Transplant and CAR T-cell Therapy for Older Adults

Celebrating a Second Chance at Life Survivorship Symposium

April 27 – May 3, 2024

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Transplant and CAR T-cell Therapy for Older Adults

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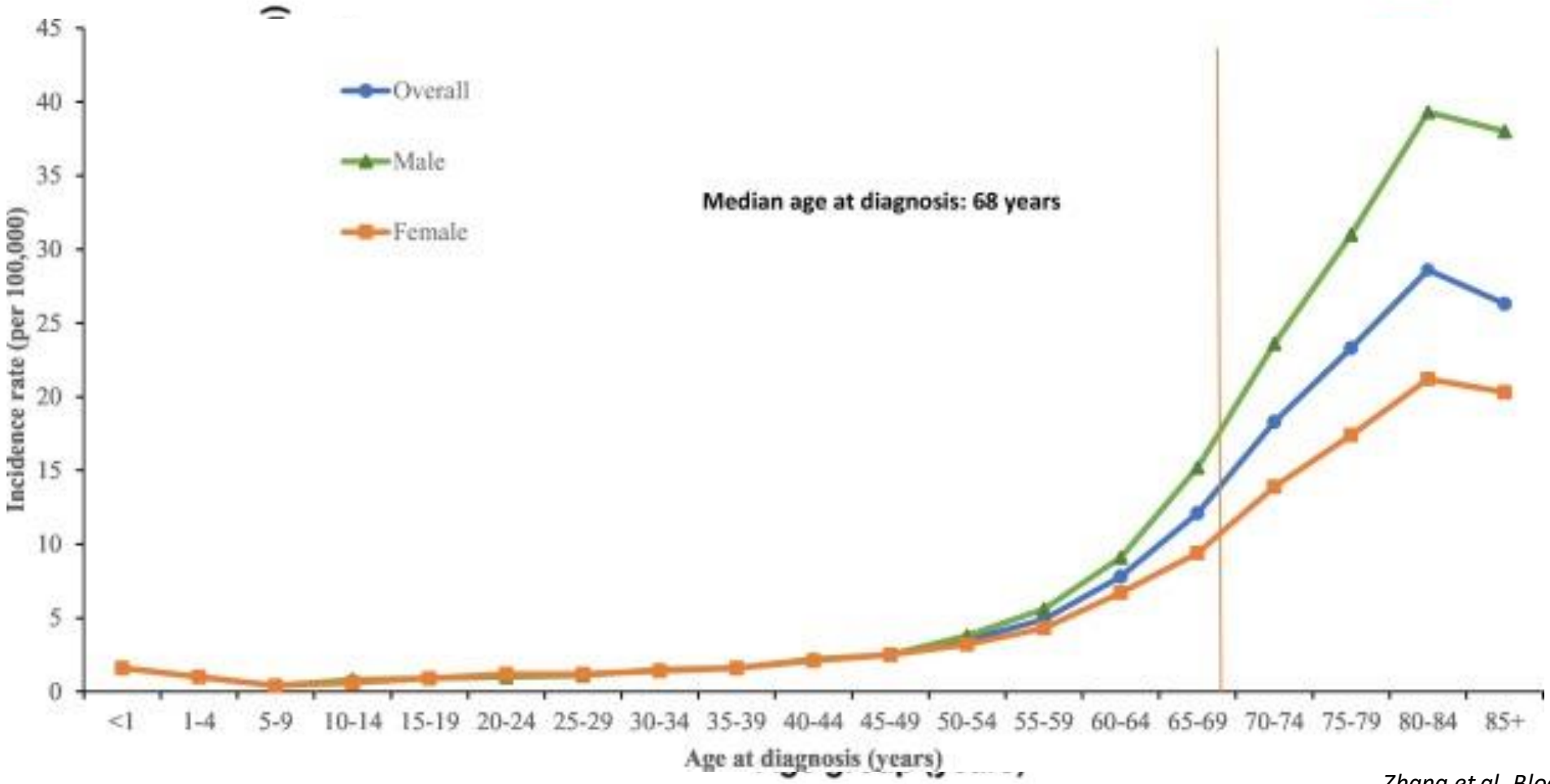
4.28.2024

Learning Objectives

- How old is too old for transplant or CAR T-cell therapy?
- Health issues that may preclude older adults from transplant or CAR T-cell therapy
- Outcomes after transplant and CAR T-cell therapy in older adults
  - Do outcomes differ in older versus younger patients?
  - Can we predict outcomes based on a patient's health status?
- Strategies to tailor the therapy to the needs of older adults

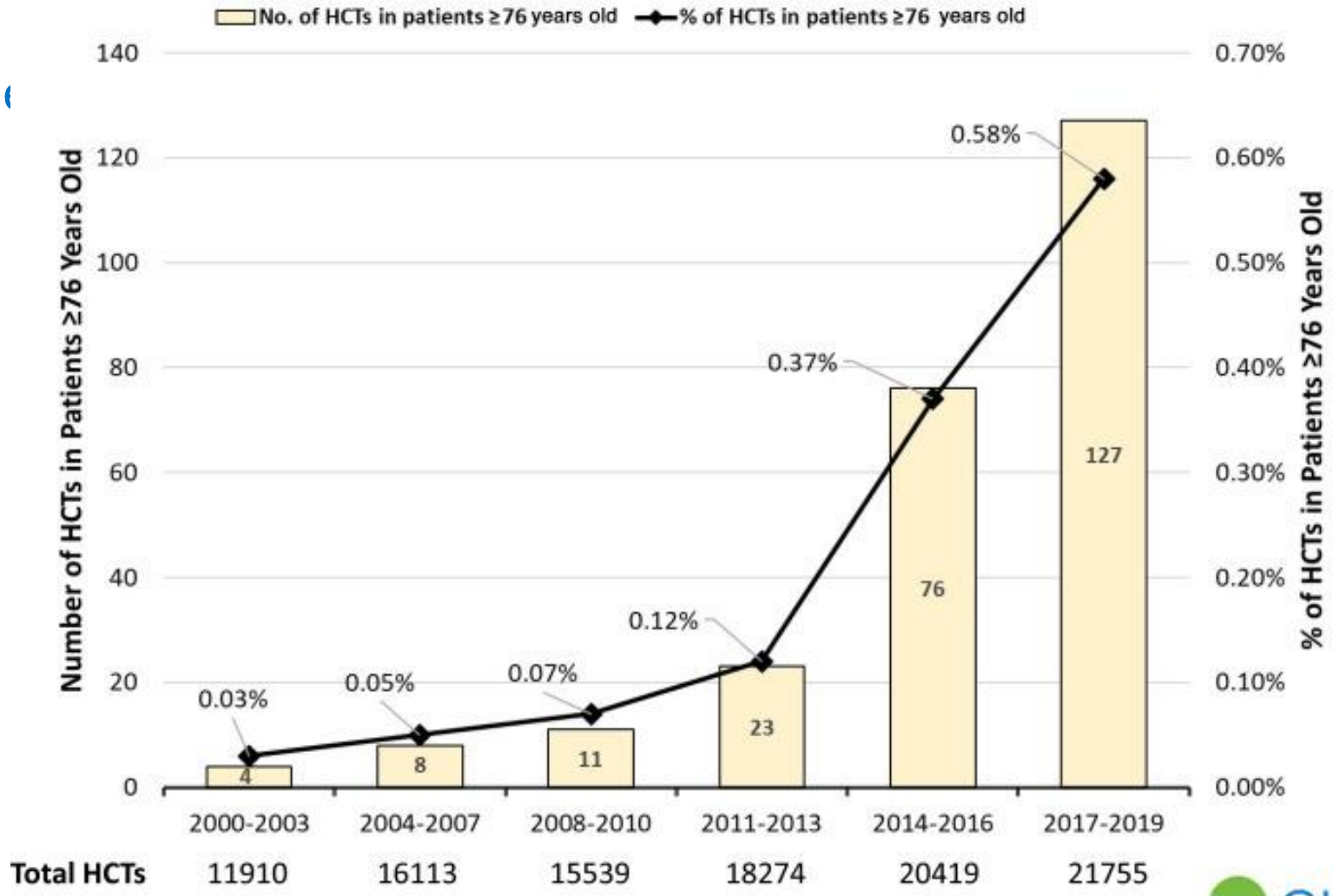
Blood cancers are primarily diseases of older adults



Zhang et al. Blood Cancer Journal 2023
Shallis et al. Blood Reviews 2019

More older adults are undergoing donor transplants…

…but th

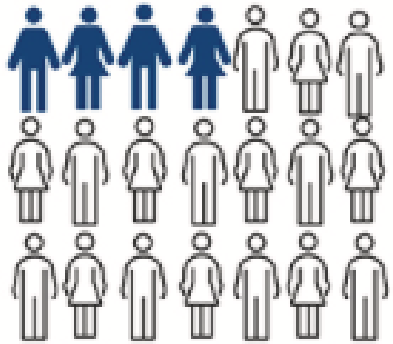


y Slide 2022

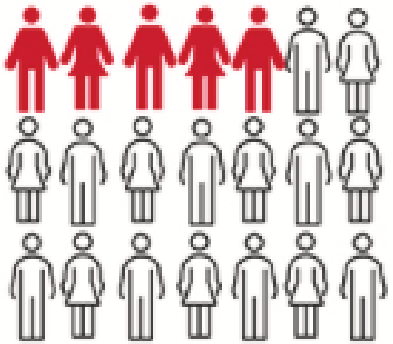
CAR T-cell usage is low in older adults with lymphomas

CAR T-cell utilization in patients with DLBCL who received two or more lines of treatments among Medicare Fee-for-Service beneficiaries:

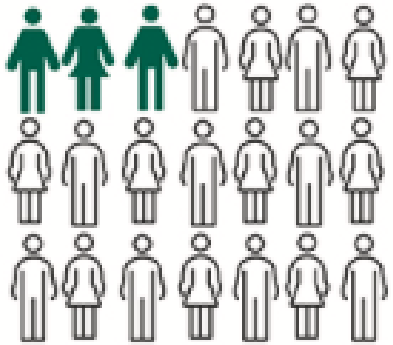
19% of DLBCL Patients Aged 65-69 Utilize CAR T



22% of DLBCL Patients Aged 70-74 Utilize CAR T



13% of DLBCL Patients Aged 75+ Utilize CAR T



"CAR T-cell therapy was not used in 80%+ of patients who received third-line treatment and beyond, highlighting significant barriers among older patients"

Chihara et al. Blood Advances 2023

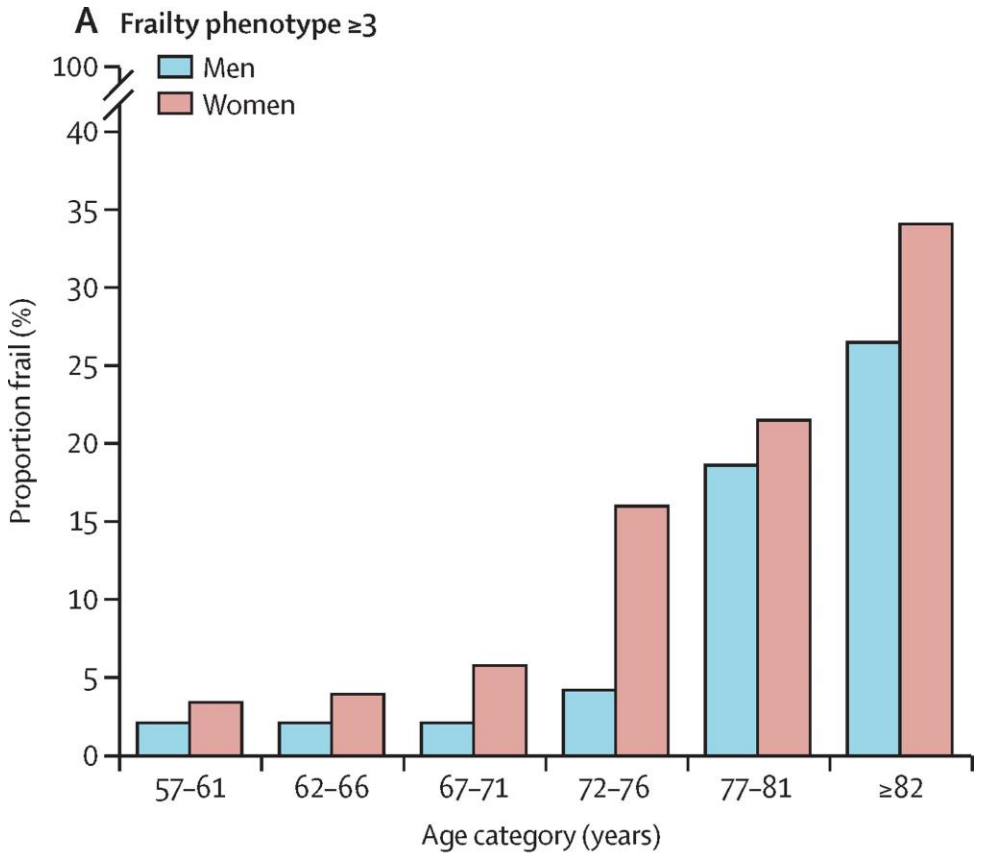
Frailty impacts outcomes after many cancer therapies

- Frailty is an aging-related syndrome of diminished physiologic reserve
- Frailty phenotype defined by presence of ≥3 of the following

FRAILTY PHENOTYPE	FRAILTY COMPONENTS
>5% BW in prior year	⇦ **Weight loss, unintentional**
In the lowest 20%	⇦ **Weakness, grip strenght**
Self report of exhaustion	⇦ **Poor endurance and energy**
Time to walk 15 feets: slowest 20%	⇦ **Slowness**
Score of Kcal/ wk: lowest 20%	⇦ **Low physical activity level**

Garcia-Gimenez et al. Int. J. Environ. Res. Public Health 2021

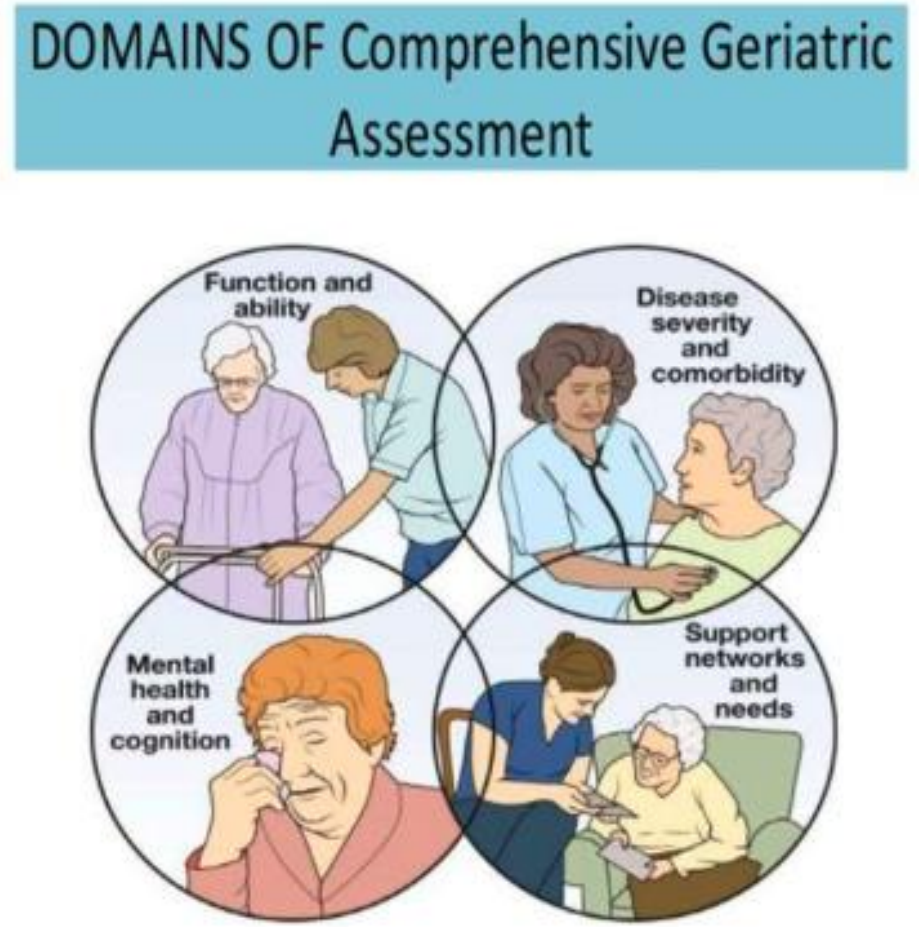
Frailty and age are correlated but are not the same



- Frailty increases with age
- It is possible to be young and frail, or old and fit
- Age is not the best determinant of a person's fitness and ability to tolerate medical stressors

Hoogendijk et al *The Lancet* 2019

The geriatric assessment evaluates health holistically

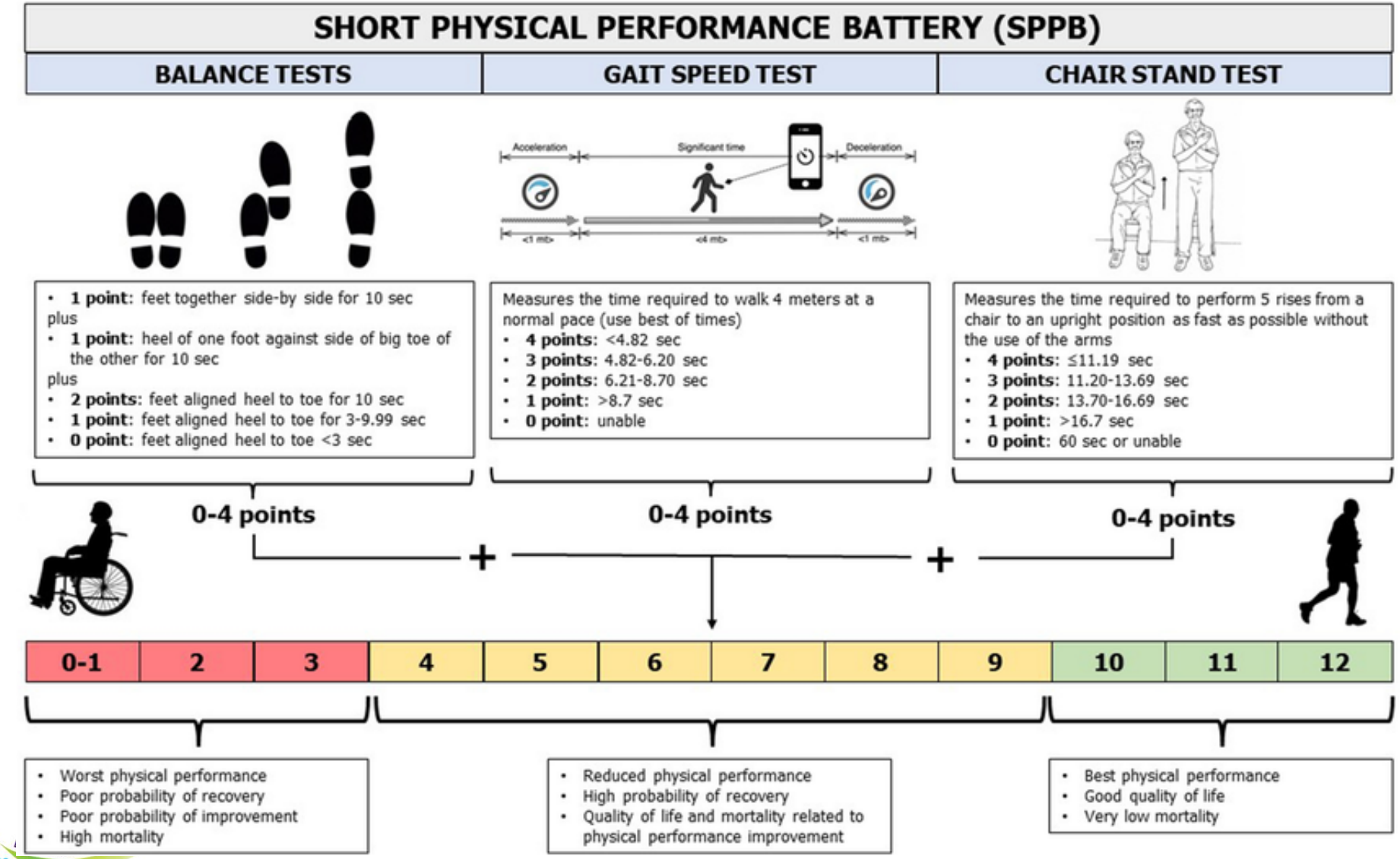


Health domains:

- Physical performance/strength
- Functional status
- Presence of other medical problems and use of medications
- Cognition
- Psychological status
- Nutritional status
- Social support in daily life

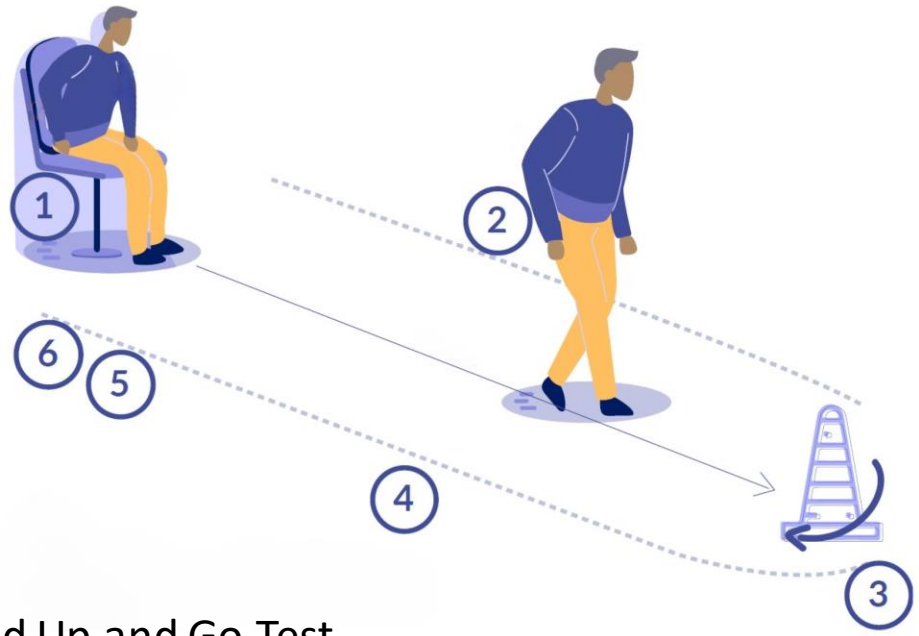
Image credit: Basicmedical Key

Tests of physical function and frailty



Tonet et al. Aging Clin Exp Res 2023

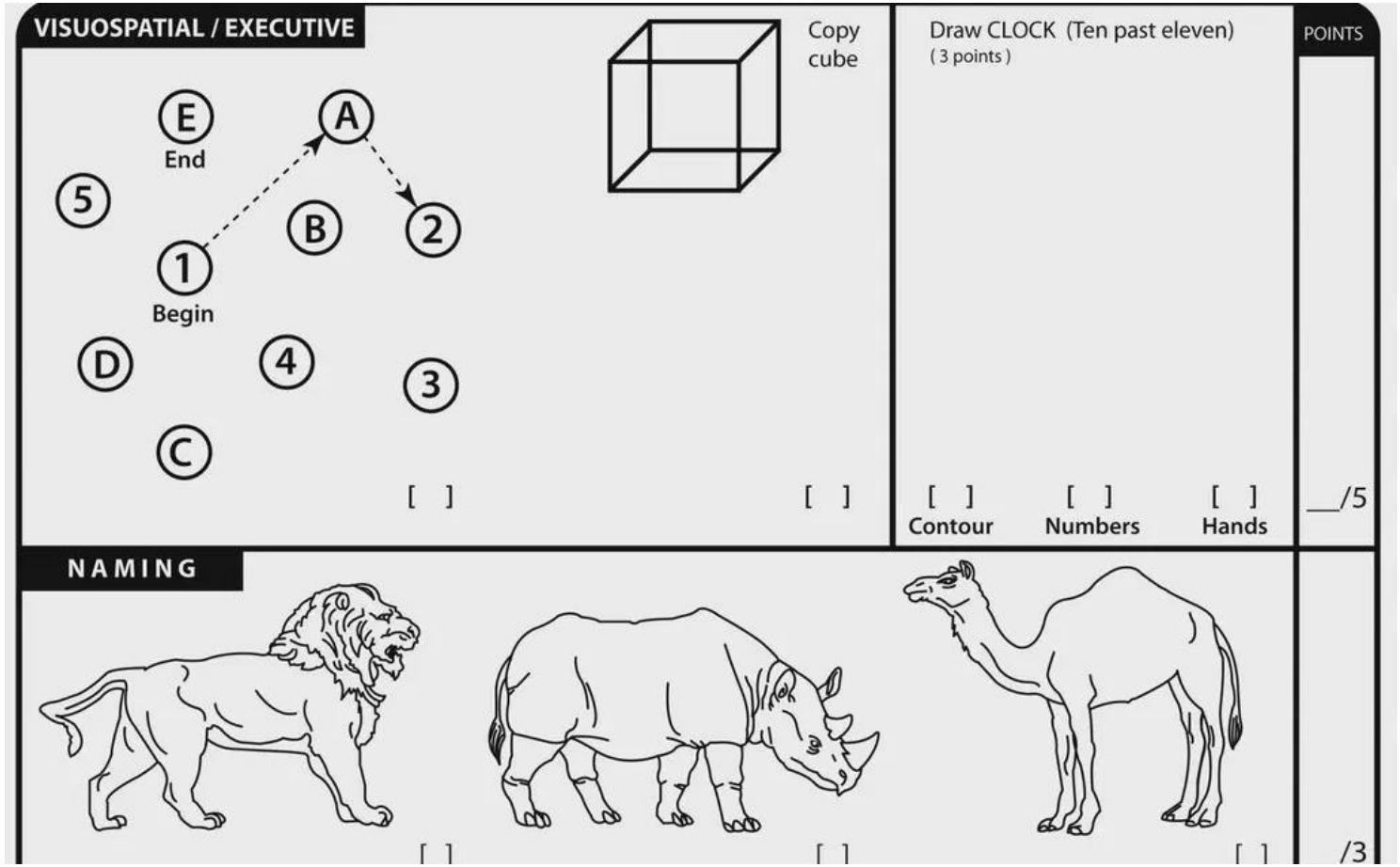
Tests of physical function and frailty



Timed Up and Go Test

Grip Strength Testing

Montreal Cognitive Assessment (MOCA)



Montreal Cognitive Assessment (MOCA)

MEMORY	Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						
ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order [ ] 2 1 8 5 4 Subject has to repeat them in the backward order [ ] 7 4 2						___/2
	Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B							___/1
	Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**							___/3
LANGUAGE	Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]							___/2
	Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)							___/1
ABSTRACTION	Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler							___/2
DELAYED RECALL	Has to recall words **WITH NO CUE**		FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only ___/5
Optional	Category cue							
	Multiple choice cue							
ORIENTATION	[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City							___/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Montreal Cognitive Assessment V 7.1

Patient-reported data is critical in this assessment!

I. Your Daily Activities

Instruc

1. Can y

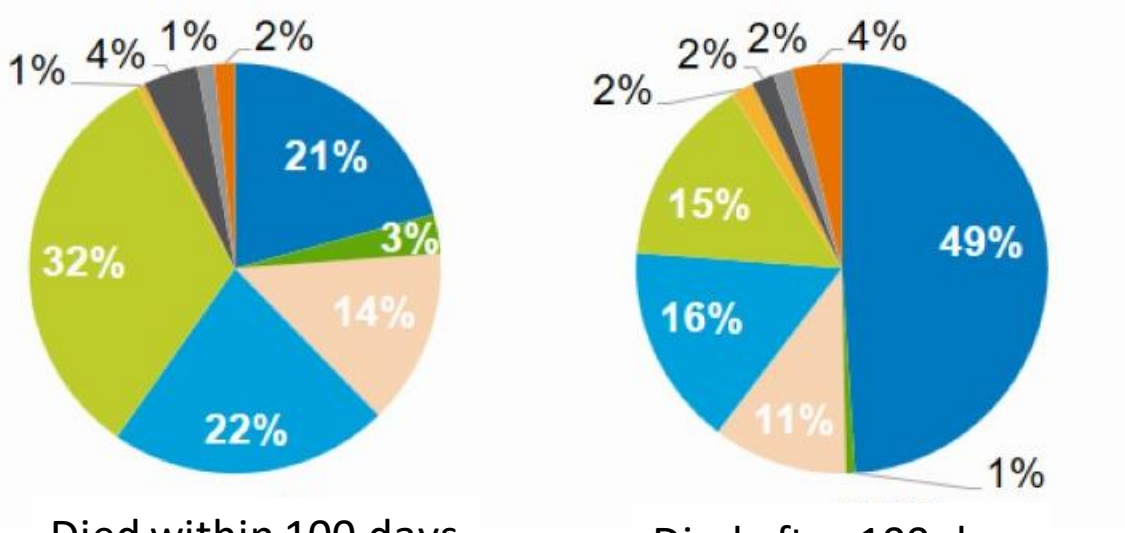
2. Can y

3. Can you go shopping for groceries or clothes (assuming you have transportation) . . .	○ **without help** (*taking care of all shopping needs yourself, assuming you had transportation*); ○ **with some help** (*need someone to go with you on all shopping trips*); **or** ○ **are you completely unable to do any shopping?**
4. Can you prepare your own meals . . .	○ **without help** (*plan and cook full meals yourself*); ○ **with some help** (*can prepare some things but unable to cook full meals yourself*); **or** ○ **are you completely unable to prepare any meals?**
5. Can you do your housework . . .	○ **without help** (*can clean floors, etc.*); ○ **with some help** (*can do light housework but need help with heavy work*); **or** ○ **are you completely unable to do any housework?**

Donor Transplants

Non-relapse mortality is a major barrier to successful donor transplants

- **Non-relapse mortality**: death unrelated to disease relapse (i.e. death due to a transplant-related complication)
- Causes of death after unrelated donor transplant, 2019-2020:



Died within 100 days of transplant

Died after 100 days of transplant

CIBMTR Summary Slide 2022

Non-relapse mortality is a major barrier to successful donor transplants

- European transplant registry (2023):
  - In adults 65+ years who undergo donor transplant, 27% will die of non-relapse mortality within 3 years*
- American transplant registry (2017):
  - In adults 70+ years who undergo donor transplant, 33-35% will die of non-relapse mortality within 2 years**

Bazarbachi et al. American Society of Hematology 2023

***Muffly et al. Blood 2017*

Do older adults experience excess non-relapse mortality after donor transplants?

- Many studies have investigated this question with slightly varying results
- In general, well selected older adults do not experience much higher rates of non-relapse mortality after donor transplants compared to younger adults
- Many studies suggest the rates may not be higher at all

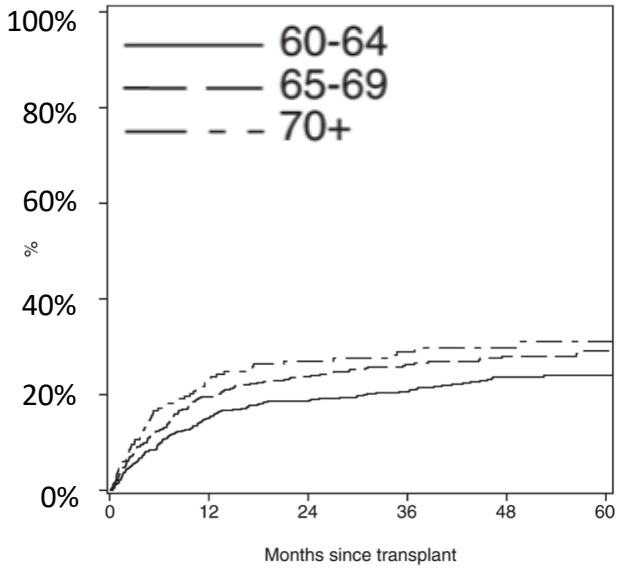
Some examples…

- In patients with **myelodysplastic syndrome**,
  - 3-year non-relapse mortality: **28%** (65+ years) vs **25%** (55-64 years)
  - 3-year overall survival **37%** (65+ years) vs **42%** (55-64 years)

  Age had no <u>significant</u> association with overall survival or non-relapse mortality

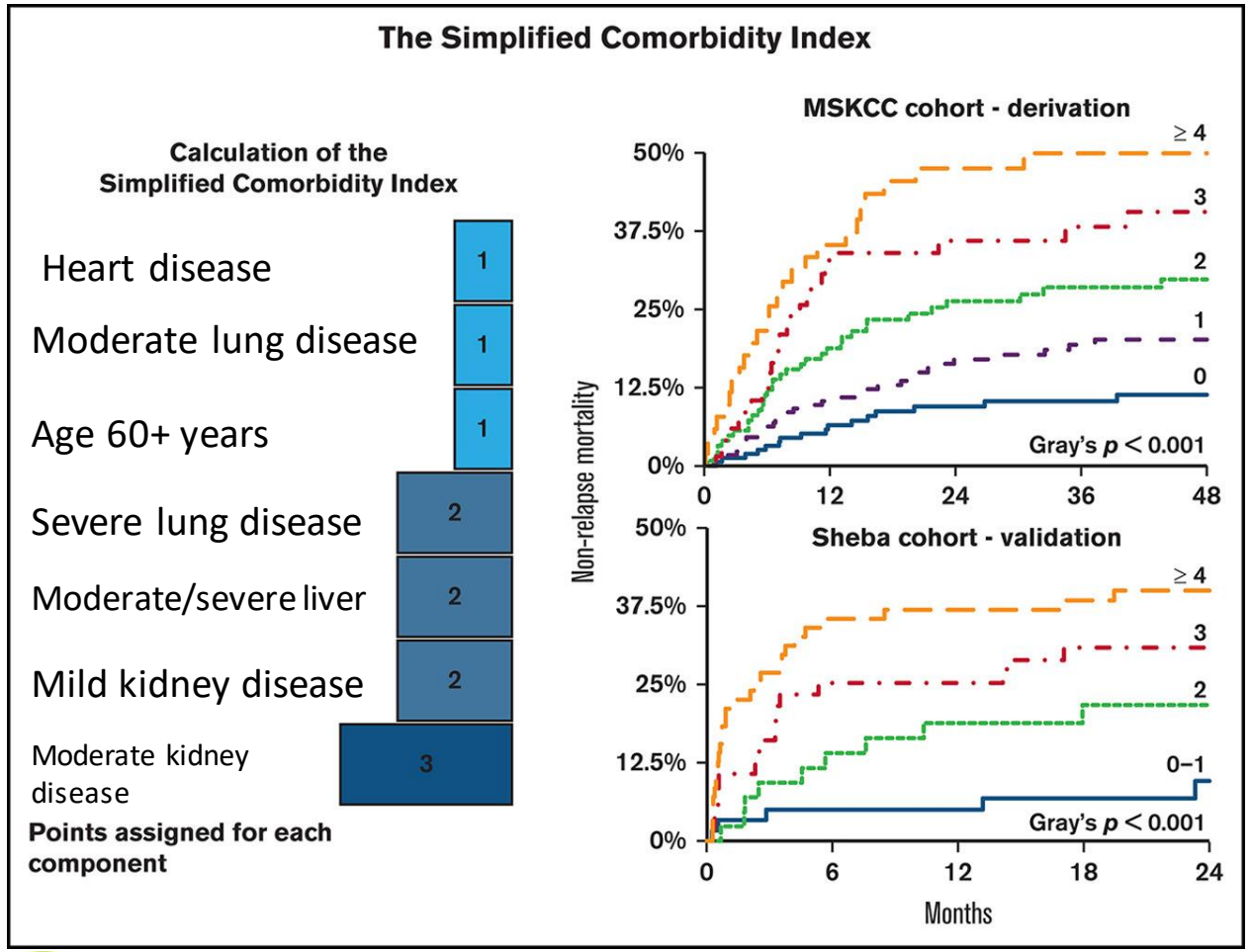
- In patients with **AML**,
  - 3-year overall survival: **49%** (60-64 years) vs **42%** (65-69 years) vs **45%** (70+ years)
  - After adjusting for other predictors, age had a <u>small effect</u> on overall survival and non-relapse mortality**

Risk of non-relapse mortality by age



*Atallah et al. JAMA Oncology 2019
**Maakaron et al. BMT 2022

↑ health issues = ↑ risk of non-relapse mortality

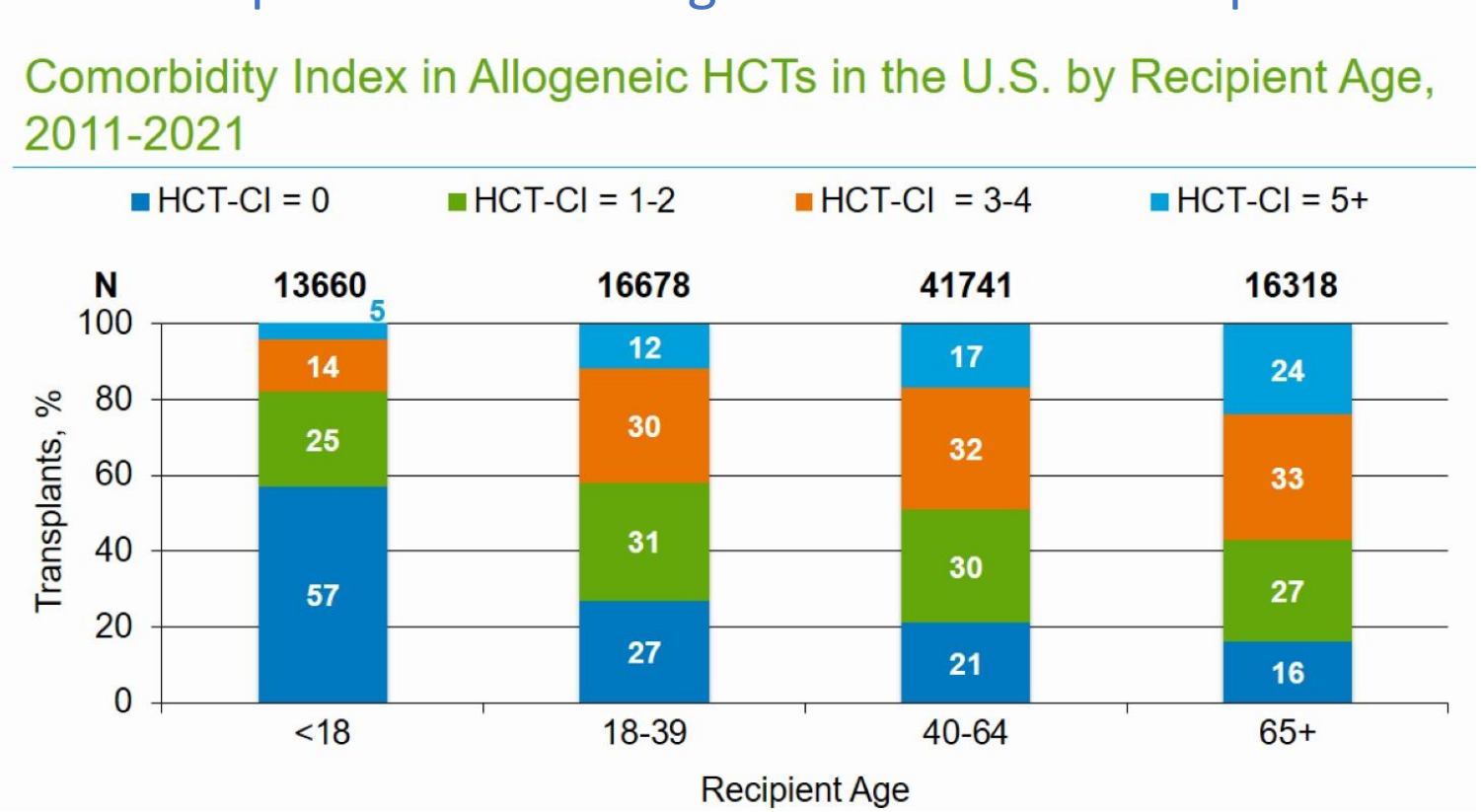


- The number and severity of a patient's health conditions can be calculated as a "score"
- The higher score, the greater the risk of fatal complications from transplant

Shouval et al. Blood Advances 2022

Older adults usually have more health issues…

… which places them at higher risk for non-relapse mortality.



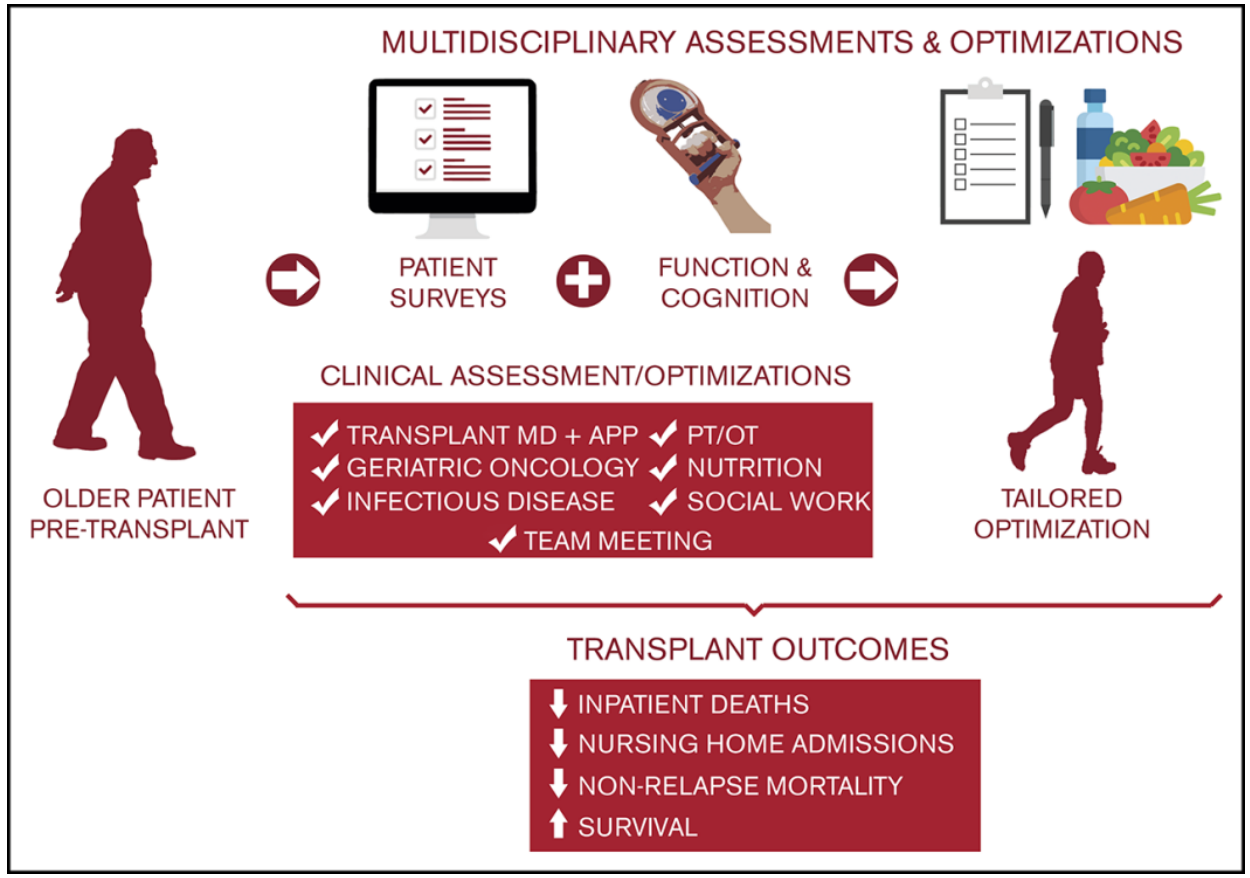
↑ number = ↑ health issues

0 = no health issues

5 = many health issues

CIBMTR Summary Slide 2022

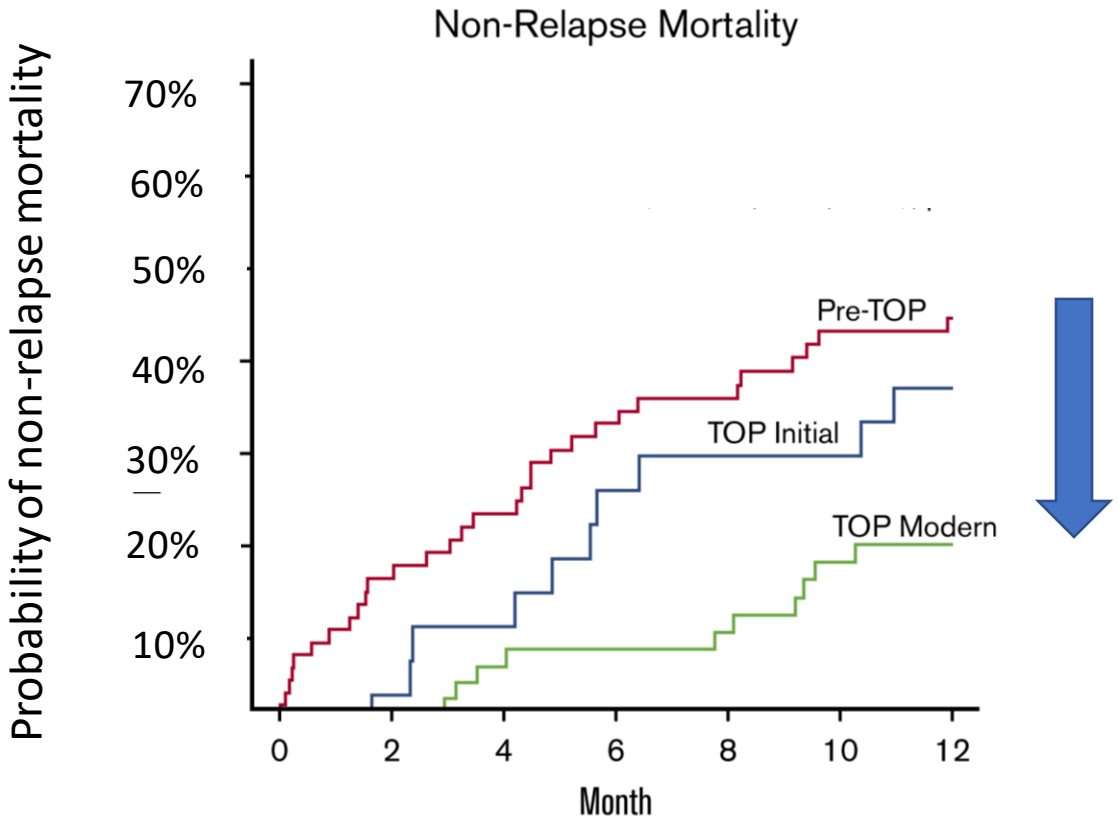
The geriatric assessment also predicts risks of donor transplant in older adults



- The geriatric assessment identifies frailty and predicts non-relapse mortality and other outcomes after transplant
- Limitations in **instrumental activities of daily living**, slow **walk speed**, and low **patient-reported functional health** were associated with worse survival after donor transplant

Derman et al. Blood Adv 2019

Evaluating older adults with a geriatric assessment before donor transplant improves survival



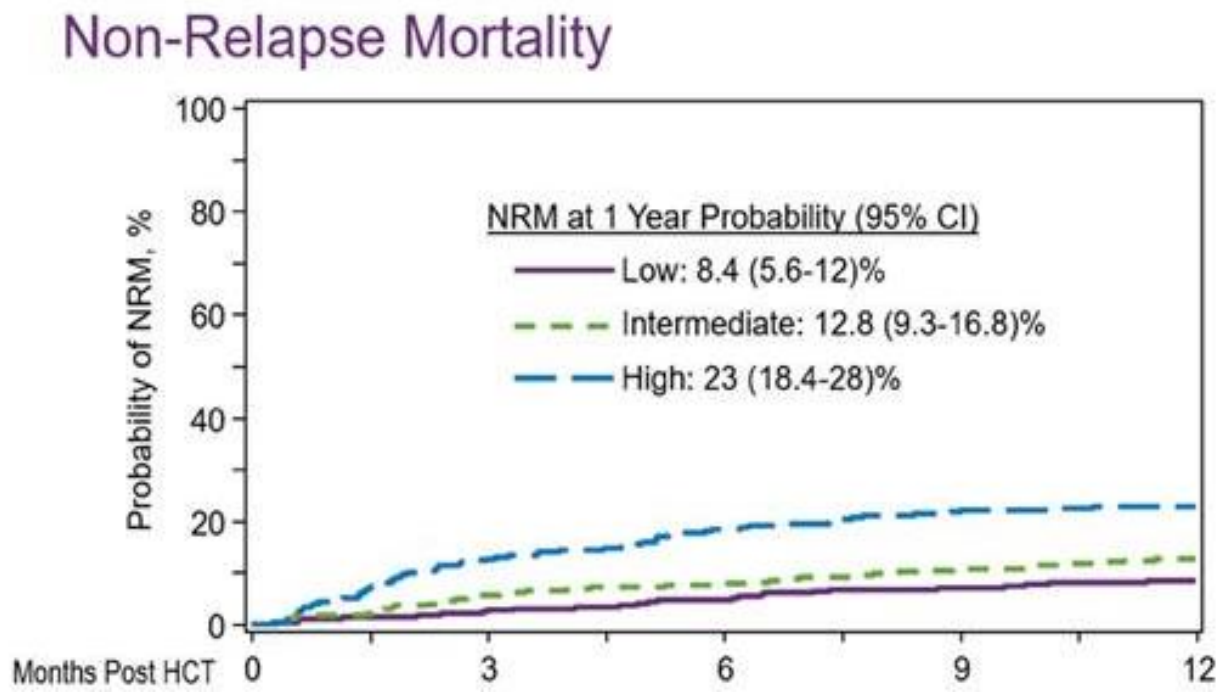
Implementing a geriatric assessment before donor transplant helped reduce non-relapse mortality and improve survival

Derman et al. Blood Adv 2019

CHARM Study:
The Composite Health Risk Assessment Model

- >1,200 adults aged 60+years undergoing donor transplants enrolled, ages **60-82**
- Geriatric assessment conducted prior to transplant
- **Albumin** (a blood marker of nutrition), **weight loss**, and a **comorbidity index** independently associated with non-relapse mortality → **CHARM score**
- Increasing age did not impact risk of non-relapse mortality!

CHARM SCORE (low, intermediate, or high)



Artz et al. American Society of Hematology 2023

How old is too old for donor transplants?

Experience in patients 80+ years is extremely limited

- From 2008-2013, only 8 patients over age 80 underwent donor transplants in the United States*
- From 2000-2021, the oldest AML transplant recipients in Europe were age 80**

**Muffly et al. Blood 2017*
***Bazarbachi et al. American Society of Hematology 2023*

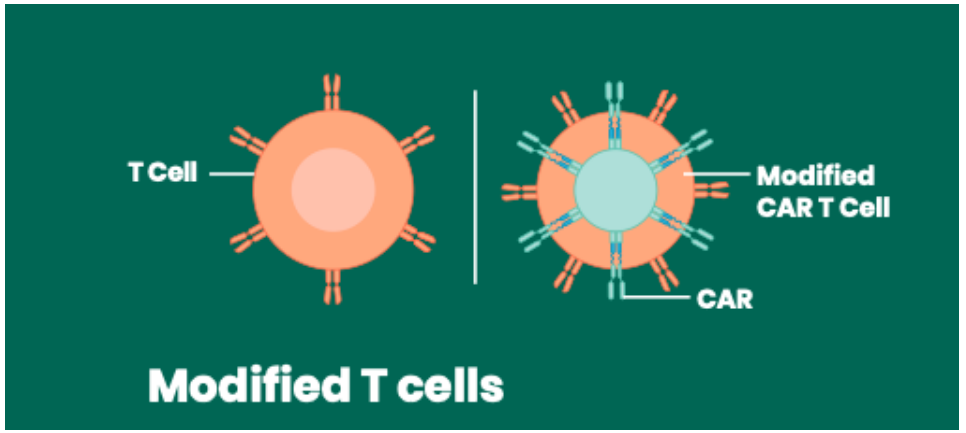
Conclusions

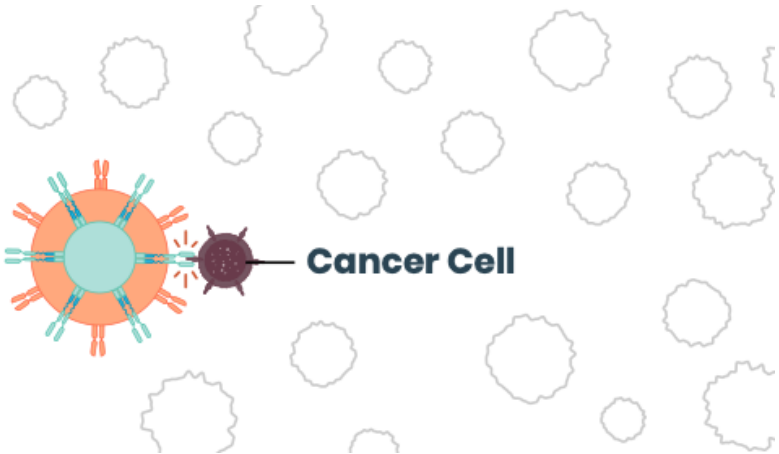
- Age alone, at least up to 75 years, should not exclude an older patient from donor transplant candidacy
- Well selected older adults do not experience dramatically higher rates of mortality after donor transplants compared to younger adults
- Health issues and the geriatric assessment, which includes frailty measurement, can determine an older patient's risk for this procedure

CAR-T Therapy

What are CAR-T cells?

To make CAR-T cells, T-cells are collected from a patient's blood and then modified in a lab. The cells then express a receptor on their surface that is better able to recognize cancer cells



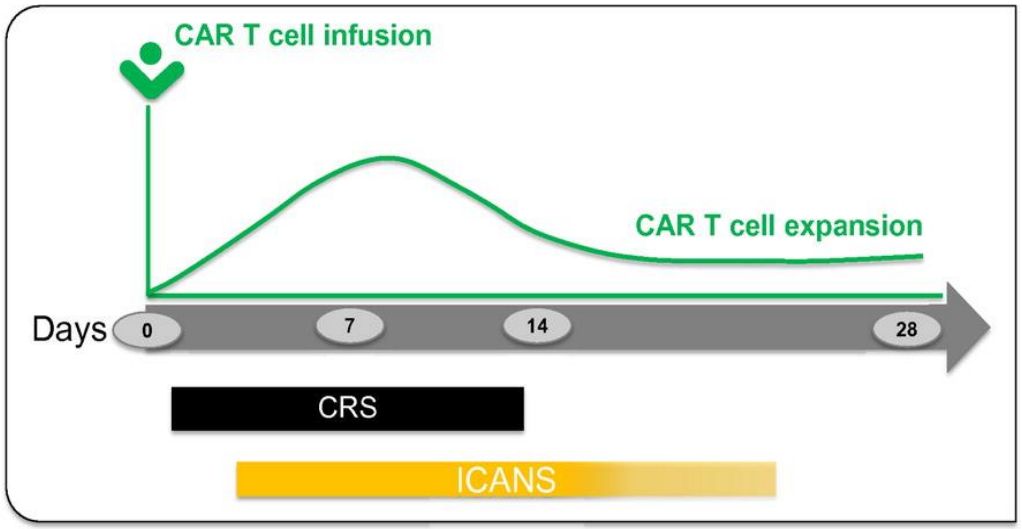


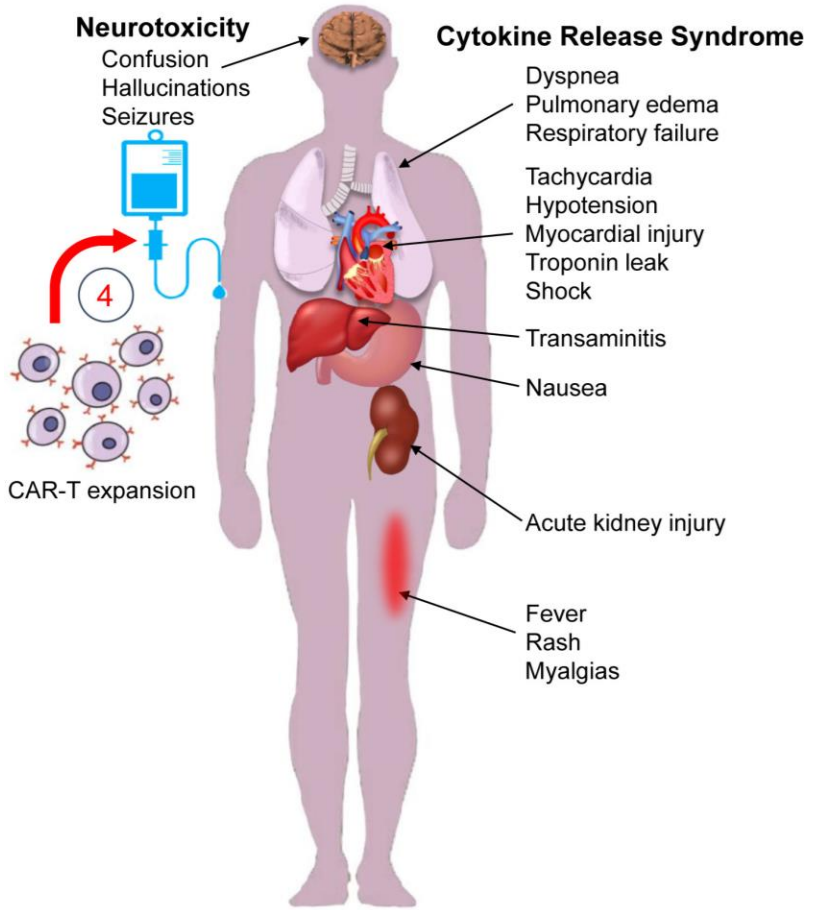
The modified T cells are infused back in the person's blood to find and destroy the cancer cells

Images taken from: American Society of Gene & Cell Therapy

Common complications after CAR-T therapy

- CAR-T cell expansion → inflammation → **cytokine release syndrome, neurotoxicity**
- Side effect profile unique to CAR-T product and disease





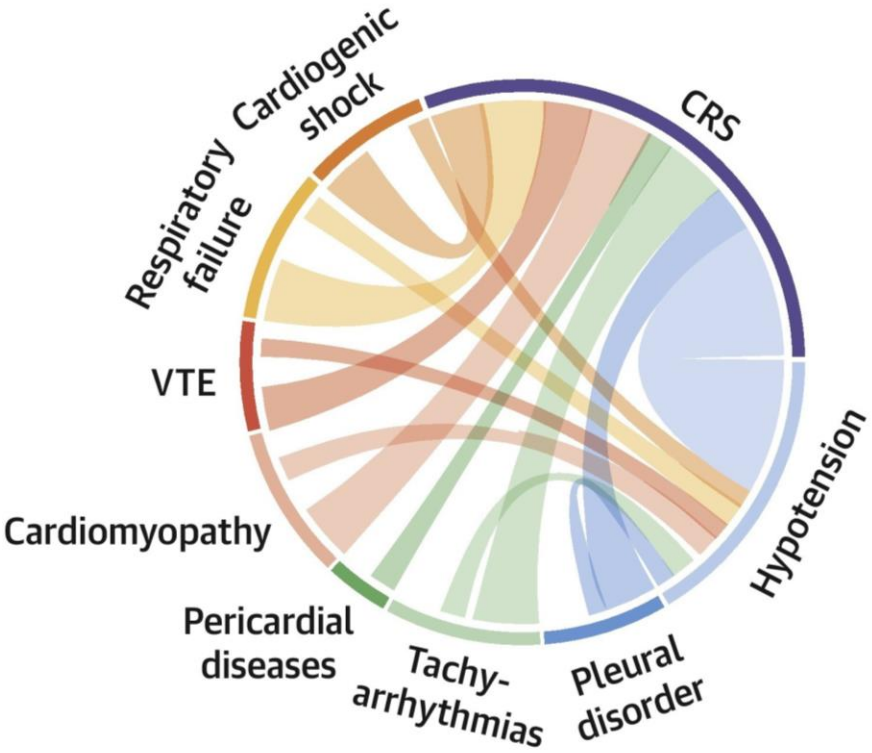
Gupta et al, Am J Kidney Dis. 2020
Image © 2019 Dr Xavier Vela Parada

CAR-T outcomes in older adults

- CAR T-cell therapy associated with favorable outcomes (disease response and survival) in older patients
- Outcomes generally comparable to those seen in younger patients
- Some side effects (neurotoxicity) and death related to treatment may be more common in older adults

Health issues can influence outcomes after CAR-T…

- **Heart** or **lung** complications can occur during cytokine release syndrome
- Pre-existing health issues involving **lungs**, **upper gastrointestinal tract**, **kidneys**, and **liver** have strongest impact on survival
- ↑ health issues = ↓ survival, ↑ rates of cytokine release syndrome, ↑ death related to treatment



Goldman et al. JACC 2021
Shouse et al Blood Advances 2023
Gutierrez Blood 2023

…but they are usually not prohibitive

According to a group of experts:

- **"Among patients with good functional status, heart & lung issues should not prevent patients from being offered CAR-T therapy"**
- **"We do not use specific ejection fraction* cut off"**
- "We generally do not … delay CAR-T for health optimization, **unless a patient is clearly not a candidate because of poor functional status and decompensated/end-stage heart or lung disease"**

*relates to heart function on ultrasound

Gutierrez et al. Blood Advances 2023

Frailty impacts outcomes after CAR-T therapy

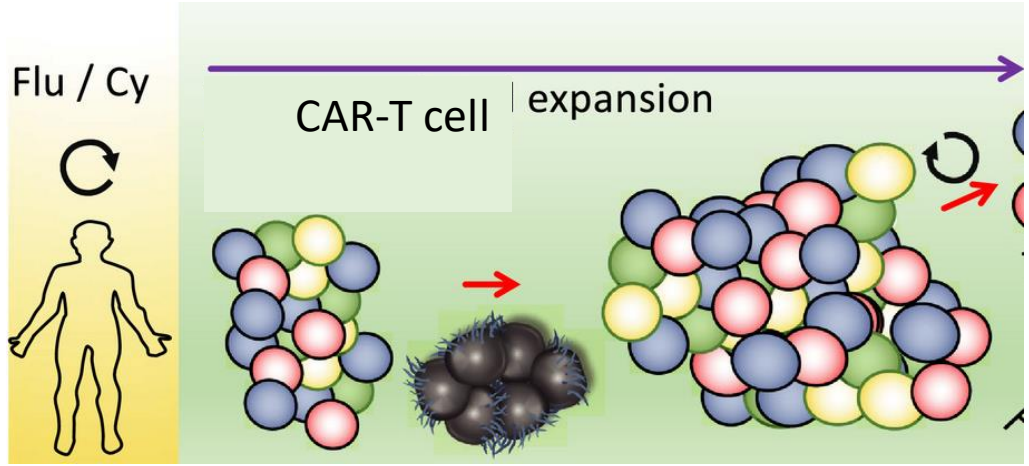
- We evaluated 61 older adults (70+ years) using the **geriatric assessment**
- Based on results, we provided recs about whether to proceed with CAR-T
- Compared to pts recommended **D/N**, pts recommended **Y** had:
  - **Shorter hospitalization**
  - **↓ discharges to rehab**
  - **↓ ICU admissions**
  - **↑ deaths related to treatment**

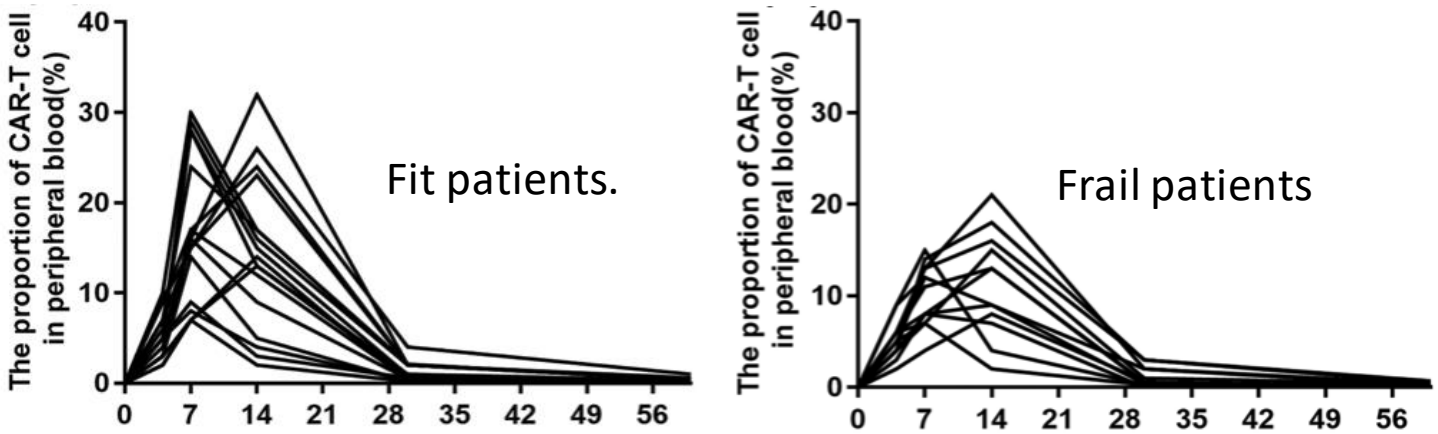
Y: *recommended yes;* **D/N**: *recommended defer/no*

Yates et al. TCT 2022 Abstract

Frail patients have worse CAR-T cell expansion

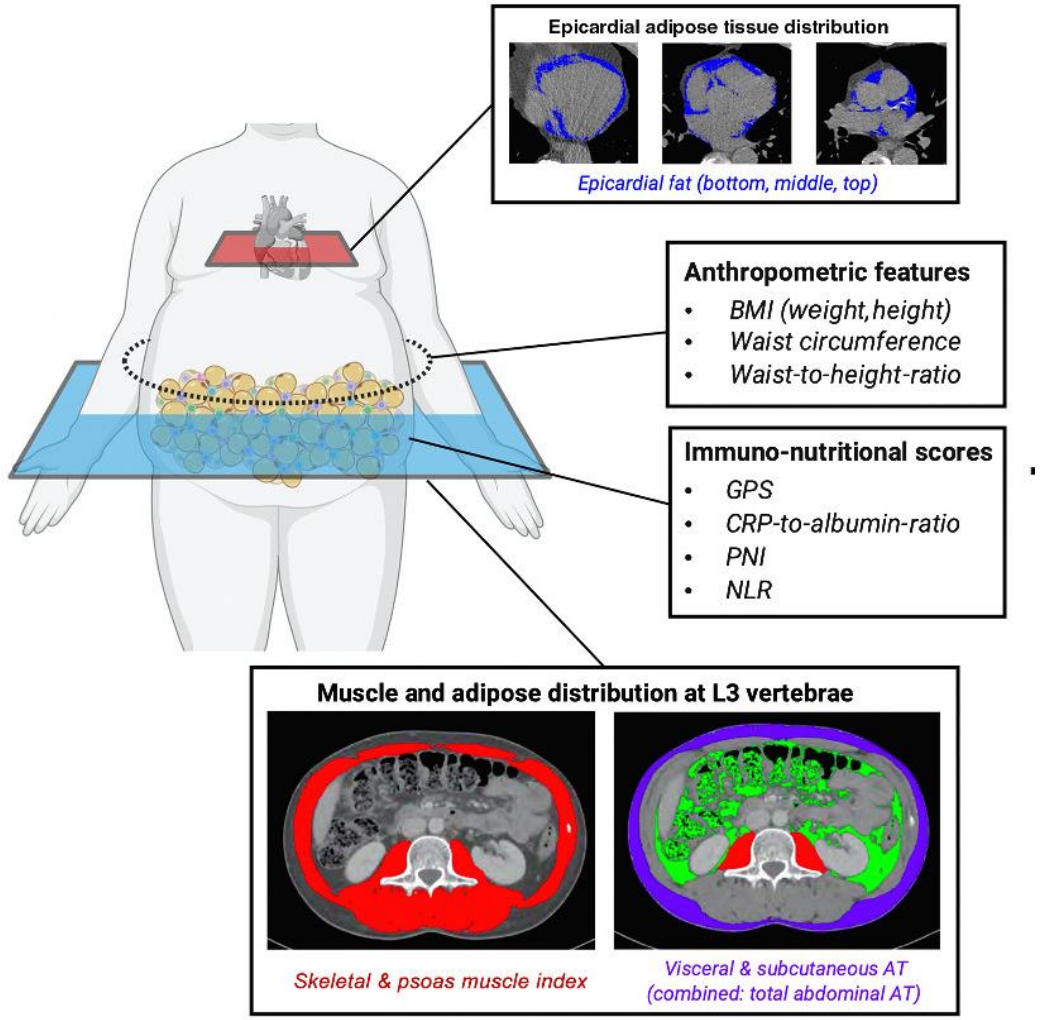
- CAR-T expansion (proliferation) important to achieving a response
- Frail patients have worse CAR-T expansion, shorter survival





McLellan et al. Immunol Cell Biol 2019
Zhang et al Leukemia & Lymphoma 2022

Body composition & nutrition impact survival after CAR-T



- ↑ abdominal fat & muscle = excellent survival after CAR-T
- Nutritional markers in the blood associate with survival

Rejeski et al Cancer Immunol Res. 2023

Conclusions

- Frailty more informative than age in determining patient candidacy for CAR-T therapy
- Based on available data, older patients (65+ years) are just as likely to benefit from CAR-T as younger patients
- A strict upper age limit for this treatment does not exist

Questions?

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