Non-HLA Barriers to Blood/Marrow Transplant

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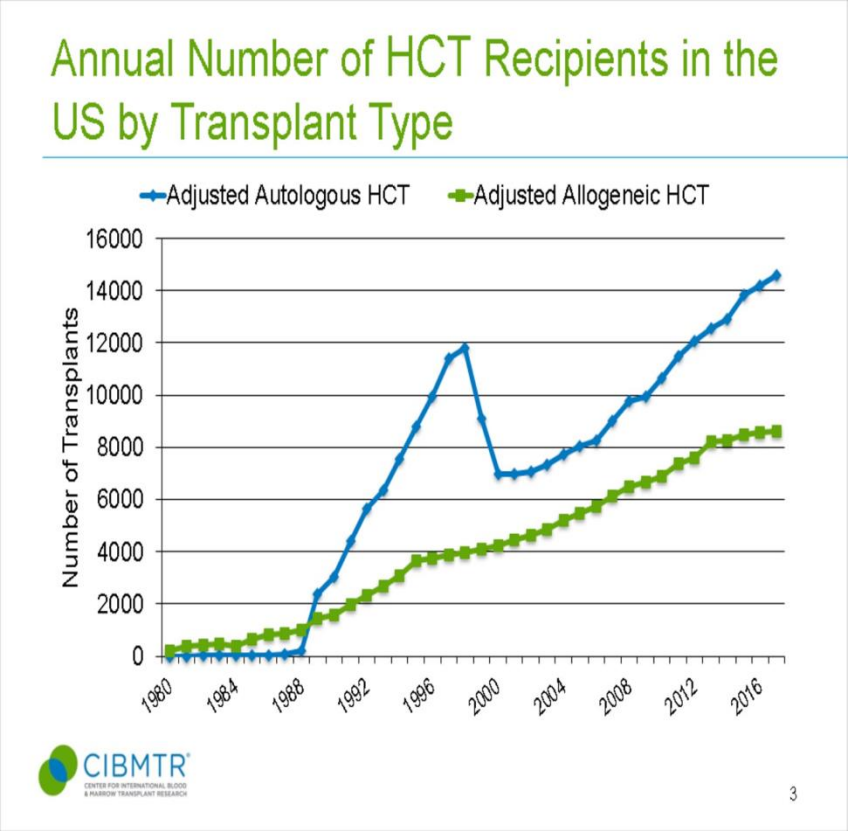
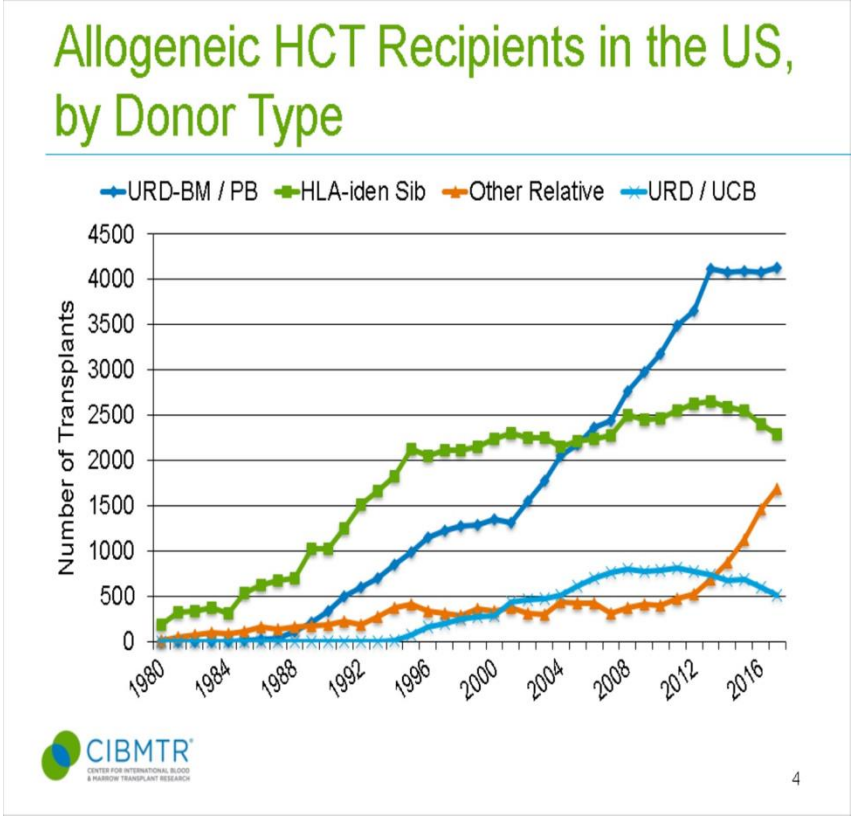
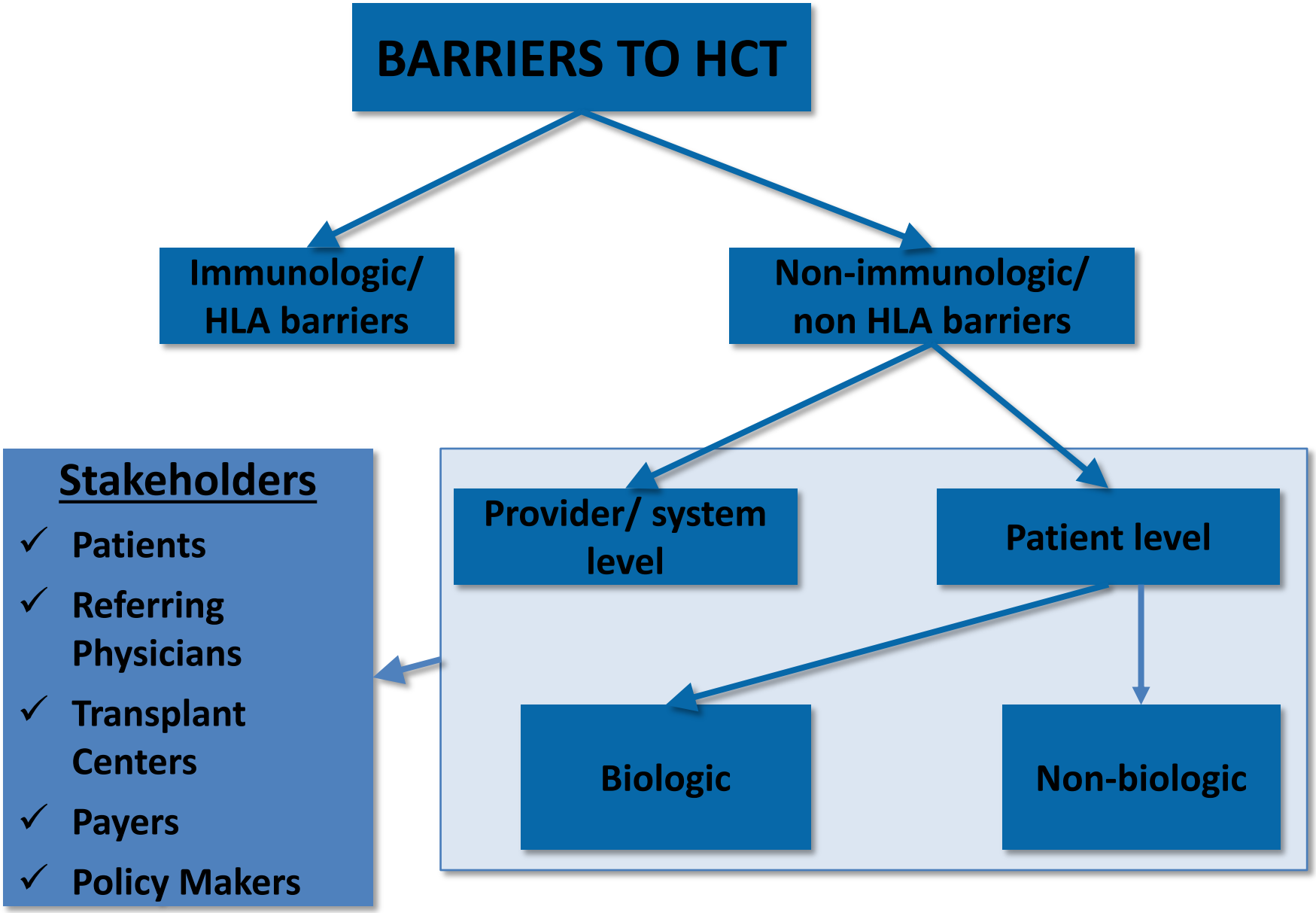
4/12/19

Trends in hematopoietic cell transplantation (HCT)





D'Souza et al. CIBMTR Summary Slides, 2018


BARRIERS TO HCT
Immunologic/ HLA barriers
Non-immunologic/ non HLA barriers
Stakeholders
✓ Patients
✓ Referring Physicians
✓ Transplant Centers
✓ Payers
✓ Policy Makers
Provider/ system level
Patient level
Biologic
Non-biologic

Case I

- 71 year old Caucasian female from Bullhead City with Aplastic Anemia
- Treated with cyclosporine and Antithymocyte globulin with no response
- Heavily transfusion dependent
- Very frail with a poor performance status
- Has a 10/10 URD available from the registry
- Social history: retired, husband recently lost job (NO STEADY INCOME), 50 pack year smoking history

Case II

- 72 y Caucasian male with MDS/ AML from Kingman, AZ
- Treated with induction chemotherapy followed by hypomethylating agent-able to go into remission
- No major comorbidities except HTN and Diabetes
- Social history: Veteran with h/o exposure to Agent Orange, 30 pack-years smoking history, lives by himself with no good caregiver options
- Progressive cognitive deficit discovered as we followed him

Case III

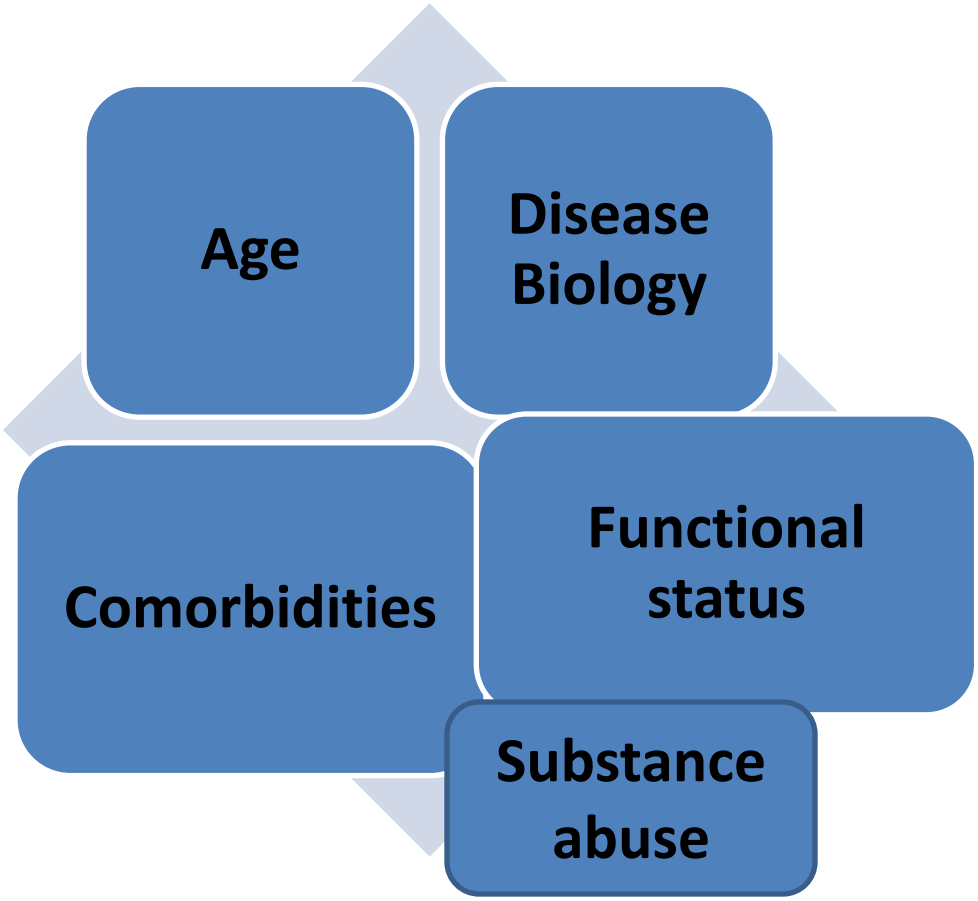
- 68 year old Native American male with high risk myelofibrosis from Navajo Reservation, Kayenta, AZ
- Increasing spleen size and WBC count
- Patient not keen on transplant because of cultural reasons
- Social history: Retired, married, reasonable caregiver support, limited income
- Did end up going to transplant after multiple meetings with the family

Case IV

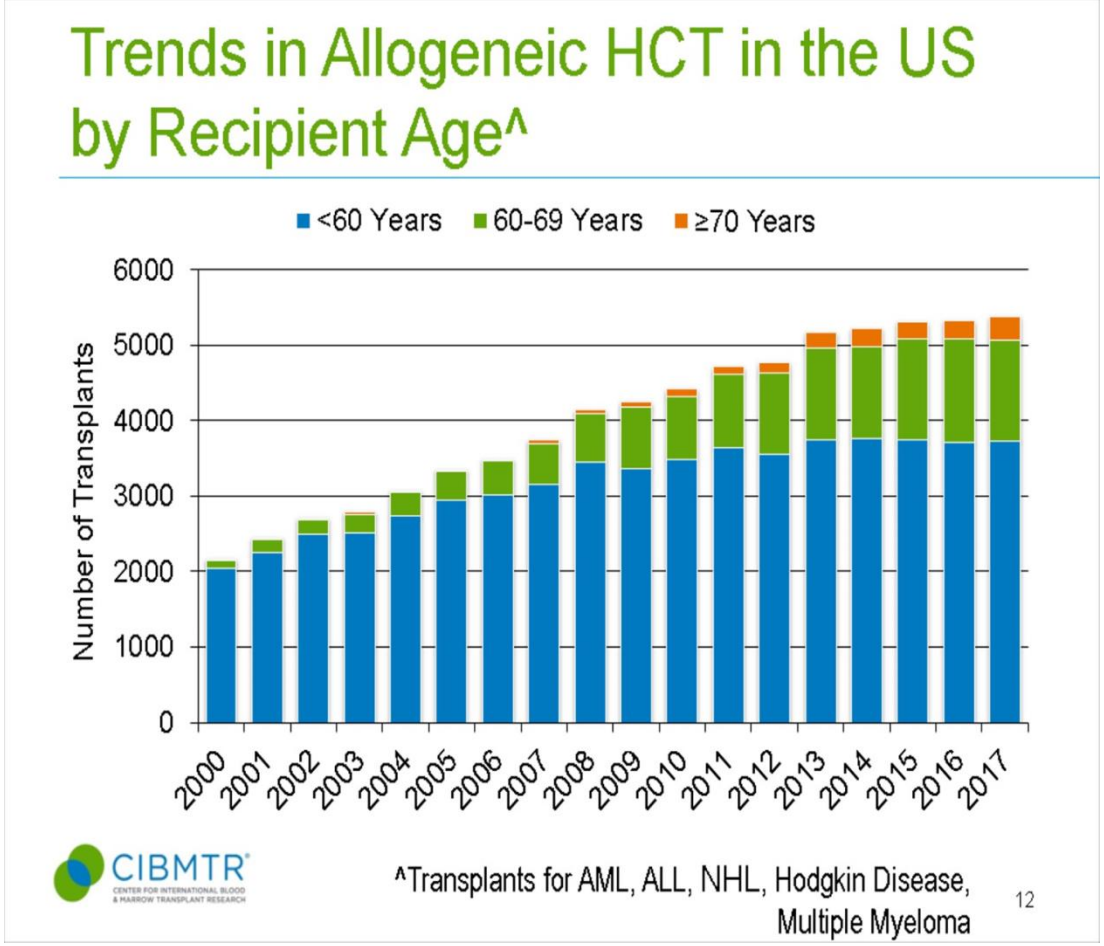
- 22-year-old Hispanic male from Yuma, AZ with a history of metastatic germ cell tumor (CNS involvement) referred for tandem autologous HCT
- Being followed at three different institutions for his care
- Delays in referral and optimal care due to which disease progressed and patient went to hospice

Patient Level Barriers To Transplant

Biologic Barriers



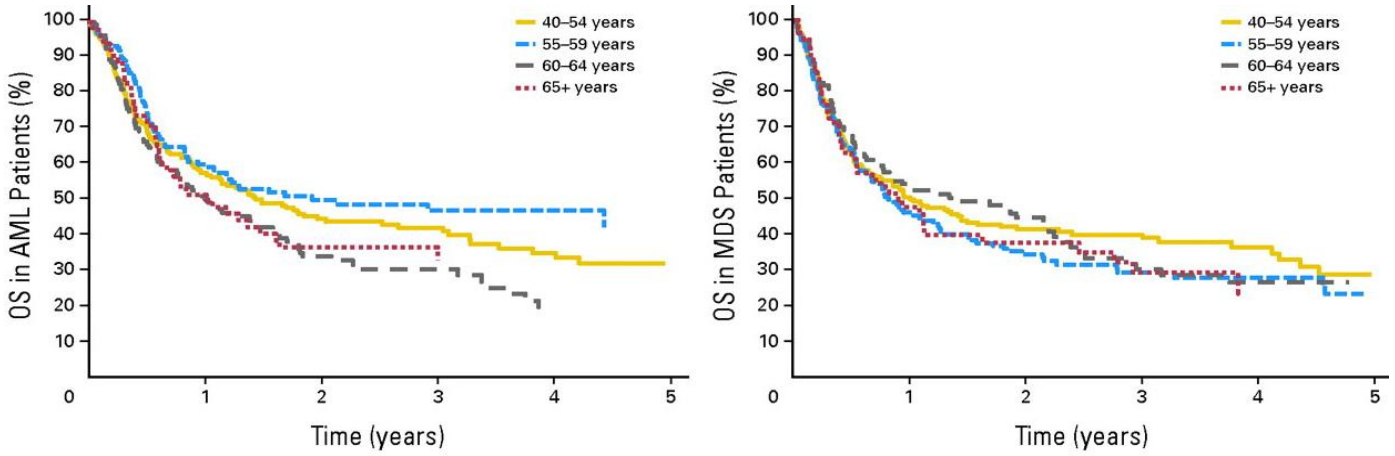
Age Barriers



- Not all older patients may be candidates for allogeneic HCT
  - Comorbidities
  - Poor functional status
  - Aggressive disease
  - Lack of adequate social support

Age Barriers: influence on outcomes

- Leukemia-free survival is higher and relapse risk is lower after allogeneic HCT vs. no HCT in older patients
- Allogeneic HCT outcomes in selected older patients are comparable to younger adults



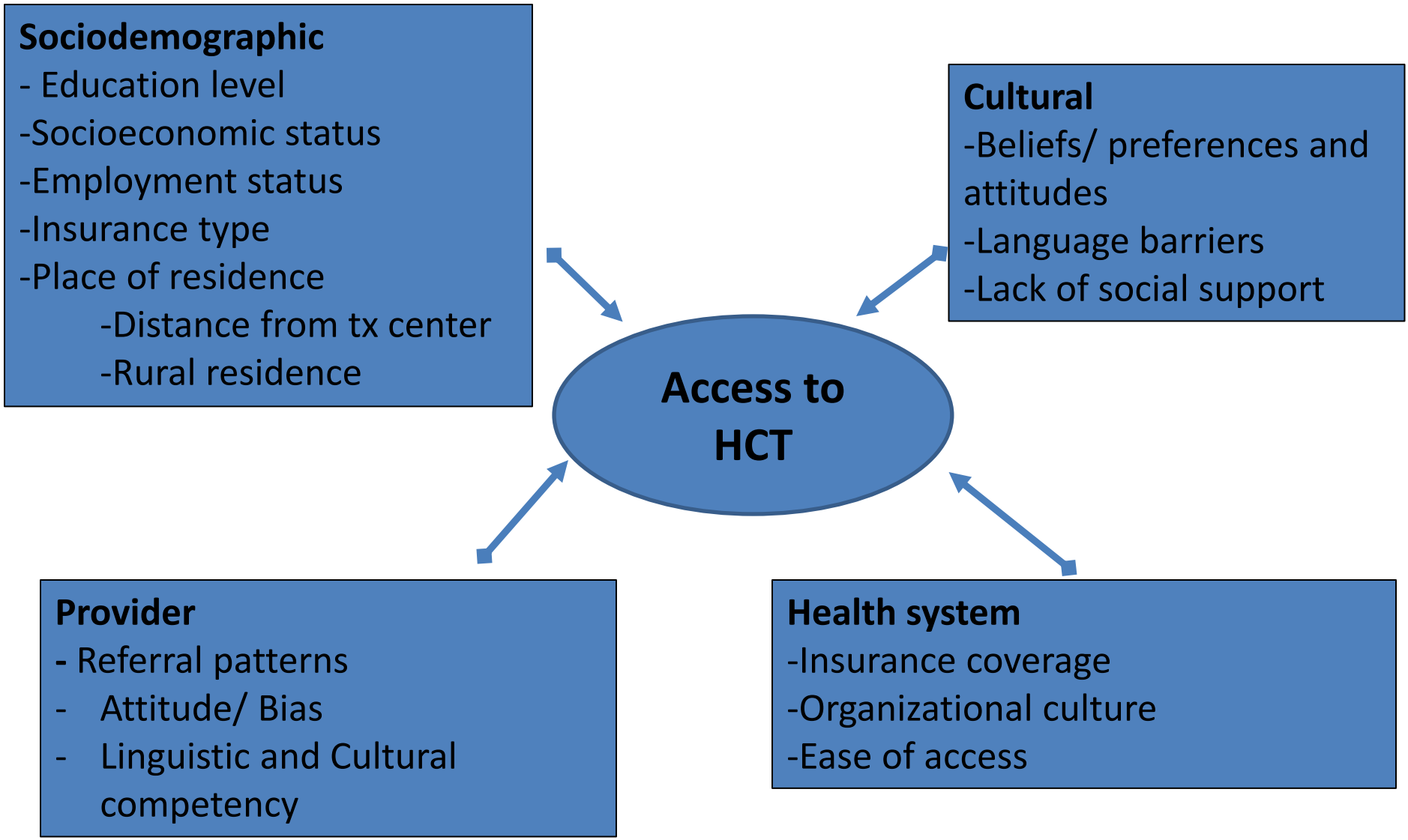
Farag SS et al. BBMT. 2011
McClune B et al. JCO. 2010

Selection of patients for transplant

Good-risk candidates
Young age
No comorbid conditions
No active infections
Disease in remission or responsive to therapy
Good socioeconomic support system
HLA-matched donor
Low risk of posttransplantation relapse
High-risk candidates
Older age
Comorbid conditions present
Refractory/relapsed disease (diagnosis-dependent)
Aggressive prior therapy
High-risk/complex karyotype

Deeg and Sandmaier. Blood 2010

Non- biologic barriers for access to HCT



Sociodemographic Barriers

Reference	Factors	Data source	N/ disease	Results
Mitchell et al (1997)	Age, sex, race, insurance	Inpatient hospital discharge data (1988-1991)	38,240 / leukemia and lymphoma	– ↓ rate in Blacks, older patients – ↑ rate in private insurance
Cho et al (2009)	Age, sex, race, education, insurance	Inpatient hospital discharge data for AZ (1997-2003)	6,435 / leukemia and lymphoma	– ↑ rate in private insurance
Joshua et al (2010)	Race	SEER and CIBMTR (1997-2002)	273,853 / leukemia, lymphoma and myeloma	– ↓ rate of auto and allo HCT in Blacks
Ailawadhi et al (2017)	Age, race/ ethnicity	SEER-Medicare (2007-2012)	5338 / myeloma	– ↑HCT utilization over time for all except Blacks
Jabo et al (2017)	Age, sex, race/ ethnicity, SES, marital status, distance from transplant center	California Cancer Registry (2003-2012)	13,250 / leukemia	– ↓ rate in older age, lower SES, unmarried, Hispanics and Blacks

Race Barriers: Auto HCT In Multiple Myeloma

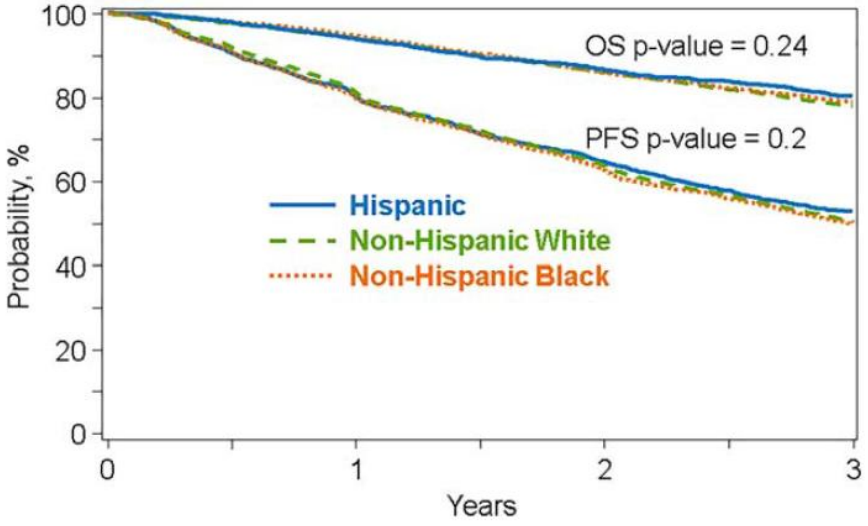
- Estimated autologous stem cell transplant utilization rates for myeloma using CIBMTR data 2008-2014 (N=28,450) and incidence rates from SEER

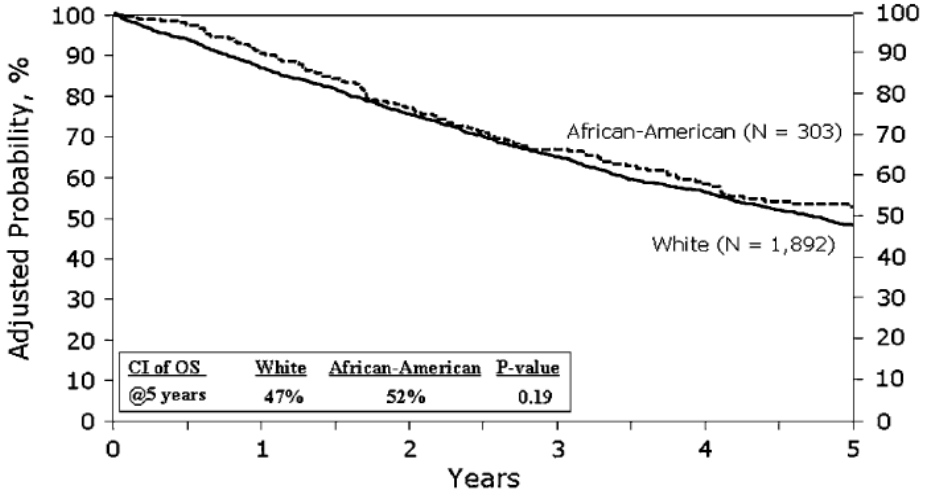
Year	All patients	Non-Hispanic Whites	Hispanics	Blacks
2008	19.1%	22.6%	12.2%	8.6%
2014	30.8%	37.8%	20.5%	16.9%

Schriber JS et al. Cancer, 2017

Race Barriers: influence on outcomes

- If racial/ethnic minorities can get to autologous HCT → outcomes similar to Whites





Schriber JS et al. Cancer, 2017
Hari P et al. Biol Blood Marrow Transplant, 2010

Race Barriers: HCT in AML

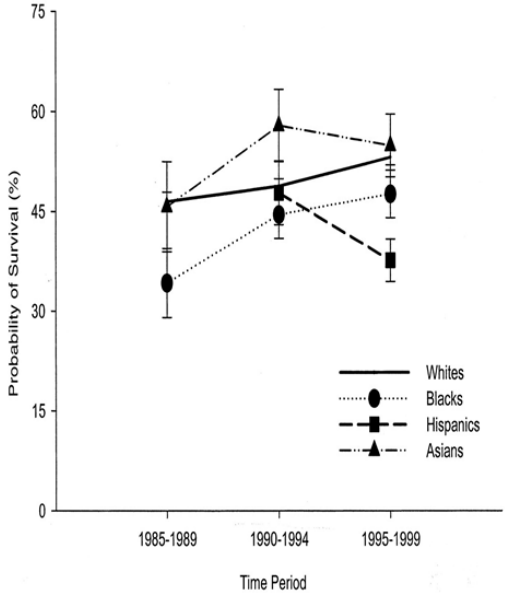
	Autologous	HLA matched sibling	Other related	Non-related
White-1st remission	87%	86%	78%	88%
Non-white-1st remission	13%	14%	22%	12%
White-2nd remission	80%	87.5%	82.5%	88.5%
Non-white-2nd remission	20%	12.5%	17.5%	11.5%
White-not in remission	*	88%	83%	90%
Non-white-not in remission	*	12%	17%	10%

Too few patients to calculate reliably.

Pulte et al. Haematologica 2013

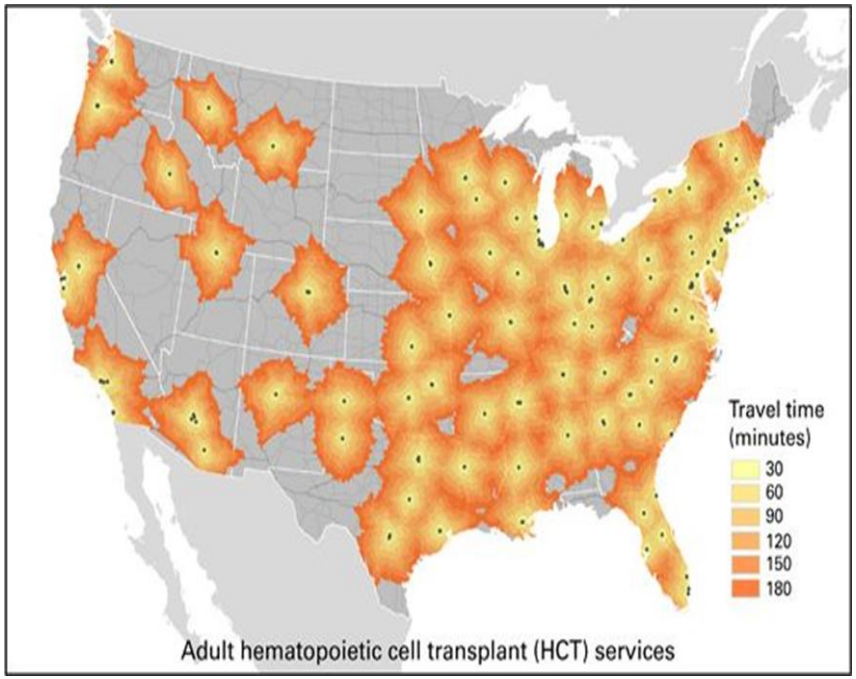
Race Barriers: influence on outcomes

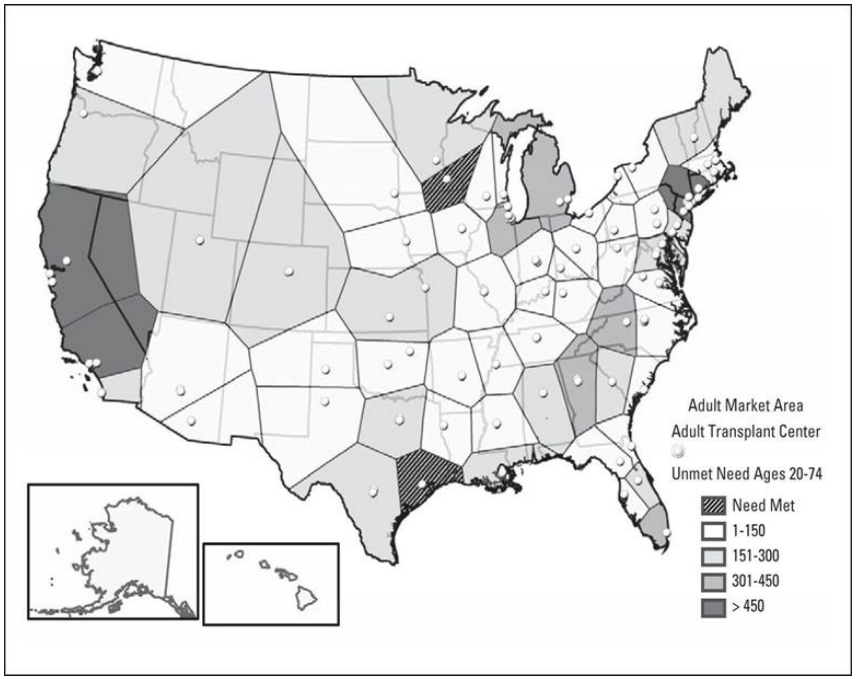
- Registry studies
  - Blacks had worse survival after unrelated donor transplantation, even after adjustment for transplant and socioeconomic factors
  - Hispanics had a higher risk of treatment failure and mortality after HCT
- Institutional studies
  - Increased mortality risk in Blacks after an allogeneic HCT
  - Comparable OS and PFS in Non-Hispanic Whites and racial ethnic minority patients



Baker et al. BBMT 2009
Baker et al. JCO 2005
Serna et al. JCO 2006
Mielcarek et al. BBMT 2005
Khera et al. Leuk Lymph 2014

Geographic Barriers

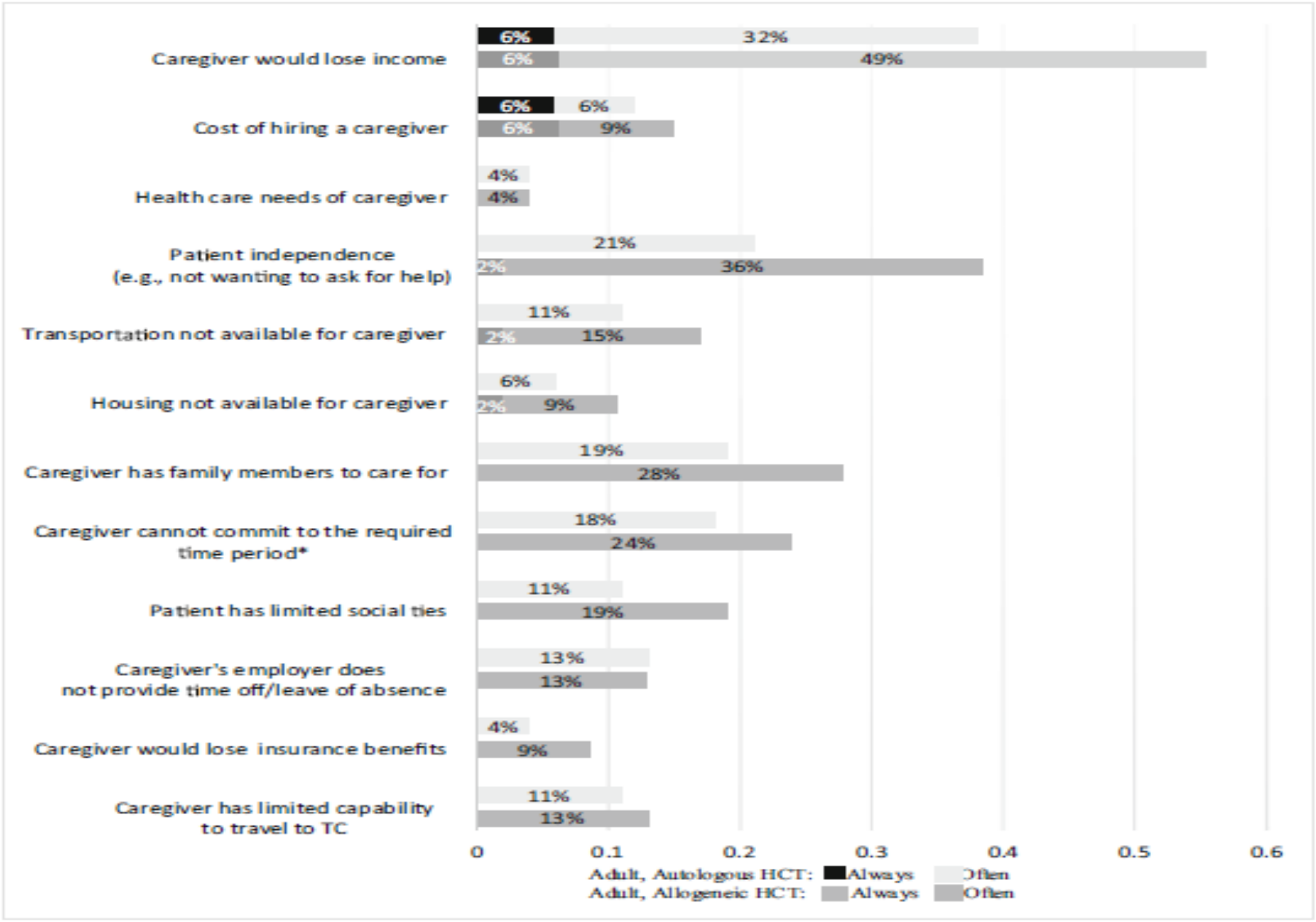




- In 2012
  -6% of the US population (> 12 million adults) resided more than 180 min from the nearest age-appropriate HCT facility
  -The national unmet need for HCT was 10,276 for adults

Delameter and Uberti. BMT 2015
Besse et al. JOP 2015

Caregiver/ social support barriers



Preussler et al. Support care cancer. 2019

Provider/ system level Barriers to transplant

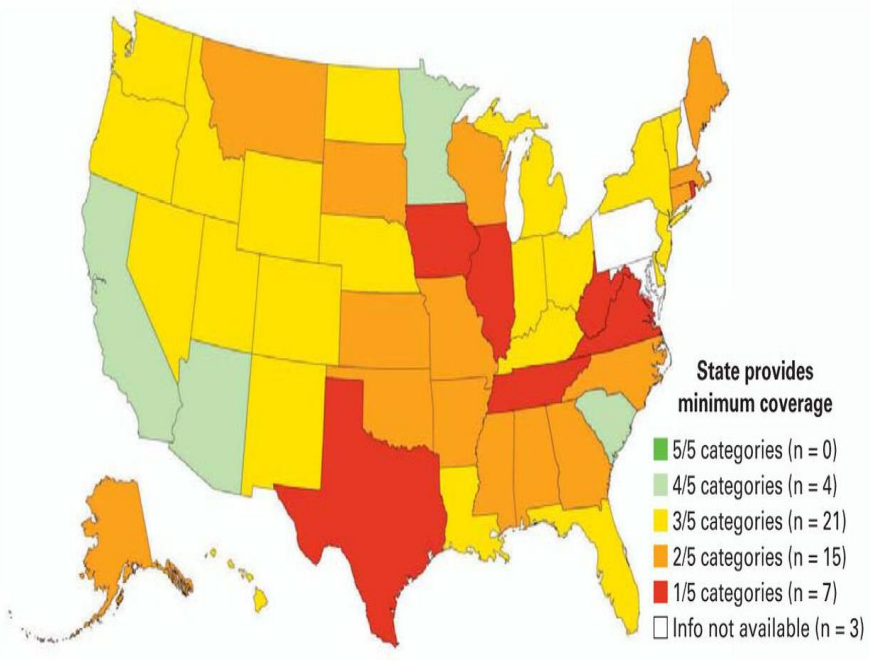
Coverage Barriers To HCT

- Essential phases that need health insurance coverage
  - Covered indication and specific transplant procedure
  - Donor search
  - Hematopoietic progenitor cell collection
  - Inpatient care and outpatient care
  - Medications
  - Unexpected costs (e.g., complications)
  - Clinical trials
  - Out-of-pocket costs (transport, lodging etc.)
- Lack of or inadequate coverage for any above can jeopardize access to and outcomes of HCT

Majhail NS. BBMT. 2015

Coverage Barriers: Example Of Medicaid

- Variation in coverage for transplant by state Medicaid programs
- Evaluated coverage for:
  - Indications
  - Donor search
  - Medications
  - Clinical trials
  - Out-of-pocket costs



Preussler JM et al. J Oncol Pract. 2014

Referring Physician Barriers

- In a Survey of hem/onc physicians, the three main reasons for non referral
  - Age 60 years (vs. 30 years): 8.29 (P<0.001)
  - Black (vs. White): 2.35 (P<0.001)
  - No HCT coverage (vs. coverage present): 6.95 (P<0.001)
- Majority reported negative perception of HCT outcomes
  - 51% agreed: "…risk or morbidity/mortality after HCT is very high"
  - 57% agreed: "…outcomes of unrelated donor HCT are much worse than sibling donor HCT"
  - 32% agreed: "…because of high risks of allo HCT, I refer only after failure of conventional chemotherapy"

Pidala J et al. Bone Marrow Transplant. 2014

Center Barriers For HCT

- Personnel and infrastructure
- Competing priorities
- Recruitment and retention of personnel

Table 3. Estimated Supply and Demand of BMT Physicians

	Adult BMT Physicians, n	Pediatric BMT Physicians, n	All BMT Physicians, n
BMT physician requirements in 2020	1991	235	2226
Current supply	959	156	1115
Projected retirements	232	15	247
New BMT physicians needed	1264	94	1358

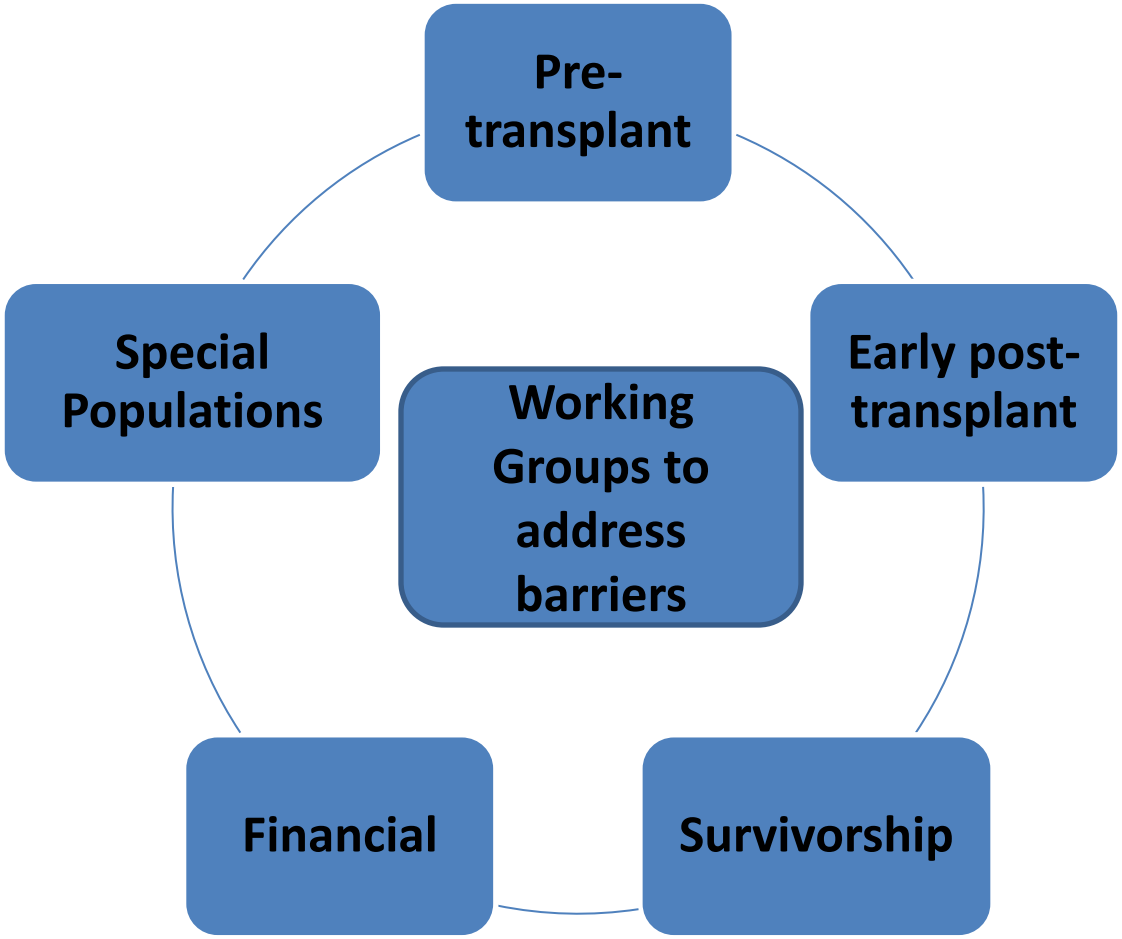
Data derived, with permission (R. Krawisz, personal communication, June 2009), from the ASBMT membership records.

Gajewski J et al. BBMT. 2009

Going back to patient cases…

	Patient I	Patient II	Patient III	Patient IV
Biologic	-Age -comorbidities -smoking H. -Frailty	-Age -smoking H. -progressive cognitive decline	-Age -Aggressive disease	-Aggressive disease
Socio-demographic	-Low income -Distance from tx center (231 mi)	-Distance from tx center(194 mi)	-Race -Limited income -Distance from tx center (294 mi)	-Ethnicity -Distance from tx center (185 mi)
Cultural	-	-Lack of social support	-Cultural beliefs	
Provider/ system level	-			-Delayed referral/ insurance issues

The National Marrow Donor Program's Symposium on Patient Advocacy in Cellular Transplantation Therapy: Addressing Barriers to Hematopoietic Cell Transplantation



Murphy E et al. BBMT 2010

Addressing Patient Barriers

- Team approach to patient care
  - Patient and caregiver education
  - Aggressive evaluation and management of comorbidities
  - Psychosocial assessment and support
  - Financial assessment and support
    - housing/ transportation
    - donor search
    - medication coverage
    - out-of-pocket costs

Addressing Patient Barriers

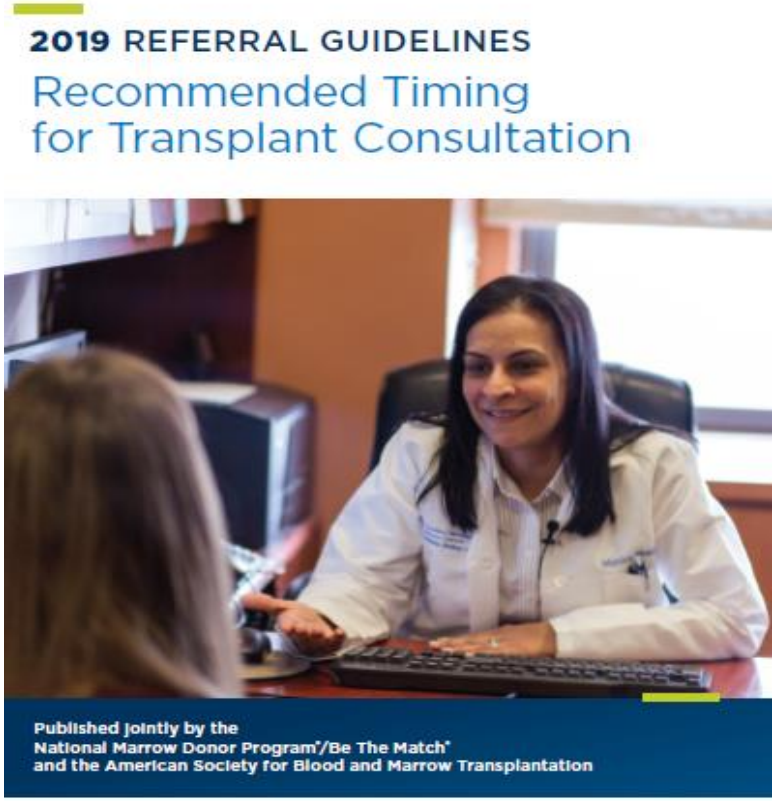
- Patient advocacy
- Local/national grants and resources for assistance
- Payer outreach and education
- Telemedicine programs

Addressing Referral Barriers

- Referring physician education
  - Local level
  - National level
- Building relationships with referring physicians
  - Accessibility to transplant center
  - Good patient outcomes
- Care coordination through payers

Referring Physician Education/Outreach

- Share information and educate about on HCT indications/outcomes
- www.asbmt.org and bethematchclinical.org



Transplant Centers: Building Capacity

- Anticipate personnel and infrastructure challenges will limit ability to serve patients who need HCT

The National Marrow Donor Program's Symposium on Hematopoietic Cell Transplantation in 2020: A Health Care Resource and Infrastructure Assessment

Navneet S. Majhail,[1,2] Elizabeth A. Murphy,[1] Ellen M. Denzen,[1] Stacy S. Ferguson,[1] Claudio Anasetti,[3] Arthur Bracey,[4] Linda Burns,[5] Richard Champlin,[6] Norman Hubbard,[7] Miriam Markowitz,[8] Richard T. Maziarz,[9] Erin Medoff,[10] Joyce Neumann,[6] Kim Schmit-Pokorny,[11] Daniel J. Weisdorf,[12] Deborah S. Yolin Raley,[13] Jeffrey Chell,[1] Edward L. Snyder[10]

Hematopoietic Cell Transplantation in 2020: Summary of Year 2 Recommendations of the National Marrow Donor Program's System Capacity Initiative

Ellen M. Denzen[1,*], Navneet S. Majhail[1,2], Stacy Stickney Ferguson[1], Claudio Anasetti[3], Arthur Bracey[4], Linda Burns[5], Richard Champlin[6], Jeffrey Chell[1], Helen Leather[7], Michael Lill[8], Richard T. Maziarz[9], Erin Medoff[10], Joyce Neumann[6], Kim Schmit-Pokorny[11], Edward L. Snyder[12], Laura Wiggins[13], Deborah S. Yolin Raley[14], Elizabeth A. Murphy[1]

Majhail NS et al. BBMT 2012
Denzen EM et al. BBMT 2013

System Capacity Initiative

- Three year multi-stakeholder deliberative process that identified and recommended solutions to address capacity challenges to HCT
- Seven working groups that worked from 2010-2012:
  - Physician Workforce
  - Advanced Practice Provider Workforce
  - Nursing Workforce
  - Social Work Workforce
  - Care Delivery Models
  - Facilities and Bed Capacity
  - Financial

Ensure Adequate Coverage For HCT

- Coverage for HCT can be restrictive and regressive
  - Ensure adequate coverage for various phases of transplantation
- Coverage for patient out-of-pocket costs
- Common standards and policies for coverage
  - Less variation among plans and states

Care Coordination

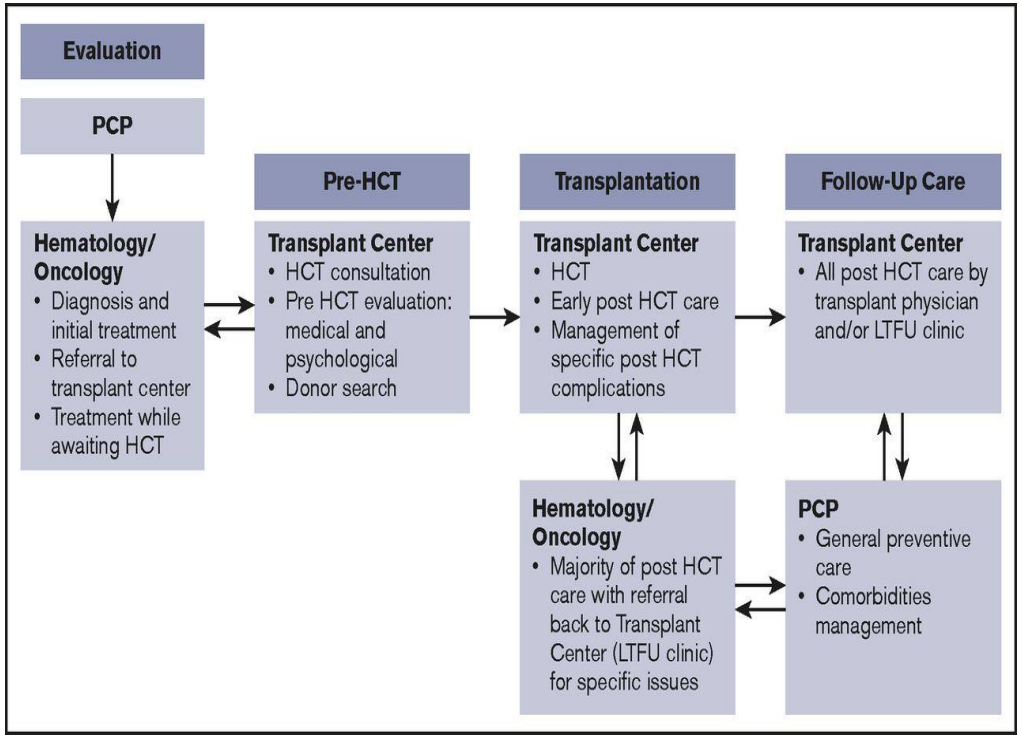
- Critical aspect of coordinating patient journey from diagnosis to transplant to survivorship
  - Collaborative effort by several stakeholders
  - Payer frequently common thread across the spectrum and sites of care - opportunity to enhance care and facilitate right care

REVIEW ARTICLE

blood advances

Patient-centered care coordination in hematopoietic cell transplantation

Nandita Khera,[1] Patricia Martin,[2] Kristen Edsall,[3] Anthony Bonagura,[4] Linda J. Burns,[5] Mark Juckett,[6] Olivia King,[5] C. Frederick LeMaistre,[7] and Navneet S. Majhail[8]



Khera N et al. Blood Advances, 2017

Barriers To BMT = Barriers To Cell Therapies

- Expect similar/ worse access barriers due to new therapy, complexity, limited availability and costs
  - Hospital will likely bear financial risk for purchase of product
  - Acquisition costs
  - Travel & Lodging
  - Medications and Complications
- If "**bridge to HCT**" in relatively short period of time:

  - contracts and pricing may face strain, with potential to be shifted to the patients as cost-sharing which maybe prohibitive

What is $475,000 (one dose of tisagenlecleucel)?

- Cost of annual insurance for 17 families of four with commercial insurance
- 6 RN salaries in US
- Cost to treat 12 people with Hepatitis C
- Annual insulin cost for 75 Type I diabetes patients
- >500,000 doses of pentavalent vaccine (DPT, HBV and H.influenza)

Ethical dilemmas…

- Should the patient selection criteria be very restrictive to aim for highest rate of success of HCT/ cellular therapies?
- How do we ensure that the benefits of rapid scientific advances in the field are enjoyed by all?
- How do we reconcile between medical recommendations and psychosocial and economic challenges?
- How is the growth in current health care expenditure sustainable?

Summary

- Continued challenges to make HCT available to every patient who needs it
  - Some may be modifiable
- Need for extensive efforts by all relevant stakeholders
  - to help overcome these barriers
  - to improve access to and coordination of care for HCT and other cellular therapies at a national and global level

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