Complications of HCT: Late Effects

WBMT Congress 2014

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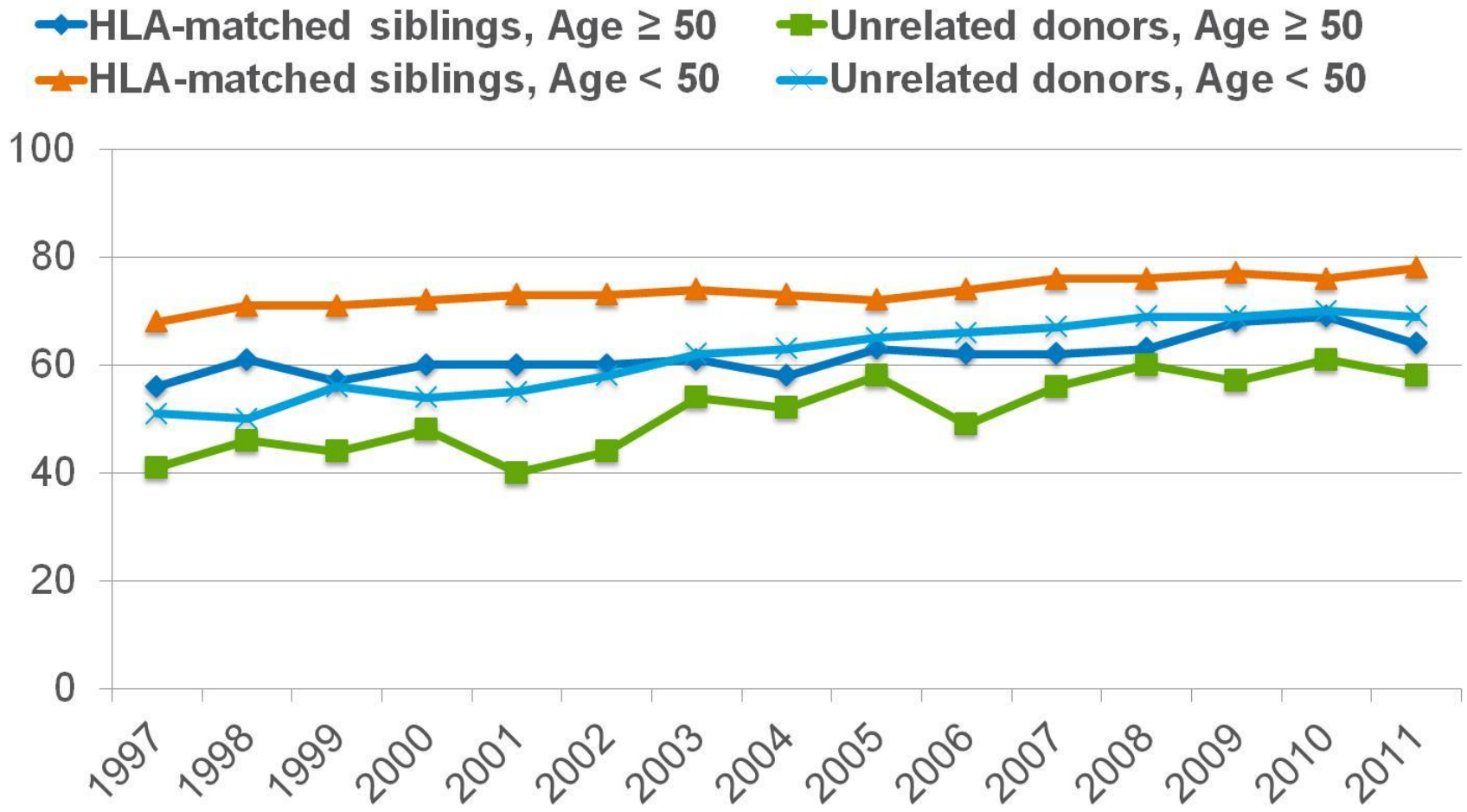
BMT Complications and Management

- Approximately 50,000 patients undergo HCT worldwide each year.
- Advances in technology and supportive care.
- Survive long term after HCT.
- Complications related to pre, peri, and post transplant exposure and risk factors.

One-year Survival by Year of Transplant, Donor and Age, Worldwide



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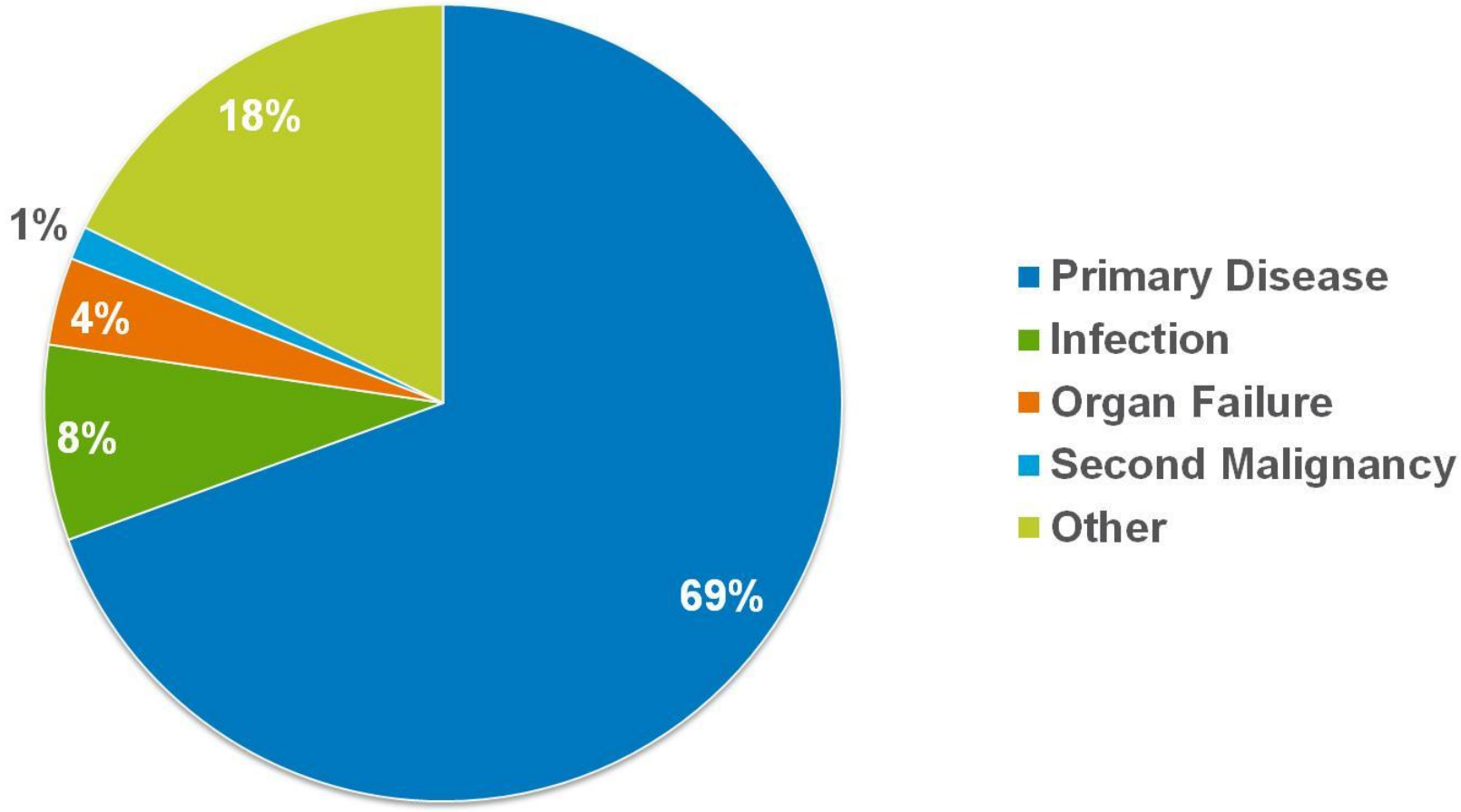
Acute Leukemia, CML or MDS early disease status.

Late Effects
Introduction

- Practice is continuously changing.
- Emerging indications for HSCT.
  - Autoimmune, sickle cell disease
- New donor sources.
  - Umbilical cord and haploidentical
- Novel therapies.
  - Post HCT maintenance. Myeloma/Leukemia
- Increasing age limit.
  - RIC and NMA
- Change in risks and constellation of complications
- **A broad facet of medical issues faced by late survivors(≥ 6 months) is presented**

Causes of Death after Autologous Transplants done in 2010-2011



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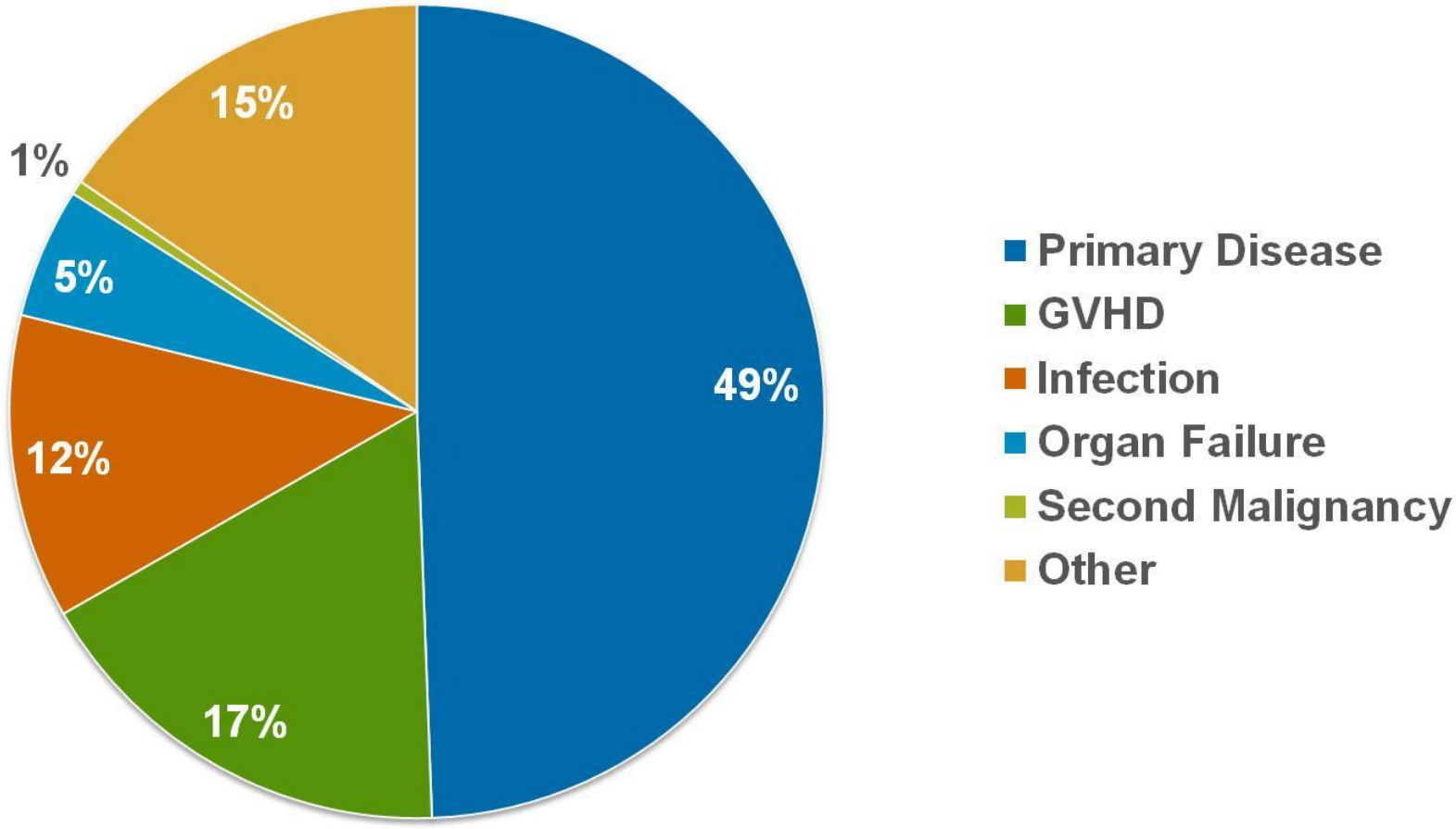
Causes of Death after HLA-identical Sibling Transplants done in 2010-2011



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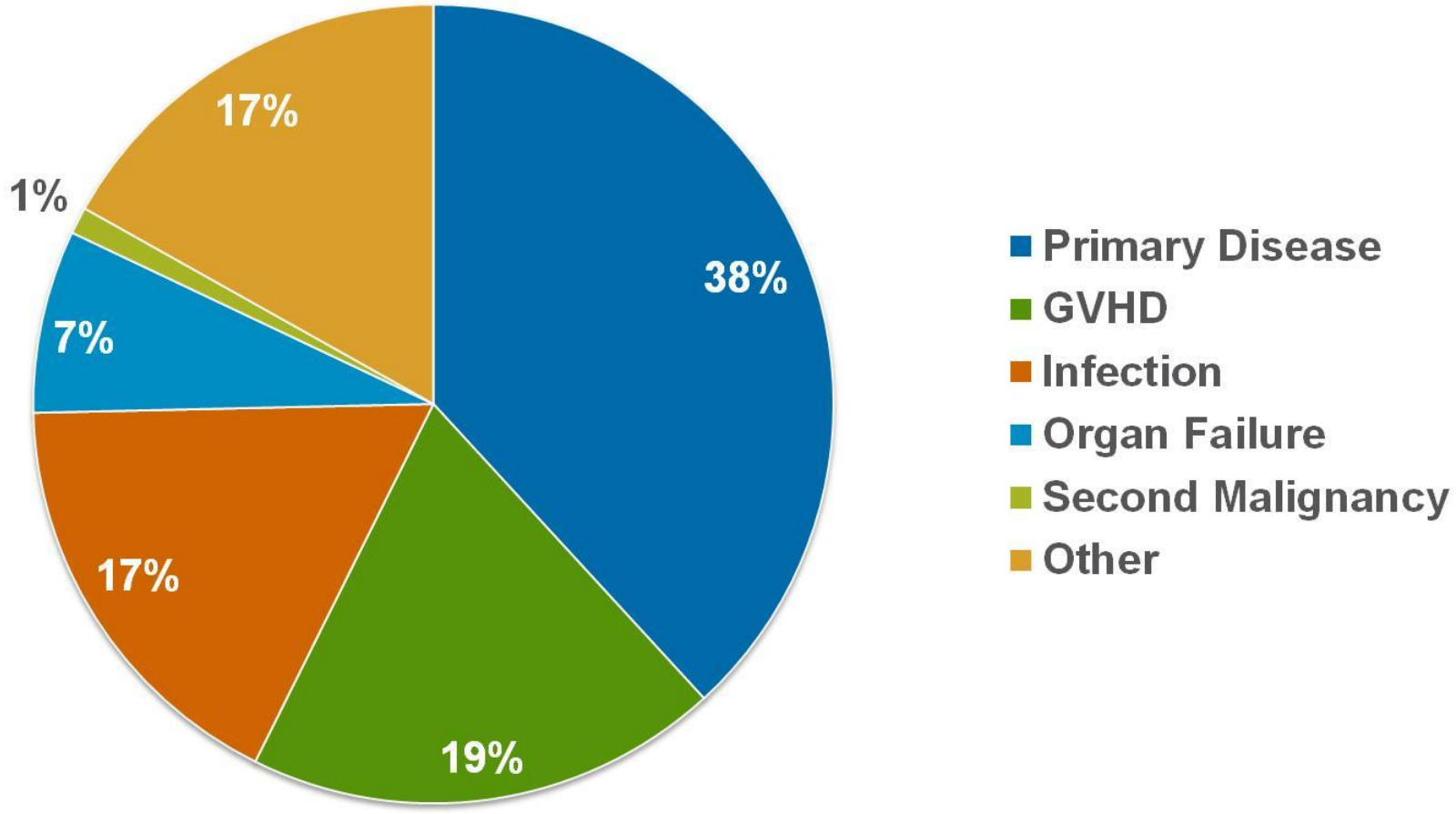
Causes of Death after Unrelated Donor Transplants done in 2010-2011



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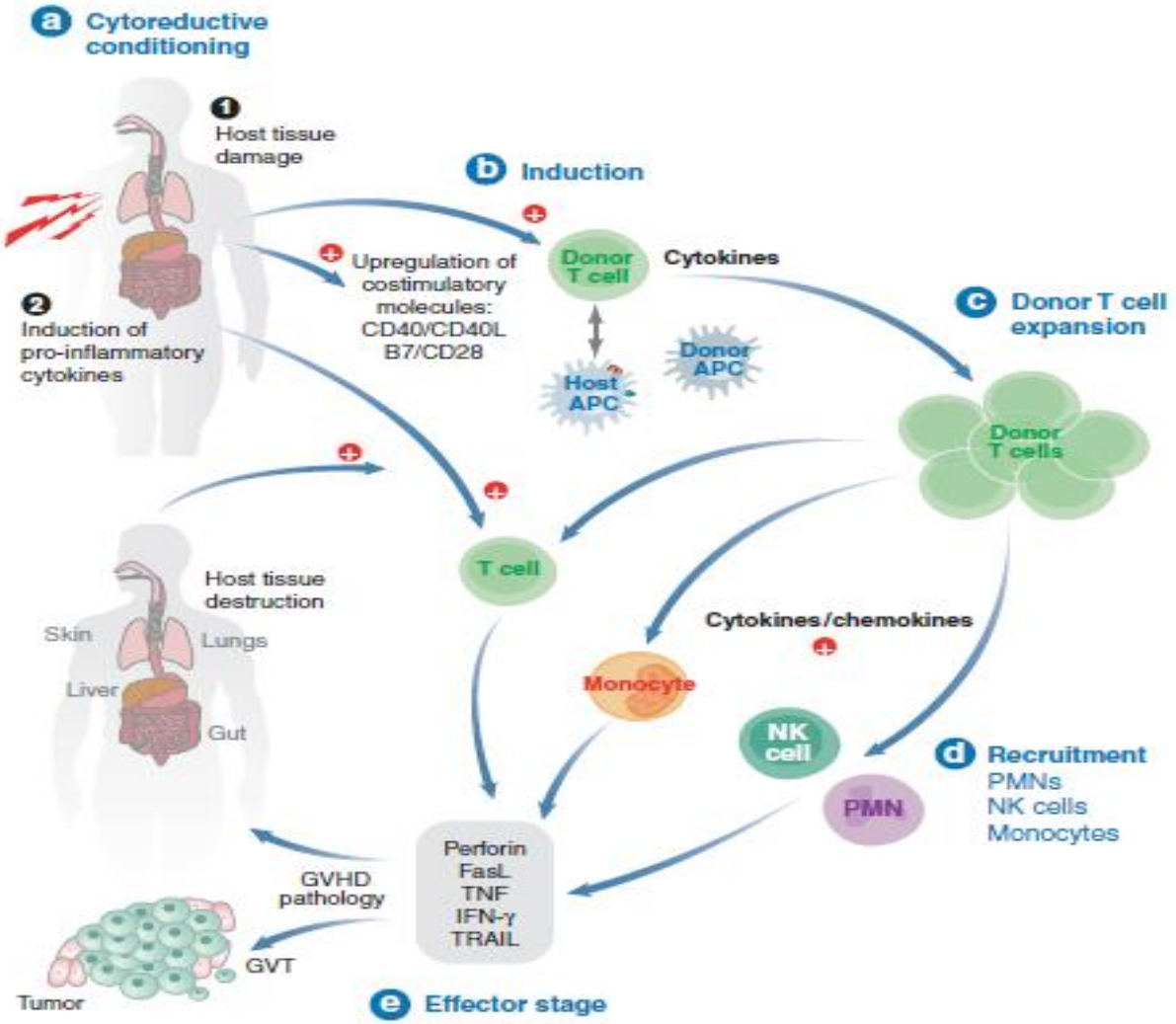

a Cytoreductive conditioning
1 Host tissue damage
2 Induction of pro-inflammatory cytokines
b Induction
Upregulation of costimulatory molecules: CD40/CD40L B7/CD28
Donor T cell
Cytokines
Donor APC
Host APC
c Donor T cell expansion
Donor T cells
T cell
Host tissue destruction
Skin
Lungs
Liver
Gut
Cytokines/chemokines
Monocyte
NK cell
PMN
d Recruitment
PMNs
NK cells
Monocytes
Perforin
FasL
TNF
IFN-γ
TRAIL
GVHD pathology
GVT
Tumor
e Effector stage

Complications/Late Effects and Management

- **Immunity and Infections**
- **Ocular Complications**
- **Oral complications**
- **Respiratory complications**
- **Cardiac and Vascular complications**
- **Liver complications**
- **Renal and genitourinary complications**
- **Complications of Muscle and Connective tissue**
- **Skeletal complications**
- **Central and Peripheral Nervous System**
- **Endocrine**
- **Muco-cutaneous**
- **Secondary cancers**
- **Psychosocial adjustment and sexual complications**
- **General screening and preventive health**

Immunity and Infections

- **Immune recovery occurs gradually(12-18mths)**
  - **Slower in allo/UCB. HLA mismatch/TCD. GVHD and prolonged IS**
- **Risk highest in 1-2 years, but may be long term.**
- **Assessment by T-Cell function**
  - **CD4 count, CD4/CD8 ratio may guide for prophylaxis**
- **Chronic GVHD:**
  - **Opsonization is impaired.**
- **Late infections:**
  - **Aspergillus of the lungs.**
  - **Late CMV with increasing pro/preemptive therapy**
  - **VZV frequently in the first year**
  - **PCP generally during first 6 months, longer in cGVHD.**
  - **Certain geographic areas. e.g., TB, malaria**

BBMT 2009:15:1143

Immunity and Infections: Recommendations

- **CGVHD:**
  - Antibiotic prophylaxis for encapsulated organism as long as IS therapy administered.
  - Antiviral and antifungal prophylaxis.
  - CMV screening based on risk factors.
- **Prophylaxis for oral procedures:**

  AHA guideline for endocarditis
- **PCP prophylaxis:**
  - Allo/Auto HCT: Prophylaxis 6 months. Longer if steroids in use or CGVHD with IS
- **Immunization with inactivated vaccines starting 6-12 months**

BBMT 2009:15:1143

Vaccine	Recommended for use after HCT	Time post-HCT to initiate vaccine	No. of doses [a]
Pneumococcal conjugate (PCV)	Yes	3-6 months	3-4 [b]
Tetanus, diphtheria, acellular pertussis [c]	Yes	6-12 months	3 [d]
Haemophilus influenzae conjugate	Yes	6-12 months	3
Meningococcal conjugate	Follow country recommendations for general population	6-12 months	1
Inactivated polio	Yes	6-12 months	3
Recombinant hepatitis B	Follow country recommendations for general population	6-12 months	3
Inactivated influenza	Yearly	4-6 months	1-2 [e]
Measles-mumps-rubella (live) [f,g]	Measles: All children and seronegative adults	24 months	1-2 [h]

BBMT/BMT/HOSCT; 3/2012

Ocular complications

1) Anterior segment.

Kerato-conjunctivitis sicca syndrome

Ocular sicca syndrome: also with xerostomia, vaginitis, skin dryness associated with chronic GVHD.

40-60% of pts with CGVHD

Cataracts

TBI exposure. At 10 years 40-70%. Older age. Steroids: 45% at 10 years. Allo HCT(risk higher than ASCT)

2) Posterior segment.

- **Ischemic micro vascular retinopathy, appears to be related to radiation exposure +/- CSA(lesions resolve on withdrawal of IS Rx)**
- **Infectious retinitis/edema/hemorrhage**

Ocular complications: Recommendations

- Routine clinical evaluation: 6 months, 1 year, then yearly.
- Ophthalmology referral, sooner with CGVHD. Frequency may depend on symptoms and presence or absence of CGVHD.
- Visual symptoms require ocular exam urgently.

Oral Complications

- **Common after HCT**
- **Risk factors:**
  - **Oral chronic GVHD**
  - **Radiation use and dose to head and neck region**
  - **Fanconi's anemia**
  - **Age**
- **Long term sequelae may continue despite resolution of GVHD**
  - **Peri-oral fasciitis or skin sclerosis. Xerostomia.**
  - **Decrease in saliva: infection/dental decay.**
  - **Oral cancers (fanconi, cGVHD are at higher risk)**
- **Young age and TBI use may lead to mandible and teeth development problems.**

Blood 2005;105
Blood 2009;113
Blood 2011;117

Oral Complications: Recommendations

- Effective cGVHD management.
- Education.
  - Avoid smoking, decrease sugar containing beverages
  - Clinical oral exam: 6mth, 1 yr and yearly.
  - High risk(cGVHD, Fanconi): every 6 month evaluation
- Dental/Oral Medicine evaluation especially for children for tooth development.

Respiratory Complications

- **Allo HCT higher risk then Auto**
- **Idiopathic pneumonia syndrome**
  - Commonly early
  - Factors: allo HCT, TBI and GVHD. Chemo may enhance TBI effects or direct damage(BCNU/BU)
- **Bronchiolitis obliterans syndrome(BOS)**
  - 2-14%. Pulmonary GVHD? Obstructive lung disease
  - PFT's: FEV1/FVC ratio< 0.7, FEV1< 75%
  - Chest CT with air trapping/Bronchiactasis
  - Absence of infection in the respiratory tract
- **Cryptogenic organizing pneumonia(COP)/BOOP**
  - Typically in 6-12 mths. Restrictive pattern. Treatment with steroids
- **Sino-pulmonary infections**.
  - Usually with delayed immune recovery.

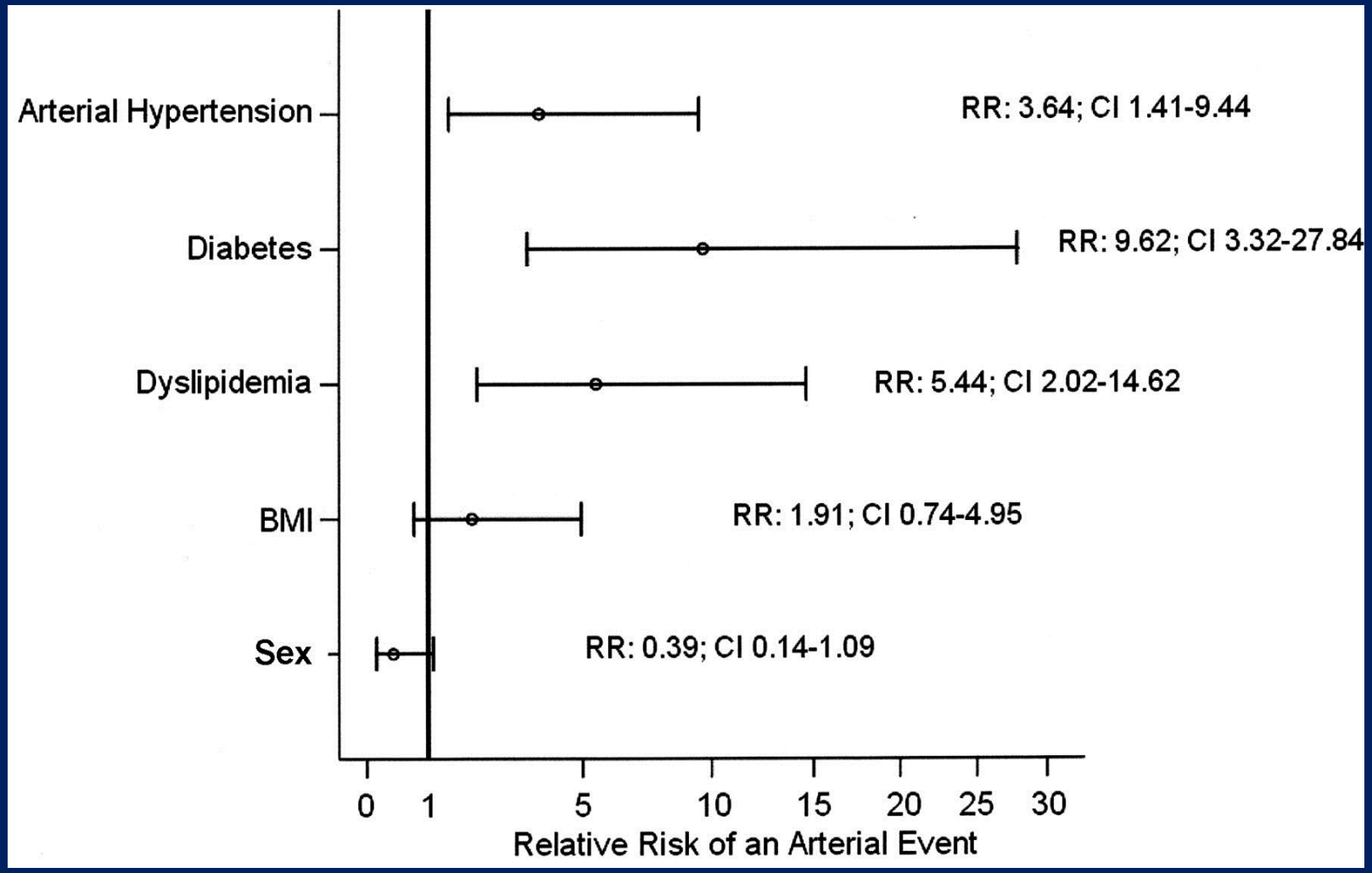
Respiratory Complications: Recommendations

- Effective treatment of GVHD and infectious complications likely to reduce COP/BOS
- Adequate steroid treatment for patient with COP
- Routine clinical assessment: 6 month, 1yr, then yearly
- Earlier and more frequent assessments in patients with CGVHD
- Counseling for smoking and passive smoking
- Pts with Symptoms and signs require focused radiological assessment and PFT’s

Cardiac and Vascular Complications

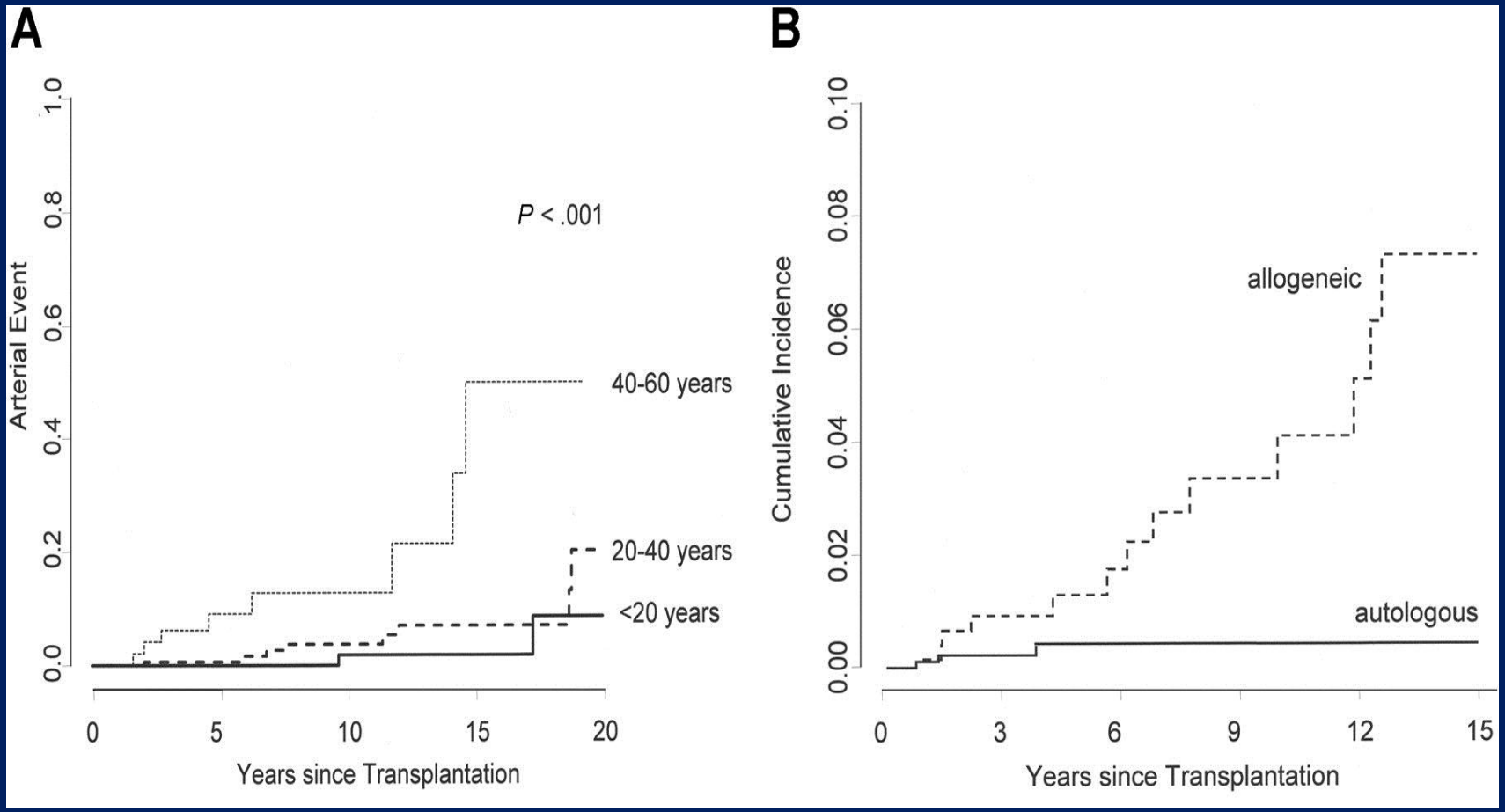
- Clinically evident complications are rare. Possibly underestimated.
- Cardiac toxic death: Auto 2%. Allo 3%
- **Factors involved**:
  - Cumulative anthracyclines
  - Chest radiation
  - Pre HCT cardiac function
  - Iron overload in non-malignant diseases.
  - Advancing age
  - Established CV risk factors
  - Conditioning regimens

Univariate analysis of risk factors for a cardiovascular event.



Tichelli A et al. Blood 2007;110:3463-3471

Cumulative incidence of an arterial event stratified by age of the patients at time of HSCT. (A) The cumulative incidence at 20 years is 8.7% for patients younger than 20 years, 20.2% for patients between 20 and 40 years, and 50.1% for patients between 40 and 60.



Tichelli A et al. Blood 2007;110:3463-3471

CV complications: Recommendations

- Proper pre HCT selection of patients and assessment of expected cardiac toxicity.
- Routine clinical assessment at 1 year then yearly.
- More frequent evaluations in pts with risk factors.
- Education on “healthy life style”
- Treatment of cardiac risk factors.

Liver Complications/Late Effects

- **Chronic GVHD** is the major cause.
  - Exclude other causes.
  - Liver biopsy if Liver dysfunction is the only manifestation of GVHD and systemic IS therapy is required.
  - Ursodeoxycholic acid may be used as adjunct
  - Liver transplant has been performed in rare cases of liver failure. *(liver transpl;2005;11)*
- Liver complications commonly related also to, medications, hepatitis B or C, Iron overload.
- PCR testing for Hep B and C. Antiviral therapy
- Iron chelation and or phlebotomy as required.

Renal and Genitourinary Complications/Late Effects

- Exposures during pre-, peri- and post HCT
- Incidence of CKD 5-65%. Apparent after 6-12 months
  - TMA, glomerulonephritis, nephrotic syndrome
  - TBI may cause radiation nephritis
  - Majority are idiopathic
- **Risk Factors:**
  - Older age, diagnosis(e.g. myeloma), baseline renal function, AGVHD, cGVHD, calcineurin inhibitors.
  - Infections, drugs, TBI
  - Post HCT H. cystitis.
  - cGVHD vulva/vagina: recurrent UTI's

Renal and Genitourinary Complications: Recommendations

- Identifying hi risk patients and early as well frequent assessment.
- Modifications in drugs and treatment of conditions causing kidney injury
- HTN screening and treatment
- Consideration of changing IS from CSA to non- nephrotoxic IS
- Renal function assessment to include urinary protein
- Workup including US or Bx in CKD or late onset renal dysfunction
- Routine assessment every 6-12 months on long term survivors

Muscle and Connective Tissue

- Steroid induced myopathy
- Fasciitis/scleroderma
- Polymyositis
- Up to 35% of pts at 10 yrs with Musculo-skeletal symptoms
  - ***JCO 2005;23:6596***
- Long term sequelae of cGVHD
  - Myositis/ Polymyositis, skin sclerosis
  - Fibrosis, joint contractures
  - Requires prolonged and aggressive IS

Skeletal Complications/Late Effects

- Bone density loss a well recognized complication
  - Osteoporosis 25%, Osteopenia 50%, AVN 4-19%
  - Rapid loss within 6-12 months
  - Elderly, women, BMI <20-25, inactivity, steroid use(≥5mg/d for >3 months)
- Other possible factors
  - Hypogonadism, sec. hyperparathyroidism, toxicity from conditioning.

Skeletal Complications: Management and Recommendations

- Dual photon densitometry at 1 year for all adult women, all allo-HCT recipients and high risk patients.
- Treatment and preventive choices:
  - Activity, vitamin D and calcium supp, bisphosphonates
  - Hormone replacement therapy
  - Screening for AVN is not recommended

HCT Late Effects and Management

- **Central and Peripheral Nervous System**
  - **Drug related, infections and metabolic encephalopathy.**
  - **Exposure to TBI and intrathecal chemo at higher risk.**
  - **Cognitive function decline may be subclinical.**
  - **Assessment at 1 year for all and frequent for higher risk.**
- **Endocrine complication**
  - **Subclinical hypothyroid in 7-15% in 1st year**
  - **Gonadal dysfunction(92%males, 99% females)**
  - **Growth in children should be monitored**
  - **Yearly evaluation and management as required**

Mucocutaneous Late Effects and Management

- **CGVHD patients with skin involvement approx. 70%**
  - **Lichen planus-like**
  - **Sclerosis, alopecia, thinning of scalp hair, nail dystrophy, skin depigmentation, sweat impairment, genital GVHD**
  - **Secondary cancers of the skin**
- **Clinical screening and preventive measures**

Late Effects of Secondary Cancers and Management

- **Secondary Cancers**
  - **2 to 3 fold increase of developing solid tumors**
  - **Nearly all cancer types**
- **Risk factors**:
  - **Radiation therapy(sarcoma, breast, thyroid)**
  - **Chronic GVHD(SCC)**
  - **Length and intensity of IS**
  - **Children with cranial radiation: Brain tumors**
  - **Fanconi's anemia: oro-pharyngeal cancers**
  - **Auto HCT: risk of sec leukemia/MDS**
  - **Post transplant lymphoproliferative disorders**
- **Earlier screening program**
- **Avoidance of exposure to UV rays, tobacco.**

HCT Late Effects and Management

- **Psychosocial Adjustment and Sexual Complications**
  - Routine evaluations at 6 monthly period
  - Fertility issues
- **General screening and preventive health**
  - Recommended screening for all patients
  - Sex specific recommendations
    - Prostate for males
    - Breast ca, Cervical ca, osteoporosis for females
  - Healthy lifestyle recommendations for all patients

Late Effects and Management Conclusions

- Late Effects Management Guidelines Implementation
  - Applicable to all patients.
  - Resource availability issues
    - Specialists
    - Procedures
    - Healthcare access
- Comprehensive evaluation and follow-up
  - Individual exposures and risk factors

Late Effects and Management Conclusions

- HCT patients require comprehensive evaluation, management and long term FU
- Survivorship care plan
  - Appropriate surveillance
  - Late effects
  - Relapse
  - Care outside HCT centers.
  - Close communication with primary care providers
- Multidisciplinary approach
- Late Effects clinics in Transplant centers?

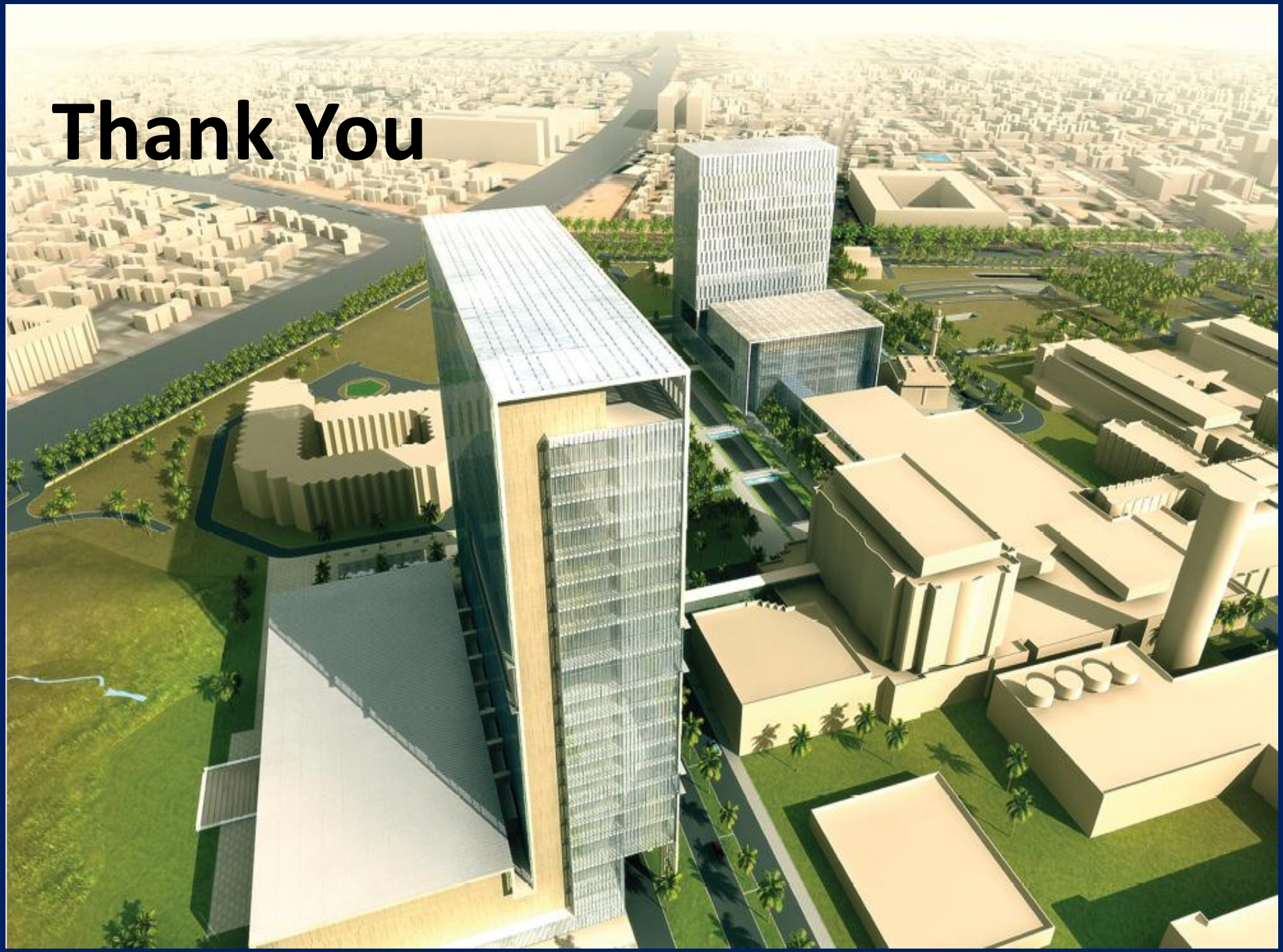
Recommended Screening and Preventive Practices for Long-term Survivors after Hematopoietic Cell Transplantation

Navneet S Majhail[1,2], J Douglas Rizzo [3], Stephanie J Lee[4], Mahmoud Aljurf[5], Yoshiko Atsuta[6], Carmem Bonfim[7], Linda J Burns[8], Naeem Chaudhri[5], Stella Davies[9], Shinichiro Okamoto[10], Adriana Seber[11], Gerard Socie[12], Jeff Szer[13], Maria Teresa Van Lint[14], John R Wingard[15], Andre Tichelli[16]

CIBMTR, ASBMT, EBMT, APBMT, BMTSANZ, EMBMT, SBTMO collaborative work.

Biology Blood Marrow transplant 18:348, 2012
Bras Hematol Hemoter. 2012;34(2):109-33.
Hematology Oncology Stem Cell Therapy, V1,Q1 2012.
Bone Marrow Transplant. 2012 Mar;47(3):337-41.

Thank You



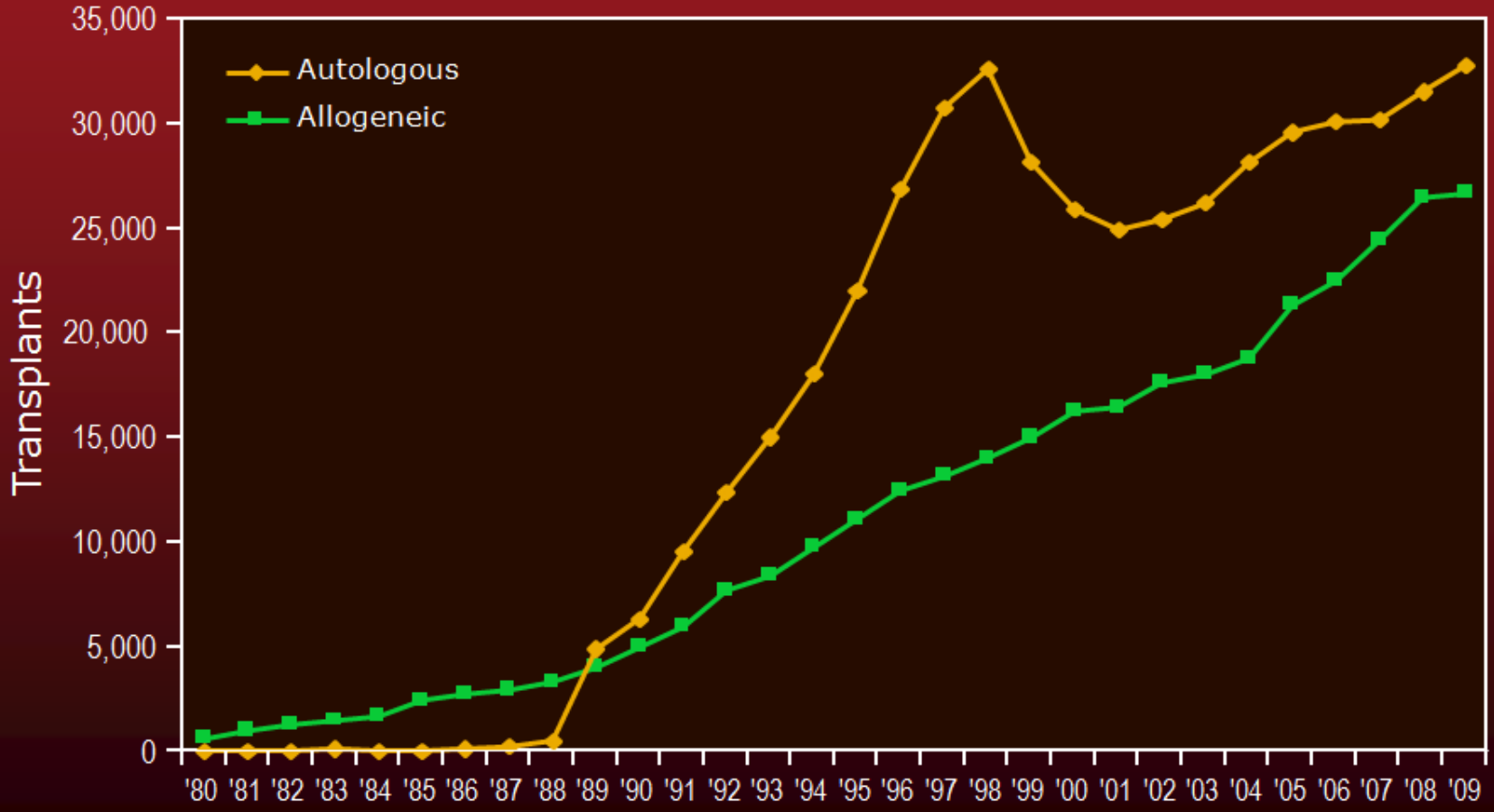
Thank You

Global Activity Survey 2006

Region	Allogeneic 1st Tx.	Autologous 1st Tx.	Total
Australia/NZ	319 (28%)	818	1137
Brazil	800 (53%)	703	1503
Canada	416 (46%)	498	914
EMRO	682 (67%)	330	1012
Europe	9661 (39%)	15389	25050
Japan	1946 (66%)	1008	2954
US	4840 (44%)	6164	11004
Total	18664 (43%)	24910	43574

Preliminary data

Transplant activity worldwide 1980-2009



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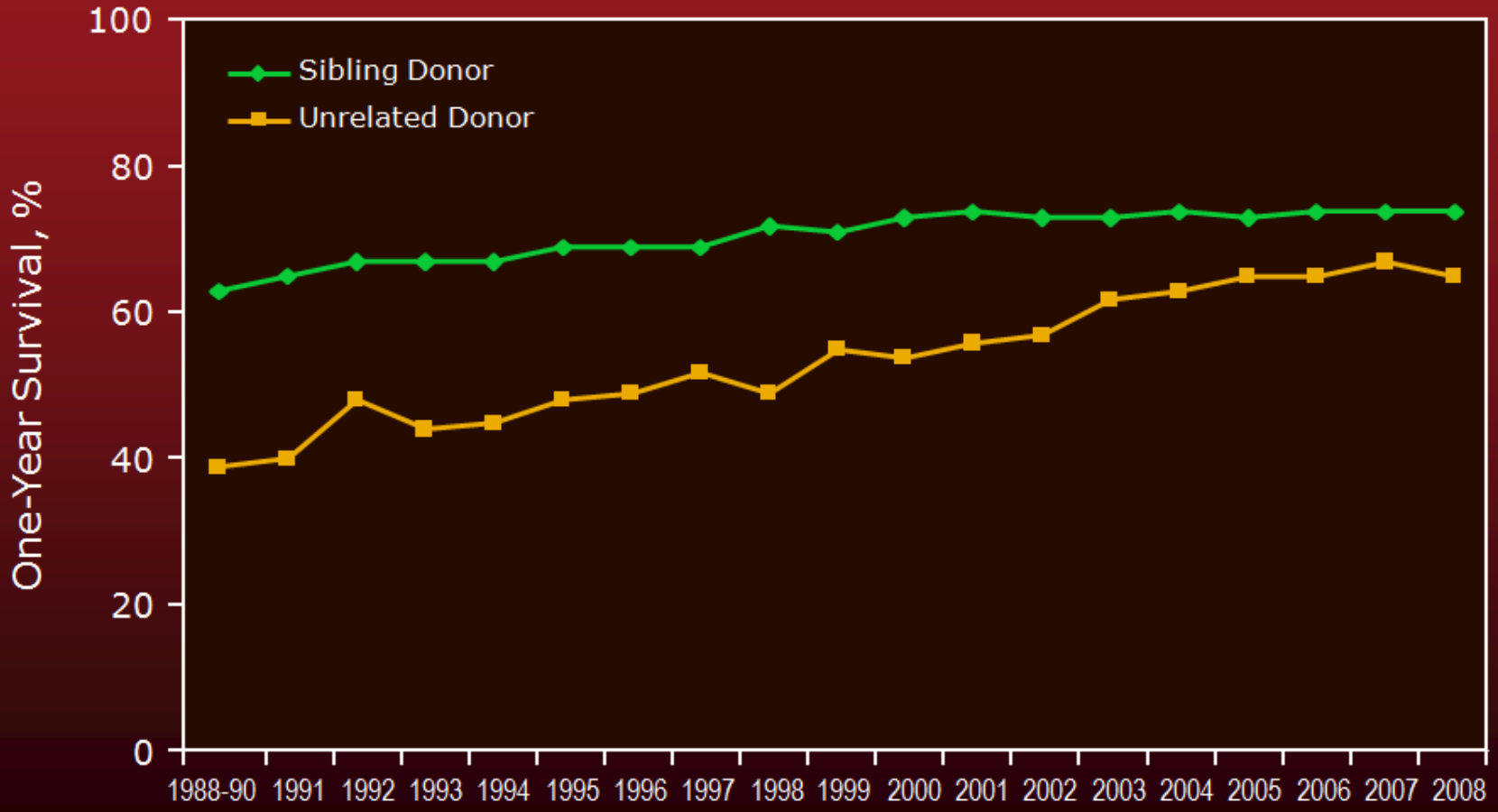
One-year survival after myeloablative conditioning for acute leukemias in any remission phase, CML or MDS, age <50 years, by year of transplant and graft source, 1988-2008



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