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Long-term Complications After Hematopoietic Cell Transplantation

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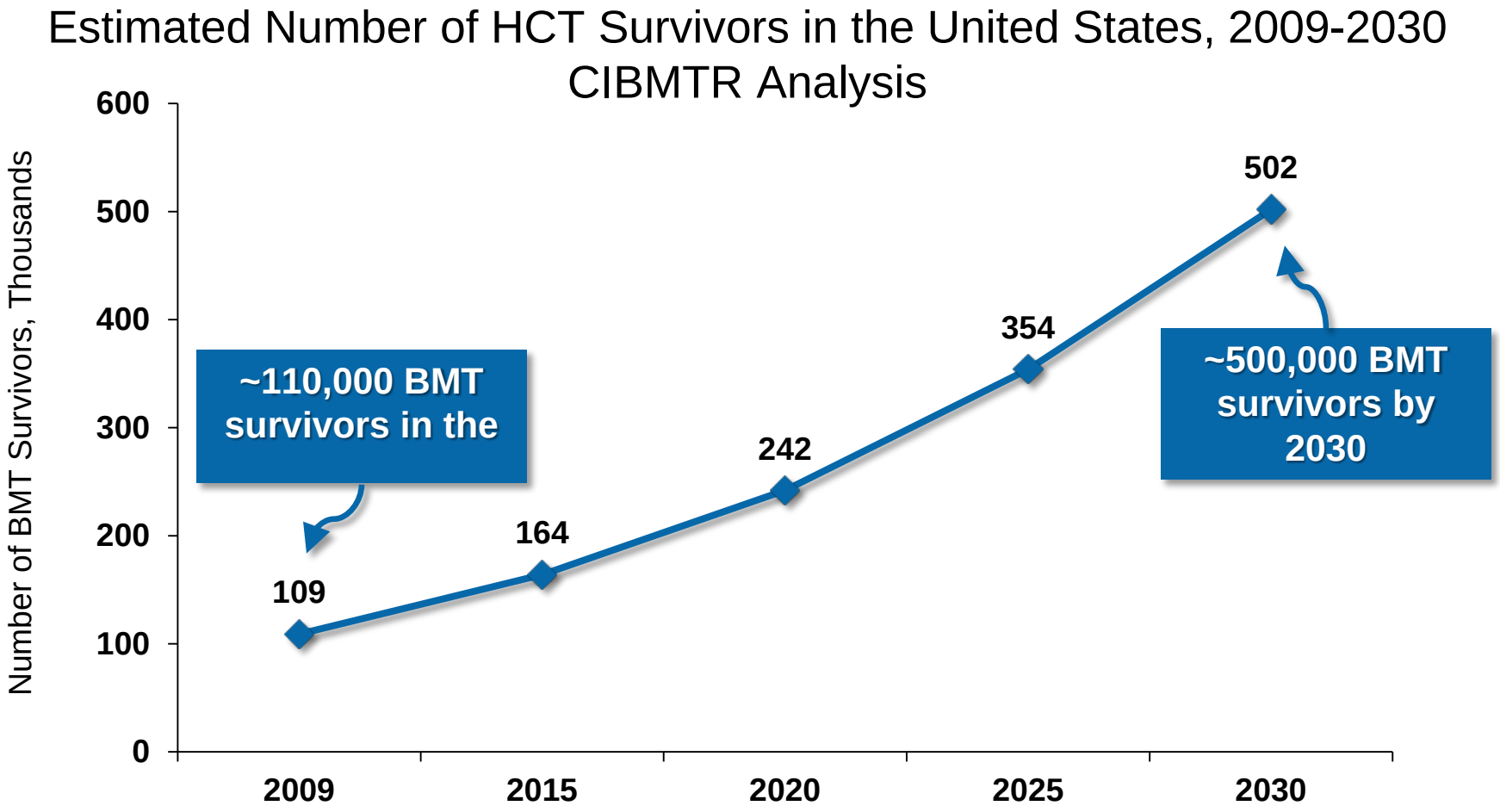
No relevant conflicts of interest to disclose

Objectives

- What are late effects of hematopoietic cell transplantation (HCT)
- How to screen and prevent late effects of HCT
- How to care for HCT survivors
- What are unmet needs and gaps in literature

Number of HCT Survivors Is Increasing



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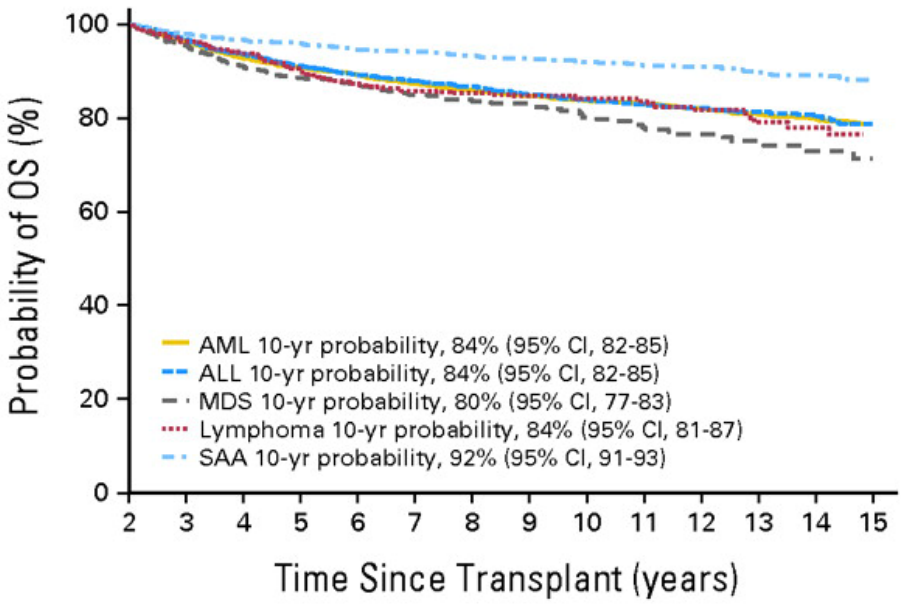
NS Majhail et al, BBMT 2013

Long-term Survival After HCT

- **10,632 allo HCT recipients surviving ≥ 2 years in remission**

Overall survival



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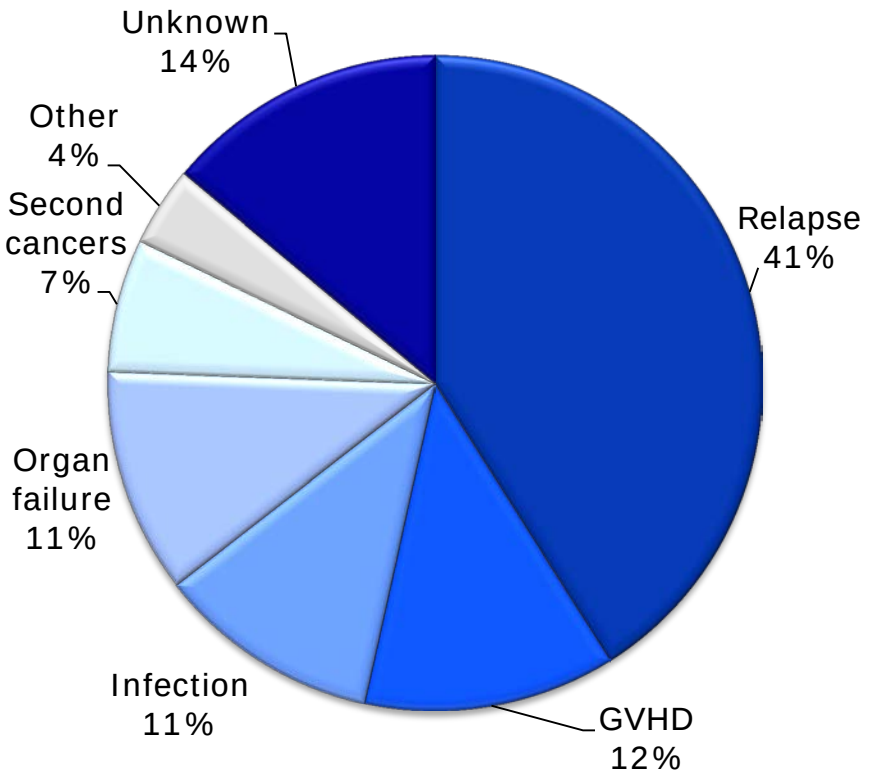
J Wingard et al, JCO 2011

Long-term Survival After HCT

- **Causes of death, ≥ 2 year survivors of allogeneic HCT**
- **Chronic GVHD consistent risk factor for mortality in all disease types**
- **Relative mortality higher than age-, gender-matched general population at 15 years**



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J Wingard et al, JCO 2011

Late Complications

- **Complications that occur late (months to years) after HCT**
  - **HCT exposures contribute to their risk**
- **Late complications**
  - **Organ toxicity**
  - **Infections**
  - **Secondary cancers**
  - **Growth and development issues**
  - **Sexual and fertility issues**
  - **Psychosocial and QOL issues**

Late Organ Dysfunction

- Neurologic – cognitive dysfunction, neuropathy
- Eye – sicca syndrome, cataracts
- Oral – xerostomia, caries
- Pulmonary – bronchiolitis obliterans
- Cardiovascular – coronary artery disease, metabolic syndrome, cardiomyopathy
- Liver – iron overload, hepatitis
- Kidney – HTN, chronic kidney disease
- Bone – osteoporosis, avascular necrosis
- Endocrine – hypothyroidism, growth disturbance

Late Infections

- **Increased risk for infections in patients with delayed immune reconstitution (e.g., chronic GVHD, prolonged steroid exposure)**
  - **Encapsulated bacteria**
  - **CMV, VZV**
  - **Aspergillus, PCP**
- **International consensus guidelines for prevention of early and late infections**
  - **Recommendations for vaccinations in transplant recipients**

M Tomblyn et al, Biol Blood Marrow Transplant, 2009
M Tomblyn et al, Bone Marrow Transplant, 2009

Vaccination Guidelines

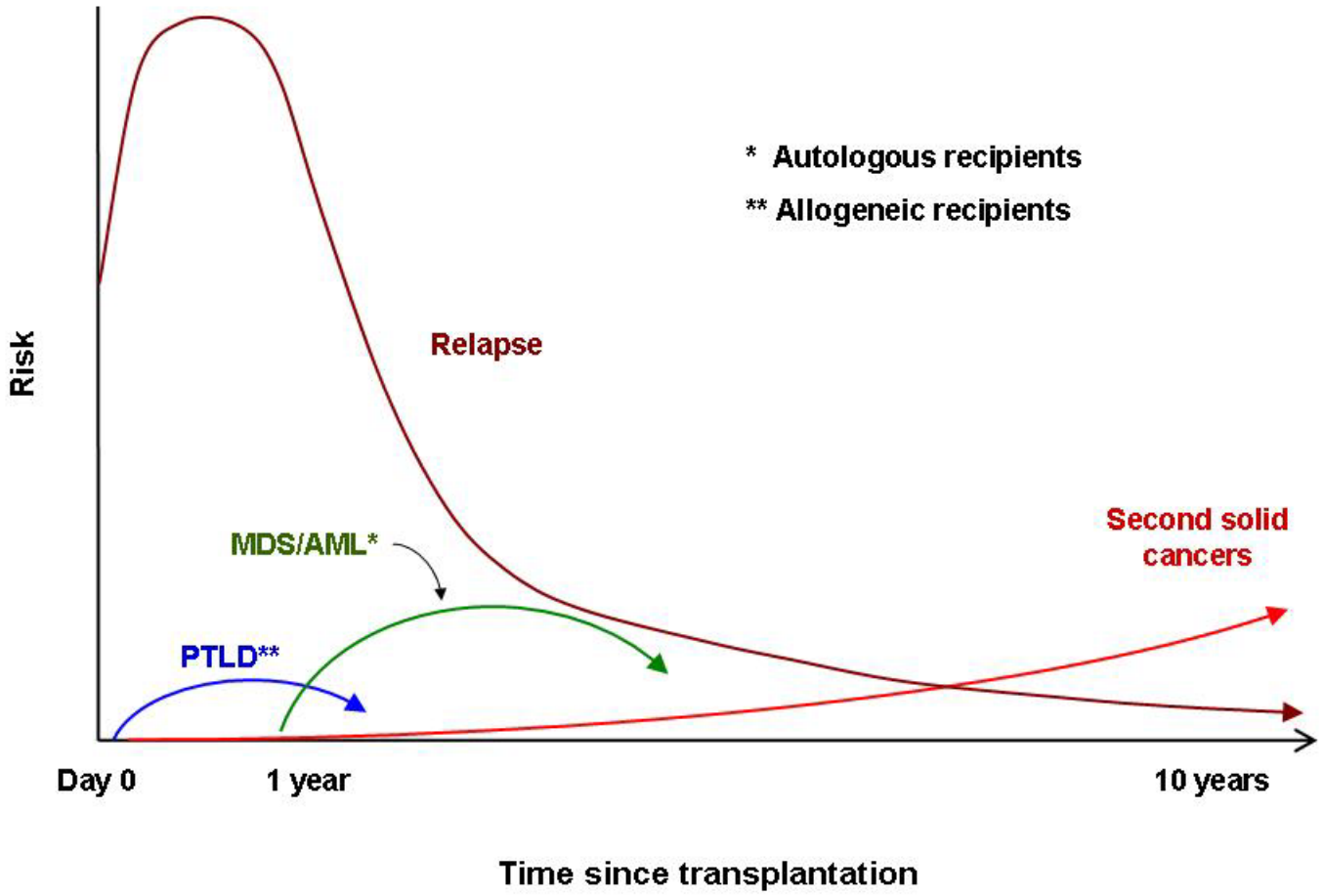
Vaccine	Recommended for use after HCT	Time post-HCT to initiate vaccine	No. of doses
Pneumococcal conjugate (PCV)	Yes	3-6 months	3-4
Tetanus, diphtheria, acellular pertussis	Yes	6-12 months	3
Haemophilus influenzae conjugate	Yes	6-12 months	3
Meningococcal conjugate	Follow general pouplation recommendations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

Secondary Cancers

- Cancers that occur after transplant
  - Different from the cancer for which transplant was performed
  - Cancer treatments may cause them or increase their risk
- Types of second cancers
  - Post-transplant lymphoproliferative disorders (PTLD)
  - MDS/AML
  - Solid cancers

N Majhail. Br J Haematol, 2011

Secondary Cancers



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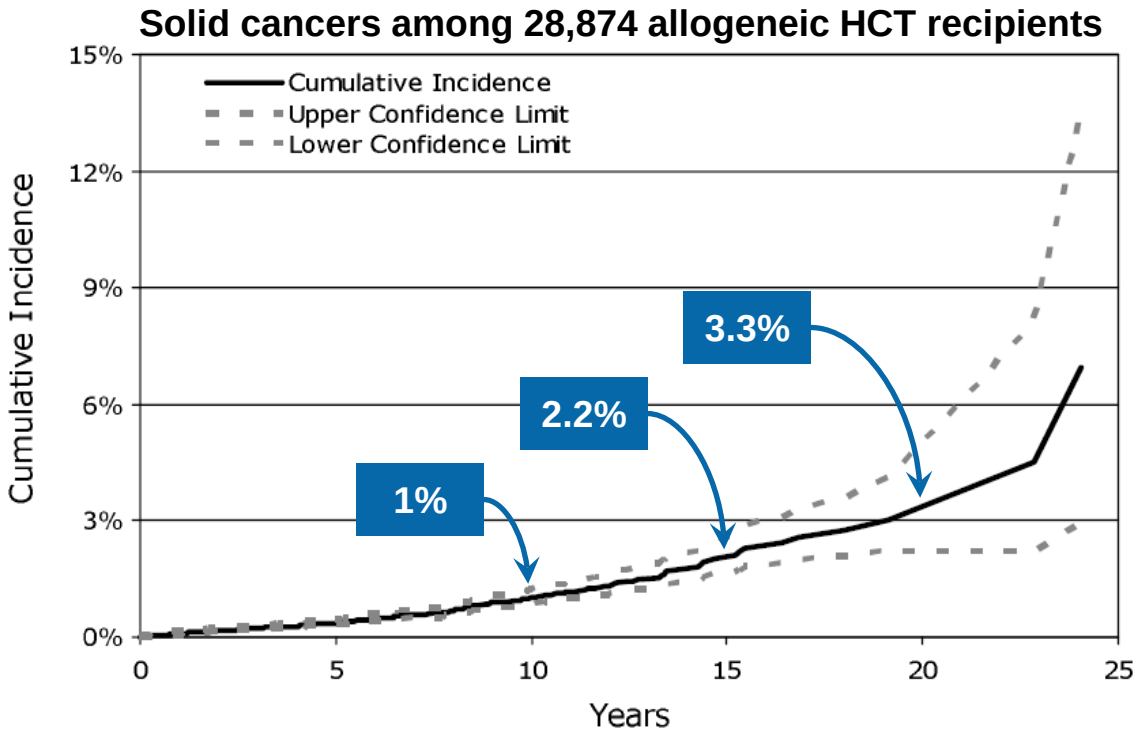
Secondary Solid Cancers

- **Latency period of 3-5 yrs, incidence increases with time**
  - **~1-2% at 5 yrs, ~1-6% at 10 yrs, ~2-15% at 15 yrs after HCT**
  - **Absolute risk is low, but is higher than general population**



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JD Rizzo et al. Blood, 2009

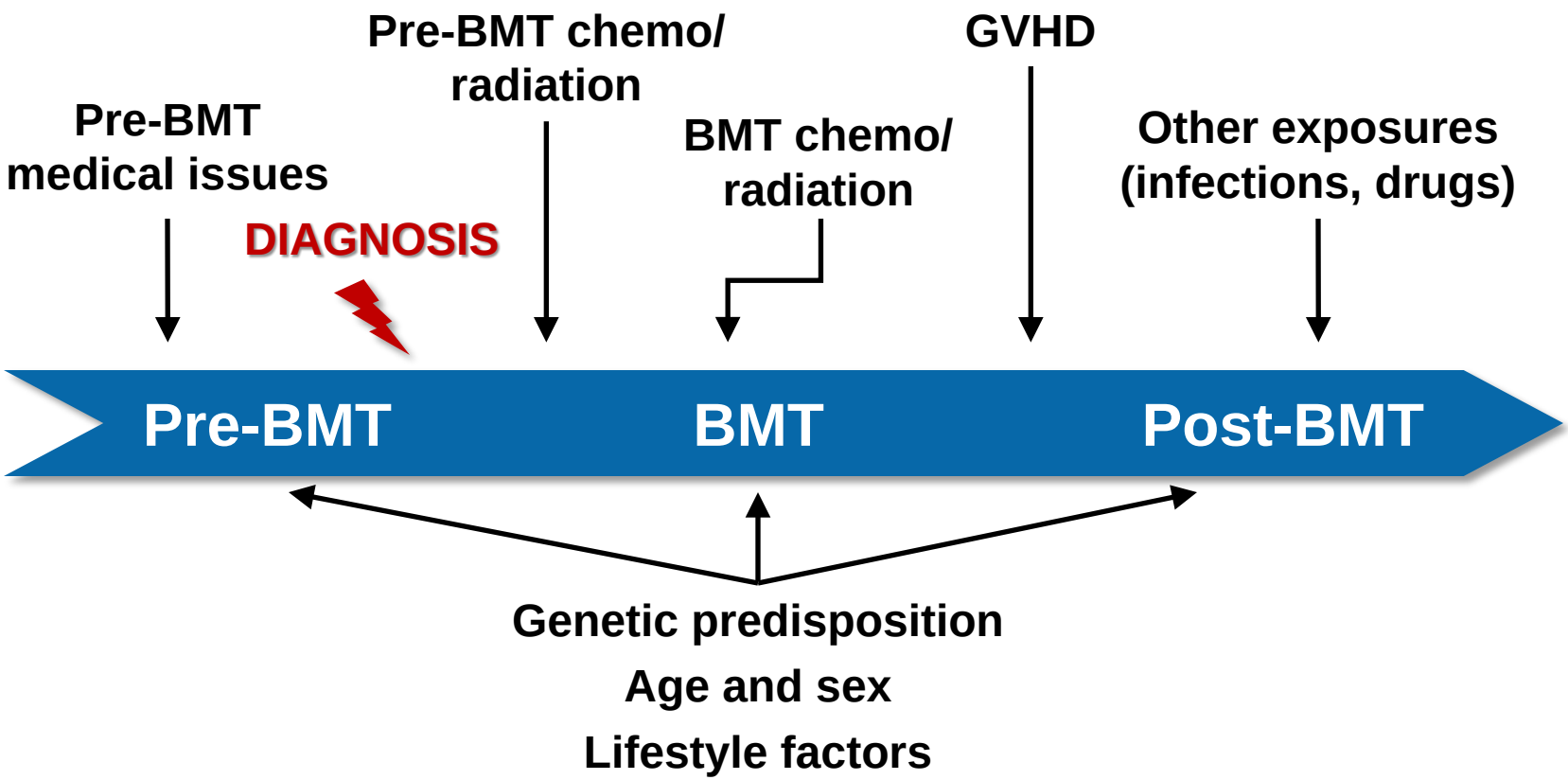
Quality of Life After HCT

- Affects all domains of QOL
  - Autologous HCT - Lowest at ~2 weeks, returns to baseline by 3 months to 1 year
  - Allogeneic HCT - Lowest at ~4 weeks, returns to baseline by 3 months to 1 year in absence of GVHD
  - Patients with chronic GVHD have persisting QOL deficits
- Continued long-term impairments compared to healthy controls
- QOL impairments and psychosocial issues in caregivers

Exposures Mediate Late Organ Toxicity

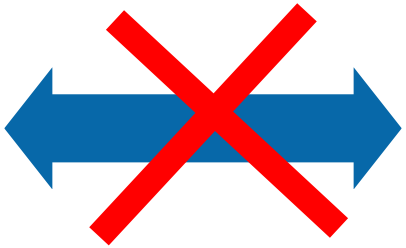
- **Chronic GVHD**
  - **Dry eye, caries, xerostomia, bronchiolitis obliterans, genitourinary issues**
  - **Squamous cell cancers (skin, oral cavity, tongue and oro-pharynx)**
- **Exposure to corticosteroids**
  - **Osteoporosis, HTN, kidney disease, myopathy**
- **TBI**
  - **Coronary artery disease, caries, dry eye, cataracts, endocrine dysfunction**
  - **Non-squamous cell cancers (breast)**

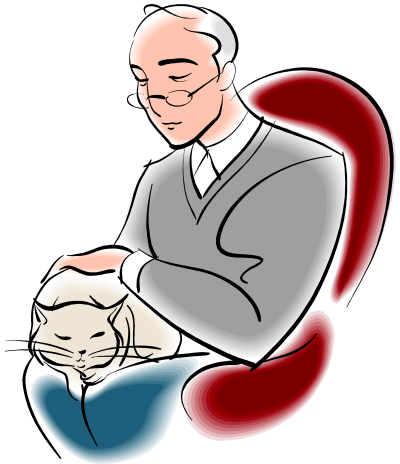
Risk Factor Based Approach To Survivorship Care



Individualized Survivor Care

LONG TERM EFFECTS ARE NOT SAME





10 year old with Fanconi anemia treated with sibling donor BMT and no GVHD

60 year old with acute leukemia treated with unrelated donor BMT and has GVHD

Long-term Followup Guidelines

GUIDELINES

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] for the Center for International Blood and Marrow Transplant Research (CIBMTR), American Society for Blood and Marrow Transplantation (ASBMT), European Group for Blood and Marrow Transplantation (EBMT), Asia-Pacific Blood and Marrow Transplantation Group (APBMT), Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ), East Mediterranean Blood and Marrow Transplantation Group (EMBMT), and Sociedade Brasileira de Transplante de Medula Ossea (SBTMO)

Co-published in:

Biology of Blood and Marrow Transplantation, 2012; 18: 348

Bone Marrow Transplantation, 2012; 47: 337

Hematology Oncology and Stem Cell Therapy, 2012; 5: 1

Revista Brasileira de Hematologia e Hemoterapia, 2012; 34: 109

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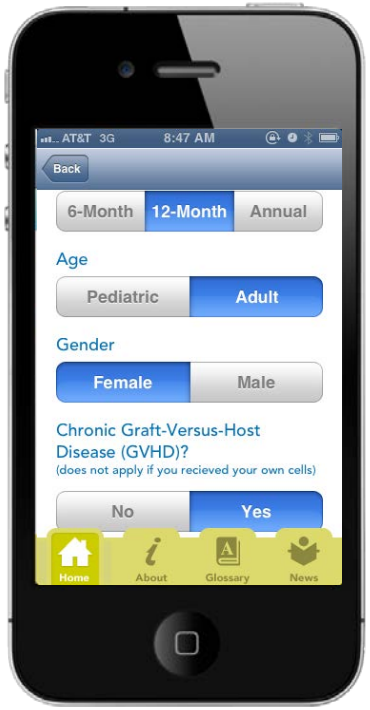
Organ Systems/Issues Considered

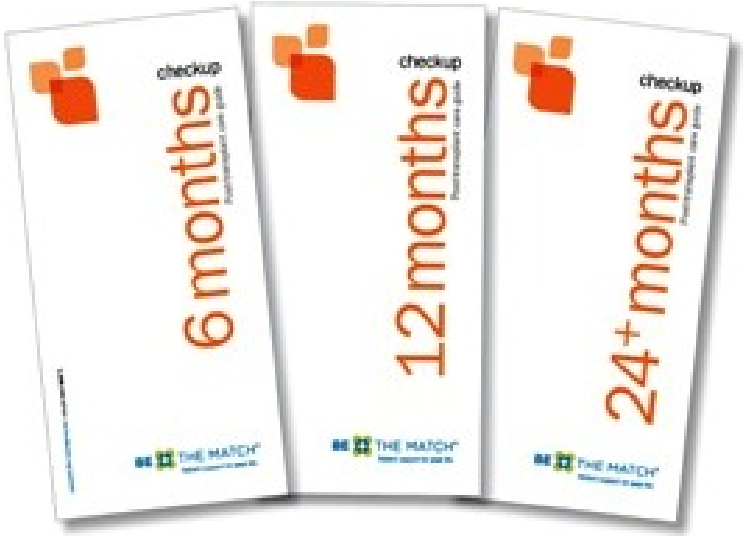
- Immune system
- Ocular
- Oral
- Respiratory
- Cardiac and vascular
- Liver
- Renal and genitourinary
- Muscle and connective tissue
- Skeletal
- Nervous system
- Endocrine
- Mucocutaneous
- Second cancers
- Psychosocial and sexual
- Fertility
- General health issues
- Healthy lifestyle

Example: Oral Complications

- **All HCT recipients**
  - Educate about preventive oral health and dental maintenance
  - Counsel to avoid smoking and chewing tobacco, avoid intraoral piercing
  - Clinical oral evaluation at 6 mo, 1 yr and then yearly
  - Dentist or oral medicine specialist evaluation at 1 yr and then yearly
- **Pediatric recipients**
  - Assessment of teeth development
- **Chronic GVHD patients**
  - Clinical oral evaluation every 6 mo
  - More frequent dentist or oral medicine specialist consultations may be considered

Resources Based on Guidelines





Physicians: www.bethmatchclinical.org

Patients: www.bethmatch.org

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Caring For HCT Survivors

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Challenges: Lost in Transition

- **Patients**
  - Distance from transplant center
  - Socio-demographic and economic barriers
  - Complex medical issues, not aware of risks
- **Providers**
  - Competing priorities, knowledge, comfort level, limited resources
- **Transplant centers**
  - Limited resources, competing priorities
- **Healthcare system**
  - Coverage for survivor care
  - Care coordination

Elements Of Patient Centered Survivorship Care

- Surveillance for disease recurrence
- Surveillance, prevention and treatment of late complications
- Screening and prevention of second cancers
- Routine health maintenance
- Health promotion and education
- Psychosocial support
- Rehabilitation
- Financial counseling
- Reintegration into society (return to work/school)

Care Delivery For HCT Survivors

- Empower patients
- Leverage technology
- Partnership and care coordination among BMT Program and other healthcare providers
- Follow guidelines
- Treatment summary and survivorship care plan
  - Details of cancer type, treatments, side effects
  - Timing and content of recommended followup
  - Recommendations for preventive practices
  - Address psychosocial services

Research Priorities For HCT Survivorship

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NIH Blood and Marrow Transplant Late Effects Consensus Conference

June 21-22, 2016 • Rockville, MD

- **Multi-stakeholder initiative**
- **Goal: Identify HCT survivorship research priorities**
- **Steering committee + six working groups**
  - **Research methodology and study design**
  - **Subsequent neoplasms**
  - **Patient centered outcomes**
  - **Immune dysregulation and pathobiology**
  - **Cardiovascular disease and associated risk factors**
  - **Health care delivery**

Working Group	Scope
Research methodology	- Methodological challenges across HCT survivor research - Historical transplantation strategies in retrospective analysis - Database/biospecimen requirements for survivorship studies
Subsequent neoplasms	- Magnitude of risk for subsequent neoplasm - Subsequent neoplasm pathogenesis, transplant- and nontransplant-related risk factors and outcomes
Patient centered outcomes	- QOL dimensions affected by HCT (physical, psychological, environmental, social, adherence, health behaviors) - Interventions tested to improve these outcomes - Methodological issues that restrict progress in this field
Immune dysregulation	- Trends in late infections among HCT survivors - Immune reconstitution in the laboratory setting - Interventions to improve immune function
Cardiovascular disease	- Arterial disease - Cardiac dysfunction - Cardiovascular risk factors
Health care delivery	- Healthcare delivery models - Coverage and value

M Battiwala et al. Biol Blood Marrow Transplant, 2017

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Editorial

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: Developing Recommendations to Improve Survivorship and Long-Term Outcomes

Minoo Battiwalla [1,*], Shahrukh Hashmi [2], Navneet Majhail [3], Steven Pavletic [4], Bipin N. Savani [5], Nonniekaye Shelburne [6]

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Cardiovascular Disease and Associated Risk Factors Working Group Report

Saro H. Armenian [1,*], Wassim Chemaitilly [2], Marcus Chen [3], Eric J. Chow [4], Christine N. Duncan [5], Lee W. Jones [6], Michael A. Pulsipher [7], Alan T. Remaley [3], Alicia Rovo [8], Nina Salooja [9], Minoo Battiwalla [10]

National Institutes of Health Blood and Marrow Transplant Late Effects Initiative: The Healthcare Delivery Working Group Report

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Lindsay M. Morton [1,*], Wael Saber [2], K. Scott Baker [3], A. John Barrett [4], Smita Bhatia [5], Eric A. Engels [6], Shahinaz M. Gadalla [7], David E. Kleiner [8], Steven Pavletic [9], Linda J. Burns [10]

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Margaret Bevans [1,*], Areej El-Jawahri [2], D. Kathryn Tierney [3], Lori Wiener [4], William A. Wood [5], Flora Hoodin [6], Erin E. Kent [7], Paul B. Jacobsen [8], Stephanie J. Lee [9], Matthew M. Hsieh [10], Ellen M. Denzen [11], Karen L. Syrjala [9]

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Immune Dysregulation and Pathobiology Working Group Report

Juan Gea-Banacloche [1,*], Krishna V. Komanduri [2], Paul Carpenter [3,4], Sophie Paczesny [5], Stefanie Sarantopoulos [6], Jo-Anne Young [7], Nahed El Kassar [8], Robert Q. Le [9], Kirk R. Schultz [10], Linda M. Griffith [11], Bipin N. Savani [12], John R. Wingard [13,14]

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Summary

- HCT survivors (1-2 years+) have high probability of long-term survival
  - At risk for late complications/non-relapse mortality
- Several challenges to providing optimal care
  - Care has to be personalized
- Need innovative models of care
  - Empower patients
  - Partnership b/w transplant centers & other providers
- Guidelines are a tool for providing clinical care
- Survivorship care needs to be individualized