The HCT Late Effects Initiative: Developing Recommendations to Improve Survivorship and Long-Term Outcomes

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Disclosures

The following faculty and planning committee staff have no financial disclosures:

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Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Jackie Foster, MPH, RN, OCN	NMDP / Be The Match	Pfizer, stock owner (spouse)

Learning objectives

At the conclusion of this session, attendees will be able to:

- Define what is meant by late effects
- Describe the late effects experienced by HCT survivors
- Identify initiatives underway to understand and mitigate late effects in HCT survivors

NMDP COUNCIL MEETING 2017
November 10-11
Sharing Our Passion For Life

The HCT Late Effects Initiative:

Late effects in long term survivors of HCT

Bipin Savani

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Case history

- 49 year old female (weight 141 kg) with recurrent HL underwent reduced-intensity matched related donor allo-SCT in 2005
- Acute GVHD, maximum grade III: 2005
- Chronic GVHD (skin, ocular, oral cavity, liver): 2005-2006
- Sclerotic skin GVHD: 2006
- Bronchiolitis obliterans June 2006 on home O2
- Hypertension, hyperlipidemia and worsening DM: 2006-7

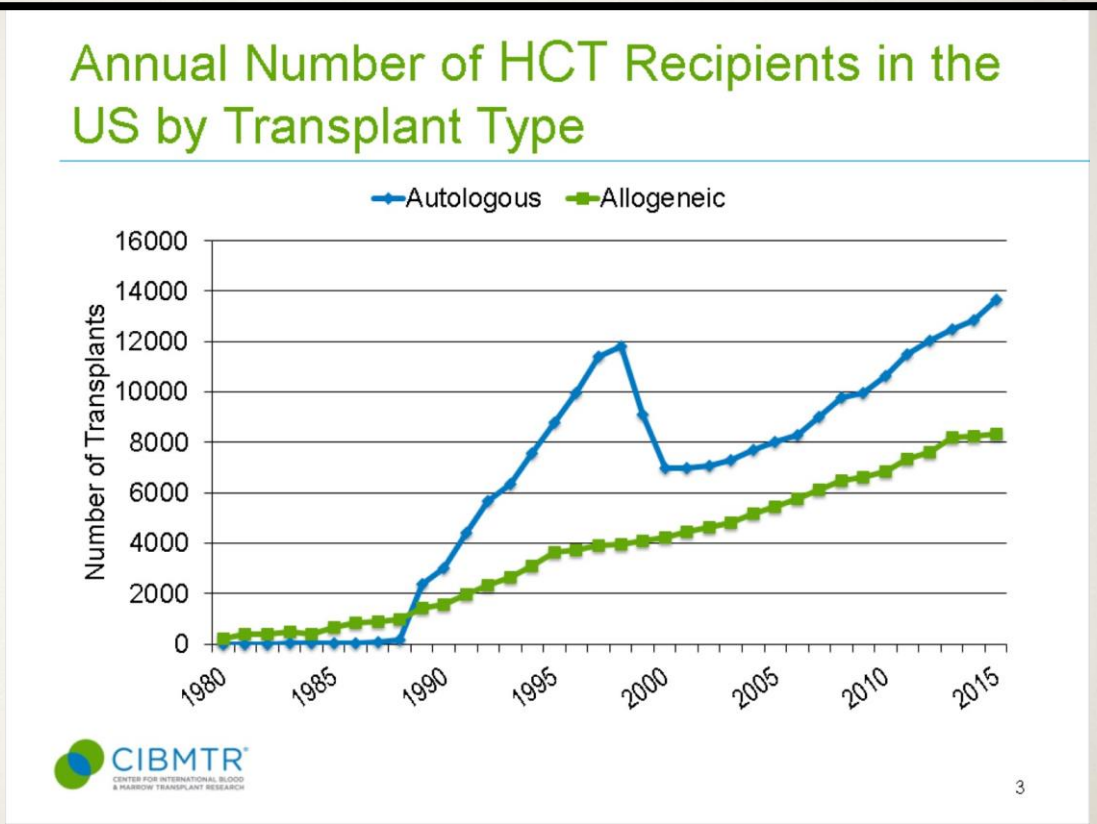
Case history

- Osteoporosis, vertebral fracture L2 after minimal trauma August 2007
- Osteonecrosis of hip bones (right hip replacement March 2008, Left July 2008)
- Decreased libido, hypothyroidism: 2006-2009
- Scleral lens for several ocular changes: 2010
- Skin cancer multiple sites (SCC): 2011
- Cervical dysplasia: 2012

Case history

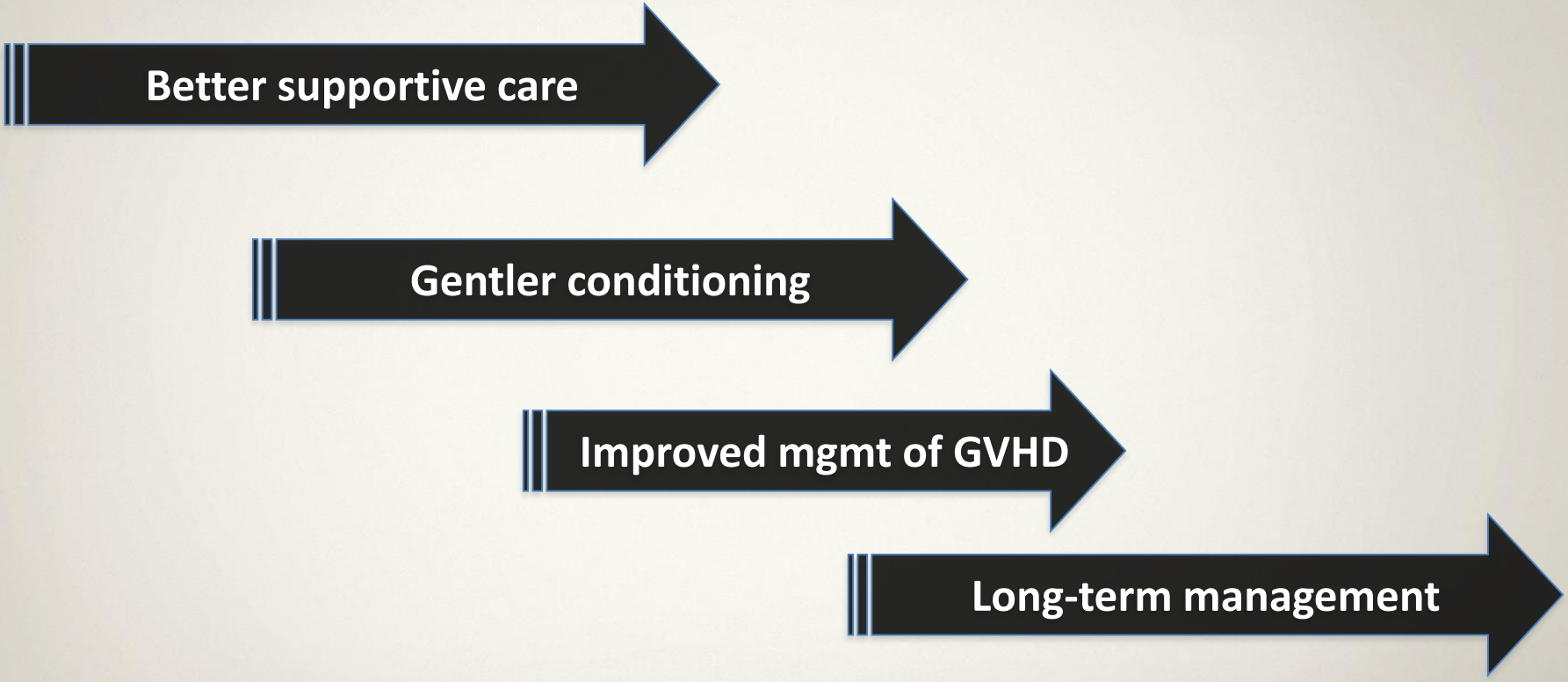
- Decreased libido
- Depression
- Sleep disturbances
- Chronic pain
- Divorced: 2010
- No job
- Lack of interest
- Fatigue
- Physical inactivity

Transplant numbers are rising



CIBMTR report 'Current Uses and Outcomes of Hematopoietic Stem Cell Transplantation 2017' accessed online Oct 21.2017
https://www.cibmtr.org/referencecenter/slidesreports/summaryslides/pages/index.aspx

Improving transplant outcome



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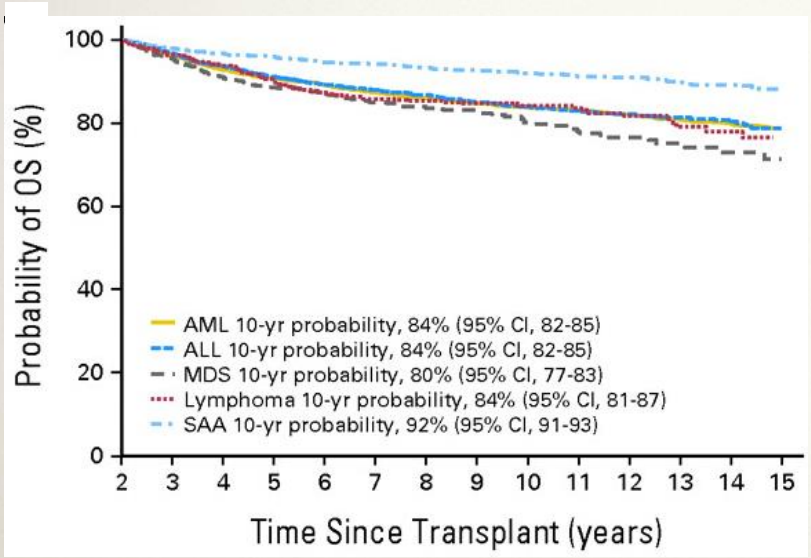
Adapted from Savani BN *et al*. Blood. 2011;117(11):3002-9.

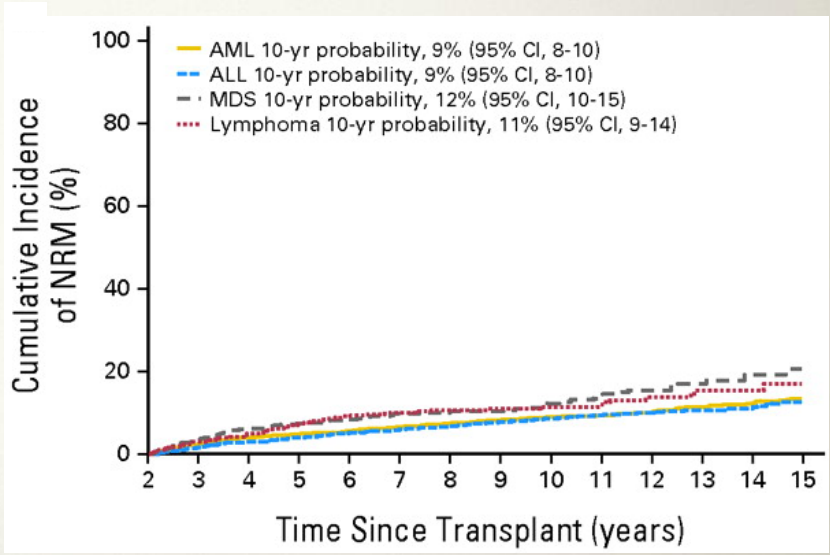
Long-term survival after HCT

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

Overall survival



Non-relapse mortality



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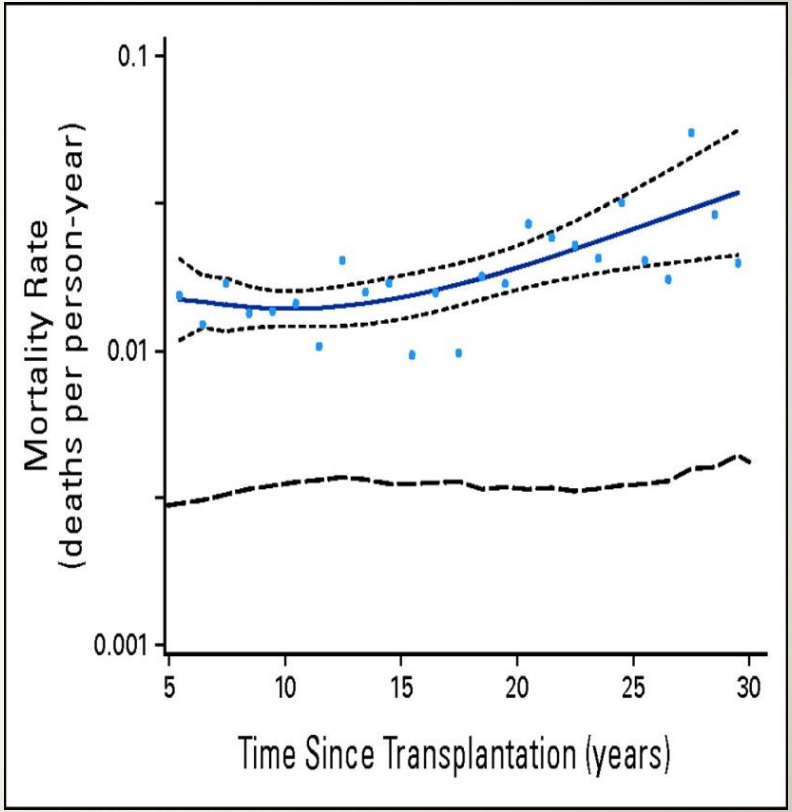
Wingard JR et al. J Clin Oncol. 2011;29(16):2230-9.

Shorter life expectancy

- Estimated survival of cohort at 20 years after SCT was 80.4%

Compared with general population:

- Mortality rate remained 4-9 times higher
- Estimated 30% lower life expectancy



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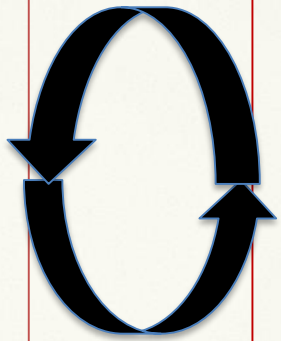
Retrospective analysis of prospectively created database (n=7984)

Adapted from Martin PJ et al , J Clin Oncol; 28:1011-1016 2010

What goes wrong: the next 30+ years

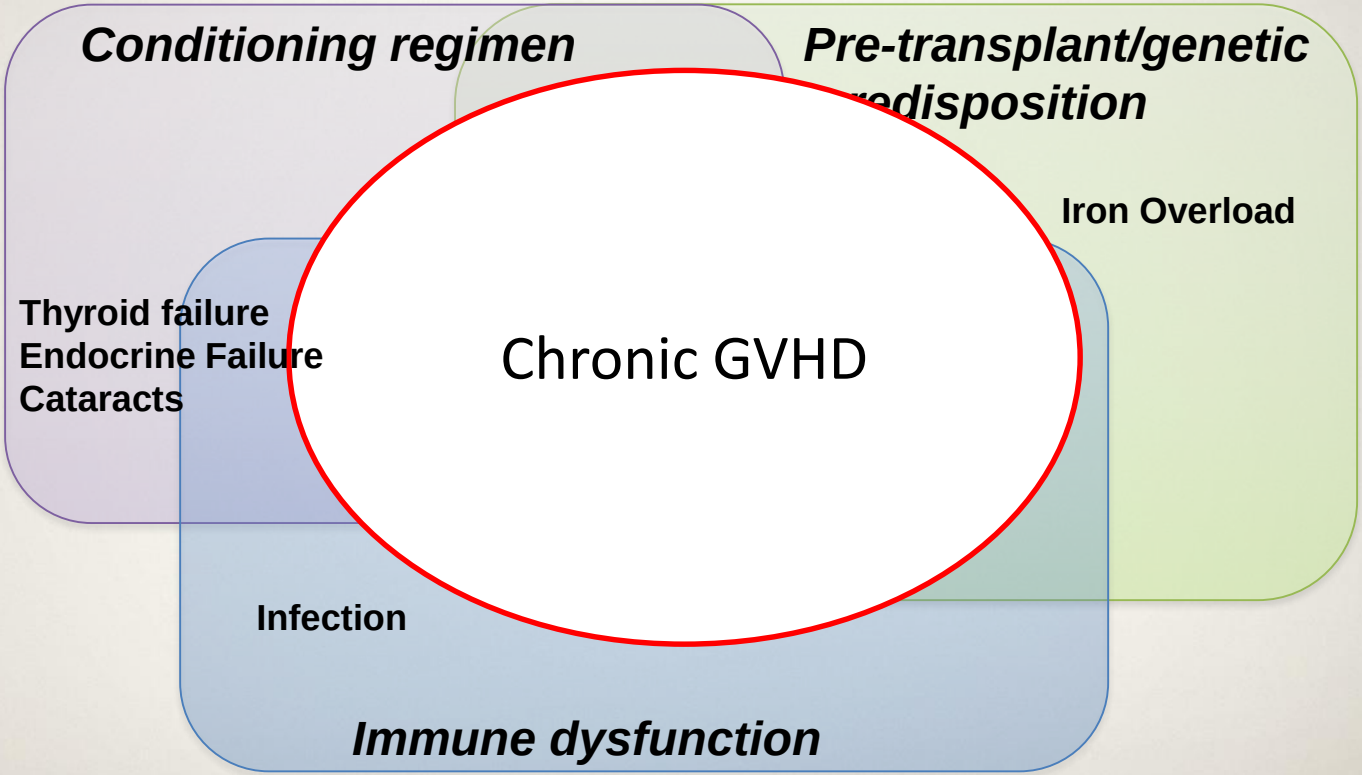
- Metabolic complications
- Pulmonary complications
- Bone loss/ AVN
- Delayed immune reconstitutions
- Renal complications
- Second malignancies



- Premature aging
- Physical symptoms
- Cognitive issues
- Loss of job
- Financial problems
- Disabilities
- Separations/ divorce
- Suicidal thoughts

Adapted from Savani BN *et al*. Blood. 2011;117(11):3002-9 and Tichelli A *et al.* Cancer. 2013;119(11):2012-21.

Immune dysfunction underpins many- late complications



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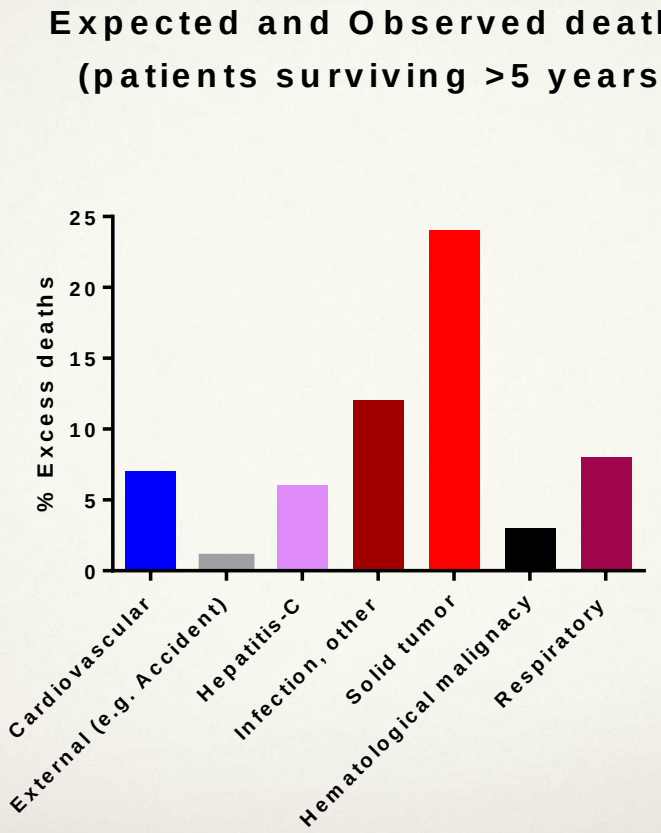
Adapted from Savani BN *et al*. Blood. 2011;117(11):3002-9.

How they die?



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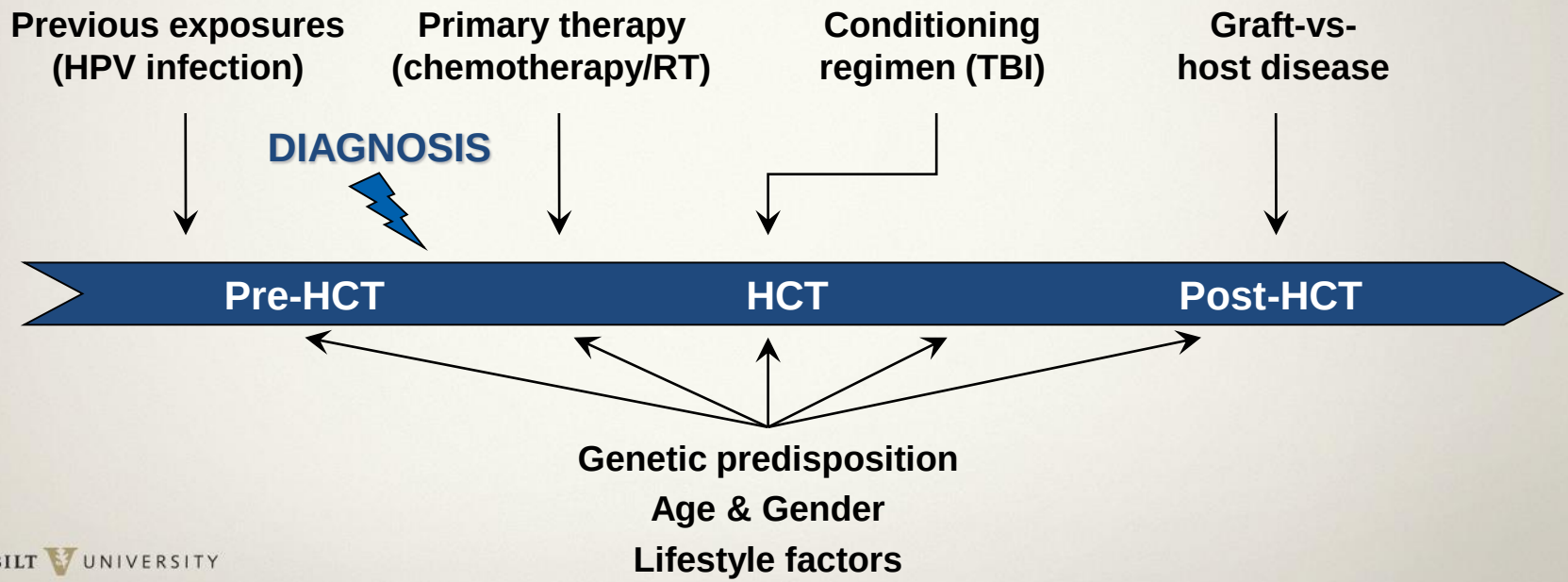
Adapted from Martin PJ et al , J Clin Oncol; 28:1011-1016 2010

New secondary solid cancers- Risk factors

Latency period of 3-5 yrs, incidence increases with time ~1-2% at 5 yrs, ~2-6% at 10 yrs, ~4-15% at >15 yrs

Risk factors for second solid cancers



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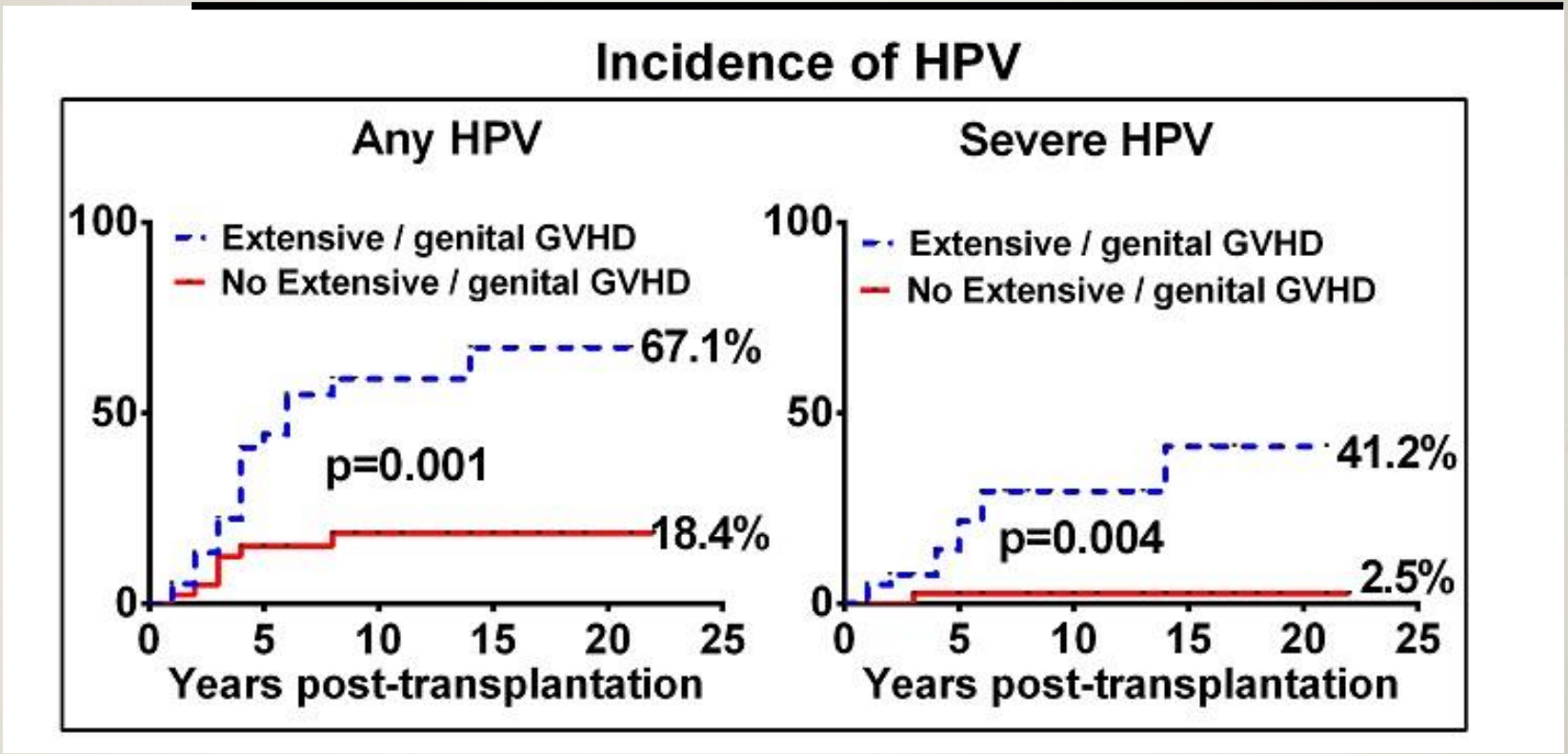
Courtesy Dr. Majhail; Inamoto *et al.* BMT 2015; Caimi PF/ Lazarus HM, Chapter 9, BMT long term management, 2014 (Ed Savani BN)

Common secondary cancers are linked to HPV

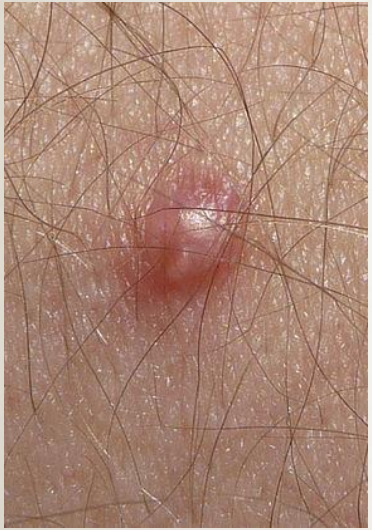


Shanis et al. Bone Marrow Transplant. 2017 Oct 16. doi: 10.1038/bmt.2017.210. [Epub]

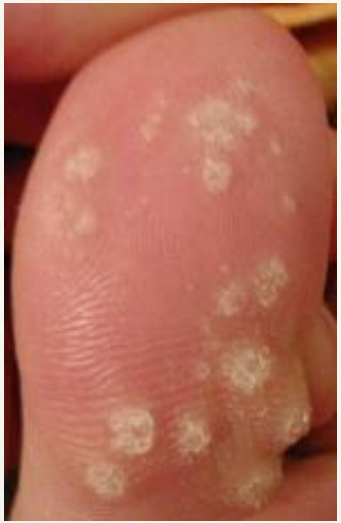
Common secondary cancers are linked to HPV

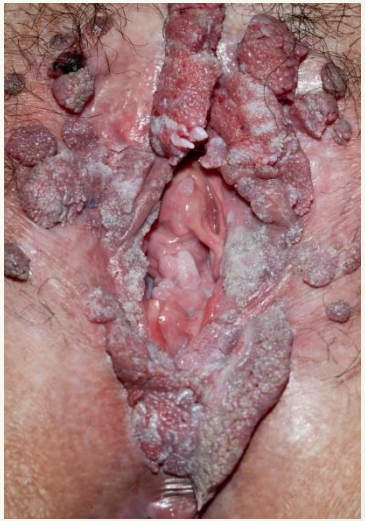
DNA virus, papillomavirus family 95% infections are subclinical Commonest STI

Papillomas

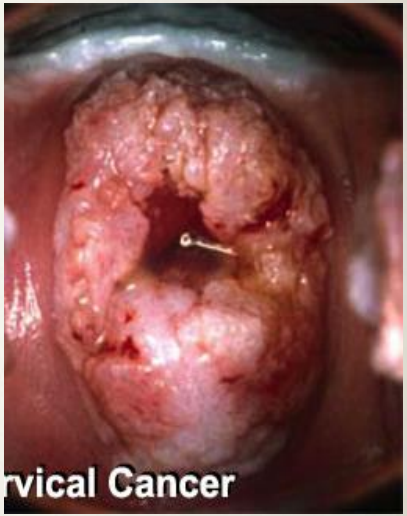


Warts





Cancer



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Merideth MA, BMT Long Term Management: Prevention and Complications 2014

Cancer screening recommendations

- A working group was established through the CIBMTR and EBMT to facilitate implementation of cancer screening appropriate to HCT recipients
- The groups reviewed guidelines and methods for cancer screening applicable to the general population, and reviewed the incidence and risk factors for secondary cancers after HCT
- A consensus approach was used to establish recommendations for individual secondary cancers
- The goals were to provide an expert review of existing, evidence-based, cancer screening guidelines applicable to the general population and adopt them to the post-HCT setting

Inamoto et al, CIBMTR and EBMT late effects writing committee members. BMT. 2015;50:1013-23

Cancer screening recommendations

Site	Screening recommendations*
Breast	• Age 20–40 years: clinical breast exam every 1–3 years • Age >40 years: annual clinical breast exam; annual mammogram Prior radiation therapy or TBI: • Age 25 years or 8 years after RT/TBI, whichever comes first, but no later than age 40 years: annual clinical breast exam, annual mammogram, annual breast MRI
Cervix	Annual Pap test and HPV DNA test
Colorectal	Fecal occult blood annually and/or flexible sigmoidoscopy or barium enema every 5 years or colonoscopy every 10 years starting age 50†
Skin	Routine skin examination in all transplant survivors, particularly for patients who had myeloablative TBI, HCT at ages <18 years or GVHD
Lung	Yearly pulmonary exam with imaging as appropriate
Oral	Screening every 12 months; every 6 months for patients with risk factors
Thyroid	Annual PE. Heightened awareness for aged ⩽ 20 years at HCT, female patients, those receiving TBI-containing CR; those who develop cGVHD

Inamoto et al, CIBMTR and EBMT late effects writing committee members. BMT. 2015;50:1013-23

Preventive strategies: recommendations

- ***HPV Vaccine Recommendations***

- The quadrivalent HPV vaccine is approved for males and females aged 9-26 years to prevent HPV-related diseases including cervical, vulvar, and vaginal cancers and precancers in females, as well as anal cancers and precancers and genital warts in both females and males.

- We offer HPV vaccinations starting at ≥12 months post-transplantation, regardless of prior sexual activity and exposure to carcinogenic strains.

Merideth MA (Chapter 23), BMT Long Term Management: Prevention and Complications 2014; Kennedy et al BBMT Oct 2017

Vaccination schedule

RE-VACCINATION SCHEDULE FOR SCT RECIPIENTS								VACCINATION OF HOUSEHOLD CONTACTS OF SCT
Inactivated Vaccine or Toxoid	**6 months**	**8 months**	**10 months**	**12 months**	**14 months**	**16 - 24 months**	**24 months**	
Tetanus, Diptheria, Pertussis (TDaP/DTaP)				X	X	X		
Haemophilus influenzas type b (Hib) conjugate				X	X	X		
Hib titers							X[4] & Annually until POS	
23-Valent Pneumococcal Polysaccharide (PPV23)				X[1]			X[1]	
13-Valent Conjugated Vaccine (Prevnar)	X[1]	X[1]	X[1]				X[1]	
PCV titers							X[4] & Annually until POS	
Inactivated polio (IPV)				X	X	X		
Influenza	X			Annually				Annually
Hepatitis B				X	X	X		
HBsAbQuant titers							X[4] & Annually until POS	
Meningococcal				X[5]				
Human Papilloma Virus (HPV)				X[6]				
Live-attenuated Vaccines*	**6 months**	**8 months**	**10 months**	**12 months**	**14 months**	**16 months**	**24 months**	
Measles/Mumps/Rubella (MMR)							X[2,3]	
Varicella Vaccine	*IN HIGHLY SELECTED PATIENTS ONLY IN CONSULTATION WITH TRANSPLANT PHYSICIAN [7,8]							

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CDC/ASBMT guidelines 2012; NIH BMT CONSORTIUM 2013; BMT LT Management: Prevention and Complications 2014

Immune responses to vaccinations after HCT

Live attenuated vaccine	Schedule	Serologic monitoring
Measles/Mumps/Rubella (MMR)	2 doses if >2 years after HCT, ≥1 year off systemic IST and no cGVHD	No recommendation[1]
Varicella-Zoster	Seronegative patients should receive 2 doses 1 month apart if >2 years after HCT, ≥1 year off systemic IST and no cGVHD	Antibody titers 1-2 months after 2nd dose
High-titer Varicella-Zoster	Contraindicated	No recommendation[1]

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Kennedy et al. Biol Blood Marrow Transplant. 2017 Oct;23(10):1614-1621

Updated vaccination recommendations

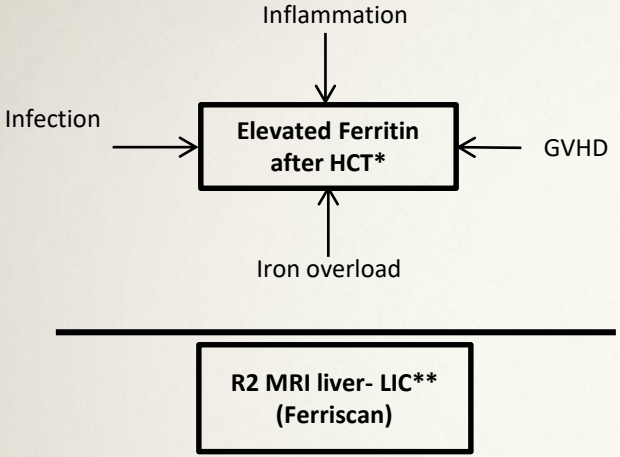
ACIP recommendations for pneumococcal vaccines (June 2012)

- Fifty percent of invasive pneumococcal disease cases were caused by serotypes contained in PCV13 (Prevnar); an additional 21% were caused by serotypes only contained in PPSV23 (Pneumovax) (CDC, unpublished data, 2011).

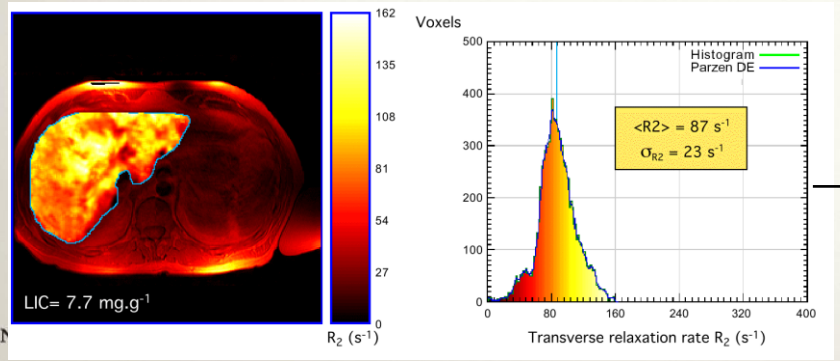
- Current vaccination guidelines recommend three doses of Prevnar followed by one dose of Pneumovax in allogeneic transplant recipients.

CDC, MMWR Morb Mortal Wkly Rep. 2012 Oct 12;61(40):816-9

Iron overload



- 30-60%, easy to overlook. Effects: Organ dysfunction, ROS, (?) Invasive fungi.
- Liver accumulates iron but most significant sequelae are cardiac and endocrine.
- Screen by ferritin, but confirm by MRI (has replaced LIC).
- Accumulating data showing “associations” w worse prognosis.



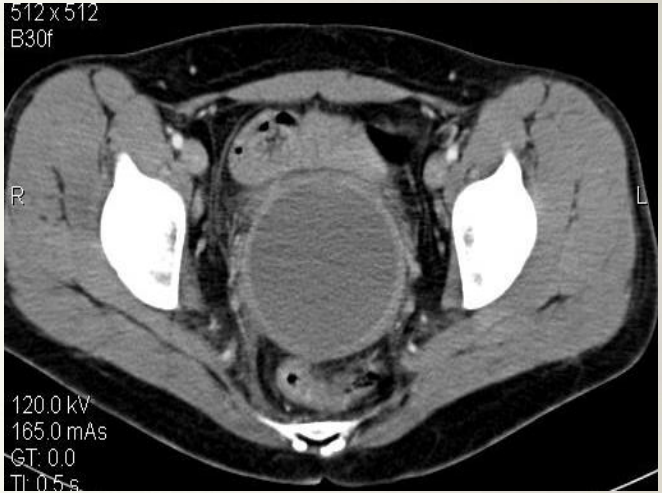
Iron overload →

Therapeutic and preventive strategies:
- Iron depletion
- Chelation post-HCT-ongoing clinical trials
- Phlebotomy- if not anemic

Savani BN, Blood. 2013 Aug 29;122(9):1539-41;
Brissot E et al. Semin Hematol 2012

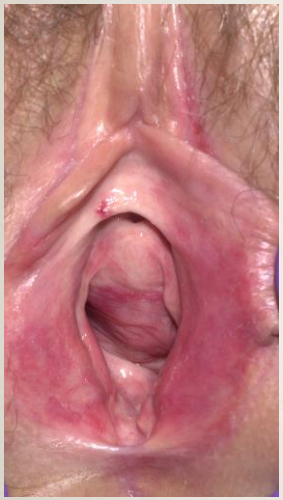
Female long term survivors

- cGVHD- vulvar and vaginal
  - 25-50%. Underreported
  - Vulvar starts in 1st year but vaginal
  - may present several years later
  - Severest form- hematocolpos
  - Regular mandatory GYN
  - screening reduces surgery
  - Rx: Topical IST, estrogens, dilators
- HRT and contraception
- HPV-related cervical dysplasia
- Infertility
- Sexual health
- Hypogonadism

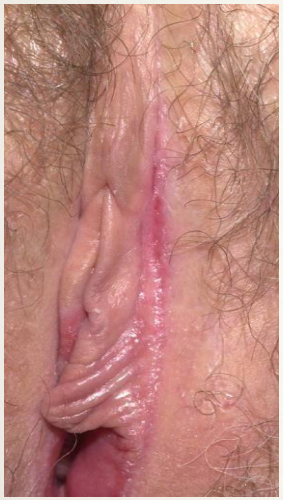


Bone Marrow Transplant. 2017 Jun;52(6):803-810
Biol Blood Marrow Transplant. 2015 Jul;21(7):1167-87
BMT Long Term Management: Prevention and Complications 2014
Shanis et al. Semin Hematol. 2012 Jan;49(1):83-93

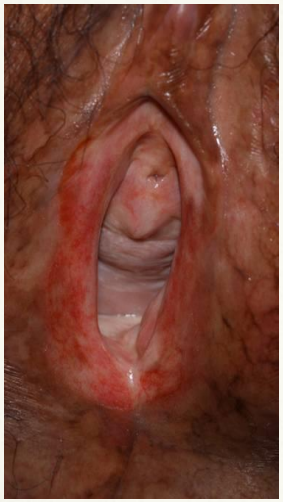
Periodic GYN examination- mandatory!



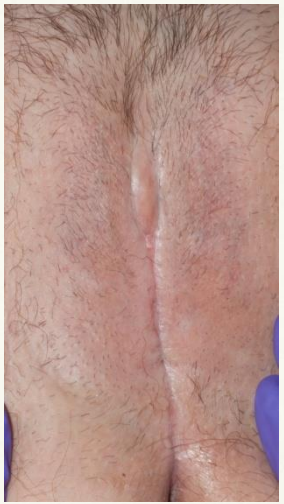
Grade I
Vulvar erythema



Grade II
Vulvar fissure



Grade II
Vulvar erosions



Grade III
Complete labial fusion

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Courtesy Dr. Pamela Stratton, MD NIH

Mild – Grade 1

- Erythema (vestibular gland, generalized, periurethral)
- Leukokeratosis r/o HPV

Moderate – Grade II

Grade I plus any of the following

- Erosions, fissures, friability
- No vaginal signs

Severe – Grade III

Grade II plus resorption of labia minora and clitoral agglutination

AND/OR

- Vaginal synechiae, hematocolpos
- Introital stenosis, myofascial pain/spasm

Cardiovascular complications

Scott JM, *et al.* Crit Rev Oncol Hematol. 2016 Feb;98:222-34

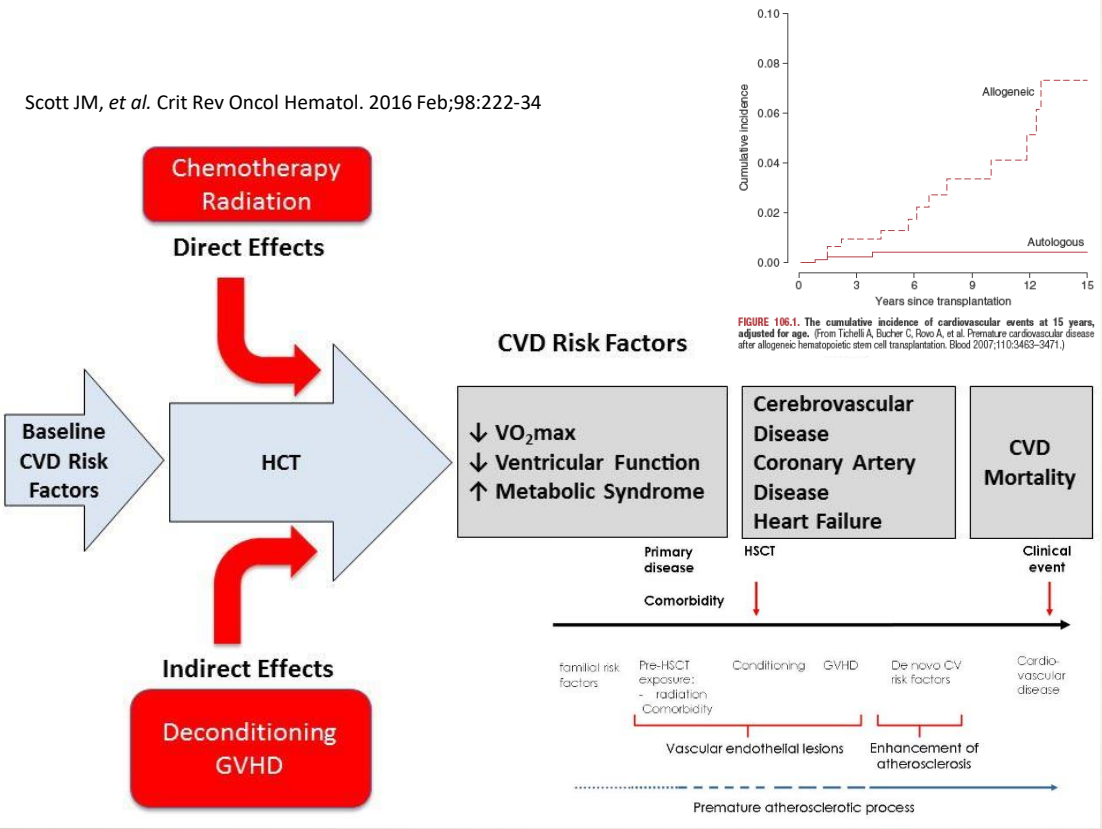

FIGURE 106.1. The cumulative incidence of cardiovascular events at 15 years, adjusted for age. (From Tichelli A, Bucher C, Rovo A, et al. Premature cardiovascular disease after allogeneic hematopoietic stem cell transplantation. Blood 2007;110:3463–3471.)

Events: CAD, CVA >>PAD

Magnitude: CVD is 3-fold higher than sibling controls

Risk factors: dyslipidemia-driven

Etiology: CR, steroids, endocrinopathy, cGVHD, age, etc

Management: address modifiable factors (lipids, DM, HTN, smoking)

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Griffith ML et al. Blood. 2010;116:1197-204; Semin Hematol. 2012;49:25-34; Tichelli A, Rovo A. BMT LT Management (Ch 24): 2014

Endocrine dysfunction

- **DM: risk is 3x that of sibling controls**
  - cGVHD, TBI, steroids. HbA1c is unreliable. Oral hypoglycemics often CI
- **Male hypogonadism:**
  - Testosterone producing Leydig cells less damaged than sperm producing Sertoli.
  - Recovery of spermatogenesis in 50-90% of non-TBI and ~ 25% of TBI survivors.
  - Supplement testosterone very selectively -low morning total testosterone level AND reduced libido/bone mass. Monitor LFTs, PSA and HCT

BMT Long Term Management: Prevention and Complications 2014; Semin Hematol. 2012 Jan;49(1):66-72; BBMT. 2017;23:529-532

Endocrine dysfunction

- **Thyroid:**
  - TSH elevations are initially subclinical. Rx- long term supplementation.
  - Thyroid adenomas and carcinomas may occur at higher rates than expected (XRT)
- **Adrenal Insuff:**
  - Overt or ACTH challenge. High prevalence (19 of 20 in one series). QOD steroids.
- **Pituitary:**
  - Growth failure, central hypogonadism or hypothyroidism.
  - TBI, young age at BMT
  - 40/141 children failed to achieve normal adult height.
  - Growth charts

BMT Long Term Management: Prevention and Complications 2014; Semin Hematol. 2012 Jan;49(1):66-72

Bone health- Avascular necrosis

- Incidence 4-19%
- Hips > knees, ankles or shoulder
- Sometimes infected. Often excruciating.
- Median at 2 years
- IST use, mainly steroids (ALL, female)
- MRI – most sensitive + extent of involvement
- Management: Conservative
  - Reduce weight bearing
  - Surgical
    - Core decompression -> joint replacement

  No role for statins or bisphosphonates!

Li X et al, Biol Blood Marrow Transplant. 2014; BMT Long Term Management: Prevention and Complications 2014

Bone health- BMD loss

- Definitions: Osteopenia, osteoporosis (T score <-2.5 or fragility fracture)
- Features: Bone loss occurs in 50-60%
- Risk factors: Steroids, hypogonadism, Vit D (diet, renal), RANK-L, inactivity
- Screening: DEXAs, Vitamin D levels
- Management: Cal/ vit D, exercise, bisphosphonates (individualize- risk of osteonecrosis, drug holiday req after 3-5 yrs), HRT for females at risk, role of androgens is unknown. Denosumbab is untested

Li X et al, Biol Blood Marrow Transplant. 2014; BMT Long Term Management: Prevention and Complications 2014

Ophthalmic complications

- #1 cGVHD
- #2 Cataracts
  - Others- xerophthalmia w/o cGVHD, corneal ulcers, glaucoma, CMV retinitis, fungal endophthalmitis, donor allergy.
  - The cumulative incidence of major ocular complications- 13%
- cGVHD
  - Lacrimal, conjunctival, lids, cornea.
  - Sicca
  - Rx: Artificial tears; tpical CSA/steroids; plugs; punctal cautery; autologous serum
- Premature Cataracts
  - 23% in peds
  - Steroids and TBI (lens shielding)
  - Rx: aggressive management of dry eyes

Cornea. 2017;36(2):258-263; BBMT. 2015;21(7):1167-87; Tichelli A, Rovo A. BMT LT Management (Book Chapter 16): 2014

Delayed chronic kidney diseases

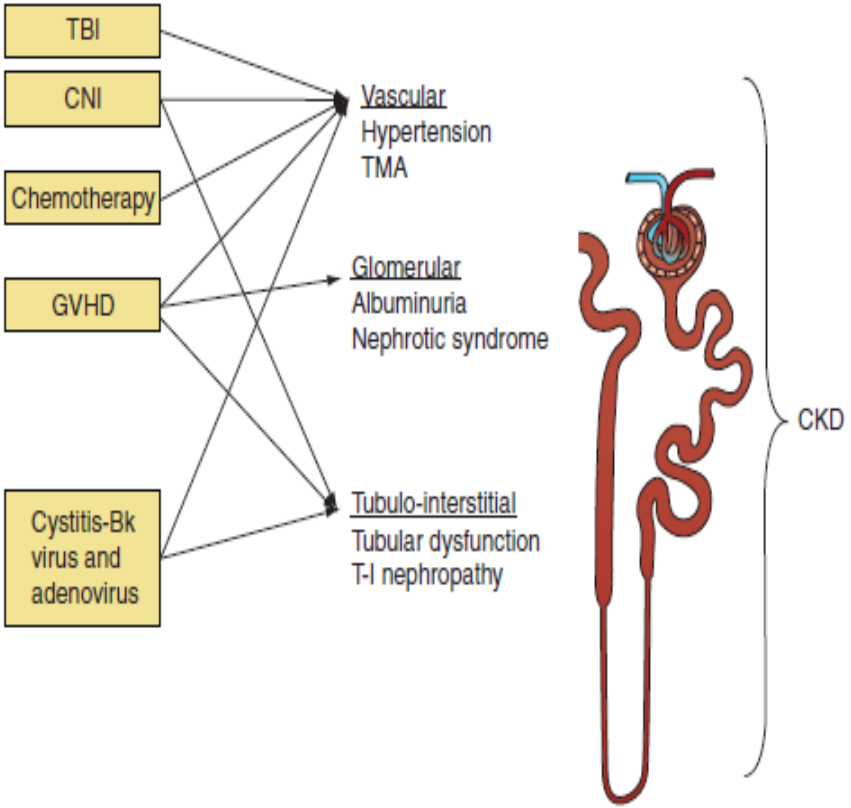

FIGURE 106.2. Types of CKD in long-term survivors of HCT: Sites of action of different renal insults with consequent clinicobiologic syndromes of kidney injury. CKD, chronic kidney disease; CNI, calcineurin inhibitor; GVHD, graft-versus-host-disease; HCT, hematopoietic cell transplant; TBI, total body irradiation; T-I nephropathy, tubulointerstitial nephropathy; TMA, thrombotic microangiopathy.

- Estimates of CKD in HCT survivors vary from 13% to 66% for adults and 62% in children.
- Often delayed up to 10 years post transplant.
- CKD defined as a sustained elevation of serum creatinine (GFR < 60) for 3 months or longer
- Mx: HTN, Renal fxn, exclude obstructive uropathies, renal biopsies for etiology.

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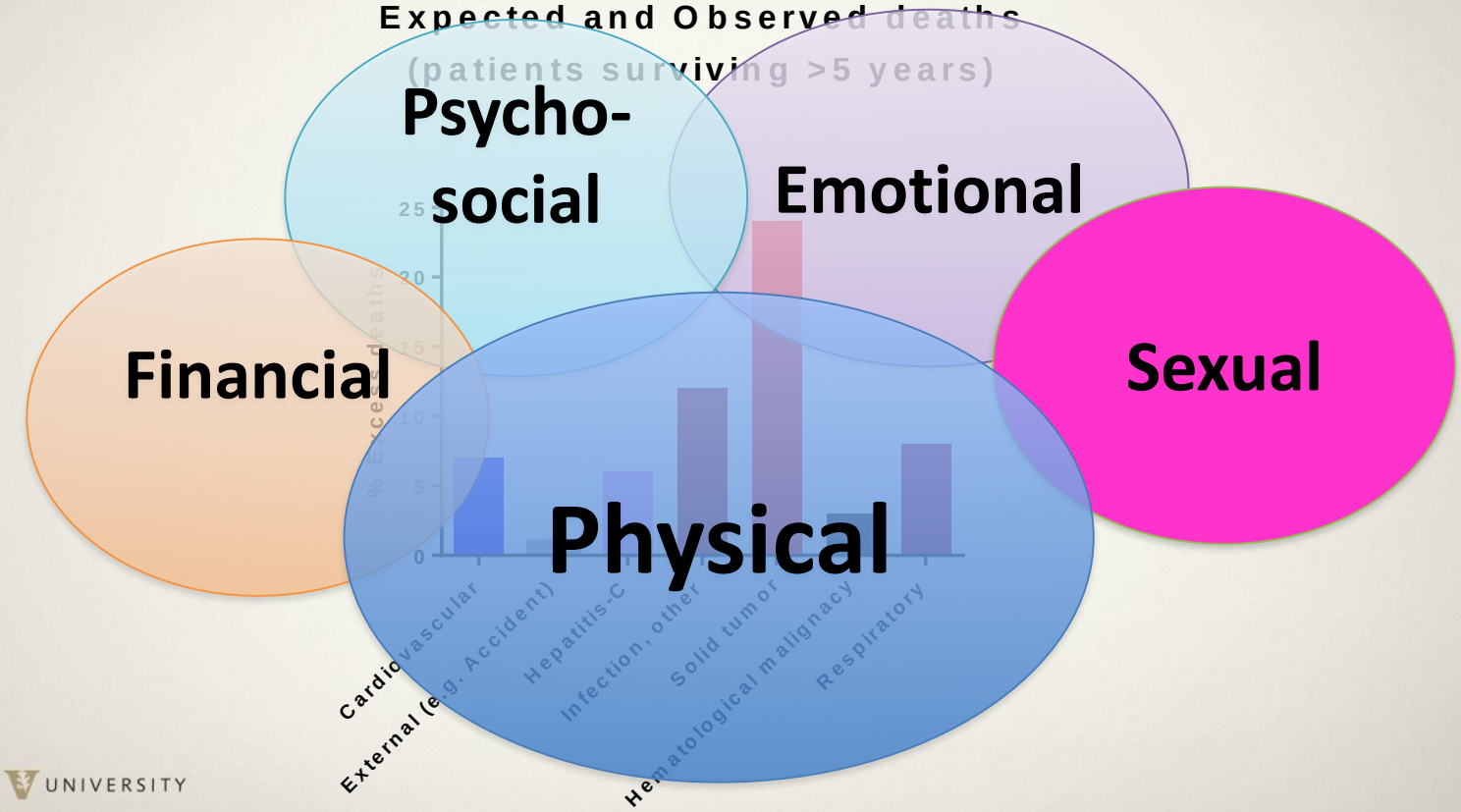
Dickenmann and Halter (Chapter 30), BMT LT Management 2014; Abboud et al. Semin Hematol. 2012 Jan;49(1):73-82

Causes of deaths in long term survivors



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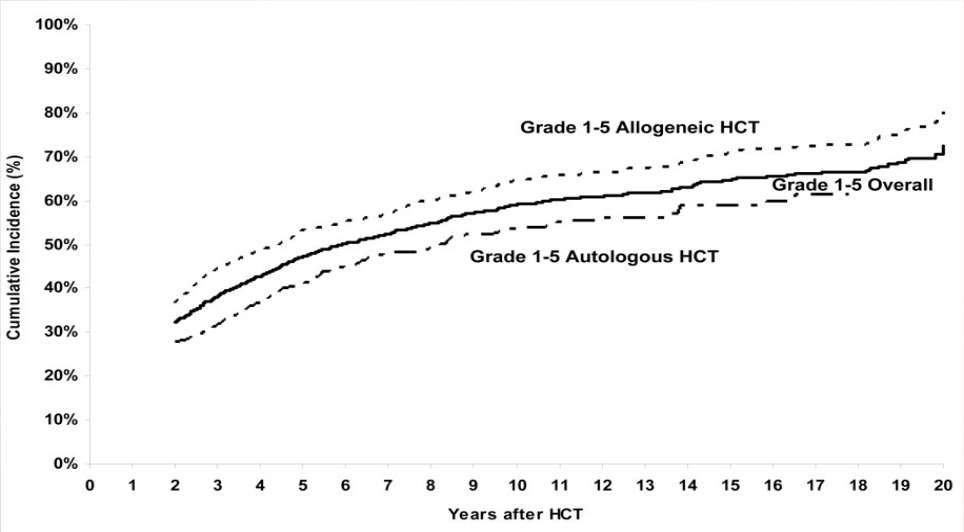
Adapted from Martin PJ et al , J Clin Oncol; 28:1011-1016 2010

Burden of late morbidity

- Late complications have a major impact on recovery and QOL post-transplant

Cumulative incidence of chronic health conditions



Bone Marrow Transplant Survivor Study (BMTSS): 1022 2-year HCT survivors

- Worse physical functioning
- More severe limitation of usual activities
- Lower likelihood of return to full-time work or study

VANDERBILT UNIVERSITY MEDICAL CENTER

Sun CL *et al*, Blood 2010; Khera N *et al*, JCO 2012

Physical symptoms after HCT- Financial burden

Financial burden

- 26% decrease of household income by >50%
- 25% withdrawing money from retirement accounts
- 9% selling/mortgaging home
- 3% bankruptcy

Causes of financial burden >3 years post-HSCT

- 30% out-of-pocket costs ≥$8000/year
- Medical copayment; median $1056 /year
- Poor coverage insurance
- Change in employment status

Khera N. et al Biol Blood Marrow Transplant. 2014;20:1375-1381

Physical symptoms after HCT- Increasing disabilities among survivors

- Work disability pension guarantees a minimum standard of living
  - Risk for long-term financial toxicity after HSCT
- 38% (76/203) survivors at 5 years or longer had partial or full work disability pension
  - compared to 3.5% in a Swiss working population (aged 18-65 years)
- Standard incidental ratio (SIR) of need disability pension was 11.8

Tichelli A. et al. et al BMT 2017

Physical symptoms after HCT- Interventions

- Interventions targeting the acute HCT period
  - Physical Exercise
  - Psychological Interventions
  - Palliative Care
- Interventions targeting the needs of HCT survivors
  - Evidence-base is lacking

Braamse AM *et al.* Bone Marrow Transplant. 2014;49(2):292-8; El-Jawahri A *et al*. JAMA. 2016;316(20):2094-2103

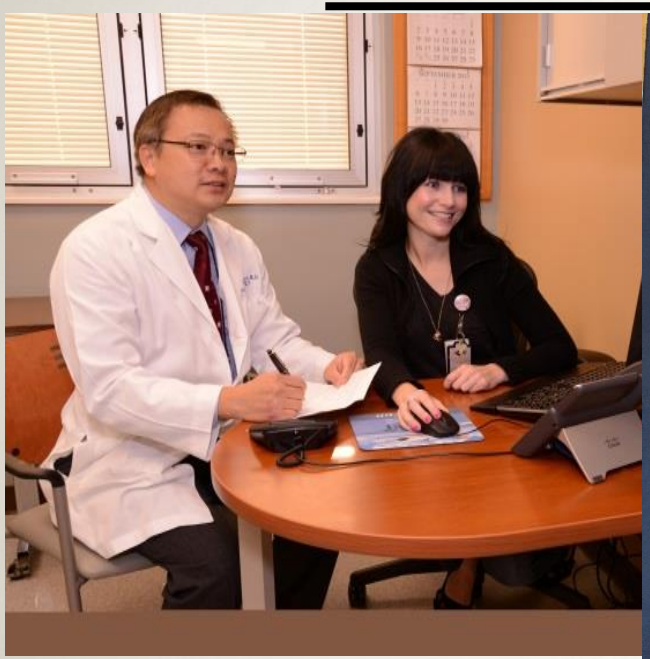
Physical symptoms after HCT- Interventions- Psychological interventions

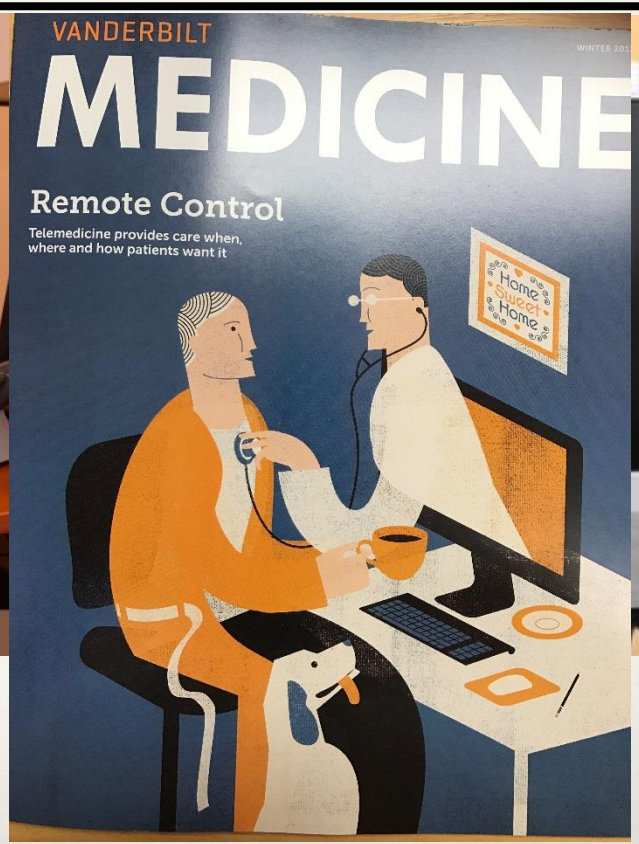
- Relaxation guided imagery
- Breathing exercises
- Progressive muscle relaxation
- Cognitive and behavioral therapy
- Face to face sessions
- Group meetings with the psychologists/ survivors

- Acupuncture
- Massage therapy
- Meditation
- Movement therapy
- Relaxation therapy
- Spinal manipulation
- Yoga
- Therapeutic touch
- Hypnotherapy

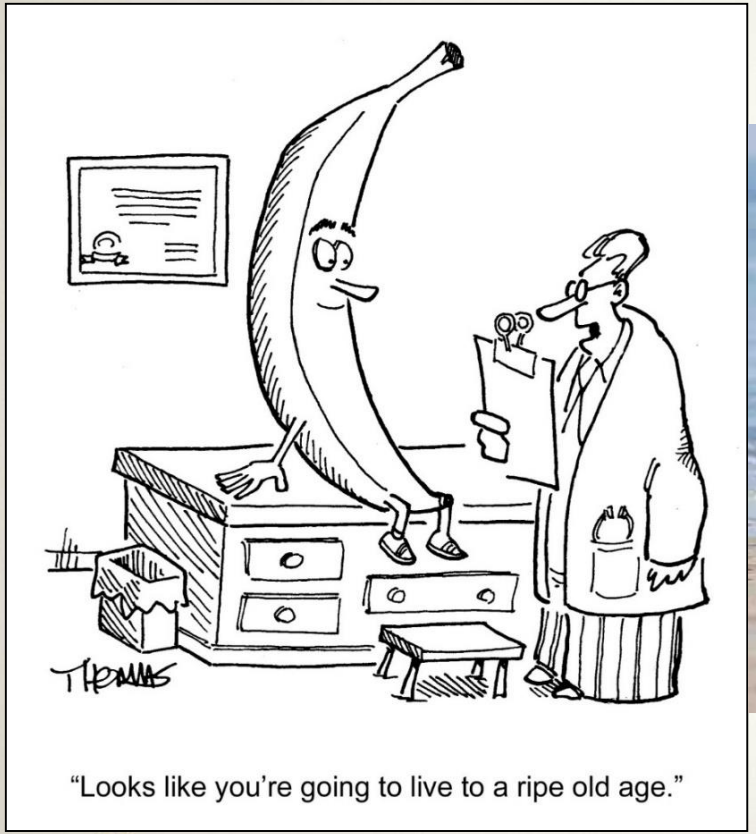
Psychooncology. 2016;25:400-411; Cancer. 2015;121:2303-2313

Next-generation long-term transplant clinics- *Telehealth*





Ultimate goal…..we are almost there



National Institutes of Health

NIH Blood and Marrow Transplant
Late Effects Consensus Conference

NMDP COUNCIL MEETING

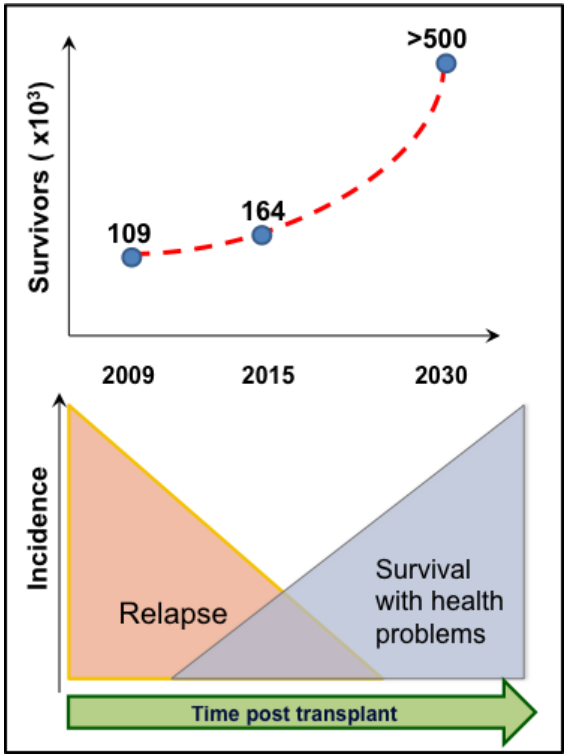
Nov10, 2017

Minoo Battiwalla, M.D., M.S.
NHLBI, NIH

INTRODUCTION

More transplants & more survivors

Needs new focus on long term survivorship



We can only wish…….

Cured, but at what cost?

40%

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

THE COST OF A CURE

Why is it different for HCT survivors?

- -age
- -extent of therapeutic exposure
- -allo-effect

How are HCT survivors unique?

How long are HCT survivors at risk? Does risk continually decline?

Who should take care of these survivors?

Can these late effects be lethal?

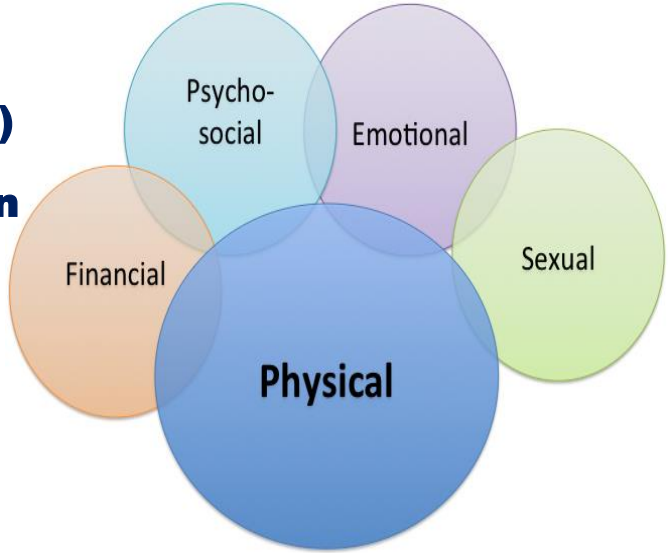
Are patient concerns adequately addressed?

What can we do together in our field to improve the situation?

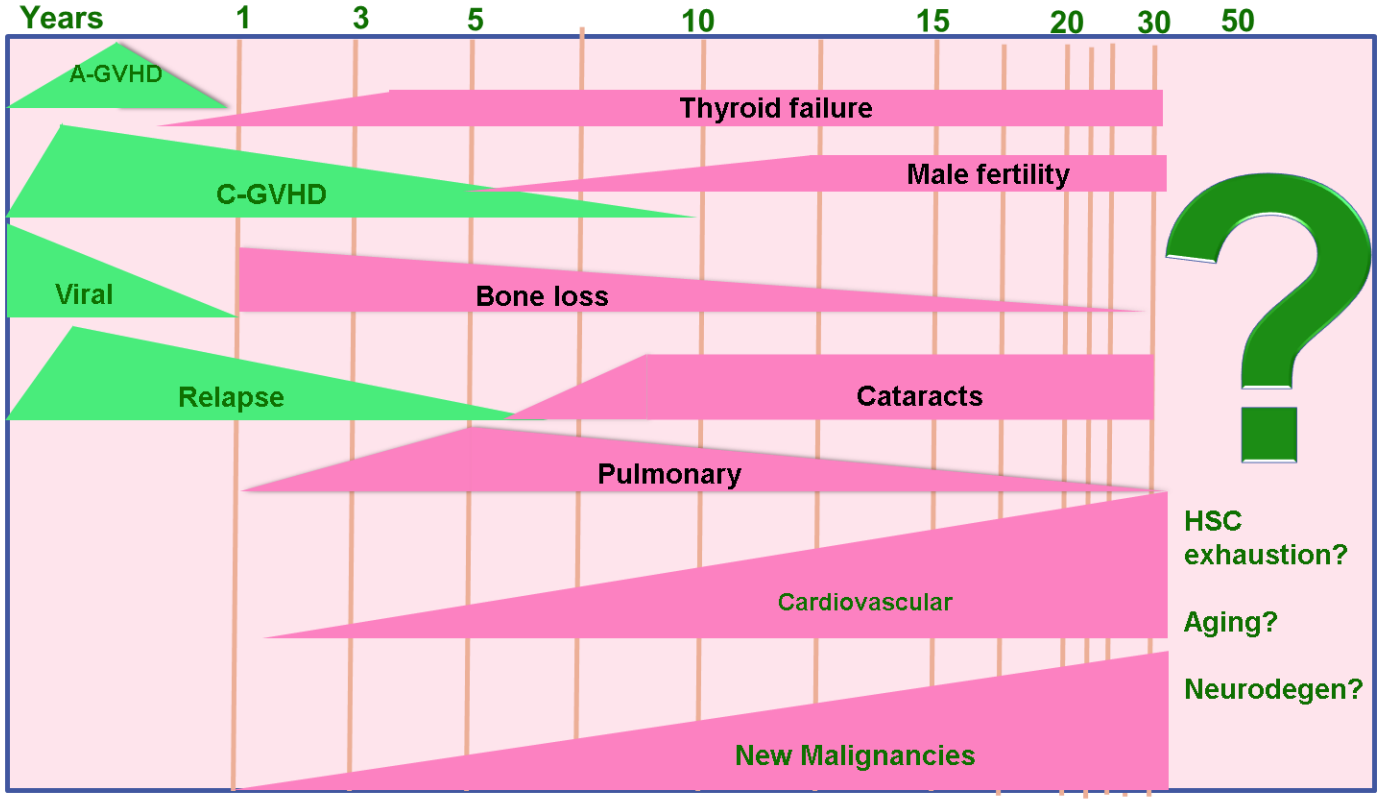
HCT LATE EFFECTS

- **Broad spectrum**
- **Diverse severity (mild – lethal)**
- **Diverse onset and progression**
- **Unique risk patterns**
- **Unique pathobiology**
- **Pediatric survivors special concern**

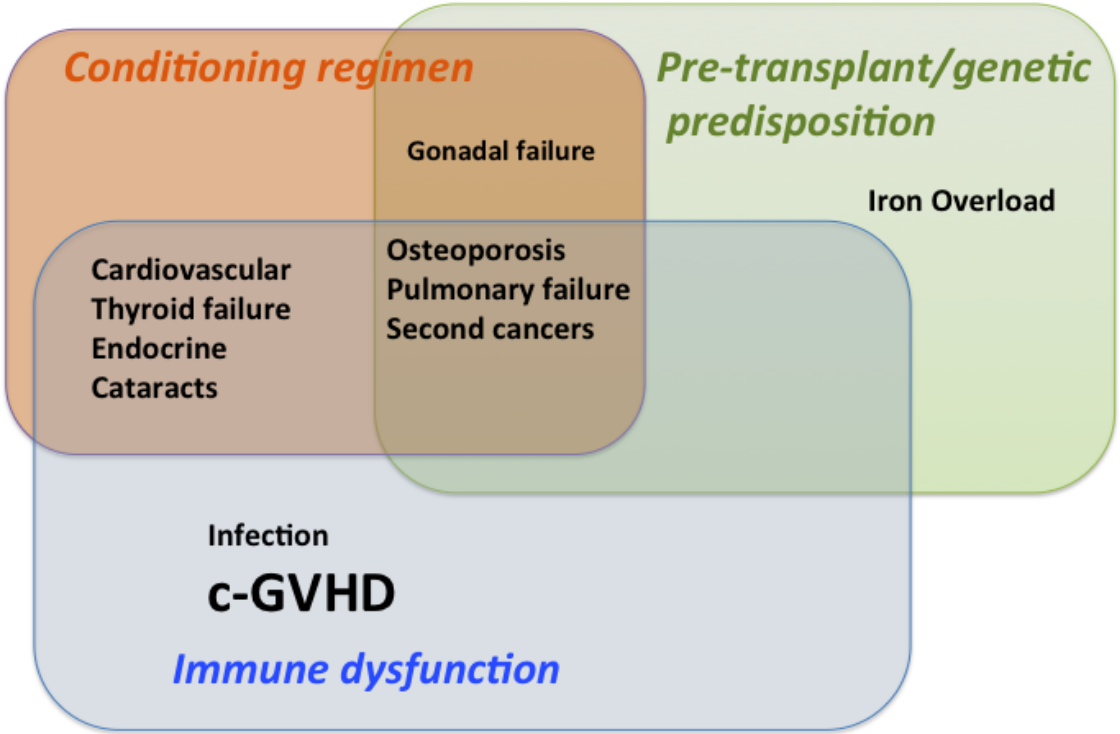
Domains of health



TIMEFRAMES FOR POST SCT COMPLICATIONS

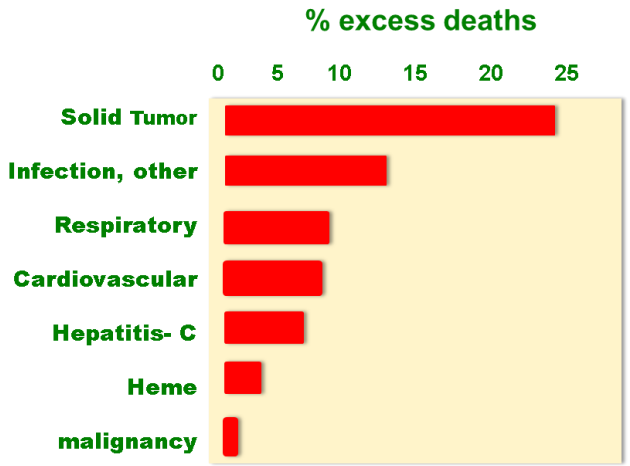


Pathobiology



Battiwalla, et al. Biol Blood Marrow Transplant. 2017 Jan

POTENTIALLY LETHAL



Adapted from Martin PJ et al, JCO 2010

- **2 years survivors have 20% mortality over 15-20y**
- **Mortality rate 4-9 x general population**
- **SMR at 15 years still ~ 2.2 x**
- **Cardiovascular and subsequent cancer risks continue to increase – no plateau at 20 yrs.**

Bhatia, et al. Blood 2007

Martin PJ et al, JCO 2010

J Wingard et al, JCO. 2011

HCT LATE EFFECTS - CHALLENGES

- **Methodology**
- **Defining mechanisms**
- **Evidence based guidelines inadequate**
- **Patient reported outcomes needed**
- **Integration into health care delivery into the future**

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

Highlights

PATIENTS >1 year after auto or allo HCT.

Scientific working groups

- **Research Methodology**
- **Health Care Delivery**
- **Cardiovascular/metabolic**
- **Immune dysfunction**
- **Subsequent neoplasms**
- **Patient reported outcomes/QOL**

- **State of the art**
- **Challenges**
- **Priorities**

- Funding discussion
- Workshop- “Starting a Late Effects Program
- Patient perspective panel

Research Methodology

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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Reports

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Research Methodology and Study Design Working Group Report

Bronwen E. Shaw [1], Theresa Hahn [2], Paul J. Martin [3], Sandra A. Mitchell [4], Effie W. Petersdorf [3], Gregory T. Armstrong [5], Nonniekaye Shelburne [6], Barry E. Storer [7], Smita Bhatia [8,*]

Research Methodology

Comprehensive data capture:

- new cohorts or expand existing cohorts
- pre-, peri- and post-HCT exposures
- extent and severity of chronic GVHD
- socio-demographic data
- PRO
- Financial

High priority areas:

- morbidity, impairment, disability and/or premature mortality,
- excess risk compared to general population
- potentially modifiable risk factors

Biospecimen Repositories:

- new vs supplement existing repositories
- before and after HCT
- biomarkers, risk factors and pathogenesis of late effects;
- germline DNA, total leukocyte, cell-specific RNA, plasma serum, and fresh frozen tissue of subsequent neoplasms

Statistical Methodology

Health Care Delivery

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journal homepage: www.bbmt.org

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

Shahrukh K. Hashmi [1], Christopher Bredeson [2], Rafael F. Duarte [3], Stephanie Farnia [4], Susan Ferrey [5], Courtney Fitzhugh [6], Mary E.D. Flowers [7], James Gajewski [8], Dennis Gastineau [1], Melissa Greenwald [9], Madan Jagasia [10], Patricia Martin [11], J. Douglas Rizzo [12], Kimberly Schmit-Pokorny [13], Navneet S. Majhail [14,*]

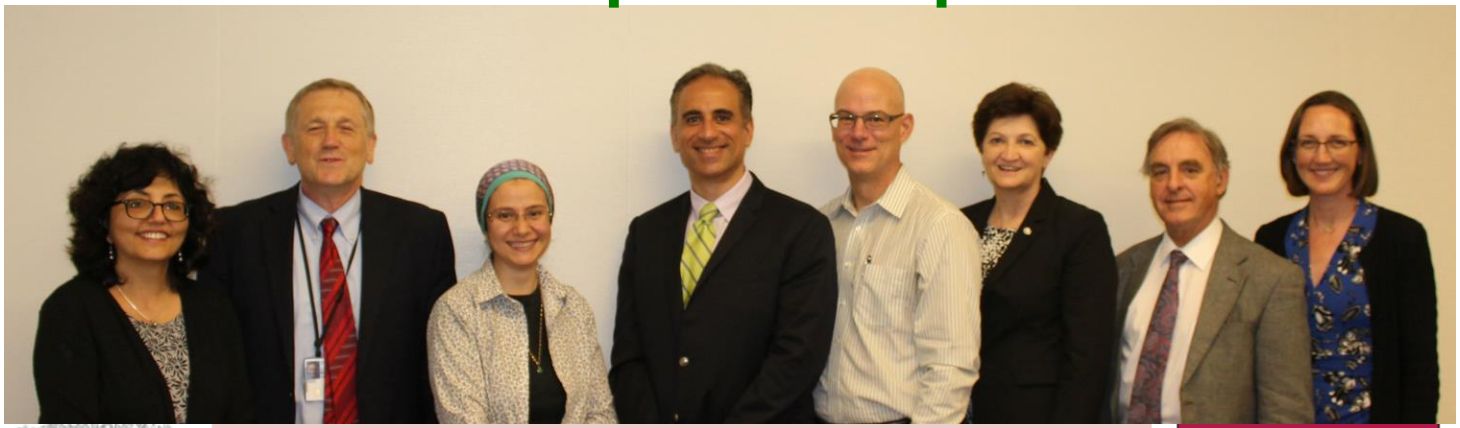
Healthcare delivery

- Identification, development, implementation and efficacy of patient-centered care delivery models,
- Novel models: IT, care coordination, non-physician providers
- Patient self-management and IT tools
- Healthcare disparities, special populations including caregivers
- Evaluate treatment summary and survivorship care plans
- Implementation of evidence-based guidelines
- Evaluate role of supportive therapies in survivorship care

Coverage and value

- Costs and value of HCT: link existing DB and EHR platforms
- Identify patient-centered coverage models for preventive care and late complications
- Investigate resource utilization, and cost-effectiveness through the care continuum
- 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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Reports

National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Subsequent Neoplasms Working Group Report

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]

Subsequent Neoplasms - Challenges

Retrospective studies, path reports

Risk factors for individual SNs not well understood

Therapeutic exposures not well captured

Mechanisms not fully understood

Prevention/screening and therapy

Subsequent Neoplasms - Priorities

Develop large scale, long-term prospective studies to:

- **Quantify risk for individual SN subtypes,**
- **Define risk factors- traditional (smoking)and HCT**
- **Identify mechanisms**
- **Optimize prevention, screening, and therapy.**

Requires:

- **Pre-transplant data (therapeutic exposures)**
- **Biological correlates (immune, genetic)**
- **Support for long term biomarkers**

Immune Dysregulation

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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]

Immune Dysregulation - Challenges

Late infections are a significant lethal complication

Cause?

- **Pathogens**
- **Immune recon / GVHD / IST**
- **Role of early and late microbiota changes**

Rational preventative management:

- **Evidence-based vaccine guidelines**
- **IVIG**

Immune Dysregulation - Priorities

Understand Late infections

- Multicenter registry to identify serious infections, pathogens, and risk factors
- Immunologic correlates using banked samples
- Microbiota changes
- Validate infection control guidelines in the prospective registry

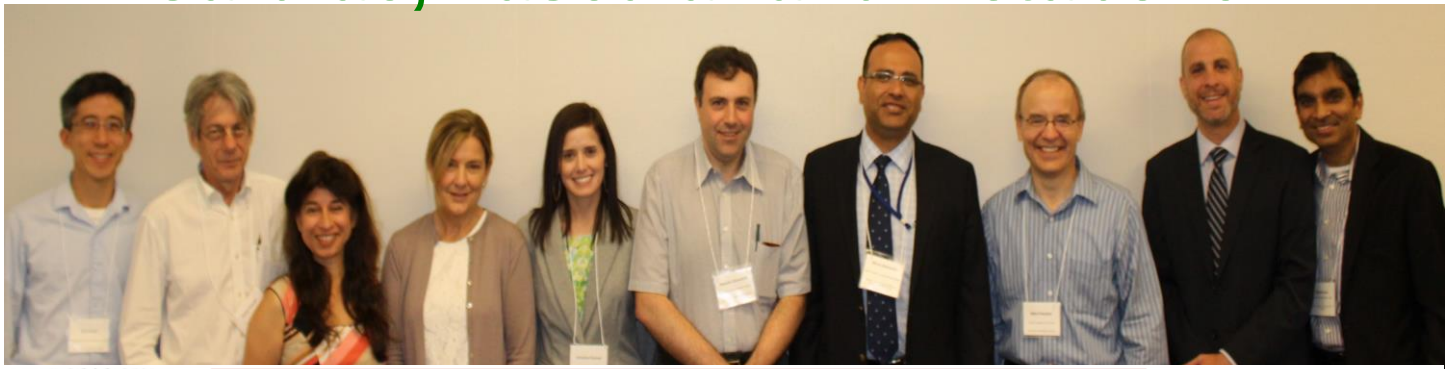
Immune reconstitution

- Molecular mechanisms of late dysfunctional adaptive immunity
- Adaptive immune system neogenesis, maturation and exhaustion
- Persistent alloreactivity, inflammation and viral infections
- Late functional pathogen-specific T and B cell responses

Prevention of infections

- Standardize thresholds for initiating vaccination based upon immune markers
- Conduct vaccination-specific prospective multicenter trials
- Assess role of other therapies such as IVIG

Cardiac, Vascular and Metabolic



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Reports

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

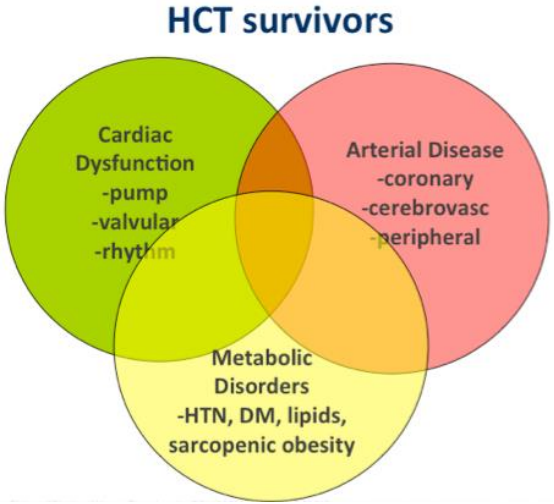
Saro H. Armenian [1,*], Wassim Chemaitilly [2], Marcus Chen [3], Eric J. Chow [4], Christine N. Duncan [5], Lee W. Jones [6], Michael A. Pulsipher [7], Alan T. Remaley [3], Alicia Rovo [8], Nina Salooja [9], Minoo Battiwalla [10]

Arterial Disease

- Incidence, risk factors, at risk populations
- HCT-specific risk prediction models
- Pathobiology- imaging and blood biomarkers screening
- Test interventions

Cardiac Dysfunction

- Pre-HCT exposures and comorbidities
- Mechanisms of enhanced cardiotoxicity
- Describe asymptomatic cardiac dysfunction
- Novel imaging and blood biomarkers for asymptomatic cardiac dysfunction and for screening
- Test interventions in high risk populations



Cardiovascular Risk Factors

Hypertension: 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

Patient Centered Outcomes

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journal homepage: www.bbmt.org

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National Institutes of Health Hematopoietic Cell Transplantation Late Effects Initiative: The Patient-Centered Outcomes Working Group Report

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]

Patient Centered Outcomes

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

- Design and test risk-targeted interventions
  - 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, resource utilization and costs

- 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

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

Ongoing and future efforts

1. Dissemination of results
   - White papers in BBMT- Editorial + 6 WG papers pre-published online
   - Scientific session at ASBMT
   - Patient outreach

2. Stimulate discussion, ideas, research projects
   - Sickle Cell
   -NCI & NHLBI funding announcements

3. Awareness in BMT societies- SIG for Late Effects in ASBMT

4. Coordination at the federal level: NCI, NHLBI, HRSA

5. Framework for multi-centric Late Effects studies:
   Redcap Database (Vanderbilt)
   Protocol (Bipin Savani)
   Bio-repository (NHLBI, John Barrett)

CONCLUSIONS

- **Increasing transplant activity and growing awareness of late complications.**
- **The NIH HCT Late Effects Initiative has identified priority areas for future effort.**
- **Further improve survival by addressing potentially lethal late effects.**

POTENTIALLY LETHAL LATE EFFECTS

- **Immune dysregulation**
- **Cardiovascular & metabolic**
- **Subsequent neoplasms**

FUTURE POSSIBILITIES?

- **FACT mandated survivorship program**

- **Active consortium to study biology of select late effects**
  - Database
  - Protocol
  - Biological samples

- **Mandated longer term outcome reporting through SCTOD.**

No survivor left behind

Acknowledgements

#NIHBMTLateEffects

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Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

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]

Questions?