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The past, present and future of hematopoietic stem cell transplants

OptumHealth Education Conference 2019, Minneapolis

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Disclosures

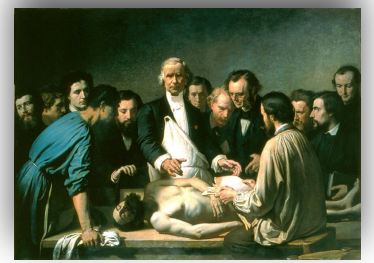
Name	Institution	Disclosure
Krishna Komanduri, MD	Sylvester Cancer Center, University of Miami	Ad hoc advisor to Kite/Gilead, Novartis, Juno/Celgene, Incyte, Atara, Helocyte, Kiadis

Goals

- Highlight evolving principles in stem cell transplantation that have increased utilization in the past two decades
- Review current indications and potential new indications
- Discuss scientific approaches that may improve outcomes
- Explore patterns of utilization and barriers to access to therapies

Alfred Velpeau describes leukemia in 1825

1825-1950: ~1000 publications about leukemia



1960s

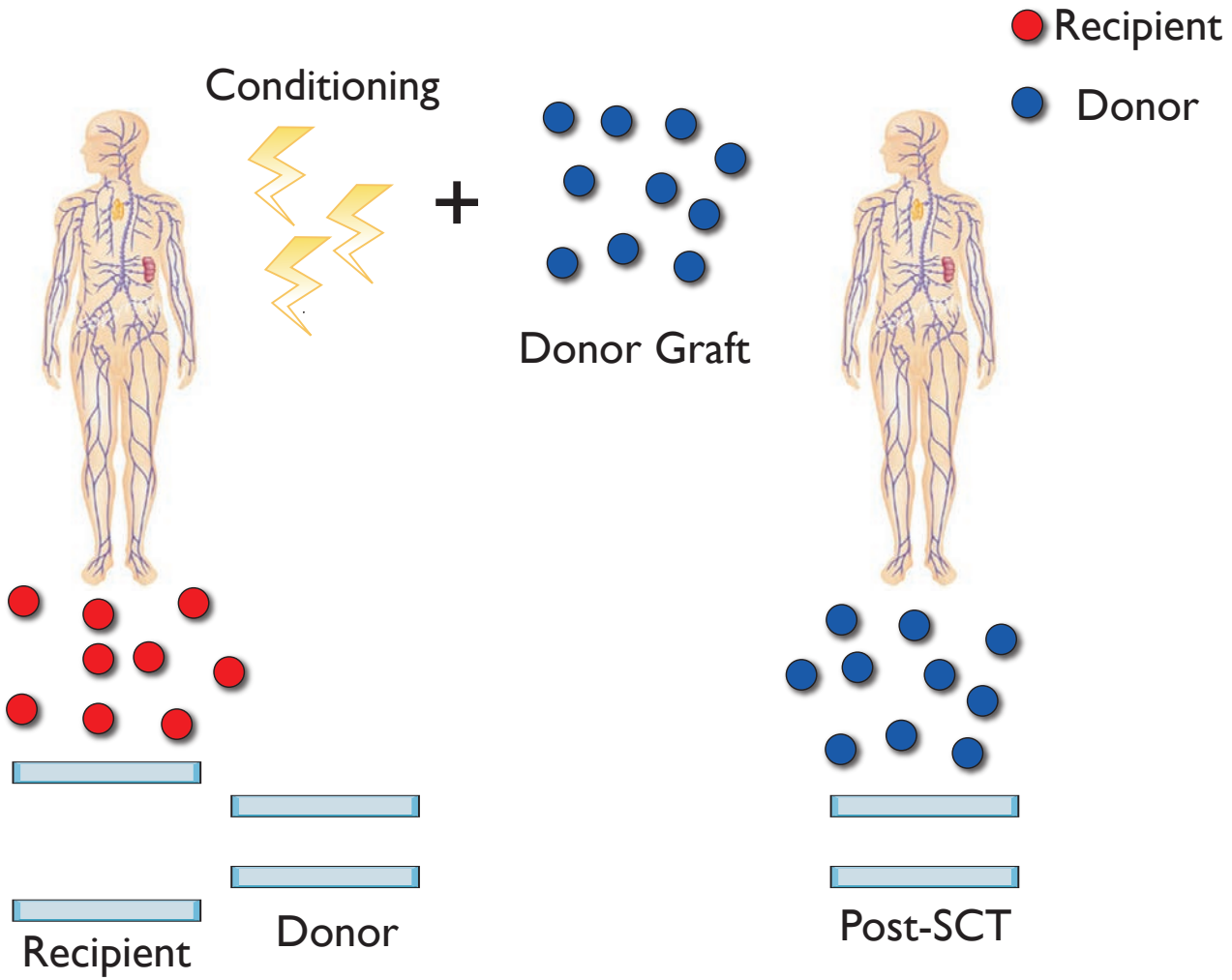
Combination
chemotherapy +
stem cell transplants

1825

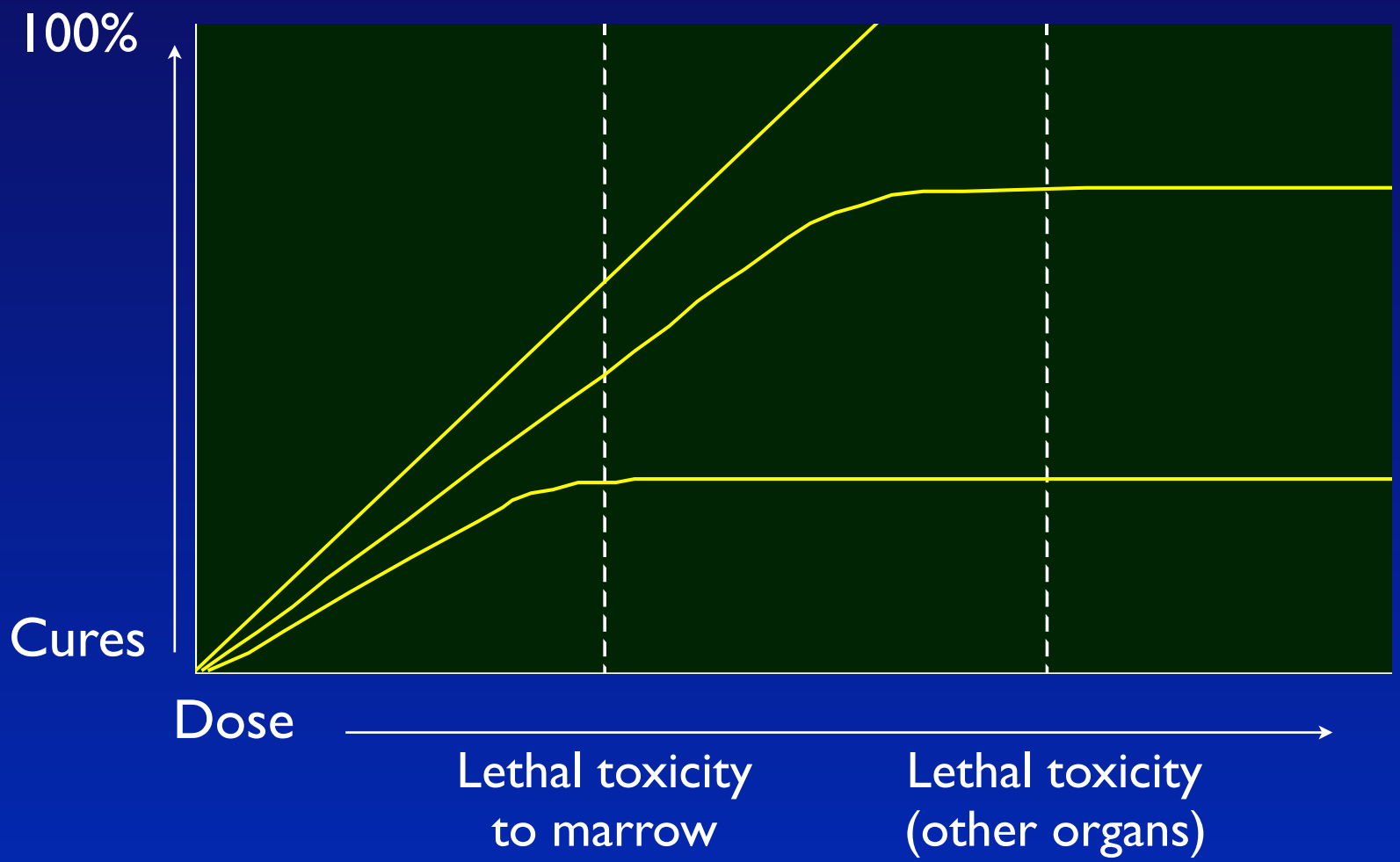
First description
of acute leukemia

1950-2000: ~175,000 publications about leukemia

Traditional Myeloablative Stem Cell Transplant

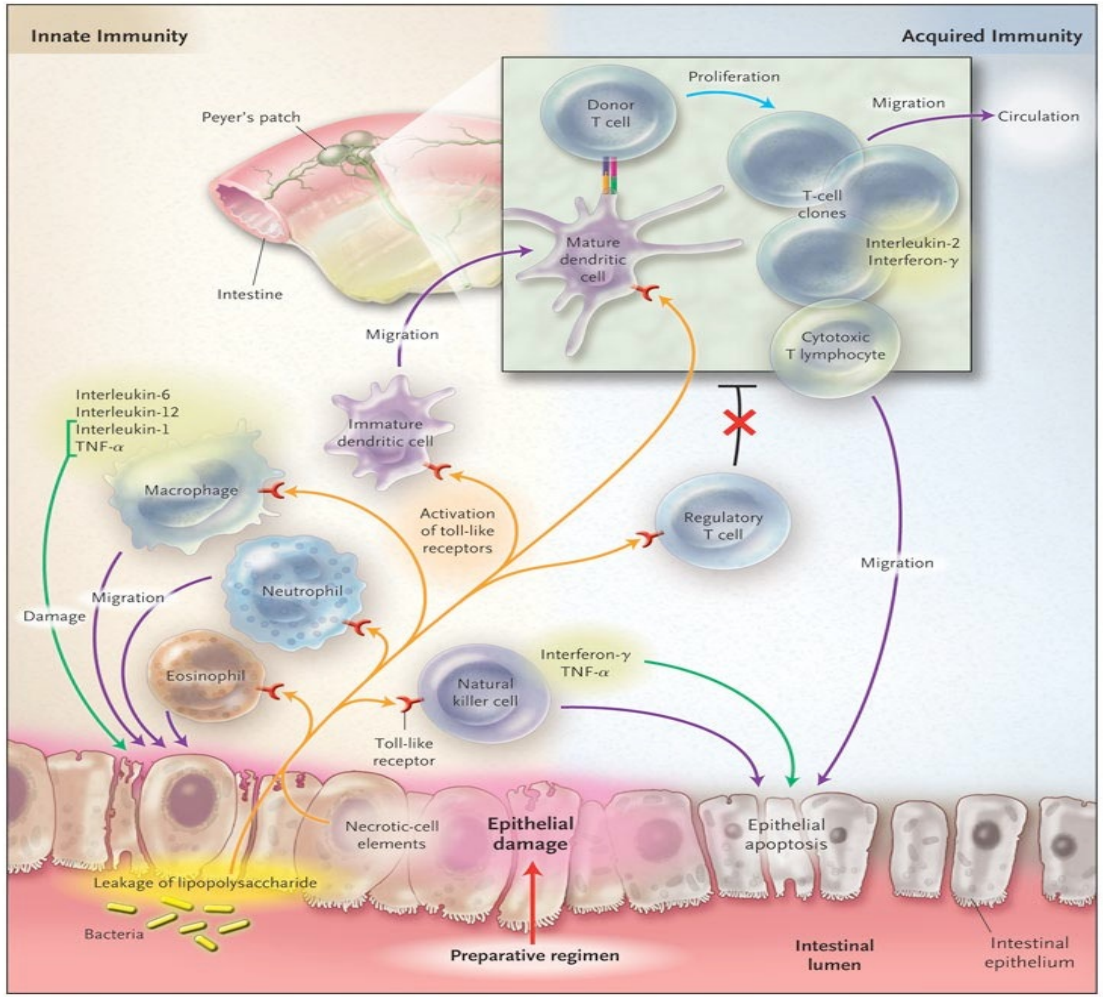


Rationale for high-dose chemotherapy with allogeneic stem cell rescue



adapted from Int'l Bone Marrow Transplant Registry

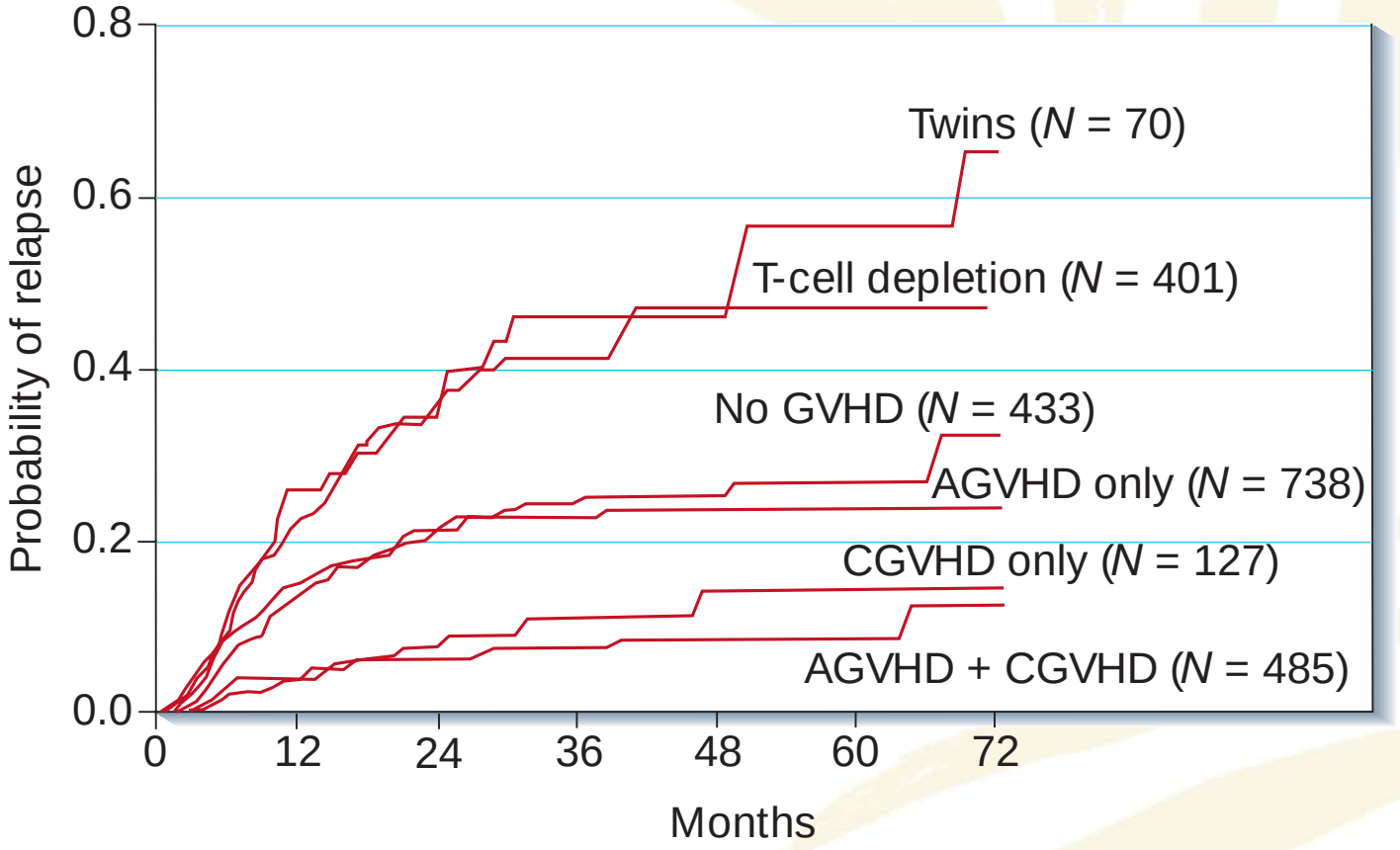
Acute GVHD: Pathophysiology



Copelan E. N Engl J Med 2006;354:1813-1826

The NEW ENGLAND JOURNAL of MEDICINE

T cell depletion increases relapse risk



Appelbaum FR. *Nature* 411: 385-389 (2001)
[from original, Horowitz M, *Blood* (1990)]

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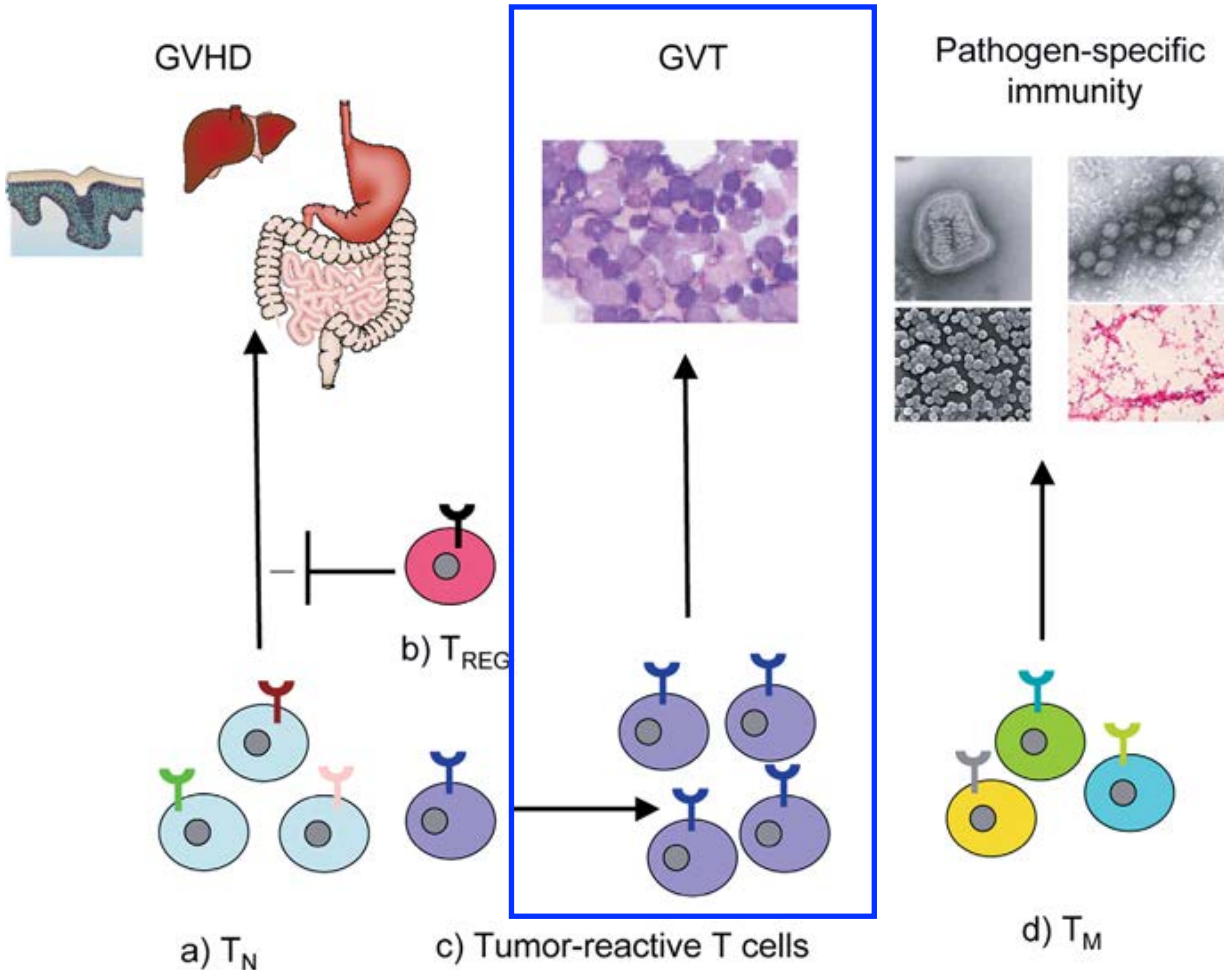
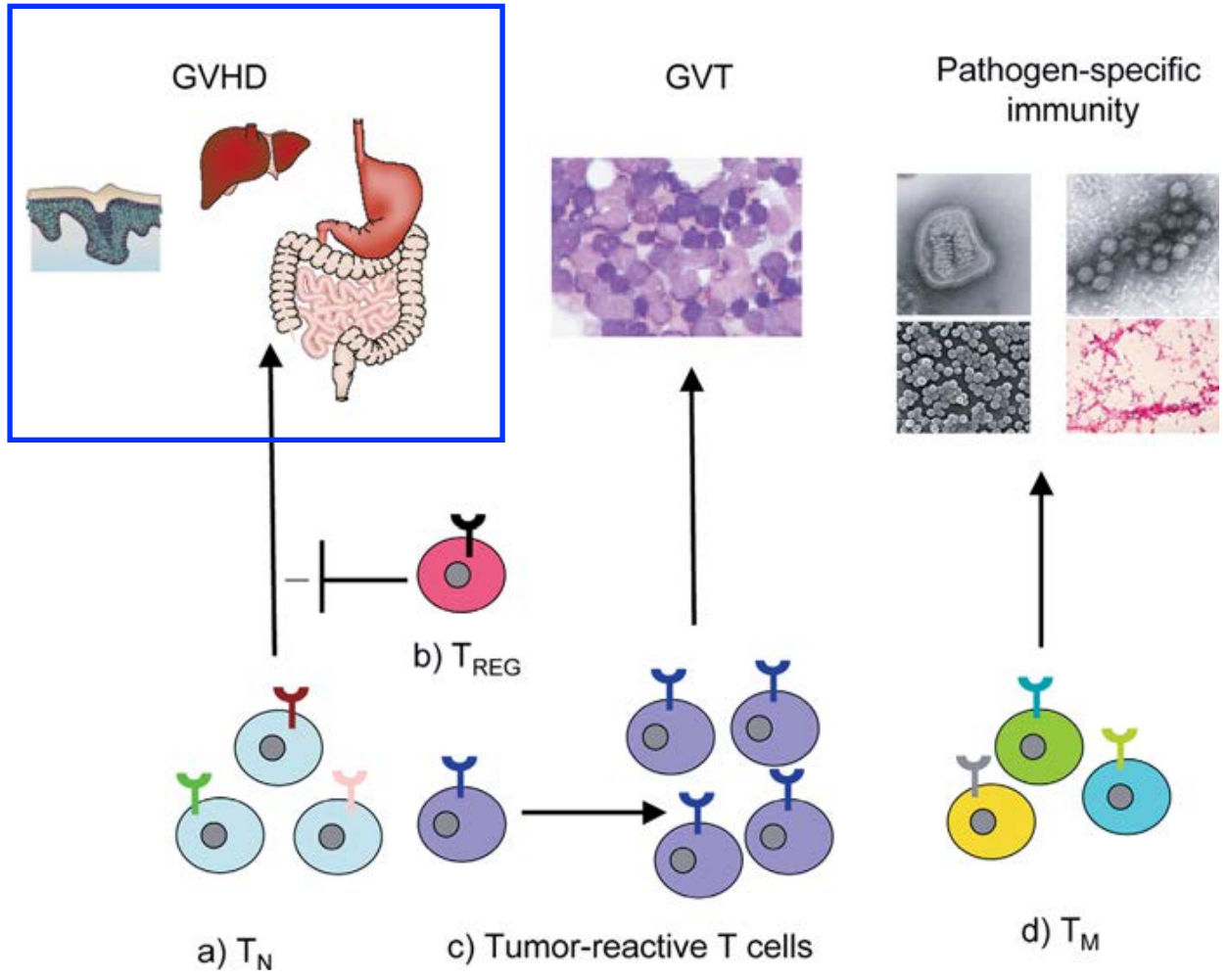
T cells in donor transplant grafts eliminate residual cancer



Riddell & Appelbaum,
Graft v. Host Disease,
PLOS Medicine, 2007

…but can also cause GVHD, with morbidity and mortality



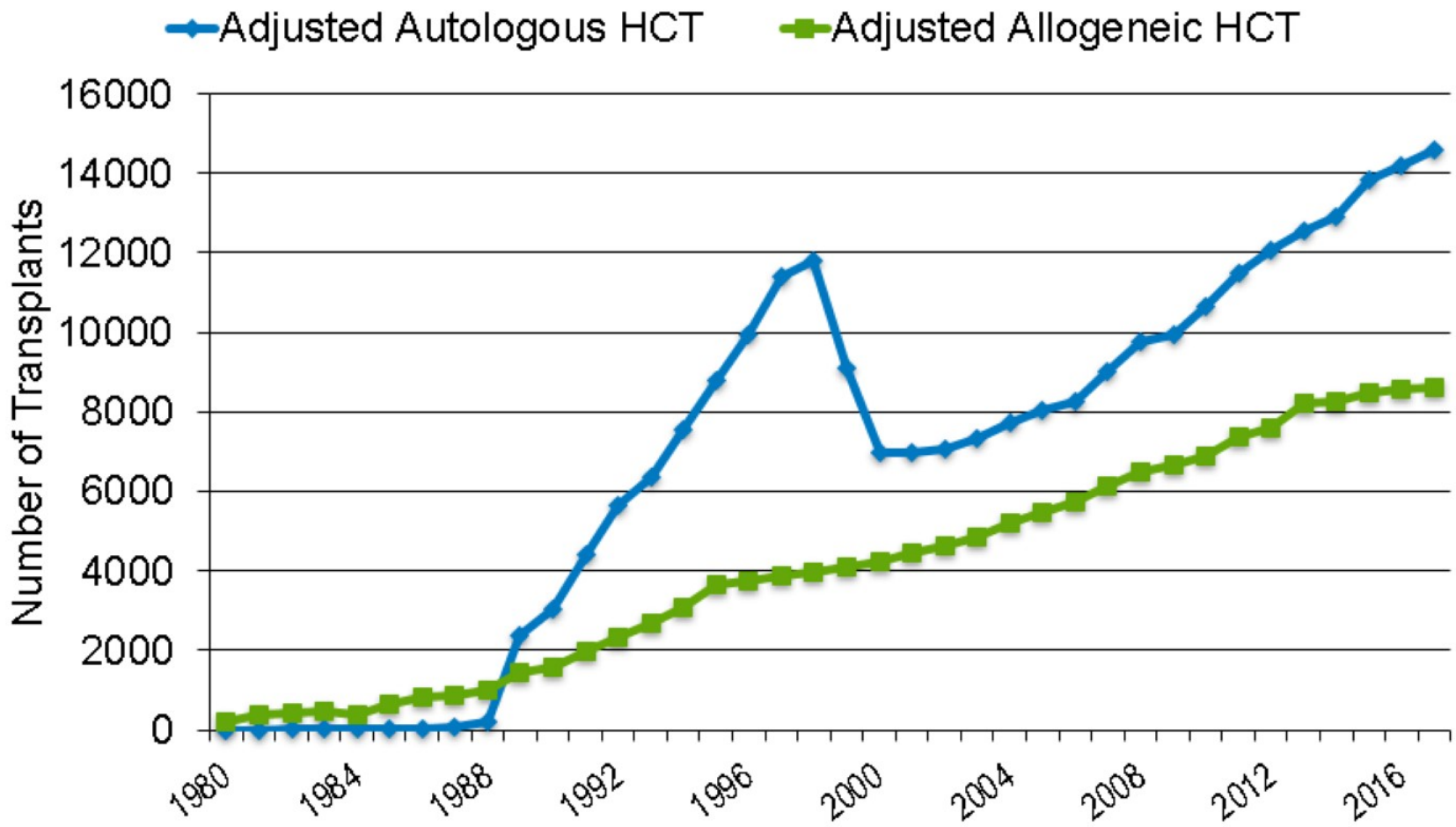
Riddell & Appelbaum,
Graft v. Host Disease,
PLOS Medicine, 2007

Evolution and Progress in Allogeneic SCT

Over the past 20 years:

- A major goal is to maximize T cell effects--*less* intense chemotherapy is often used
- Older patients are commonly transplanted (to 75 vs. 55)
- Peripheral blood (vs. marrow) is commonly used as a stem cell source (correct?)
- 100-day mortality now typically 5-10% (from 20-40%)
- Almost all patients now have a donor (sibling, registry MUD, cord or haplo)

Annual Number of HCT Recipients in the US by Transplant Type



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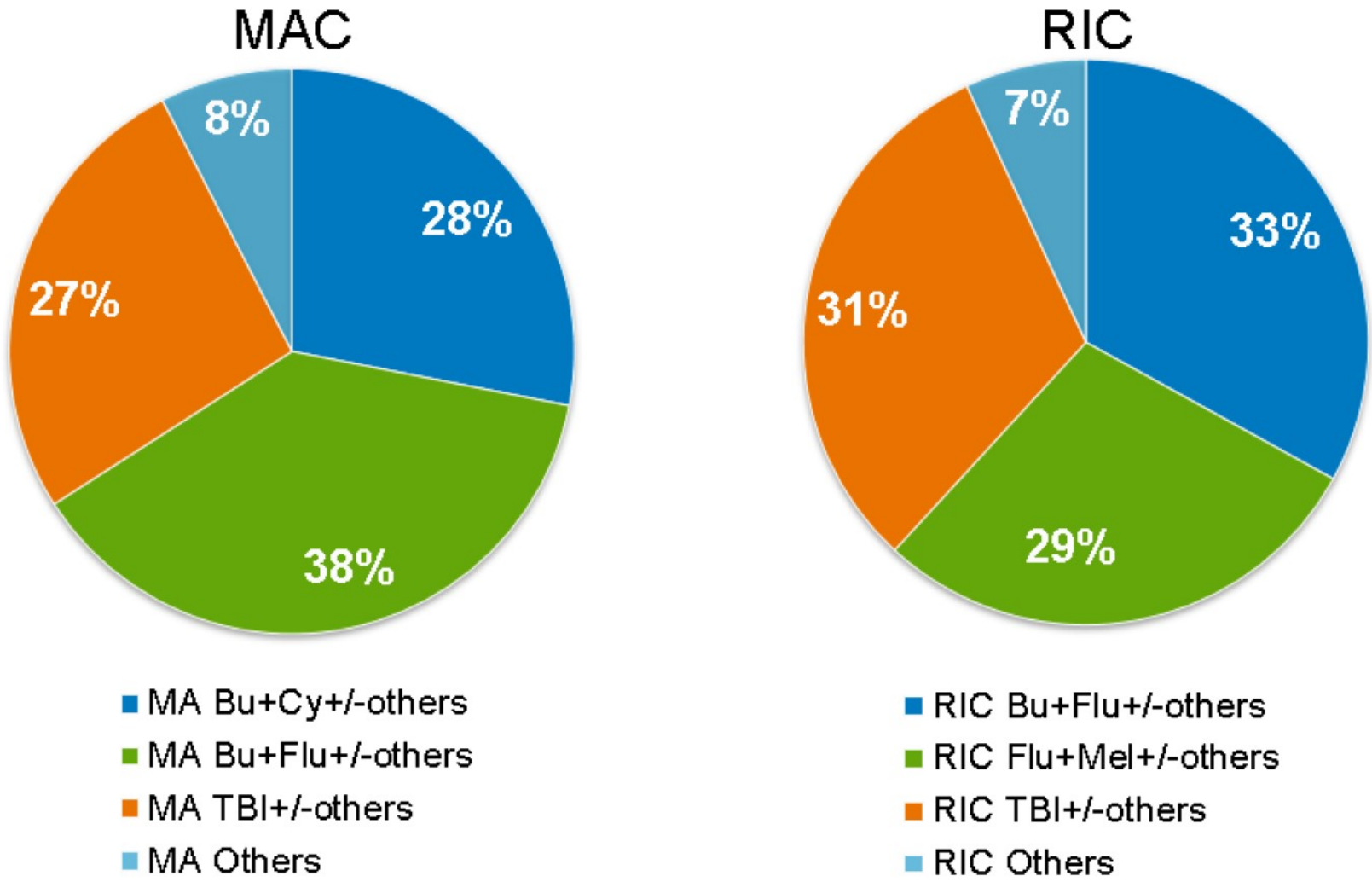
Common Conditioning Regimens in AML or MDS Allogeneic HCT in the US in 2007-2017



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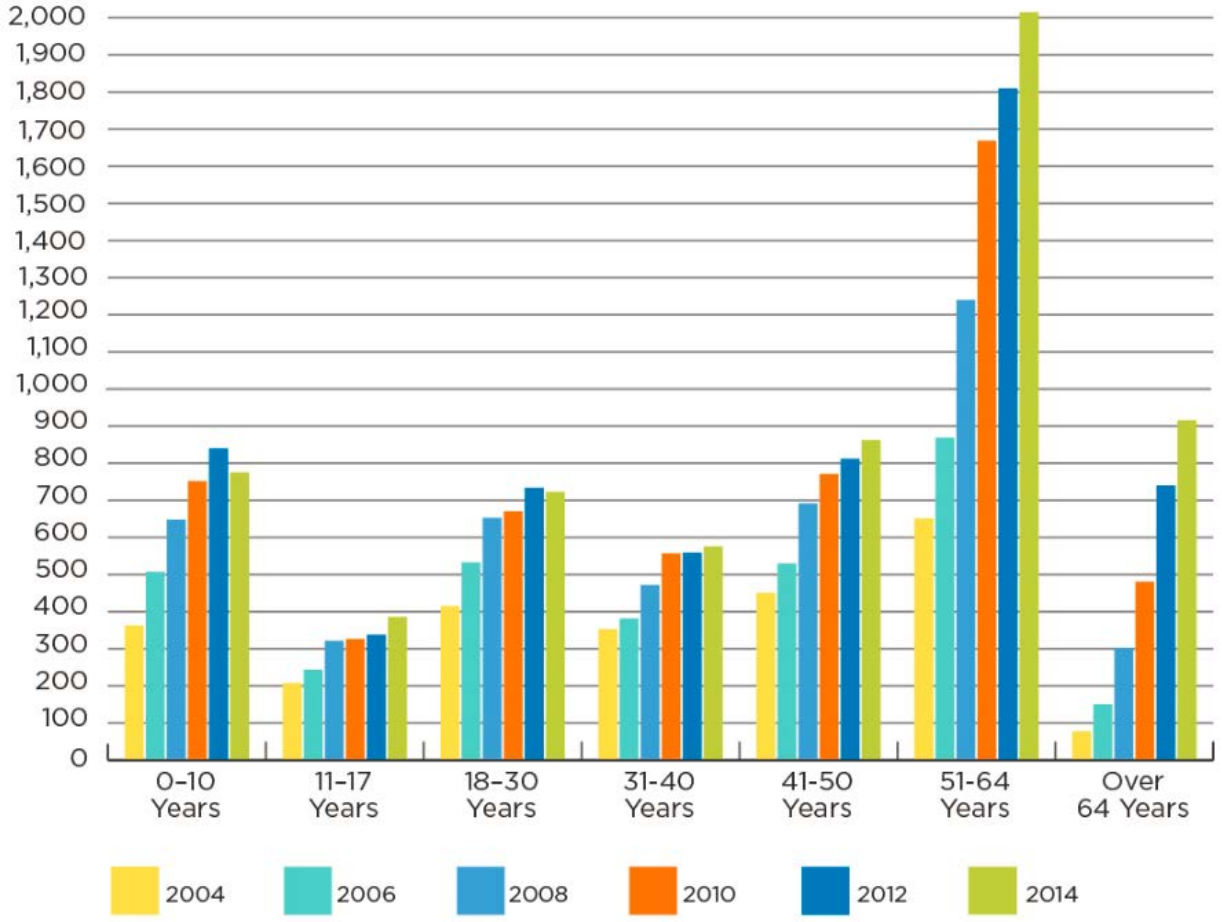
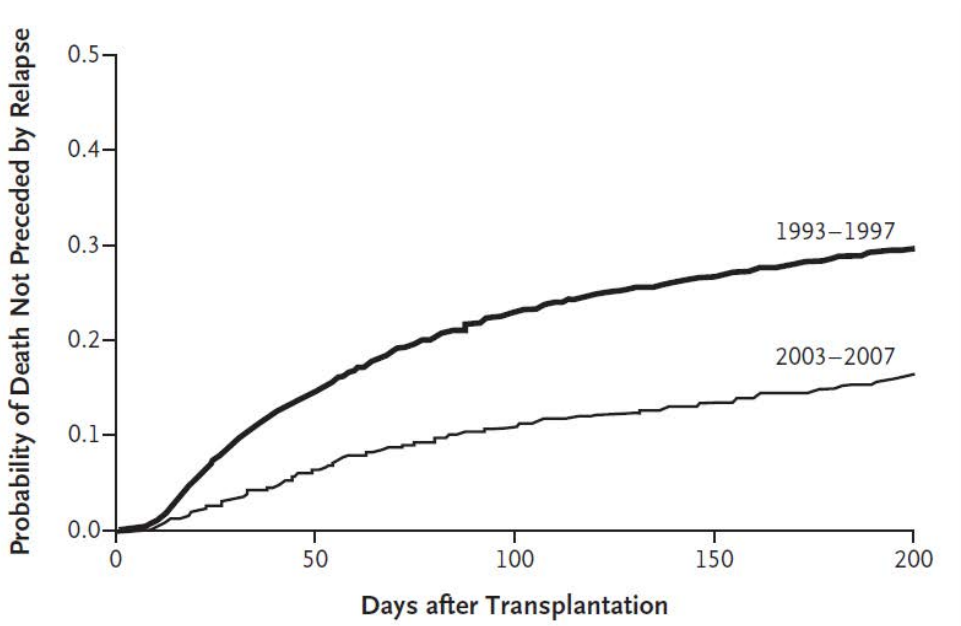
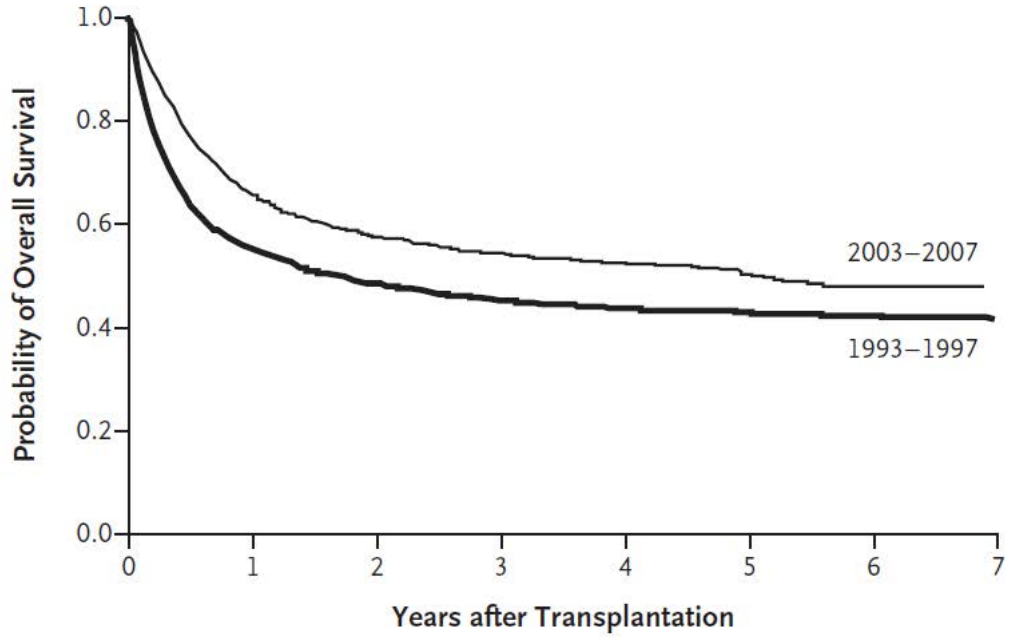
Transplants by Recipient Age



Source: National Marrow Donor Program/Be The Match FY 2014

Reduced Mortality after Allogeneic Hematopoietic Cell Transplant[1]



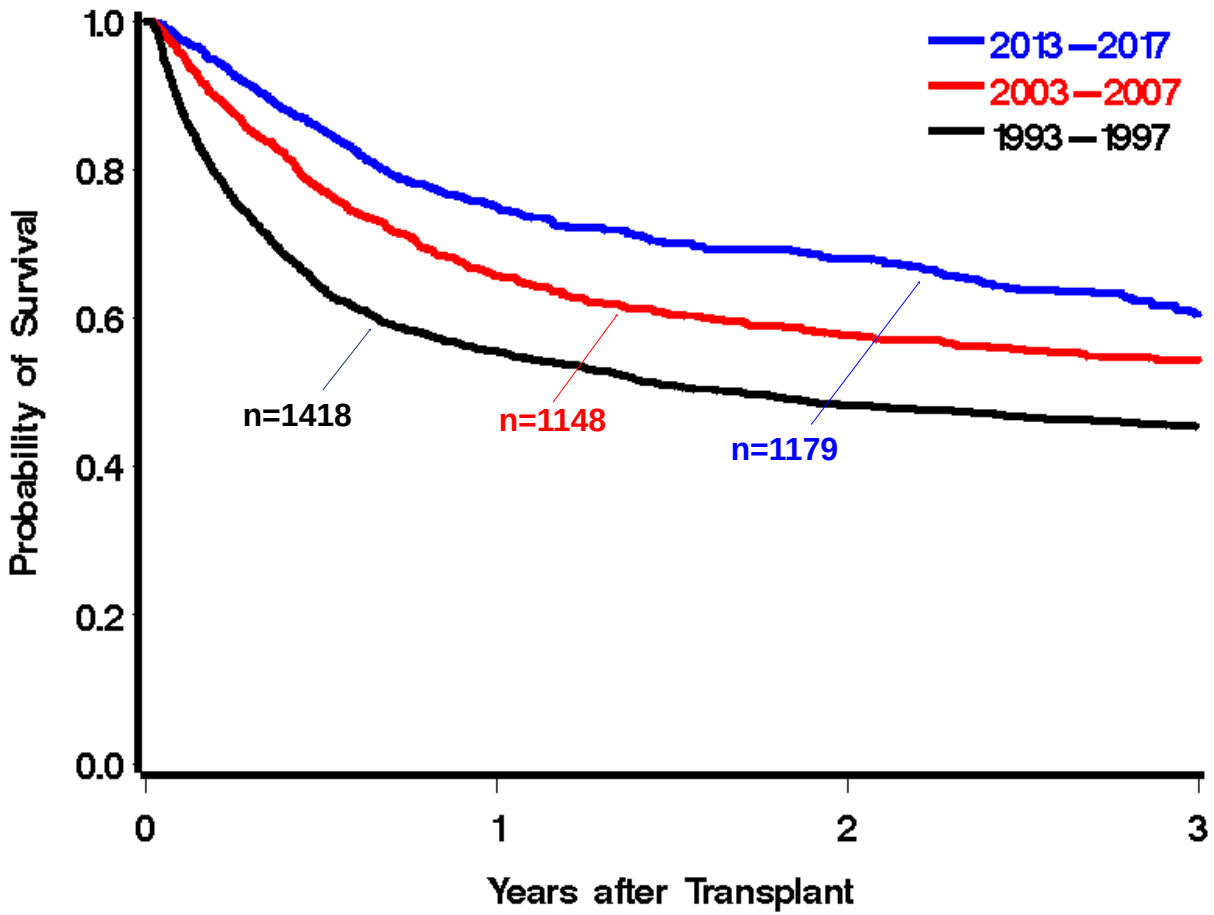


Gooley et al. NEJM 363: 2091 – 2101, 2010

FRED HUTCH

Slide: Fred Applebaum, Fred Hutch

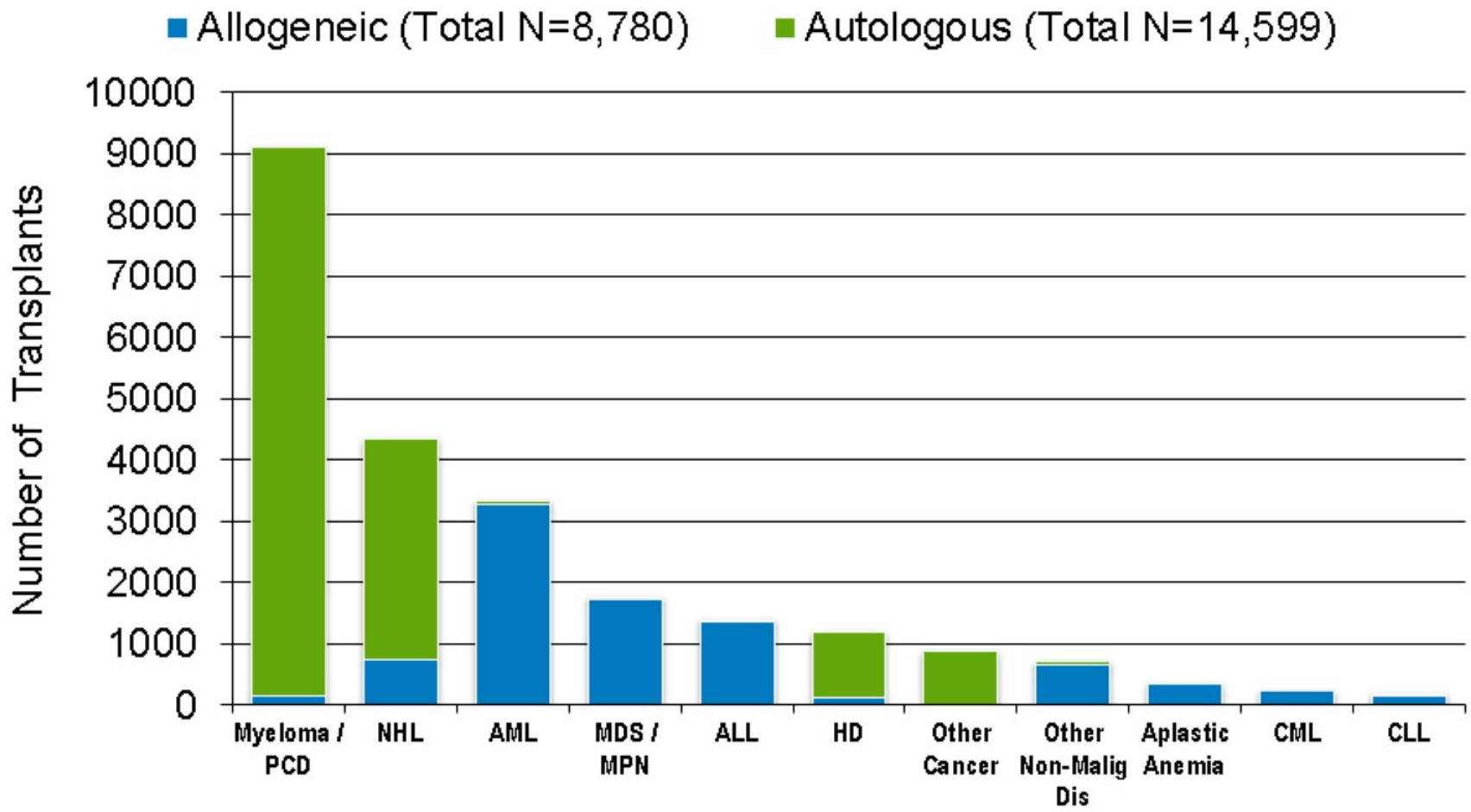
Survival following Allogeneic Hematopoietic Cell Transplantation for Hematologic Malignancies



FRED HUTCH

Slide: Fred Applebaum, Fred Hutch

Indications for Hematopoietic Cell Transplant in the US, 2017



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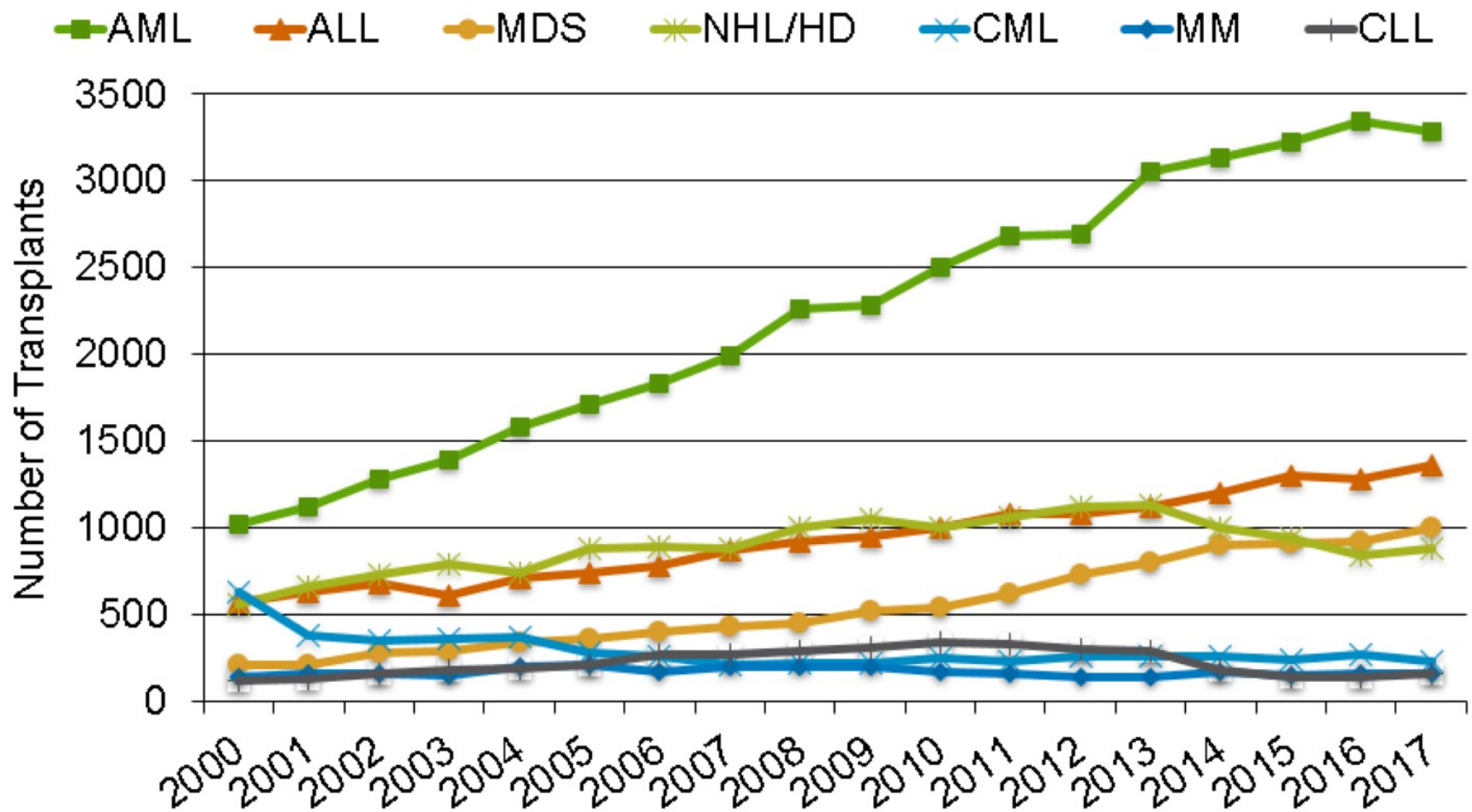
Selected Disease Trends for Allogeneic HCT in the US



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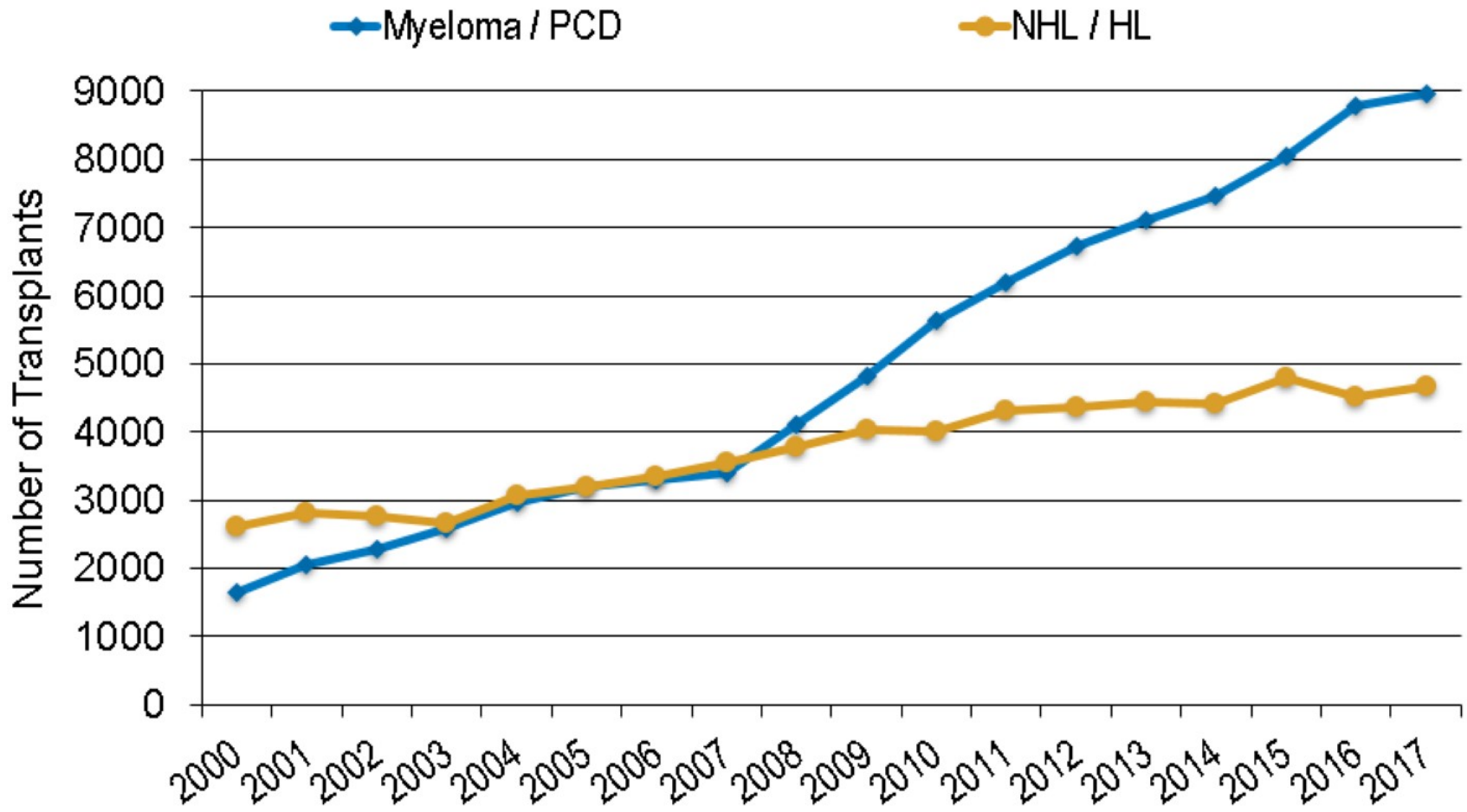
Selected Disease Trends for Autologous HCT in the US



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Changes in graft types used for stem cell transplants

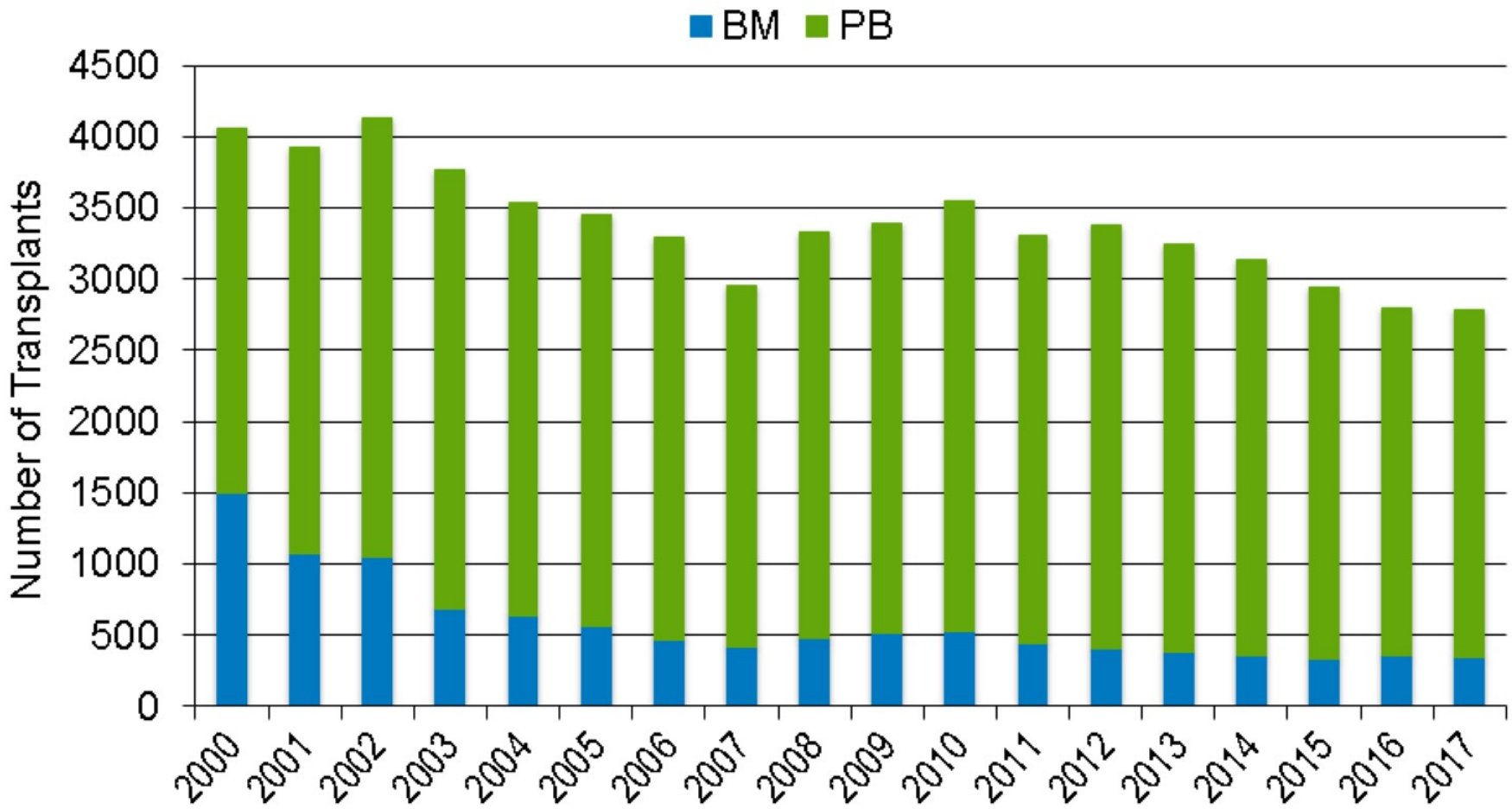
- Historically outcomes were much poorer for patients who didn't have matched family donors. *Each sibling has 1 in 4 chance of matching, so a patient with two siblings has ~50% chance of a family match.*

- Increases in size of volunteer donor registries dramatically improved outcomes for unrelated donor transplantation (but less so for underrepresented minorities)

- Rise in cord blood transplantation and, more recently, improvements in haploidentical (half-matched) transplants have improved outcomes for patients lacking family donors (now nearly equivalent!)

- *Nearly everyone has a donor now!*

HLA-Matched Sibling Donor Allogeneic HCT in Patients Age ≥18 Years



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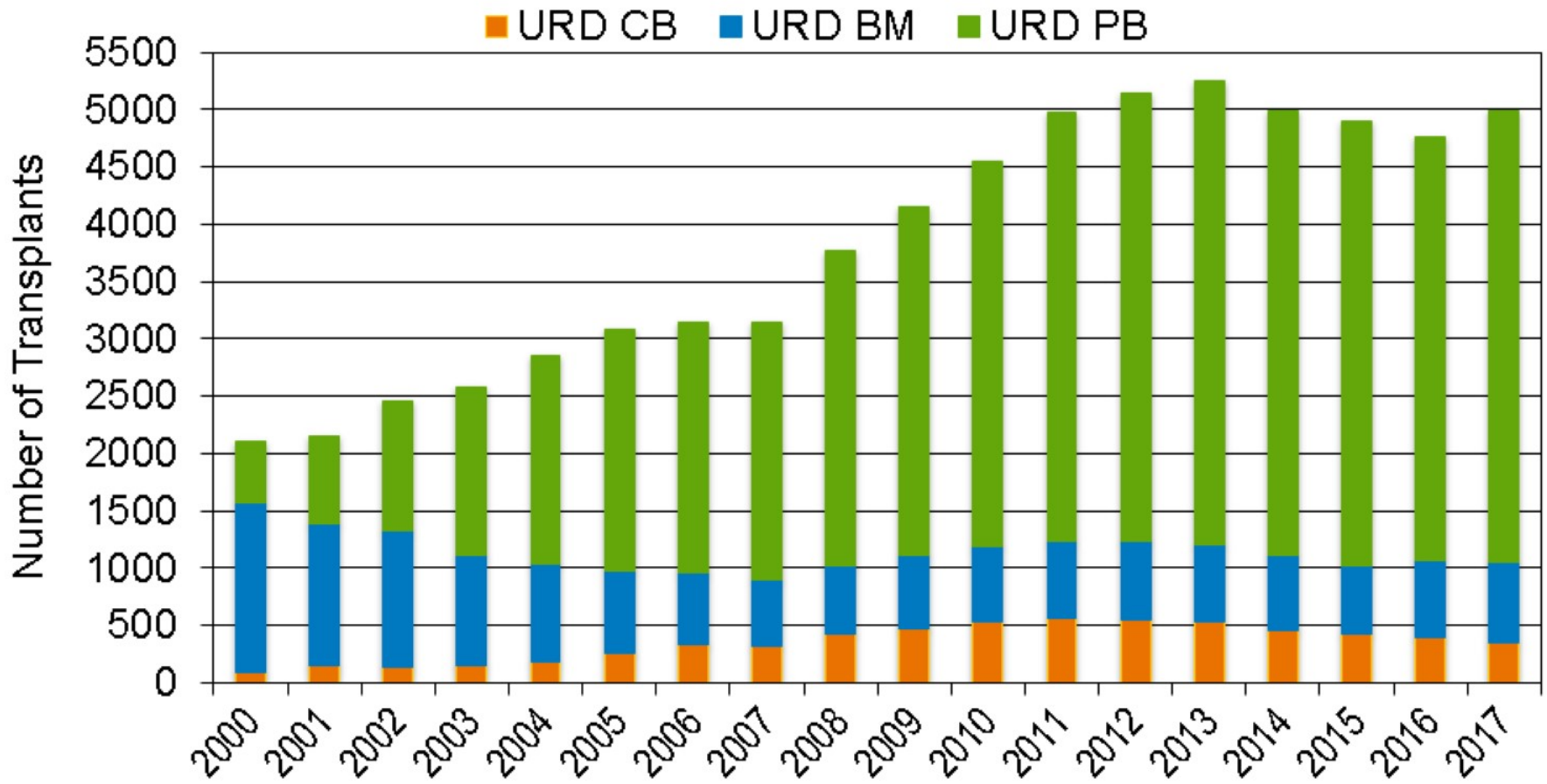
Unrelated Donor Allogeneic HCT in Patients Age ≥18 Years



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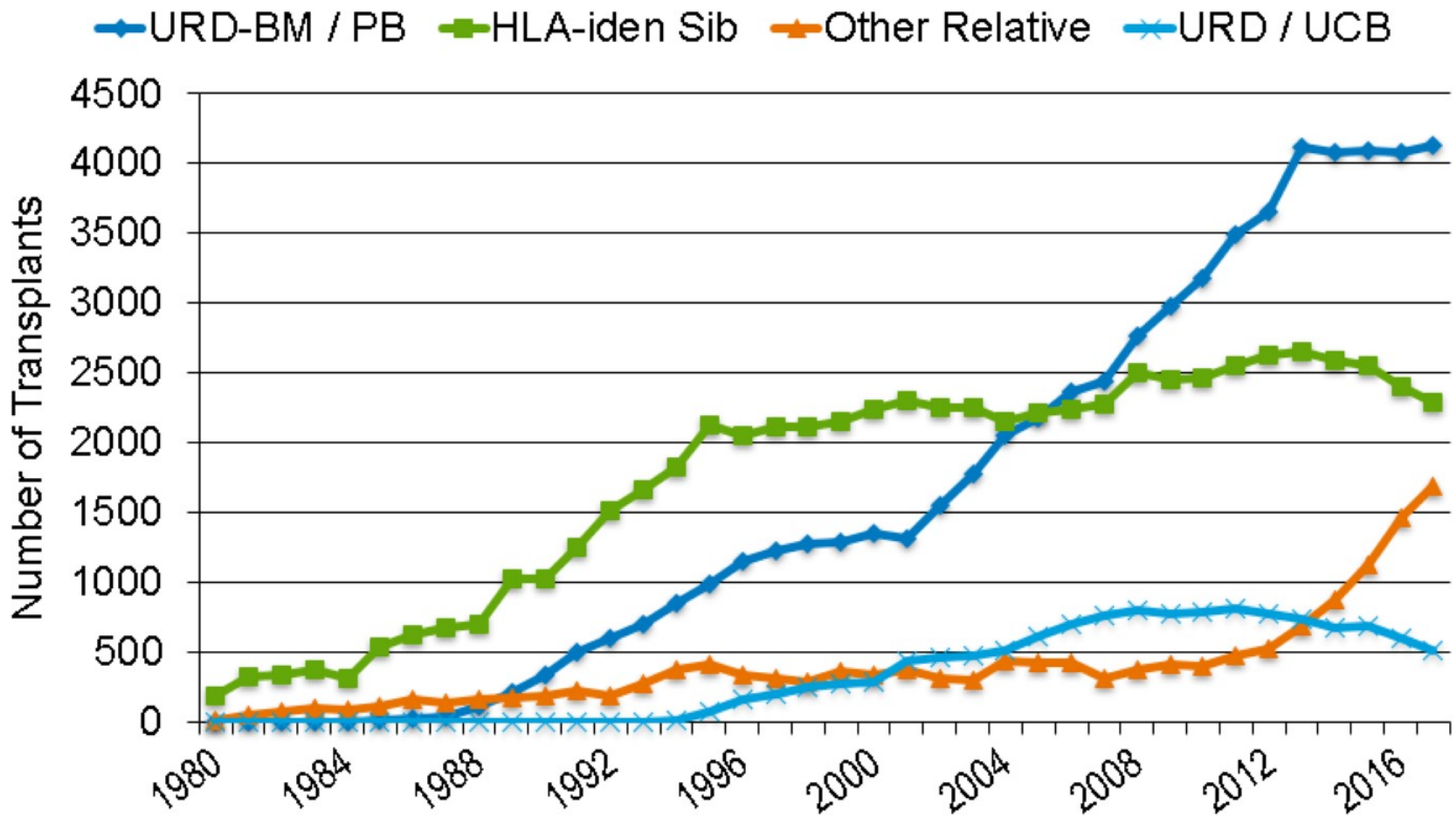
Allogeneic HCT Recipients in the US, by Donor Type



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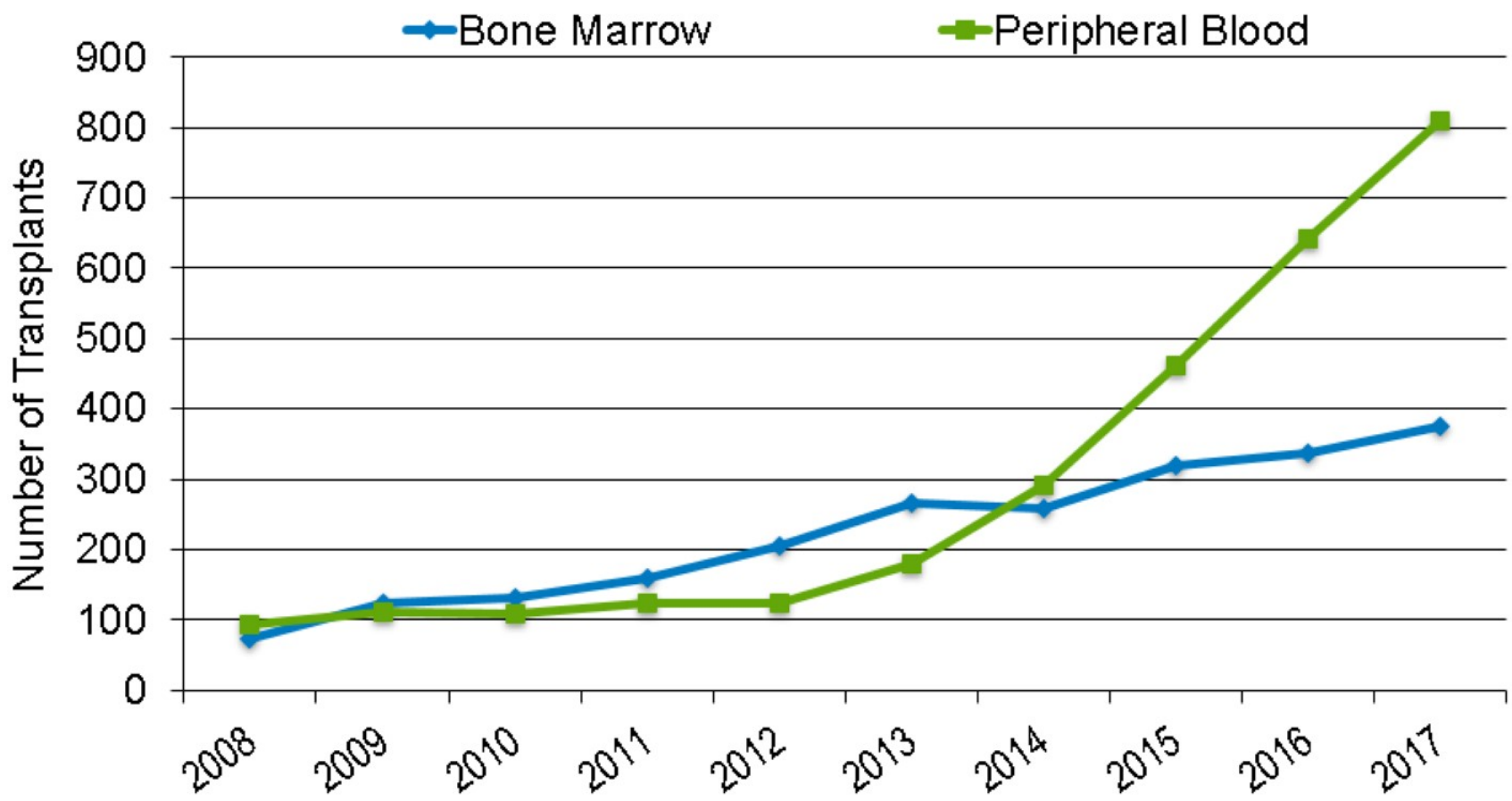
Haploidentical HCT Recipients in the US, by Graft Type



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Potential changes in utilization of SCT by disease

- Improvement of non-transplant therapies in myeloma are improving outcomes independent of transplant. *Despite multiple studies demonstrating that transplantation further improves outcomes, there appears to be a plateau in utilization*

- Relapsed and refractory lymphoma respond to CAR-T therapies *Role for earlier use of CAR-T therapies being explored. These studies may either reaffirm the role of autologous SCT or subsets that may do better with CAR-T*

- Acute myeloid leukemia therapy has evolved little over decades, except for subsets that may respond to targeted therapies. *Immunotherapy is likely to still require transplantation due to ablation of healthy bone marrow cells*

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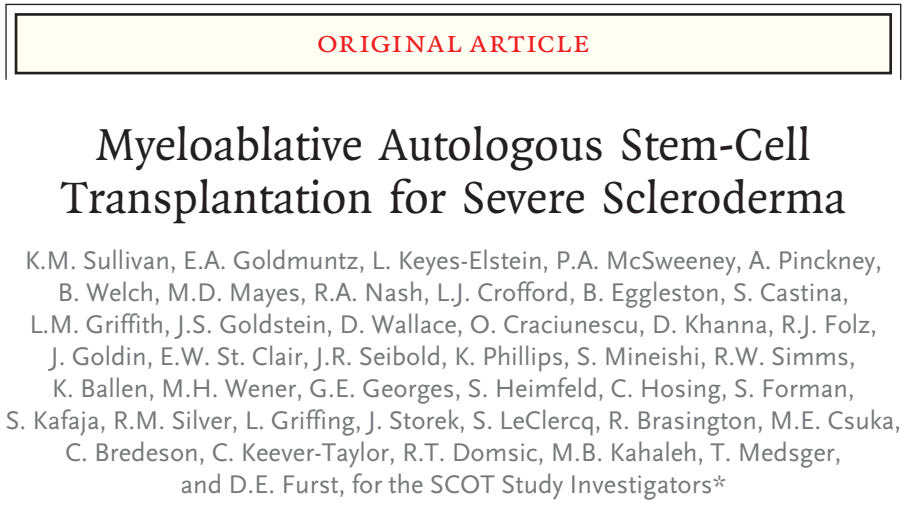
Potential new indications

- Hemoglobinopathies (Sickle cell anemia and thalassemia) are major populations that can benefit from curative stem cell transplantation
- Use of allogeneic transplantation has been limited, due to concerns about potentially fatal outcomes for "benign" diseases.
- Emerging gene therapies are exciting, but many involve autologous transplantation of genetically modified cells that produce corrected genes

Autoimmune disease

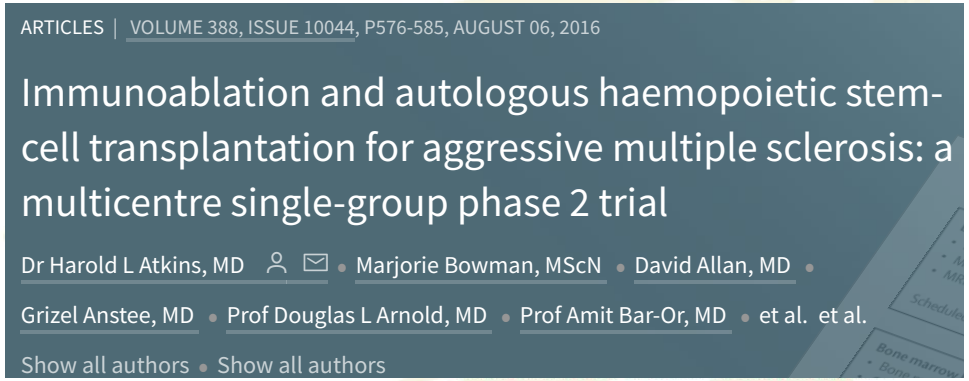
- Impressive results in well controlled trials have been seen in systemic sclerosis (scleroderma) and multiple sclerosis (Sullivan, NEJM 2018, Atkins, Lancet 2016)

- These "benign" diseases, in subsets of advanced patients, are associated with severe limitation of function and even high rates of mortality. *While utilization is increasing, it remains very limited.*


ORIGINAL ARTICLE

Myeloablative Autologous Stem-Cell Transplantation for Severe Scleroderma

K.M. Sullivan, E.A. Goldmuntz, L. Keyes-Elstein, P.A. McSweeney, A. Pinckney, B. Welch, M.D. Mayes, R.A. Nash, L.J. Crofford, B. Eggleston, S. Castina, L.M. Griffith, J.S. Goldstein, D. Wallace, O. Craciunescu, D. Khanna, R.J. Folz, J. Goldin, E.W. St. Clair, J.R. Seibold, K. Phillips, S. Mineishi, R.W. Simms, K. Ballen, M.H. Wener, G.E. Georges, S. Heimfeld, C. Hosing, S. Forman, S. Kafaja, R.M. Silver, L. Griffing, J. Storek, S. LeClercq, R. Brasington, M.E. Csuka, C. Bredeson, C. Keever-Taylor, R.T. Domsic, M.B. Kahaleh, T. Medsger, and D.E. Furst, for the SCOT Study Investigators*


ARTICLES | VOLUME 388, ISSUE 10044, P576-585, AUGUST 06, 2016

Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial

Dr Harold L Atkins, MD • Marjorie Bowman, MScN • David Allan, MD • Grizel Anstee, MD • Prof Douglas L Arnold, MD • Prof Amit Bar-Or, MD • et al. et al.

Show all authors • Show all authors

What hasn't changed much?

- Risk stratification for most diseases (e.g., acute myeloid leukemia, the primary indication for allo SCT) has evolved very little, despite the 'omic' revolution
- In most cases, we still infuse donor grafts as collected, without enrichment or manipulation of cell subsets
- Strategies to prevent and/or treat GVHD have not significantly evolved in over 25 years, despite many attempts and the advent of targeted and biologic therapies
- Beyond conditioning, no therapies have typically been used to reduce relapse risk

What can we do to decrease relapse after SCT?

- Select patients most likely to benefit from allogeneic SCT
- Manipulate the graft (to selectively inhibit GVHD, improve GVL)
- Develop more selective pharmacologic approaches to inhibit GVHD
- Apply post-transplant maintenance therapy

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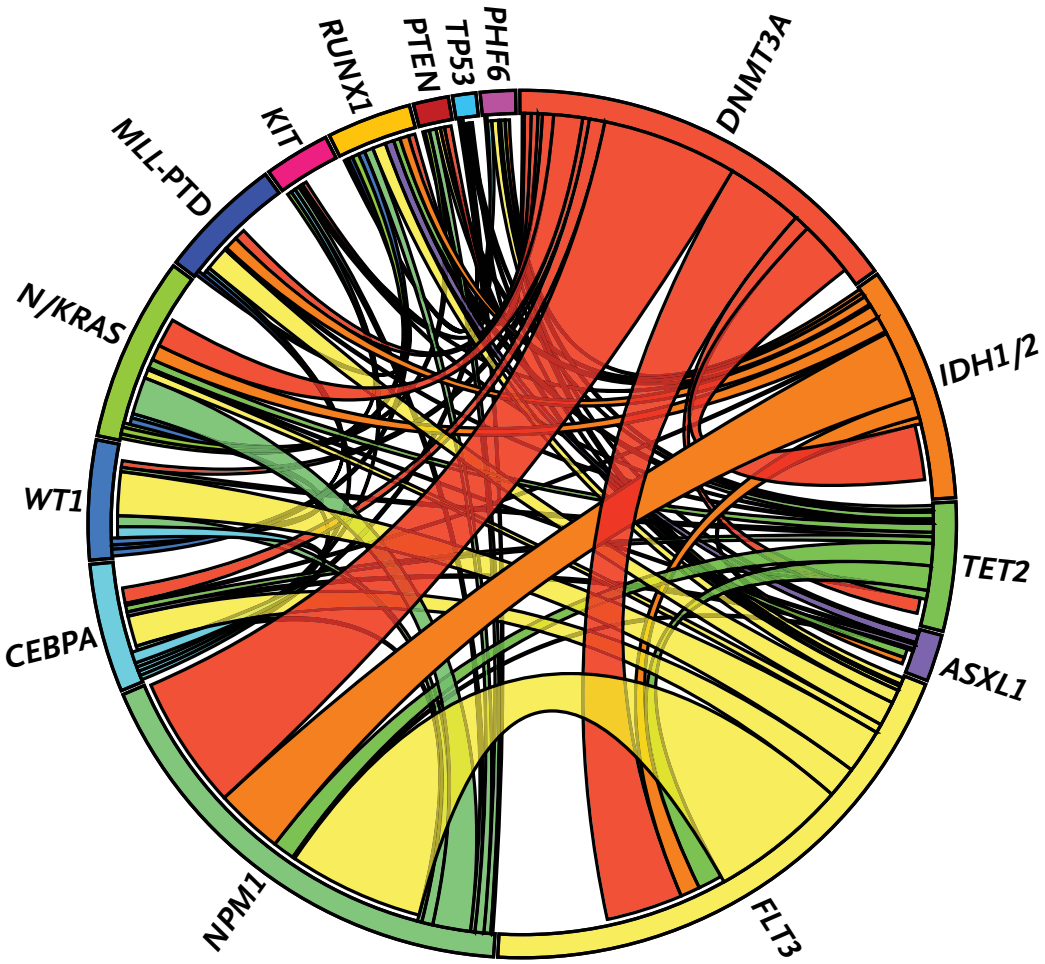
Personalized medicine in AML

- Molecular profiling (incompletely done, in most centers) may add significantly to conventional pathology/cytogenetics and predict risk of relapse
- Further studies are needed to determine how new stratification schemes may predict relapse after transplantation, and identify patients most likely to benefit from SCT (*if and when)*
- Targeted therapies will likely be used in a tailored fashion before and after SCT (induction therapy and post-SCT maintenance)

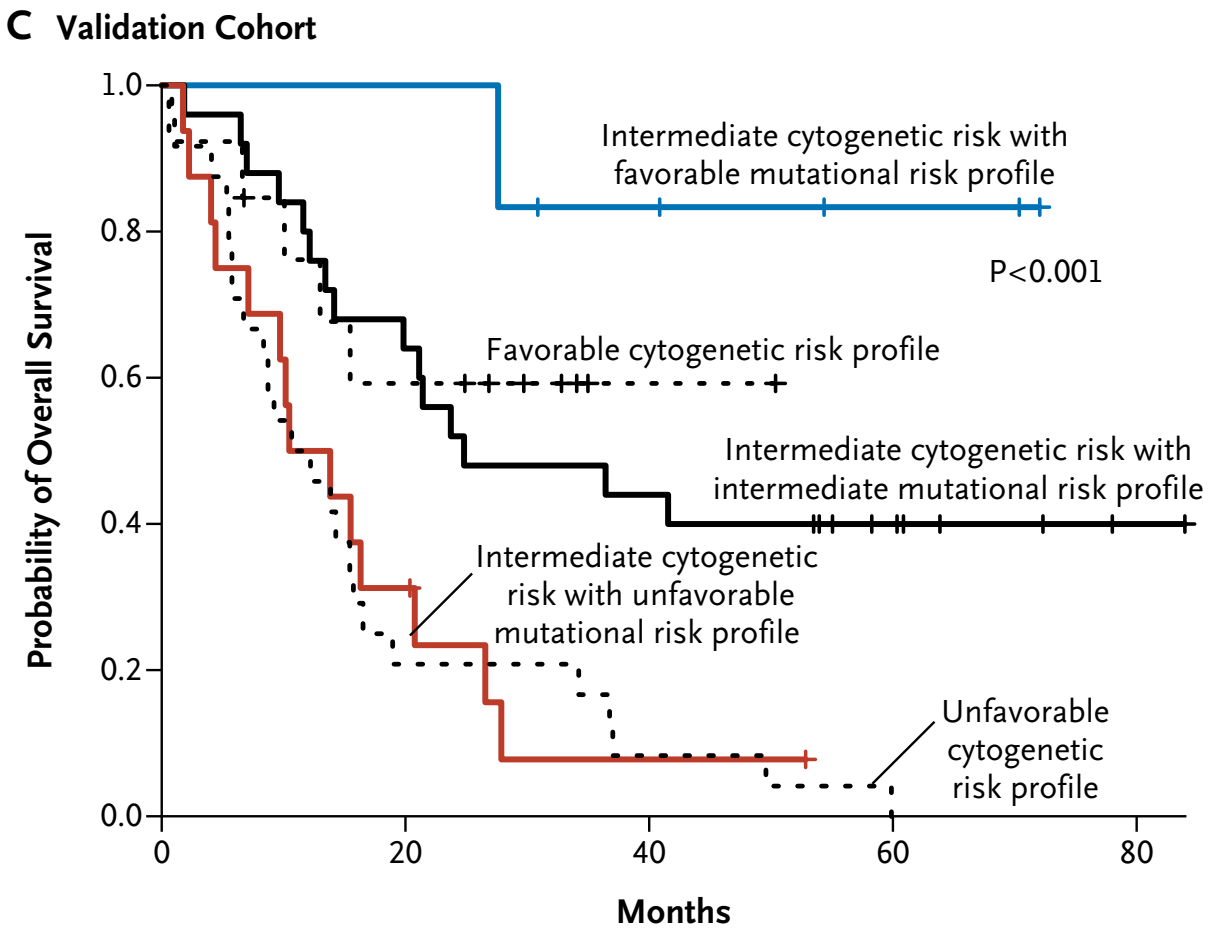
A **Total Cohort**



Gene	Overall Frequency (%)
FLT3 (ITD, TKD)	37 (30, 7)
NPM1	29
DNMT3A	23
NRAS	10
CEBPA	9
TET2	8
WT1	8
IDH2	8
IDH1	7
KIT	6
RUNX1	5
MLL-PTD	5
ASXL1	3
PHF6	3
KRAS	2
PTEN	2
TP53	2
HRAS	0
EZH2	0

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 22, 2012 VOL. 366 NO. 12

Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia

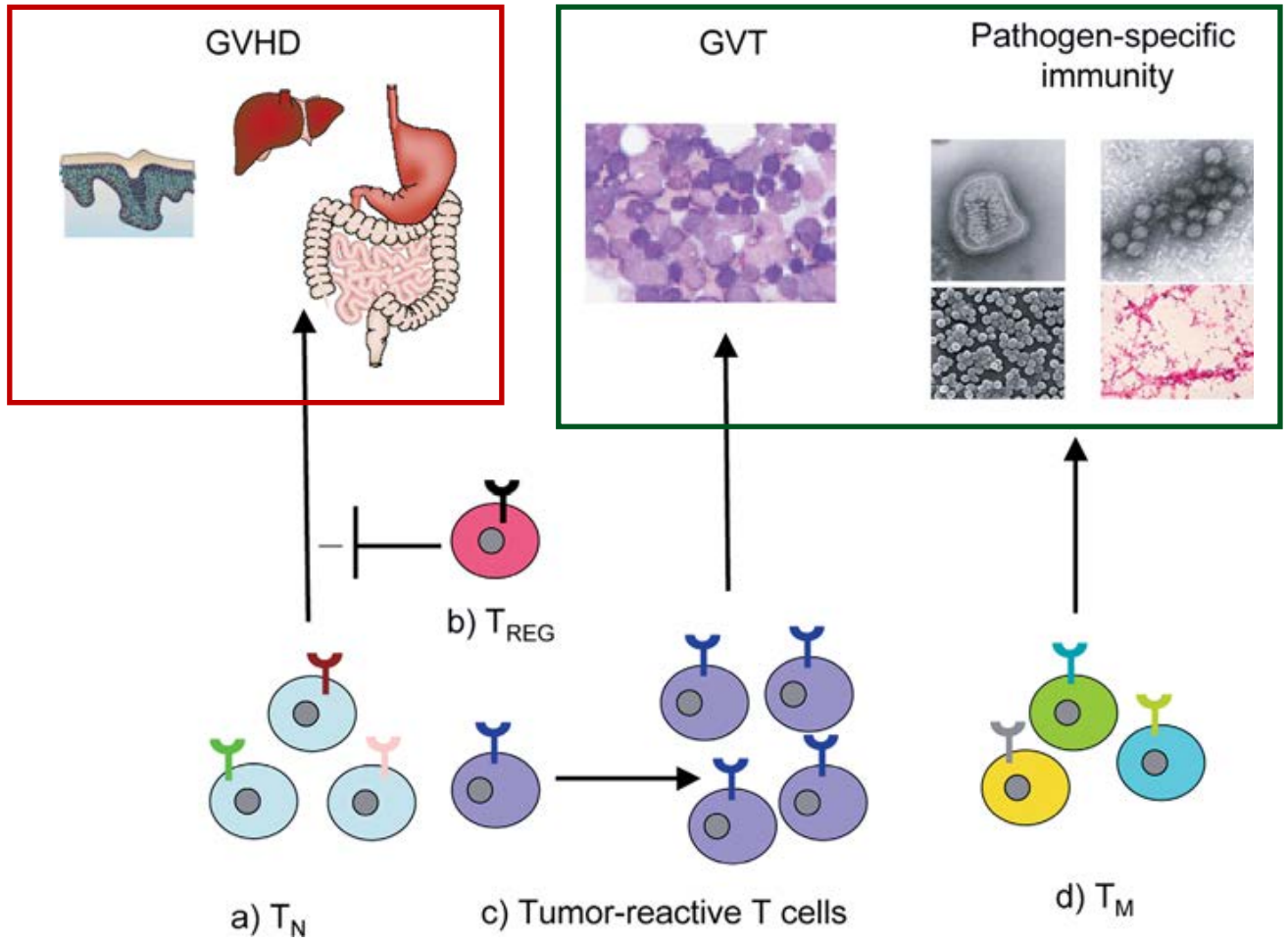


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 22, 2012 VOL. 366 NO. 12

Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia

Improving immune outcomes of stem cell transplants

Can we selectively inhibit these...



But not these?

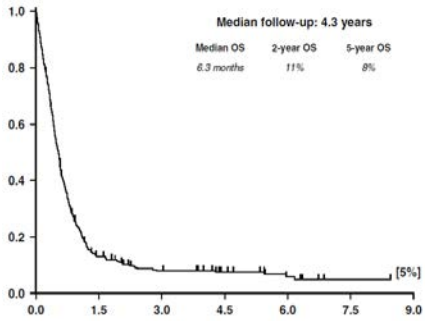
Riddell & Appelbaum, Graft v. Host Disease, PLOS Medicine, 2007

What can we do to decrease relapse after SCT?

- Select patients most likely to benefit from allogeneic SCT
- Manipulate the graft (to selectively inhibit GVHD, improve GVL)
- Develop more selective pharmacologic approaches to inhibit GVHD
- Apply post-transplant maintenance therapy

What are the unmet needs in HCT in 2018?

Disease control pre-HCT

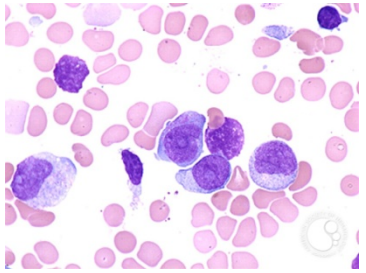


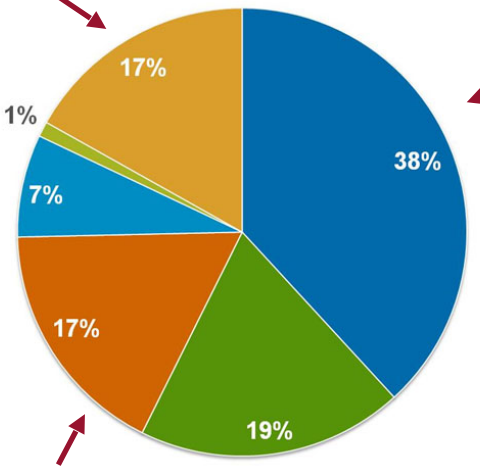
Donor/Access

Causes of death after Unrelated donor HCT

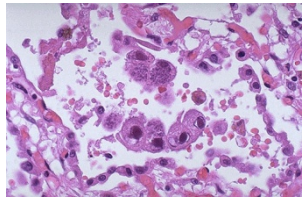
Toxicity

Relapse

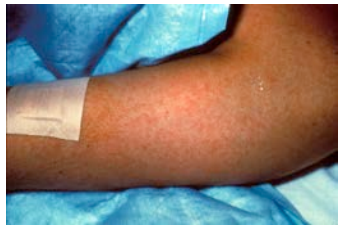




Infection



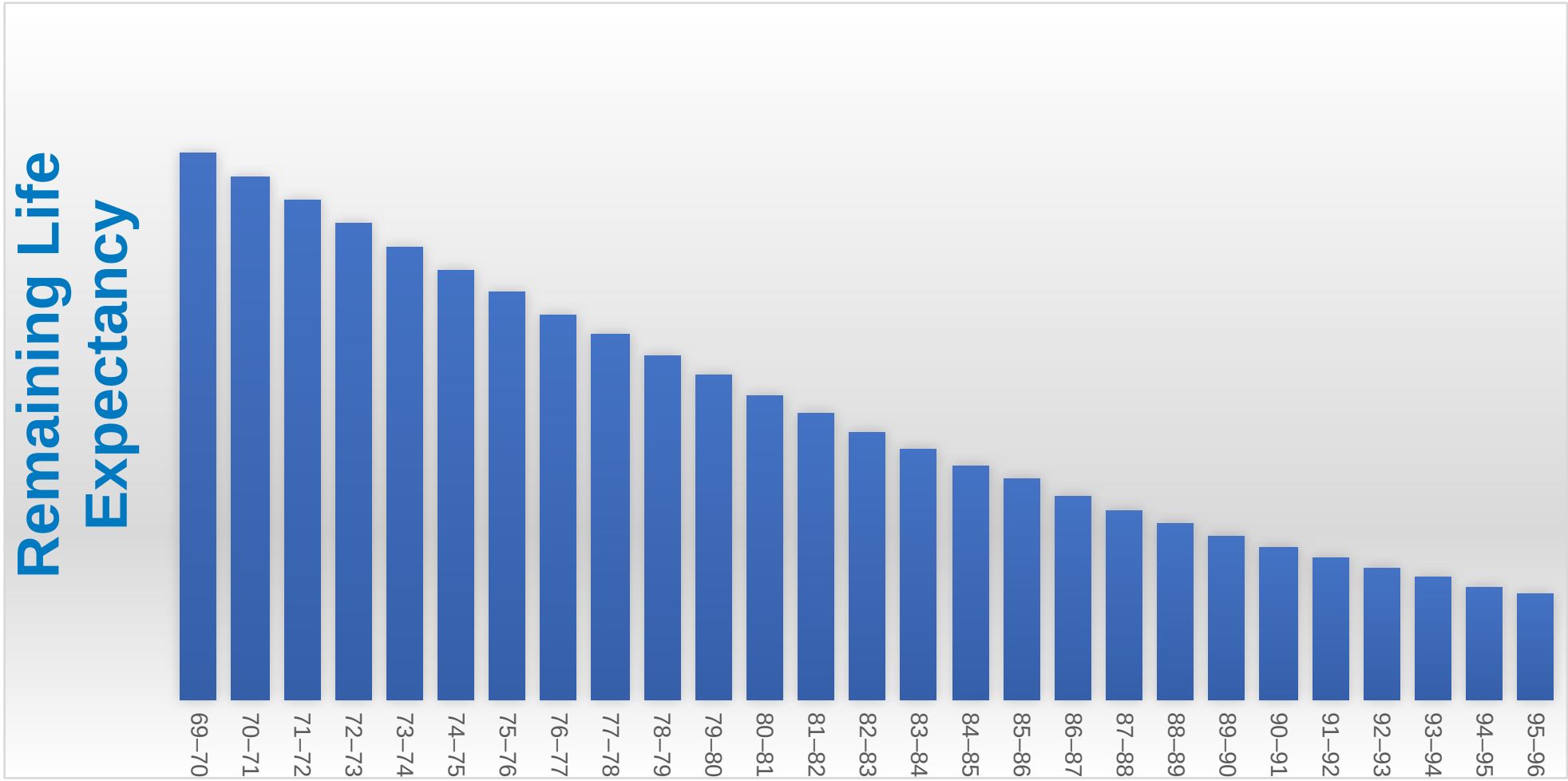
GVHD



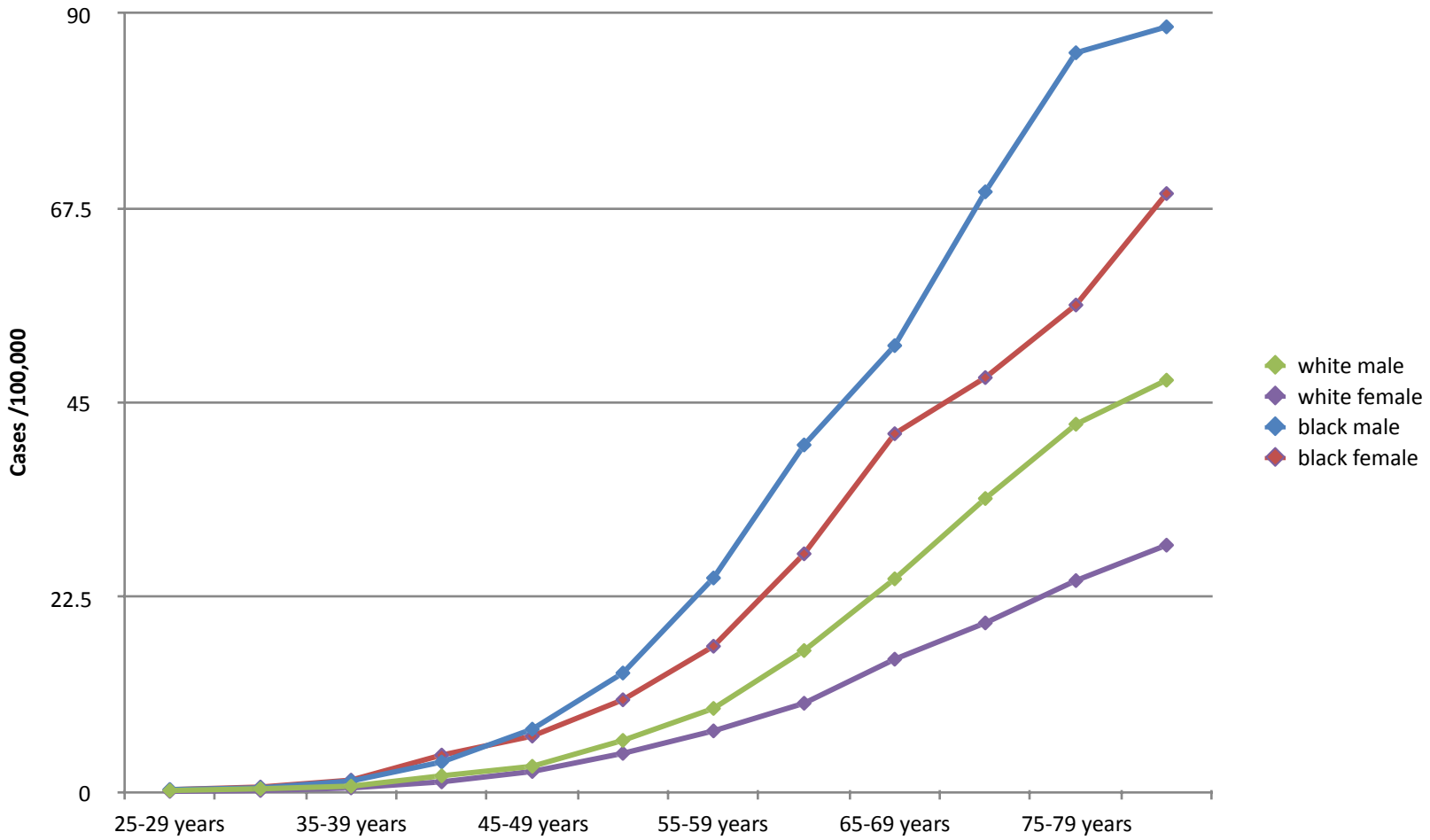
MM provides an optimal setting to understand socio-demographic disparities in transplant utilization

- Most common disease treated with transplantation
- Transplant is SOC as initial therapy
- Vast majority of transplants are autologous, therefore not limited by donor availability
- Higher incidence in Blacks
- Incidence increases with age

2013 US Census Data: Life Expectancy vs Age

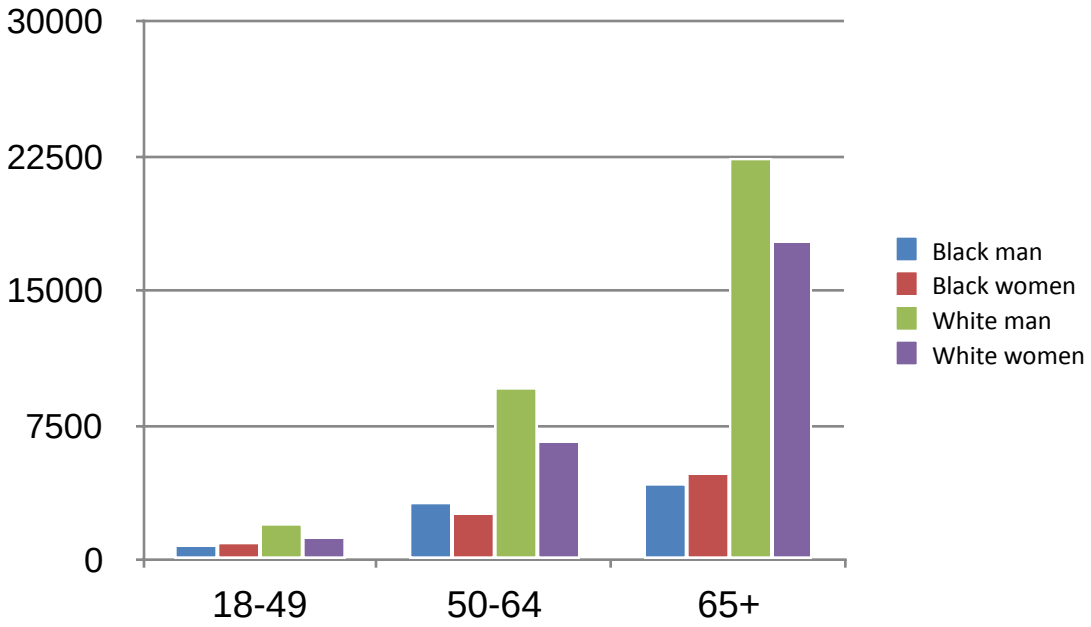


Incidence of Multiple Myeloma

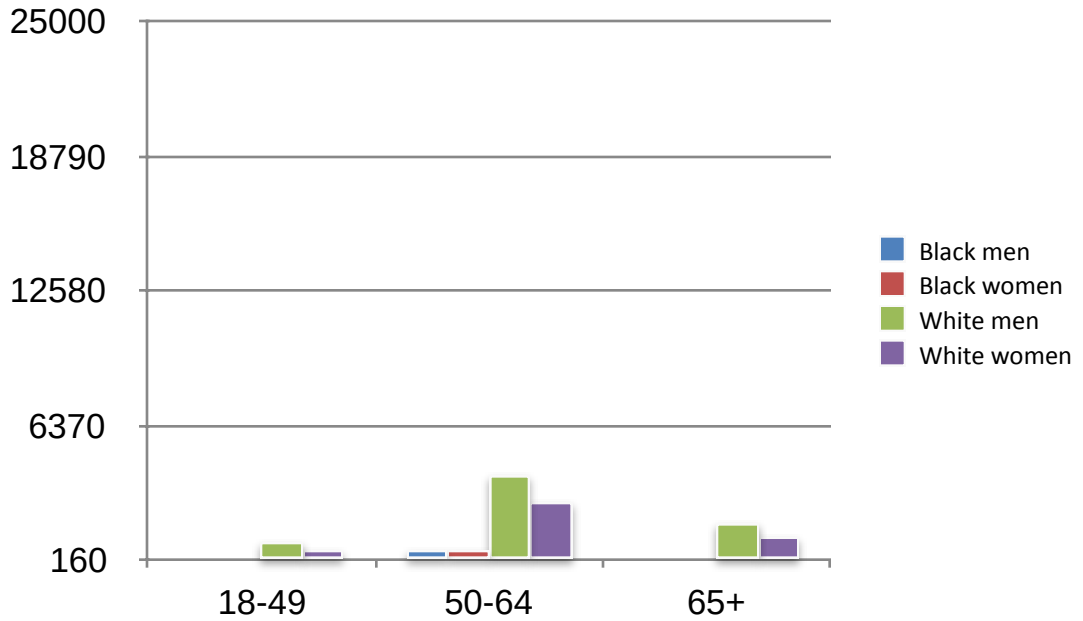


AHPCT utilization in Multiple Myeloma

Number of newly diagnosed cases



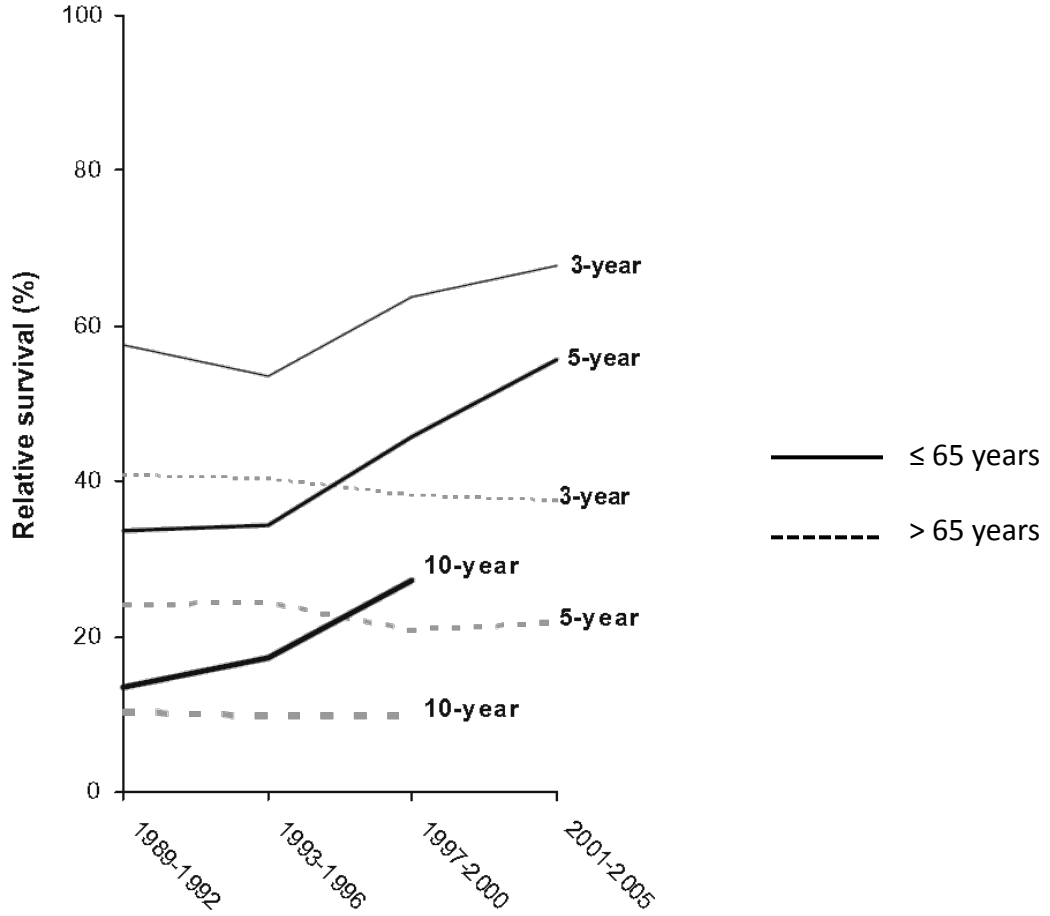
•Number of first AHPCT



Only ~ 1 in 5 MM patients undergo AHPCT

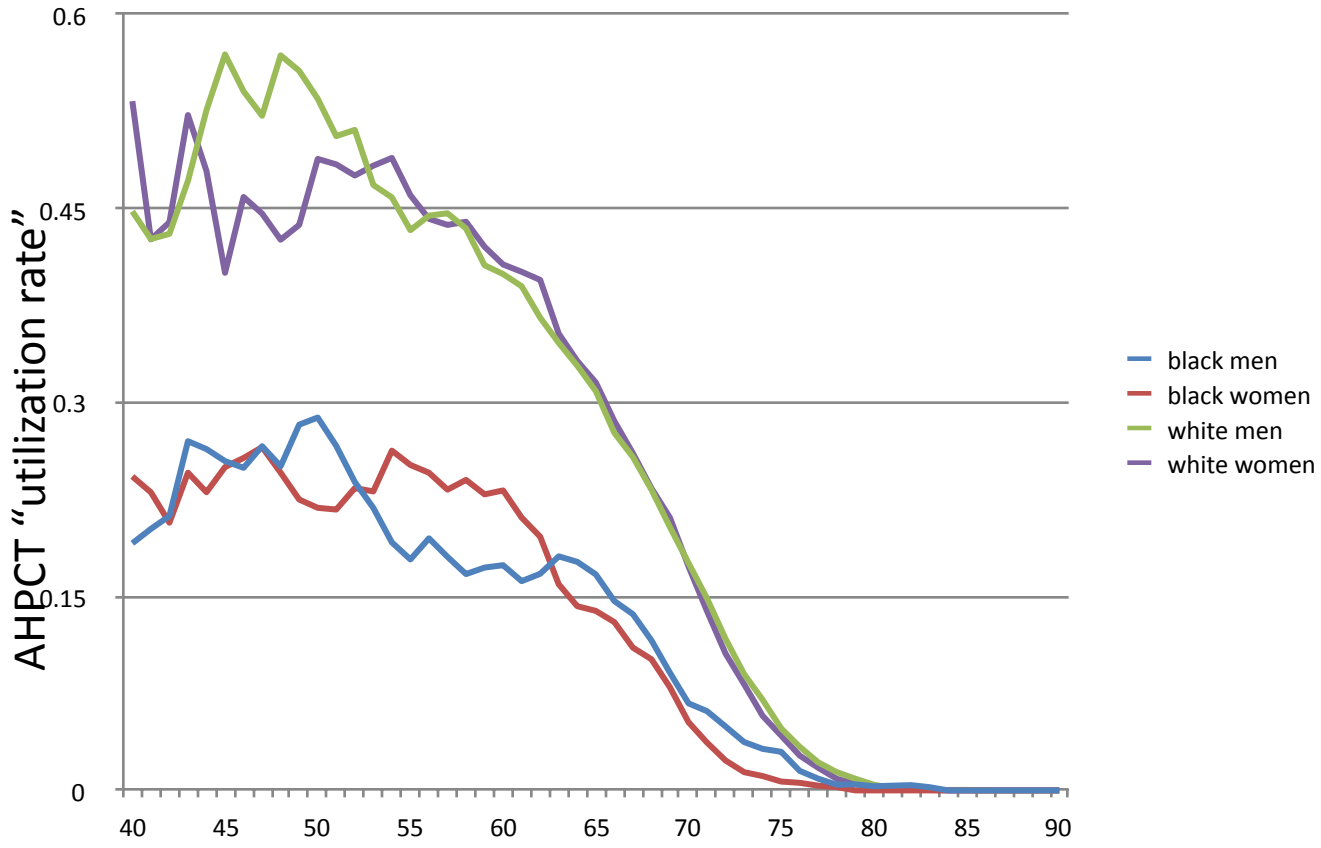
AHPCT changed MM outcome. Population-level data

Changes in MM relative survival ratio in the Netherlands



Schaapveld M, Eur J Cancer 46: 160, 2009

AHPCT utilization greatly affected by race, race and sex



Race Barriers: Auto HCT In Multiple Myeloma

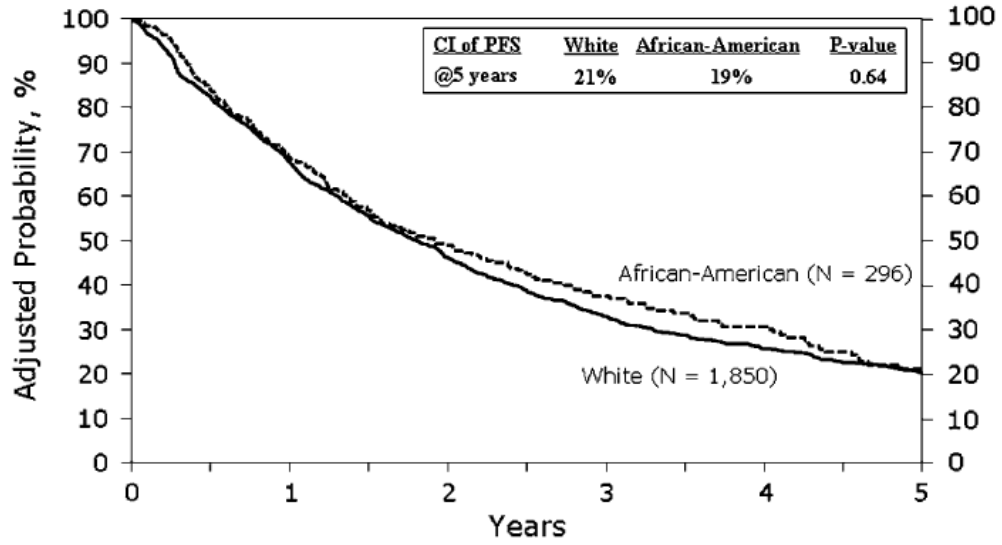
- Estimated autologous stem cell transplant utilization rates (STUR) for myeloma using CIBMTR data 2008-2014 (N=28,450) and incidence rates from SEER

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%**

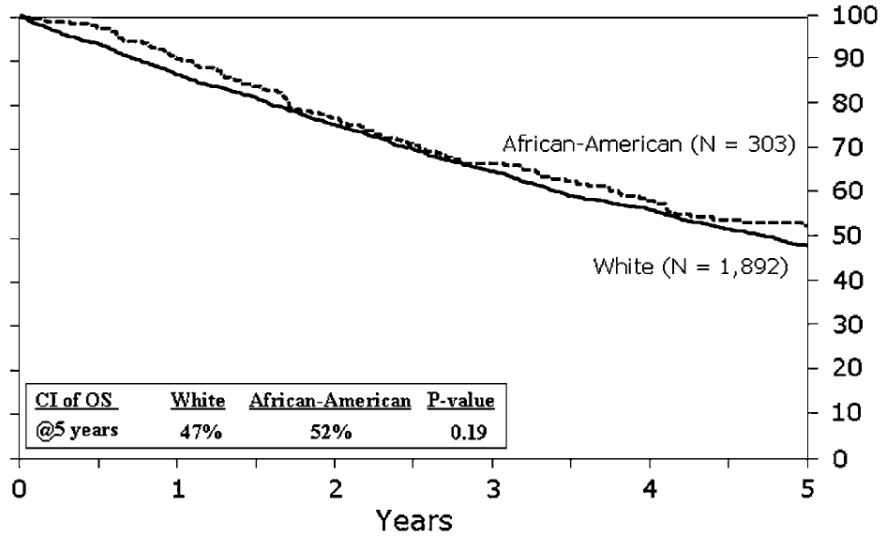
Schriber JS et al. Cancer, 2017

Similar treatment*, similar outcome

Progression-free survival



Overall survival

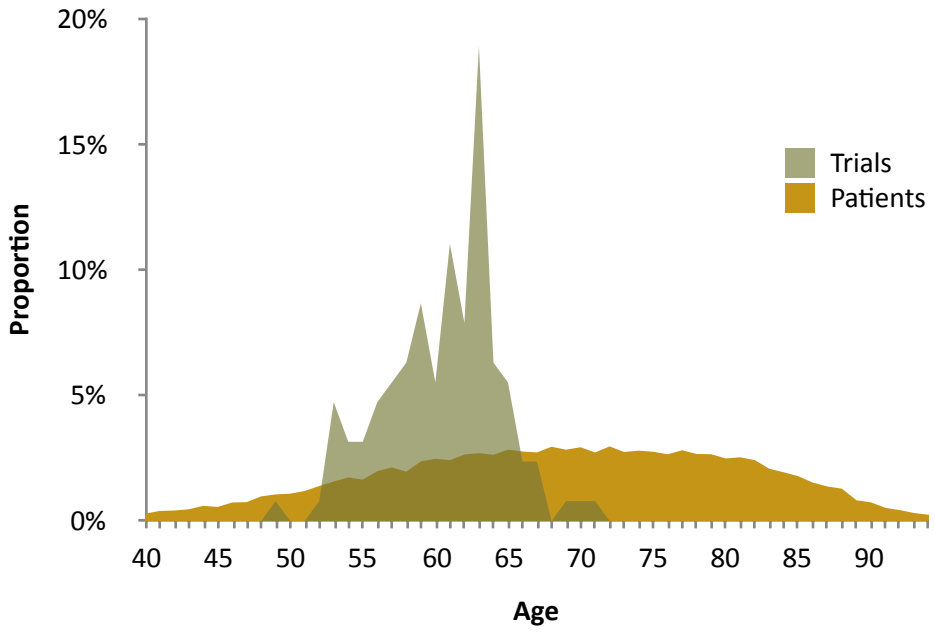


*AHPCT

Hari P Net al, Biol Blood Marrow Transplant 16: 395, 2010

HCT clinical trial populations are often selected

➢ Median of median age of subjects 61 years vs. 69 years in unselected patients.



➢ 58.4% subjects were men vs. expected 56.9% (O:E ratio 1.03, 95% C.I. 0.99-1.05)

Underutilization of HCT in Myeloma: Conclusions

•Availability of Autologous SCT impacts MM outcomes at the population level

•Autologous SCT still vastly underutilized in the US

•Underutilization more pronounced among blacks and patients older than 65 years, with no medical justification

•Reasons are unknown, likely interconnection of race, education, income, geographic distribution, physician and patient bias

Underutilization of AlloHCT: AML

- 887 adults with non-APL AML dx'd in 2007 from SEER PoC study (14 US registries)
- Cytogenetic risk not reported
- 27.5% < age 60 received alloHCT, 2.7% > age 60

Table IV. AML (non-APL), predictors of receiving allogeneic transplant, multivariate logistic regression model.

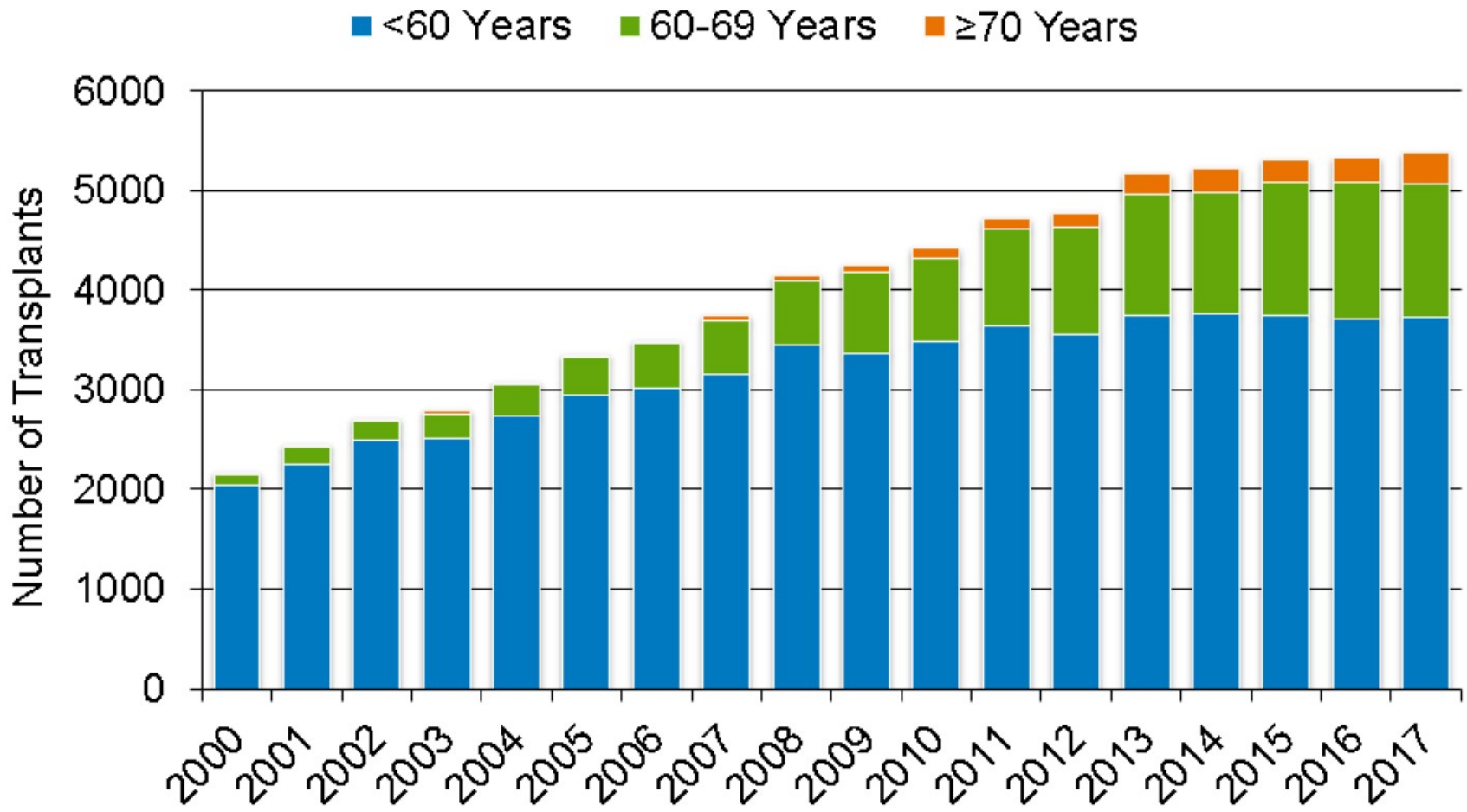
	Treated			
Predictor	No.	%*	OR	95% CI
Age				
<40	30	31.4	1.00	Referent
40–49	24	27.8	0.65	0.27–1.54
50–59	35	21.4	0.41	0.19–0.92
60+	7	1.5	0.02	0.01–0.06
Sex				
Male	43	10.1	1.00	Referent
Female	53	15.3	1.48	0.80–2.73
Race/ethnicity				
White	59	13.3	1.00	Referent
Black	10	8.3	0.47	0.19–1.18
Hispanic	11	9.4	0.38	0.16–0.92
Other	16	13.0	0.73	0.32–1.66
Median household income (quartiles)				
<$40 142	27	11.9	1.00	Referent
$40 142–$53 817	23	10.9	0.74	0.26–2.11
$53 818–$70 899	16	9.5	0.58	0.18–1.85
$70 900+	30	17.7	1.55	0.44–5.46
Marital status				
Married/living as	58	11.9	1.00	Referent
Other	38	13.2	1.55	0.79–3.01
Insurance status				
Private	82	15.4	1.00	Referent
Public/no insurance	14	5.2	0.27	0.12–0.60
Residency program				
No	17	7.0	1.00	Referent
Yes	79	16.2	2.28	1.04–4.99
Charlson comorbidity score				
0	74	14.9	1.00	Referent
1+	22	7.7	0.75	0.39–1.46

Doria-Rose et al., Leuk Lymphoma 2014

Unique challenges in older patients

- Increased rates and poorer outcomes due to complications (infections and GVHD)
- Poorer tolerance of immunosuppression (e.g., steroids)
- Greater likelihood of Comorbidities
- Caregiver challenges are more common
- May be less connected or more apprehensive about novel therapies
- Lower incomes and greater dependence on Medicare

Trends in Allogeneic HCT in the US by Recipient Age^



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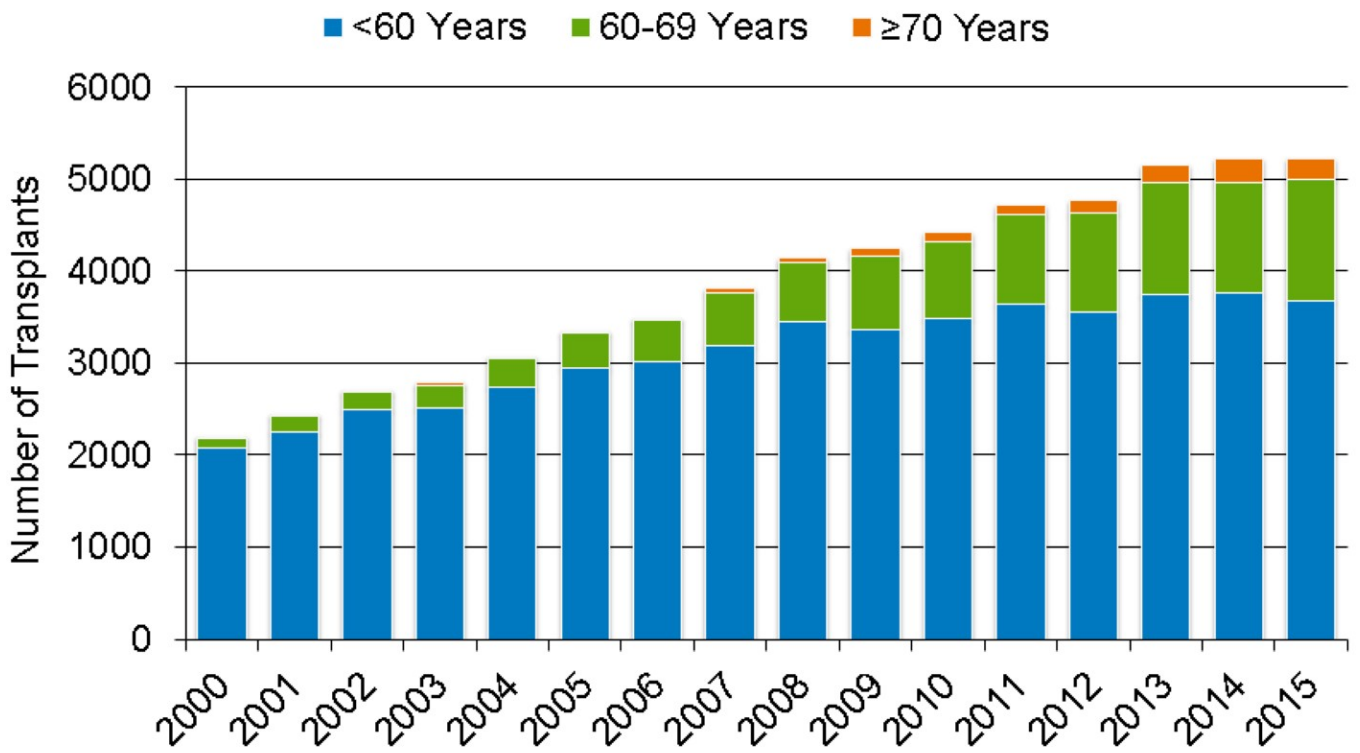
^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

Age Barriers: Allo HCT In AML



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^Transplants for AML, ALL, NHL, Hodgkin Disease, Multiple Myeloma

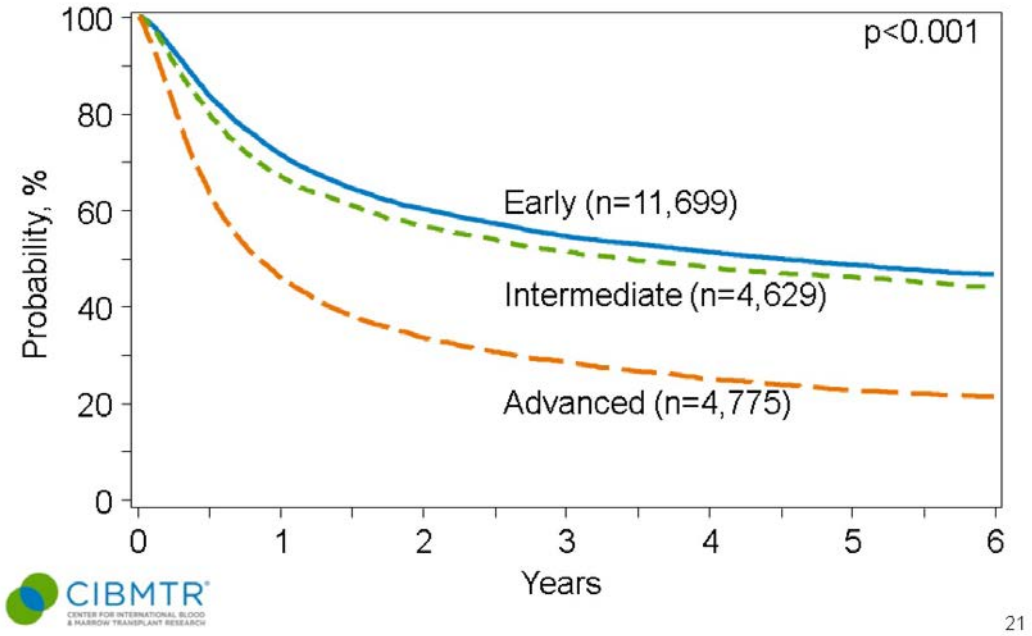
12

~3-6% patients age 60-75 years receive allogeneic HCT *

Ustun C et al. Bone Marrow Transplant, 2013
Doria- Rose VP et al. Leuk & Lymphoma, 2014

Transplantation: Timing matters

Survival after Unrelated Donor HCT for AML, 2006-2016



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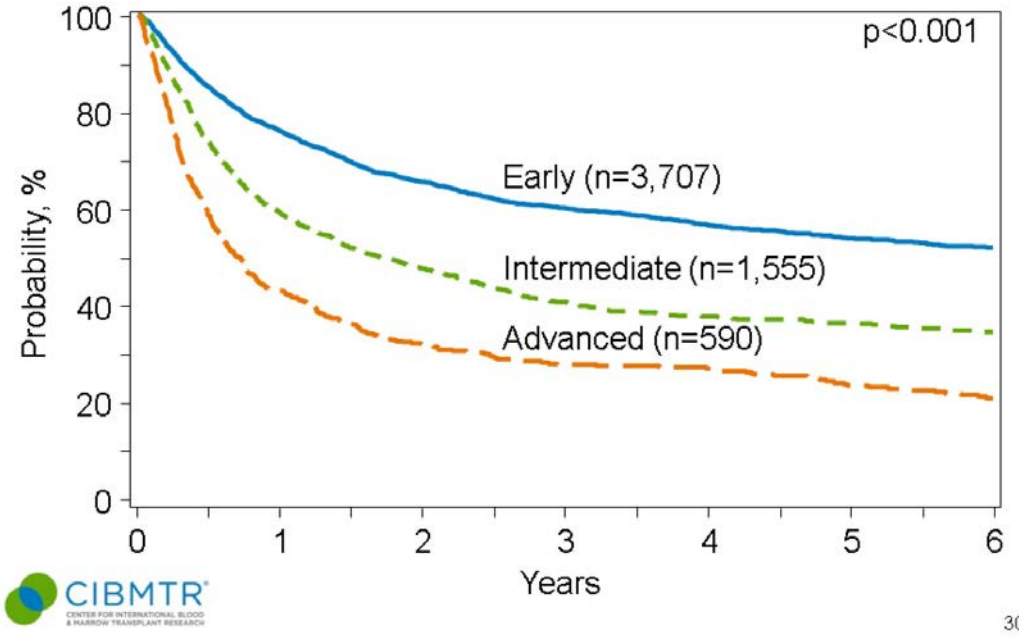
Survival after Unrelated Donor HCT for ALL, ≥18 Years, 2006-2016



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Timely Referral Affects Survival

Because disease stage at the time of transplant is the only factor under direct control of a physician, an **early referral is perhaps the single most important step that can affect survival.**

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Lee SJ, et al. Blood; 2007;110(13):4576-4583

Patient | **Oncologist** | **BMT Program**

CONSULT

- ✓ Demographics
- ✓ SES
- ✓ Coverage
- ✓ Literacy
- ✓ Cultural
- ✓ Preferences
- ✓ Other health disparity factors

- ✓ Knowledge
- ✓ Perceptions
- ✓ Experience with other patients
- ✓ Other biases that prevent referral

PATIENT SPECIFIC

- ✓ Demographics
- ✓ SES
- ✓ Coverage
- ✓ Caregivers
- ✓ Distance
- ✓ Other health disparity factors

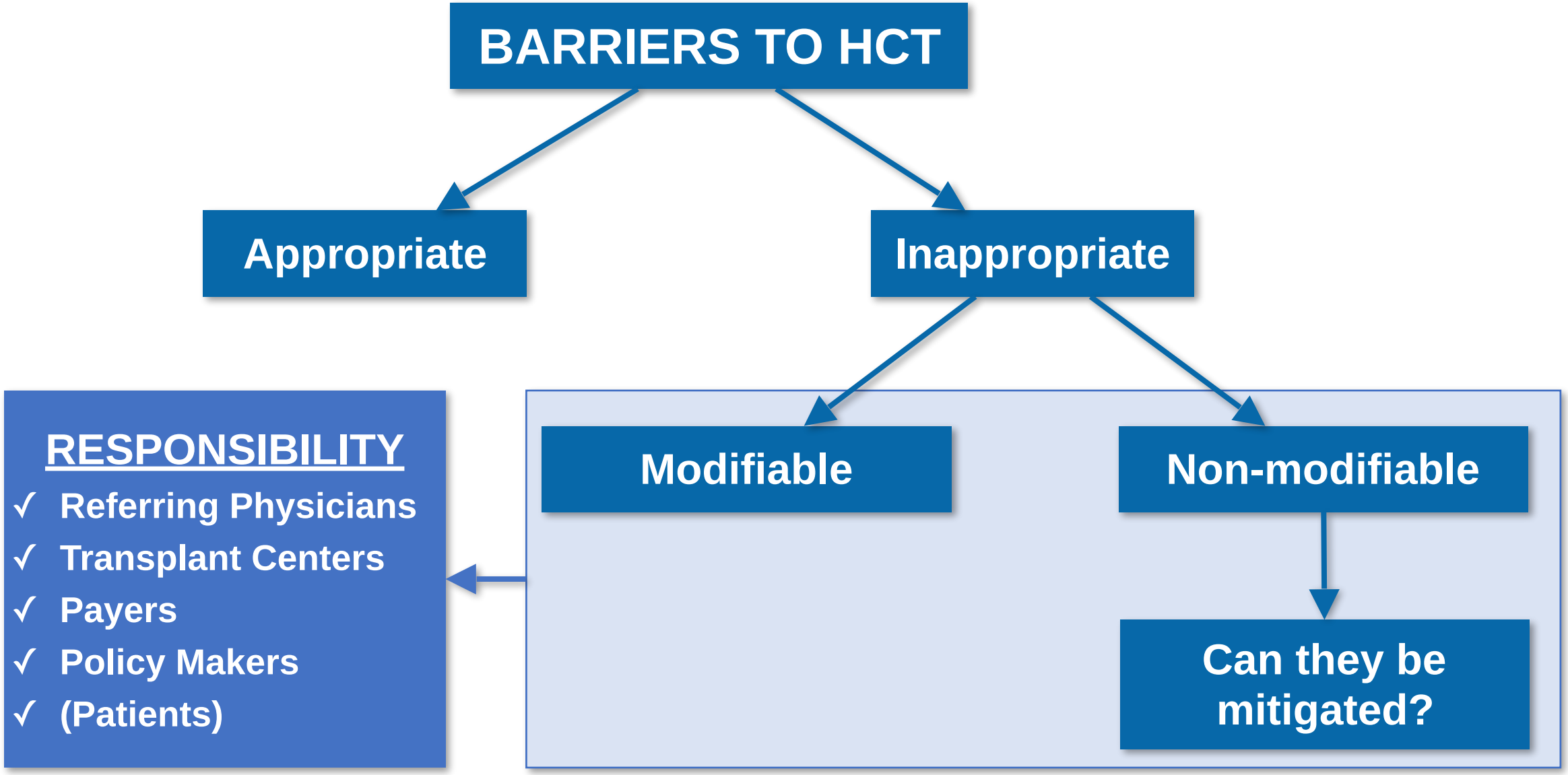
BMT SPECIFIC

- ✓ Donor
- ✓ Comorbidities
- ✓ Disease status

CENTER SPECIFIC

- ✓ Expertise
- ✓ Capacity

Slide: Navneet Majhail, Cleveland Clinic



Slide: Navneet Majhail, Cleveland Clinic

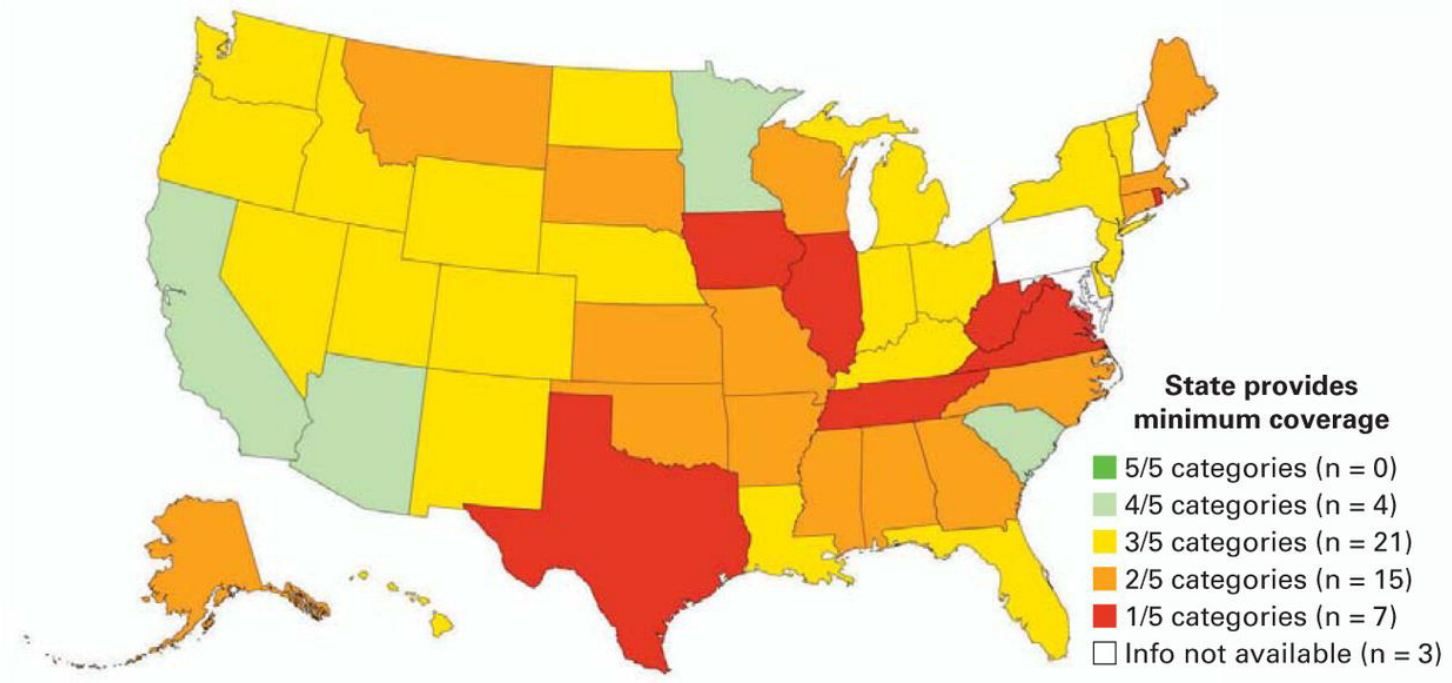
Coverage Barriers To HCT

- 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
- Lack of or inadequate coverage for any above can jeopardize access to and outcomes of HCT

Majhail NS. Biol Blood Marrow Transplant. 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

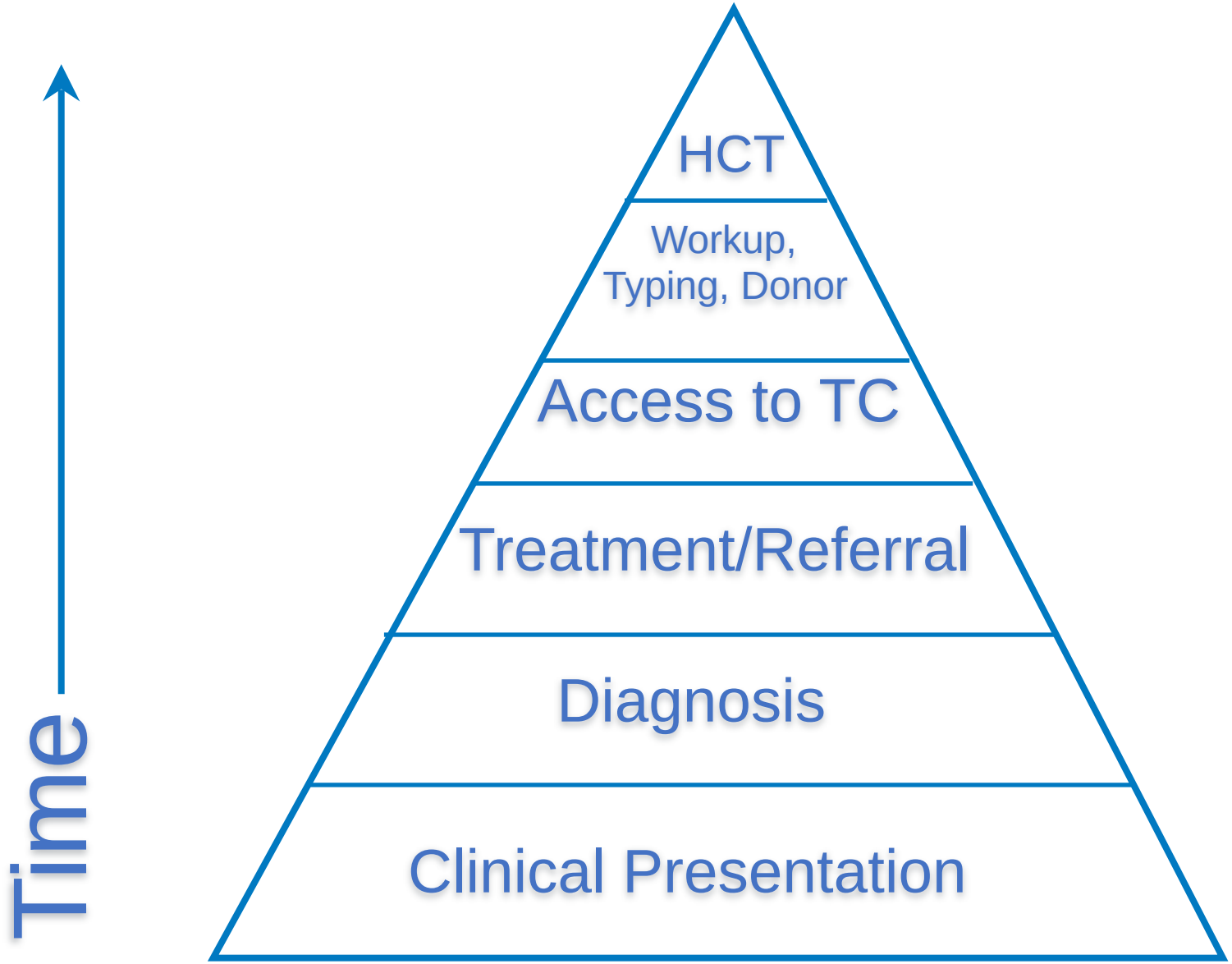
Ensure Adequate Coverage For HCT

- 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

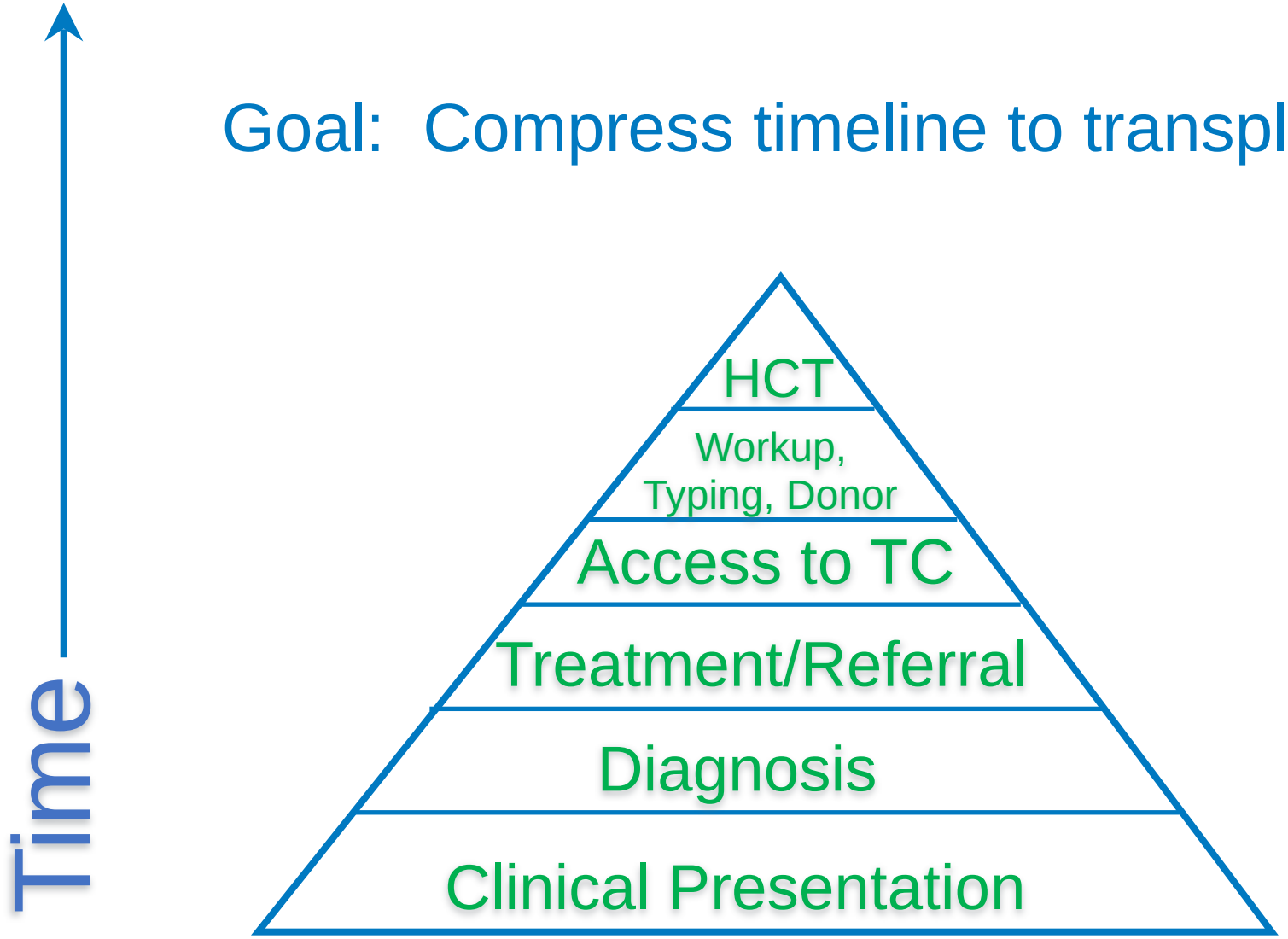
Referring Physician Barriers For Allo HCT

- Survey of hem/onc's (N=113 respondents; ~10% response rate)
- Case vignettes of accepted indications (AML, ALL, CML, MDS); odds ratio for no HCT 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"

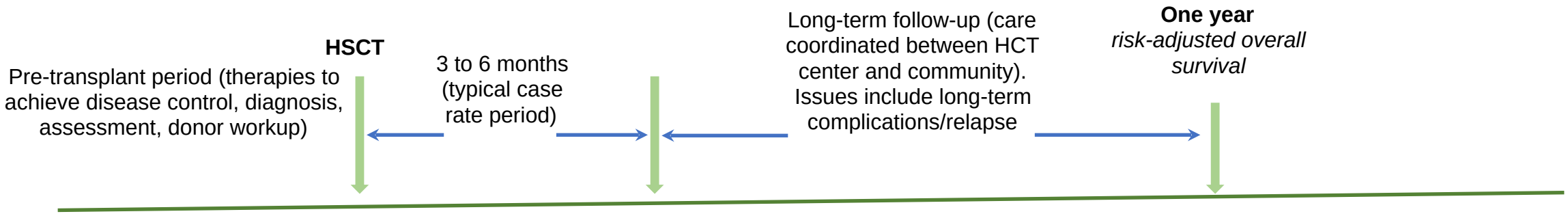
Pidala J et al. Bone Marrow Transplant. 2014


Time
HCT
Workup,
Typing, Donor
Access to TC
Treatment/Referral
Diagnosis
Clinical Presentation

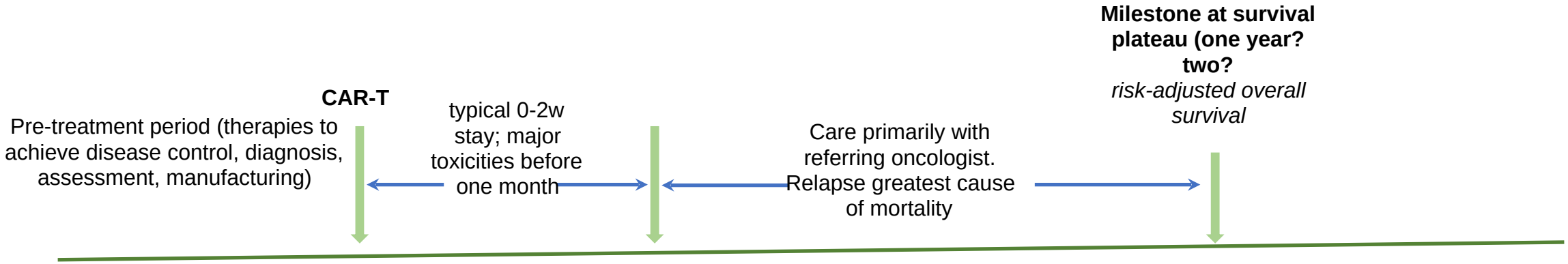
Goal: Compress timeline to transplant



Parallels between HSCT and CAR-T therapy (phases of care)



In HSCT, a critical dyad between payer and transplant center



*For T cell therapies, a **triad** is necessary (payer, transplant center, developer)*

Overall conclusions

- Stem cell transplantation has seen radical scientific and clinical changes that have dramatically improved application to older subjects with reduced morbidity and mortality
- Novel graft sources and approaches to conditioning have made transplantation available and safe for most patients under 75
- Access problems increase with age and are also associated with race and socioeconomic status
- Expanding indications include hemoglobin disorders and greater application in autoimmune disease
- Scientific improvements in risk stratification, GVHD therapies and combination of SCT with other therapies will further improve outcomes

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Acknowledgments

Source Slides:

Fred Appelbaum (Fred Hutch)

Navneet Majhail (Cleveland Clinic)

Sergio Giralt (MSKCC)

Miguel Perales (MSKCC)

Luciano Costa (UAB)

Bill Wood (UNC)

ASTCT:

Stephanie Farnia

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