Hospital Universitario Fundación Jiménez Díaz
Grupo quirónsalud

Hematogeriatría:
Valoración de la fragilidad. Conceptos.

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Sociedad Española de Hematología y Hemoterapia (SEHH)

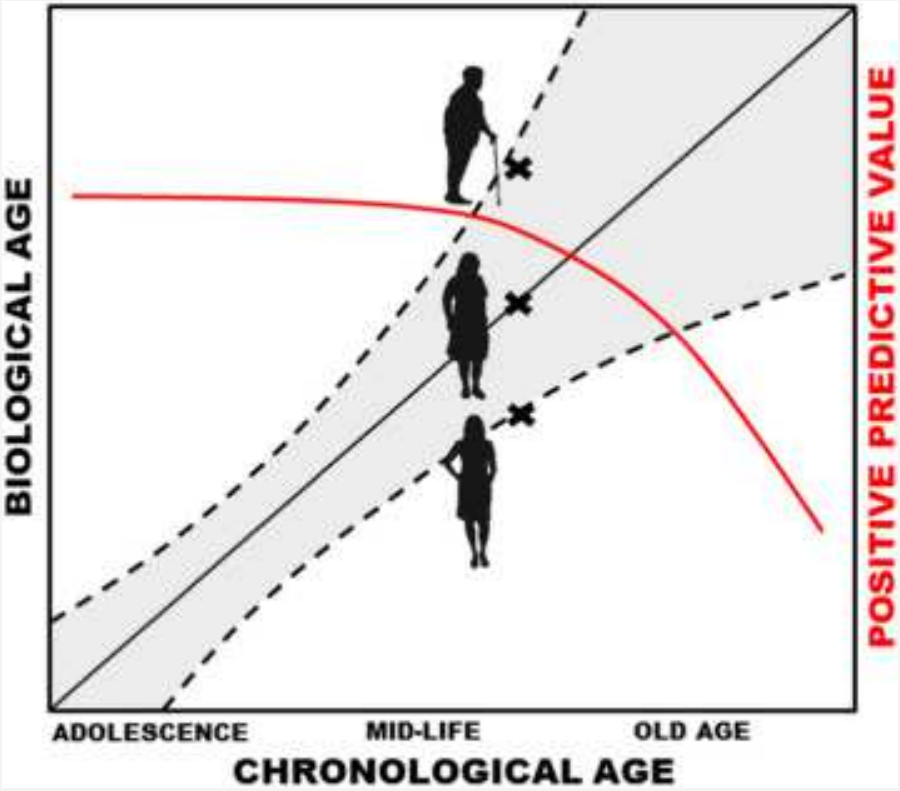
ATENCIÓN FARMACÉUTICA AL PACIENTE ONCOHEMATOLÓGICO

Tercera Reunión Anual del grupo:
GEDEFO
Grupo de Farmacia Oncológica de la SEFH

Introduction

- Geriatric Hematology is a novel area of knowledge
- Centered in elderly patients with hematologic malignancies
- Aim to tailor treatments and individualise patients' care

Biological vs chronological age



Jylhava J et al. EBioMedicine 2017;21:29-36

Biological vs chronological age

- "**Aging** is associated with common trends that include a **decreased functional reserve** of multiple organ systems"

  Poor tolerability

- "and an **increased susceptibility to diseases and injuries**"

  More iatrogenic risk

Balducci et al. Cancer Control 2014; Jul;21(3):215-20

Biological vs chronological age

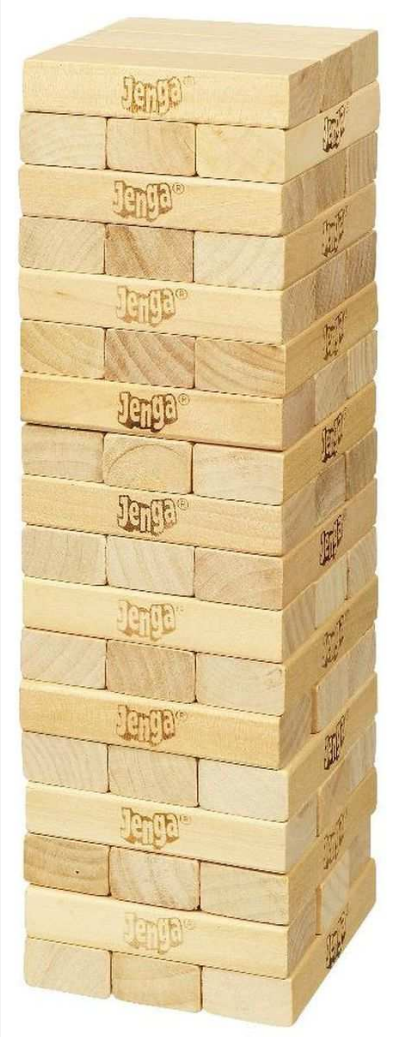
- “Chronological age may be used as a landmark to establish when the assessment of physiological age becomes necessary ”

  Balducci et al. Cancer Control 2014; Jul;21(3):215-20

- This landmark is commonly established to be **70 years** of age

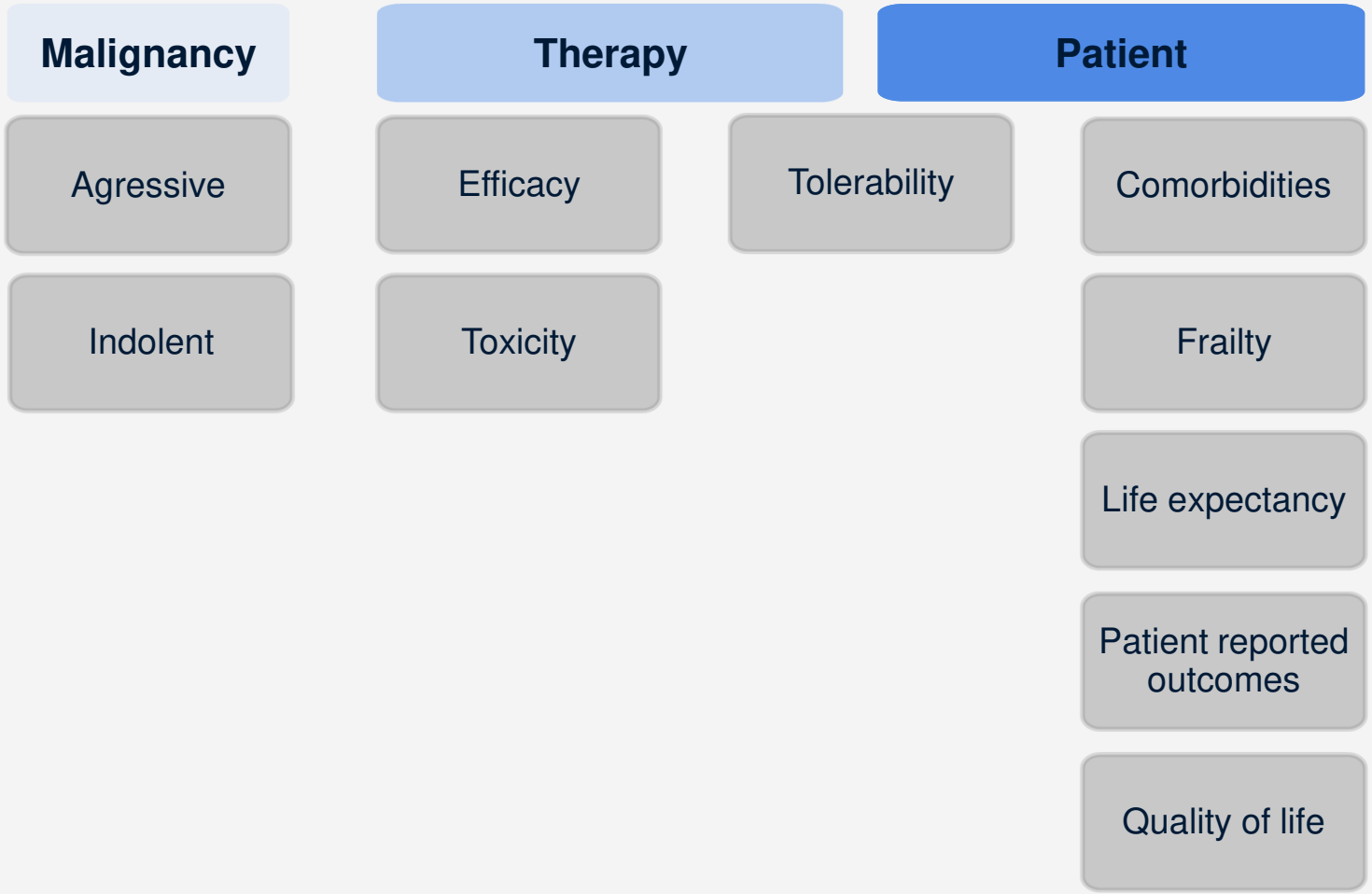
  Hurria A, et al. J Natl Compr Cancer Netw. 2014;12(1):82-126

Biological vs chronological age



Biological vs chronological age

Treatment decission in older patients with cancer

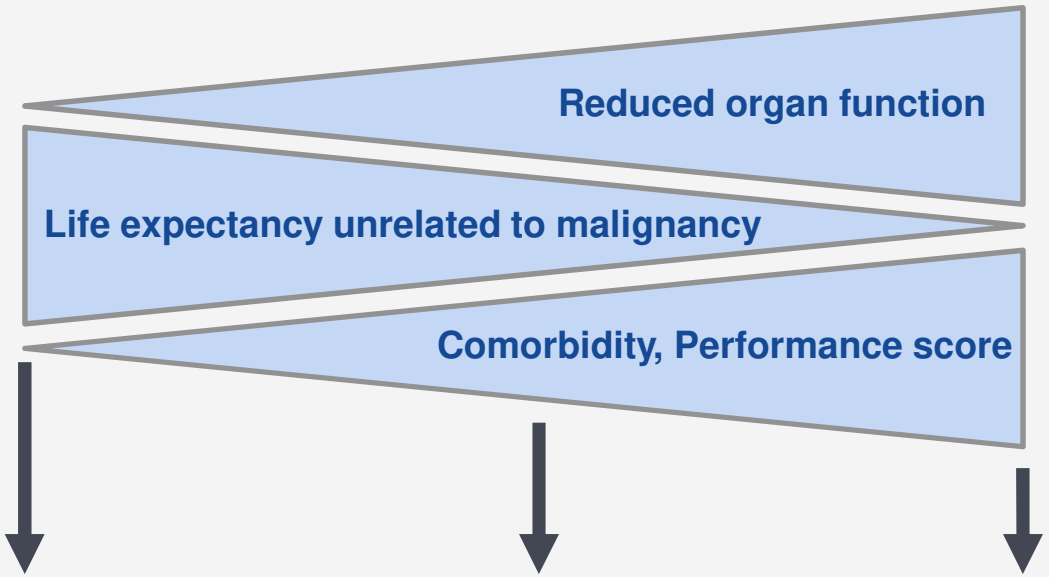


Tailoring treatments

Criteria for treatment selection

- The goal with our patient
- Comorbidities profile
- Frailty phenotype
- Predictive factors for outcome

Individualizing goals



Phenotype	Robust or “fit”	Vulnerable or “frail”	Palliative or “unfit”
Treatment strategy	Improve outcome / survival	Balance efficacy /toxicity	Do not harm
Goal	CR (MRD)	Good response	Palliation
Priority	Efficacy	Combination of efficacy with low toxicity	Low toxicity

Adapted from: http://www.newevidence.com/oncology/fit-vs-frail-assessment-strategies-in-cll/

Comorbidity ≠ Frailty

- **Comorbidity**: the concurrent presence of two or more medically diagnosed diseases in the same individual
- **Frailty**: state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality
- **Disability**: difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently in a home, and desired activities important to one's quality of life

Fried LP et al. J Gerontol A Biol Sci Med Sci 2004; 59(3):255-63

Comorbidity

Comorbidity

- CIRS-G
- CCI Charlson Comorbidity Index

CIRS-G

Please rate each of the following individual body system

	0	1	2	3	4
Cardiac					
Vascular					
Hematological					
Respiratory					
Ophthalmological and ORL					
Upper gastrointestinal					
Lower gastrointestinal					
Hepatic and pancreatic					
Renal					
Genitourinary					
Musculoskeletal and tegumental					
Neurological					
Endocrine, metabolic, breast					
Psychiatric					

Miller et al. Psychiatry Res 1992; 41:237-48

CCI Charlson

1. AIDS*	☐	0
2. Metastatic solid tumor *item #6*	☐	0
3. Moderate or severe liver disease *item #11*	☐	0
4. Malignant lymphoma	☐	0
5. Leukemia*	☐	0
6. Any non-metastatic solid tumor*	☐	0
7. Diabetes with end organ damage* *item #10*	☐	0
8. Moderate or severe renal disease	☐	0
9. Hemiplegia *item #16*	☐	0
10. Diabetes without end organ damage*	☐	0
11. Mild liver disease*	☐	0
12. Ulcer disease	☐	0
13. Connective tissue disease	☐	0
14. Chronic pulmonary disease	☐	0
15. Dementia	☐	0
16. Cerebrovascular disease	☐	0
17. Peripheral vascular disease*	☐	0
18. Congestive heart failure	☐	0
19. Myocardial infarction*	☐	0
		=

Charlson et al. J Chronic Dis. 1987;40:373-83

Frailty

Frailty

- G8
- VES13

G8

Items	Possible responses (score)
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 = Severe decrease in food intake 1 = Moderate decrease in food intake 2 = No decrease in food intake
Weight loss during the last 3 months?	0 = Weight loss >3 kg 1 = Does not know 2 = Weight loss between 1 and 3 kg 3 = No weight loss
Mobility?	0 = Bed or chair bound 1 = Able to get out of bed/ chair but does not go out 2 = Goes out
Neuropsychological problems?	0 = Severe dementia or depression 1 = Mild dementia 2 = No psychological problems
Body mass index (BMI)? (weight in kilograms) / (height in square metres)	0 = BMI <19 1 = BMI 19 to <21 2=BMI 21 to <23 3 = BMI ≥23
Takes more than three prescription drugs per day?	0 = Yes 1 = No
In comparison with other people of the same age, how does the patient consider his/her health status?	0.0 = Not as good 0.5 = Does not know 1.0 = As good 2.0 = Better
Age	0 = >85 1 = 80–85 2 = <80
Total score 0–17	Cut-off ≤ 14

Hamaker ME et al. Ann Hematol (2014) 93:1031–1040

G8 tool in hematology

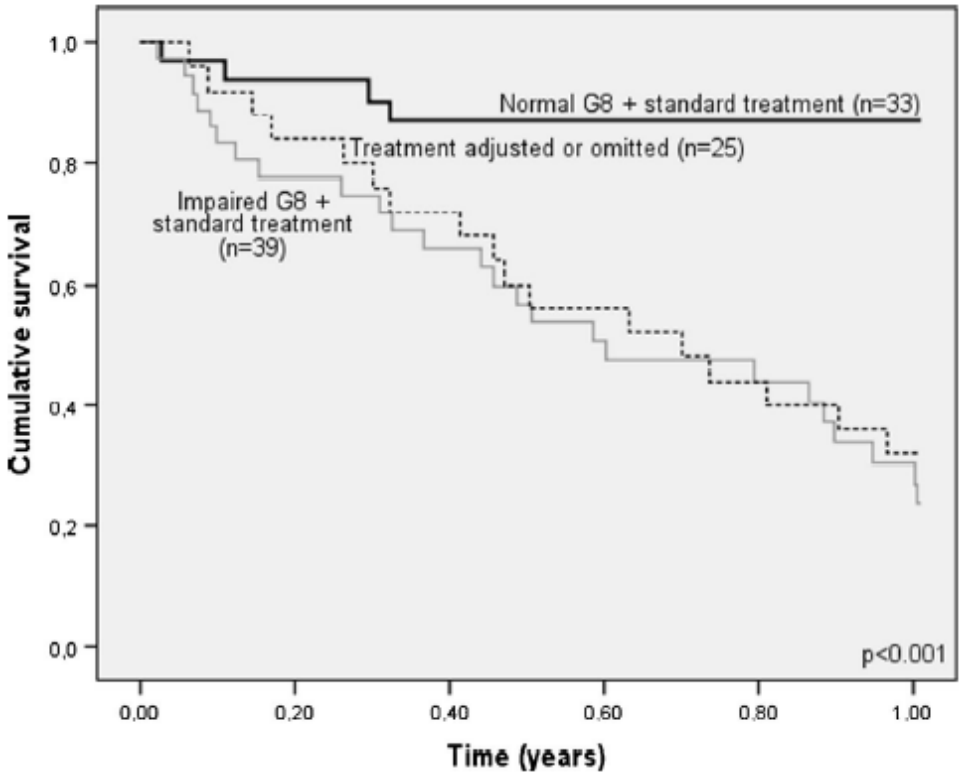
Ann Hematol (2014) 93:1031–1040
DOI 10.1007/s00277-013-2001-0

ORIGINAL ARTICLE

The G8 screening tool detects relevant geriatric impairments and predicts survival in elderly patients with a haematological malignancy

Marije E. Hamaker · M. Mitrovic · R. Stauder

- 108 consecutive patients
- Median age of these patients was 78.2 years (range 67.1–98.9 years) and 13 % of patients were older than 85 years of age.
- The WHO performance status was 0 in 19 patients (18 %), 1 in 38 (35 %), 2 in 42 (39 %) and 3 in 9 (8 %).
- Most common diagnoses were acute myeloid leukaemia (AML) (29 %), aggressive non-Hodgkin lymphoma (29 %) and myelodysplastic syndromes (23 %);
74 % of patients had unfavourable tumour characteristics
-The median total CIRS-G comorbidity score was 6.5 (range 0–20), with 31 % of patients having at least one grade 4 (extremely severe) or two grade 3 (severe) comorbidities.



VES13 (vulnerable elderly survey)

Element of assessment	Score
Age	
75–84	1
≥85	3
Self-reported health	
Good or excellent	0
Fair or poor	1
ADL/IADL—needs helps in:	
Shopping	1
Money management	1
Light housework	1
Transferring	1
Bathing	1
Activities—needs help in	
Stooping, crouching or kneeling	1
Lifting or carrying 10 lbs	1
Writing or handling small objects	1
Reaching or extending arm above shoulder	1
Walking 1/4 mile	1
Heavy housework	1

Saliba S. Journal of the American Geriatric Society 2001; 49:1691-9

Comprehensive Geriatric Assessment

Comprehensive Geriatric Assessment

Domain	Clinical Application
Functional Status	
Activities of daily living	Relation to life expectancy
Instrumental activities of daily living	Functional dependence
	Tolerance of stress
Comorbidity	
Number of comorbid conditions and comorbidity indices	Relation to life expectancy
	Tolerance of stress
Mental Status	
Mini-Mental State Examination (Folstein test)	Relation to life expectancy and dependence
Emotional Conditions	
Geriatric Depression Scale	Relation to survival
	May indicate motivation to receive treatment

Balducci et al. Cancer Control 2014; Jul;21(3):215-20

Comprehensive Geriatric Assessment

Nutritional Status	
Mini Nutritional Assessment	Reversible condition Possible relationship to survival
Polypharmacy	Risk of drug interactions
Geriatric Syndromes	
Delirium	Relationship to survival and stress tolerance
Dementia	Functional dependence
Depression	May be reversible to some extent
Falls	
Incontinence	
Spontaneous bone fractures	
Neglect and abuse	
Failure to thrive	

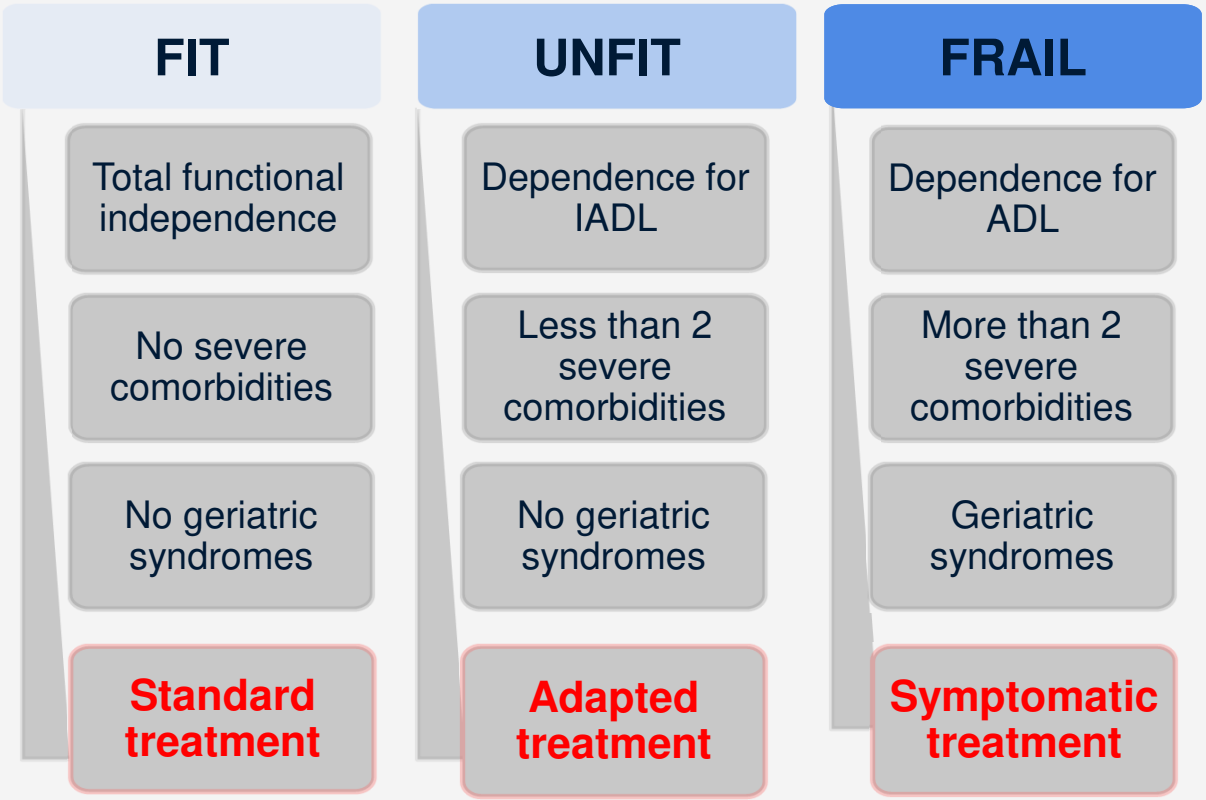
Balducci et al. Cancer Control 2014; Jul;21(3):215-20

Balducci Classification

- **Robust**: Fit patients may benefit from standard cancer treatment
- **Vulnerable**: vulnerable patients from adapted care
- **Frail**: frail patients from palliative care

Balducci L et al. Crit Rev Oncol Hematol 2000;35:147-154
Balducci L et al. Oncologist 2000; 5:224-237

Balducci Classification



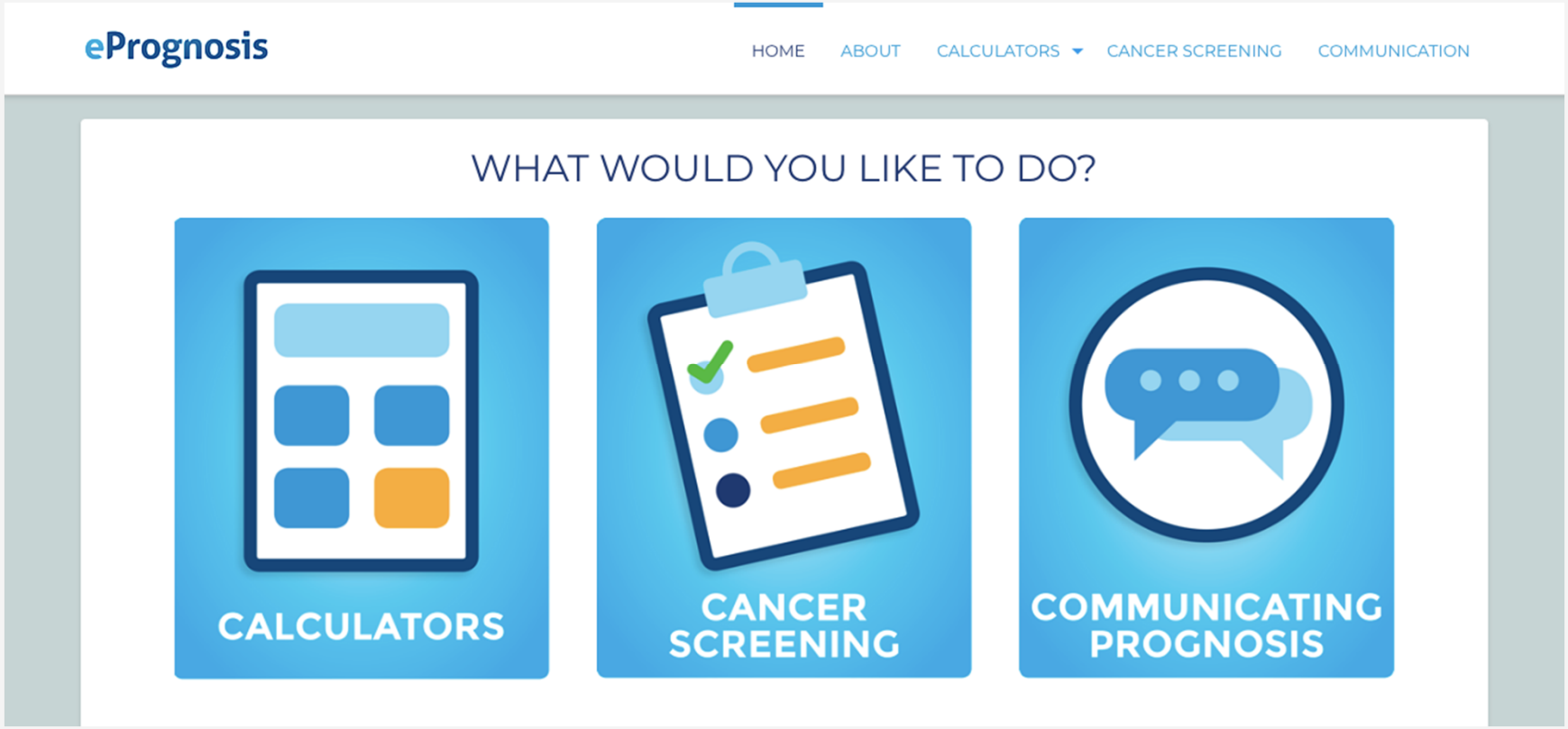
Life expectancy

Life expectancy by age

Years of Age	Average Life Expectancy	Leading Causes of Death	# Alive Out of 100,000 born
70 Add to Compare	**Female: 16.3 years** **Male: 14.1 years**	• Cancer • Heart disease • Chronic lower respiratory diseases	 78,048
80 Add to Compare	**Female: 9.6 years** **Male: 8.1 years**	• Cancer • Heart disease • Chronic lower respiratory diseases	 56,648
85 Add to Compare	**Female: 6.9 years** **Male: 5.8 years**	• Heart disease • Cancer • Stroke	 40,692
90 Add to Compare	**Female: 4.8 years** **Male: 4.0 years**	• Heart disease • Cancer • Stroke	 22,948

http://life-span.healthgrove.com/

ePrognosis



http://eprognosis.ucsf.edu/

ePrognosis

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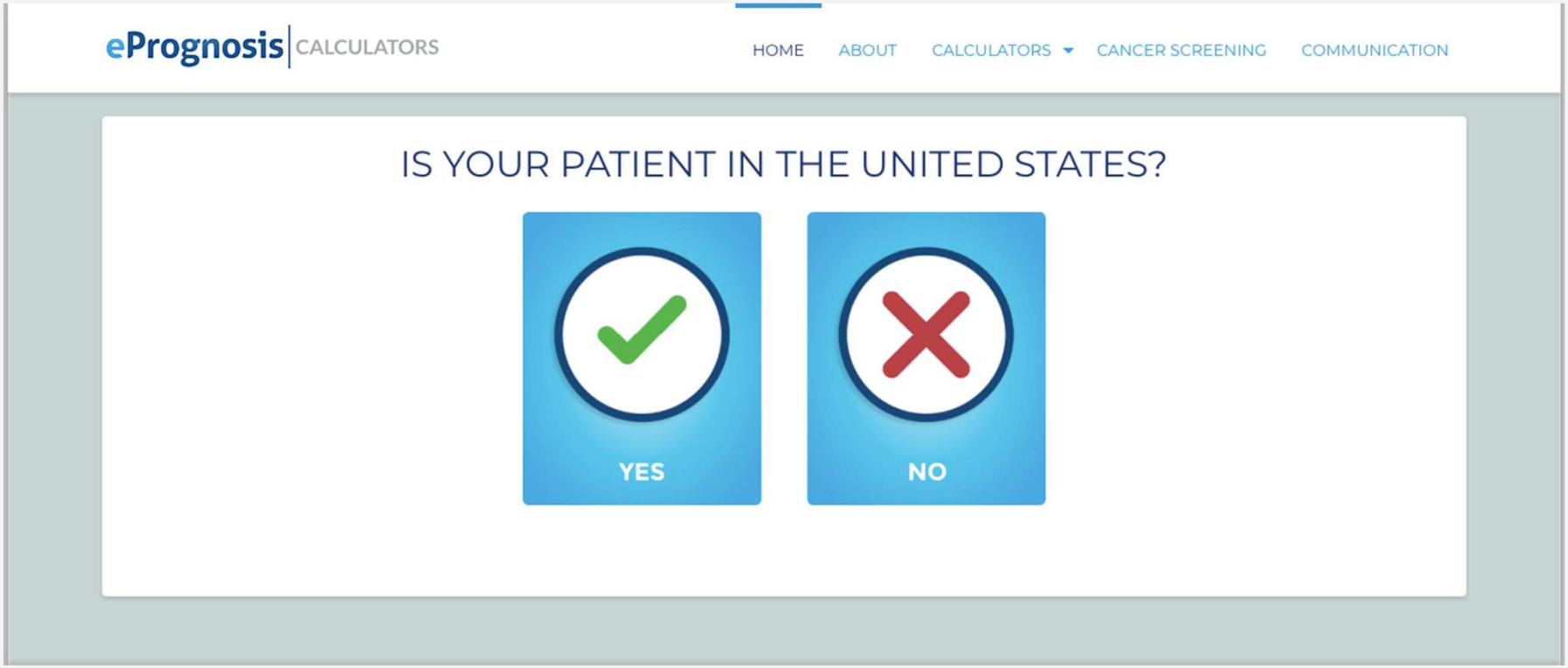

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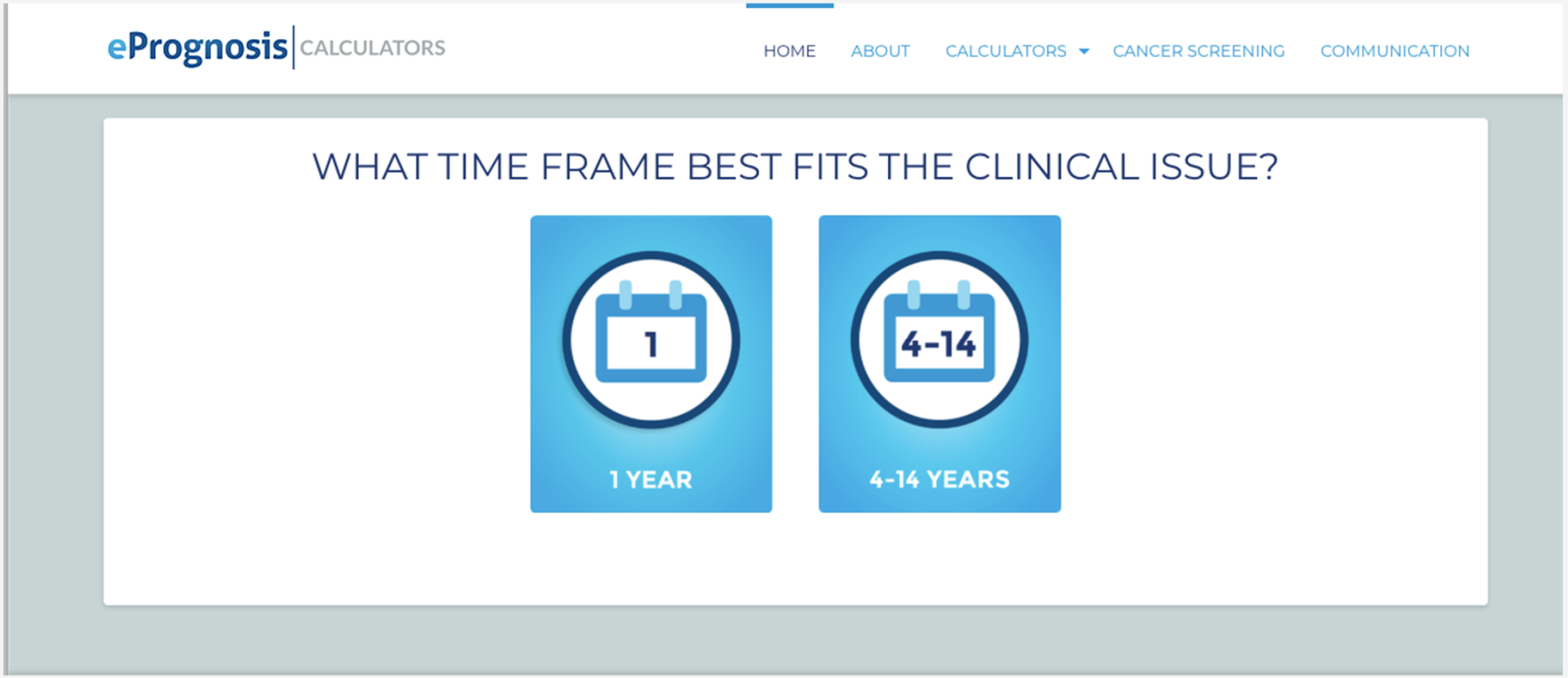

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Lee Index

- This index was developed in 11,701 community-dwelling adults from the eastern, western and central United States who were interviewed in the Health Retirement Survey in 1998 (mean age 67, 57% female, 81% white, 12% 4-year mortality)
- The index was internally validated in 8009 Health Retirement Survey interviewees from the southern United States (mean age 67, 57% female, 71% white, 13% 4-year mortality) and externally validated in 7042 English Longitudinal Study on Ageing interviewees.
- Discrimination: This risk calculator sorts patients who died from patients who lived correctly 82% of the time (c-statistic). The life expectancy calculator sorts patients who lived longer from patients who lived shorter correctly 78-80% of the time in the validation studies.

- Calibration: The model was well calibrated across all risk levels with less than 3% difference between estimated and actual mortality rates.

Schonberg Index

- This index was developed in 16,077 community dwelling older adults who responded to the 1997-2000 National Health Interview (NHIS) (27% >80 years old, 60% female, 85% white, 17% 5-year mortality)
- The index was internally validated in a random sample of 8038 from respondents from the same data source from 2001-2004 and followed through 2006 (27% >80 years old, 60% female, 85% white, 17% 5-year mortality). The index was internally validated in 16,063 respondents from the original development cohort and 8,027 respondents from the original validation cohort from 1997-2000 and followed through 2011 (10 and 14-year mortality).
- Discrimination: This risk calculator sorts patients who died within 5 years from patients who lived correctly 75% of the time (c-statistic). The discrimination was the same in the independent validation study. For 10 year and 14 year mortality the calculator sorts patients correctly 73% and 72% of the time.

- Calibration: The model was well calibrated across all risk levels with less than 10% difference between estimated and actual mortality.

http://eprognosis.ucsf.edu/

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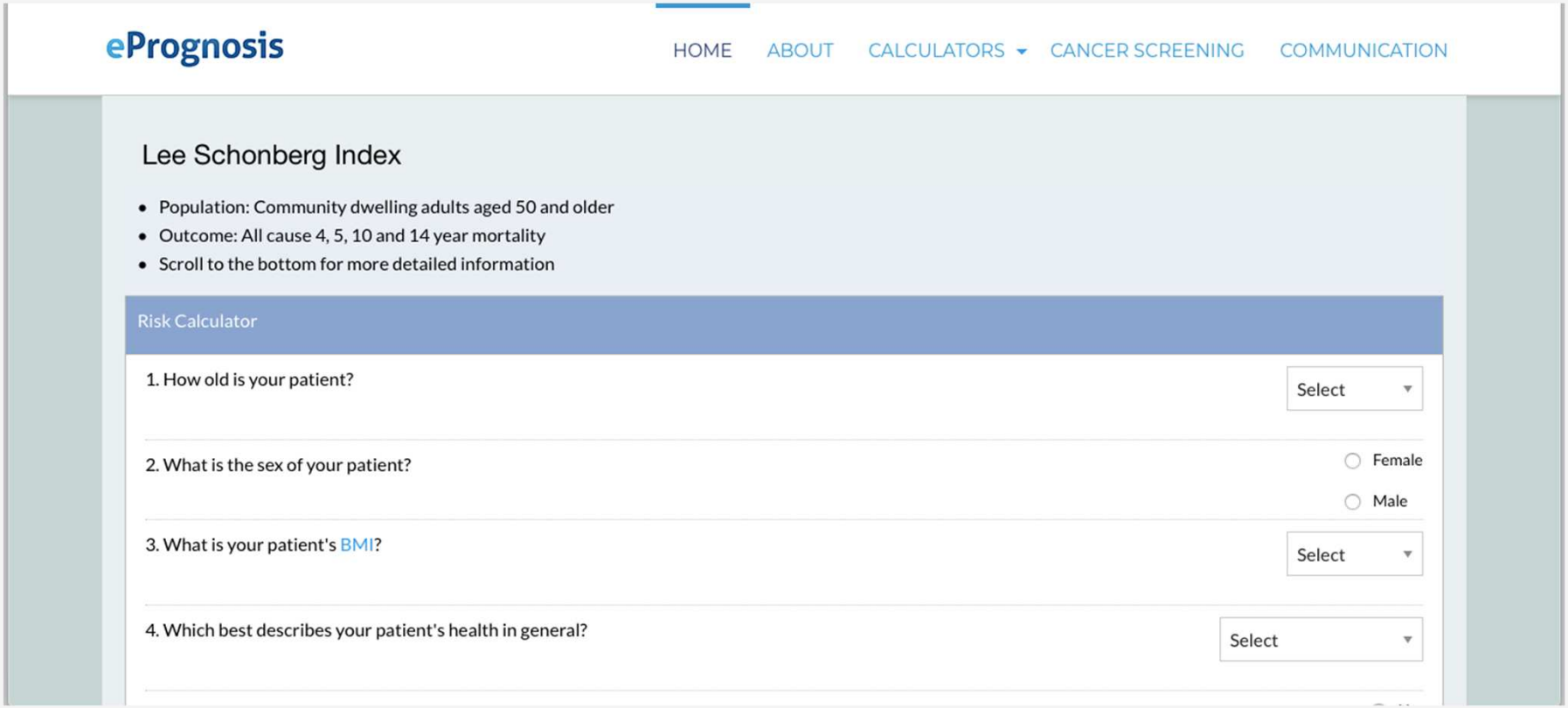

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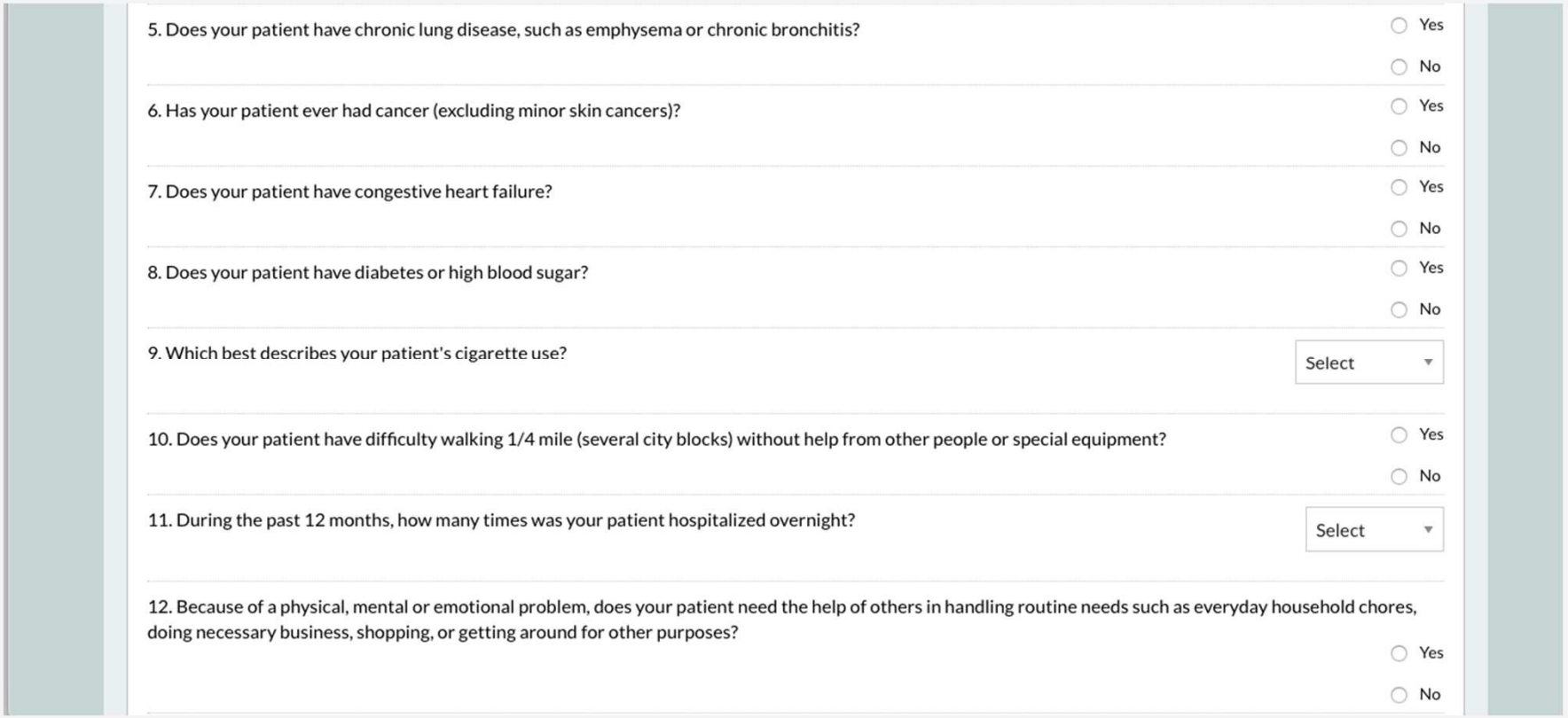

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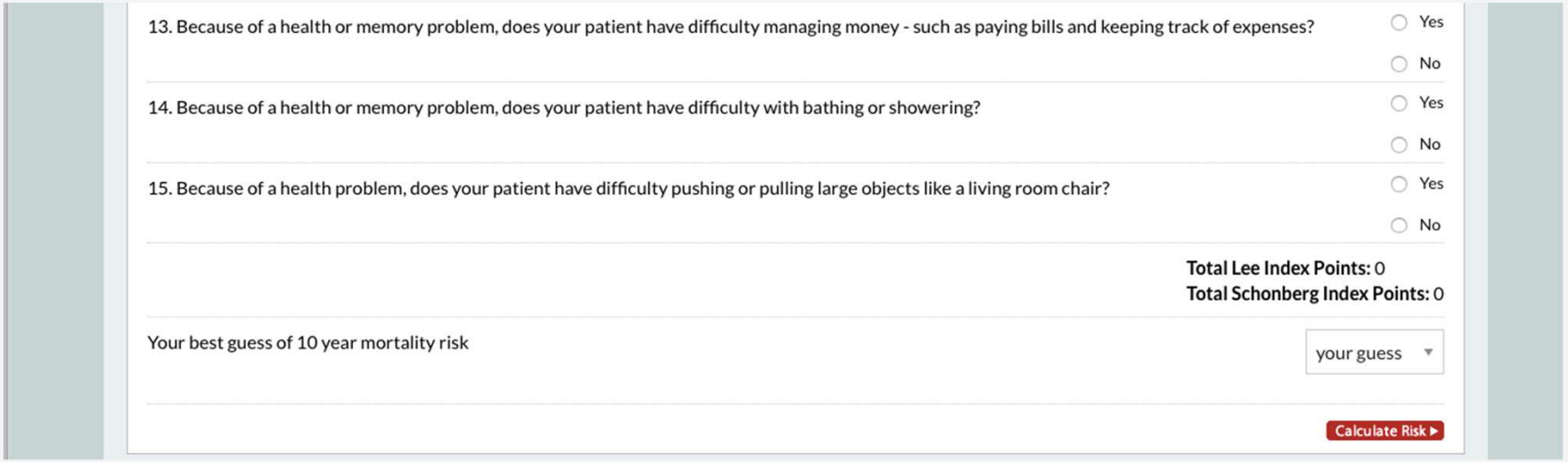

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Mortality Risk for Schonberg Index

Points	Risk of FIVE YEAR mortality	Risk of TEN YEAR mortality	Risk of FOURTEEN YEAR mortality
0 - 1	<3%	5 - 11%	19 - 21%
2 - 3	3 - 6%	9 - 12%	19 - 24%
4 - 5	7 - 8%	15 - 21%	27 - 36%
6 - 7	10 - 12%	26 - 37%	42 - 52%
8 - 9	17 - 27%	37 - 44%	42 - 52%
10 - 11	26 - 29%	53 - 60	74 - 78%
12 - 13	37 - 41%	60 - 68	81 - 83%
14 - 15	47 - 52%	74 - 76	87 - 88%
16 - 17	60 - 61%	86 - 87	100%
≥17	70%	92%	100%

Patients that have >50% chance of death in a specific time interval have an estimated life expectancy less than that time interval. For example, a patient with a 60% mortality risk at 5 years has a life expectancy <5 years.

http://eprognosis.ucsf.edu/

Disease-specific prognostic index

Table 5. IPSS-R prognostic risk category clinical outcomes

	No. of patients	Very low	Low	Intermediate	High	Very high
Patients, %	7012	19	38	20	13	10
Survival, all*		8.8	5.3	3.0	1.6	0.8
		(7.8-9.9)	(5.1-5.7)	(2.7-3.3)	(1.5-1.7)	(0.7-0.8)
Hazard ratio		0.5	1.0	2.0	3.2	8.0
(95% CI)		(0.46-0.59)	(0.93-1.1)	(1.8-2.1)	(2.9-3.5)	(7.2-8.8)
Patients, %	6485	19	37	20	13	11
AML/25%*†		NR	10.8	3.2	1.4	0.73
		(14.5-NR)	(9.2-NR)	(2.8-4.4)	(1.1-1.7)	(0.7-0.9)
Hazard ratio		0.5	1.0	3.0	6.2	12.7
(95% CI)		(0.4-0.6)	(0.9-1.2)	(2.7-3.5)	(5.4-7.2)	(10.6-15.2)

NR indicates not reached.
*Medians, years (95% CI), $P < .001$.
†Median time to 25% AML evolution (95% CIs), $P < .001$.

Greenberg et al. Blood. 2012; 120(12): 2454–2465

Treatment tolerability

Different safety profile

Type of Change	Comments
Pharmacokinetics	
Absorption	Effects of aging on absorption are unknown Reasonable to assume a progressive decrease in absorption due to atrophic gastritis, decreased gastric motility, and decreased splanchnic circulation
Volume of distribution	Changes in body composition; increased fat and decreased water content
Metabolism	Hepatic metabolism reduced from progressive loss of liver mass and decreased splanchnic circulation
Renal excretion	Glomerular filtration rate declines with age in nearly all individuals
Hepatic excretion	Biliary excretion appears to remain intact

Balducci et al. Cancer Control 2014; Jul;21(3):215-20

Different safety profile

Pharmacodynamics	
Hematopoietic system	Decreased concentration of early hematopoietic progenitors Decreased lymphocytic production Homing abnormality may reduce concentration of early progenitors in bone marrow
Mucosa epithelium	Decreased epithelial stem cells Increased proliferation of differentiated cells
Heart	Reduction in myocardial sarcomeres Increased fibrosis and degenerative processes (amyloid)
Peripheral nervous system	Increased degenerative processes
Central nervous system	Atrophy Increase in degenerative processes with decreased circulation

Balducci et al. Cancer Control 2014; Jul;21(3):215-20

CARG score

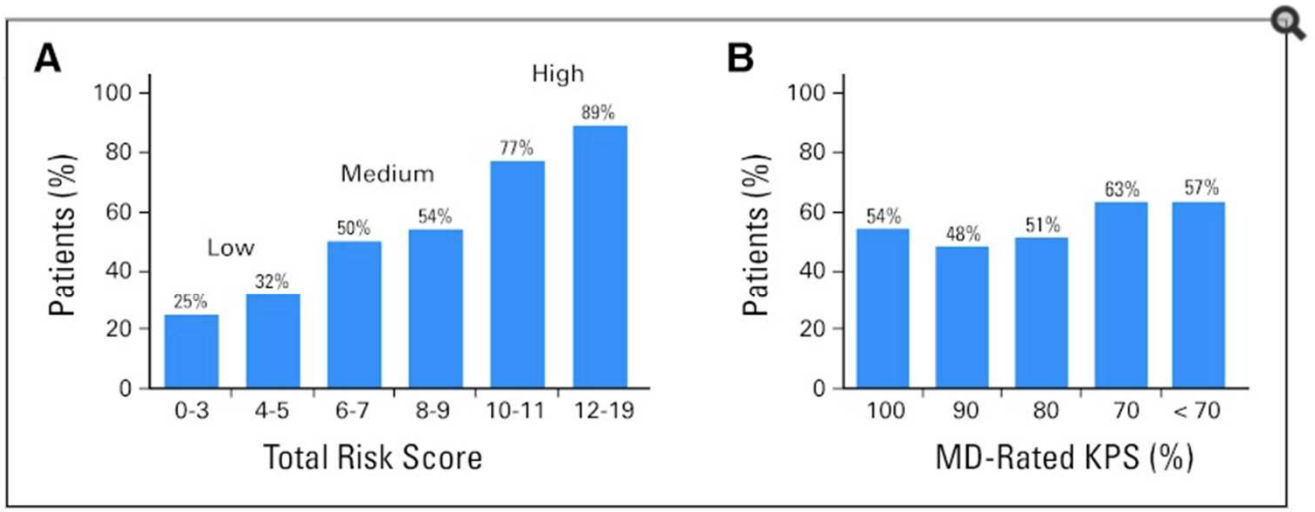
Predictive Model

Risk Factor	Prevalence		Grades 3 to 5 Toxicity		OR	95% CI	Score
	No.	%	No.	%			
Age ≥ 72 years	270	54	163	60	1.85	1.22 to 2.82	2
Cancer type GI or GU	185	37	120	65	2.13	1.39 to 3.24	2
Chemotherapy dosing, standard dose	380	76	204	54	2.13	1.29 to 3.52	2
No. of chemotherapy drugs, polychemotherapy	351	70	192	55	1.69	1.08 to 2.65	2
Hemoglobin < 11 g/dL (male), < 10 g/dL (female)	62	12	46	74	2.31	1.15 to 4.64	3
Creatinine clearance (Jelliffe, ideal weight) < 34 mL/min	44	9	34	77	2.46	1.11 to 5.44	3
Hearing, fair or worse	123	25	76	62	1.67	1.04 to 2.69	2
No. of falls in last 6 months, 1 or more	91	18	61	67	2.47	1.43 to 4.27	3
IADL: Taking medications, with some help/unable	39	8	28	72	1.50	0.66 to 3.38	1
MOS: Walking 1 block, somewhat limited/limited a lot	109	22	69	63	1.71	1.02 to 2.86	2
MOS: Decreased social activity because of physical/emotional health, limited at least sometimes	218	44	126	58	1.36	0.90 to 2.06	1

Abbreviations: GU, genitourinary; IADL, instrumental activities of daily living; MOS, Medical Outcomes Study; OR, odds ratio.

Hurria A et al. J Clin Oncol. 2011; 29(25): 3457–3465.

CARG score



Ability of (A) risk score versus (B) physician-rated Karnofsky performance status (KPS) to predict chemotherapy toxicity. Graphs show grade 3 to 5 toxicity.

Hurria A et al. J Clin Oncol. 2011; 29(25): 3457–3465.

CRASH score

Table 4. The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) Score

	Points		
Predictors	**0**	**1**	**2**
Hematologic score [a]			
Diastolic BP	≤72	>72	
IADL	26-29	10-25	
LDH (if ULN 618 U/L; otherwise, 0.74 /L*ULN)	0-459		>459
Chemotox [b]	0-0.44	0.45- 0.57	>0.57
Nonhematologic score [a]			
ECOG PS	0	1-2	3-4
MMS	30		<30
MNA	28-30		<28
Chemotox [b]	0-0.44	0.45-0.57	>0.57

Abbreviations: BP, blood pressure; Chemotox, toxicity of the chemotherapy regimen (for details, see text); ECOG PS, Eastern Cooperative Oncology Group performance status; IALD, Instrumental Activities of Daily Living; LDH, lactate dehydrogenase; MMS, Mini Mental Health Status; MNA, Mini Nutritional Assessment; ULN, upper limit of normal.

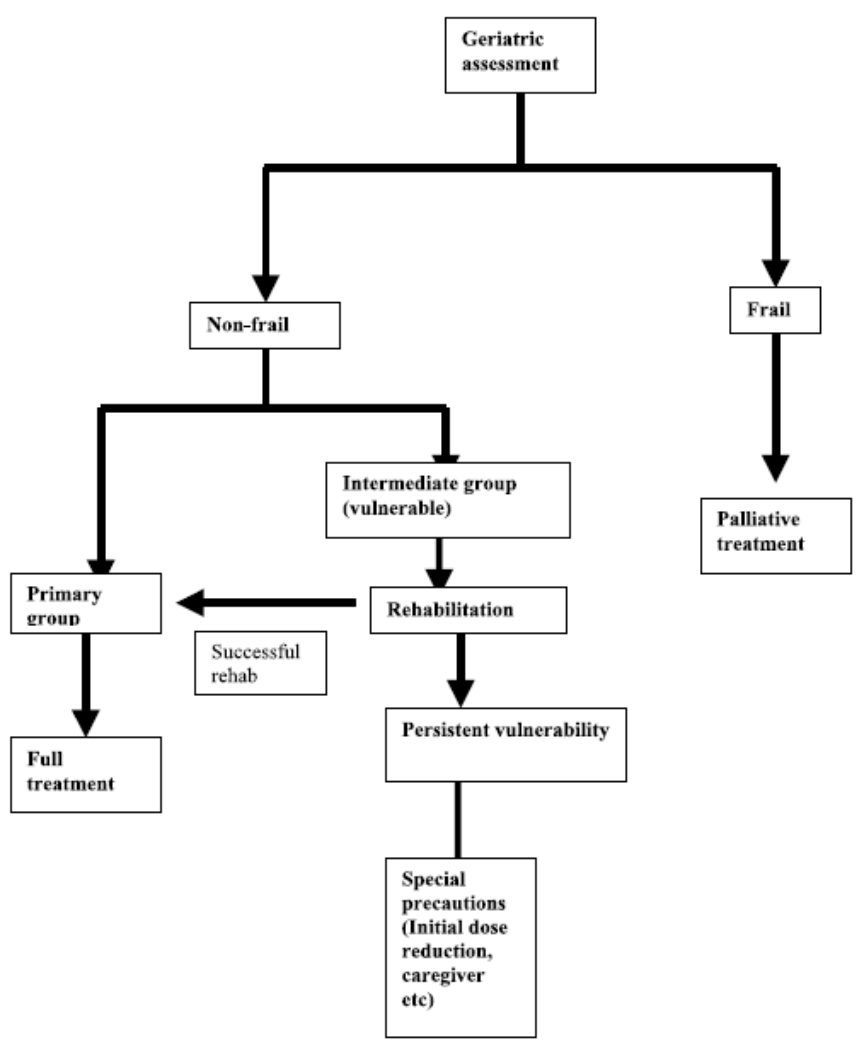
Extermann M et al. Cancer 2012;118(13):3377-3386

CRASH score

CRASH Points[b]		
0	1	2
Capecitabine 2g	Capecitabine 2.5 g	5-FU/LV (Roswell-Park)
Cisplatin/pemetrexed	Carboplatin/gemcitabine AUC 4-6/1 g d1,d8	5-FU/LV (Mayo)
Dacarbazine	Carboplatin/pemetrexed	5-FU/LV and bevacizumab
Docetaxel weekly	Carboplatin/paclitaxel q3w	CAF
FOLFIRI	Cisplatin/gemcitabine d1,d8	Carboplatin/docetaxel q3w
Gemcitabine 1 g 3/4 wk	ECF	CHOP
Gemcitabine 1.25 g 3/4 wk	Fludarabine	Cisplatin/docetaxel 75/75
Paclitaxel weekly	FOLFOX 85 mg	Cisplatin/etoposide
Pemetrexed	Gemcitabine 7/8 wk then 3/4 wk	Cisplatin/gemcitabine d1,d8,d15
	Gemcitabine/irinotecan	Cisplatin/paclitaxel 135-24 h q3w
	PEG doxorubicin 50 mg q4w	CMF classic
	Topotecan weekly	Doxorubicin q3w
	XELOX	FOLFOX 100-130 mg

Extermann M et al. Cancer 2012;118(13):3377-3386

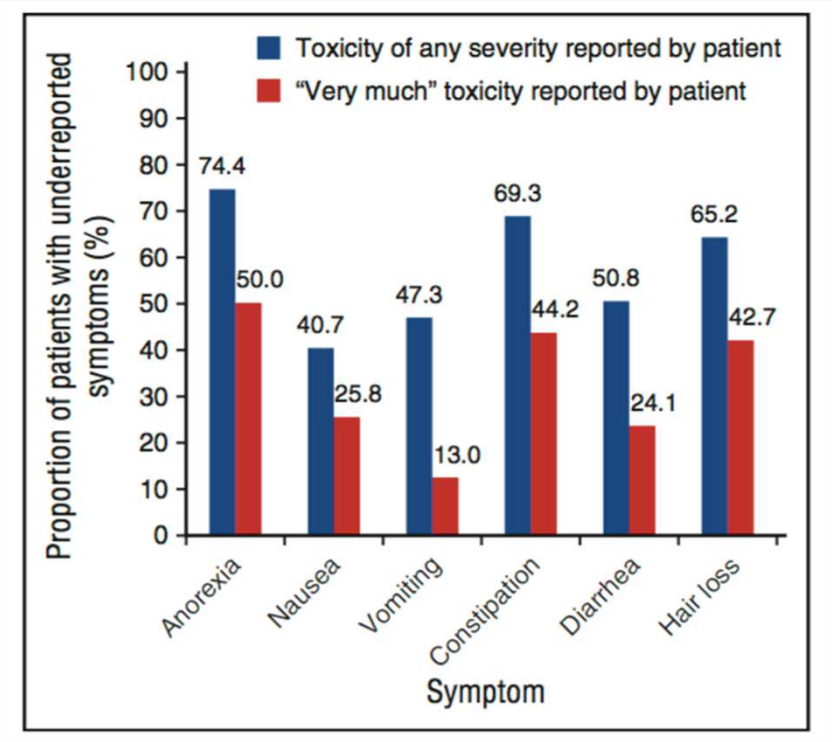
Treatment guidance



Balducci L. Critical Reviews in Oncology/Hematology 46 (2003) 211/220

Patient reported outcomes (PROs)

PROs in hematology



Underreporting of treatment-related toxicities by physicians, relative to patients

Efficace F. Blood 2017 130:859-866

PROs questionaires

https://healthcaredelivery.cancer.gov/pro-ctcae/

Quality of life (QoL)

HRQoL

- EuroQoL-5D
- FACT

Multidisciplinary approach

Multidisciplinary approach

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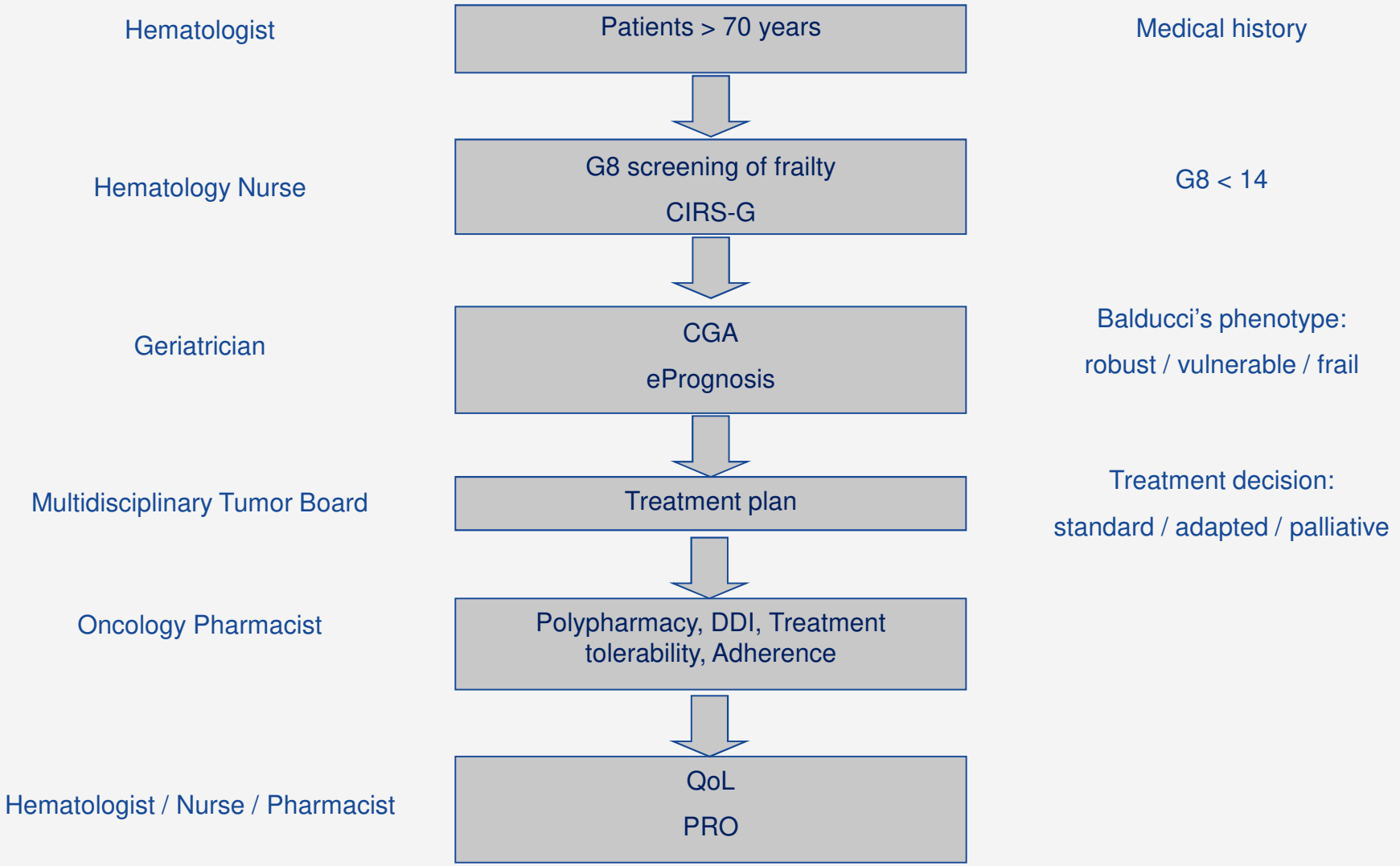

Role of the Oncology Pharmacist in a Geriatric Hematology Program?

- Assessment of polypharmacy
- Check for DDI
- Help geriatricians in START/STOP
- Help hematologists in assessment of treatment tolerability (CARG, CRASH)
- Check doses prescribed
- Monitor adherence
- Help hematologists in PROs

Take home messages

- The treatment strategy for our patients with hematologic malignancies should be individualized on basis of disease and patient's features
- We need to identify which is the goal with our patient at the begining of therapy
- We must assess comorbidities and frailty in order to adapt treatments to our older patients with hematologic malignancies
- The Oncology Pharmacists will play a relevant role in a Geriatric Hematology program

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