Pediatric Cancer Survivorship: Late Health Effects, Risk-Based Screening, and Optimizing Care Delivery

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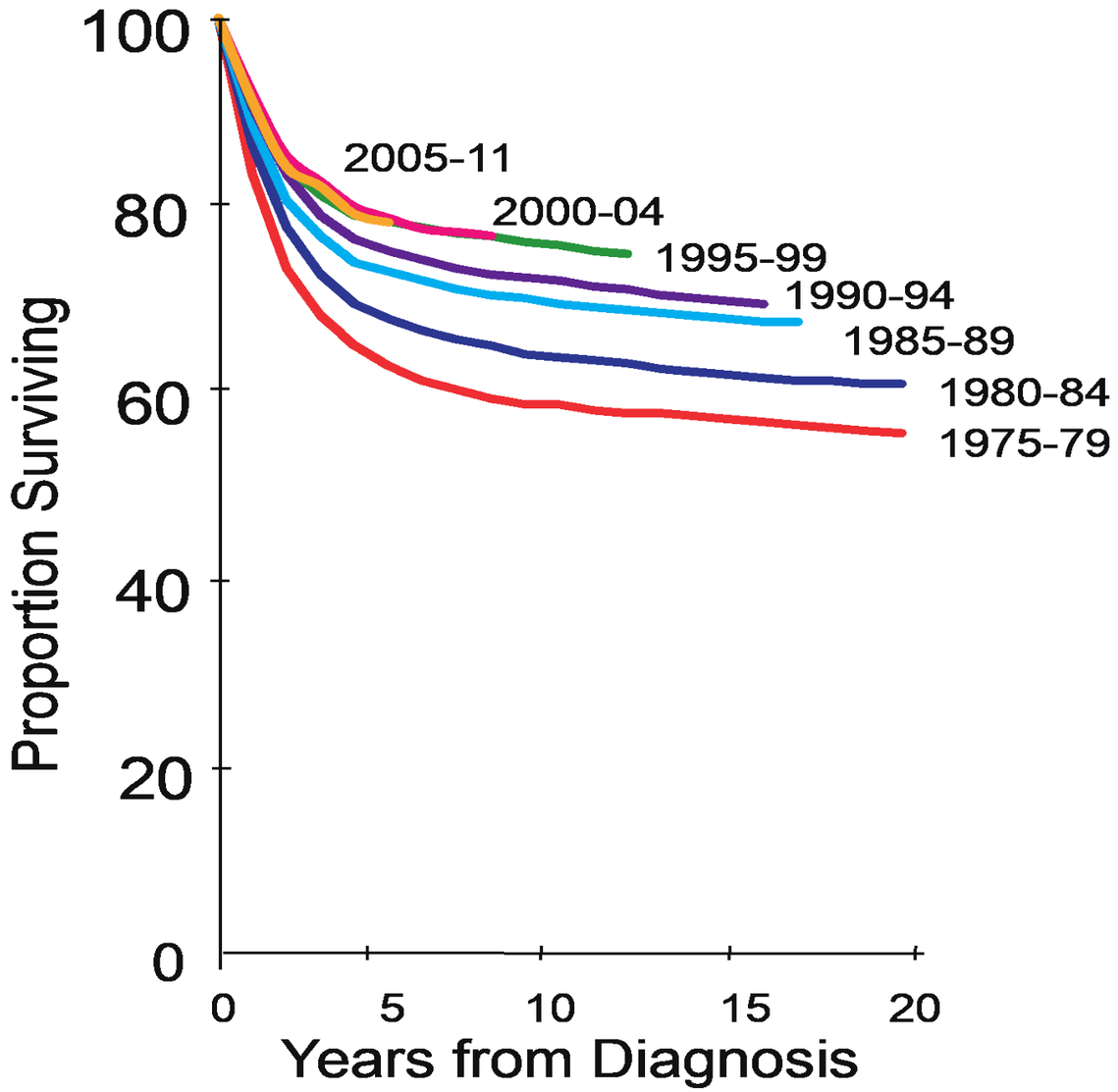
Disclosures

- I have no financial interest or other relationship with any manufacturer/s of any commercial products.

Objectives

- Discuss the long-term health conditions commonly experienced by survivors of childhood cancer.
- Explore ways in which treatment should be tailored individually to each patient to reduce long-term consequences.
- Review measures for the monitoring, prevention and management of long-term health conditions in childhood cancer survivors.
- Explore strategies to facilitate collaborative long-term, interdisciplinary care for survivors of childhood cancer.

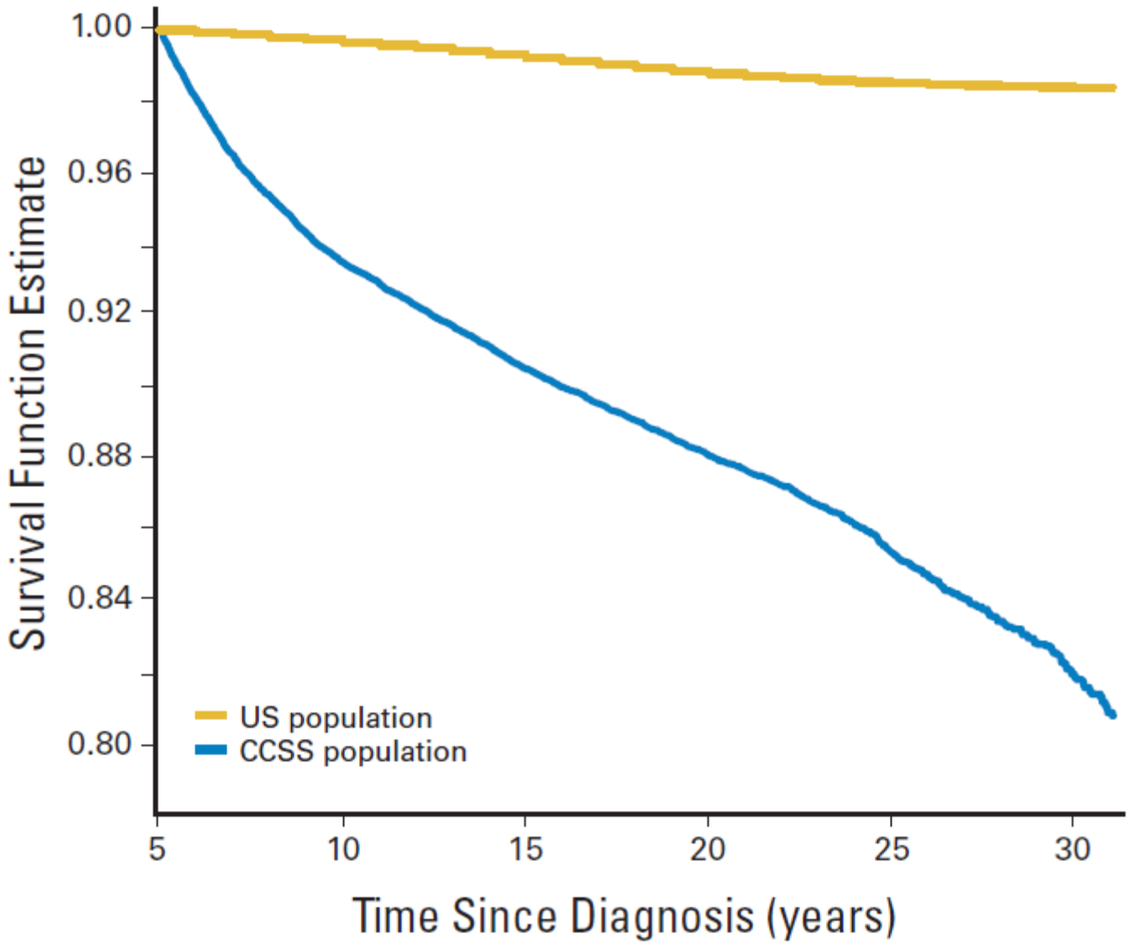
Emerging Survivor Population



- >84% of children diagnosed with cancer will achieve 5-year survival.
- 1 in 750 individuals in the U.S. is a childhood cancer survivor.
- 500,000 childhood cancer survivors are estimated to be living in the U.S.

Howlader et al, SEER Cancer Statistics Review 1975-2012
Robison & Hudson, *Nature Reviews Cancer* 2014

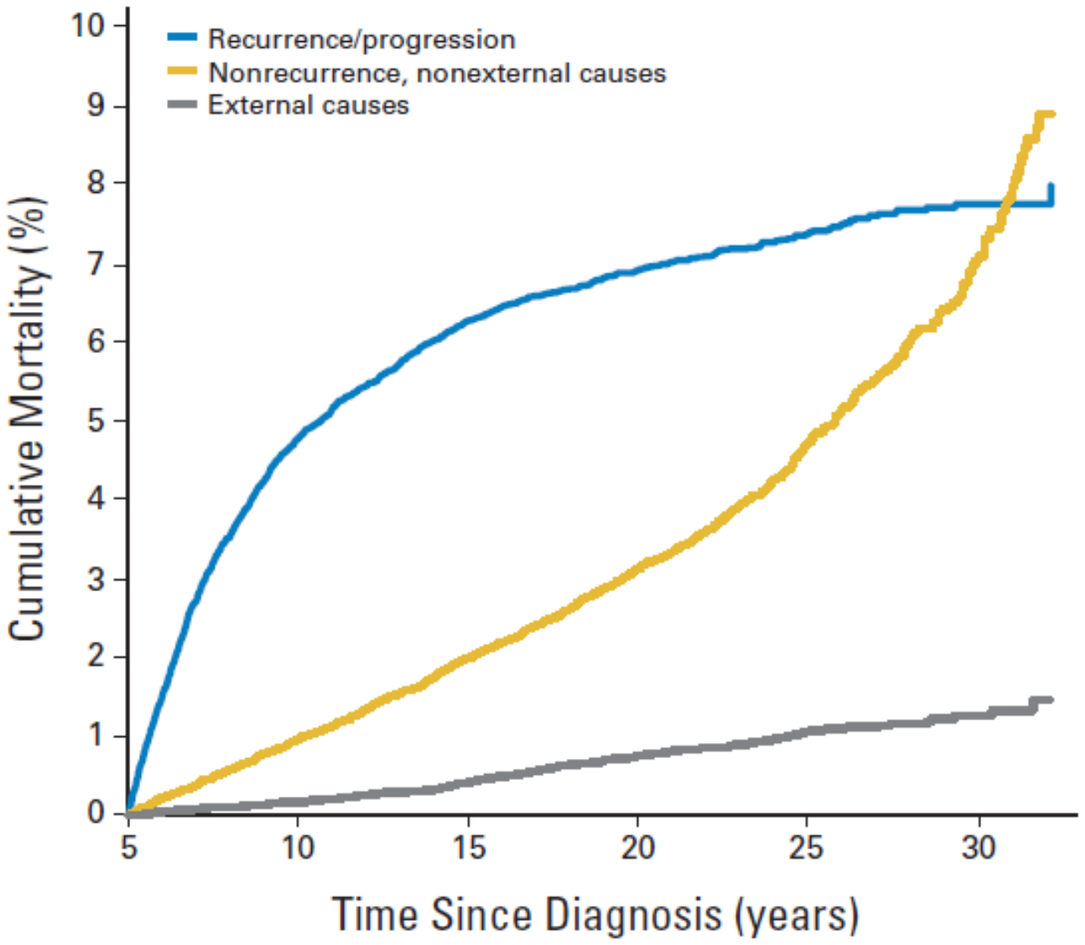
Survivor Mortality



- Childhood cancer survivors experience increased mortality risk compared to the U.S. population.

Armstrong et al, *J Clin Oncol* 2009

Survivor Mortality



- Childhood cancer survivors experience increased mortality risk compared to the U.S. population.
- By 30 years from cancer diagnosis, chronic health conditions surpass recurrent or progressive disease as the leading cause of death.

Armstrong et al, *J Clin Oncol* 2009

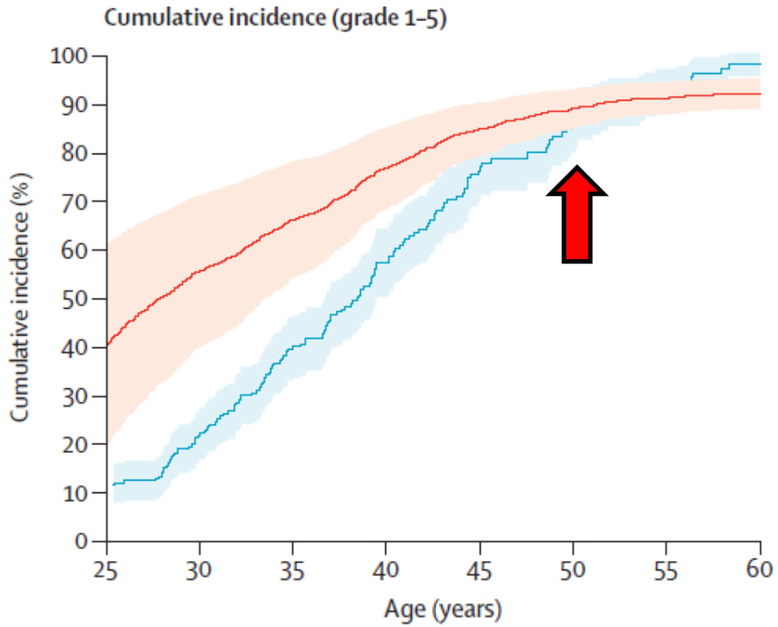
Late Effects of Cancer Treatment

Cohort Size/Citation	≥ 1 Problem	≥ 2 Problems	Severe Problems
290 *Eur J Cancer 1998;24:694-8*	**58%**	**32%**	**–**
288 *AJPHO 1994;16:143-52*	**69%**	**–**	**21%**
96 *Cancer 2000;88:1687-95*	**69%**	**36%**	**30%**
10,397 *NEJM 2006;355:1572-82*	**67%**	**33%**	**33%**
1,713 *JAMA 2013;309:2371-2381*	**95.5%**	**–**	**80.5%**

Modified from Bhatia 2006

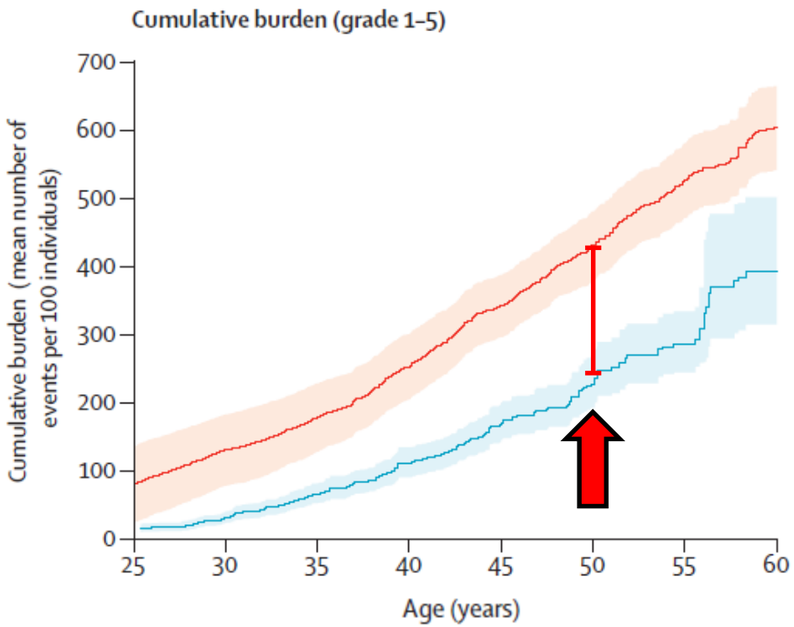
Cumulative Incidence vs. Cumulative Burden

Cardiovascular Conditions in SJLIFE Hodgkin Lymphoma Survivors



SJLIFE-eligible survivors
Community controls

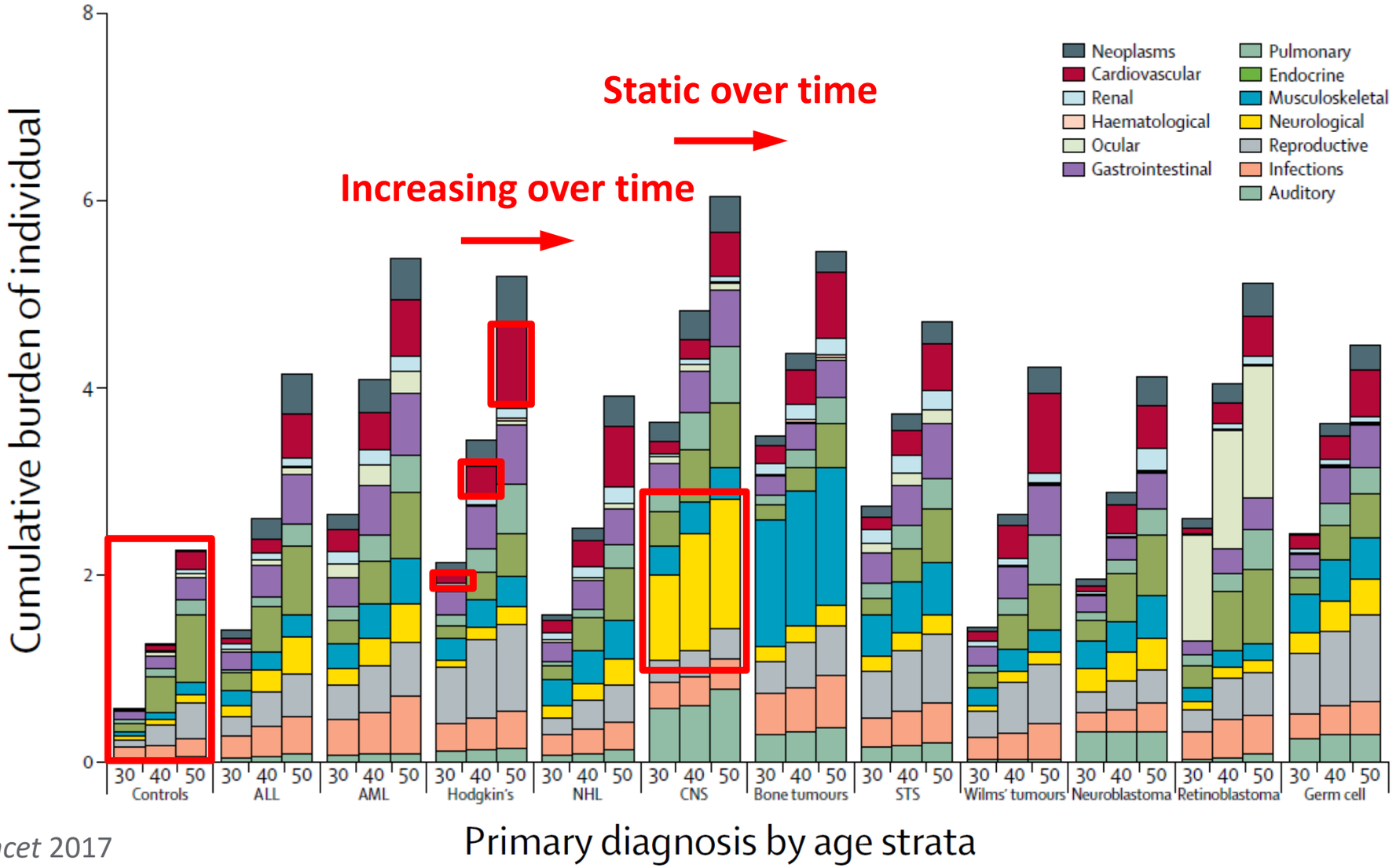
Bhakta, et al *Lancet Oncol* 2016



Cumulative Burden of Chronic Conditions in Childhood Cancer Survivors				
Attained Age	Grade 1-5		Grade 3-5	
	Survivors	Controls	Survivors	Controls
30	7.7	2.0	2.1	0.6
50	17.1	9.6	4.7	2.3

Bhakta, et al *Lancet* 2017

Grades 3-5 Chronic Health Conditions

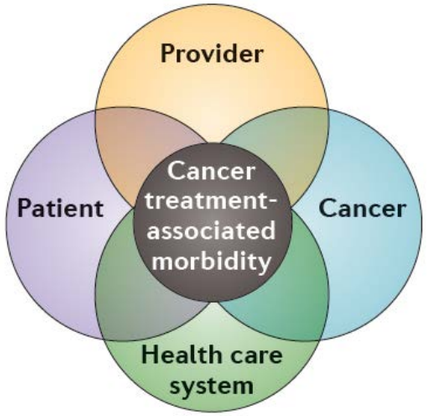


Bhakta et al, *Lancet* 2017

Factors Influencing Survivor's Health Outcomes

- Survivorship education or training
- Survivorship experience
- Practice style
- Perceptions regarding preventive care
- Access to survivorship resources
- Knowledge or access to individual survivor health history

- Age at treatment and attained age
- Sex, race or ethnicity
- Familial or genetic factors
- Pre- or co-morbid conditions
- Health behaviours
- Cognitive or developmental status
- Health knowledge
- Health risk perceptions
- Self-efficacy
- Insurance or health care access

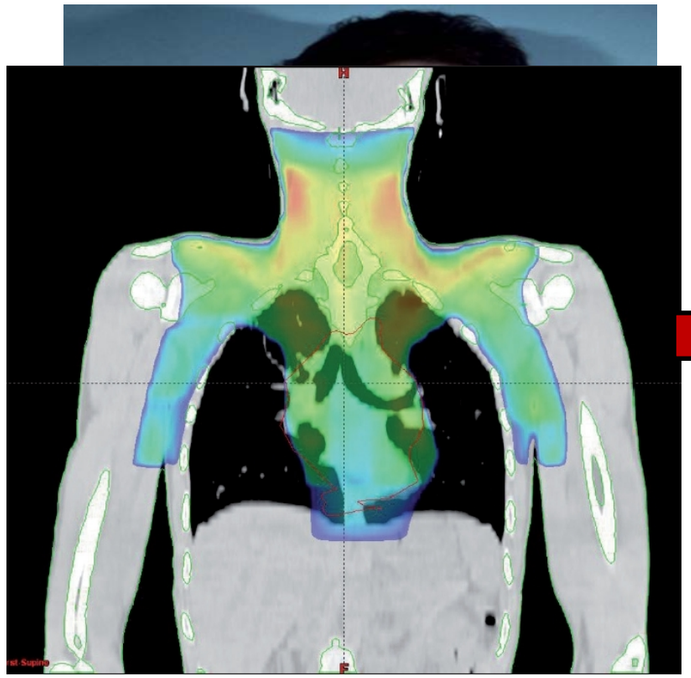


- Histology or involved sites
- Biology or response
- Treatment
- Surgery
- Chemotherapy
- Radiotherapy
- Transplantation
- Transfusion
- Treatment events

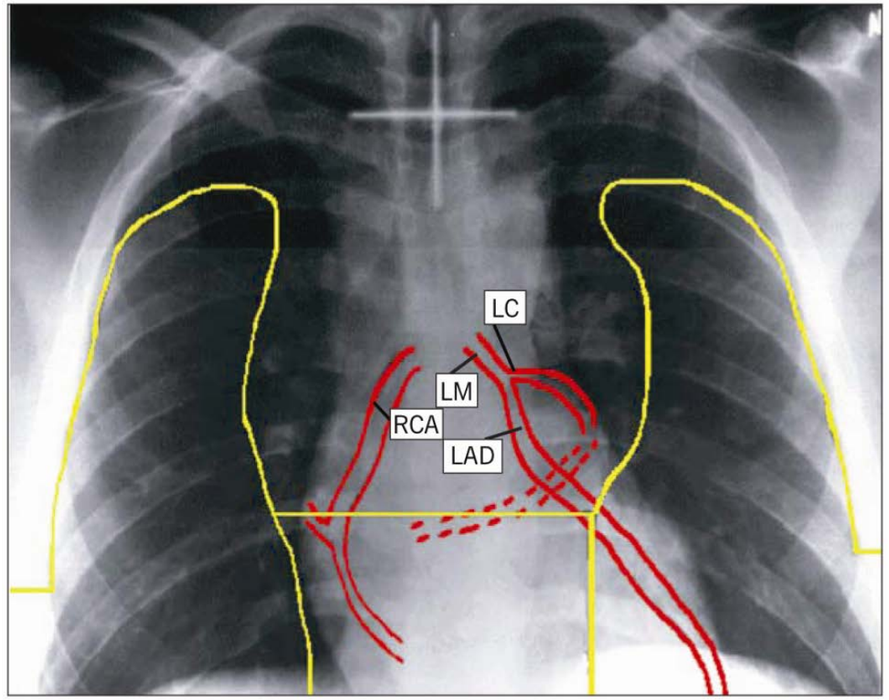
- Financing and payment policies
- Organization and affiliation of providers
- Data systems and information sharing
- Models of survivorship care
- Insurance coverage and benefits supporting survivorship care (especially preventive and psychosocial services)
- Community resources
- Survivorship advocacy activity

Robison and Hudson, *Nat Rev Cancer* 2014

Late Effects as Stimulus for Change



Musculoskeletal



Cardiac

Subsequent cancers

Finding the Balance: Cost of Cure

Cumulative Doses Associated with Long-Term Sequelae in Comparable Pediatric Hodgkin Regimens (mg/m²)

	Stanford V	GPOH-HD 2002	HLHR13	CCG 59704		
				Rapid Responders		Slow Responders
	+ Radiation	OEPA/COPDac ± Radiation	AEPA/CAPDac ± Radiation	BEACOPP+ABVD + Radiation (Males)	BEACOPP+COPP/ABV - (Females)	BEACOPP + Radiation (Both)
Doxorubicin	150	160	160	340	280	280
Bleomycin	30			120	80	80
Etoposide	360	1250	1250	2400	2400	4800
Cyclophosphamide		2000	4000	4800	7600	9600
Procarbazine				2800	4480	5600
Dacarbazine		3000	3000	1500		
Mechlorethamine	18					
Brentuximab vedotin (mg/kg)			16.8			
Prednisone	1120	4200	4200	2240	4480	4480

Flerlage, *personal communication*

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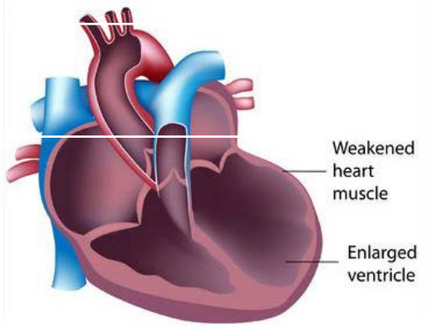

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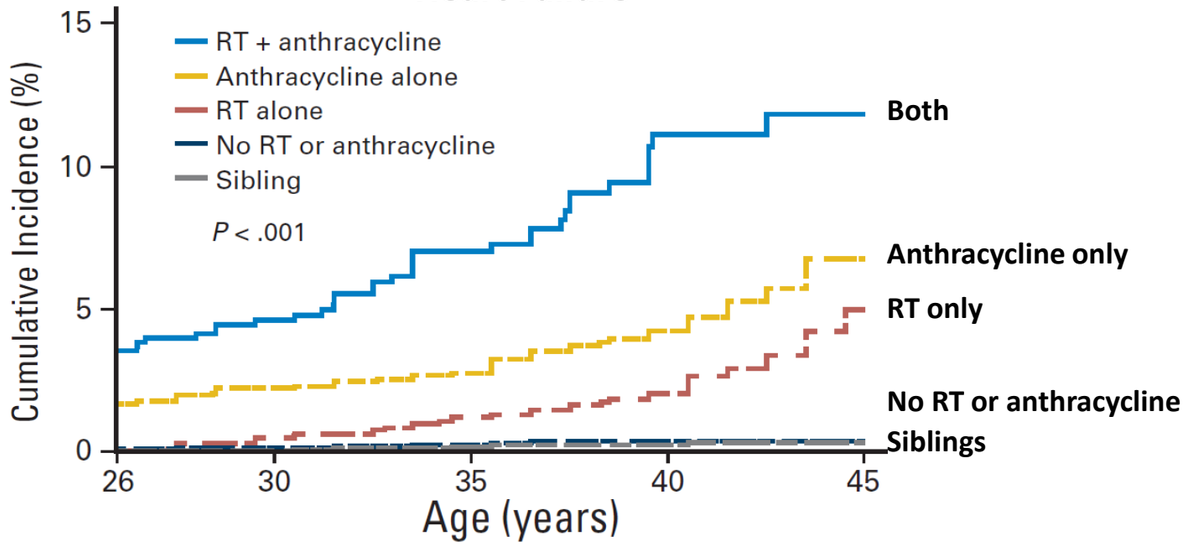
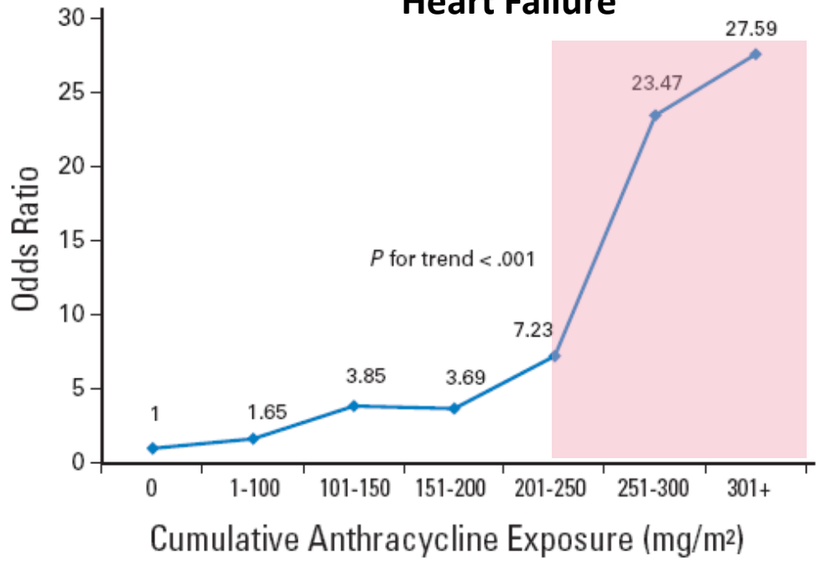
Doxorubicin	150	160	160	340	280	280

Heart Failure



Armstrong et al, *J Clin Oncol* 2013

Heart Failure



Blanco et al, *J Clin Oncol* 2012

Finding the Balance: Cost of Cure

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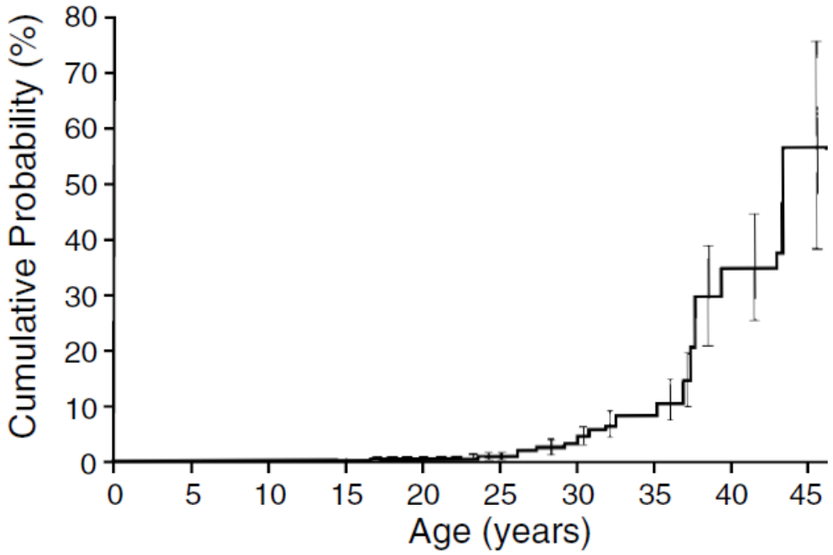
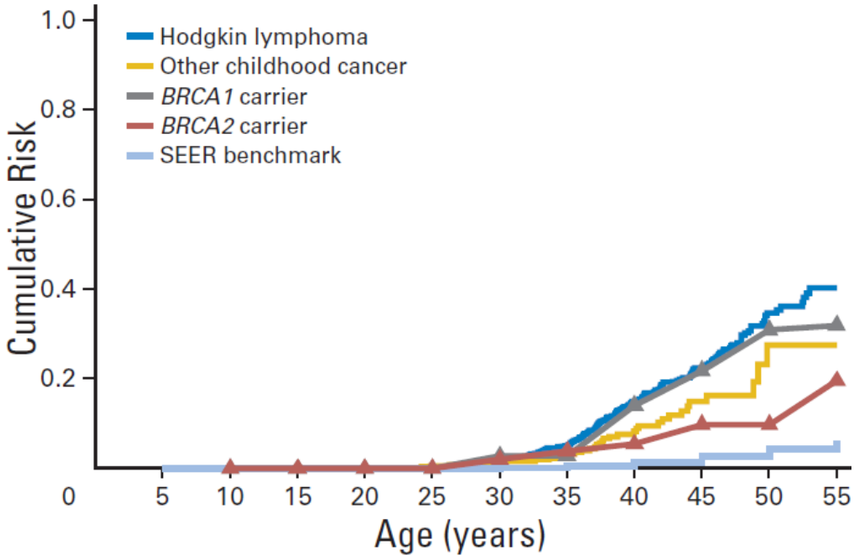
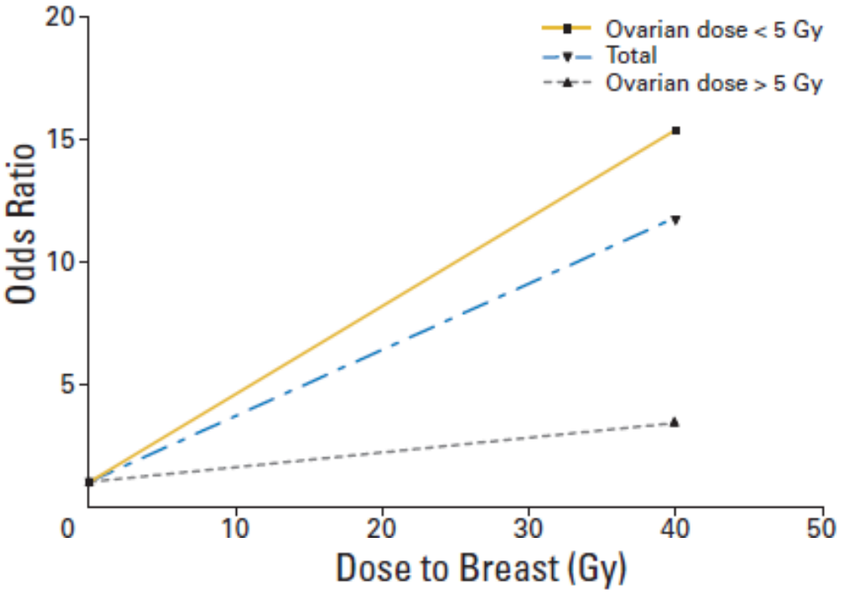
Stanford V	GPOH-HD 2002	HLHR13	CCG 59704		
			Rapid Responders		Slow Responders
	OEPA/COPDac	AEPA/CAPDac	BEACOPP+ABVD	BEACOPP+COPP/ABV	BEACOPP
+ Radiation	± Radiation	± Radiation	+ Radiation (Males)	- (Females)	+ Radiation (Both)



Bhatia et al, *N Engl J Med* 1996



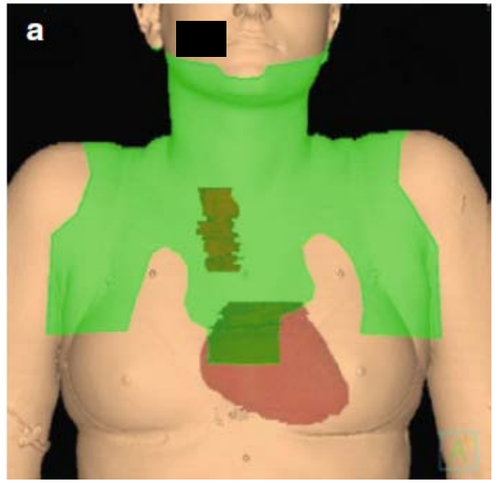
Moskowitz et al, *J Clin Oncol 2014*



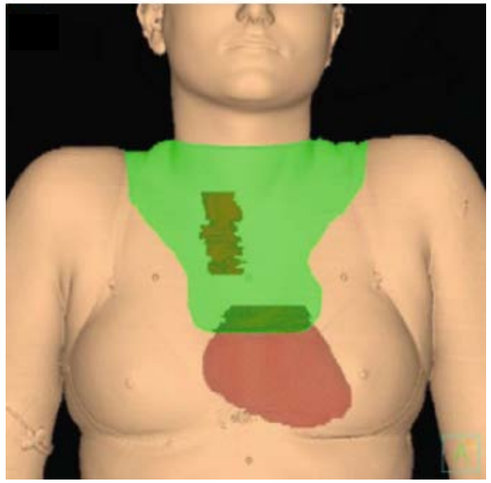
Inskip et al, *J Clin Oncol* 2009

Finding the Balance: Cost of Cure

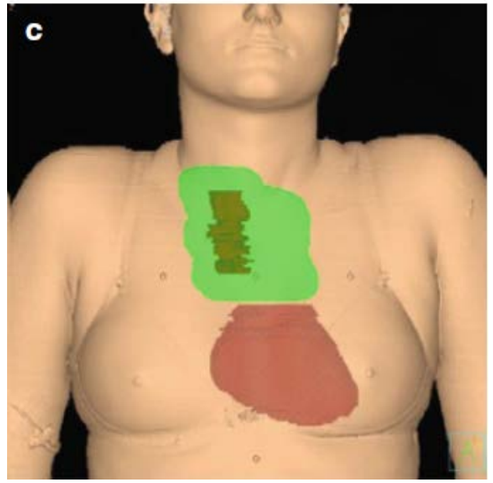
Mantle Radiation

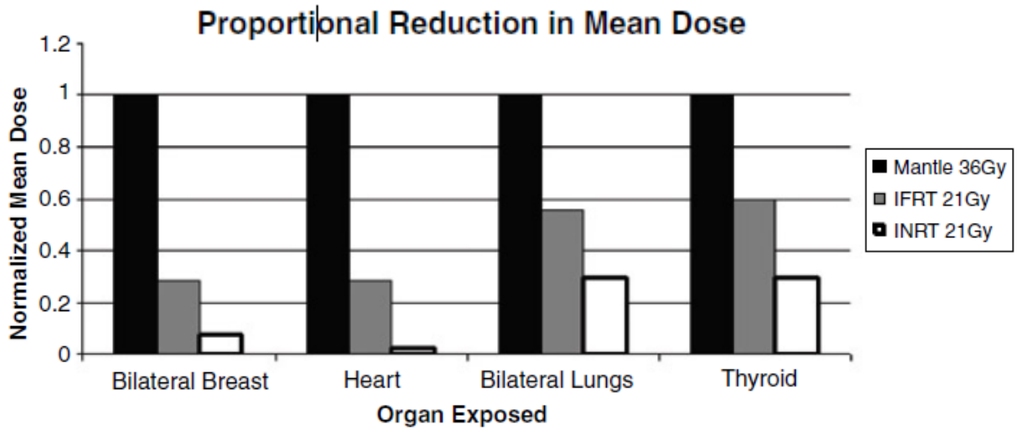


Involved Field Radiation



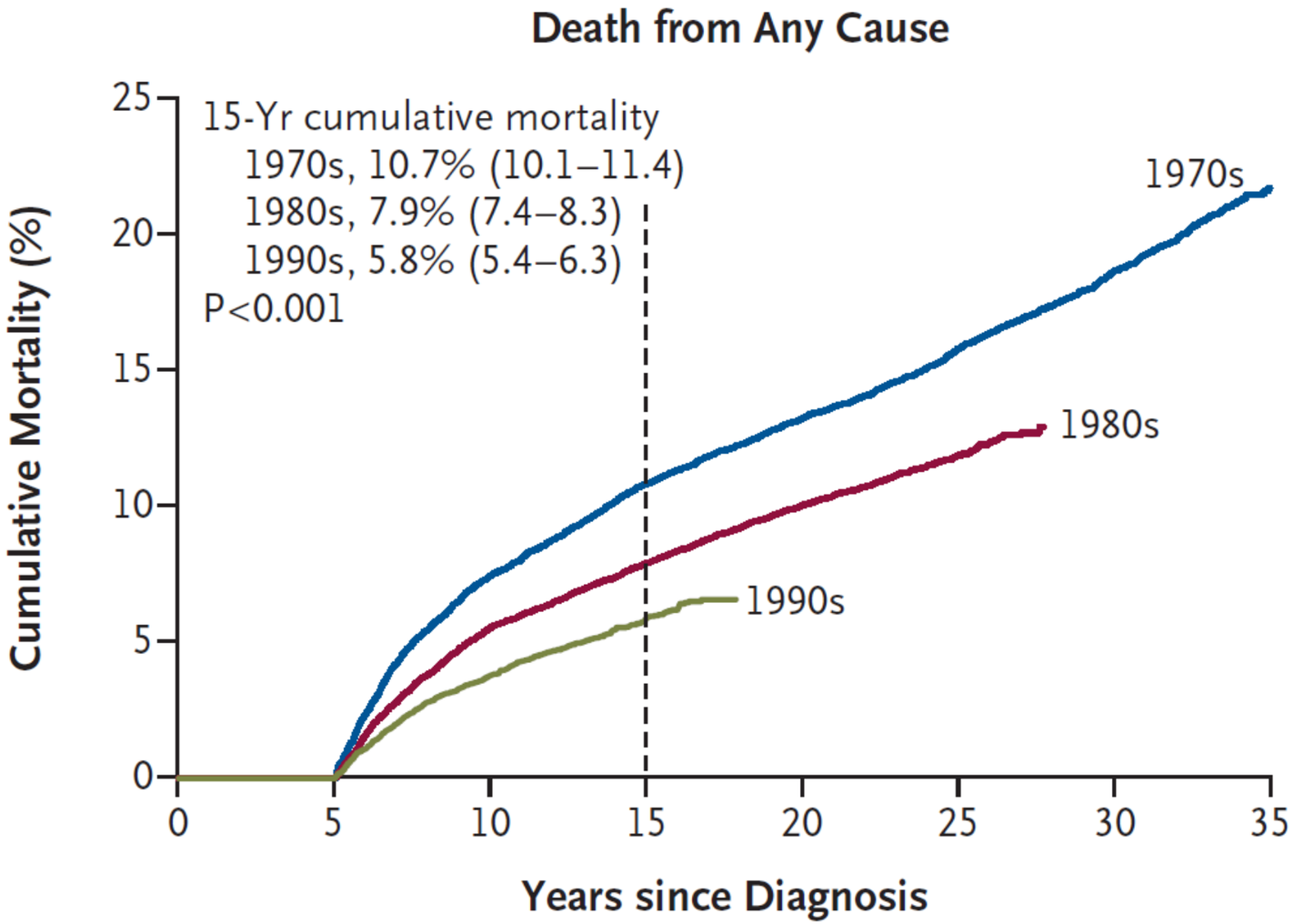
Involved Node Radiation





Specht and Yahalom. Radiotherapy for Hodgkin Lymphoma. 2011.

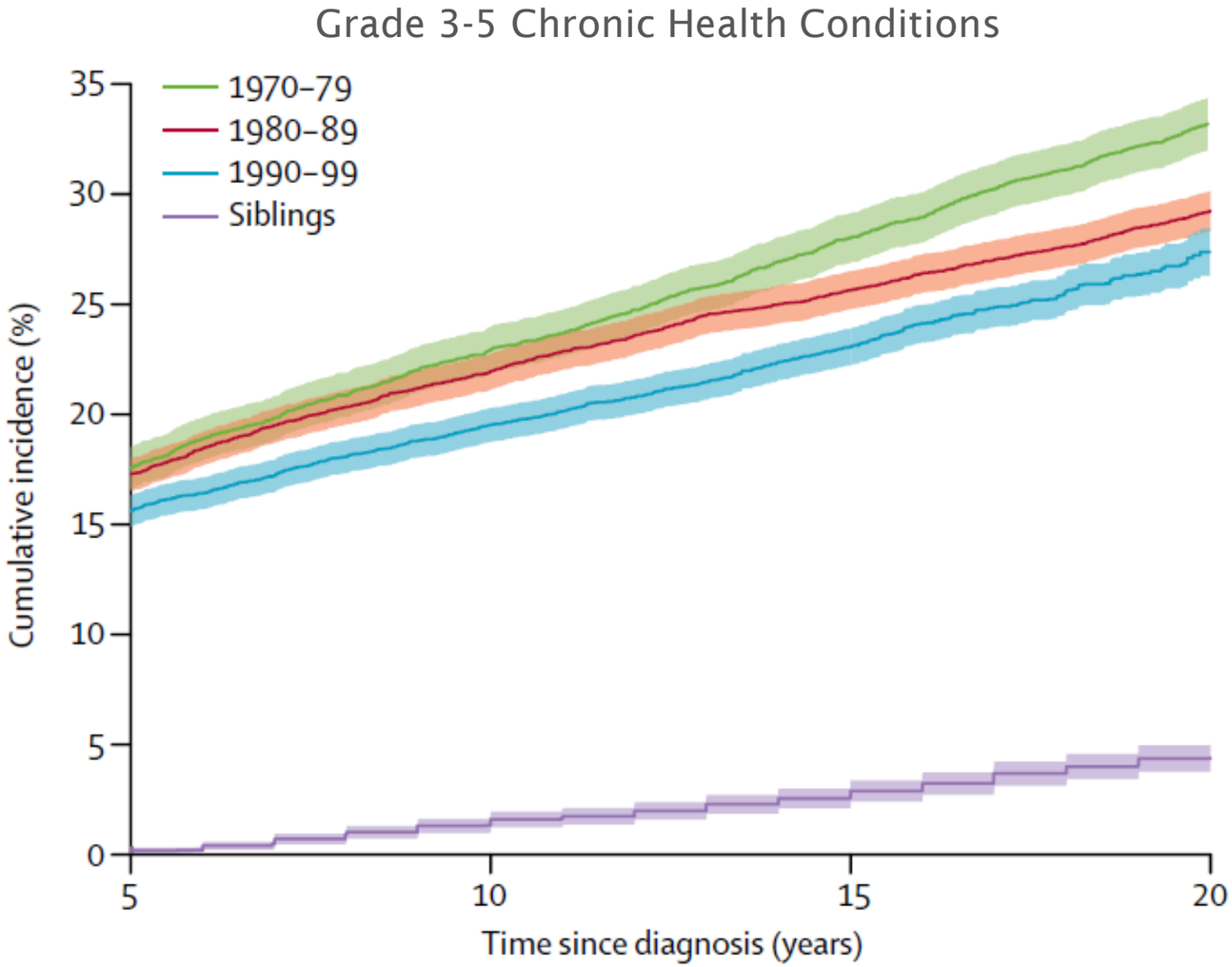
Temporal Trends in Mortality and Morbidity



Armstrong et al, *N Engl J Med* 2016

- Strategies of lowering treatment exposures have led to reductions in survivor ***mortality*** over time.

Temporal Trends in Mortality and Morbidity

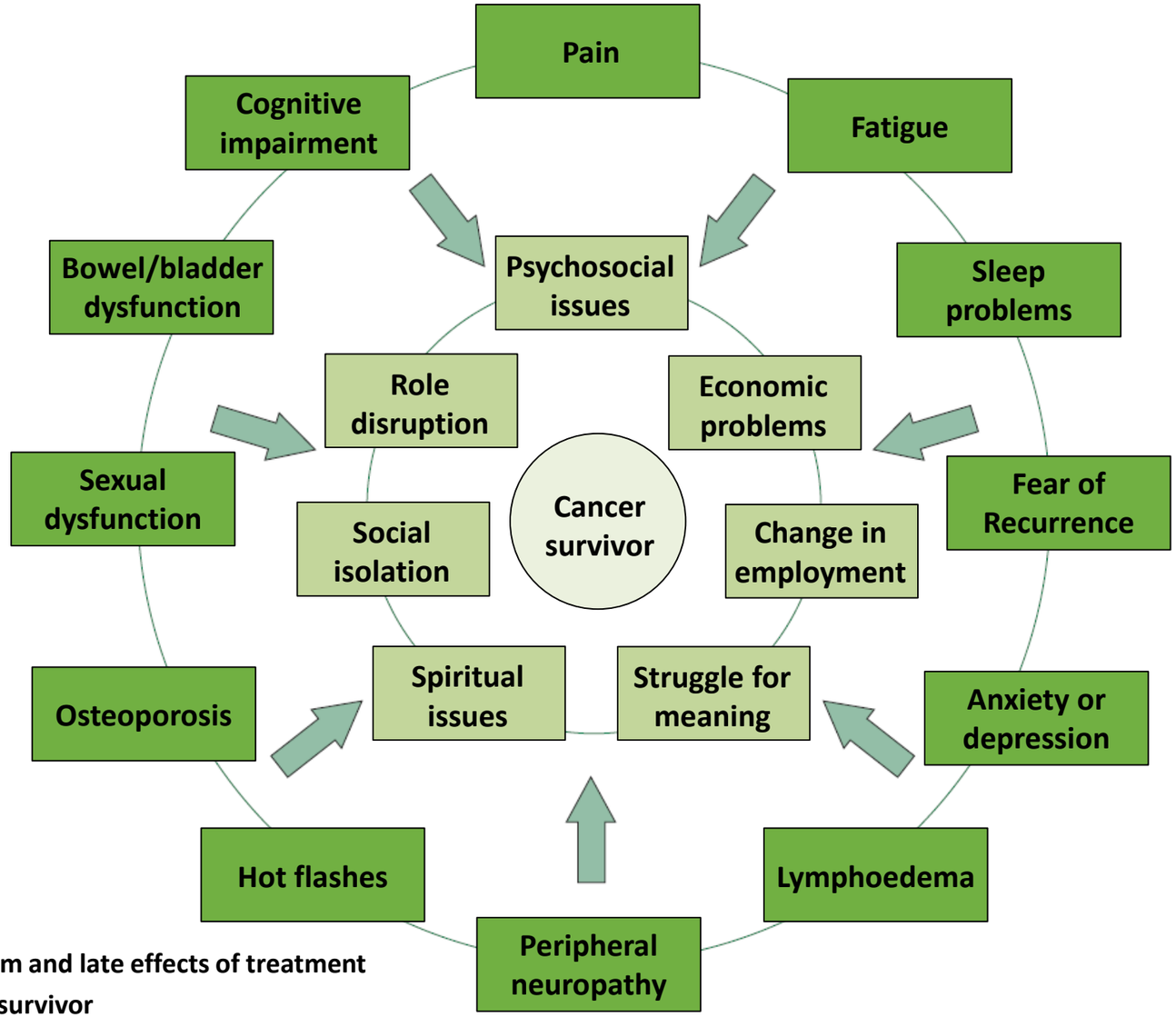


Gibson et al, *Lancet Oncol* 2018

- Strategies of lowering treatment exposures have led to reductions in survivor ***mortality*** over time
- Strategies of lowering treatment exposures have led to reductions in survivor ***morbidity*** over time.

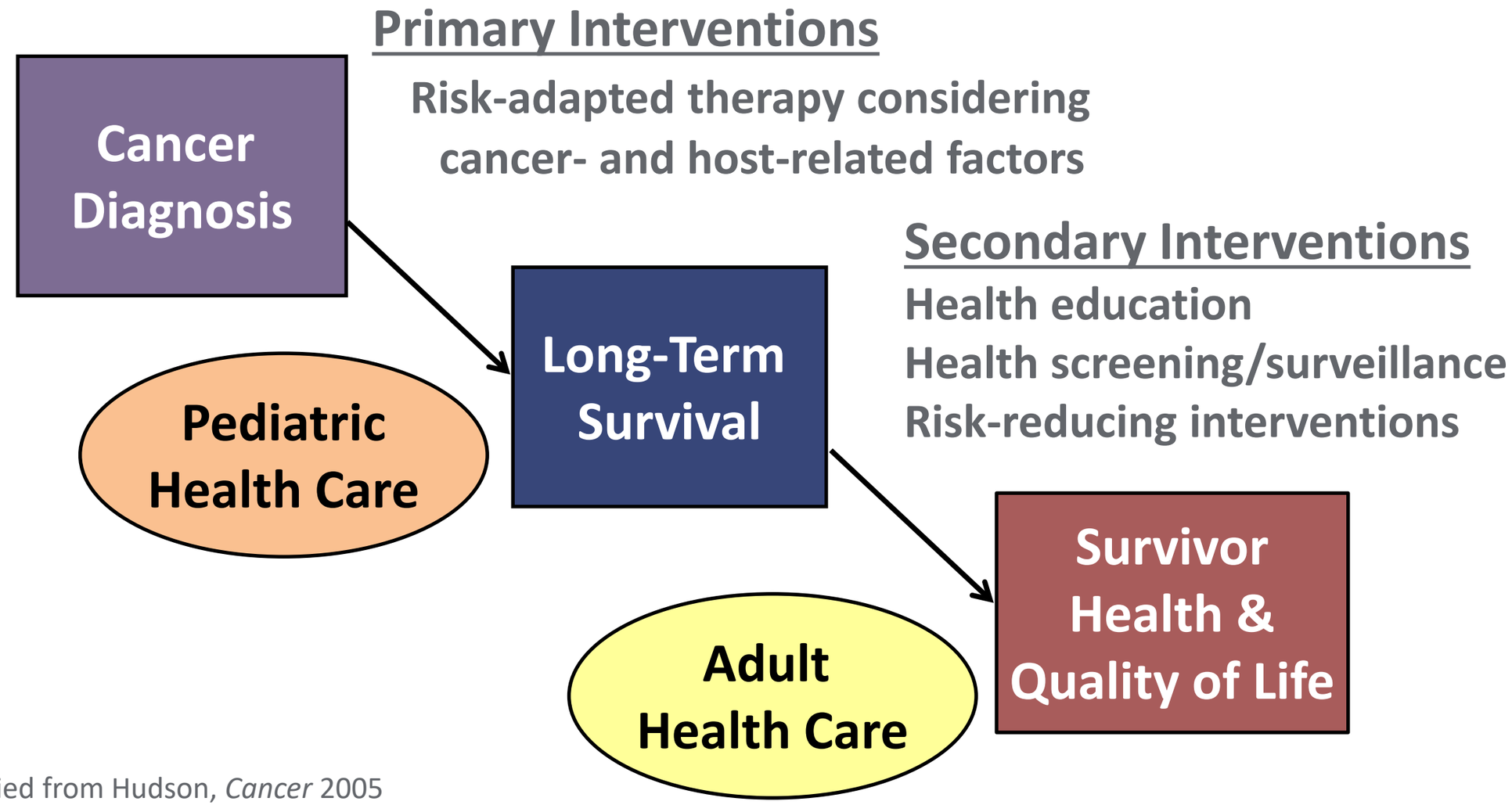
Late Effects and Impact on Survivors

- Medically complex population with diverse healthcare needs.
- At risk for adverse psychosocial and medical outcomes.



Jacobs et al, *Lancet Oncol* 2017

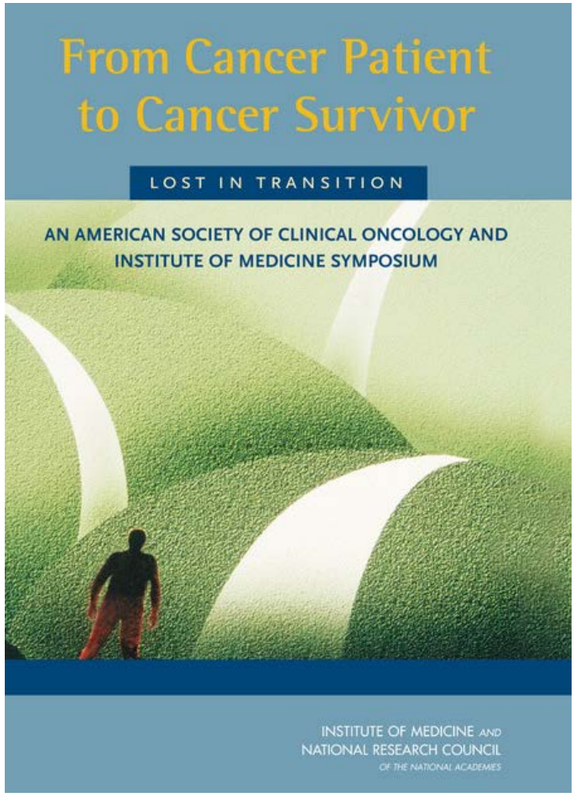
Model for Care Across the Cancer Continuum



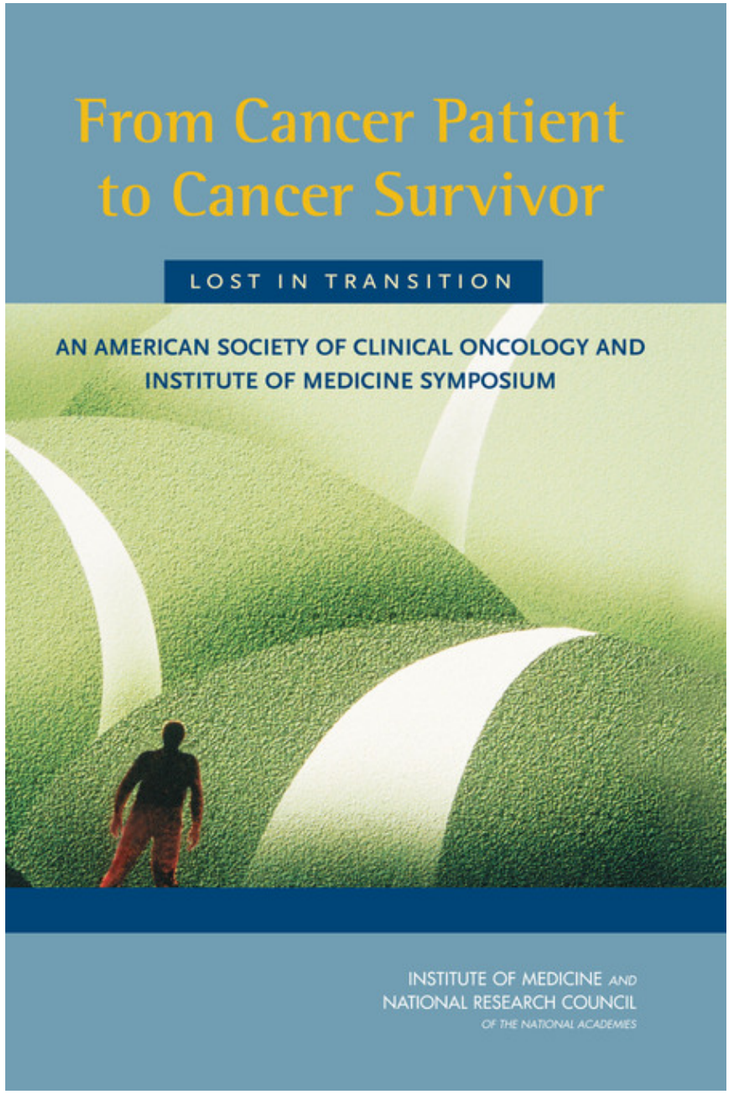
Modified from Hudson, *Cancer* 2005

Emergence of Cancer Survivorship

- 1986 – National Coalition for Cancer Survivorship
  - Change perspective from “cancer victim” with “cancer survivor”
  - Influence government agencies and policymakers
- 2005 – Institute of Medicine Publication Essential Aims for Survivorship Care
  - Prevention of recurrent/new cancer and late effects
  - Cancer surveillance (progression, recurrence, or secondary)
  - Assessment of medical and psychosocial late effects
  - Intervention for consequences of cancer and its treatment
  - Coordination between specialists and primary care providers to ensure survivors' health needs are met



Essential Components of Survivorship Care

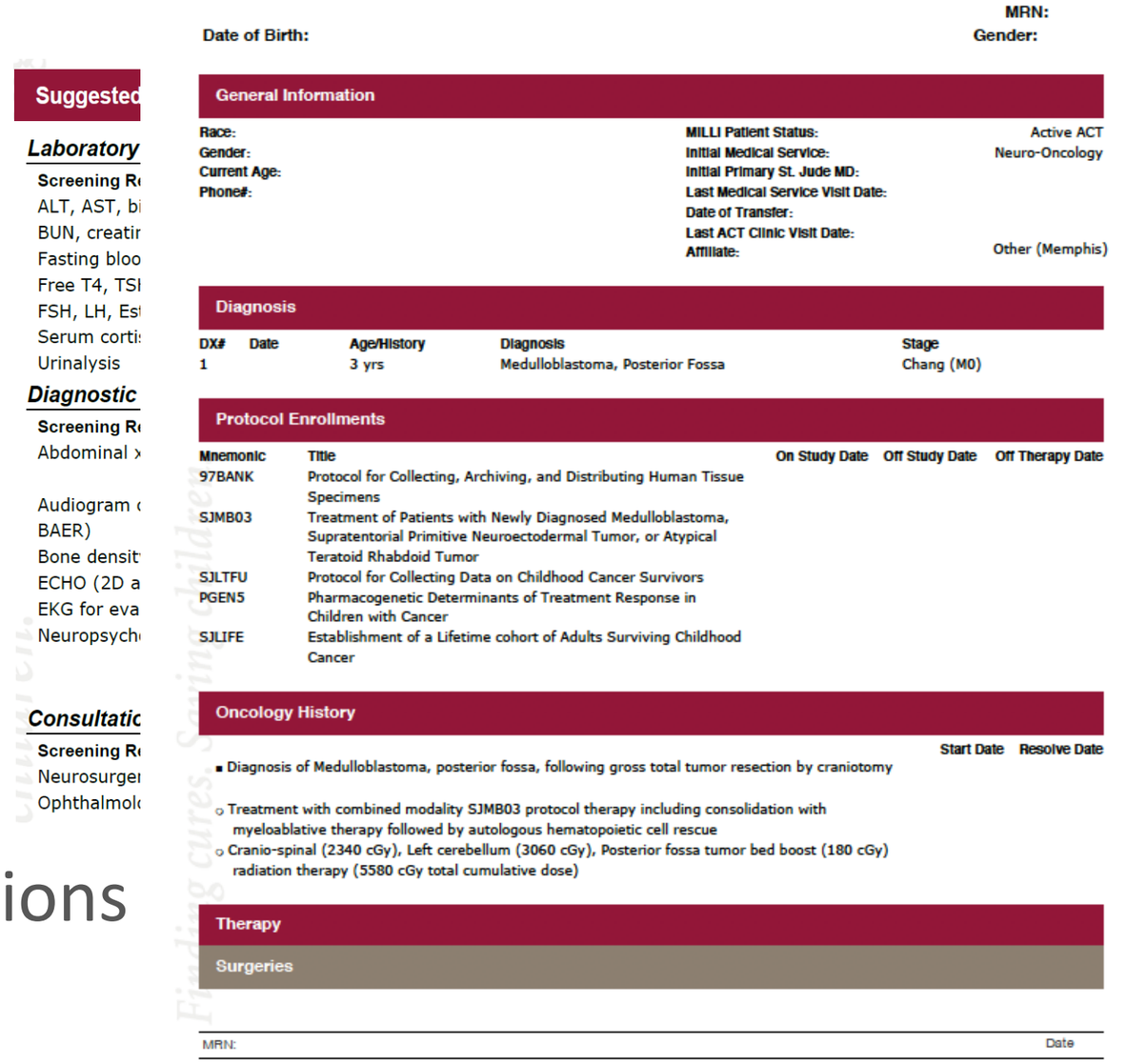


Institute of Medicine, 2005 Recommendation:

"Patients completing primary treatment should be provided with a comprehensive care summary and follow-up plan that is clearly and effectively explained."

Survivorship Care Plans

- Diagnostic (cancer) information
- Cumulative treatment exposures
- Clinical events and status
- Transfusion history
- Family history
- Cancer-related health risks
- Health behaviors modifying risks
- Risk-based screening recommendations



Suggested

Laboratory

Screening R
ALT, AST, bi
BUN, creatir
Fasting bloo
Free T4, TSI
FSH, LH, Est
Serum corti
Urinalysis

Diagnostic

Screening R
Abdominal x

Audiogram
BAER)
Bone densit
ECHO (2D a
EKG for eva
Neuropsych

Consultatic

Screening R
Neurosurger
Ophthalmol

MRN:
Date of Birth:
Gender:

General Information

Race:		MILLI Patient Status:	Active ACT
Gender:		Initial Medical Service:	Neuro-Oncology
Current Age:		Initial Primary St. Jude MD:	
Phone#:		Last Medical Service Visit Date:	
		Date of Transfer:	
		Last ACT Clinic Visit Date:	
		Affiliate:	Other (Memphis)

Diagnosis

DX#	Date	Age/History	Diagnosis	Stage
1		3 yrs	Medulloblastoma, Posterior Fossa	Chang (M0)

Protocol Enrollments

Mnemonic	Title	On Study Date	Off Study Date	Off Therapy Date
97BANK	Protocol for Collecting, Archiving, and Distributing Human Tissue Specimens			
SJMB03	Treatment of Patients with Newly Diagnosed Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumor, or Atypical Teratoid Rhabdoid Tumor			
SJLTFU	Protocol for Collecting Data on Childhood Cancer Survivors			
PGEN5	Pharmacogenetic Determinants of Treatment Response in Children with Cancer			
SJLIFE	Establishment of a Lifetime cohort of Adults Surviving Childhood Cancer			

Oncology History

Start Date Resolve Date

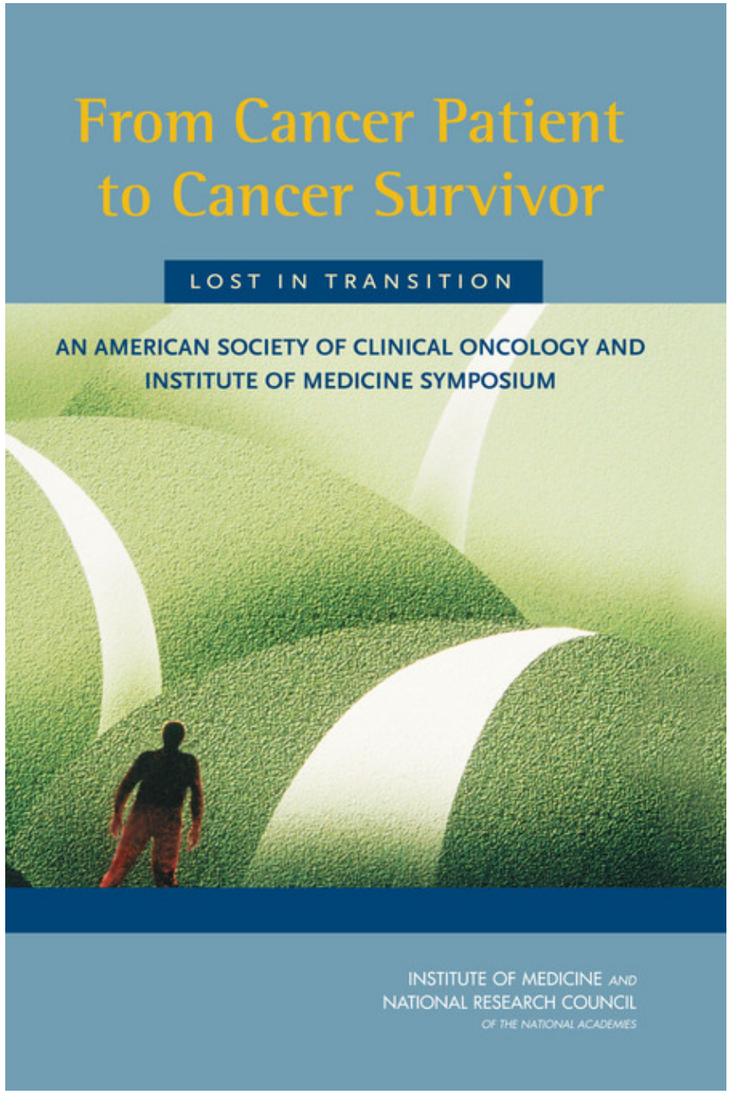
- Diagnosis of Medulloblastoma, posterior fossa, following gross total tumor resection by craniotomy
  - Treatment with combined modality SJMB03 protocol therapy including consolidation with myeloablative therapy followed by autologous hematopoietic cell rescue
  - Cranio-spinal (2340 cGy), Left cerebellum (3060 cGy), Posterior fossa tumor bed boost (180 cGy) radiation therapy (5580 cGy total cumulative dose)

Therapy

Surgeries

MRN: Date

Essential Components of Survivorship Care



Institute of Medicine, 2005 Recommendation:

"Health care providers should use systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to identify and manage late effects of cancer and its treatment."

Clinical Practice Guidelines

- Exposure-based
  - Includes screening and counseling based on specific chemotherapy, radiation doses/volumes and surgery
- Disease-based
  - Focuses on modalities and health concerns related to a specific malignancy (e.g., NCCN breast, prostate)
- Organ-system based
  - Considers specific organ systems affected by cancer or cancer therapy
- Symptom-based
  - Targets symptoms common to many cancer diagnoses and treatment (e.g., fatigue, sleep, cognition)

CHILDREN'S ONCOLOGY GROUP Foundation

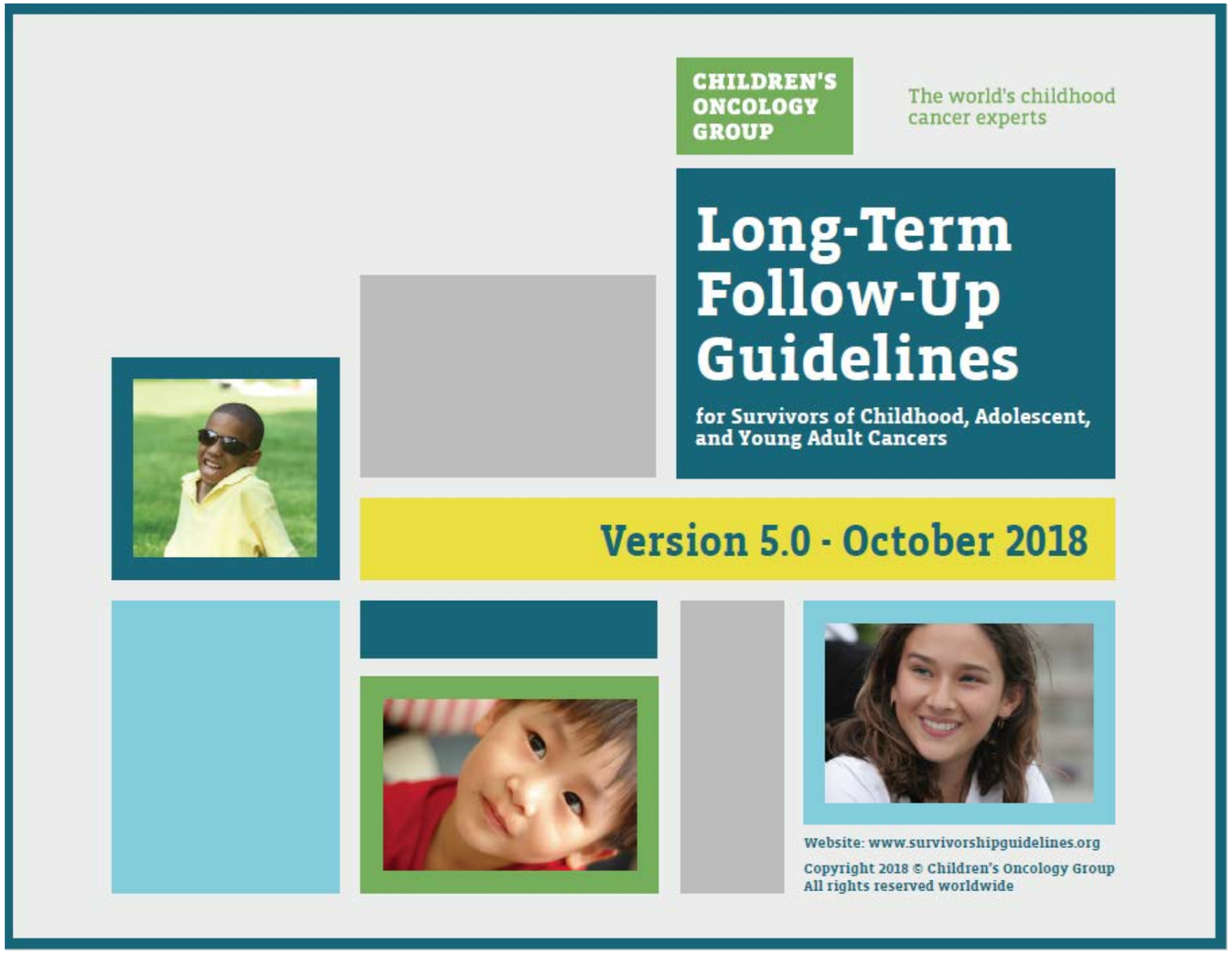
Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies
PanCareSurFup

SIGN
Scottish Intercollegiate Guidelines Network

DCOG LATER
Longterm effects after childhood cancer

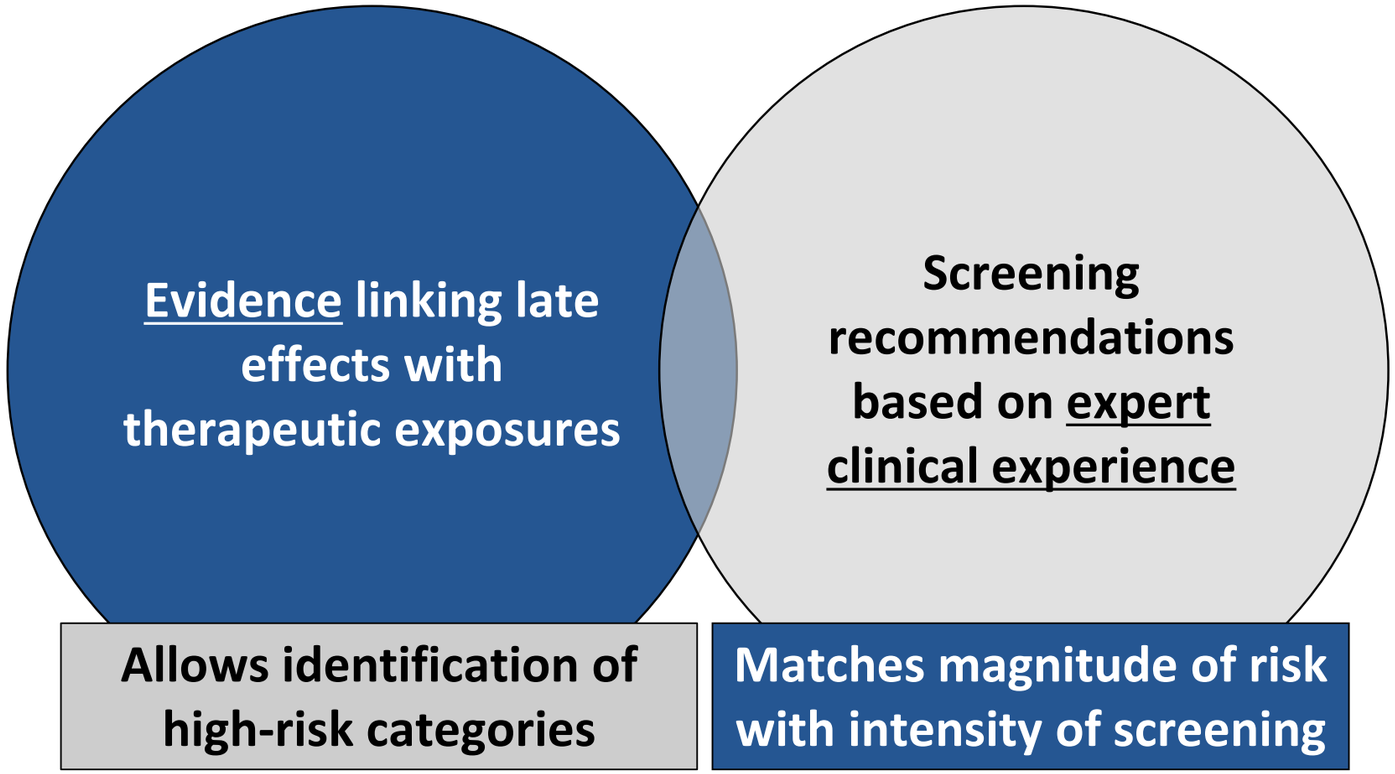
Children's Cancer and Leukaemia Group
Working together to beat childhood cancer

Children's Oncology Group Survivorship Guidelines



- survivorshipguidelines.org
- Updated every 5 years
- Comprehensive literature search and grading of evidence

Children's Oncology Group Survivorship Guidelines



- survivorshipguidelines.org
- Updated every 5 years
- Comprehensive literature search and grading of evidence
- Consensus based recommendations – hybrid of evidence and expert opinion

Children's Oncology Group Survivorship Guidelines

CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** **Recommended Frequency of Echocardiogram** *Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

Organized around risk-based exposure, including corresponding offending agents

Children's Oncology Group Survivorship Guidelines

CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	**Cardiac toxicity** Cardiomyopathy Subclinical left ventricular dysfunction Congestive heart failure Arrhythmia	**HISTORY** **Shortness of breath** **Dyspnea on exertion** **Orthopnea** **Chest pain** **Palpitations** **If under 25 yrs: abdominal symptoms (nausea, vomiting)** Yearly **PHYSICAL** **Blood pressure** **Cardiac exam** Yearly **SCREENING** **ECHO (or comparable imaging to evaluate cardiac function)** **Recommended Frequency of Echocardiogram** *Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33. **Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76. **EKG (include evaluation of QTc interval)** Baseline at entry into long-term follow-up, repeat as clinically indicated	**HEALTH LINKS** **Heart Health** **Cardiovascular Risk Factors** **Diet and Physical Activity** **COUNSELING** Maintain appropriate weight, blood pressure and heart-healthy diet. Regarding exercise: - Regular exercise is generally safe and should be encouraged for patients who have normal LV systolic function. - Survivors with asymptomatic cardiomyopathy should consult cardiology to define limits and precautions for physical activity. - Cardiology consultation may be reasonable to define limits and precautions for physical activity for high risk survivors (i.e., those requiring an ECHO every 2 years) who plan to participate in intensive exercise. If QTc interval is prolonged: Caution regarding use of medications that may further prolong the QTc interval (e.g., tricyclic anti-depressants, antifungals, macrolide antibiotics, metronidazole). **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal. Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval. Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: - ≥250 mg/m² anthracyclines - ≥35 Gy chest radiation, or - Anthracycline (any dose) combined with chest radiation (≥15 Gy) Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure. **SYSTEM = Cardiovascular** **SCORE = 1**

Anthracycline Dose*	Radiation Dose**	Recommended Frequency
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

Additional Information

Although Mitoxantrone technically belongs to the anthracenedione class of anti-tumor antibiotics, it is related to the anthracycline family and is included in this section because of its cardiotoxic potential.

- Organized around risk-based exposure, including corresponding offending agents
- Pertinent late effects are individually listed

Children's Oncology Group Survivorship Guidelines

CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

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Suggested evaluations are outlined pertinent to the exposure and degree of risk

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CHEMOTHERAPY

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Additional Information

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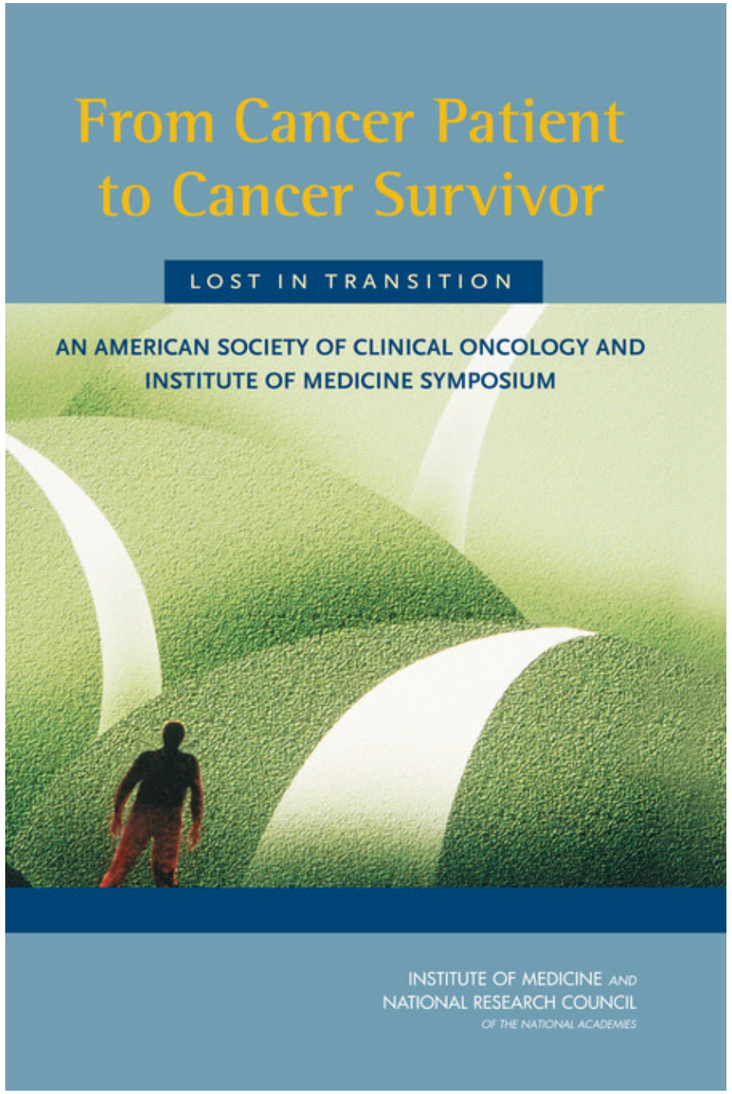
- Suggested evaluations are outlined pertinent to the exposure and degree of risk
- Further considerations and the level of evidence (scored according to the National Comprehensive Cancer Network "Categories of Consensus") are provided

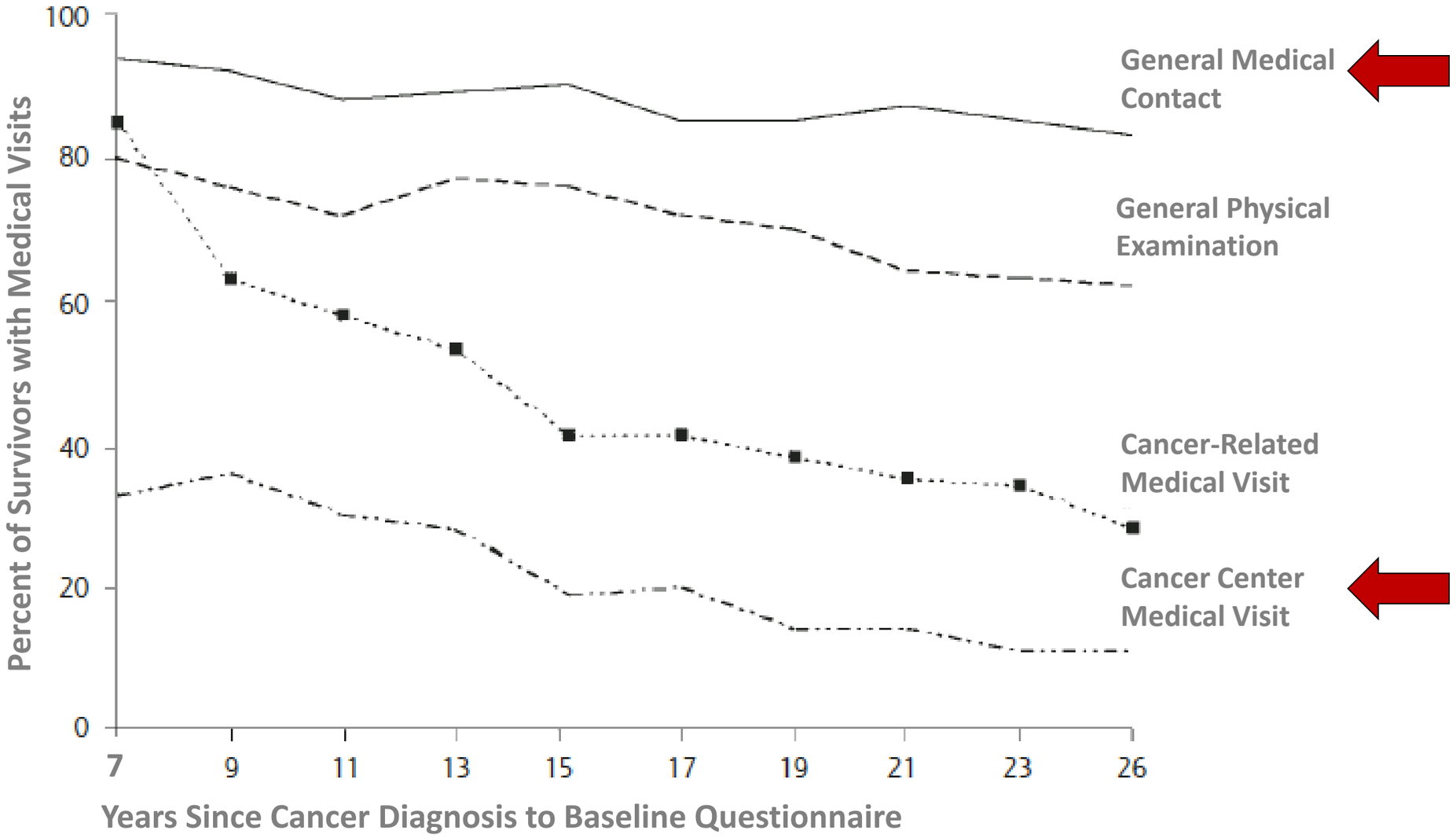
Essential Components of Survivorship Care



Institute of Medicine, 2005 Recommendation:

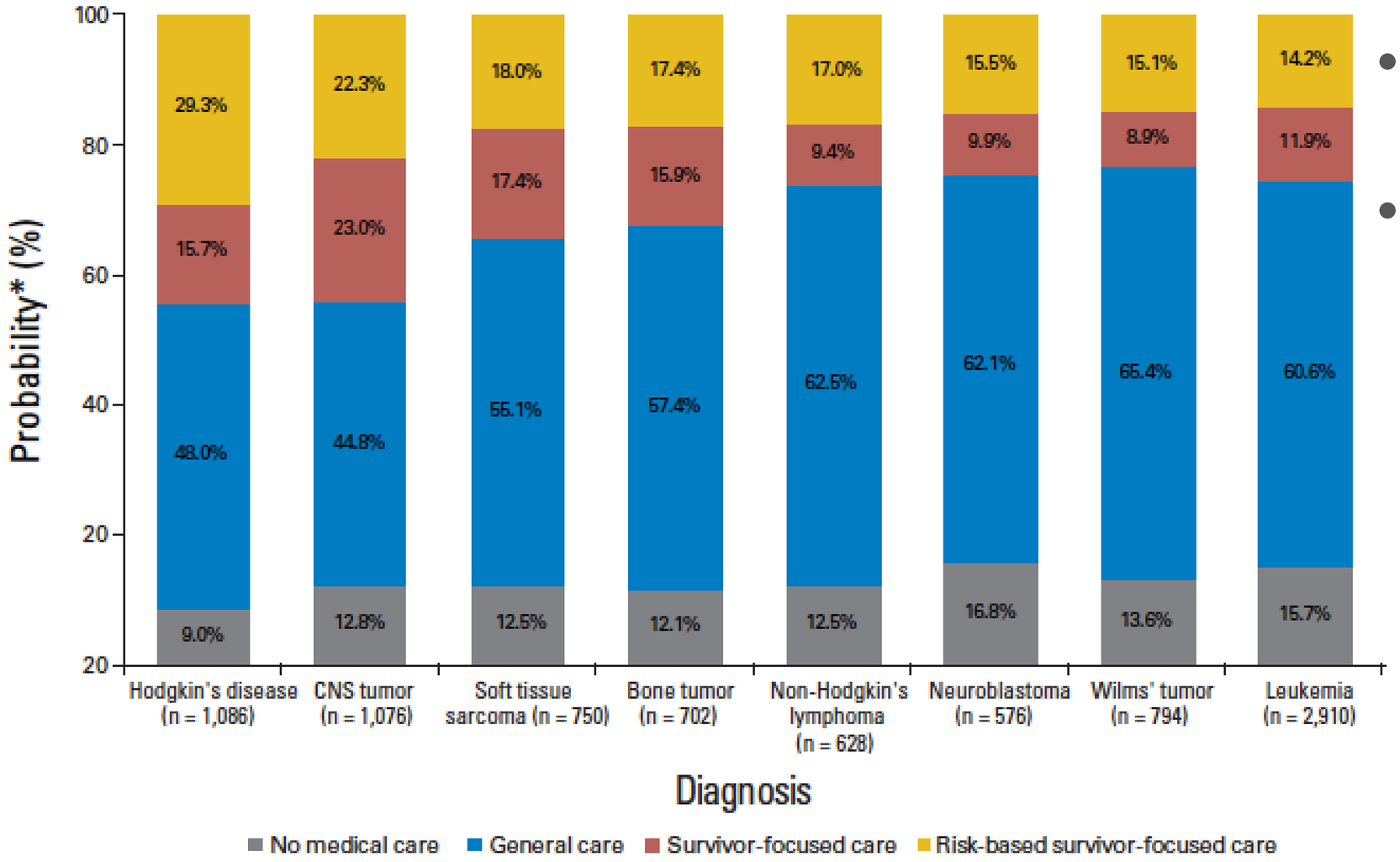
"…qualified organizations should support demonstration programs to test models of coordinated, interdisciplinary survivorship care in diverse communities and across systems of care."

Adult Survivors' Medical Visits in Past 2 Years



Oeffinger et al, *Ann Fam Med* 2004

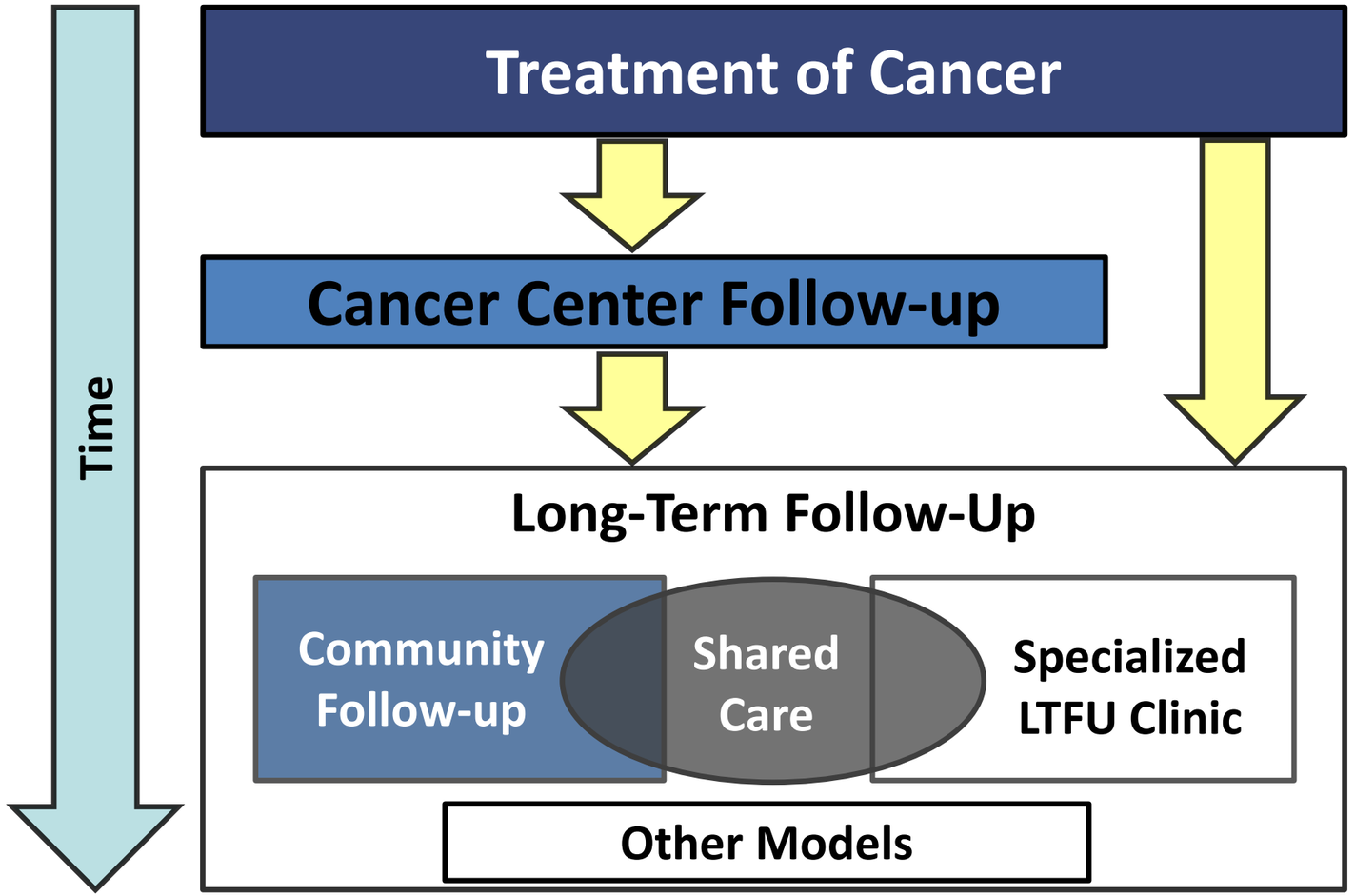
What Care Do Survivors Receive?



- 88.8% reported ≥ 1 medical visit during previous 2 years
- Reported care
  - –No medical care (11.2%)
  - –General medical care (57.3%)
  - –General survivor care (13.7%)
  - –Risk-based survivor care (17.8%)

Nathan et al, *J Clin Oncol* 2008

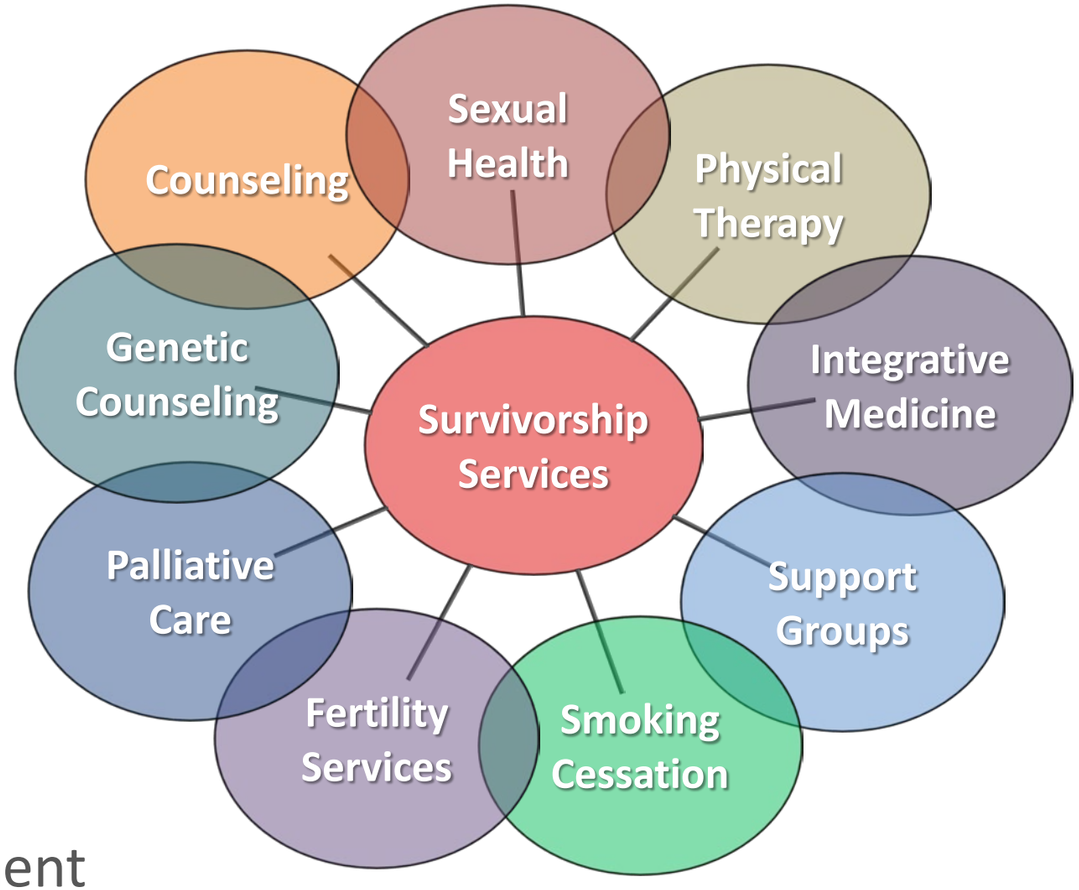
Models of Survivorship Care



Adapted from Singer et al, *Pediatr Blood Cancer* 2013

Factors Influencing Model Selection

- Risk of recurrence and late effects
- Type of services to be provided
  - Medical
  - Psychological
  - Social
  - Rehabilitative
  - Financial
- Timing of the services
  - Transition visit at the end of therapy
  - Specified time after completion of treatment
  - Ongoing care



Most Effective Care Delivery Model

- Existing studies vary by disease group, comparative delivery models, and outcomes.

Outcomes Studied in Previous Cancer Survivorship Model Trials

Type of Survivorship Intervention	Author and Year	Quality of Life	Depression	Anxiety/ Distress	Well-Being	Satisfaction	Resource Use	Adherence to Planned Follow-Up	Disease-Free Period	Overall Survival	Recurrence	Perceptions of Health	Engage–ment in Health-Promoting Activities	Cancer Survivors' Knowledge	Coor–dination/ Conti–nuity of Care	Unmet Needs
Physician-led	Cannon et al, 2010[51]	X	–	–	–	X	X	–	–	–	–	–	–	–	–	–
	Kokko et al, 2005[52]	X	–	–	–	–	X	–	X	X	X	–	–	–	–	–
	Wattchow et al, 2006[53]	X	X	X	–	X	X	–	–	X	X	–	–	–	–	–
Nurse-led	Gates et al, 2012[55]	–	–	–	–	–	–	–	–	–	–	X	X	–	–	–
	Knowles et al, 2007[54]	X		–		X	–	X	–	–	X	–	–	–	–	–
SCP development a key component	Curcio et al, 2011[56]	–		X	–	X	–	X	–	–	–	–	–	X	–	–
	Grunfeld et al, 2011[57]	X		X	–	X	–	–	–	–	X	–	–	–	X	–
	Jefford et al, 2011[18]	X		X	–	X	–	–	–	–	–	–	–	–	–	X
Comparing group *v* individual counseling	Naumann et al, 2012[19]	X	–		X	–	–	–	–	–	–	–	–	–	–	–

Halpern et al, *J Oncol Pract 2015*

- No model has demonstrated superiority in all healthcare environments.
- The preferred model is that which can be implemented within the available resources.

Summary

- Childhood cancer survivors are at increased risk for chronic health conditions compared to the general population.
- Cancer treatment has been modified over time in order to reduce treatment-related exposures that increase risk for adverse health.
- Risk-based guidelines provide recommendations regarding care delivery for this medically complex population.
- A variety of care delivery models exist and should be adapted to local resource availability.

Questions?