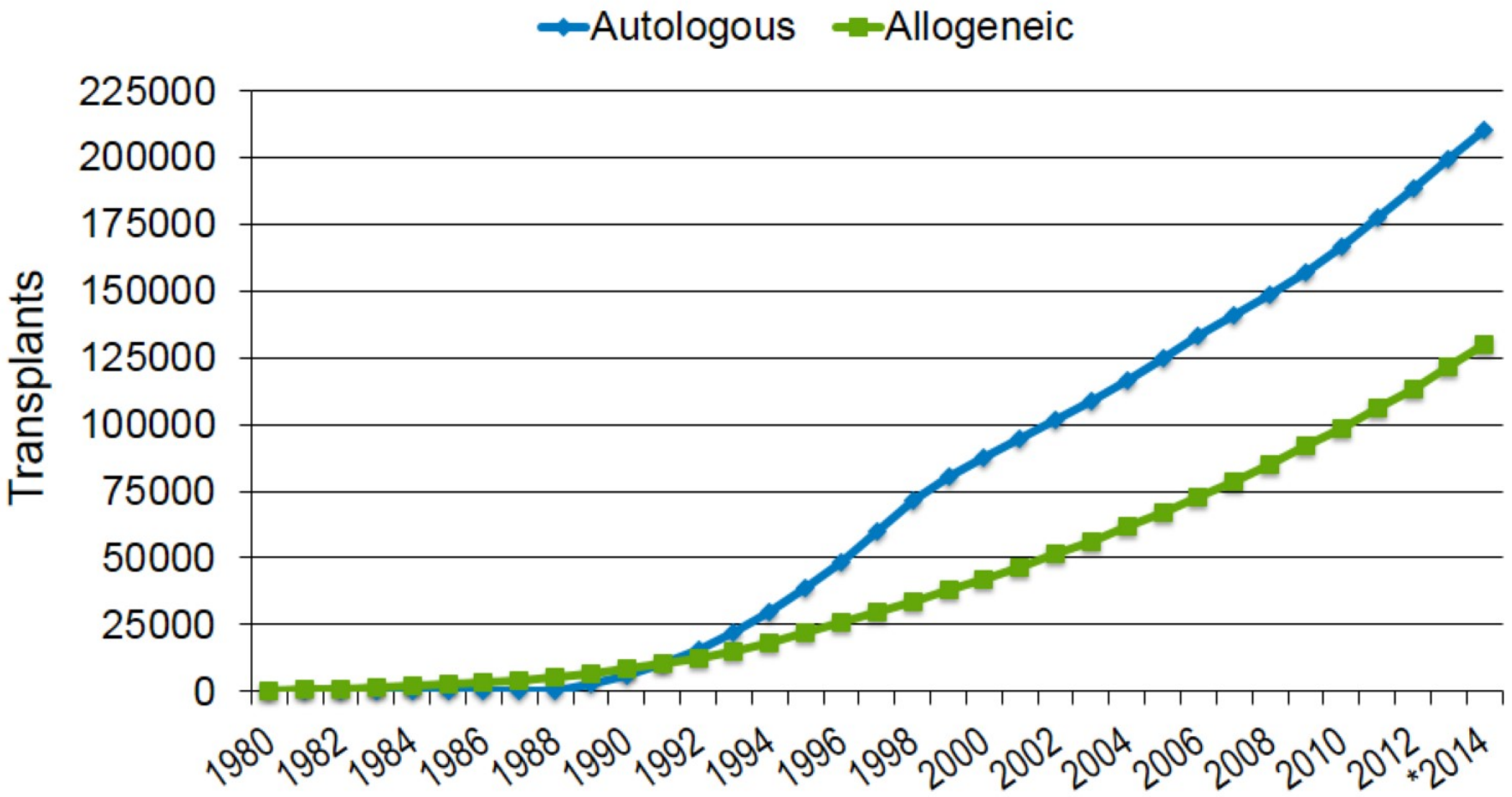
National Institutes of Health

NIH Blood and Marrow Transplant
Late Effects Consensus Conference

Initiative Overview

Minoo Battiwalla, M.D., M.S.

Cumulative Plot of Transplant Recipients in the US by Transplant Type

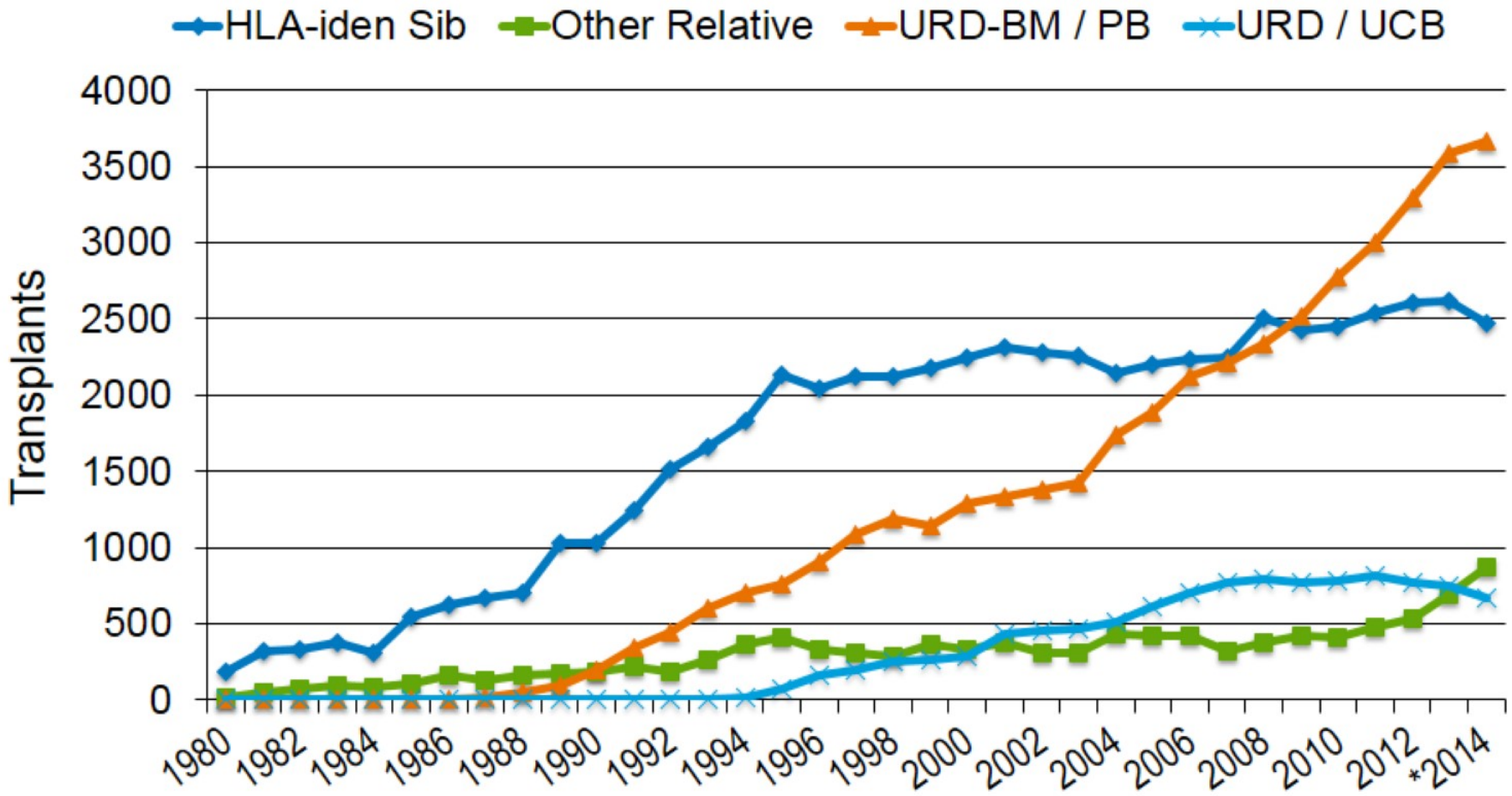


CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

CIBMTR report 'Current Uses and Outcomes of Hematopoietic Stem Cell Transplantation 2013' accessed online 08.26.14
http://www.cibmtr.org/search/pages/results.aspx?k=Hematopoietic%20%20Stem%20Cell%20Transplantation&s=Entire%20Site

*2014 Data incomplete

Allogeneic Transplant Recipients in the US, by Donor Type



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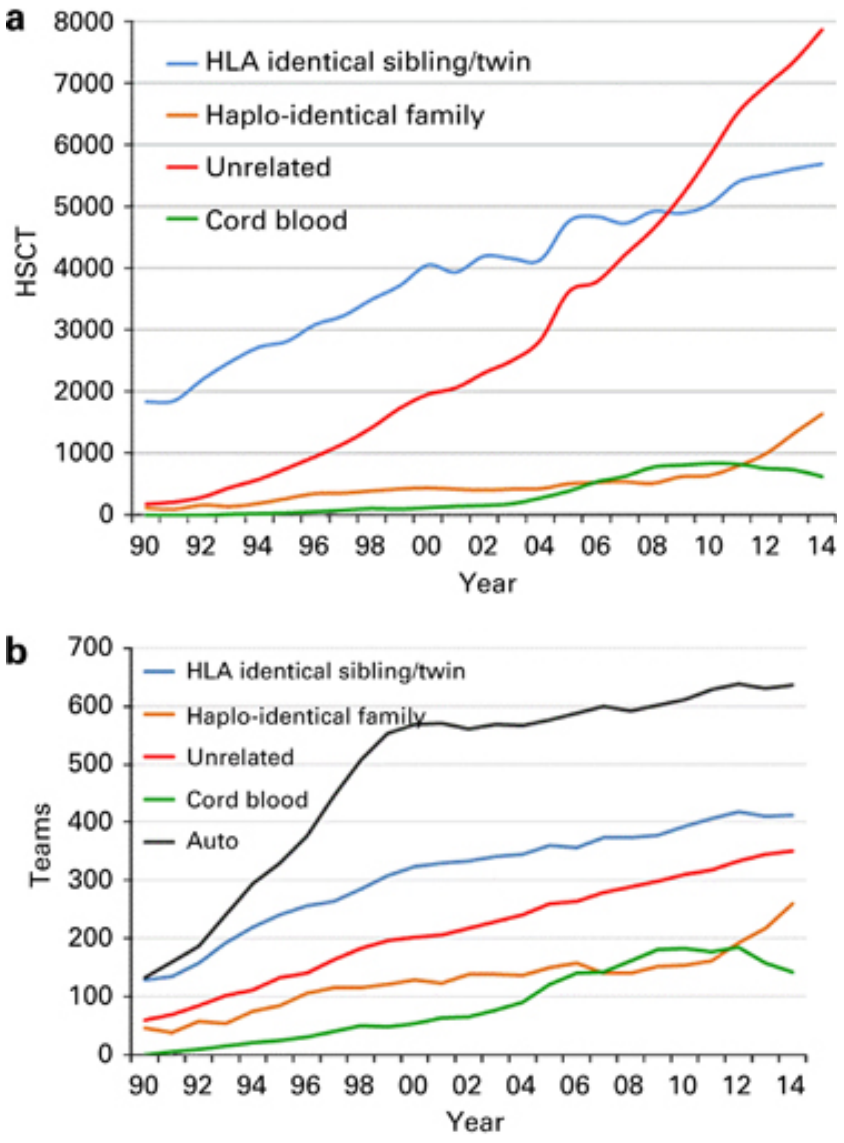
http://www.cibmtr.org/search/pages/results.aspx?k=Hematopoietic%20%20Stem%20Cell%20Transplantation&s=Entire%20Site

*2014 Data incomplete

Transplant Activity in Europe

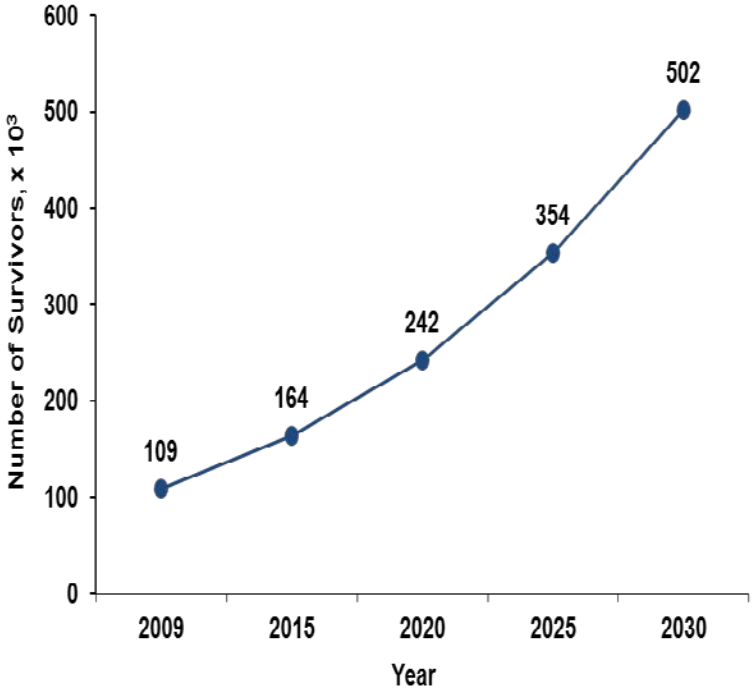


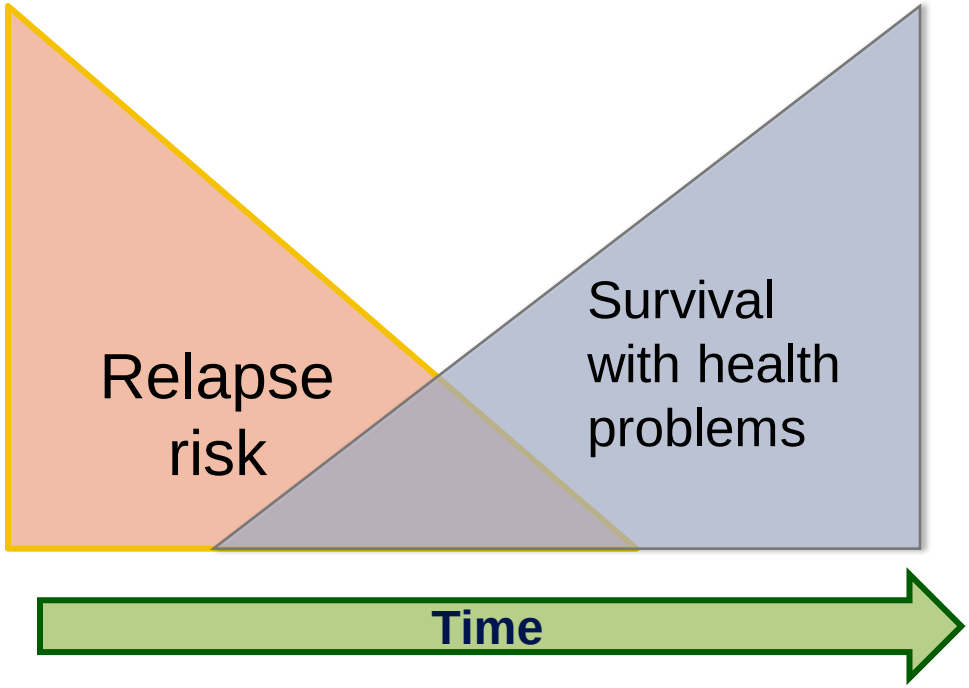
Bone Marrow Transplantation advance online publication 22 February 2016; doi:10.1038/bmt.2016.20

Number of Survivors are Increasing

Estimated ~110,000 HCT survivors in the US in 2009

- >~5X increase by 2030 if transplant rates stay stable





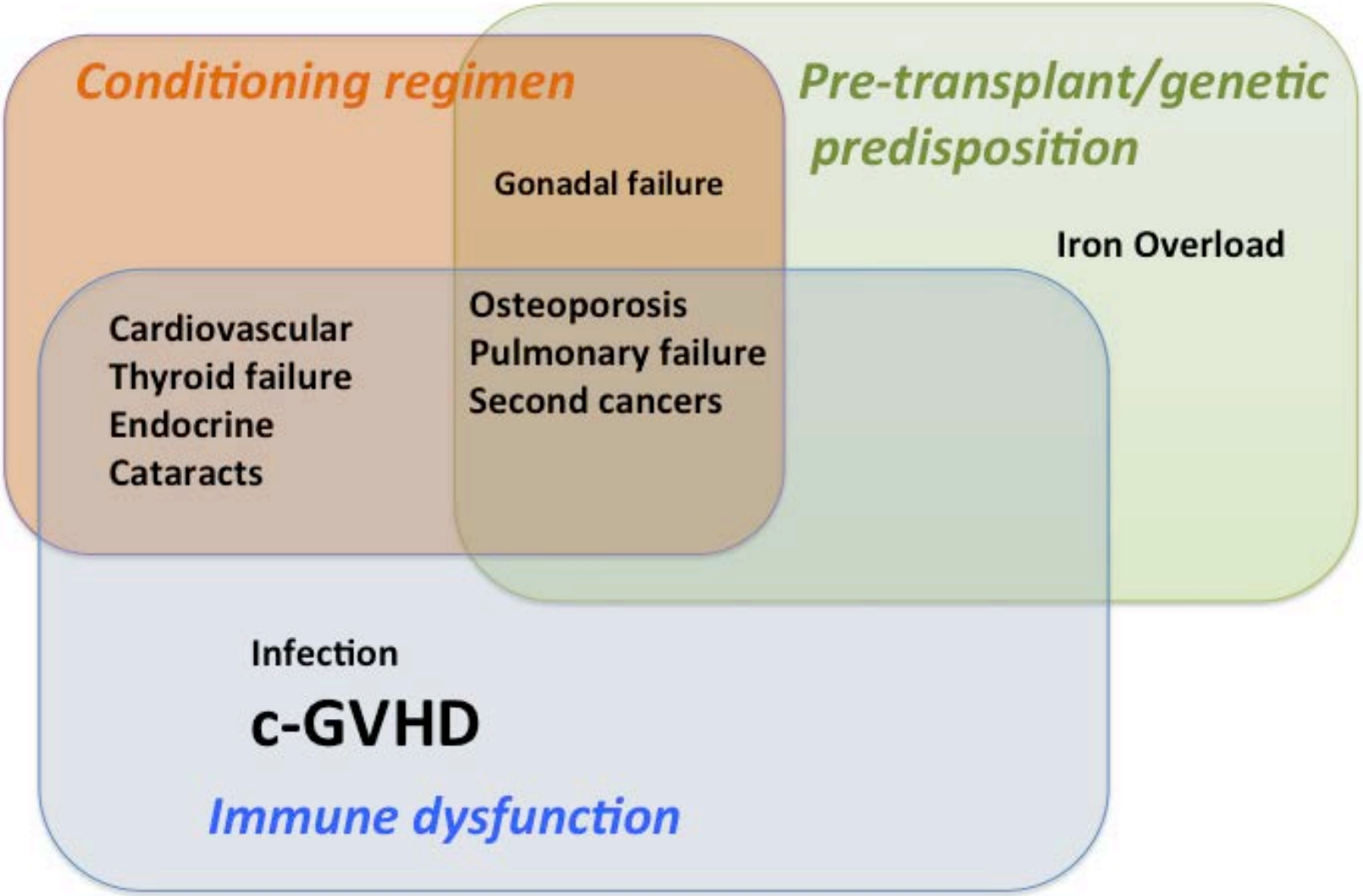
We can only wish…….

Cured, but at what cost?

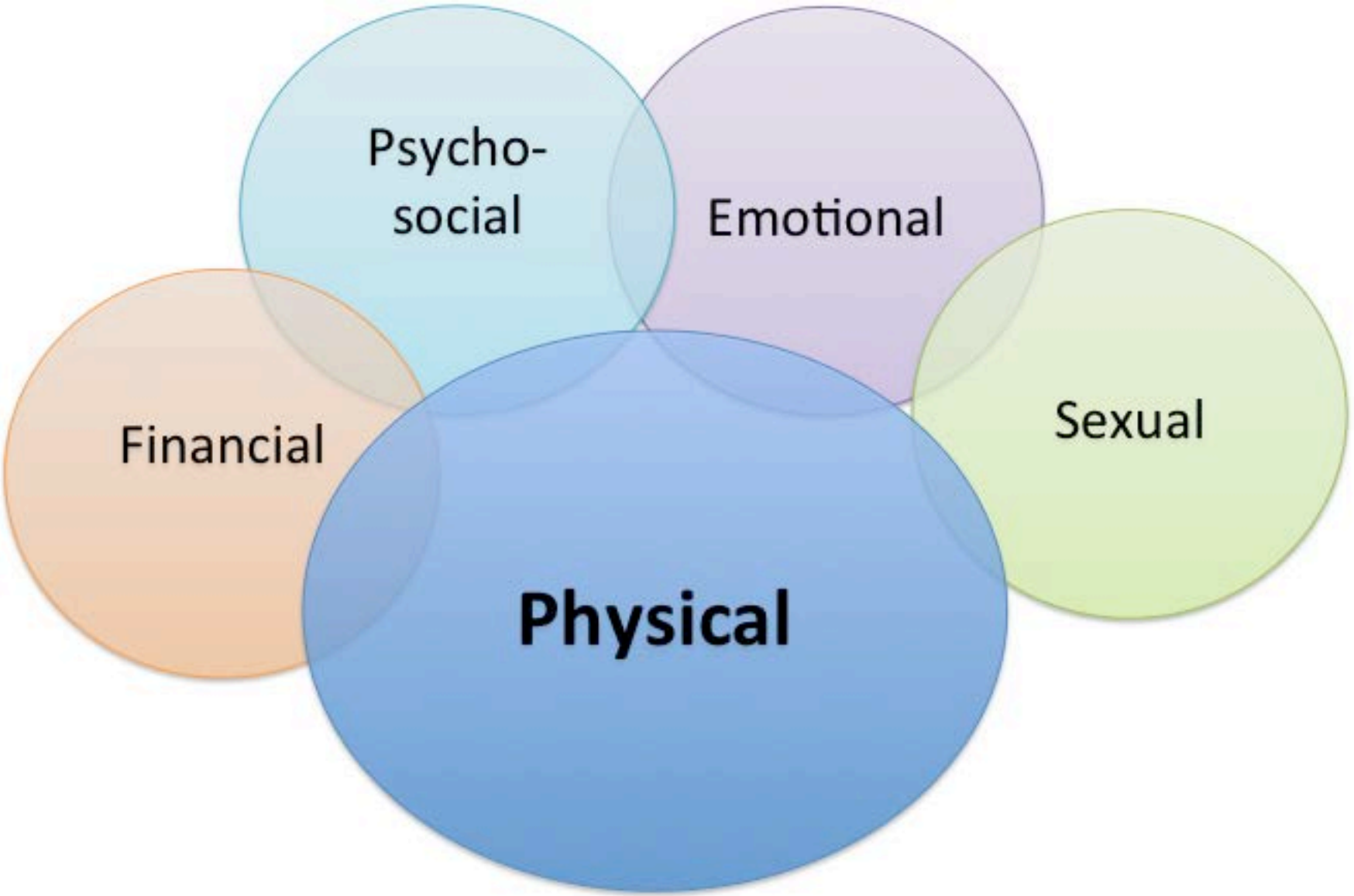
40%

OF CHILDHOOD CANCER SURVIVORS HAVE SEVERE ILLNESSES OR DIE FROM SUCH ILLNESSES[13]

Pathobiology



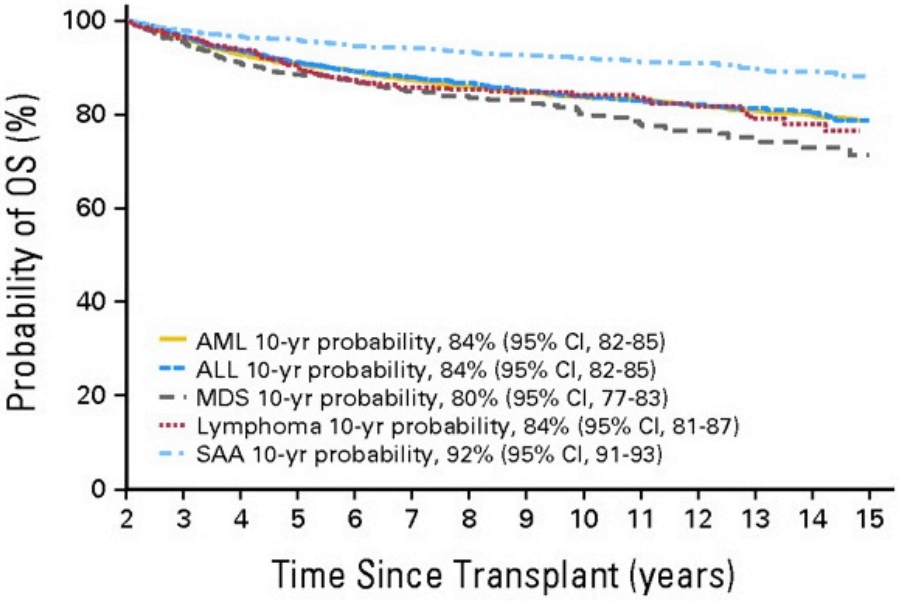
Impact on multiple domains of health



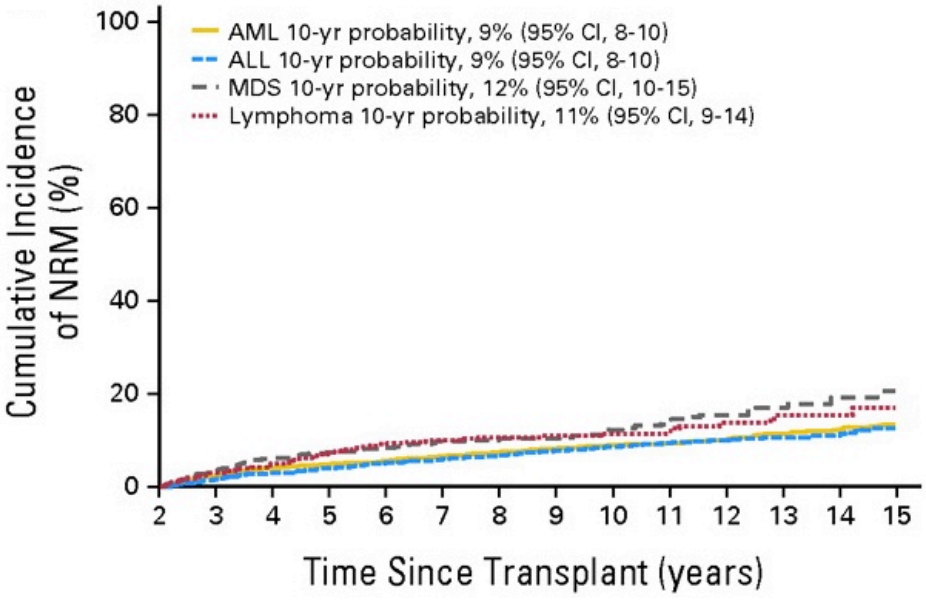
Long-term Survival after HCT

CIBMTR study of 10,632 allogeneic HCT recipients surviving ≥ 2 years in remission (median follow-up 9 years)

Overall survival



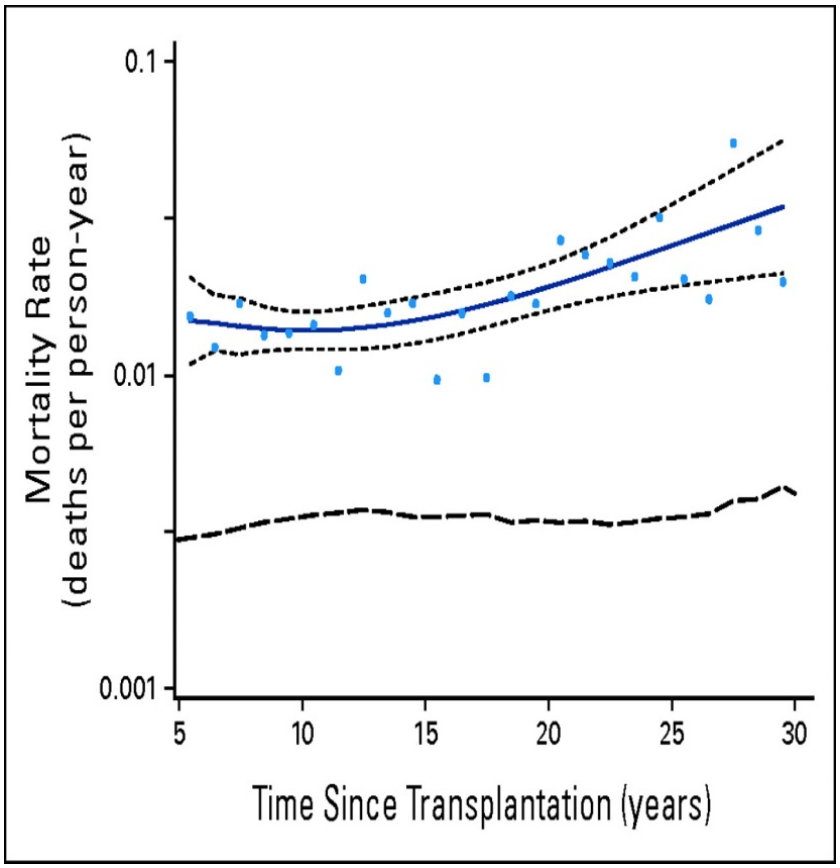
Non-relapse mortality

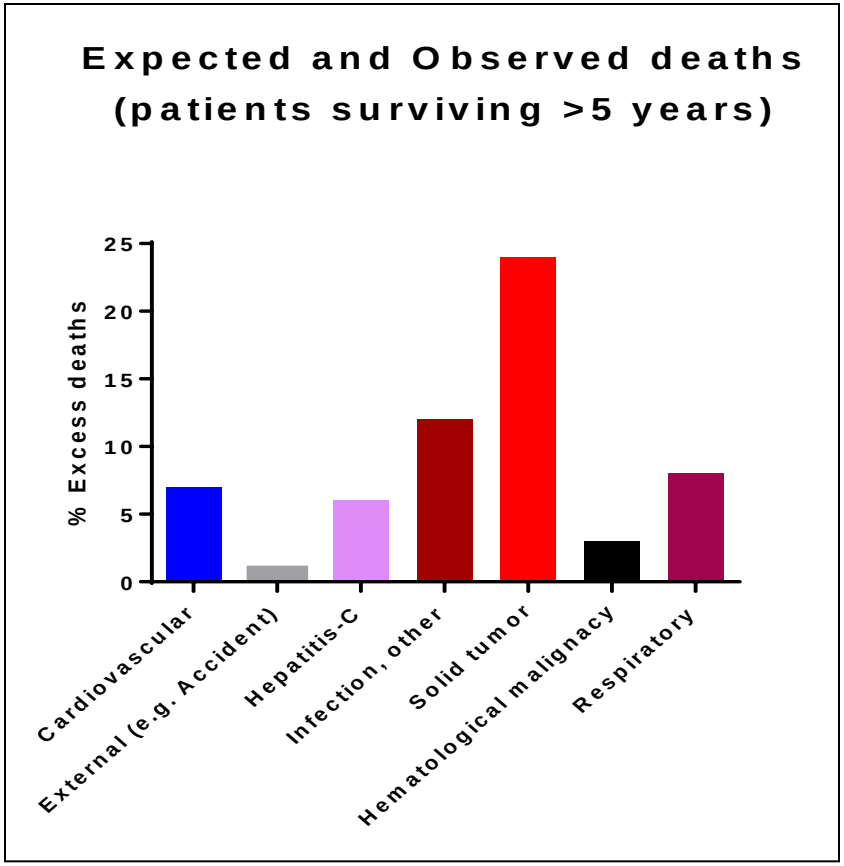


J Wingard et al, J Clin Oncol. 2011 Jun 1;29(16):2230-9

LIFE EXPECTANCY IN THOSE SURVIVING BEYOND 5 YEARS

- **Estimated survival of cohort at 20 years after SCT was 80.4%**
- **Mortality rate remained 4-9 times higher than general population**



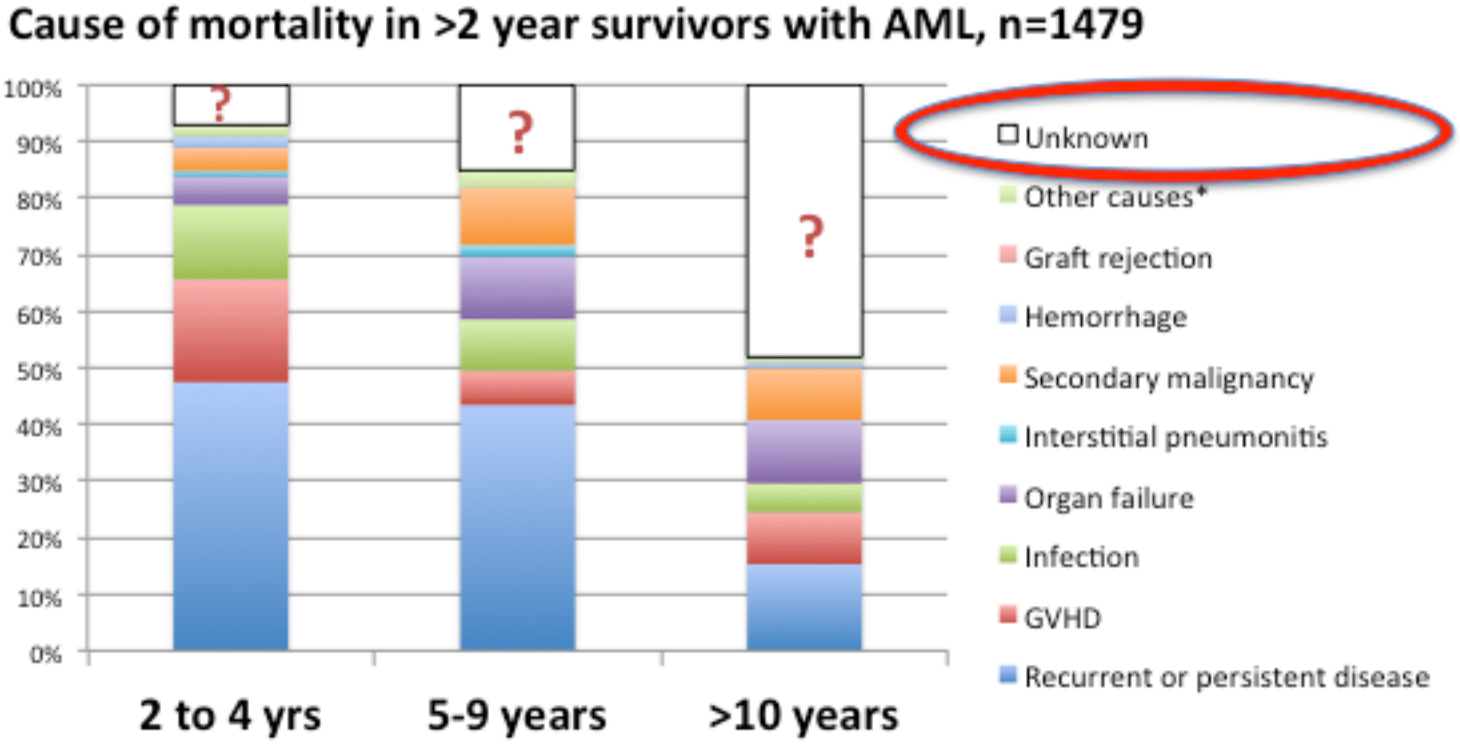


Retrospective analysis of prospective created database. N=7984

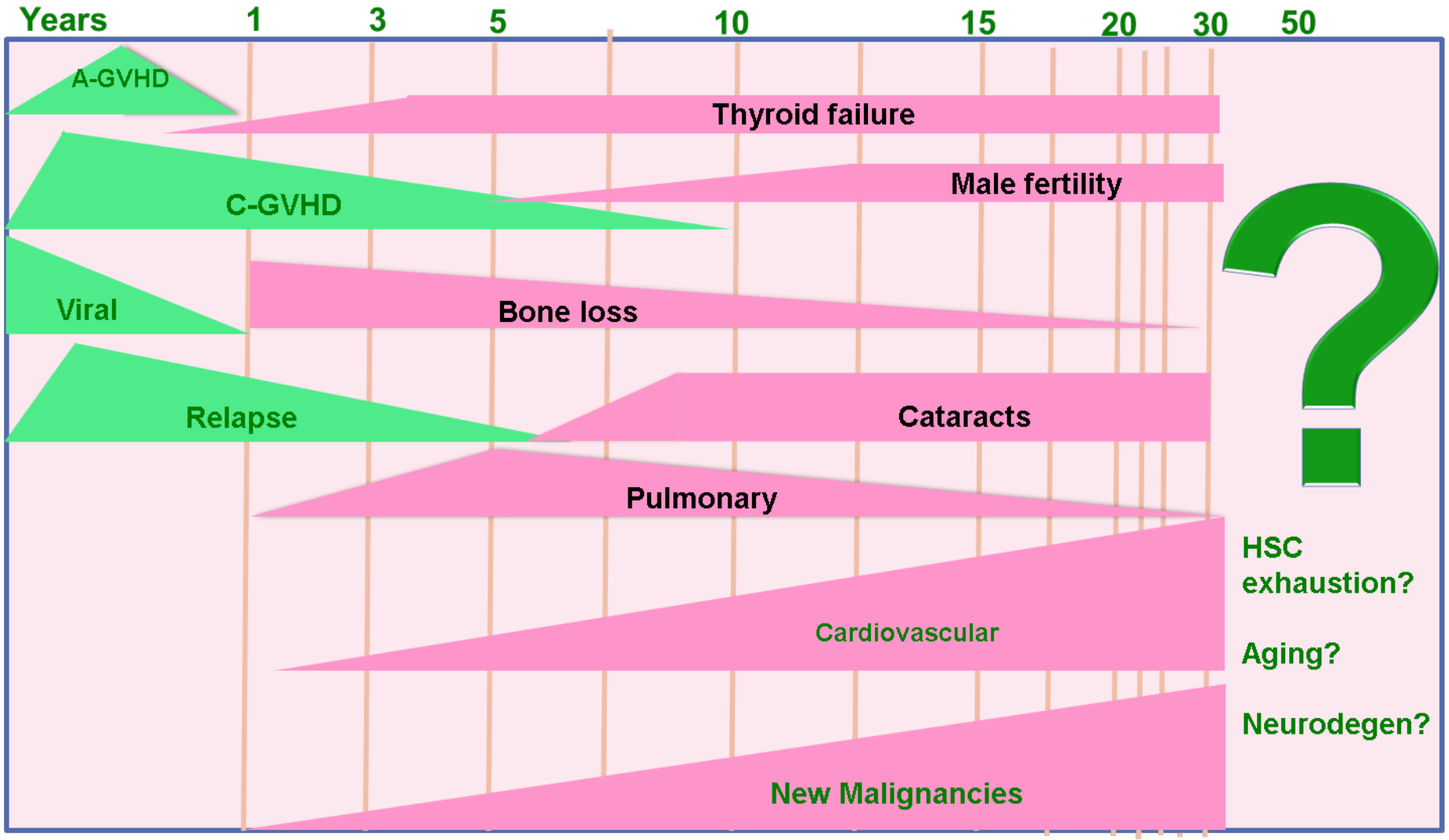
Increased mortality in survivors

- In the Bone Marrow Transplant Survivor Study (BMTSS) relative mortality was found to be ***9.9*** .
- At 15 years after HSCT (standardized mortality ratio [SMR] = ***2.2***).

Bhatia, S., et al. Blood (2007). Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the Bone Marrow Transplant Survivor Study.



TIMEFRAMES FOR POST SCT COMPLICATIONS



Delayed complications may be lethal!

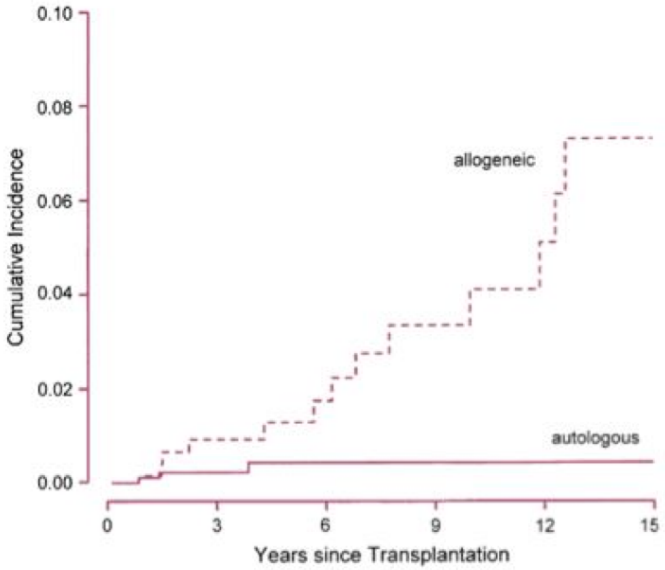


FIG 1. The cumulative incidence of cardiovascular event at 15 years, adjusted for age (Tichelli A. et al. Blood. 2007)

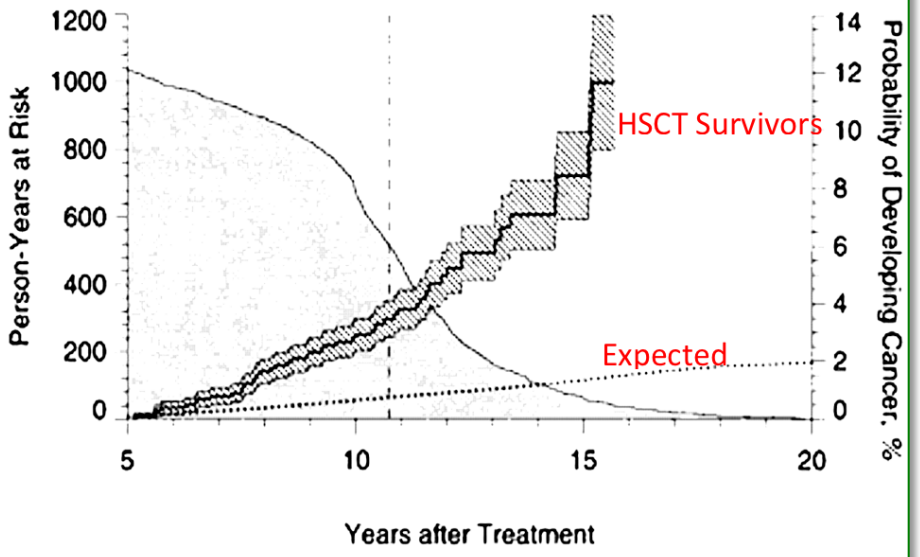


FIG 2. The cumulative incidence of new malignancy in HSCT survivors (Kolb, H.J. et al. Ann Intern Med. 1999)

Justification

METHODS

Observational studies, registry limitations, latency measurable in decades, minimal cross-disciplinary involvement

INCENTIVES LACKING

FACT, SCTOD, reimbursement, framework

OVERLAP

Chronic GVHD, pediatric initiatives, other oncology survivorship

WIDE SPECTRUM

- disorders, latency, lethality, disciplines
- patient-centric Vs. pathobiology

UNKNOWNS

- pathobiology poorly understood
- effectiveness of preventive guidelines
- ultra-late effects and aging

The NIH Late Effects Initiative

OBJECTIVES

- to define the critical issues and barriers in the field
- to set research priorities
- create a successful organizational framework for studying late–effects

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June 21-22, 2016 • Rockville, MD

PROGRESS TIMELINE

March, 2015

Steering committee formed

June 26, 2015

Planning Meeting: (Arlington, VA)
Steering committee, WC chairs, federal stakeholders, ex-officio (ASBMT/CIBMTR/NMDP)

Aug '15

Working Committee Teleconferences

Feb '16

Working Committee Draft Presentations: Tandem BMT conference. Honolulu. HI. 2016

June 21-22 2016

Final NIH Consensus Conference:
NCI, Shady Grove

Guidance for Working Committees

•**Focus**: Survival > 1 year, not covered by chronic GVHD initiative, unique to BMT. Only the most critical challenges that will improve health, advance the science OR change guidelines/clinical care/standard approach.

•**Multidisciplinary:** International, adults/peds, subject matter experts, Governmental, advocacy groups, transplant societies.

•**Cross fertilization:**

- Pediatric oncology & HIV.
- Unique problems in this field may lead to generalizable solutions.

•**Goals**: identify knowledge gaps, give evidence-based recommendations and set research agenda to improve BMT survivor monitoring and management.

Program Highlights

- Participation
- Research Roadmaps- CV, ID, SN, QOL
- Methodology
- HCD- Improve follow up!
- Patient perspective panel
- Funding discussion
- Workshop- “Starting a Late Effects Program”
- Consensus publications BBMT

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Research Methodology

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Establish new cohorts or expand existing cohorts to study late effects using comprehensive and complete capture of pre-, peri- and post-HCT exposures and follow-up of HCT recipients and include detailed information on extent and severity of chronic GVHD, socio-demographic data, patient reported outcomes and healthcare costs

High priority areas for data collection are late effects that have high incidence of morbidity, impairment, disability and/or premature mortality, have excess risk compared to general population and have potentially modifiable risk factors

Develop or supplement existing repositories of biospecimens before and after HCT to facilitate investigations of biomarkers, risk factors and pathogenesis of late effects; high priority specimen collection areas include germline DNA, total leukocyte of cell-specific RNA, plasma serum, and fresh frozen tissue of subsequent neoplasms

Health Care Delivery

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Healthcare delivery models

Identification, development, implementation and efficacy of patient-centered care delivery models, including novel models that integrate information technology in healthcare delivery and evaluate care coordination and role of non-physician providers

Evaluate patient self-management and information technology tools for enhancing patient participation in survivorship care

Evaluate healthcare disparities in HCT survivorship care and issues in special populations including caregivers

Assess models for implementation and utilization of treatment summary and survivorship care plans

Evaluate development and implementation of evidence-based late effects screening and prevention guidelines

Evaluate role of supportive therapies in survivorship care

Coverage and value

Establish infrastructure and databases to conduct studies on costs and value of HCT, including linkage of existing databases and electronic health record platforms

Identify patient-centered coverage models for preventive care and late complications

Investigate resource utilization, costs and cost-effectiveness of healthcare delivery models including innovative models for coverage through the care continuum and coverage of other services required to provide survivorship care

Assess impact of health policy (e.g., Affordable Care Act, Medicare payment reform) on HCT survivorship care

Evaluate prevalence, risk factors and interventions for short-term and long-term financial toxicity of HCT to patients and caregivers

Evaluate patient reported outcomes to inform value and coverage models

Subsequent Neoplasms

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Establish multicenter mechanisms to conduct prospective large-scale long-term studies of HCT survivors that capture detailed data on pre-, peri- and post-transplant exposures

Define magnitude of risks for specific subsequent neoplasms

Evaluate interaction between traditional risk factors (e.g. smoking) with transplant related risk factors

Bank cryopreserved donor and recipient blood and marrow cells and subsequent neoplasm tissues for laboratory investigations of susceptibility and pathogenesis

Assess genetic risk factors

Investigate validity, cost-effectiveness, magnitude of risk-reduction, and optimal techniques and timing of screening for specific subsequent neoplasms and its impact on HCT outcomes

Validate cancer prevention interventions (e.g., HPV vaccination) in HCT survivors

Immune Dysregulation

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Late infections

- Conduct long-term multicenter prospective studies of late infectious events in HCT survivors to identify serious infections, types of pathogens, and risk factors
- Evaluate immunologic correlates for late infections using banked samples
- Evaluate association of early and late microbiota changes after HCT with late infections and immune reconstitution
- Understand effectiveness of consensus infection control guidelines by creating registry of vaccine-preventable and other rare infectious diseases

Immune reconstitution

- Identify the molecular mechanisms of late dysfunctional adaptive immunity
- Investigate adaptive immune system neogenesis, maturation and exhaustion and the influence of persistent alloreactivity, inflammation and viral infections
- Asses late functional pathogen-specific T- and B-cell responses to pathogens

Prevention

- Correlate immune reconstitution markers with vaccine responses to standardize thresholds for initiating vaccination
- Conduct vaccination specific prospective multicenter trials
- Assess role of other therapies such as IVIG

Cardiac, Vascular and Metabolic

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Arterial Disease

- Describe incidence, risk factors (including allo-effect) and at risk populations
- Establish HCT-specific risk prediction models
- Clarify pathobiology and evaluate novel imaging and blood biomarkers for screening
- Test interventions on risk reduction in HCT survivors

Cardiac Dysfunction

- Describe contribution of pre-HCT exposures and comorbidities
- Examine mechanisms of enhanced cardiotoxicity in patients with cardiovascular risk factors
- Describe asymptomatic cardiac dysfunction
- Novel imaging and blood biomarkers for asymptomatic cardiac dysfunction and for screening
- Test preventive interventions in high risk populations

Cardiovascular Risk Factors

Hypertension: Evaluate optimal timing of interventions based on markers of vascular and endothelial dysfunction; assess magnitude of under-treatment and barriers to treatment

Hyperglycemia: Assess effects of pre-HCT metabolic status and exposures; evaluate optimal timing and methods for screening; investigate pharmacologic and non-pharmacologic interventions in prediabetic states

Dyslipidemia: Define high-risk populations; evaluate association of dyslipidemia with inflammation after HCT and immunomodulatory aspects of statins; assess effect of lifestyle and lipid-lowering therapy on risk reduction

Sarcopenic obesity: Evaluate longitudinal changes in body composition in HCT survivors and association with outcomes, Assess risk factors and exposures and effect of exercise or dietary modification on fat/muscle mass

QOL & Psychosocial

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- Establish registry for prospective collection of patient reported outcomes that includes underrepresented groups

- Design and test risk-targeted interventions that address resource utilization and costs, process measures including feasibility and treatment fidelity, sustainability and dissemination potential; priority domains include sexual dysfunction, fatigue/sleep disruption, non-adherence, health behaviors such as physical inactivity, and psychological dysfunction

- Convene stakeholders to design a consensus-based methodological framework for outcomes evaluation including standardized time points and longitudinal prospective designs

- Evaluate and compare existing practices for integrating patient-centered outcome screening across HCT survivorship programs to identify best practices and barriers; address opportunities to incorporate patient centered outcome data into electronic medical records

Future plans:

1. Dissemination of results
   - White papers in BBMT
   - Educational session at ASBMT, ? EBMT
   - Patient outreach

2. Stimulate discussion, ideas, research projects

3. Stimulate awareness in BMT societies- ASBMT SIG

4. Coordinate and align recommendations with existing BMT initiatives, such as CTN

5. Stimulate funding discussion at federal level
   – IAA between NHLBI and HRSA

#NIHBMTLateEffects

NIHBMTConference@icfi.com

Steering committee

- Minoo Battiwalla, NHLBI/HB
- Shahrukh Hashmi, Mayo Clinic
- Navneet Majhail, Cleveland Clinic
- Steve Pavletic, NCI/ETIB
- Bipin Savani, Vanderbilt University
- Nonniekaye Shelburne, NCI/DCCPS