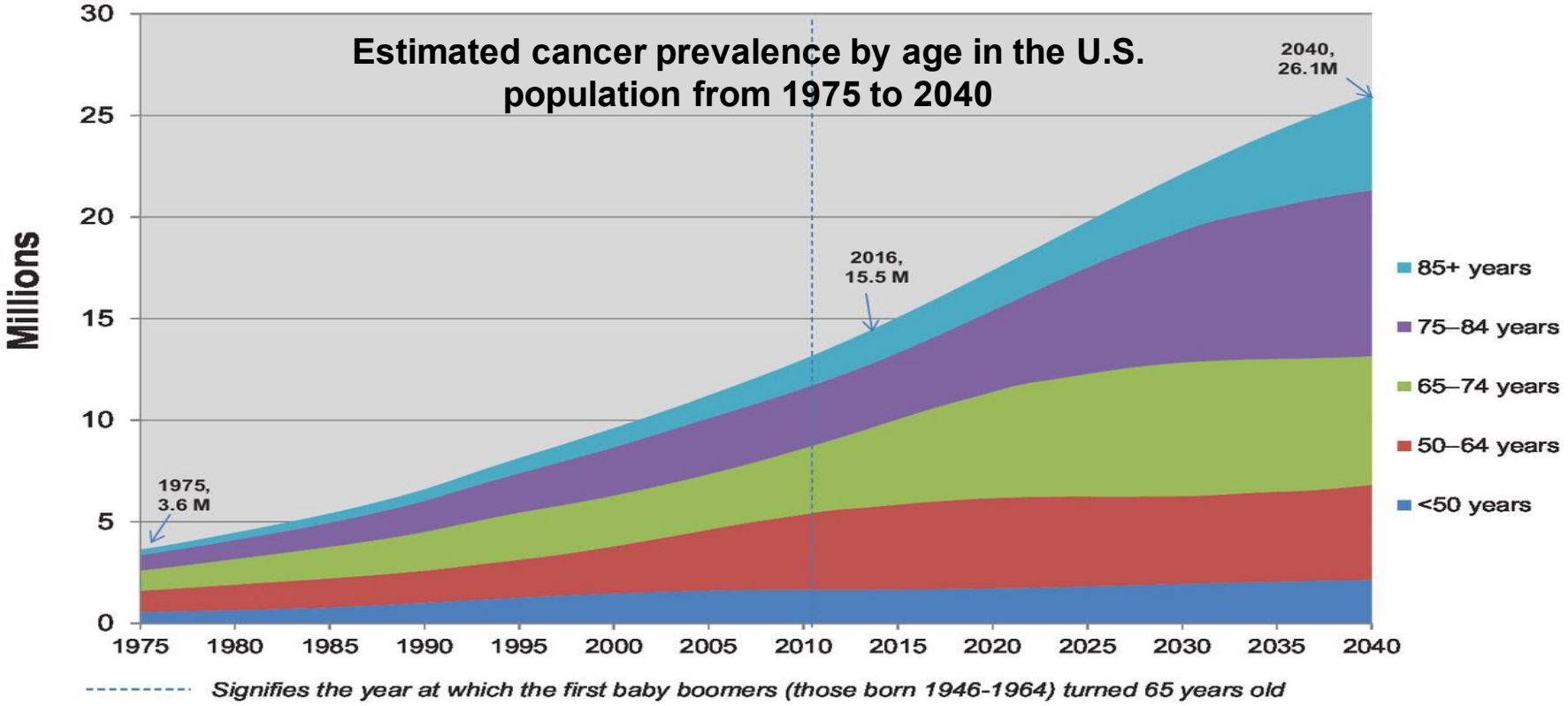
3. Describe how the geriatric assessment can be used to identify vulnerabilities when selecting treatment options for older adults with cancer

Worldwide Population is Aging



https://www.businessinsider.com/population-over-60-map-2014-5

U.S. Cancer Prevalence by Age



https://cebp.aacrjournals.org/content/25/7/1029.figures-only

Image displayed with permission from Bluethmann SM et al. Cancer Epidemiol Biomarkers Prev 2016;25:1029-1036.

The Aging Spectrum

Pediatrics

Unique Populations

- Age-related physiologic changes
- Vulnerability to toxicity
- Dependence in activities of daily living
- Concerns with long-term effects of therapy

Geriatrics

https://timesofmalta.com/articles/view/Do-we-age-to-become-ill-.485470

What's the Relationship Between Chronologic Age and Functional Age?

Start here

- Copies sounds
- Begins to sit without support

6 Months

- Likes to play with others, especially parents
- Responds to own name

- String vowels together when babbling ("ah", "eh", "oh")

12 Months (1 Year)

- Uses simple gestures such as shaking head for "no" or waving "bye bye"
- Copies gestures

- Respond to simple spoken requests

18 Months (1 ½ Year)

- Says "mama" and "dada"
- Pulks up to stand

- Plays simple pretend, such as feeding a doll
- Points to show others something interesting

2 Years

- Follows simple instructions
- Kicks a ball

- Says several single words
- Walk alone

- Points to things or pictures when they're named

3 Years

- Says sentences with 2 to 4 words
- Gets excited when with other children

- Knows what ordinary things are for; for example, telephone, brush, spoon

- Carries on a conversation using 2 to 3 sentences
- Climbs well

- Hopes and stands on one foot for up to 2 seconds

4 Years

- Draws a person with 2 to 4 body parts
- Plays cooperatively

- Copies adults and friends (like running when other children run)

- Plays make-believe with dolls, animals and people
- Shows affection for friends without prompting

- Would rather play with other children than alone
- Tells stories

Chronologic Age Versus Functional Age in Older Adults with Cancer

Chronologic age = 80 years

Chronological age alone is often a poor indicator of the physiological and functional status of older adults; age alone should not be the main factor guiding treatment decisions in oncology.

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Soto-Perez-de-Celis E, Li D, Yuan Y, et al. The Lancet Oncology. 2018;19(6):e305-16.

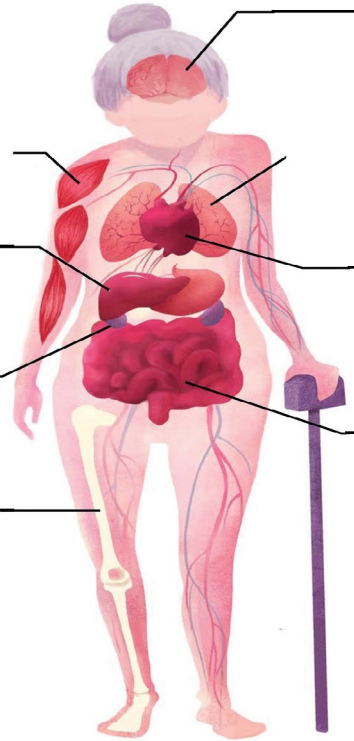
Age-related Physiologic Changes Influence Clinical Pharmacology and Dosage Selection

Age-related Physiologic Changes (Pharmacokinetic Considerations)

Liver
- ↓ Volume
- ↓ Blood Flow
- ↓ First-pass Metabolism
- ↓ Drug Clearance

Kidneys
- ↓ Glomerular Filtration
- ↓ Renal Mass
- ↓ Drug Clearance

Bone
- ↓ Bone Mineral Density
- ↑ Fracture Risk



CNS
- ↓ Synaptic Density
- ↓ Processing Speed
- ↓ Attention
- ↓ Memory

Cardiovascular system
- ↓ Cardiac Output
- ↓ Heart Rate Modulation
- ↑ Arterial Stiffness
- Myocardial Hypertrophy

Digestive system
- ↓ Acid Secretion
- ↓ Drug Absorption

Soto-Perez-de-Celis E, Li D, Yuan Y, et al. The Lancet Oncology. 2018;19(6):e305-16.
Nightingale G, Schwartz R, Kachur E, et al. Journal of Geriatric Oncology. 2019;10(1):4-30.

Age-related Physiologic Changes (Pharmacodynamic Considerations)

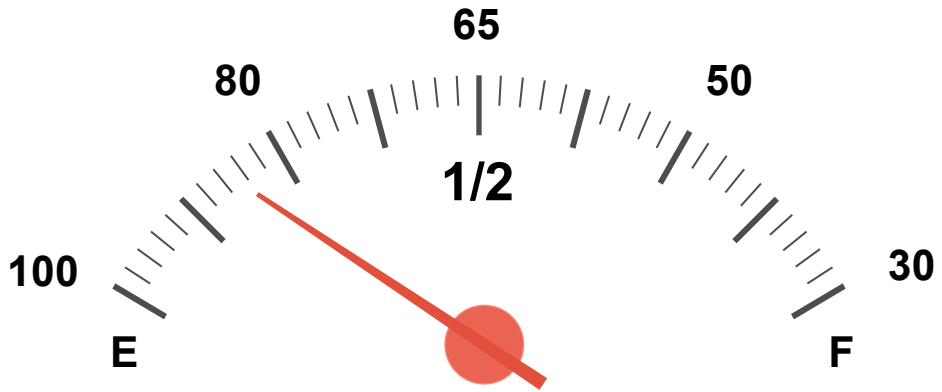
Pharmacodynamics is defined as the correlation between drug concentration at the receptor and the resulting effect (influenced by variations in receptor number, receptor affinity, cellular response) and by changes in functional organ reserves.

Examples:

- Older adults have increased sensitivity to anthracycline-induced cardiovascular effects, increased risk of cardiomyopathy
- Older adults have reduced bone marrow reserve which increases the risk for chemotherapy-induced myelosuppression

Dimitrow MS, Airaksinen MS, Kivelä SL, et al. Journal of the American Geriatrics society. 2011;59(8):1521-30.
Nightingale G, Schwartz R, Kachur E, et al. Journal of Geriatric Oncology. 2019;10(1):4-30.

Hallmarks of aging: Reduced physiologic reserve



Physiologic reserve = Fuel available

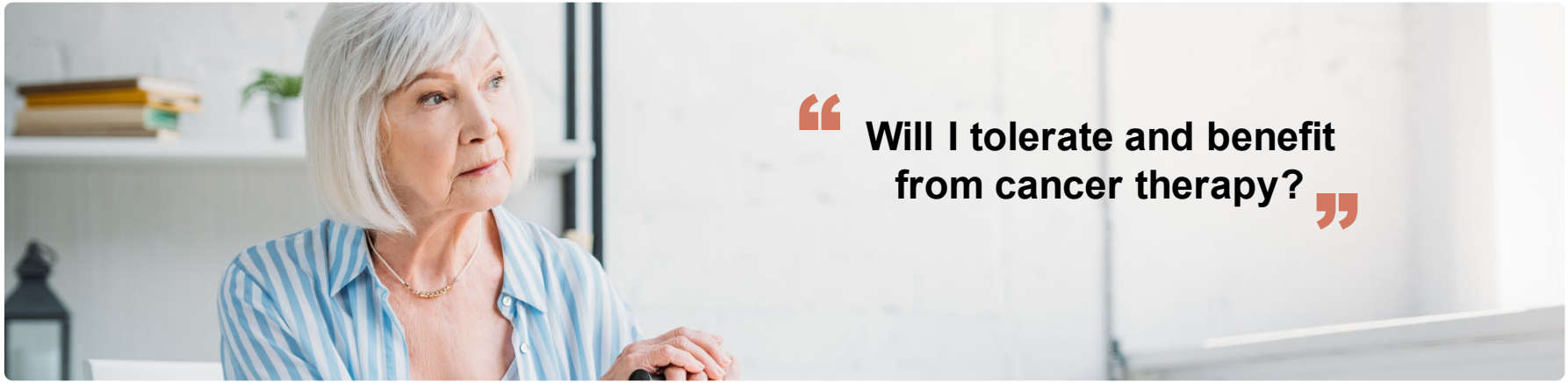
- May not be obvious at rest
- Becomes apparent with a stressor

There is little clinical trial evidence to guide treatment decisions for (many) older adults

Older adults are underrepresented on cancer clinical trials

Older adults on clinical trials are often not representative of patients seen in clinical practice

Talarico L et al. Journal of Clinical Oncology. 2004;22:4626-4631.
Dale W, Klepin HD, Williams GR, Alibhai SM, et al. Journal of Clinical Oncology. 2023;41(26):4293-312.



Factors Affecting Individualized Treatment Decisions

- **Characteristics of the tumor** (e.g., tumor genetics, molecular findings)
- **Characteristics of the anti-cancer treatment regimen** (e.g., safety profile)
- **Characteristics of the patient** (e.g., physiologic reserve, comorbidities)

Integrating Geriatric Assessments into Oncology Practice

Intersection of Geriatrics and Oncology

Geriatric Assessment (GA)

Factors other than chronologic age predict treatment related morbidity/ mortality in older adults with cancer

Key Domains for Assessment

- Functional status (ADL, IADL*, mobility)
- Comorbid medical conditions (Severity, compensated)
- Nutritional status (Access to nutrition support, BMI**)
- Cognitive function (Cognition screening)
- Psychological state (Depression, distress)
- Social support (caregivers, transportation, finances)
- Medications (adherence, polypharmacy, high risk drugs)

Fit

- Minimal co-morbidities
- Independence with ADLs, IADLs
- Similar to younger age counterparts

Vulnerable

- Controlled co-morbidities
- Some dependence with IADLs
- Geriatric syndrome

Frail

- Several co-morbidities
- Dependence with ADLs
- Significant geriatric syndromes

*Instrumental activities of daily living, **Body mass index

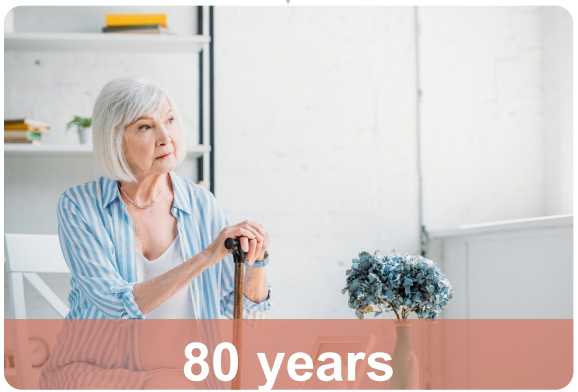
2023 NCCN Clinical Practice Guidelines in Oncology – Older Adult Oncology
Available at: https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf Accessed 9/7/2023

A Tailored, Personalized Approach

Tailoring Cancer Treatment and Dosage Selection

80 years

No major comorbidity, exercises regularly, no geriatric syndromes, life expectancy ~ 13years*



80 years

Compensated comorbidity, independent with activities, 1 fall in the past 6 months, life expectancy ~ 8.5 years*

80 years

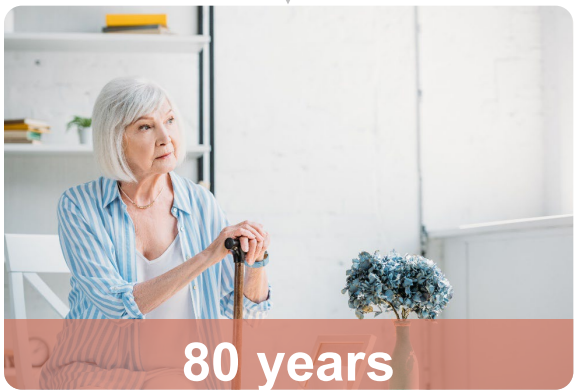
Moderate cognitive impairment, dependent with activities, 3 falls, life expectancy < 5 years*

*life expectancy estimated with e-Prognosis

A Tailored, Personalized Approach

Tailoring Cancer Treatment and Dosage Selection

FIT: Similar tolerance and benefit as middle-aged patient.



Vulnerable: Decreased treatment tolerance. Consider a modified therapy plan.

Frail: Not likely to tolerate anti-cancer therapy; Consider supportive care.

*life expectancy estimated with e-Prognosis

Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update

Recommendations

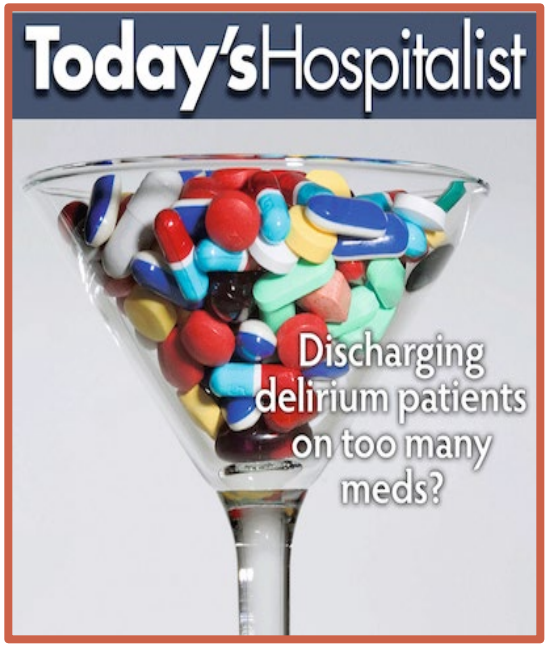
- The geriatric assessment (GA) should be used to identify vulnerabilities or impairments that are not routinely captured in oncology assessments for all patients over 65 years old with cancer
- A GA should include high priority aging related domains known to be associated with outcomes in older adults with cancer: physical and cognitive function, emotional health, comorbid conditions, polypharmacy, nutrition, and social support

In patients over 65 years receiving chemotherapy, geriatric assessment should be used to identify vulnerabilities that are not routinely captured in oncology assessments.

Dale W, Klepin HD, Williams GR, Alibhai SM, et al. Journal of Clinical Oncology. 2023;41(26):4293-312.

Polypharmacy: The Other Drug Problem?

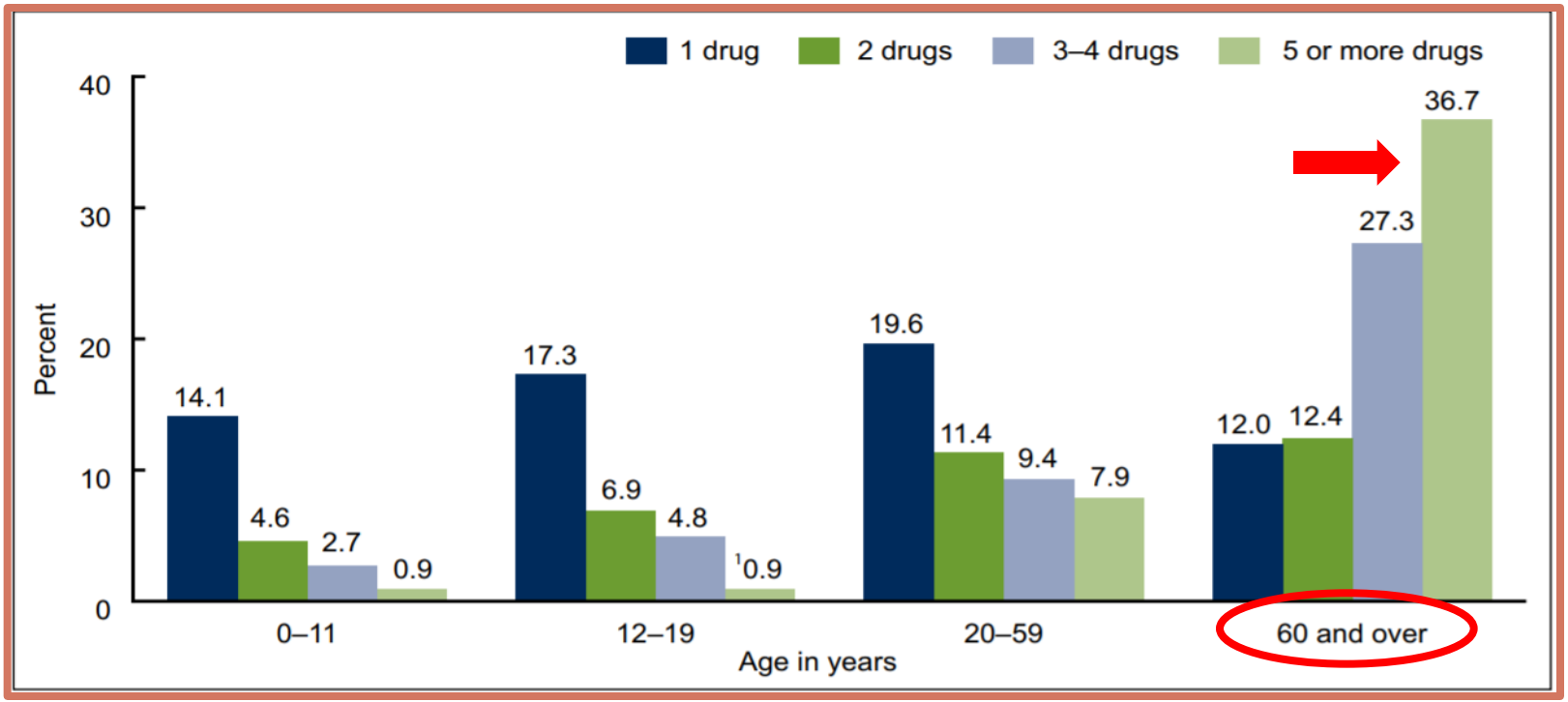
Defined as the use of ≥ 5 medications or the use of high-risk drugs



Masnoon N, Shakib S, Kalisch-Ellett L, et al. BMC Geriatrics. 2017;17:1-10.
Hajjar ER, Cafiero AC, Hanlon JT. The American Journal of Geriatric Pharmacotherapy. 2007;5(4):345-51.

Polypharmacy: The Other Drug Problem?

More than an 1/3 of older Americans use ≥ 5 prescription drugs



CDC/NCHS, National Health and Nutrition Examination Survey

The Influence of Polypharmacy in Older Adults with Cancer

- Risk of adverse drug events
- Risk of cognitive impairment
- Risk of depression
- Risk of disability
- Risk of falls
- Risk of healthcare resource utilization
- Risk of post-operative complications
- Risk of caregiver burden
- Risk of mortality
- Risk of drug-drug interactions

Mohamed MR, Ramsdale E, Loh KP, et al. The Oncologist. 2020;25(1):e94-108.
Lu-Yao G, Nightingale G, Nikita N, et al. Journal of Geriatric Oncology. 2020;11(4):579-85.
Nightingale G, Pizzi LT, Barlow A, et al. Journal of Geriatric Oncology. 2018;9(5):526-33.
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Pamoukdjian F, Aparicio T, Zelek L, et al. Journal of Geriatric Oncology. 2017;8(3):190-5.
Canoui-Poitrine F, Reinald N, Laurent M, et al. Psycho-Oncology. 2016;25(1):104-11.

In Summary:

- Unique challenges exist when considering cancer treatment (dosage selection) in older adults with cancer. Chronological age, alone, is insufficient to guide treatment decisions.

- Functional age, determined by a geriatric assessment, can be useful to tailor cancer treatment in older adults with cancer.

- Broadening cancer therapy trials to capture not only chronologic age but functional age would allow clinicians to better identify subsets of older adults who are most vulnerable to morbidity and mortality.

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