Committee Recommendations for Center Outcomes Forum 2025

Optimizing Handling of Comorbidities in Adults and Pediatric Transplant Recipients

Working Group Expert Panel Members

Presenters	**Adult Expertise**
A. Artz, M. Sorror	R. Jayani-Kosarzycki
	N. Khera
Pediatric Expertise	M. Nawas
L. Broglie	S. McCurdy
B. Friend	A. Sung
M. Thakar	S. Wall

Recommendations

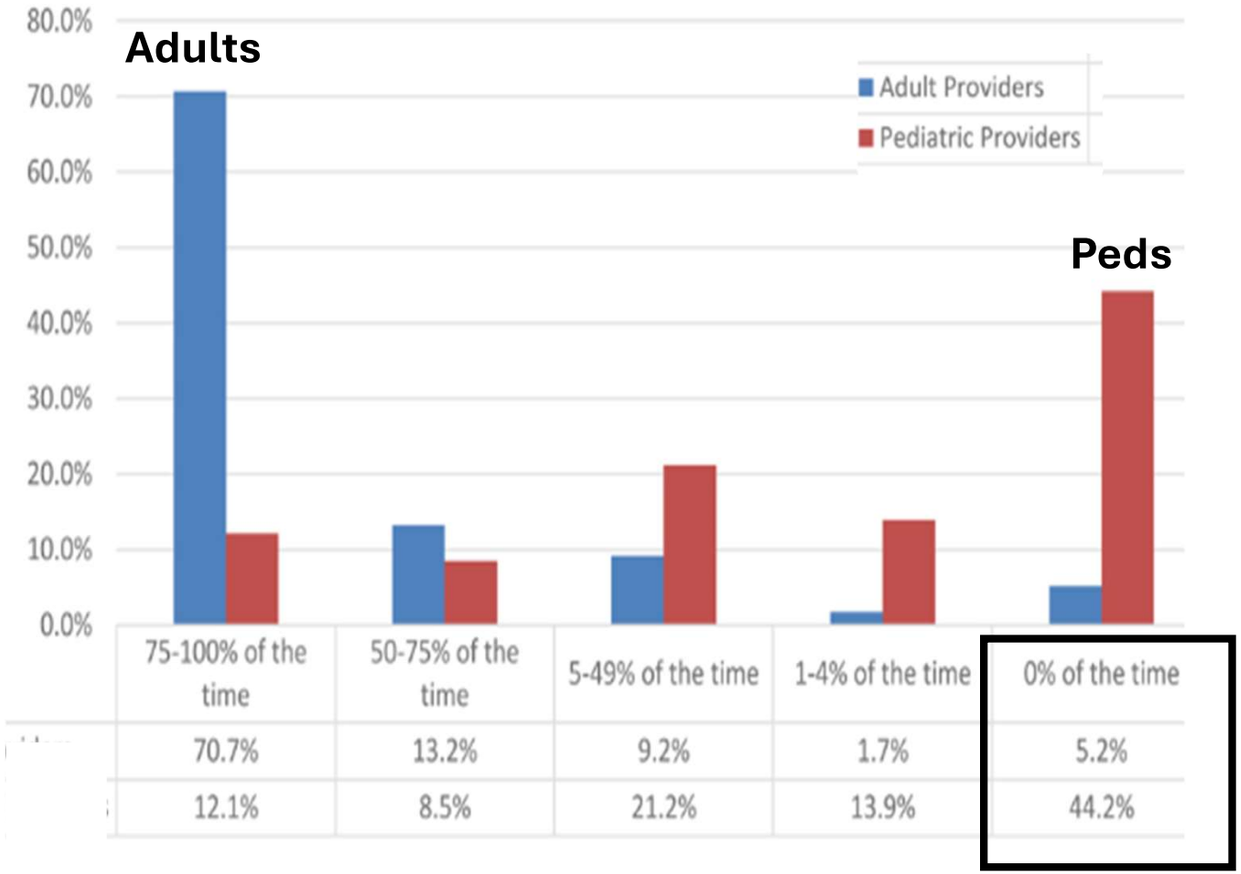
1. Inclusion from Currently Collected Data For Future Testing
    - Renal Dysfunction by 2021 CKD EPI Creatinine formula **
2. Pediatric Comorbidity Adequate pending further validation ***
    - Per the adapted HCT-CI for malignant and non-malignant diseases ***
    - For Hemoglobinopathies - continue liver iron content and RBC Dependence **
3. New Fields or Adjustment
    - Calculate CHARM for HCT recipients aged ≥60 years old ***:
        - Continue to collect to Albumin, recipient age and HCT-CI ***
        - Start collecting Pt reported KPS, hs CRP, % weight loss over a year, and MoCA ***
4. Other Considerations
    - Consider collecting CHARM variables for all adults younger than 60 yrs old for testing *
    - Gait speed (4-meter walk test) for older pts given some results on prognostic impact *
    - Vitamin D level for both adult and pediatric pts given some results on prognostic impact *

Level of recommendation: * weak, ** moderate, and *** severe

Youth Malignant & Non-Malignant HCT-CI

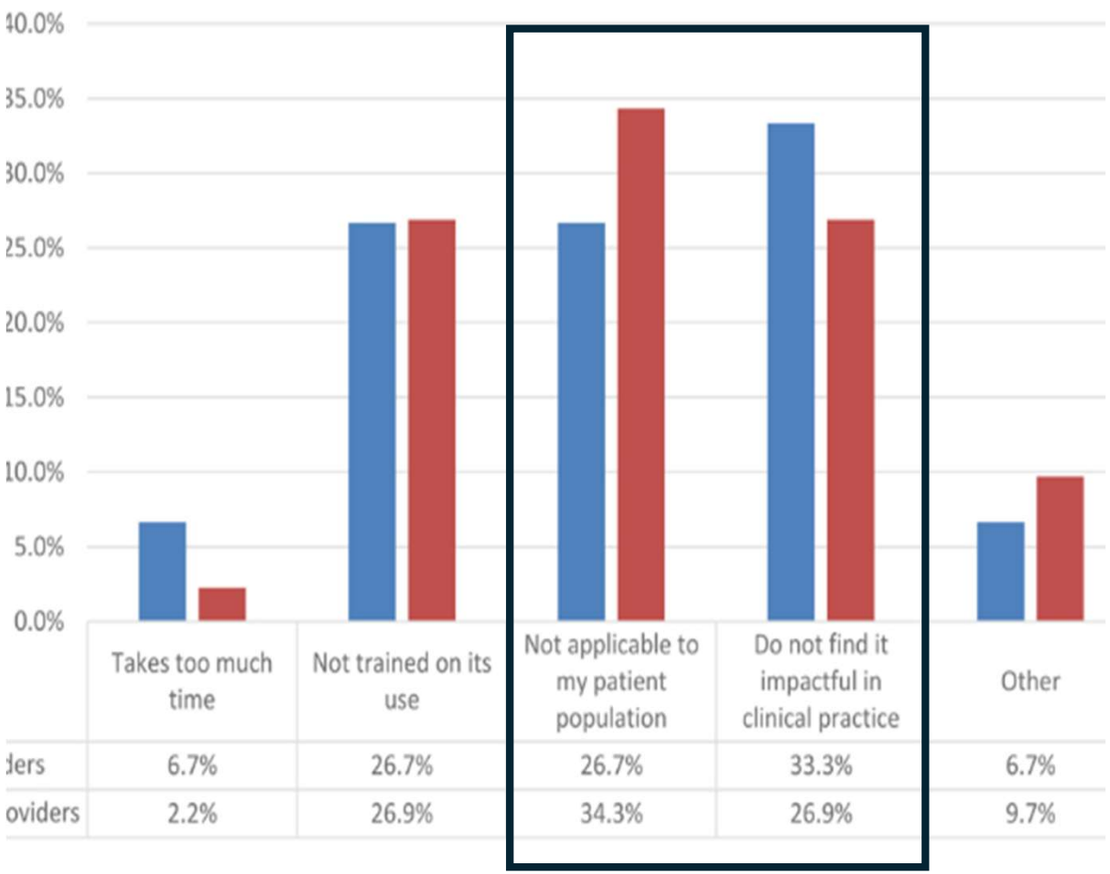
A survey of transplant physicians showed limited use of the HCT-CI by pediatric transplanters

How often do you use the HCT-CI?



	75-100% of the time	50-75% of the time	5-49% of the time	1-4% of the time	0% of the time
	70.7%	13.2%	9.2%	1.7%	5.2%
	12.1%	8.5%	21.2%	13.9%	44.2%

What limits you from using the HCT-CI?



	Takes too much time	Not trained on its use	Not applicable to my patient population	Do not find it impactful in clinical practice	Other
ders	6.7%	26.7%	26.7%	33.3%	6.7%
oviders	2.2%	26.9%	34.3%	26.9%	9.7%

Broglie, Thakar, Sorror et al, Leuk Lymphoma 2023

Expanding the HCT-CI for younger patients

- Why did pediatric transplant physicians not use the HCT-CI?
  - Pediatric comorbidity burden generally less than adults
  - Adult definitions cannot always apply to pediatrics
    - Ie, young children cannot perform PFTs
  - Certain comorbidities extremely rare
    - Ie, peptic ulcer disease very rare in pediatrics, common in adults
  - Other comorbidities seen in pediatrics not collected in HCT-CI
    - Ie, failure to thrive seen more often than obesity

- Effort began in 2018 to expand the HCT-CI relevance in pediatrics

Comorbidity definitions needed updating for younger patients

ELSEVIER

Transplantation and Cellular Therapy

Volume 27, Issue 1, January 2021, Pages 74.e1-74.e9

Pediatric

Limitations of Applying the Hematopoietic Cell Transplantation Comorbidity Index in Pediatric Patients Receiving Allogeneic Hematopoietic Cell Transplantation

Larisa Broglie [1], Jenny Ruiz [1 2], Zhezhen Jin [3], Justine M. Kahn [1], Monica Bhatia [1], Diane George [1], James Garvin [1], Prakash Satwani [1]

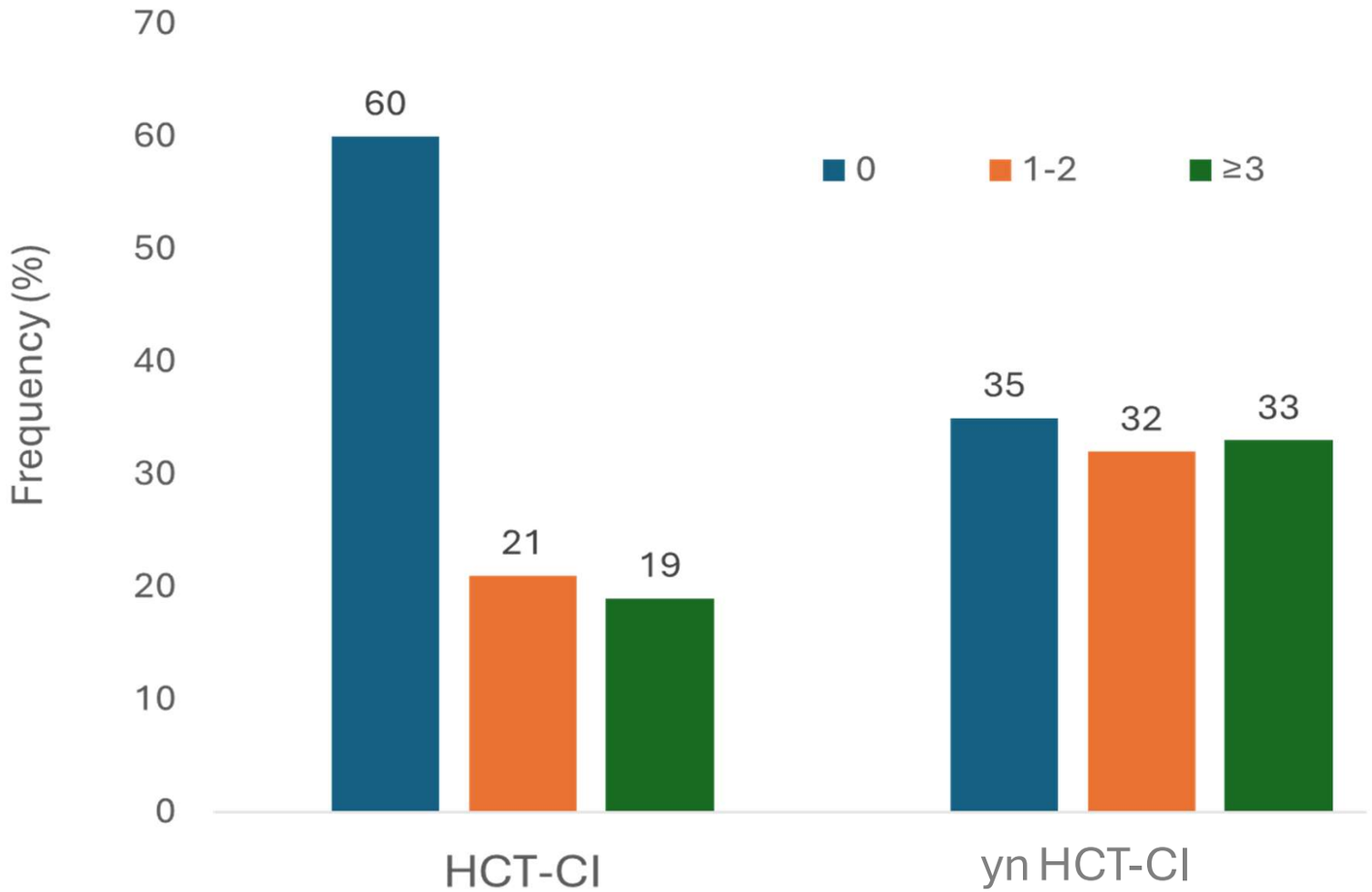
Highlights

- The hematopoietic cell transplantation comorbidity index did not affect survival or nonrelapse mortality in our pediatric cohort.
- Forty-five percent could not perform pulmonary function testing, underestimating pulmonary disease.
- Hepatic disease was common in hemoglobinopathies and hyperbilirubinemia from hemolysis.
- No patients had creatinine >2 mg/dL, but 5% had abnormal renal function by glomerular filtration rate.
- Assessment of pulmonary, renal, and hepatic function should be amended for children.

Comorbidity	Definition	HCT-CI	Expanded youth HCT-CI		Simplified youth HCT-CI	
			Malignant	Nonmalignant	Malignant	Nonmalignant
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias	1	1	1	0	0
Cardiac disease	Coronary artery disease, congestive heart failure, myocardial infarction, or EF ≤50% on most recent test	1	1	1	1	1
Heart valve disease	Except asymptomatic mitral valve prolapse	3	3	3	3	3
Inflammatory bowel disease	Crohn disease or ulcerative colitis	1	1	1	0	1
Diabetes	Requiring treatment with insulin or oral hypoglycemics, but not diet alone	1	1	1	1	1
Psychiatric disease	Requiring psychiatric consult or treatment in the last 4 weeks	1	1	1	0	0
Cerebrovascular	Any history of transient ischemic attack, subarachnoid hemorrhage, or cerebrovascular accident	1	1	1	0	1
Infection*	Requiring antimicrobial treatment for serious infection that continues through conditioning	1	1	1	1	1
	Or history of invasive fungal disease (proven, suspected, and/or documented)	N/A				
Obesity*	>35 kg/m^2	1	1	1	1	0
	BMI >95th percentile by CDC guidelines for (≤18 years old)	N/A				
Underweight*	Underweight: BMI <5th percentile by CDC guidelines for (≤18 years old) or <18 kg/m^2 (>18 years old)	N/A	0	1	0	1
Mild hepatic disease	Chronic hepatitis, bilirubin >upper limit of normal to 1.5 × upper limit of normal, or AST/ALT upper limit of normal to 2.5 × upper limit of normal	1	1	1	0	0
Moderate/severe hepatic disease	Liver cirrhosis, bilirubin >1.5 × upper limit of normal, or AST/ALT >2.5 × upper limit of normal	3	3	3	3	3
Mild renal disease*	Creatinine >2 mg/dL or prior renal transplant; or on dialysis	2[a]	N/A	N/A	N/A	N/A
	or eGFR 60-89 mL/min/1.73 m^2 (by Bedside Schwartz calculation for <18 years old, CKD-EPI calculation for ≥18 years old)	N/A	2	N/A	2	N/A
	eGFR 60-89 mL/min/1.73 m^2 (by Bedside Schwartz calculation for <18 years old, CKD-EPI calculation for ≥18 years old)	N/A	N/A	1	N/A	1
Moderate/severe renal disease*	Creatinine >2 mg/dL, or prior renal transplant, or on dialysis	2[a]	N/A	N/A	N/A	N/A
	Creatinine >2 mg/dL, on dialysis, or prior renal transplant; or eGFR <60 mL/min/1.73 m^2 (by Bedside Schwartz calculation for <18 years old, CKD-EPI calculation for ≥18 years old)	N/A	N/A	2	N/A	2
	On dialysis	N/A	3	N/A	3	N/A
Moderate pulmonary disease	Corrected diffusion capacity of carbon monoxide and/or FEV_1 66%-80%, or dyspnea on slight activity	2	2	2	0	0
Severe pulmonary disease*	Corrected diffusion capacity of carbon monoxide and/or FEV_1 ≤65%, dyspnea at rest, or requiring oxygen	3	3	3	3	3
	Or prior history of mechanical ventilation	N/A				
Peptic ulcer disease	Confirmed by endoscopy and requiring treatment	2	2	2	0	2
Rheumatologic disease	Systemic lupus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rheumatica requiring treatment	2	2	2	0	2
Prior solid tumor	At any point in patient's history, excluding nonmelanoma skin cancer, leukemia, lymphoma, or multiple myeloma; does not count if patient is being transplanted for indication of solid tumor	3	3	3	3	3

Thakar and Sorror, ASH Education book 2023

Youth Scores Better Classify Comorbidity for younger patients

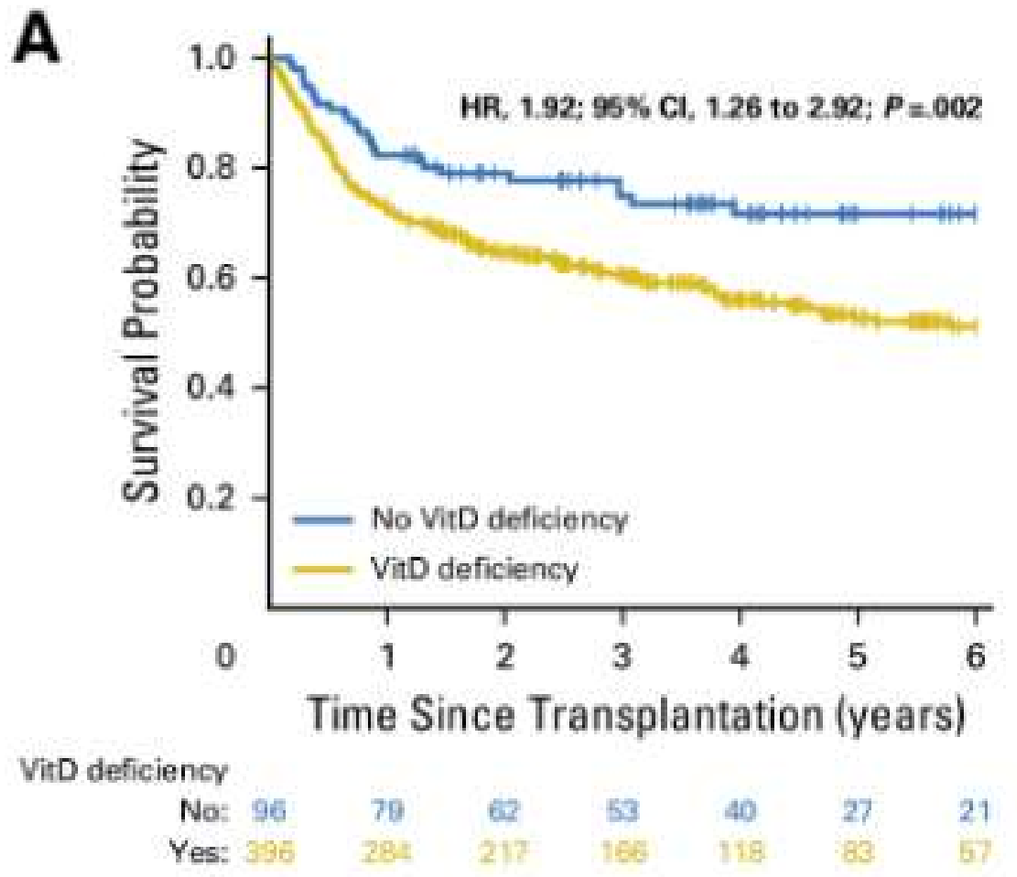


Adults- Expanding on HCT-CI

Low Vitamin D pre-HCT is associated with worse outcomes post-HCT

- Vit D can affect multiple signaling pathways controlling proliferation, apoptosis, differentiation, angiogenesis, and metastasis and modulate innate and adaptive immune responses

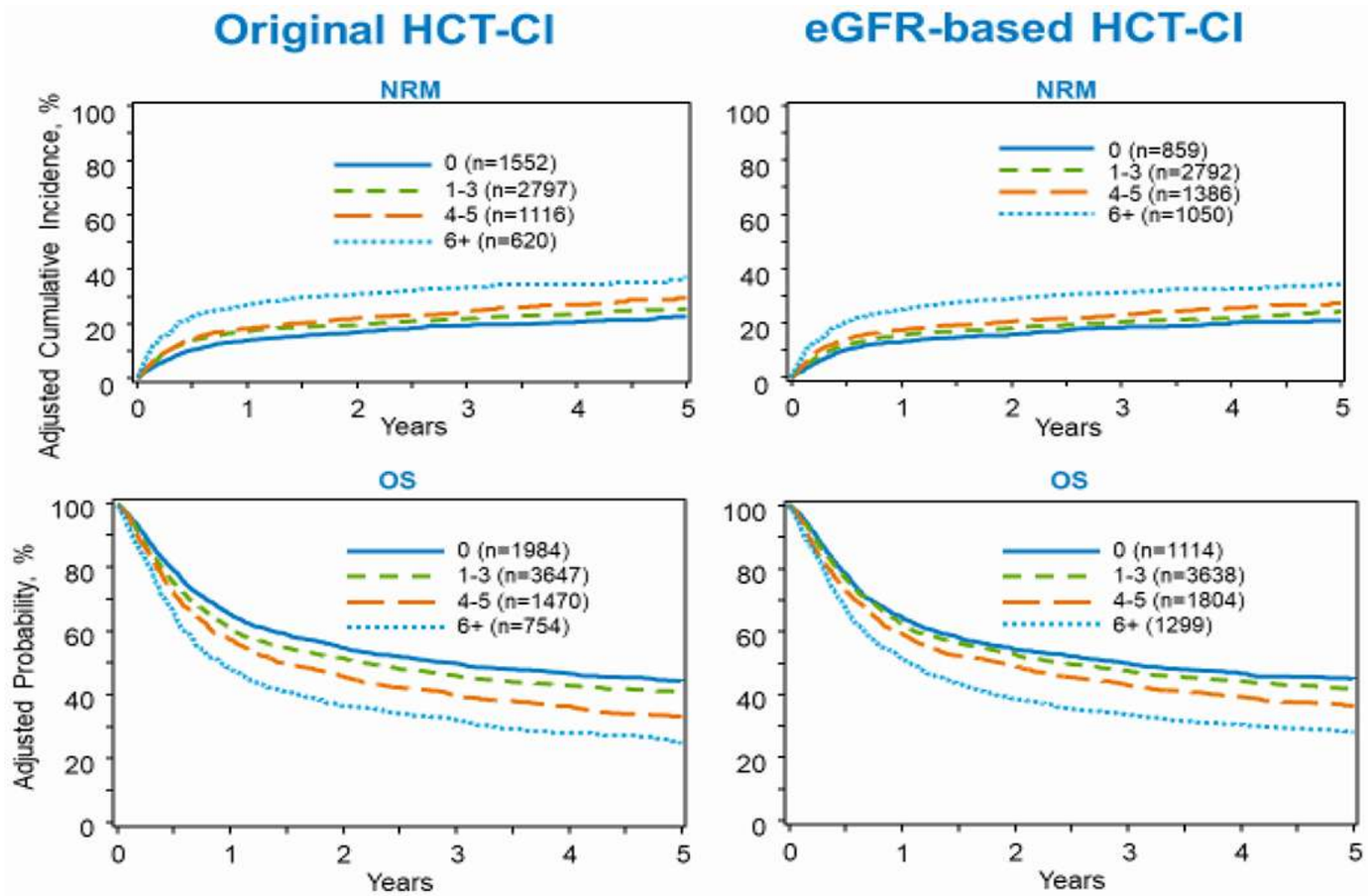
- Several reports demonstrating lower OS, higher relapse, higher GVHD in peds pts with low vit D levels (Hansson et al, BBMT 2015; Wallace et al, BBMT 2015)



Worse OS in AML related to increased relapse in training (n=396) & validation (n=348) sets (Radujkovic JCO 2017)

Renal Insufficiency with HCT-CI

n=13505, patients 40 years and older
CKD-EPI 2009 without cystatin C



Overall Survival		
	HCT-CI	HCT-CI eGFR
C-statistics validation set N= 5403	0.6277	0.6289

Farhadfar N…Paquini M, Transplant Cel Ther 2022; PMID 33775617

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BLOOD & MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Composite Health Assessment Risk Model (CHARM) for Older Adults:

A New Milestone in Predicting Non-Relapse Mortality in Older Recipients of Allogeneic HCT

Study Design: Primary Objective

A large, prospective, multicenter, observational study to determine the set of factors that could together constitute a robust and valid composite health risk-model for accurate estimation of 1-year NRM

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Study Design: Secondary Objectives

To assess the prognostic ability of the model over 1-year:

1) OS
2) Frailty
3) Development of disability
4) Incidence of nursing facility admission
5) Cognitive decline (day 100)
6) Trajectories in QOL
7) Cum incidence of aGVHD and cGVHD
8) Cum incidence of serious organ toxicity (day 100)
9) Survival after acute GVHD

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Eligibility

- ≥60 years of age
- First alloHCT for hematologic malignancies
- Eligible per institution
- English, Spanish or Mandarin speaking

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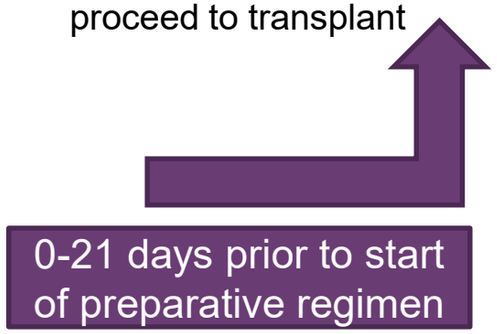
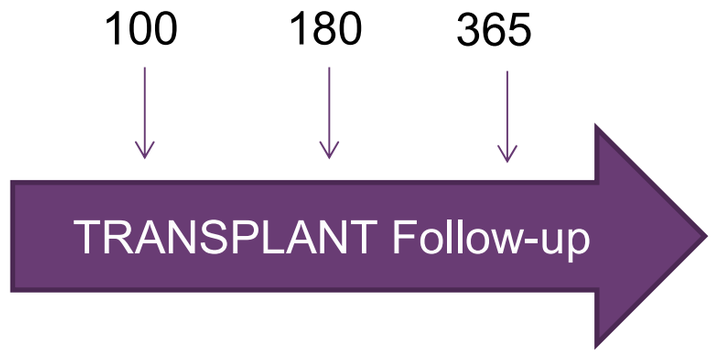
SCHEMA 1704

Off-Study – obtain reason why subject did not proceed to transplant





Baseline
HCT-CI*
GA** + Frailty Phenotype***
CRP, Albumin* (0-14 days prior to preparative regimen)
QOL by PROMIS Depression, Physical Function, Anxiety
MD Prognostication Survey

Core Outcome Measures at Each Follow-Up	
GA + QoL	**Standard of Care**
Frailty Phenotype***	NRM*
IADL	Survival*
Skilled Nursing Facility Admissions	GVHD*
QOL by PROMIS	OS after GVHD*
MoCA (d100)	Organ toxicities* (d100)

*** Standard of care**

**** GA: KPS, IADL, MoCA, falls, medications**

***** Frailty: grip, walk, exhaustion, activity, weight loss**

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Statistical

-Prospectively identified 13 pt specific health variables to test for CHARM to predict 1-year NRM

-To select covariates, MVA Fine-Gray model with multiple imputation to handle missingness

-Grouped penalized variable selection using SCAD* to identify variables to retain in model

-Variables modeled as continuous and assessed for linearity and proportional hazards

-Considered adjustment for conditioning intensity, CMV serostatus and donor type.

-AUC calculated to validate CHARM and compare to HCT-CI alone, with boostrap sampling to correct for optimism in the within-sample AUC.

-MVA for 1-year OS used CHARM score adjusted for other significant variables from stepwise regression.

*smoothly clipped absolute deviation

Statistical Team	Organization or Role
B. Logan	CTN, NMDP, CIBMTR
J. Kou	CTN, NMDP, CIBMTR
N. Geller	NHLB statistician
A. Bellach	NHLBI statistician
W. Saber	Scientific Officer

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Select Baseline Characteristics

Characteristic	N(%)
Age yrs, median	67 (range 60-82)
Sex, Male	704 (64)
Race	
White	984 (89)
Black or AA	44 (4)
Asian	44 (4)
Disease	
AML	498 (45)
MDS	236 (30)
MPN	108 (10)
Ref DRI, Intermediate	639 (58)

Characteristic	N(%)
Donor	
HLA-iden Sib	169 (15)
MUD	625 (57)
Haplo	227 (21)
MMUD	84 (8)
Conditioning	
MAC	144 (13)
RIC	753 (68)
NMA	208 (19)
GVHD Ppx	
Tac +/- other	577 (52)
Cyclophos +/- other	465 (42)

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Baseline Characteristics and Completeness of Proposed CHARM Factors

- **BOLD were in final CHARM model**
- **Note: we had 100% completion of all 13 variables for the study calculated sample size of 880 patients**

Characteristic	Source	% Evaluable	Median, (IQR)
Age	**Team**	**100**	**67.5 (64.1 - 71.2)**
Walk Speed	Team	100	1.0 (0.8 - 1.1)
Albumin, g/dL	**CIBMTR**	**100**	**4.0 (3.7 - 4.2)**
HCT-CI	**CIBMTR**	**100**	**3 (1 - 4)**
MoCA	**Team**	**97**	**26 (24 - 28)**
Weight loss	**PRO and Team**	**92**	**3.2 (0 - 8.2)**
IADL	PRO	89	14 (13 - 14)
PROMIS Depression	PRO	88	44 (38 - 50)
PROMIS Phys. Func	PRO	88	44 (39 - 50)
KPS, pt report	**PRO**	**88**	**90 (80 - 100)**
Falls	PRO	88	0 (0 - 0)
CRP, mg/L	**Local Lab**	**87**	**2 (0.9 - 6.0)**
# of Rx'd meds	PRO	78	5 (3 - 7)

Team= Research Team, CIBMTR= CIBMTR forms, PRO= patient reported outcome, Lab-local laboratory

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Outcomes (N=1105)

Outcomes at 1 year	Prob (95% CI)
NRM	**14.4 (12.-4-16.6)**
Survival	72 (69.3-74.6)
Relapse	25.3 (22.7-27.9)
Leading causes of death	N=308 deaths
Disease	114 (37%)
organ failure	52 (17%)
Infection	41 (13%)
aGVHD	31 (10%)

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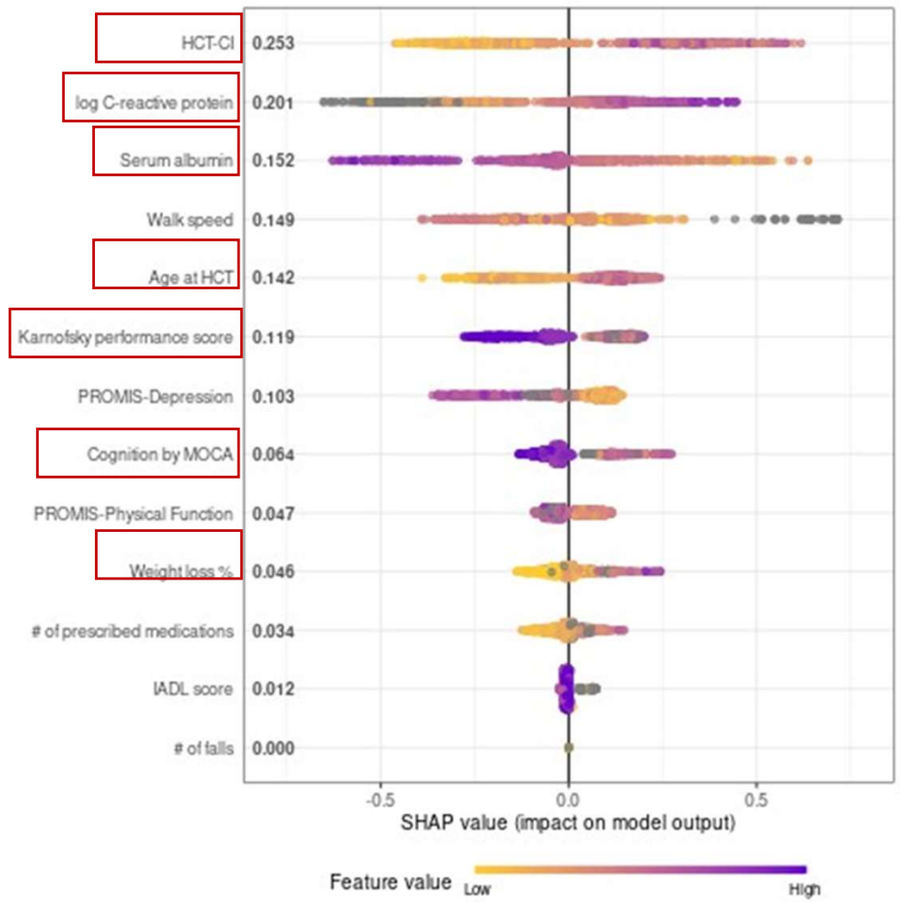
MVA by individual covariates

Variable	Coefficient (Log HR scale)*	p-value	Coefficient (adjusted for non-CHARM variables)**
HCTCI	0.1296686	<0.0001	0.1357042
Log(CRP)*	0.1118738	0.0493	0.1141597
albumin	-0.5989142	0.0008	-0.5920071
weight loss^2	0.001110624	0.0089	0.001190834
PROkps^2	-6.45035E-05	0.1115	-6.74881E-05
Age at HCT	0.03748089	0.0317	0.04346934
MoCA	-0.04649406	0.1106	-0.04011149

CHARM CALCULATOR
0.1296686 * HCTCI + 0.1118738 * Log (CRP) - 0.5989142*albumin
+0.001110624 * Weight loss^2 - 0.0000645035*KPS^2 + 0.03748089*Age at HCT - 0.04649406 * MoCA.

Calculator https://cibmtr.org/CIBMTR/OffNav/DevSandbox/CHARM-Risk-NRM-Calculator.

Shapley Value of Cox Boosting Model for NRM



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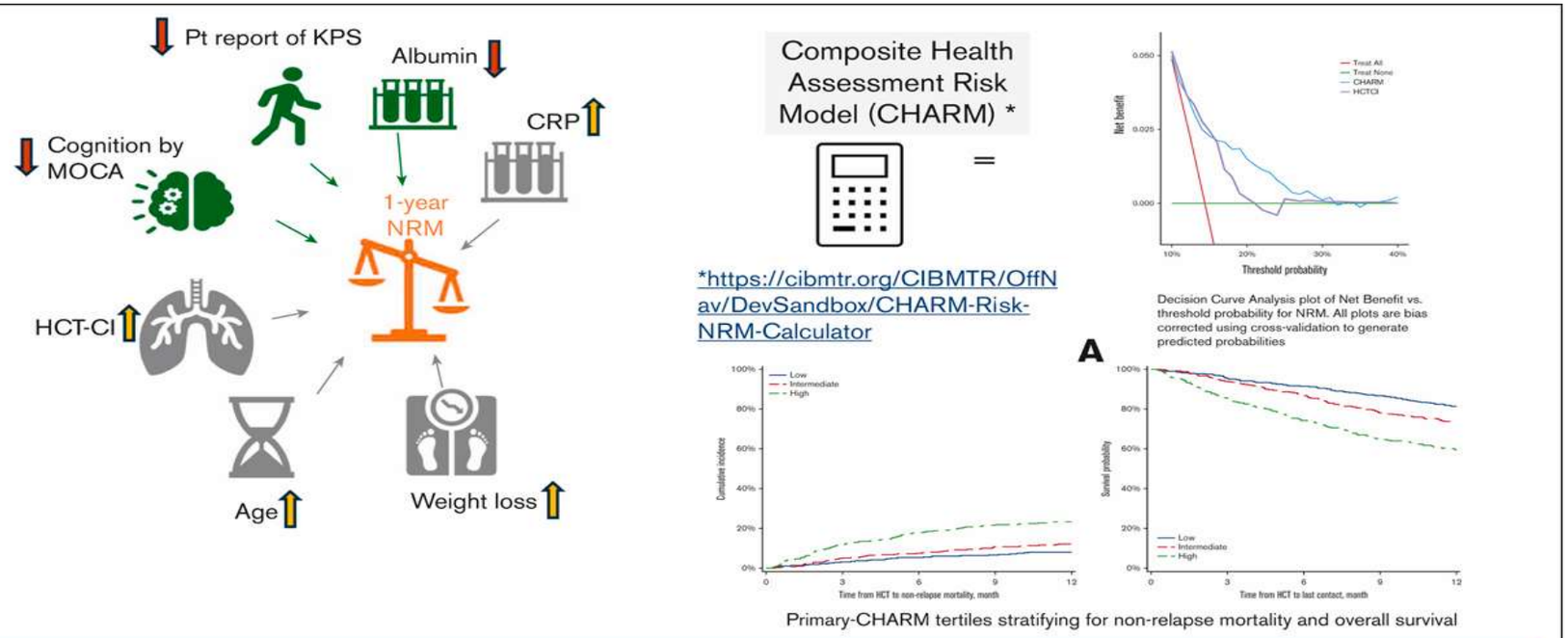
Shapley value plots summarize the contribution and rank of all health variables in the Cox Boosting ML-CHARM on patient specific predictions of NRM risk, where variables with wider Shapley value ranges indicate larger impact on NRM risks across individuals.

Novel composite health assessment risk model for older allogeneic transplant recipients: BMT-CTN 1704



Primary-CHARM tertiles stratifying for non-relapse mortality and overall survival

Conclusions: CHARM is a tool to risk-stratify older recipients of allo-HCT for risks of NRM. It complements DRI to predict survival. Utilizing CHARM could help increase referrals to allo-HCT and novel strategies to reduce NRM.

*Sorror et al. DOI: 10.1182/**bloodadvances**.2025015793*

blood advances® Visual Abstract

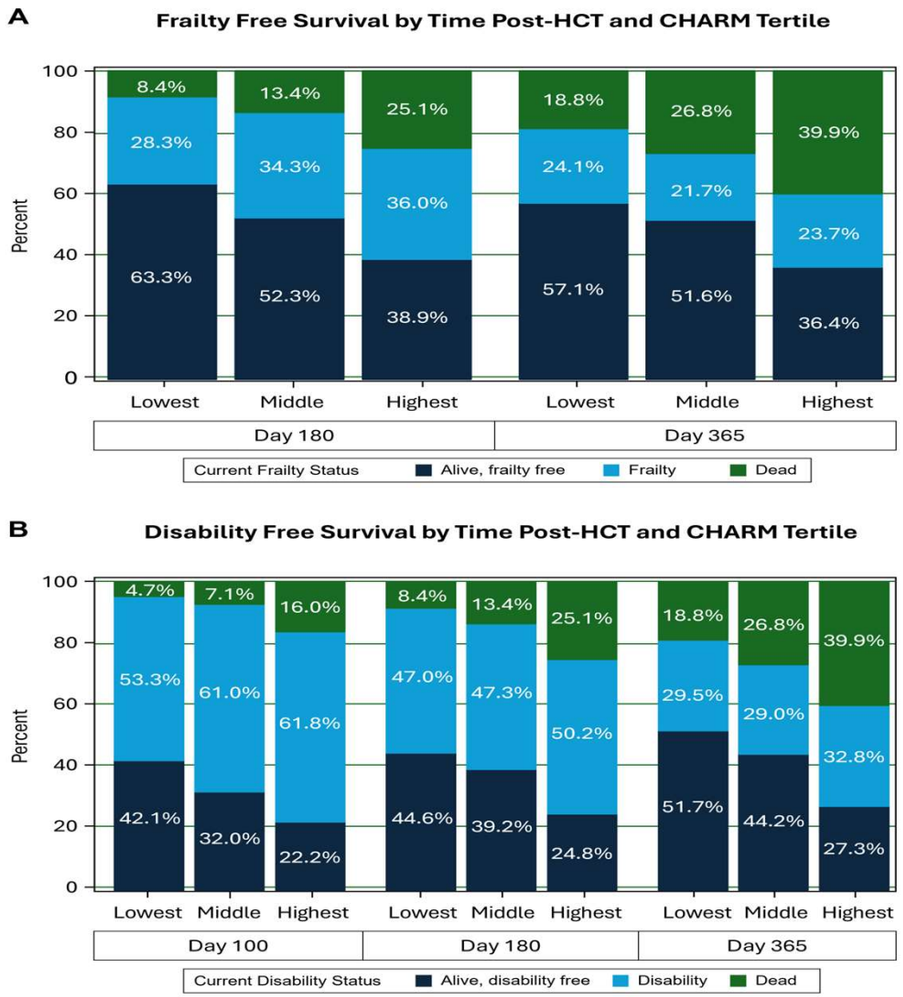
MVA for OS from CHARM 1704

Table 3: Multivariate model for overall survival through 1 year

Variable	HR	Lower	Upper	p-value
Primary-CHARM scores	2.060	1.676	2.531	<0.0001
DRI Low/Intermediate	1.000			Overall 0.0057
DRI High/Very High	1.537	1.164	2.031	0.0025
DRI unknown	1.495	0.935	2.391	0.0931
PhysQ: 75-90%	1.000			Overall 0.056
PhysQ: 90-100%	0.874	0.418	1.830	0.7218
PhysQ: 50-74%	1.033	0.758	1.408	0.8357
PhysQ: 25-49%	1.058	0.730	1.534	0.7664
PhysQ: 0-24%	2.532	1.339	4.788	0.0043

DRI = Disease Risk Index; PhysQ = physician questionnaire about patient survival

CHARM Predicts Functional Limitation-Free Survival



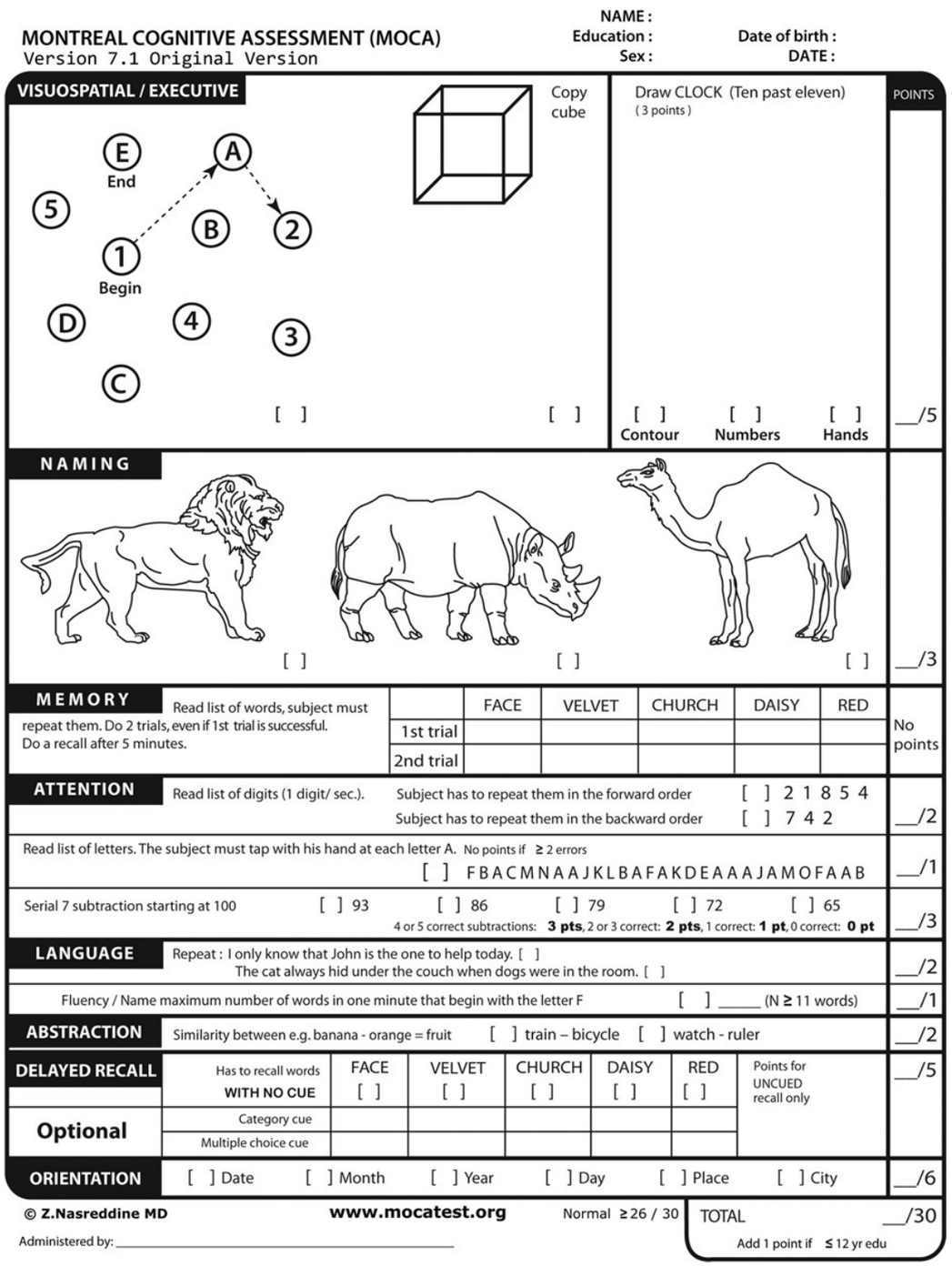
Artz A.…Sorror M, Blood Adv *in press*.

Data Capture for CHARM

Tool	Health Care/Patient Reported Outcomes (PRO)	Additional effort	Challenges	Prone to Bias (Minimal, mild, moderate, large)
HCT-CI	Health Care	None	CIBMTR	Mild
Albumin	Health Care	None	CIBMTR	No
Recipient Age	Health Care	None	CIBMTR	No
CRP, highly sensitive	**Health care**	**Mild**	**Timing and insurance**	**Minimal**
Pt reported KPS	**PRO**	**Mild**	**Method to capture by center**	**Mild**
Weight loss	**Health Care or PRO**	**Mild**	**Availability of data**	**Minimal**
MoCA	**Health Care**	**Moderate**	**Training, licensure and version**	**Mild**

NEW

Montreal Cognitive Assessment



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] Contour [ ] Numbers [ ] Hands __/5

NAMING __/3

[ ] [ ] [ ]

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — No points

	FACE	VELVET	CHURCH	DAISY	RED
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 __/3
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

LANGUAGE Repeat : I only know that John is the one to help today. [ ] __/2
The cat always hid under the couch when dogs were in the room. [ ]

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 __/5

	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
Has to recall words WITH NO CUE	[ ]	[ ]	[ ]	[ ]	[ ]	
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: _____

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CMS Aging Friendly Hospital Measure for Hospital Inpatient Quality Reporting

5 domains

- Eliciting Patient Goals
- Responsible Medication Management
- Frailty Screening and Intervention
- Social vulnerability
- Age-friendly care leadership

Meeting the Measure

- What Matters
- Medications
- Mentation
- Mobility

“Domain 3: Frailty Screening and Intervention (i.e., Mobility, Mentation, and Malnutrition): This domain aims to screen patients for geriatric issues related to frailty including cognitive impairment/delirium, deficits in physical function, mobility, and malnutrition for the purpose of early detection and intervention where appropriate. “

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