Chronic Graft-versus-Host Disease and Hematopoietic Cell Transplant Survivorship Care Models

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No conflict of interest to disclosure

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Disclosures

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- **Major Shareholder**: No disclosure
-

Ibrutinib is the only FDA approved therapy for chronic GVHD that failed corticosteroids

Outline

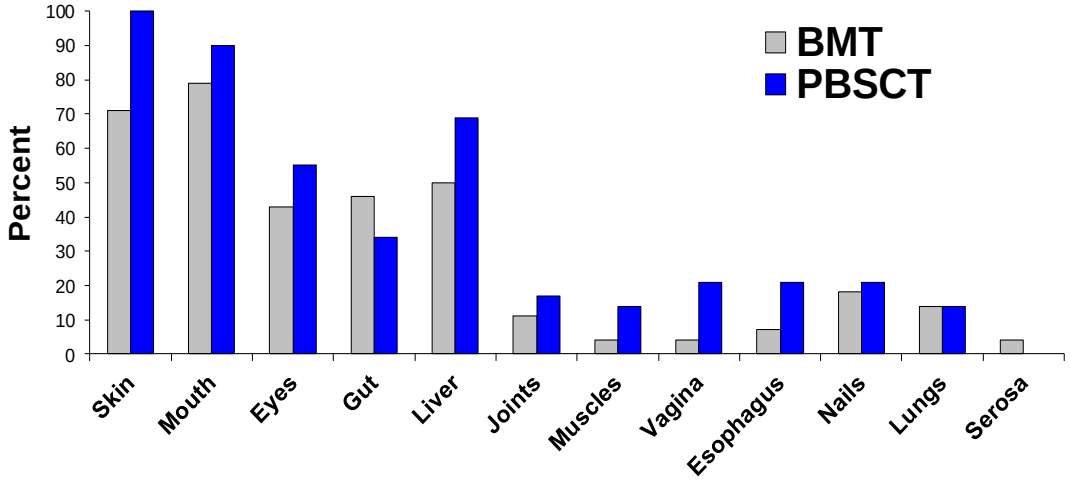
- What is chronic Graft-versus-Host Disease (GVHD)
- Challenges of patients with chronic GVHD
- Quality of life and functional of hematopoietic cell transplant (HCT) recipients with chronic GVHD
- Quality of life and functional of caregivers of transplant recipients
- HCT Survivorship Care Models

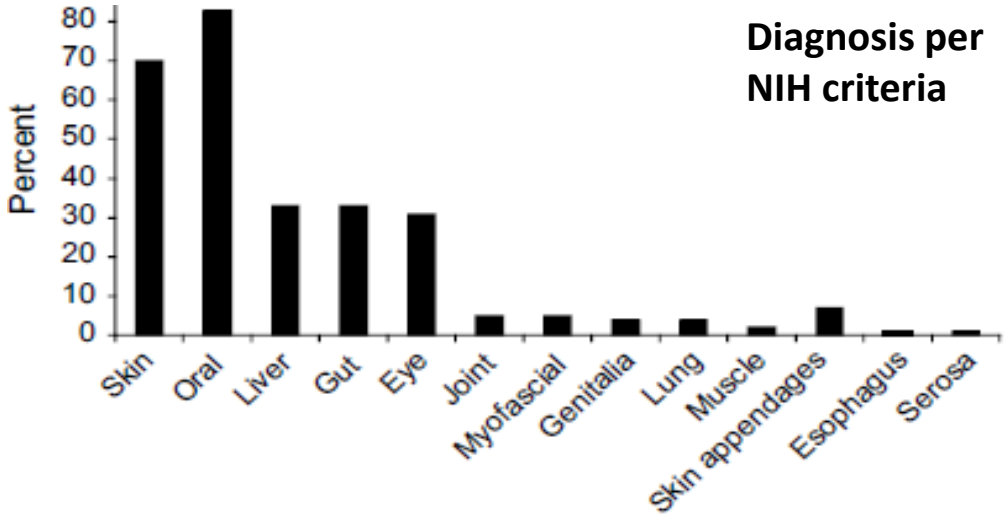
Chronic Graft-versus-Host-Disease (GVHD)

- Major barrier of otherwise successful allogeneic hematopoietic stem cell transplantation (HCT)
- Results from an immunological assault of the allogeneic "graft" against the transplant recipient (host)
- ~40 % cumulative incidence by 1 year after transplant
- Median onset 6 months after HCT (10% > 1 year after HCT)
- Median duration of treatment 2 -3 years (some cases require systemic immunosuppression beyond 10 years)
- Associated with poor quality of life
- Associated with lower risk of relapse of original malignancy

Sites affected by chronic GVHD

At time of initiation of systemic treatment





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Flowers et al, Blood 2002

Flowers et al Biol Blood Marrow Transplant 2008

What are the severe manifestations of cGVHD

- Severe ocular sicca (eyes)
- Sclerotic features (skin)
- Joint contractures/Fasciitis (muscle/joint)
- Esophageal stricture (difficult swallowing)
- Bronchiolitis obliterans (lungs)
- Severe oral sicca and ulcers (mouth)

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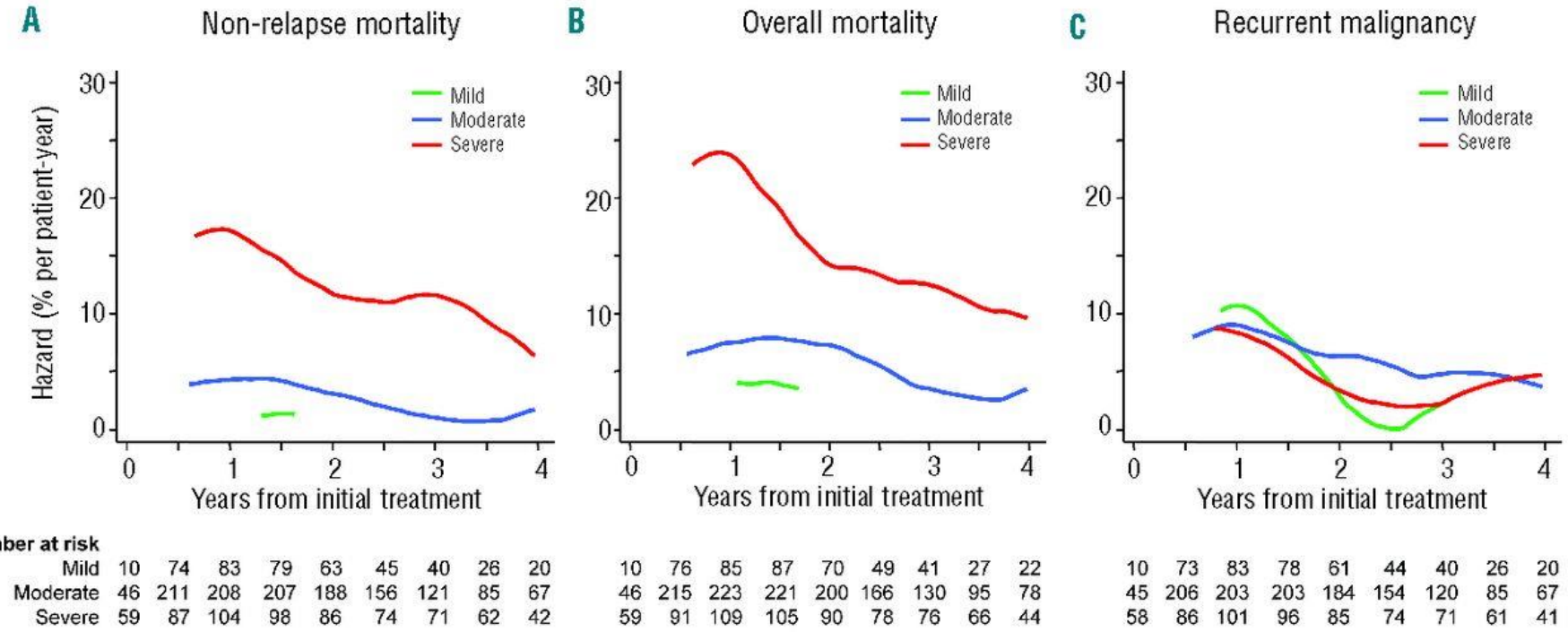
Flowers M et al. Blood 2002; 100: 415-419

Impact of severity of chronic GVHD on NRM, OS and *Graft-vs.-Leukemia*



NIH global score	Non-relapse mortality N. of patients*	HR† (95% CI)	P	Overall mortality N. of patients*	HR† (95% CI)	P	Recurrent malignancy N. of patients*	HR‡ (95% CI)	P
Mild	196	1.00 (reference)		196	1.00 (reference)		194	1.00 (reference)	
Moderate	455	4.27 (0.99-18.4)	0.051	455	2.79 (1.24-6.30)	0.013	447	1.26 (0.68-2.35)	0.46
Severe	320	17.1 (4.12-71.3)	<0.001	320	7.59 (3.42-16.9)	<0.001	314	1.27 (0.64-2.52)	0.49

**Total number of patients contributing to the category at one or more visits. †Models were adjusted for time after transplantation, transplant center, patients' age, stem cell source, disease risk, cytomegalovirus status, HLA and donor type, gender mismatch, conditioning intensity, prior acute GVHD and thrombocytopenia at the visit. ‡Models were adjusted for time after transplantation, transplant center and disease risk.*

Inamoto Y et al, Haematologica 2014: 99:1619

Challenges Faced by Patients with Chronic GVHD

Neuropsychologic effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

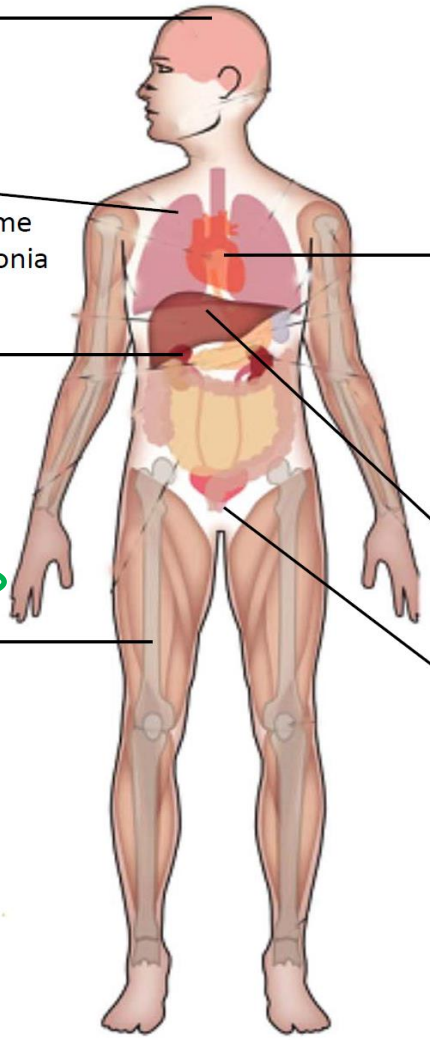
Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic CKD
- Persistent acute kidney injury
- BK virus nephropathy

Impact on quality of life

Bone diseases
- Osteopenia
- Osteoporosis
- Avascular necrosis

Endocrine diseases
- Thyroid dysfunction
- Gonadal dysfunction
- Diabetes
- Dyslipidemia
- Metabolic syndrome
- Adrenal insufficiency



Solid cancers
- Oral cavity
- Skin
- Breast
- Thyroid
- Other sites

Cardiovascular diseases
- Cardiomyopathy
- Congestive heart failure
- Valvar dysfunction
- Arrhythmia
- Pericarditis
- Coronary artery disease

Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- *Pneumocystis jirovecci*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus

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Adapted from Inamoto Y, Lee SJ. Haematologica 2017

Chronic GVHD impacts overall health and quality of live (QOL) after transplantation

Patient-reported outcomes and health status associated with chronic GVHD

Study objectives:

- Describe the quality of live (QOL) scores and health status of patients with chronic GVHD of differing severity compared to those with resolved chronic GVHD or those who had never had chronic GVHD.
- Investigate the PROMIS* measures in chronic GVHD relative to established measures of QOL in long-term transplant survivors.

Patient-Reported Outcomes Measurement Information System *is a set of person-centered measures that evaluates and monitors physical, mental, and social health.*

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Lee. S et al. Haematologica 2018, 103(9):1535-1541

Patient-reported outcomes and health status associated with chronic GVHD

- We surveyed allogeneic transplant recipients about their quality of life, symptoms, health status, comorbid conditions and medication.
- Of 3027 surveys sent to recipients surviving ≥ 1 year after transplantation, 1377 (45%) responded.

Lee. S et al. Haematologica 2018, 103(9):1535-1541

Patient-reported outcomes and health status associated with chronic GVHD

- Of 1377 responders, they reported their chronic GVHD as
  - Mild (18.7%)
  - Moderate (8.0%)
  - Severe (1.8%)
- Another 377 (27.4%) never had chronic GVHD
- And 280 (20.3%) had chronic GVHD but it had resolved.

Lee. S et al. Haematologica 2018, 103(9):1535-1541

Patient-reported outcomes and health status (n = 1377)

Population characteristics						
	Never (n=377)	Resolved (n=280)	Mild (n=257)	Moderate (n=110)	Severe (n=25)	P-value
Female, n (%)	209 (55.4)	135 (48.2)	113 (44.0)	49 (44.5)	9 (36.0)	0.02
Age, mean years (SD)	53.9 (13.5)	58.8 (12.3)	57.2 (12.6)	58.3 (10.8)	57.6 (15.0)	<0.001
Matched related	212 (56.2)	136(48.6)	88 (34.2)	40 (36.4)	7 (28.0)	<.001
Mismatched related	16 (4.2)	19 (6.8)	4 (1.6)	1 (0.9)	1 (4.0)	
Haplo-identical related	11 (2.9)	7 (2.5)	10 (3.9)	2 (8.1)	1 (4.0)	
Matched unrelated	95 (25.2)	81 (28.9)	114 (44.4)	54 (49.1)	11 (44.0)	
Mismatched unrelated	17 (4.5)	33 (11.8)	31 (12.1)	13 (11.8)	4 (16.0)	
Cord	19 (5.0)	4 (1.4)	9 (3.5)	0	0	
Syngeneic	6 (1.6)	0	1 (0.4)	0	0	
Peripheral blood, n (%)	150 (39.8)	110 (39.3)	187 (72.8)	97 (88.2)	20 (80.0)	<.001
Myeloablative, n (%)	309 (82.0)	242 (86.4)	172 (66.9)	64 (58.2)	14 (56.0)	<.001
High dose TBI, n (%)	133 (35.3)	131 (46.8)	59 (23.0)	18 (16.4)	3 (12.0)	<.001
Years since HCT, mean, (SD)	**14.9 (11.3)**	**17.5 (8.4)**	**8.4 (7.5)**	**7.2 (5.8)**	**9.0 (8.1)**	**<.001**

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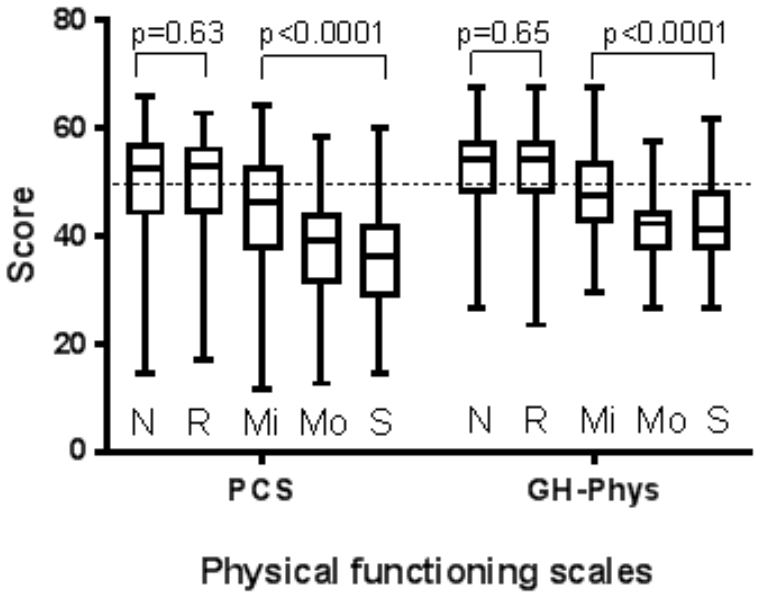
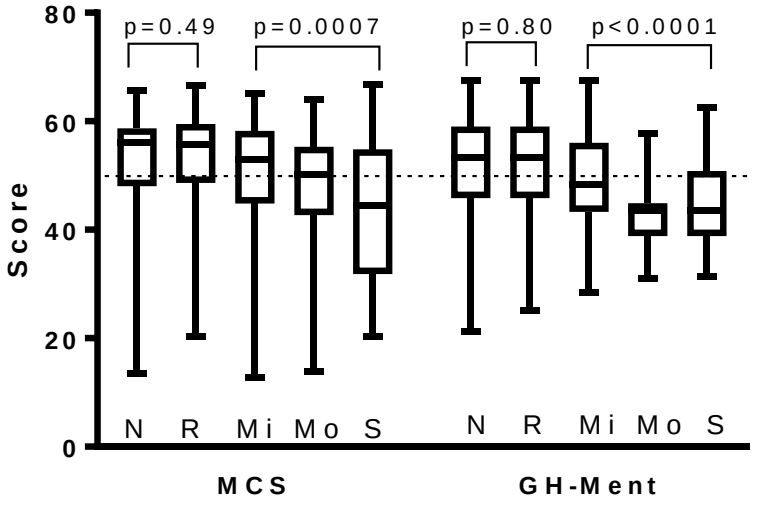
Lee, S. et al. Haematologica 2018, 103(9):1535-1541

SF-36 Physical (PCS) and Mental (MCS) Component Score and PROMIS Global Health Health Physical (GH-Phys) and Mental score (GH-Ment)



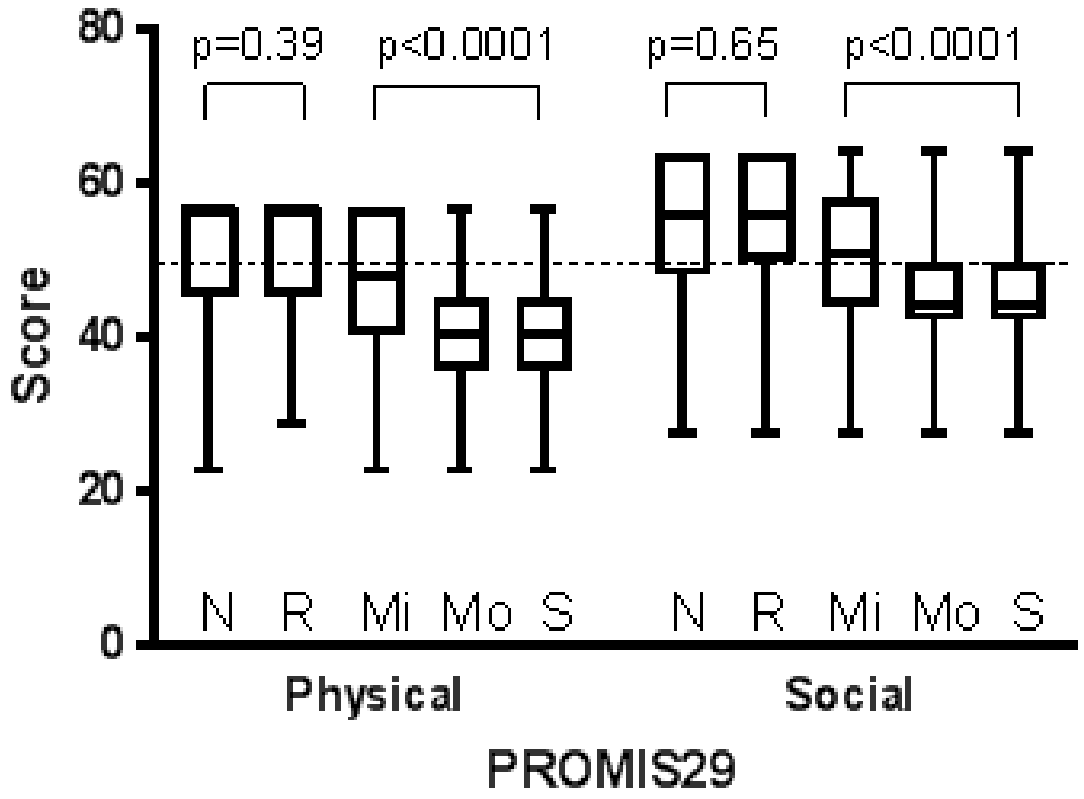
Physical functioning scales



Mental Functioning

Lee. S et al. Haematologica 2018, 103(9):1535-1541

PROMIS 29 subscales of physical and social functioning



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Conclusions

- Patients with moderate or severe cGVHD reported worse quality of life, lower performance status, a higher symptom burden and were more likely to be taking prescription medications for pain, anxiety and depression compared to those with resolved cGVHD.
- Self-reported measures were similar between patients with resolved cGVHD and those who never had it.
- Our data suggest that the PROMIS measures can replace the SF-36 in cGVHD assessment.
- Between 26.7-39.4% of people with active cGVHD were unable to work due to health reasons, compared with 12.1% whose cGVHD had resolved and 15.4% who never had cGVHD.
- Mouth, eye and nutrition symptoms persisted after resolution of cGVHD.
- These results show that better prevention of and treatment for cGVHD is needed to improve survivorship after allogeneic transplantation

Lee. S et al. Haematologica 2018, 103(9):1535-1541

Quality of live of Caregivers of Recipients of Hematopoietic Cell Transplantation (HCT)

Quality of Life of Caregivers of Hematopoietic Cell Transplant (HCT) Recipient

- Caregiver burden is a well-recognized problem when patients have chronic illnesses.
- Caregiver burden is defined as the emotional, physical, social, and financial suffering that they experience as a result of providing care.
- Studies have found that early after HCT, caregivers experience significant levels of distress and burden and declining quality of life (QOL).
- Given the complex care needs and prolonged recovery for transplant recipients, effects on caregiver health and QoL are expected.
- We surveyed allogeneic transplant recipients about their quality of life, symptoms, health status, comorbid conditions and medication.

Jamani, K et al. BBMT 2018 (24):2271-2276

Quality of Life (QoL) of Caregivers of Hematopoietic Cell Transplant (HCT) Recipient

- In this study we surveyed 4446 caregiver-recipient pairs in the post-HCT period to describe their QoL and its determinants.
- Survey was sent between July 2015 to July 2016
- 849 caregiver-recipient pairs at a median of 6 years (range, 0.4 to 44) after autologous or allogeneic HCT responded (~20%).

Jamani, K et al. BBMT 2018 (24):2271-2276

Characteristics of Caregiver Population

Characteristics	Recipient	Caregiver
Age, median (range) years	62 (18-87)	63 (18-90)
Sex, n (%)		
Male	502 (56)	290 (33)
Female	390 (44)	594 (67)
Ethnicity		
Non-Hispanic	863 (97)	764 (86)
Hispanic	15 (2)	14 (2)
Missing	14 (2)	114 (13)
Education		
<High school		11 (1%)
2 year college/trade degree		97 (11%)
4 year college/trade degree		228 (26%)
Graduate degree		254 (28%)
Missing		24 (3%)
2 year college/trade degree		97 (11%)

Jamani, K et al. BBMT 2018 (24):2271-2276

Characteristics of Caregivers Population (Continue)

Characteristics	
Caregiver relationship, n (%)	
Spouse	698 (78)
Live in partner	21 (2)
Parent	92 (10)
Child	28 (3)
Other	33 (4)
Friend	9 (1)
Paid caregiver	2 (0)
Missing	9 (1)
Caregiver still living with HCT recipient, n (%)	
Yes	760 (85)
Missing	21 (2)
Caregiver still providing care of HCT recipient, n (%)	
Yes	608 (68)
Missing	32 (4)

Quality of Life (QoL) of Caregivers of HCT Recipient Results

- Of 849 responding caregivers, 67% were women and 68% were still providing care to the HCT recipient.
- Mean and median QoL measures of caregivers were at or above general population norms; but approximately 20% of reported poor QoL relative to general population norms.
- Multivariate analysis revealed that caregiver age, gender, and educational attainment, were important determinants of caregiver QoL.
- Other determinants of caregiver QoL were recipient QoL, relapse after autologous HCT, and ongoing use of immunosuppression after allogeneic HCT.
- Prevalence of depression and sleep disorders appeared to be higher in caregivers than in the general population.

Jamani, K et al. BBMT 2018 (24):2271-2276

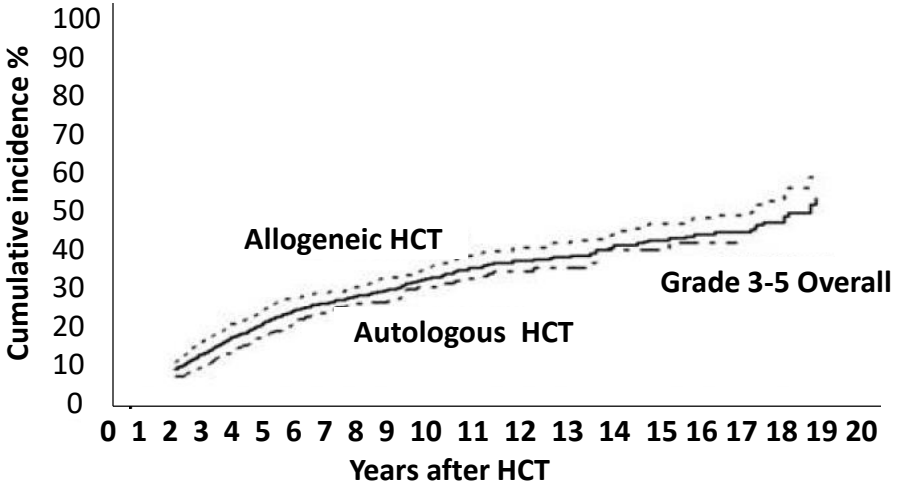
Quality of Life (QoL) of Caregivers of HCT Recipient
Conclusions

- We identified a population of caregivers who may benefit from interventions aimed at improving QoL and health outcomes.
- HCT clinical practice should also consider caregiver well-being

Autologous and Allogeneic HCT survivors have higher risk of chronic health problems compared with siblings

HCT survivors have higher risk of chronic health problems in compared with siblings

Chronic problems



Sun CL et al, Blood 2010

Relative risk (RR) compared with HCT siblings

Chronic problems	RR	95% CI
Overall	**1.88**	**1.39-2.11**
Grade 3-5	**3.52**	**2.31-5.38**

The Fred Hutch BMT Program at the Seattle Cancer Care Alliance

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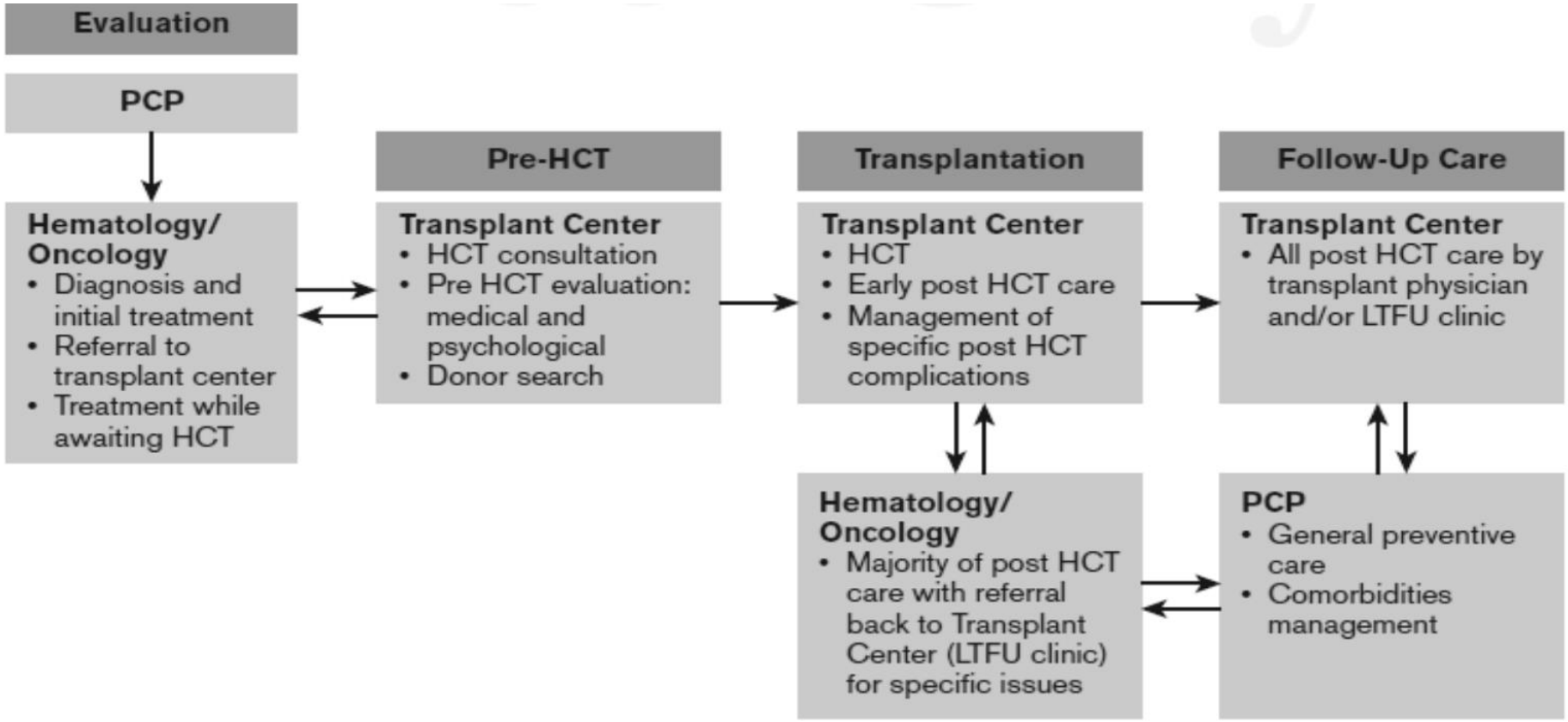
Gaps in the Care of HCT survivors

- Lack of evidence of care delivery models for HCT survivors
- Models of care delivery for HCT survivors vary and depend on many factors.

[1]Khera,N. et al. *Blood Advances* *2017*
[2]Hashmi,S. et al. *Biol Blood Marrow Transplant*, *2018*

Phases in the HCT continuum and Main stakeholders



Khera et al. Blood Advances 2017

Opportunities in HCT Survivorship Care

- Patient-centered care coordination in hematopoietic cell transplantation has been reviewed[1]
- ASBMT Practice Guidelines Committee Survey on Long Term Follow-Up Clinics for HCT Survivors has recently been published[2]

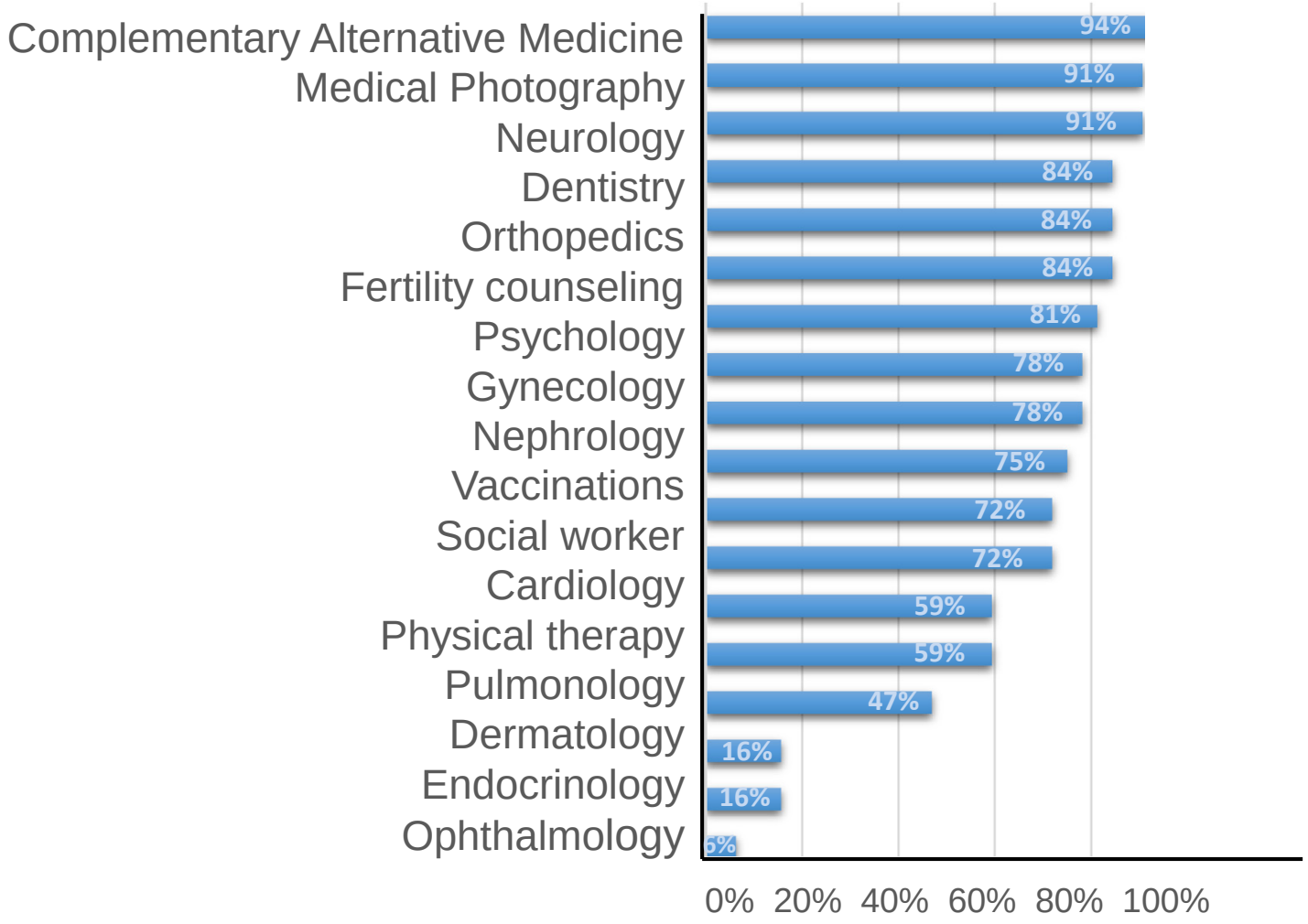
[1]Khera,N. et al. *Blood Advances* 2017
[2]Hashmi,S. et al. *Biol Blood Marrow Transplant*, 2018

Survey on Long-Term Follow-Up Clinics for Hematopoietic Cell Transplant Survivors

- Among 77 programs (38.5%) that responded, 45% indicated that they had a LTFU clinic, however, their care models varied with respect to services provided, specialist availability, type of patients served, and staffing.
- Among 55% of programs without an LTFU clinic, 100% agreed that allogeneic HCT survivors have unique needs separate from graft-versus-host disease and that complications could arise during the transition of care either from pediatric to adult settings or away from the HCT center.
- Obstacles identified to establish HCT survivorship care clinic included lack of expertise, logistics and financial issues.

Hashmi, SK. et al *Biol Blood Marrow Transplant* 2018

Availability of specialty services at centers with already established HCT-LTFU Clinics



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Hashmi, SK. et al *Biol Blood Marrow Transplant* 2018

Results of Survey among HCT Centers with Etablished LTFU Clinics

Statements	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree
Helpful in providing preventive ASBMT guidelines for HCT survivors (n=34)	3%	6%	6%	32%	53%
Advance practice practitioners (NP/PA) are essential part of LTFU Clinic (n=34)	3%	3%	6%	18%	70%
All allogeneic HCT survivors are seen/followed lifelong (n=32)	6%	9%	9%	31%	44%
All Autologous HCT survivors are seen/followed lifelong (n=32)	16%	31%	25%	16%	12%
Provides survivorship care plans for longitudinal care and transitional of care of HCT survivors (n=33)	3%	6%	3%	45%	44%

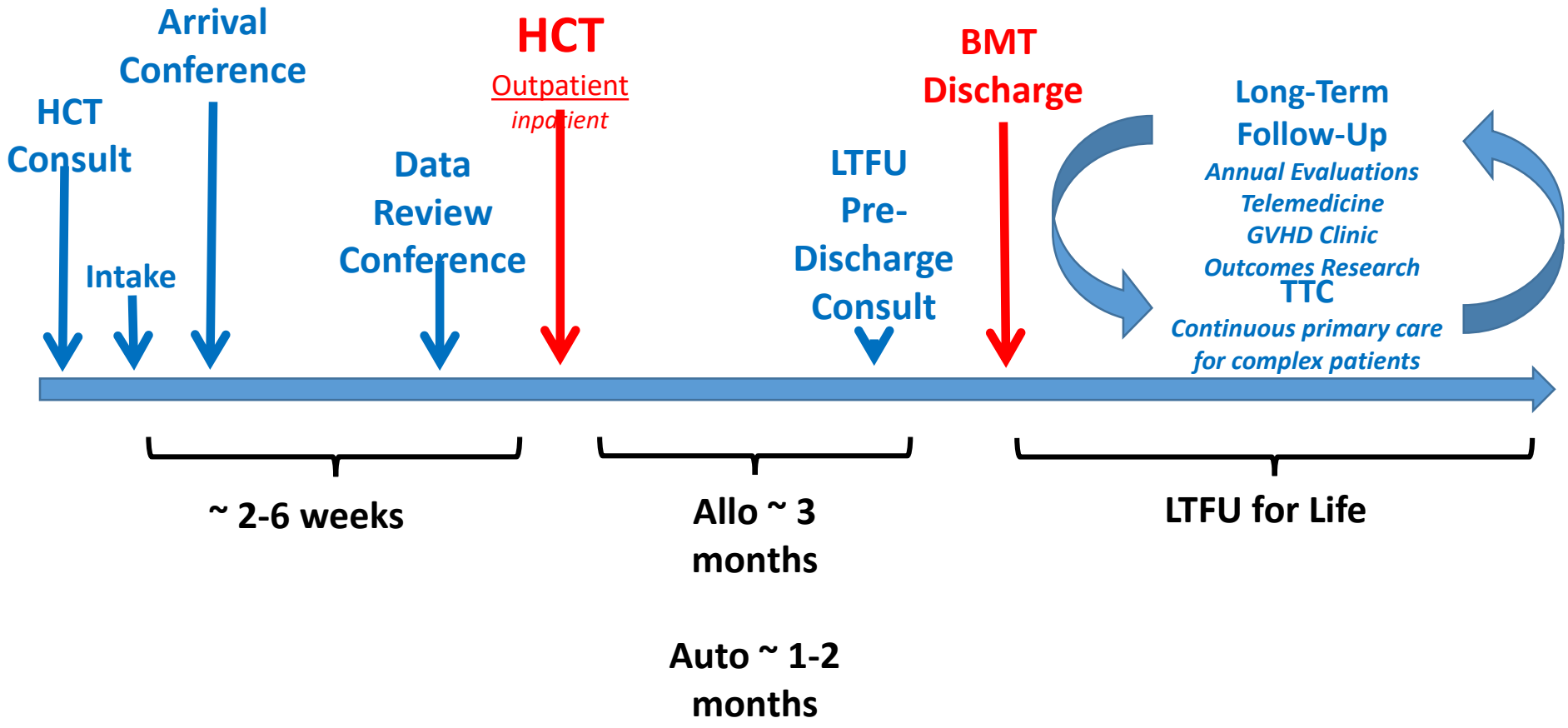
Hashmi, SK. et al *Biol Blood Marrow Transplant* 2018

Survey on Long-Term Follow-Up Clinics for HCT Survivors
Conclusions

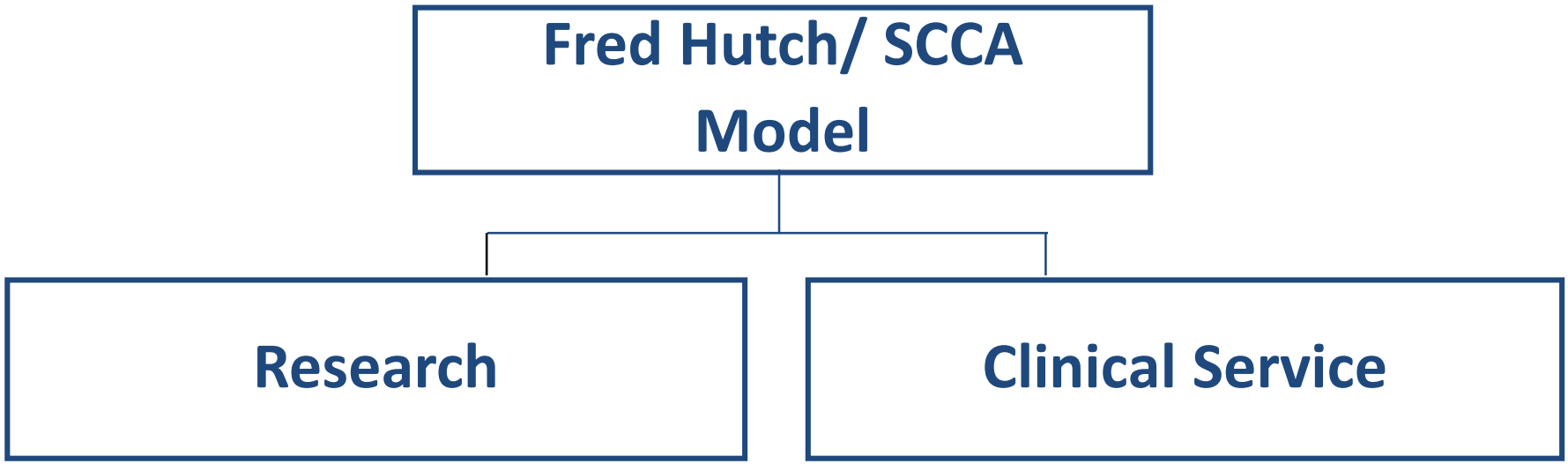
- Results of this survey hopefully will help policymakers, HCT providers, and institutions in establishing HCT survivorship care models.
- Many studies have documented substantial morbidity and mortality from late effects after HCT, thus, delivering recommended screening and expert management of any detected late effects is paramount in HCT survivors.
- The American Society of Blood and Marrow Transplantation (ASBMT) Clinical Practice Committee recommends that delivering guidelines-driven screening and expert management of late effects is the goal of first-rate HCT survivorship care.

Hashmi, SK. et al *Biol Blood Marrow Transplant* 2018

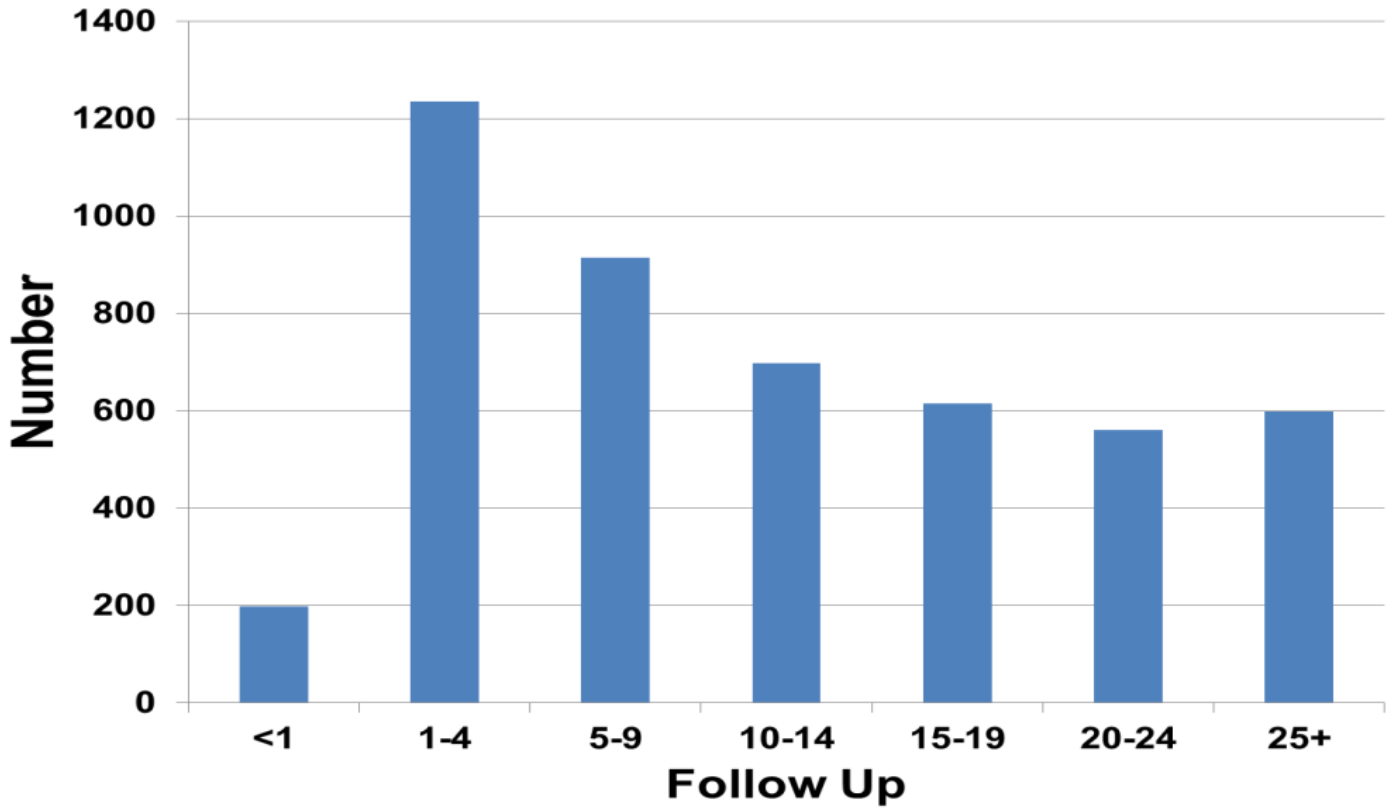
Fred Hutch/ SCCA
Transplant Timeline - Clinical Care



HCT Long-Term Follow Up (LTFU) Survivorship Clinical Care and Research Model



Fred Hutch/SCCA LTFU Population in 2014
N = 4,819



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LTFU Patients currently being followed*

Diagnoses	Time interval from treatment (years)							
	< 1	1-4	5-9	10-14	15-19	20-24	25+	Total
Acute Leukemias	40	331	274	223	127	118	2889	1402
Aplastic Anemia	9	39	24	22	12	23	175	304
MDS	26	124	101	87	69	41	31	479
CML	3	19	22	60	181	181	278	744
Lymphoma	44	275	274	188	93	79	67	1020
Multiple Myeloma	55	299	214	77	33	6	3	687
CLL	0	7	16	12	10	2	1	48
Solid Tumors	4	27	23	16	35	49	7	161
Other**	8	81	81	30	29	7	24	260
Multiple diagnoses	0	24	40	10	6	5	0	85
Total	**189**	**1226**	**1069**	**725**	**595**	**511**	**875**	**5190**

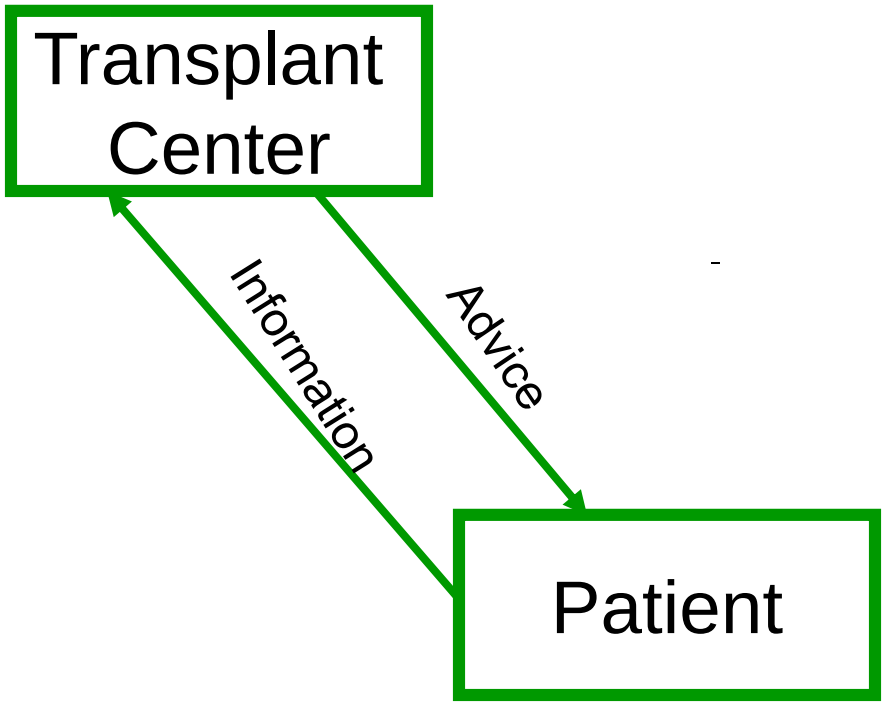
* As of 4/11/18, sent a PRQ since 2014

** Neoplasms, disorders of hematopoietic or immunologic and metabolic inborn errors

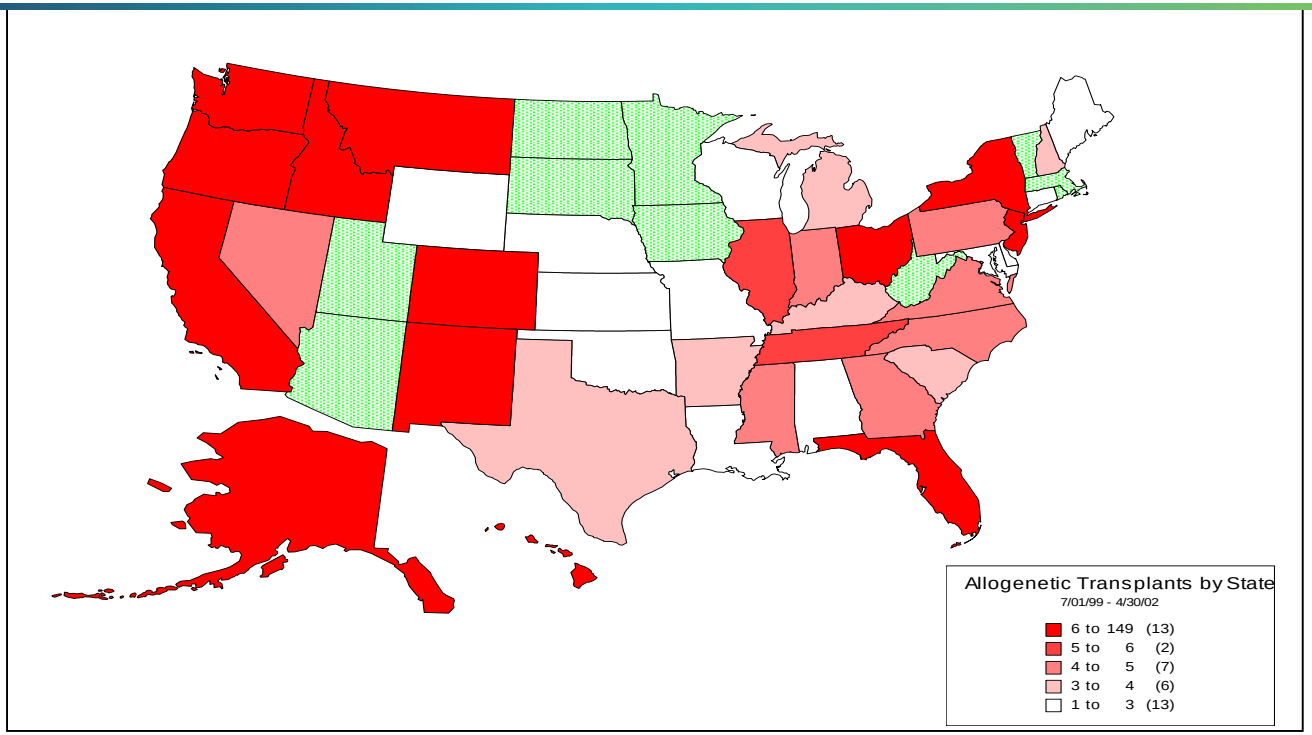
Fred Hutch/SCCA HCT Survivorship Care Model

- Utilizes primary care providers and/or non-transplant hemo/oncologist in the care of HCT survivors but require coordination and collaboration.

Traditional Management Model



Geographic Dispersion of Patients Transplanted at Fred Hutch/SCCA



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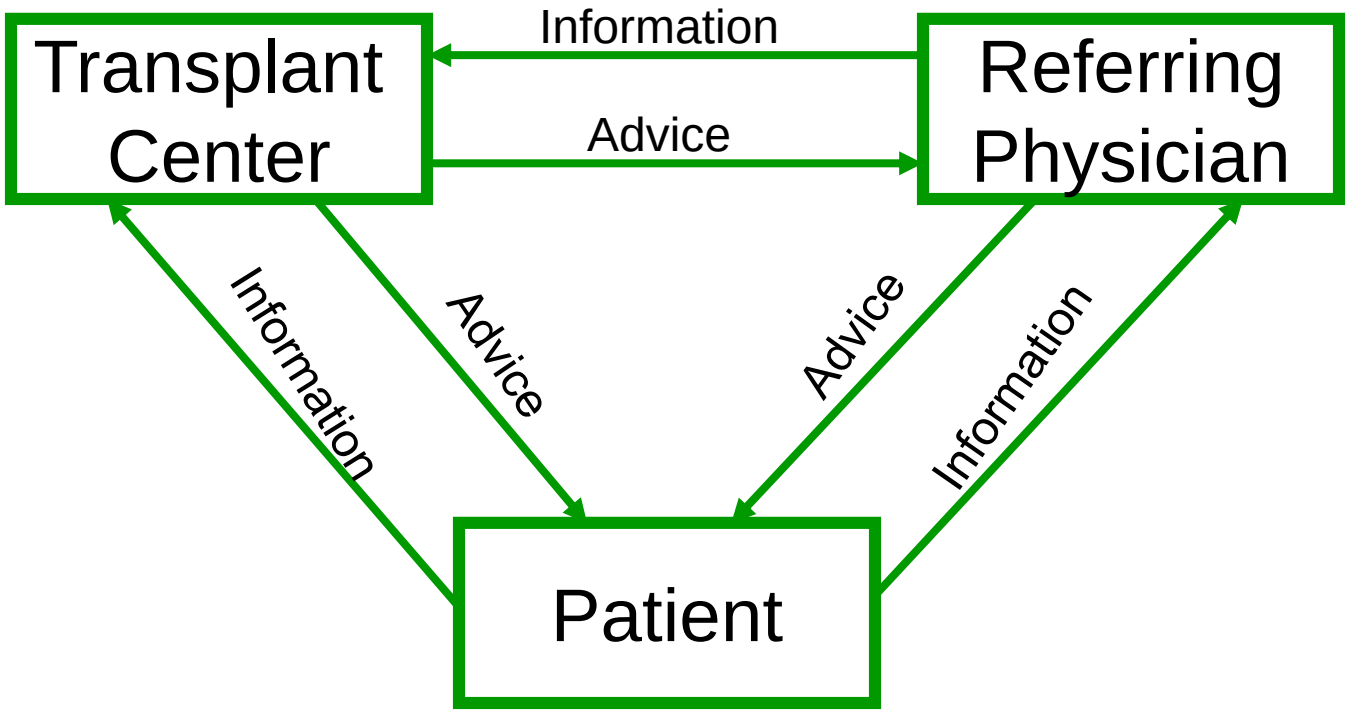
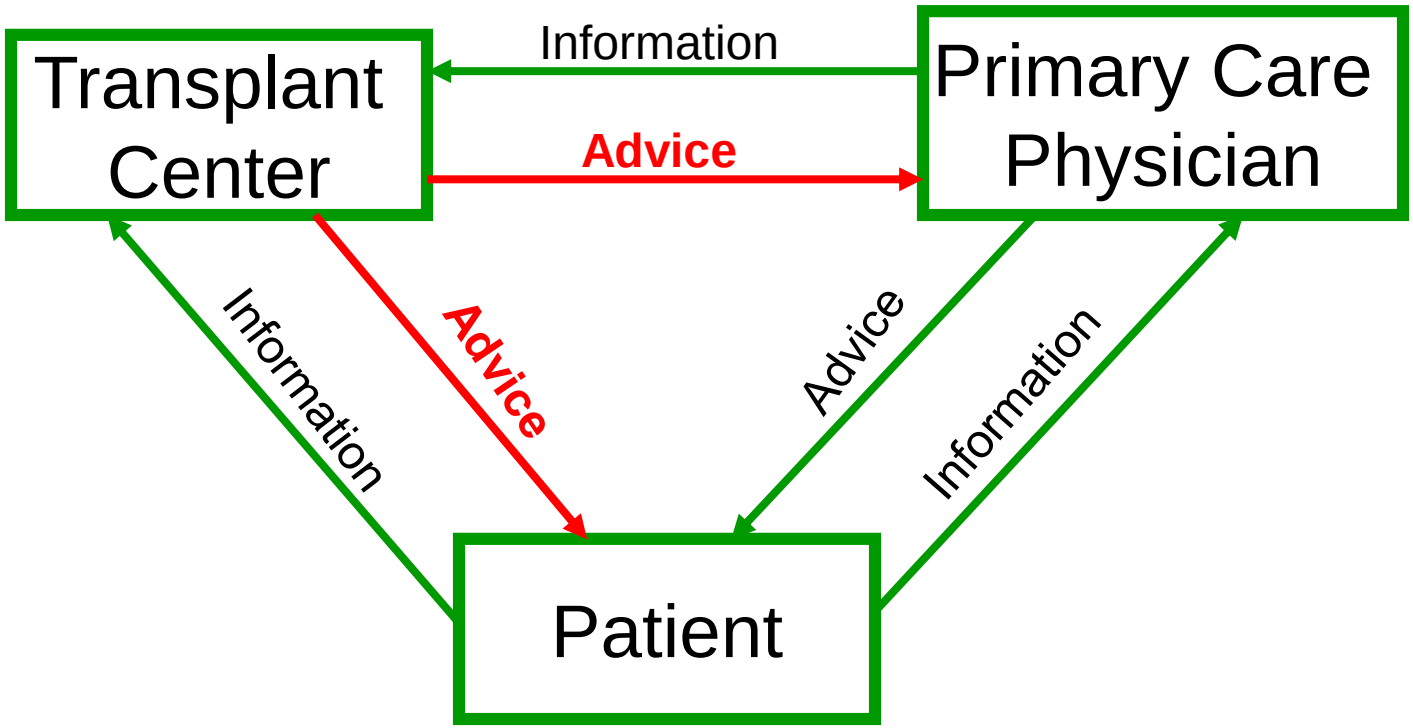
Collaborative Management Model



Collaborative Care Model



Fred Hutch / SCCA HCT Survivorship Care Delivery *"Collaborative Care Model"*

- **Consultation Service**
  - Pre-discharge Home LTFU Consultation Clinic (*between days 80-100 posttransplant)*
  - Telemedicine consultation to patients and primary care providers
  - Chronic GVHD Clinic
  - Comprehensive annual evaluation
- **Primary care (Transitional Transplant Clinic)**
  - Transitional continuity of care to HCT survivors with severe or lingering complications that requires complex management by experts
  - Alleviate the high burden of care by primary care providers

FHCRC/SCCA HCT Survivors Care Delivery Model

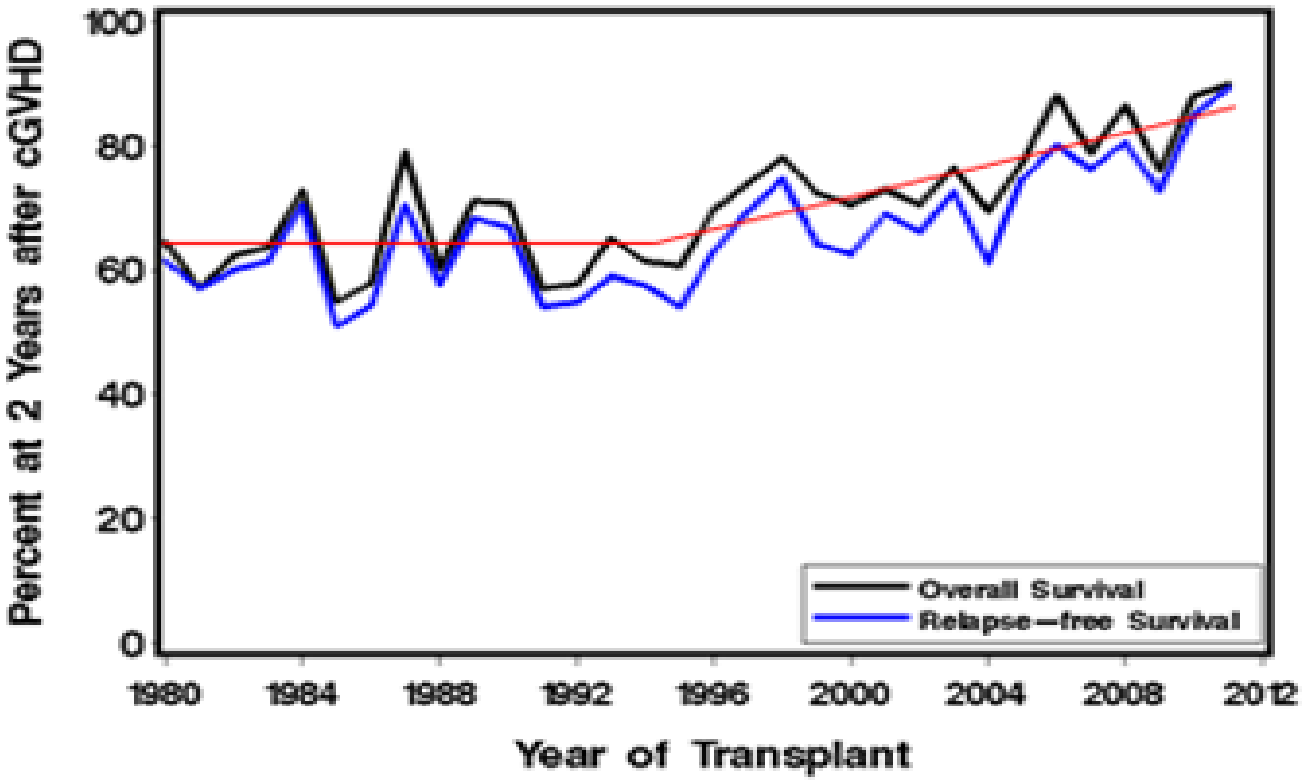
- Multidisciplinary long-term hematopoietic stem cell transplant care model
- Consultation
- Primary care for complex health needs (transitional transplant clinic)
- Collaborative management with non-transplant primary care providers

Reasons for HCT Survivorship Care Delivery Model
Collaborative Management Model

- Geographical dispersion of HCT survivors
- Necessary for long-term follow up continuity of care
- Important for research

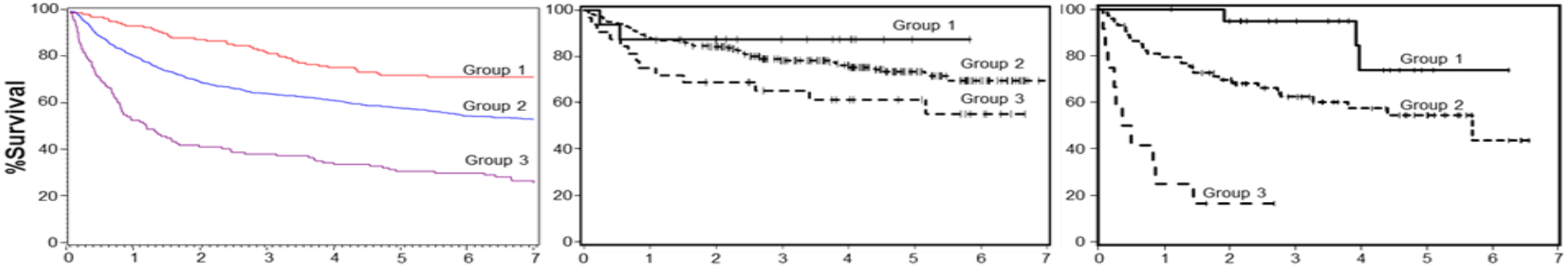
Does a dedicated HCT-LTFU Model matter?

Survival after chronic GVHD over time



What may account for difference in survival in patients with high risk CIBMTR chronic GVHD score?

CIBMTR (n=1128)* Seattle (n=268)† Toronto (n=108)†



* Arora M, Flowers, Pavletic S. et al BBMT 2015 (Supp. Figure)
†Inamoto, Kim, Flowers et al. BLOOD 2014

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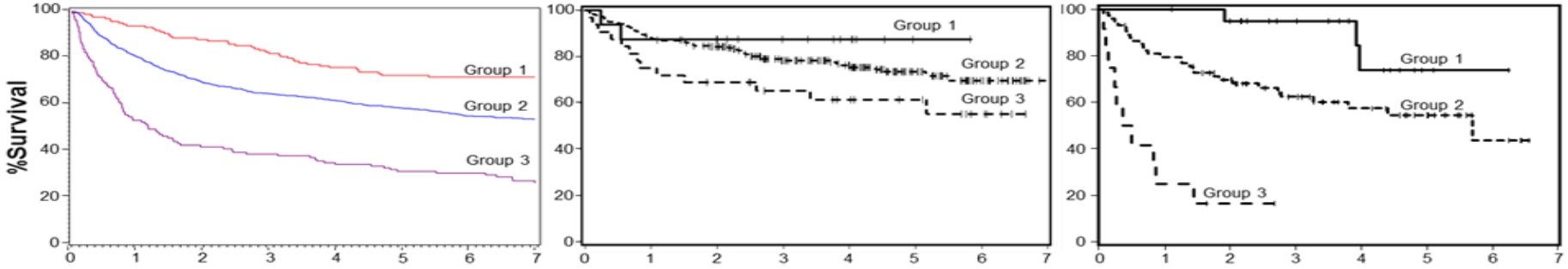
CIBMTR (n=1128)* Seattle (n=268)† Toronto (n=108)†



Could a dedicate LTFU service account for better survival?

* Arora M, Flowers, Pavletic S. et al BBMT 2015 (Supp. Figure)
†Inamoto, Kim, Flowers et al. BLOOD 2014

Conclusions

- Increased interest in HCT survivorship care in the past 5 years
- Future studies are needed to evaluate HCT survivorship care delivery models
- Severity of chronic GVHD needs to be considered when evaluating HCT survivorship care models
- Collaboration between the transplant center and patient PCP are important for care of HCT survivors

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