INSTITUTE FOR CANCER OUTCOMES & SURVIVORSHIP

The University of Alabama at Birmingham

Prediction and Prevention of Morbidity across the Disease Trajectory

…Lessons learned from our Children with Cancer

Smita Bhatia, MD, MPH, FASCO

Gay and Bew White Endowed Chair in Pediatric Oncology

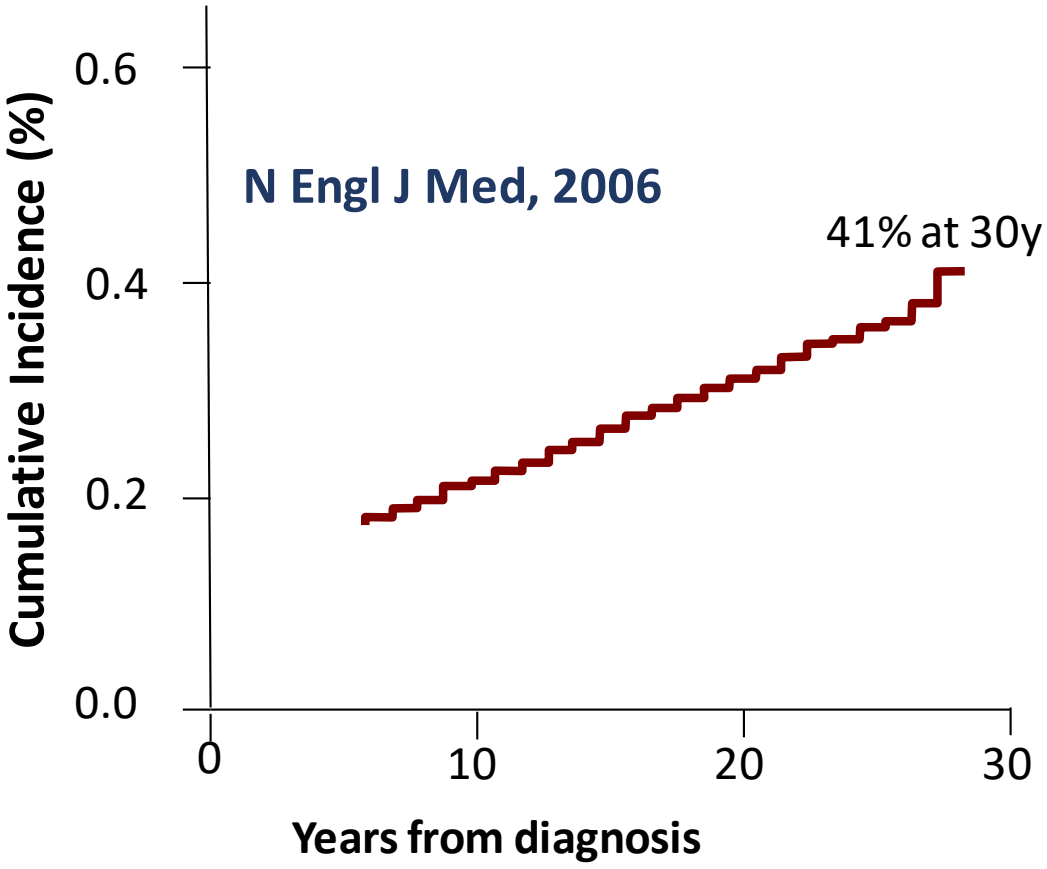
Director, Institute for Cancer Outcomes and Survivorship

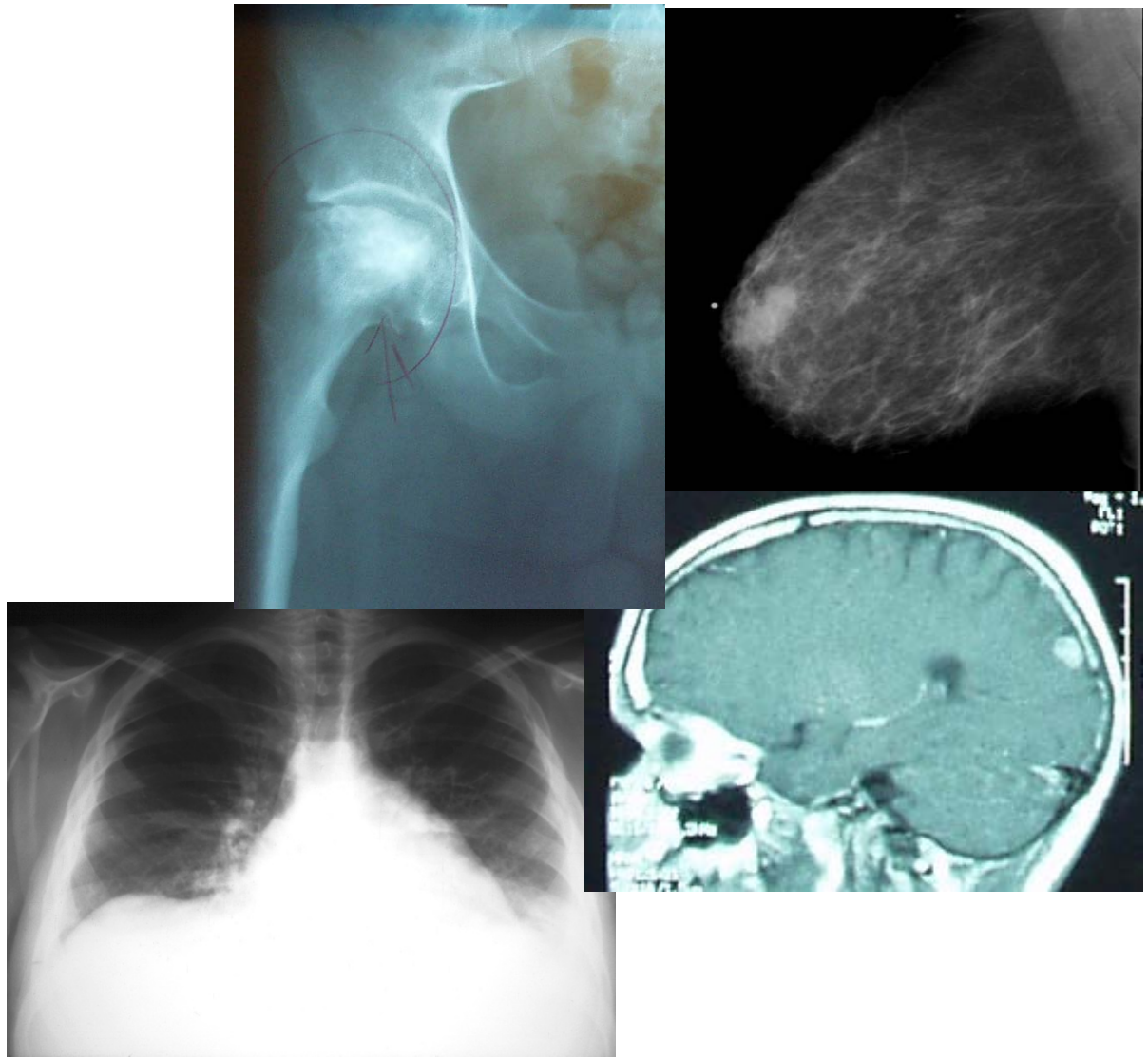
School of Medicine

University of Alabama at Birmingham

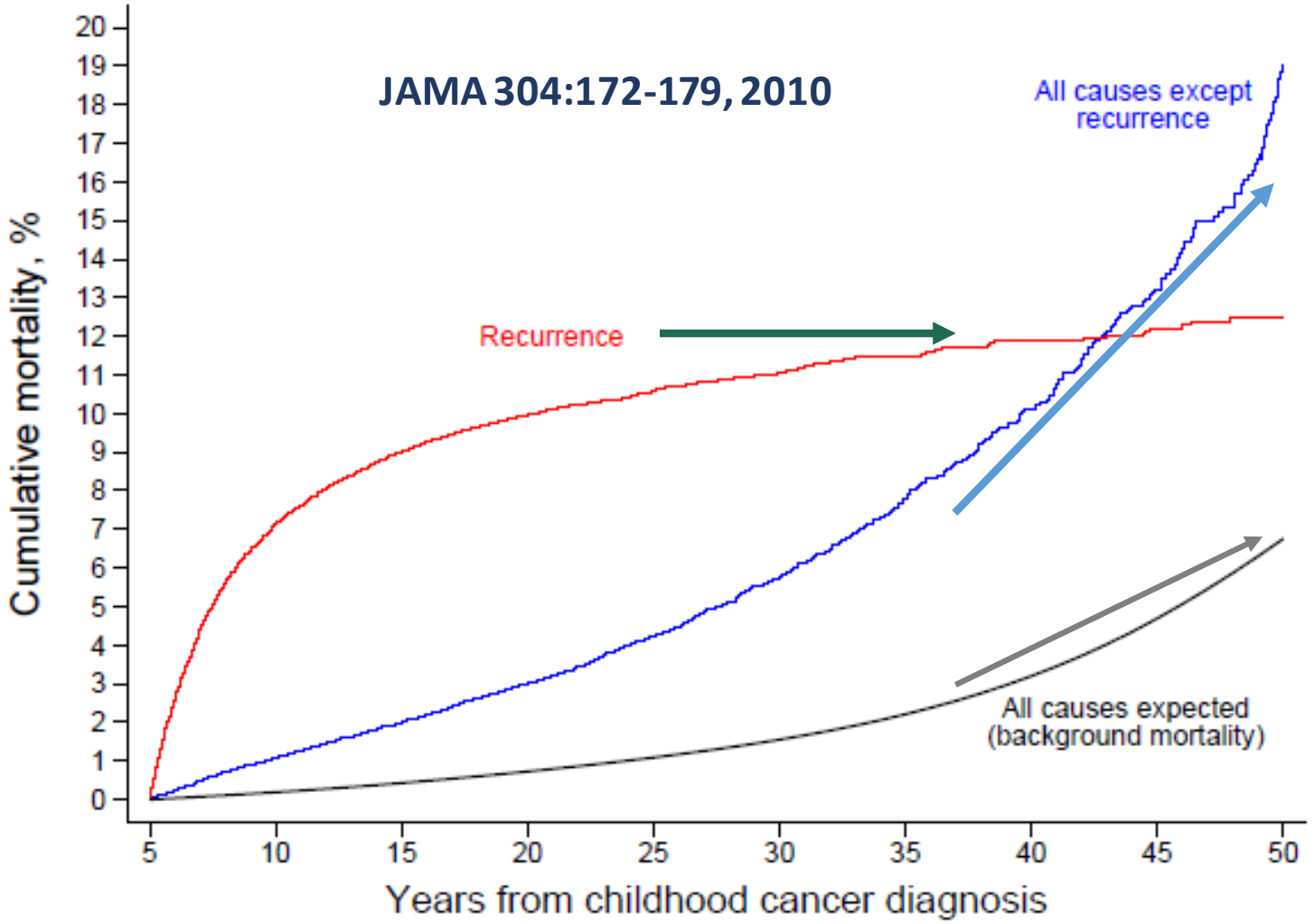
Burden of Morbidity in Childhood Cancer Survivors

Severe/ Life-threatening Chronic Health Conditions

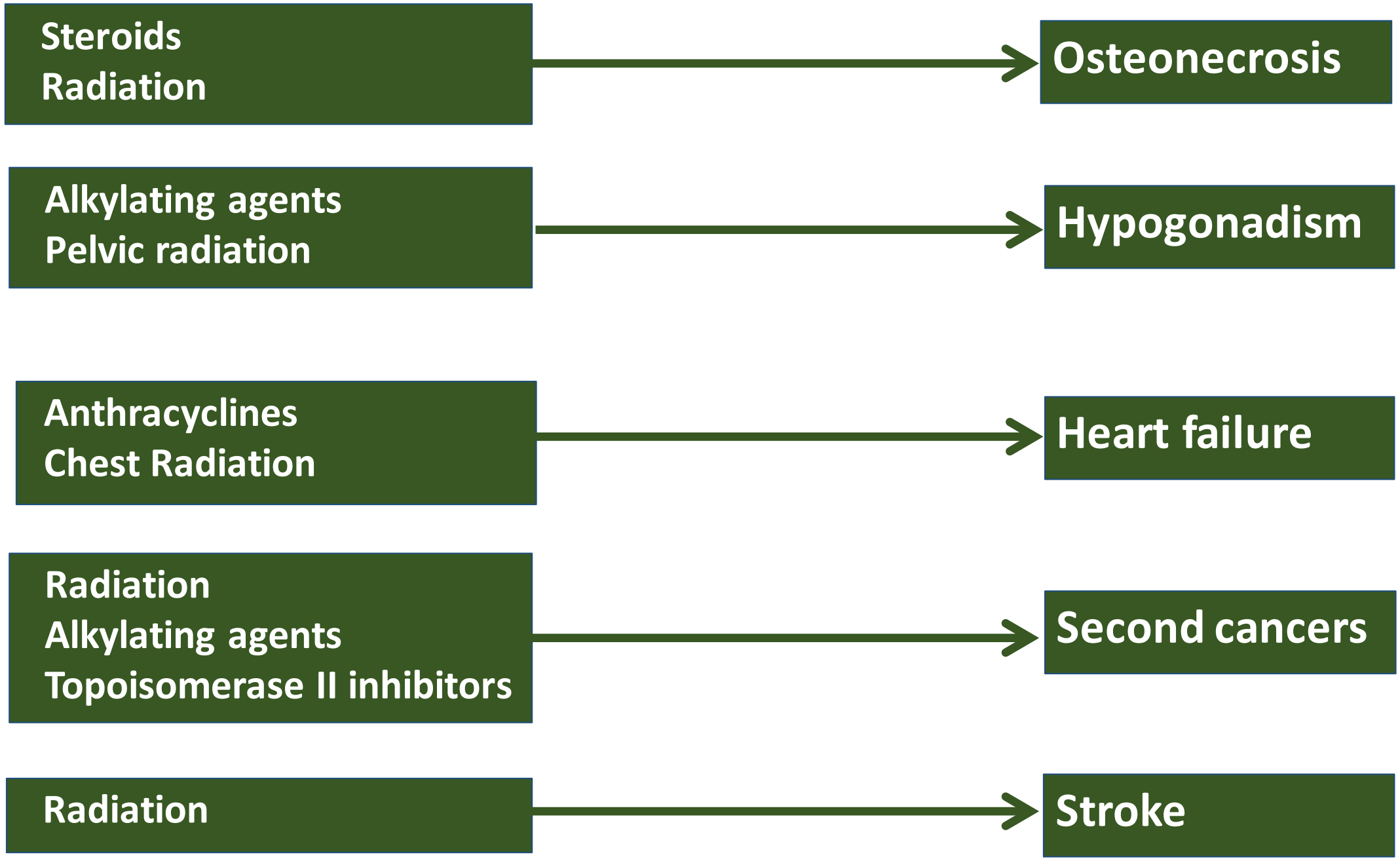


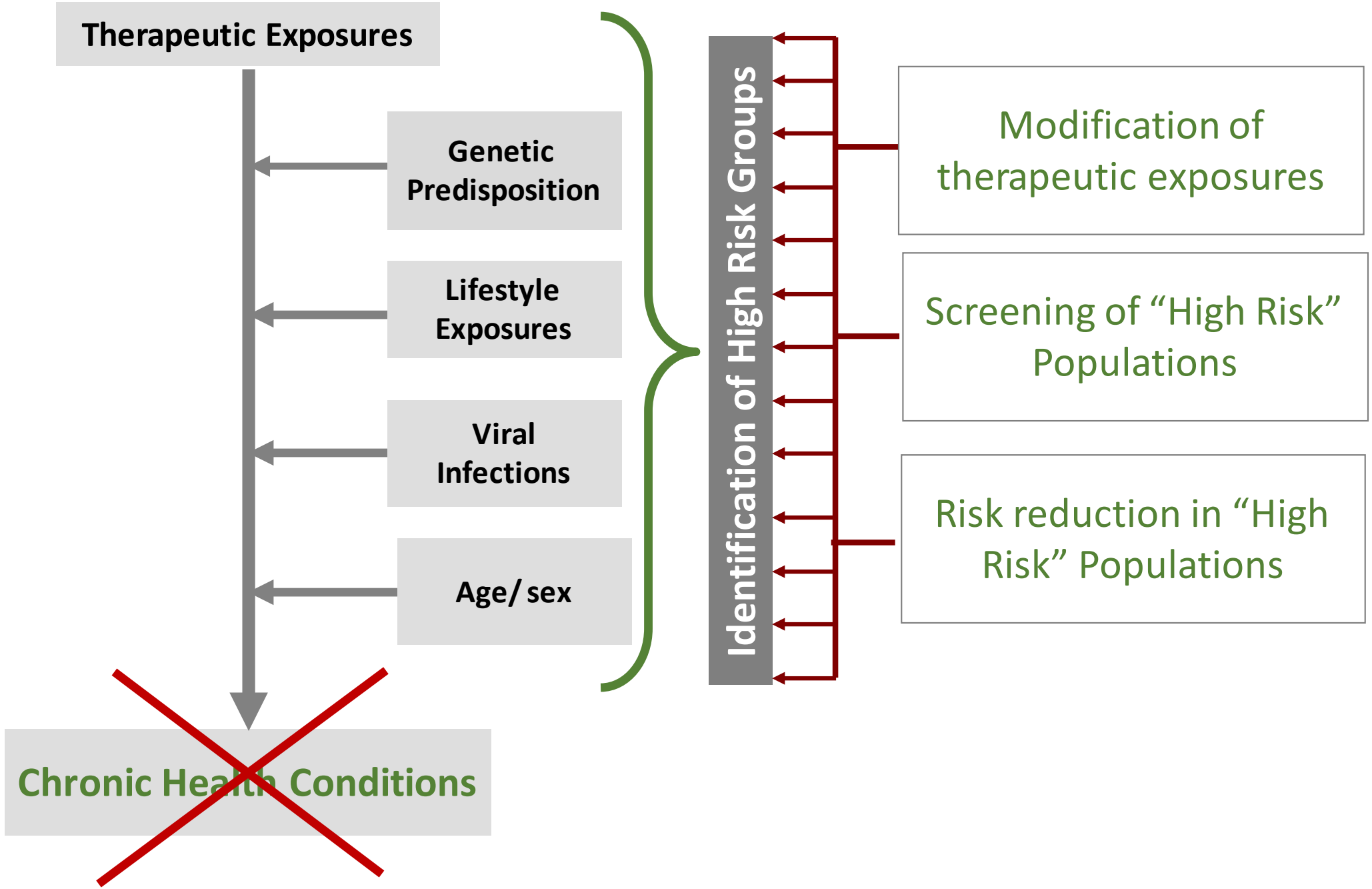


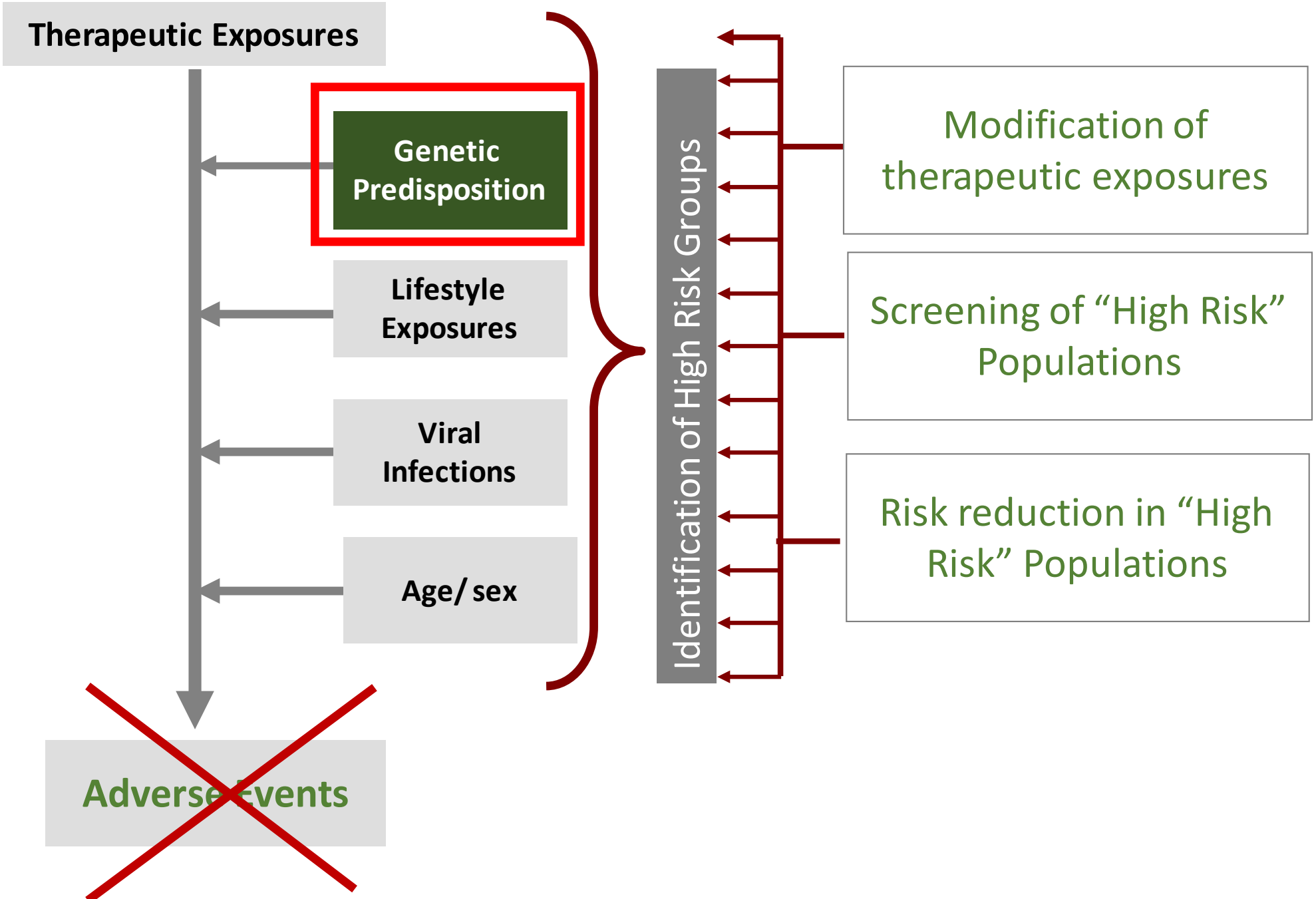
Cumulative Cause-specific Mortality among 5-year Childhood Cancer Survivors

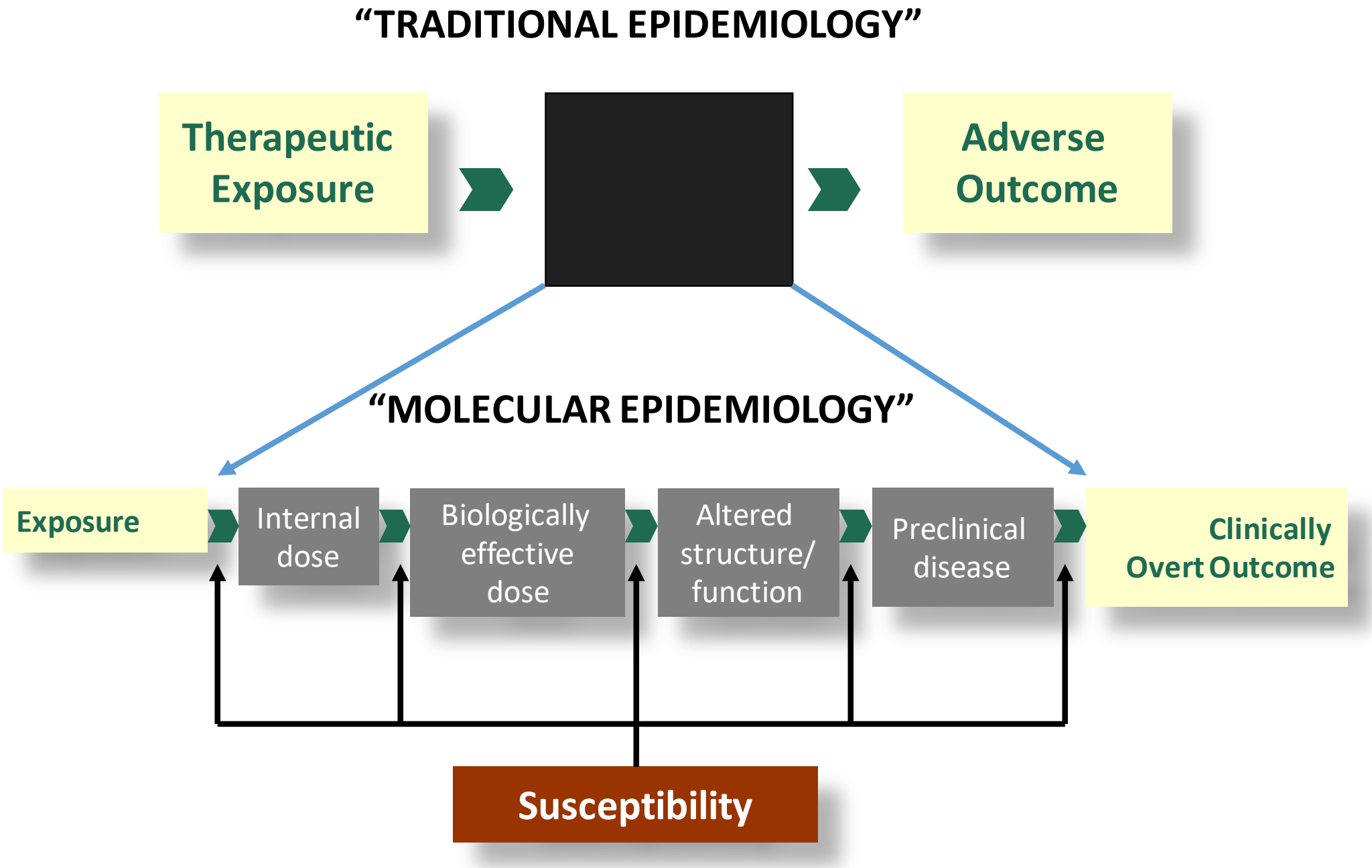


Clearly-defined association between therapeutic exposures and specific chronic health conditions


Steroids
Radiation
Osteonecrosis
Alkylating agents
Pelvic radiation
Hypogonadism
Anthracyclines
Chest Radiation
Heart failure
Radiation
Alkylating agents
Topoisomerase II inhibitors
Second cancers
Radiation
Stroke


Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Chronic Health Conditions
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations


Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations


"TRADITIONAL EPIDEMIOLOGY"
Therapeutic Exposure
Adverse Outcome
"MOLECULAR EPIDEMIOLOGY"
Exposure
Internal dose
Biologically effective dose
Altered structure/ function
Preclinical disease
Clinically Overt Outcome
Susceptibility

Case-control study of key adverse events after childhood cancer

COG ALTE03N1

Leukemia/ Lymphoma Society
National Cancer Institute (R01 CA139633)
National Cancer Institute (R35 CA220502)
The V Foundation

Study Design

Eligibility - Cases

1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. Subsequent development of a key adverse event

Matching Criteria

Primary cancer diagnosis
Year of diagnosis (±5y)
Race/ethnicity
Time since primary cancer

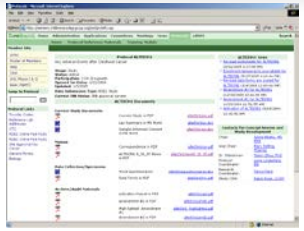
Eligibility - Controls

1. Individuals diagnosed with a primary cancer at age 21 years or younger
2. No evidence of key adverse events

Collect DNA from **Cases and controls**

Self-report of **comorbidities**

Summarize therapeutic exposures for cases and controls



Source documentation (Cases only)

Osteonecrosis *(diagnostic radiology)*

Subsequent neoplasms *(pathology report)*

Congestive Heart Failure *(echocardiogram report)*

Stroke *(diagnostic radiology)*

Cardiac Toxicity in Cancer Survivors

Cardiomyopathy → congestive heart failure

Risk factors

Anthracycline chemotherapy

Risk modifiers

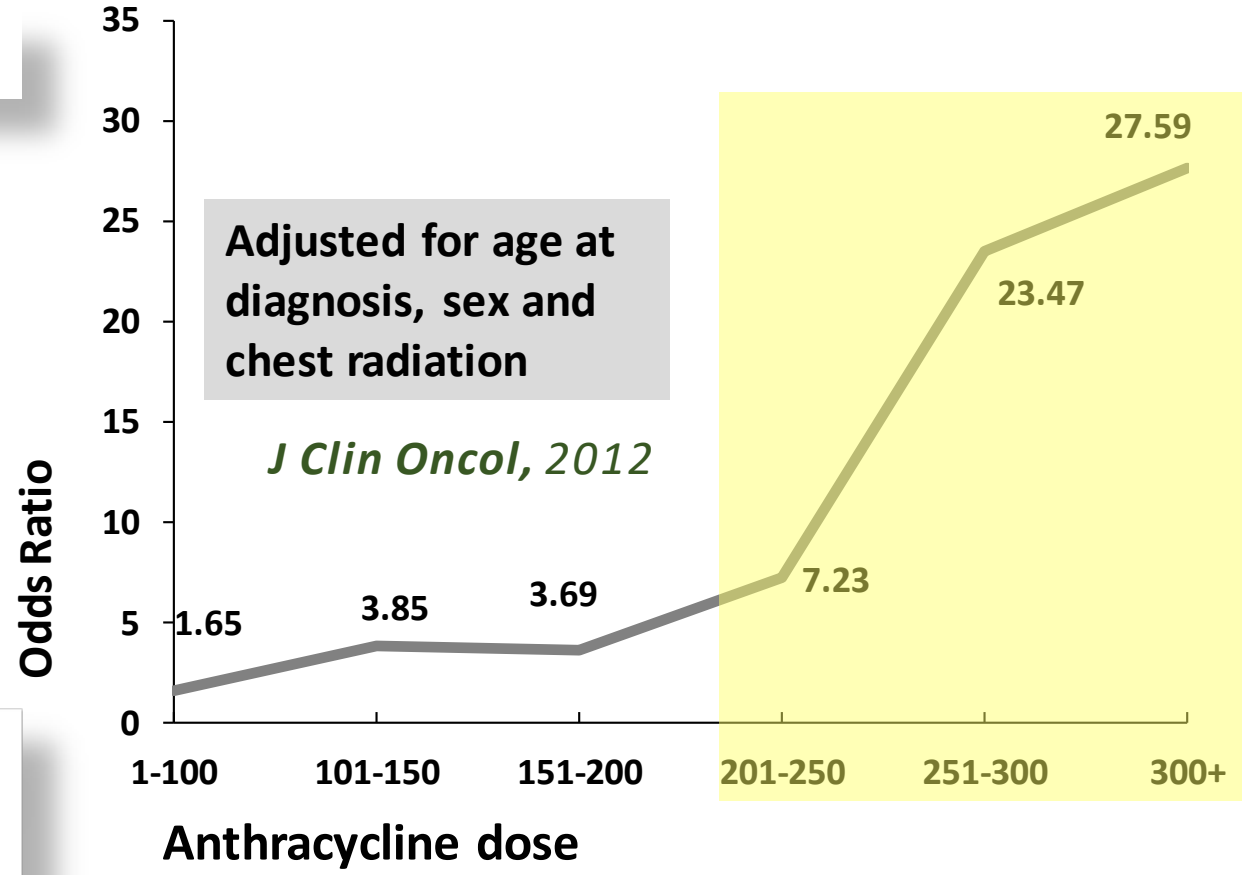
Chest radiation

Young age at exposure

Female sex

~60% of children exposed to high-dose anthracyclines develop cardiotoxicity

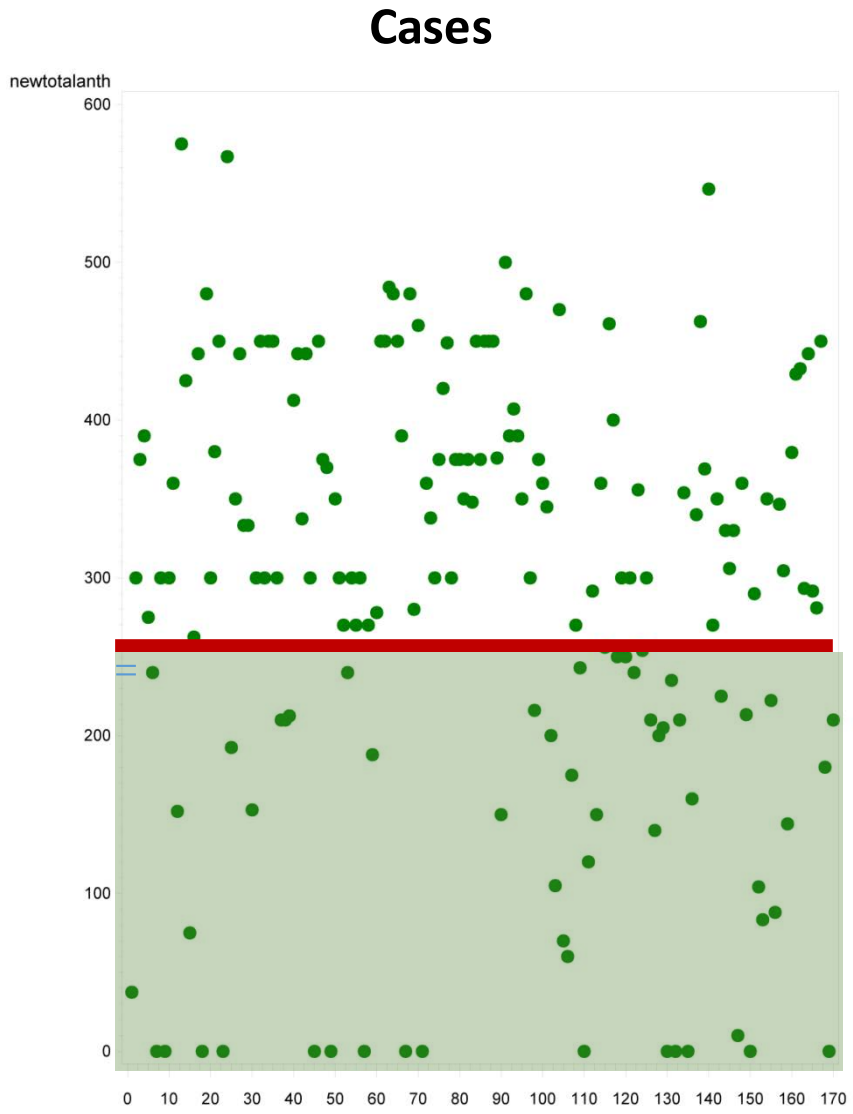
Circulation, 2013

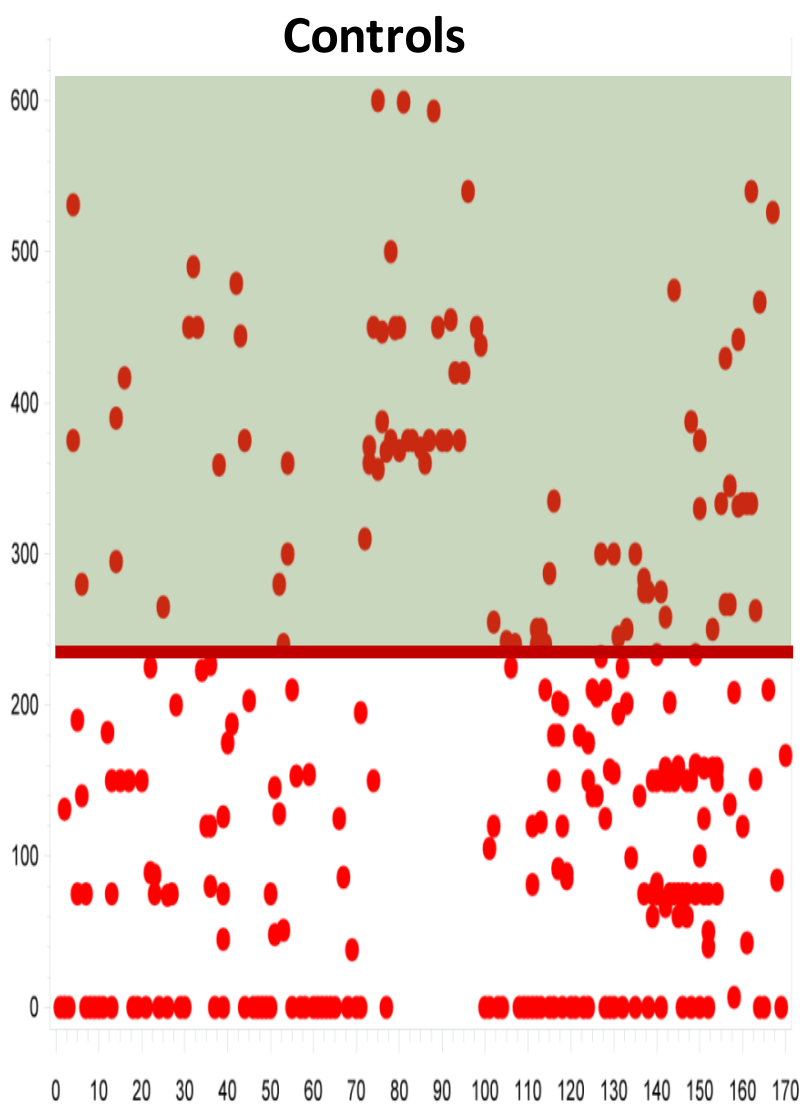


5-year survival rates of less than 50% after CHF diagnosis

N Engl J Med, 2000

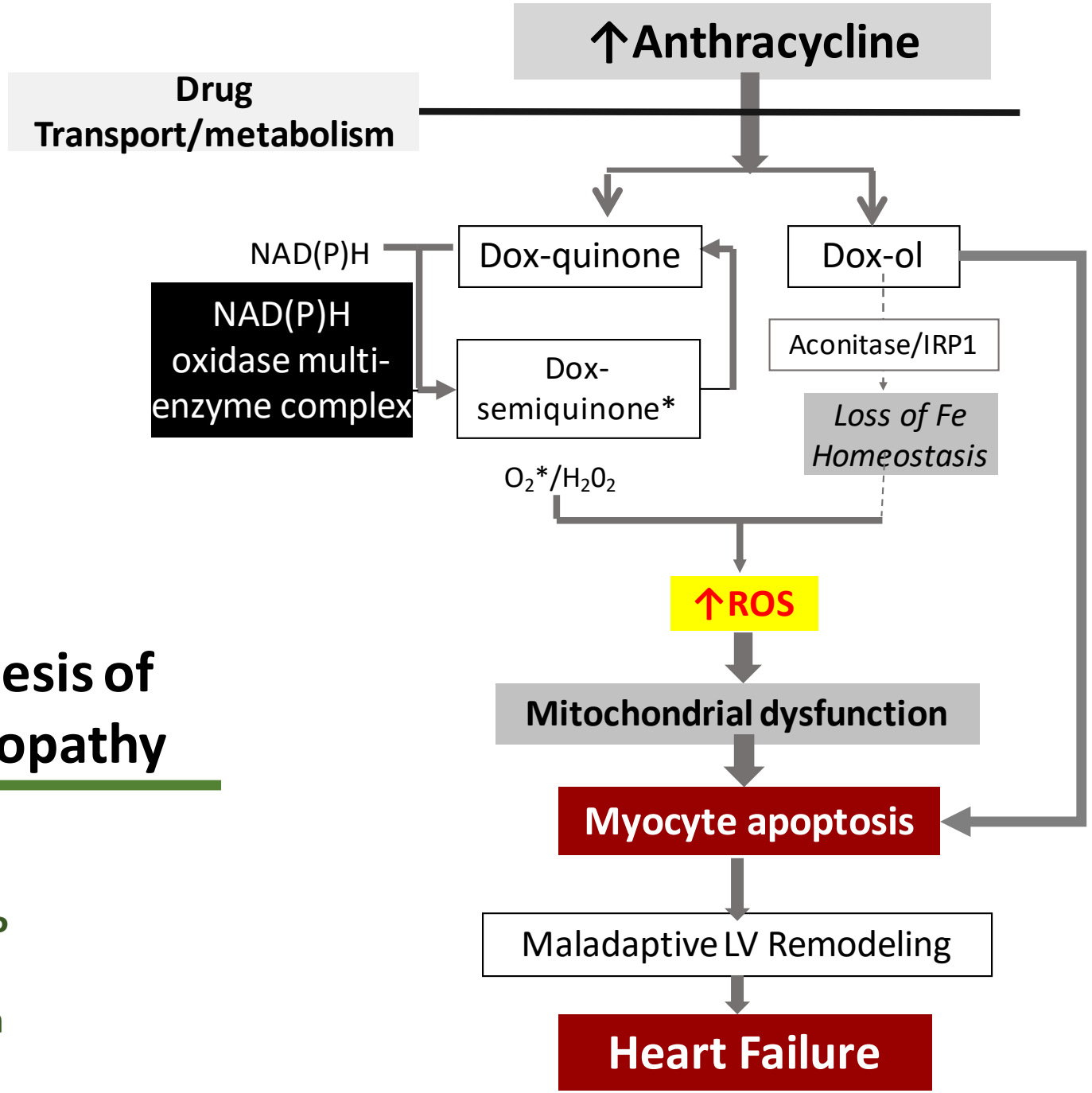
Inter-individual variability in risk of anthracycline-related cardiomyopathy





Role for genetic susceptibility?

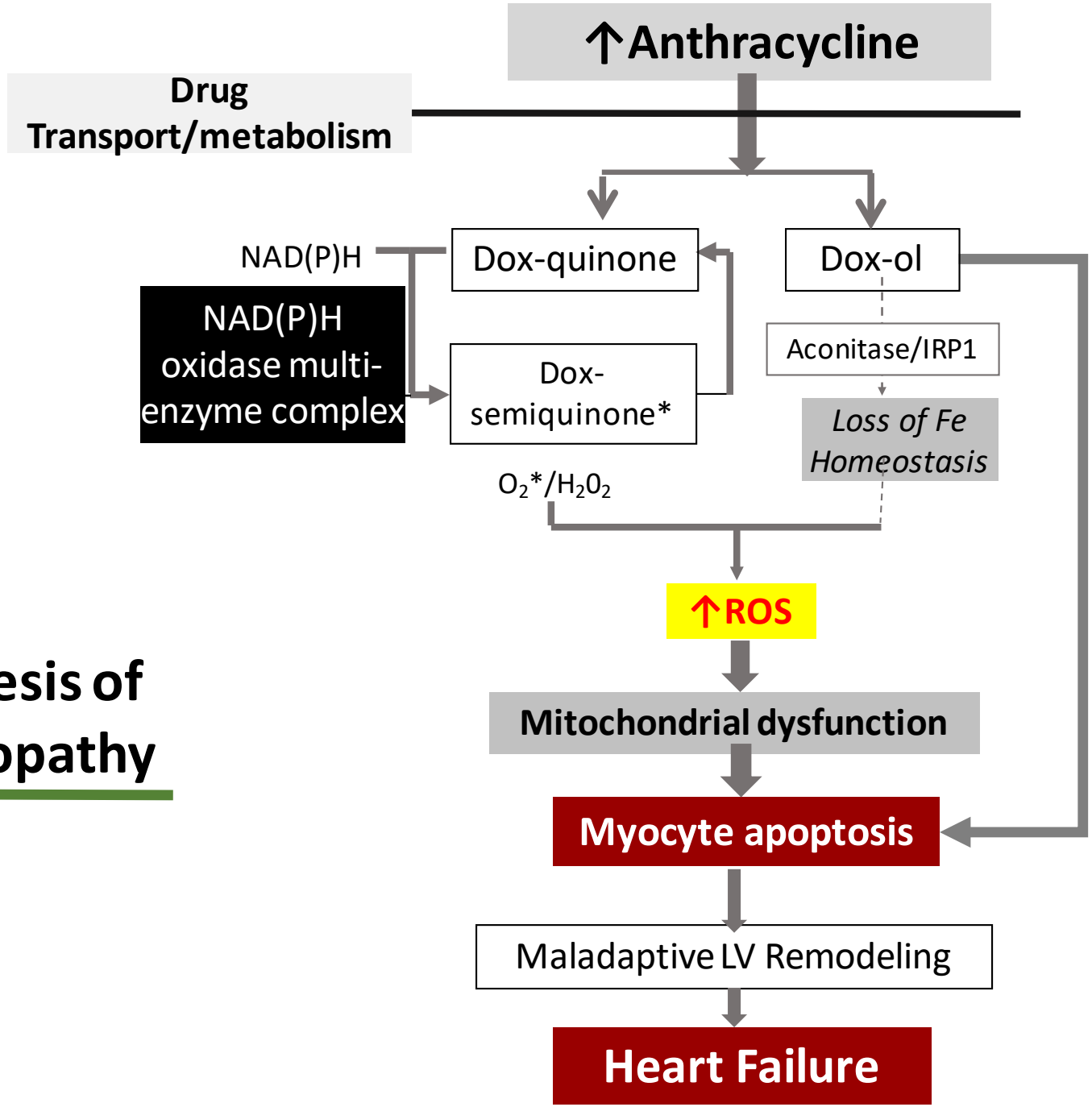
Pathogenesis of cardiomyopathy



Funding:

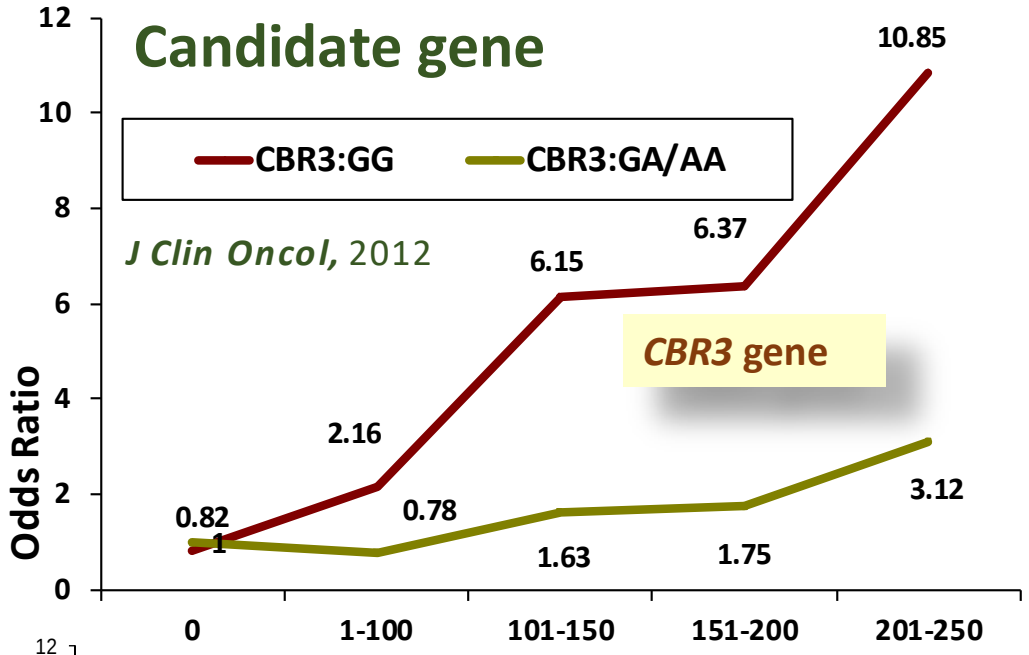
62771-11 LLS TRP
R35 CA220502
The V Foundation

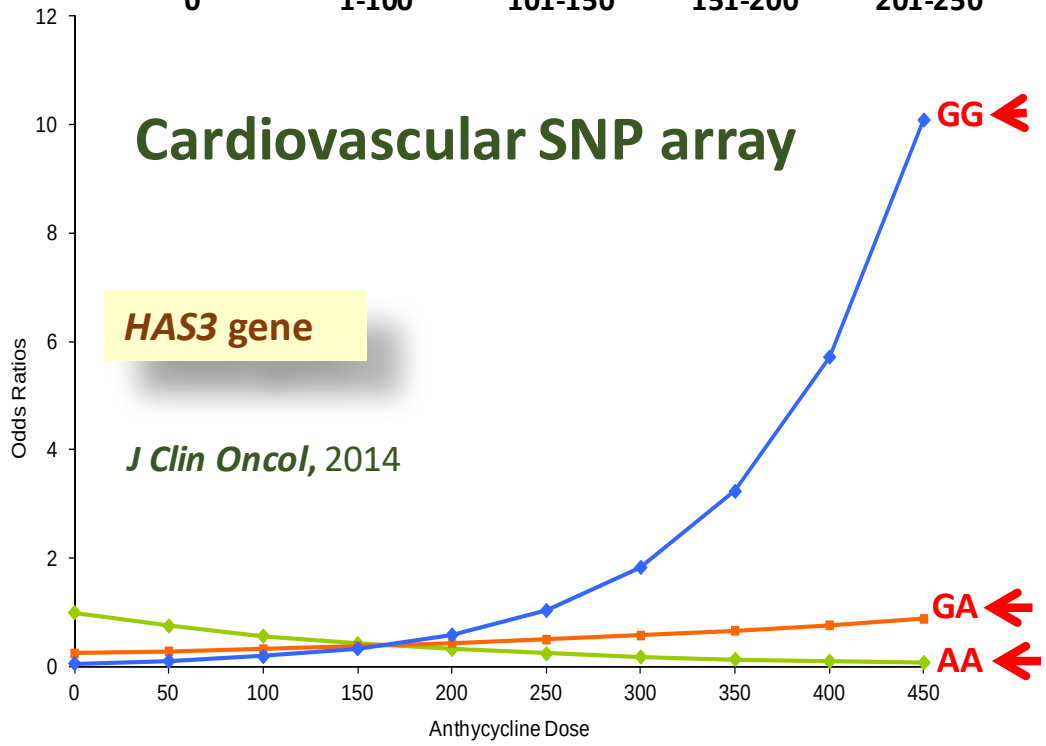
Pathogenesis of cardiomyopathy

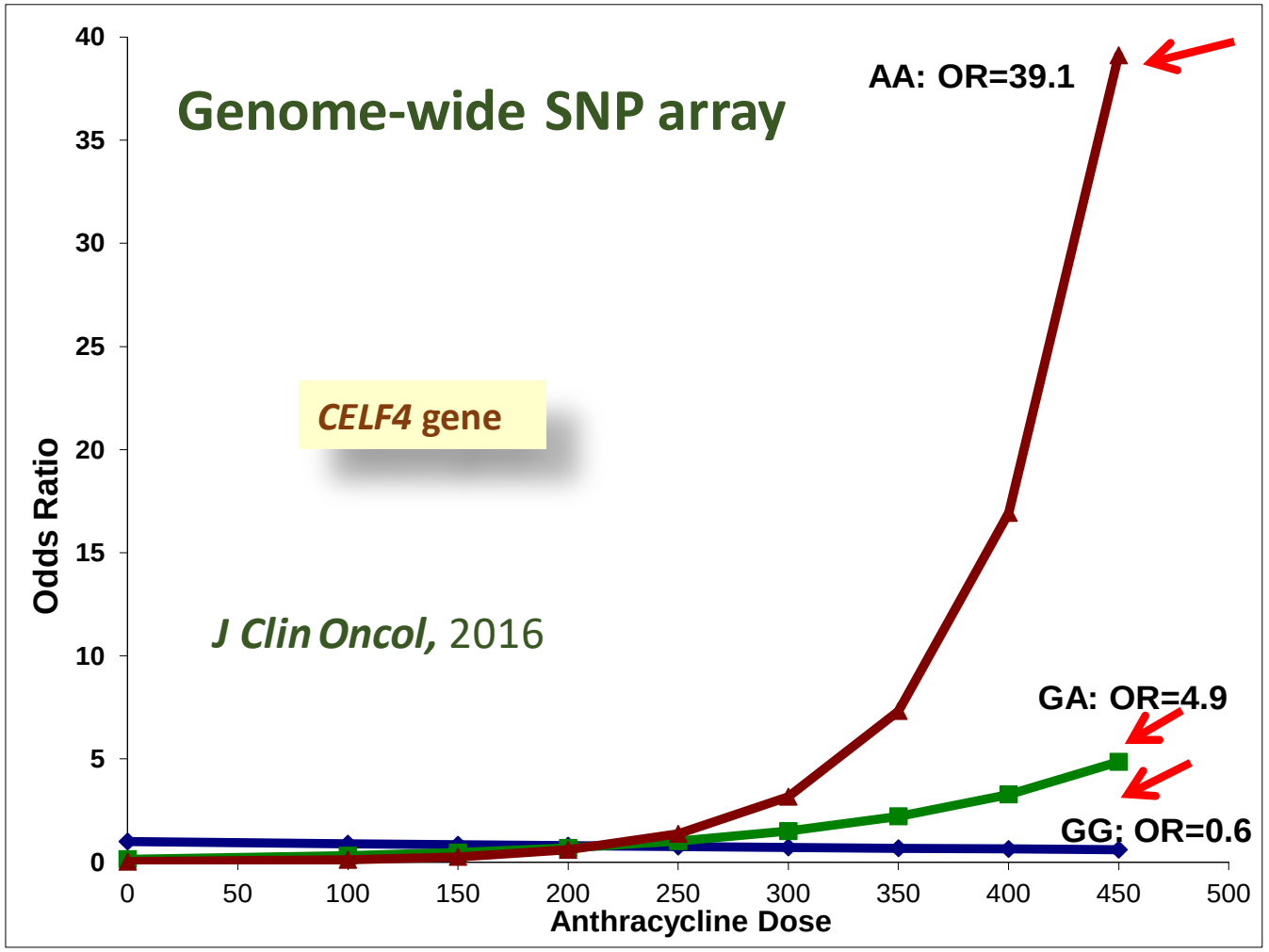


1. Candidate gene approach
2. Carefully-curated SNP arrays
3. Agnostic-genome wide association studies
4. Functional studies

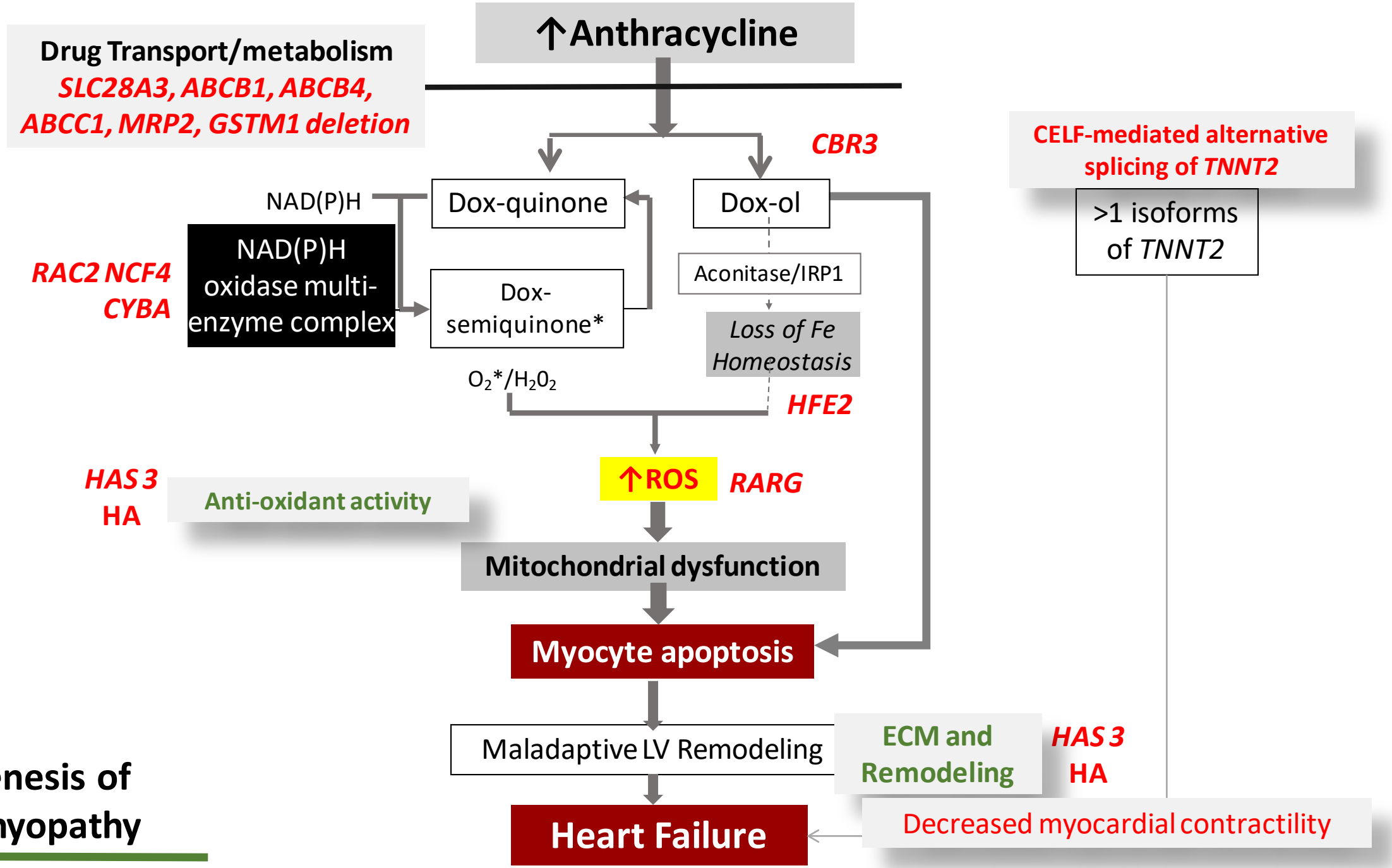
Genetic Associations

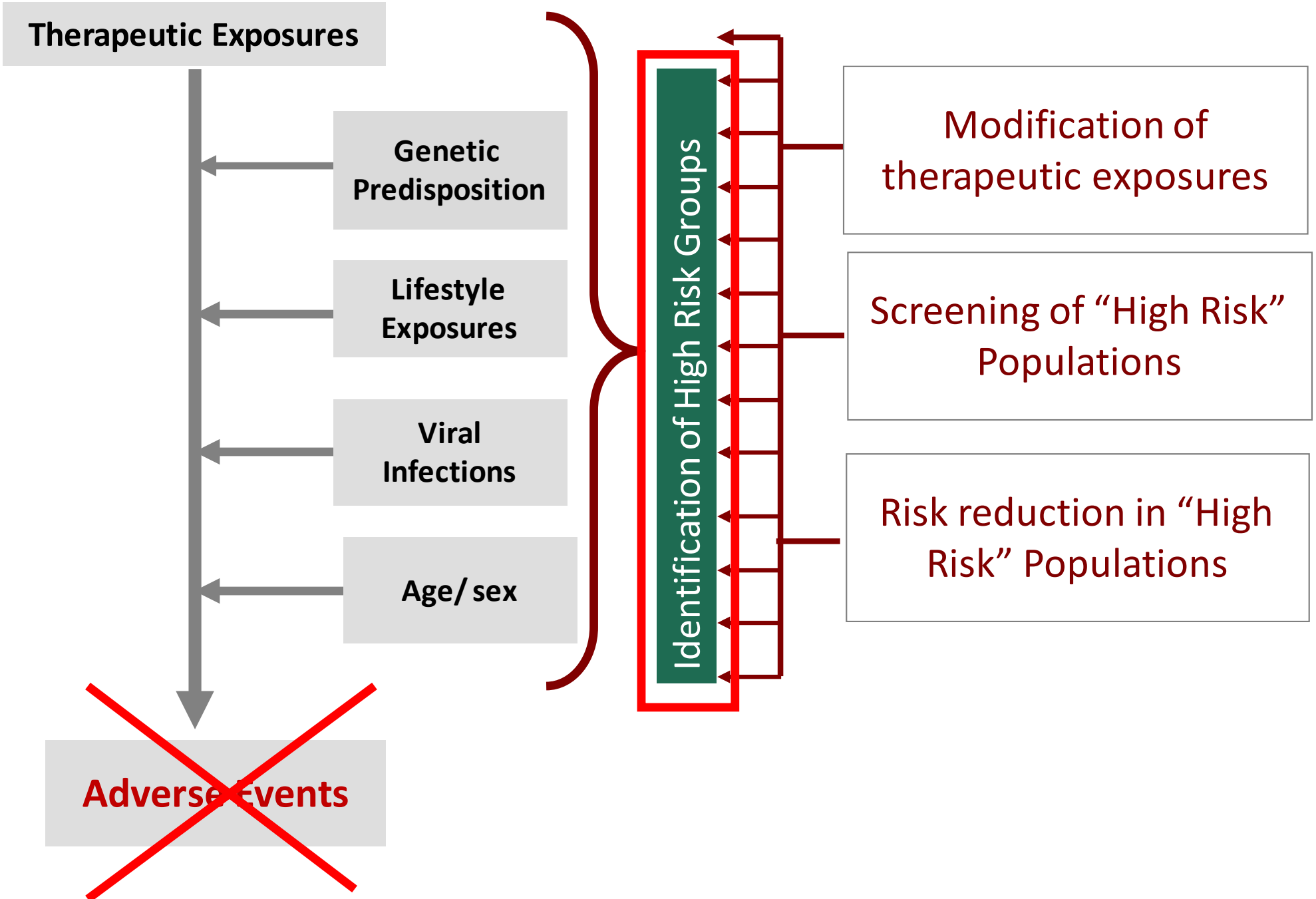




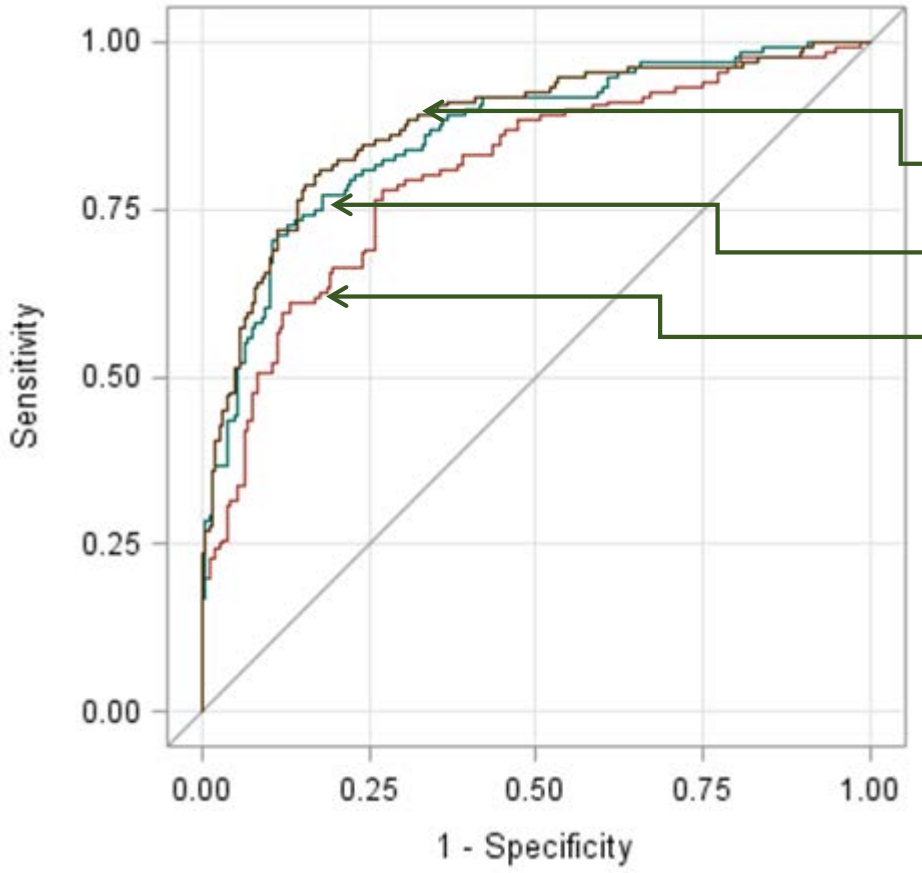


Pathogenesis of Cardiomyopathy




Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations

Risk prediction models for anthracycline-related cardiomyopathy

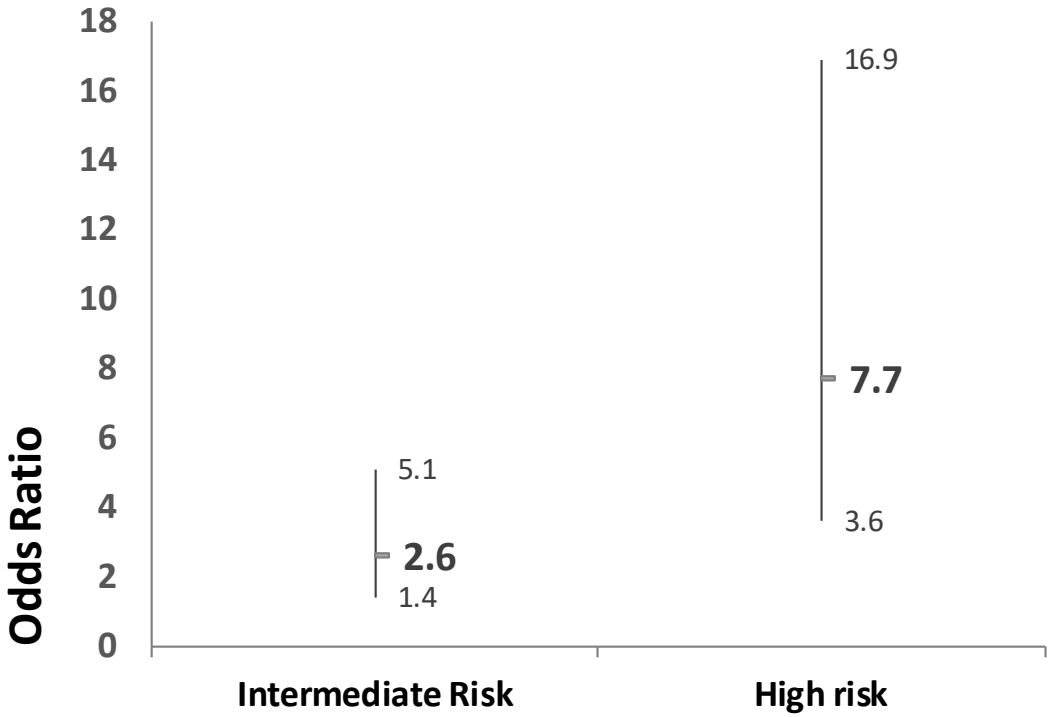


Final Model (AUC=0.88)

Clinical + Genetic Model (AUC=0.86)

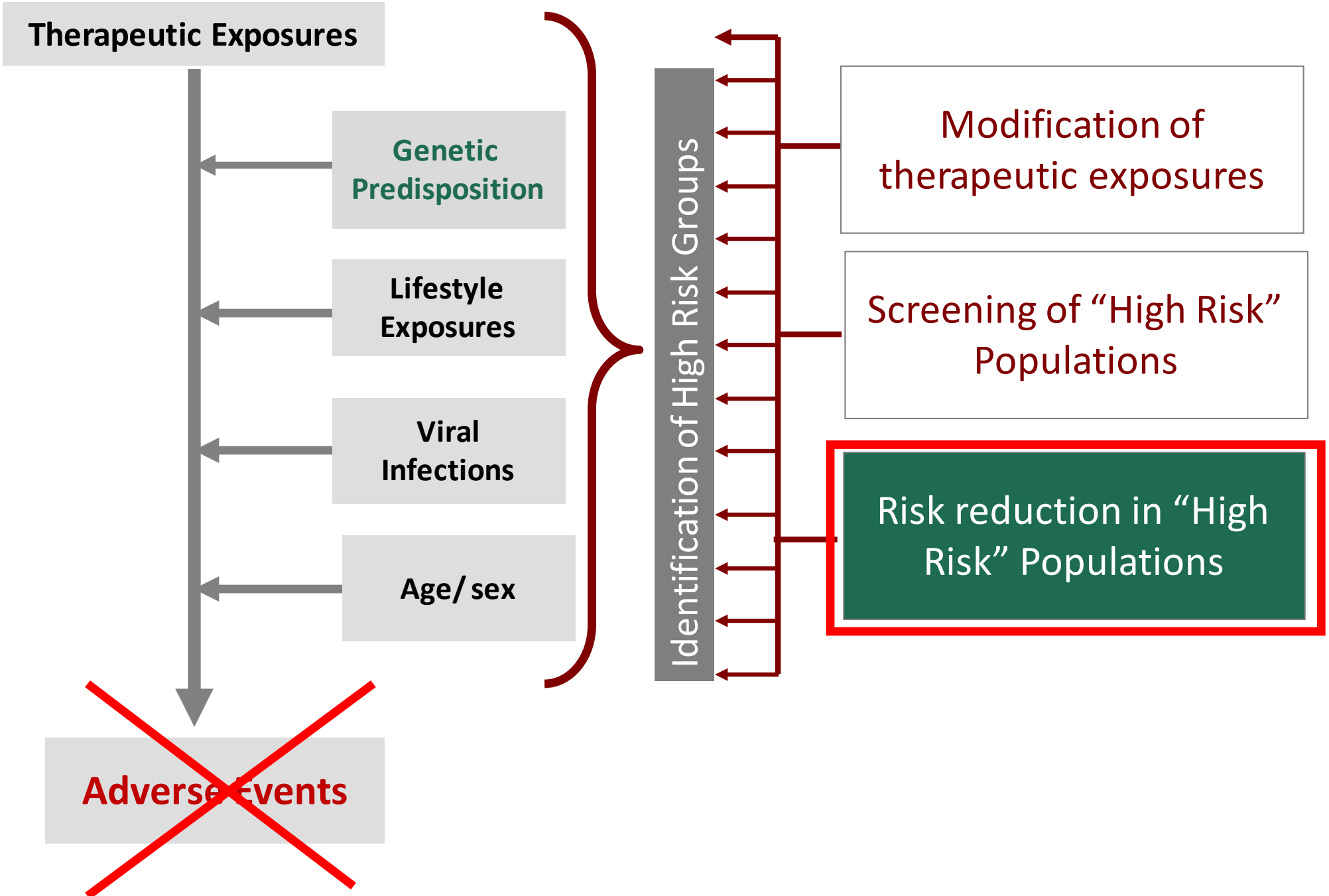
Clinical Model (AUC=0.80)

P <0.0001



Prediction model was successfully replicated in CCSS

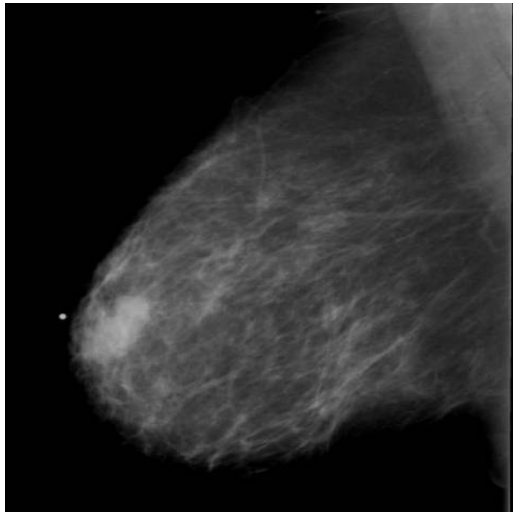
- **Final Model performed significantly better than the Clinical Model, *P*=0.02.**

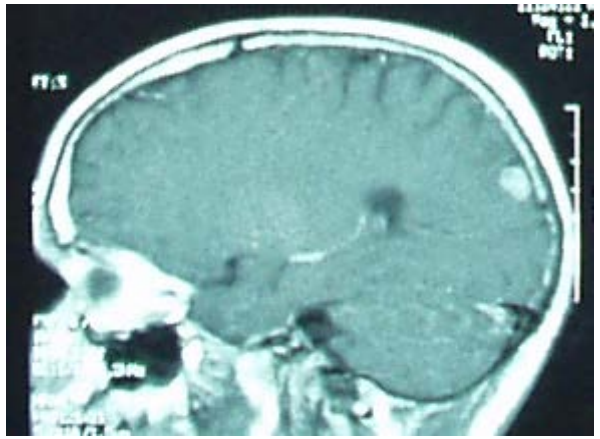

Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations

Subsequent Neoplasms

Case-control study of key adverse events after childhood cancer

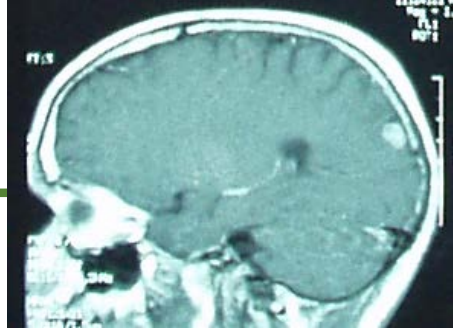
COG ALTE03N1





Leukemia/ Lymphoma Society
National Cancer Institute R01 CA139633
National Cancer Institute R35 CA220502

Background



- Childhood cancer survivors are at a 10-fold increased risk for developing histologically distinct subsequent CNS tumors c/w general population

- High-grade gliomas and meningiomas are most common types of subsequent CNS tumors
  - significant morbidity and mortality
    - Five-year survival is <20% for gliomas
    - Meningiomas are often accompanied by significant morbidity

***JNCI.* 2010**
***Lancet Oncol.* 2013**

Risk factors

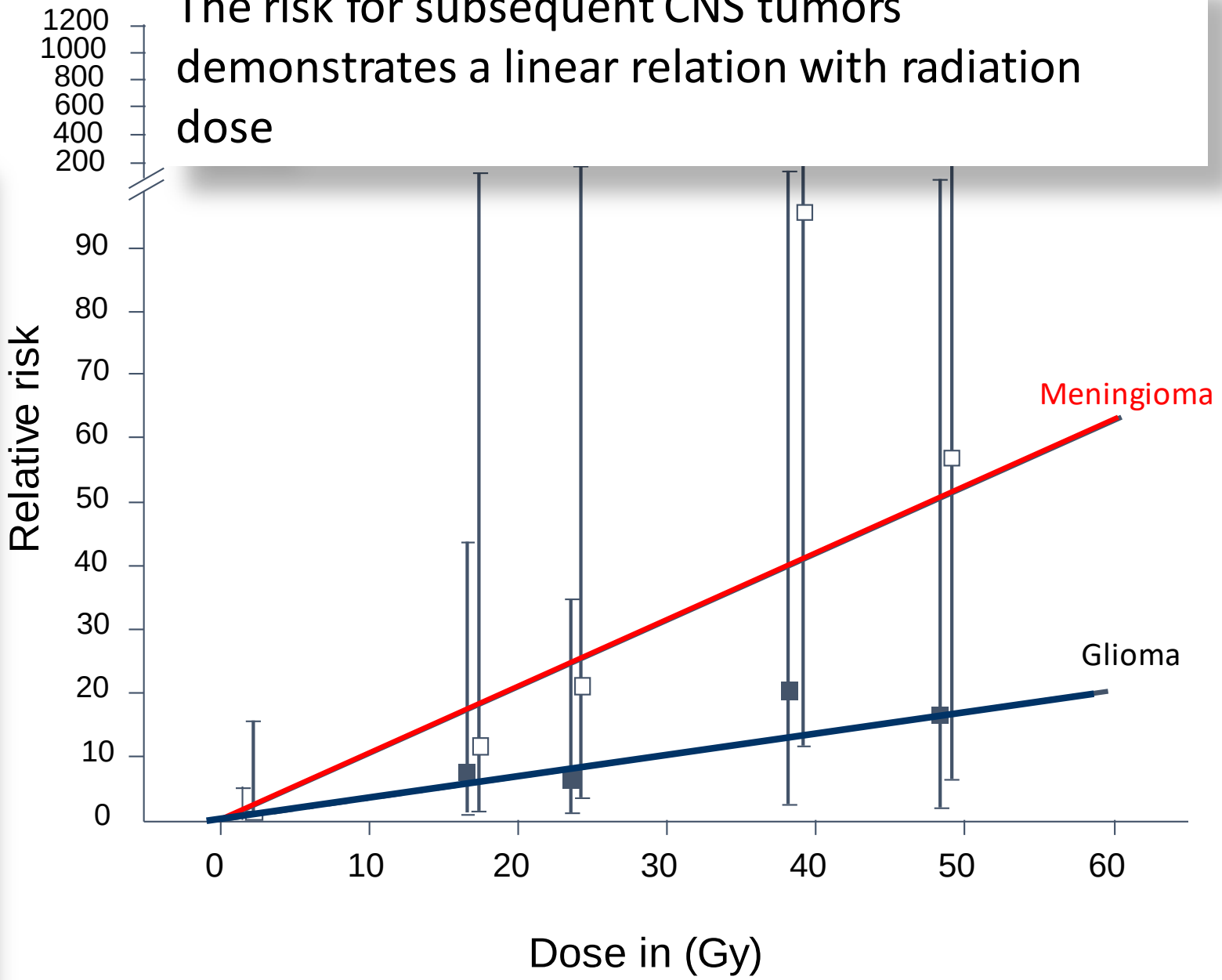
- Exposure to cranial radiation is the major risk factor
- The risk is especially increased after exposure to radiation at a very young age

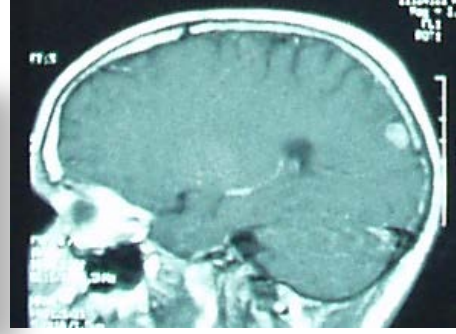
The risk for subsequent CNS tumors demonstrates a linear relation with radiation dose

Risk factors

- Exposure to cranial radiation is the major risk factor
- The risk is especially increased after exposure to radiation at a very young age

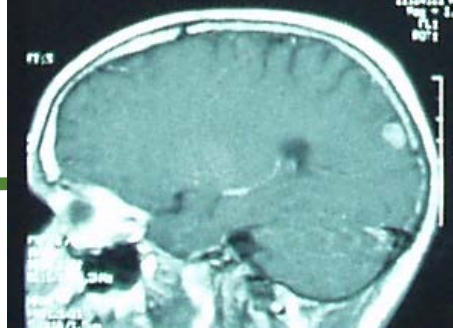
The risk for subsequent CNS tumors demonstrates a linear relation with radiation dose

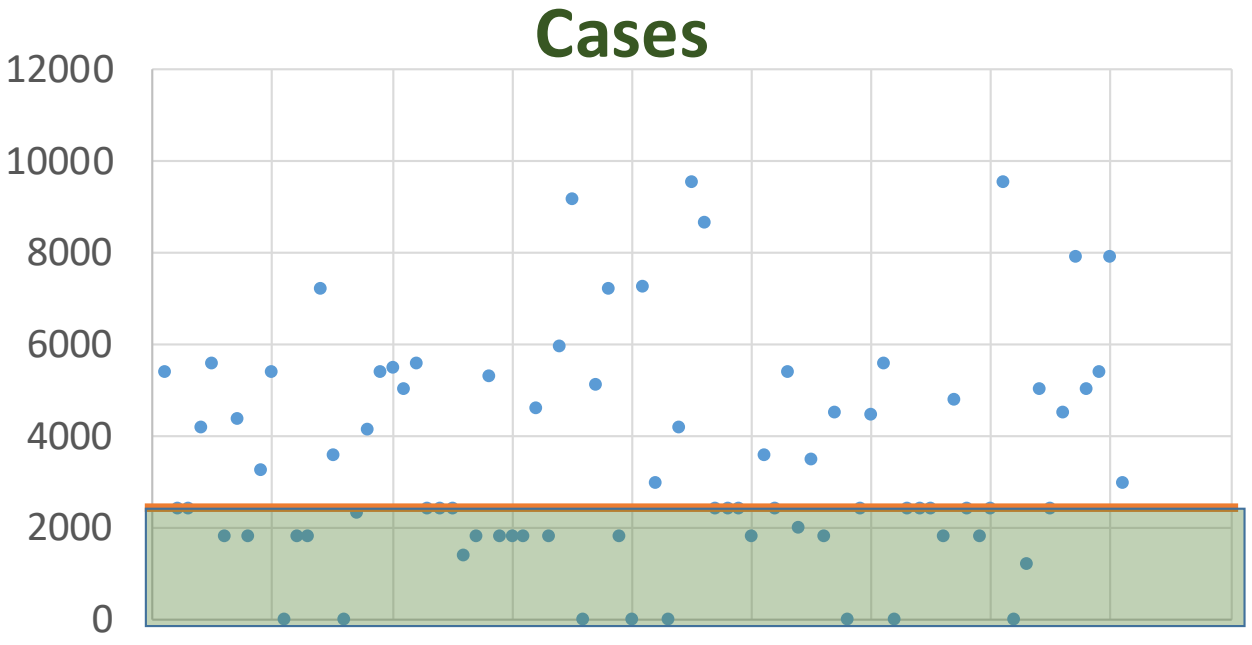


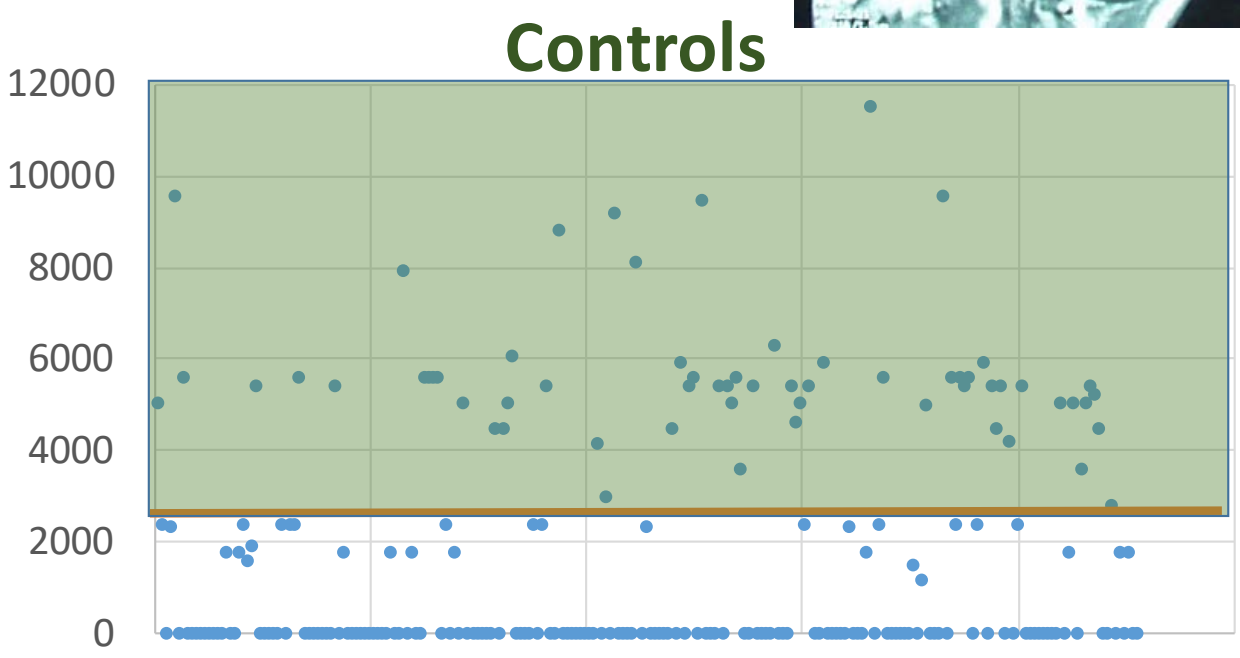


JNCI. 2010

Cranial radiation dose and subsequent CNS tumors - inter-individual variability in risk





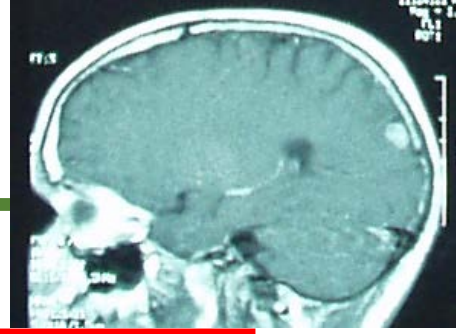


Role for Genetic Susceptibility?

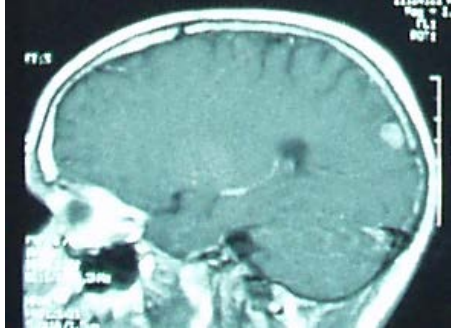
Candidate gene approach

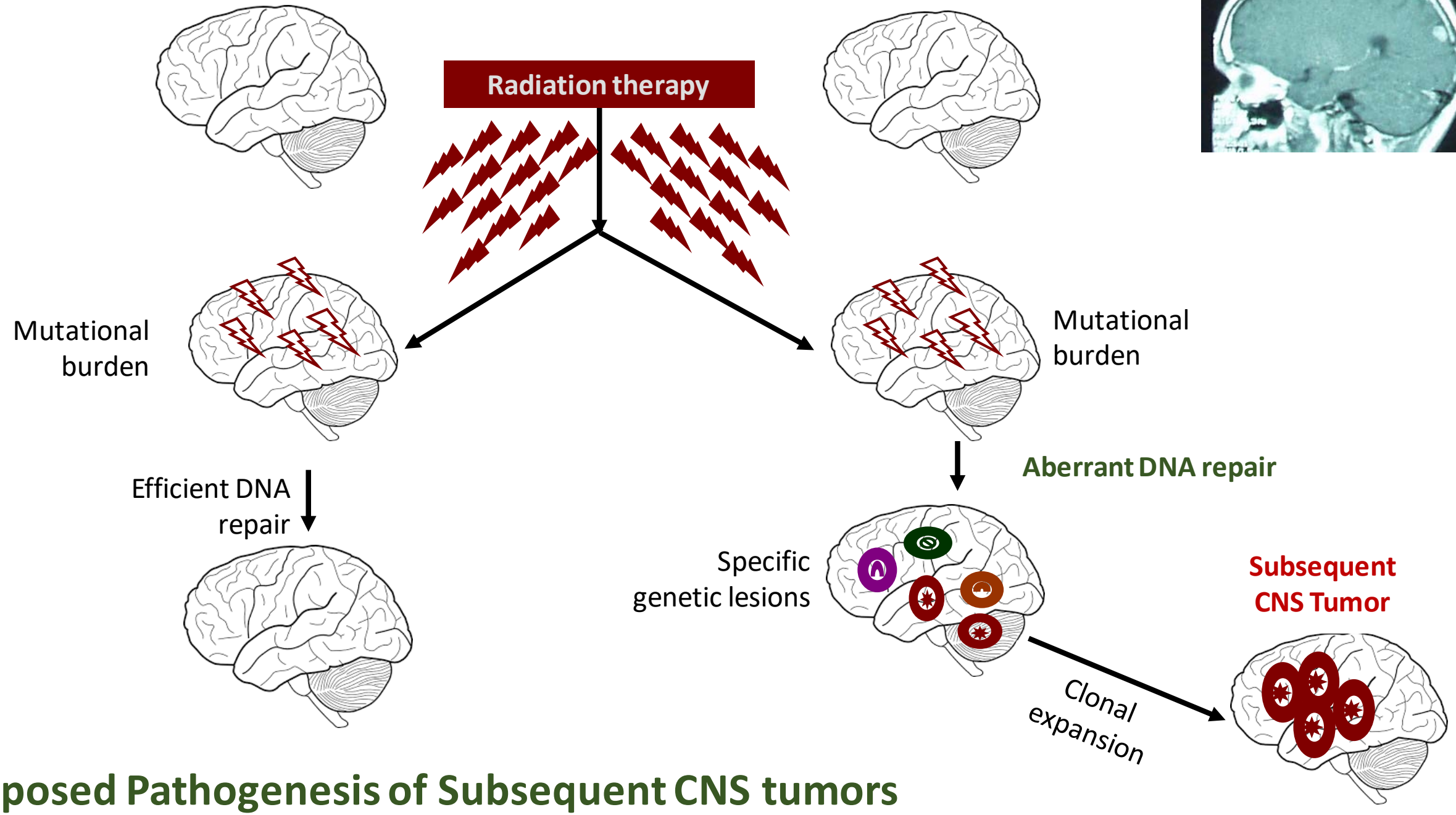
- Examined genetic variants associated with *de novo* brain tumors

Replication of Candidate SNPs – Results

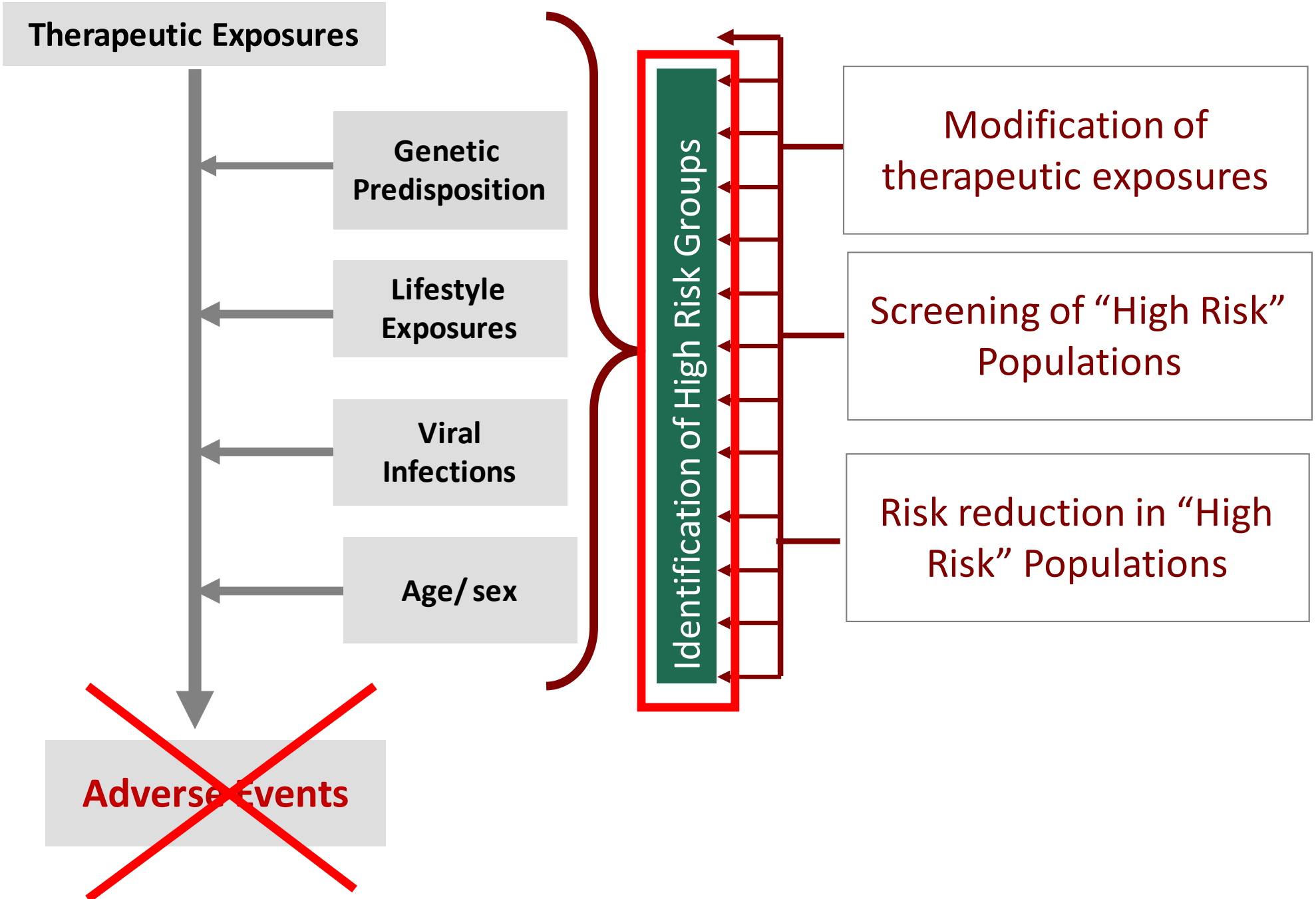


SNP	Chromosome	MAF_ca	MAF_co	Gene	Function
rs15869	**Chr13**	0.32	0.19	***BRCA2***	**DNA repair**
rs1805389	**Chr13**	0.09	0.04	***LIG4***	**DNA repair**
rs1673041	**Ch19**	0.29	0.24	***POLD1***	**DNA repair**
rs8079544	**Ch17**	0.2	0.07	***TP53***	**DNA damage response**
rs25489	**Ch19**	0.2	0.07	***XRCC1***	**DNA repair**
rs11615	**Ch19**	0.29	0.24	***ERCC1***	**DNA repair**

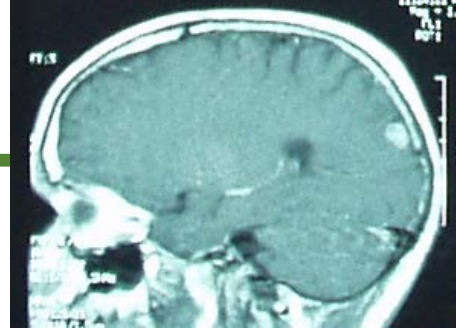


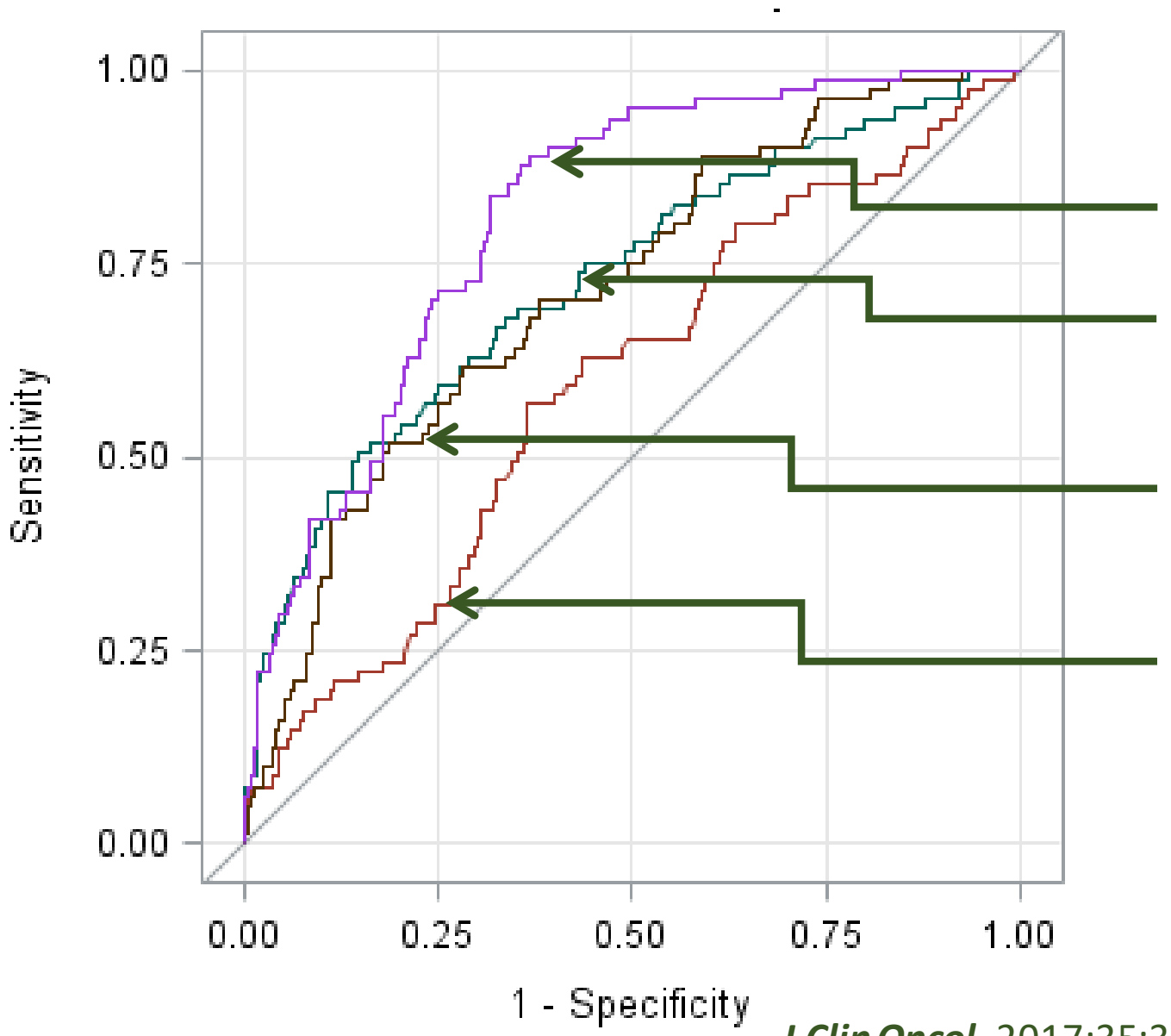


Proposed Pathogenesis of Subsequent CNS tumors


Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations

Risk prediction models for subsequent CNS tumors





Final Model
AUC=0.81

Clinical Model
AUC=0.73

P=0.002

Genetic Model
AUC=0.71

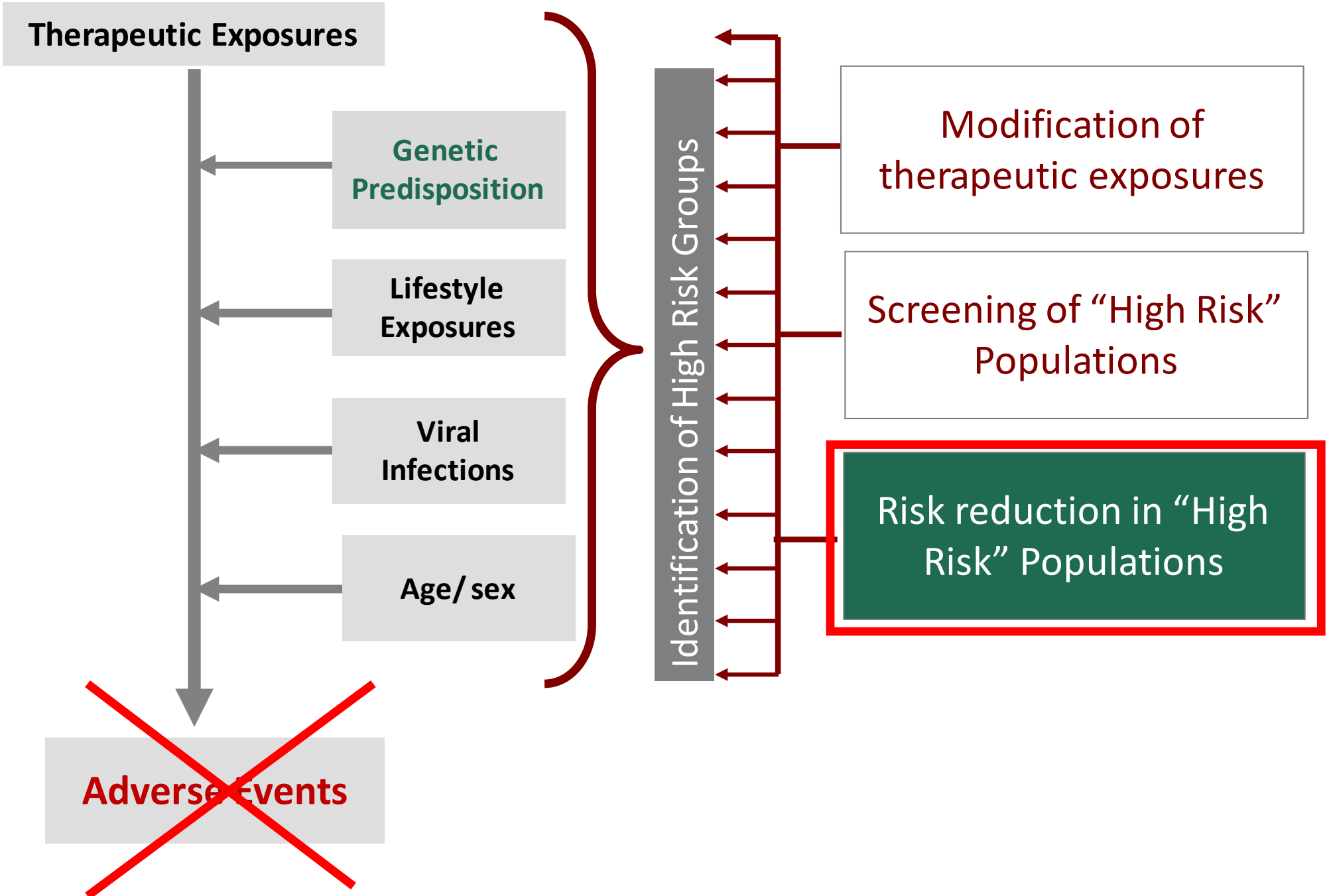
Base Model
AUC=0.59

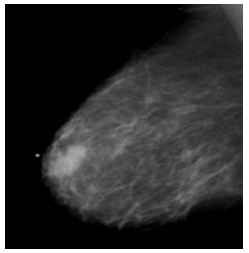
rs15869 [***BRCA2***]
rs8079544 [***TP53***]
rs498872 [***PHLB1***]
rs1673041 [***POLD1***]
rs25489 [***XRCC1***]
rs11615 [***ERCC1***]
rs828699 [***XRCC5***]

Replication case-control set

- AUC_{CL} **73%**
- AUC_{F} **89%**

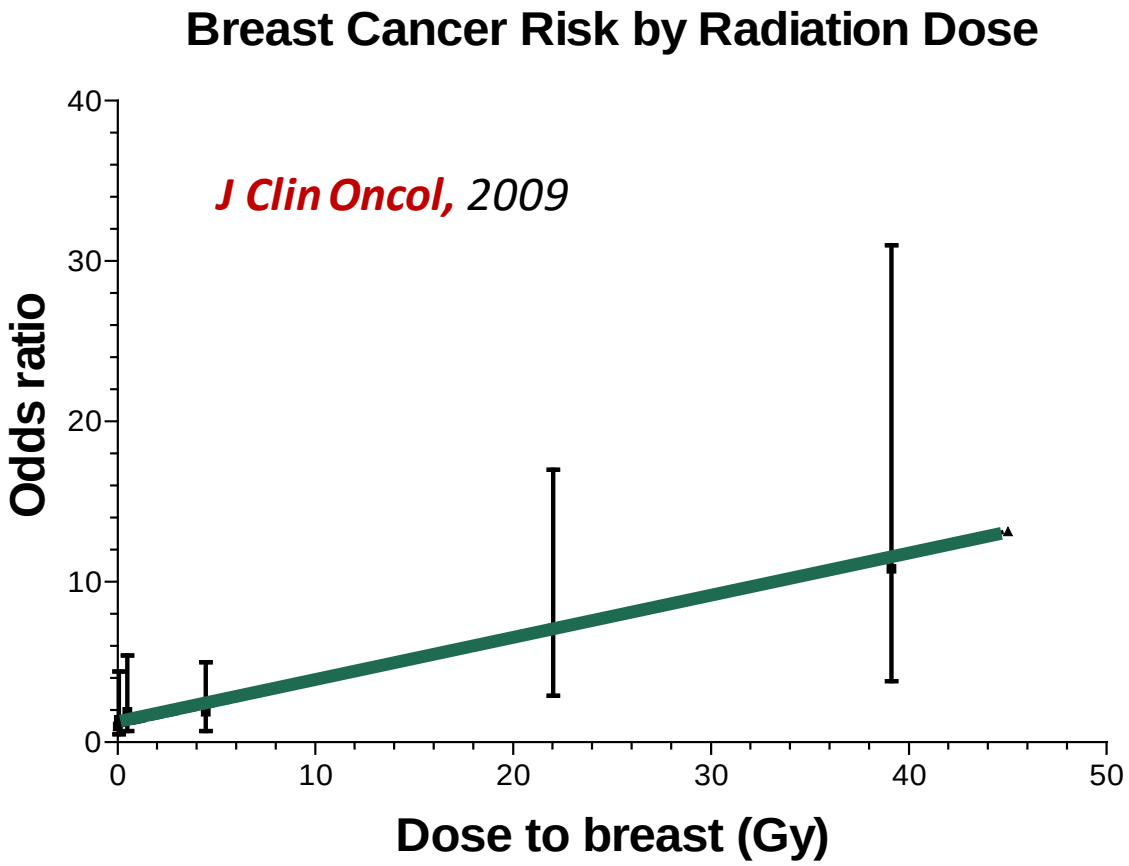
J Clin Oncol, 2017;35:3688-96


Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations

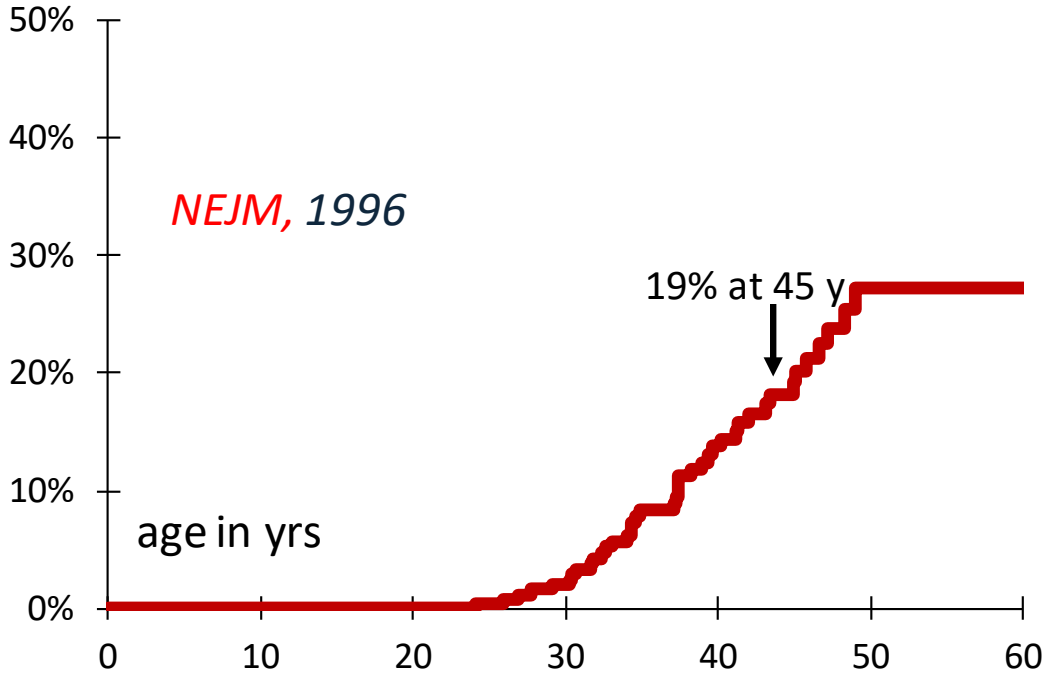


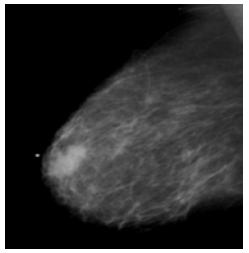
Radiation-induced Breast Cancer

Radiation increases the risk of breast ca



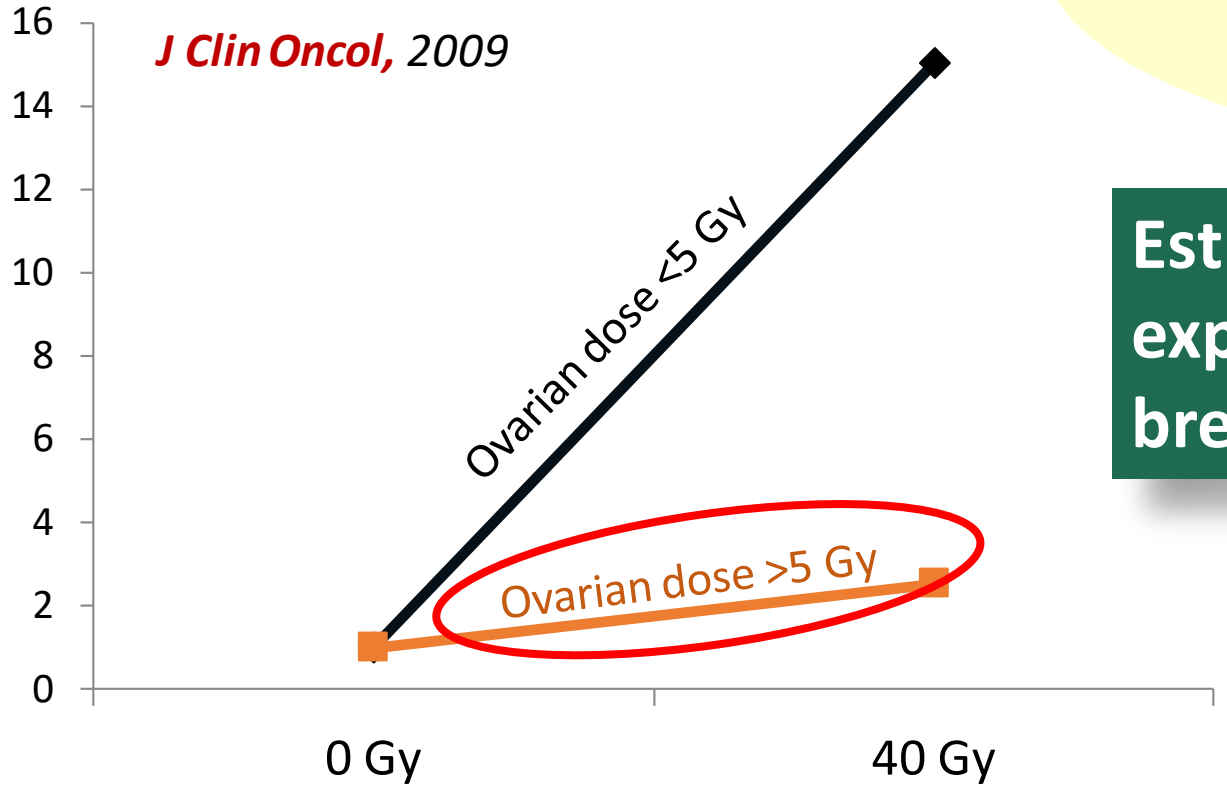
Increased risk similar to *BRCA* mutation





Radiation-induced Breast Cancer

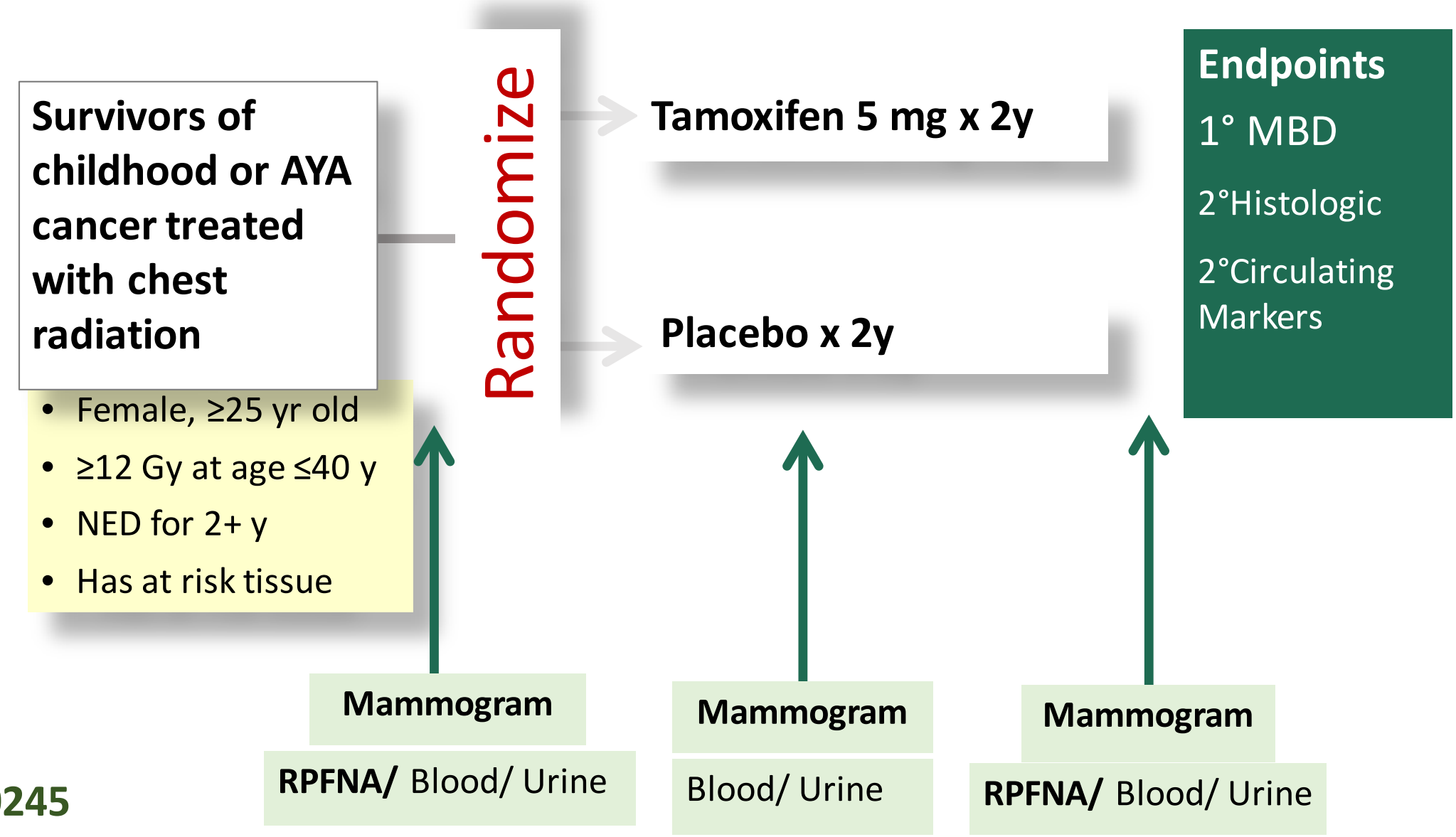
Endogenous estrogen modifies breast c



The only FDA-approved chemopreventive option in both pre- and post-menopausal women is tamoxifen

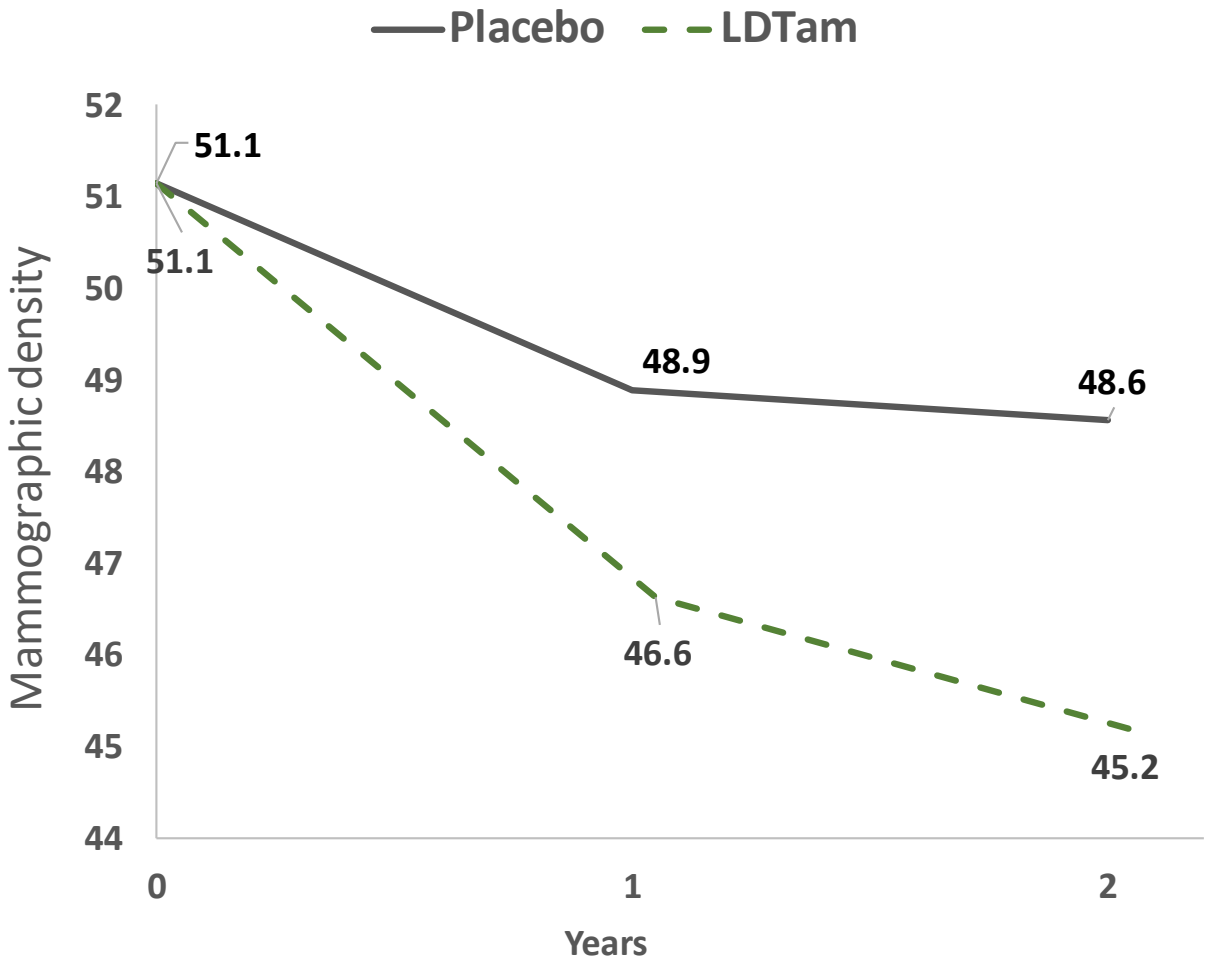
Estrogen-blocking intervention is expected to prevent radiation-induced breast cancer in survivors

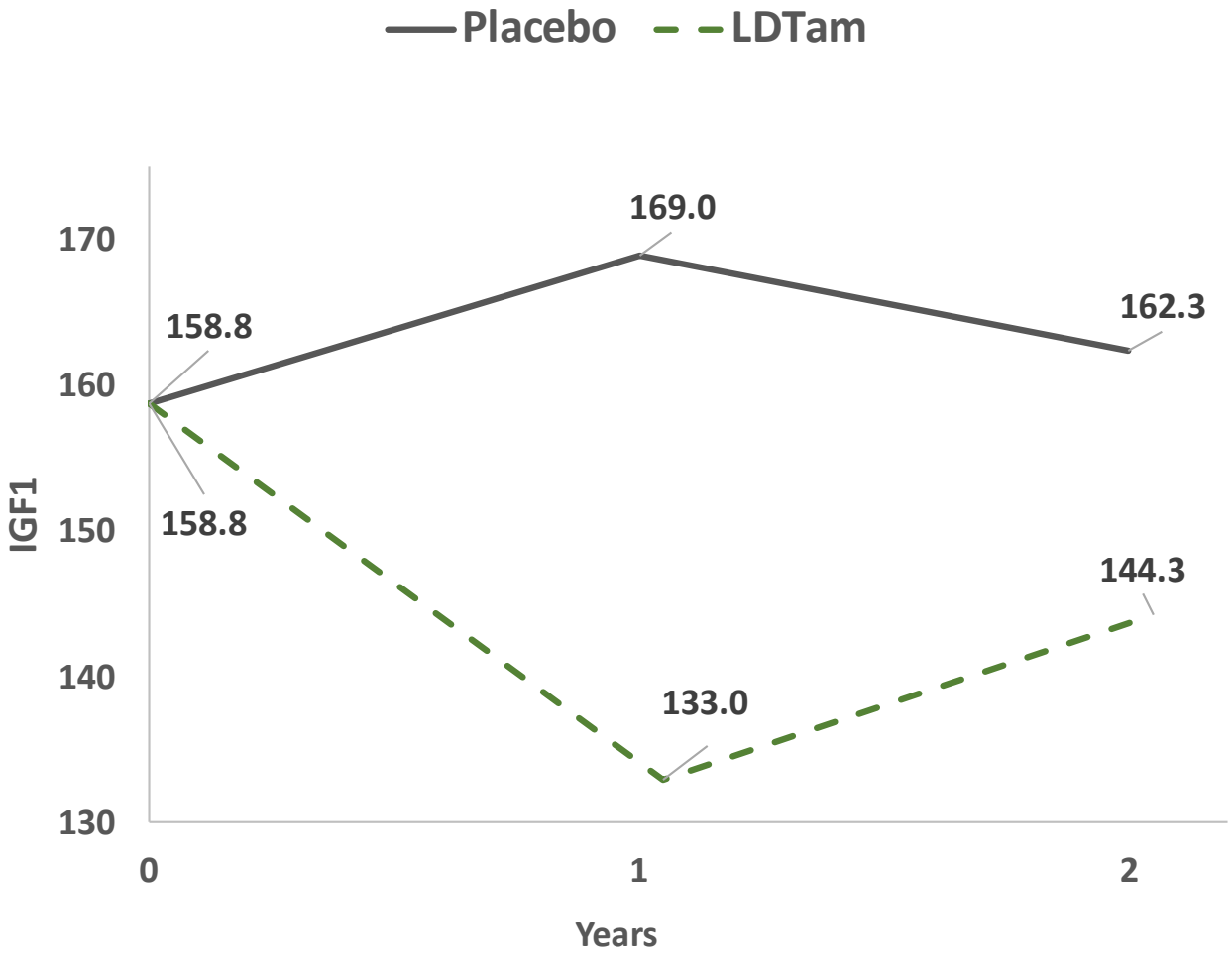
Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction

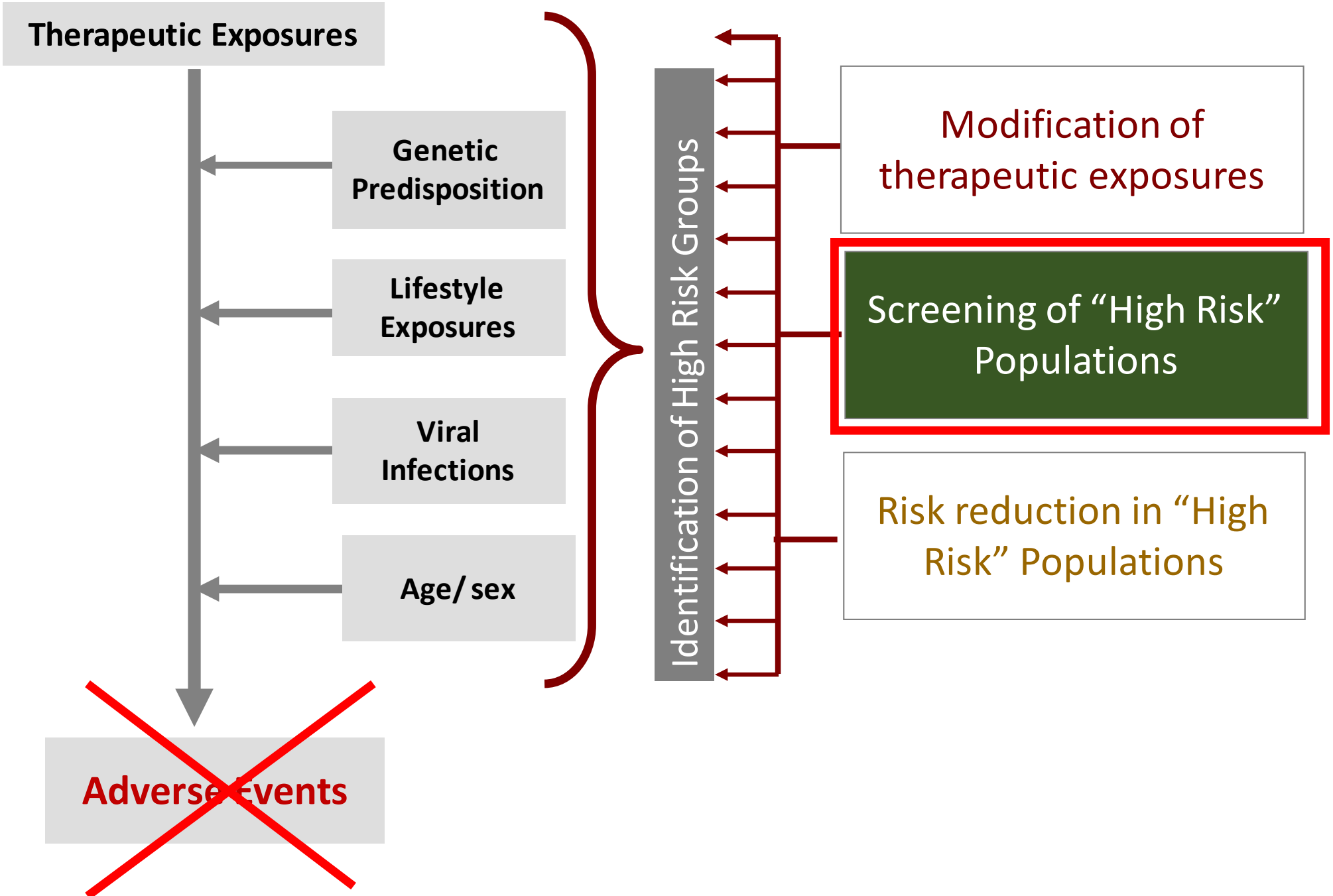


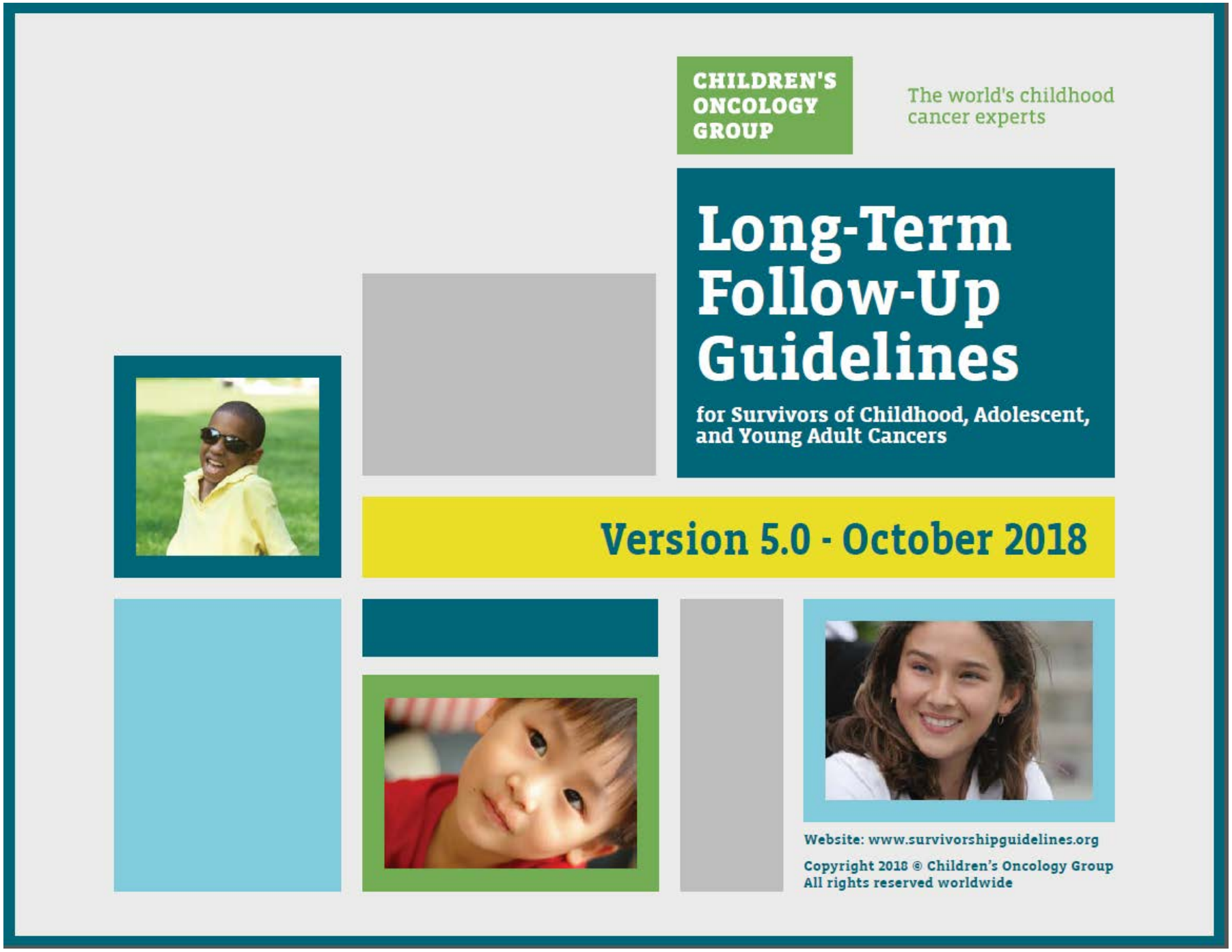
Funding:
R01 CA140245

Low Dose Tamoxifen for Radiation-Induced Breast Cancer Risk Reduction



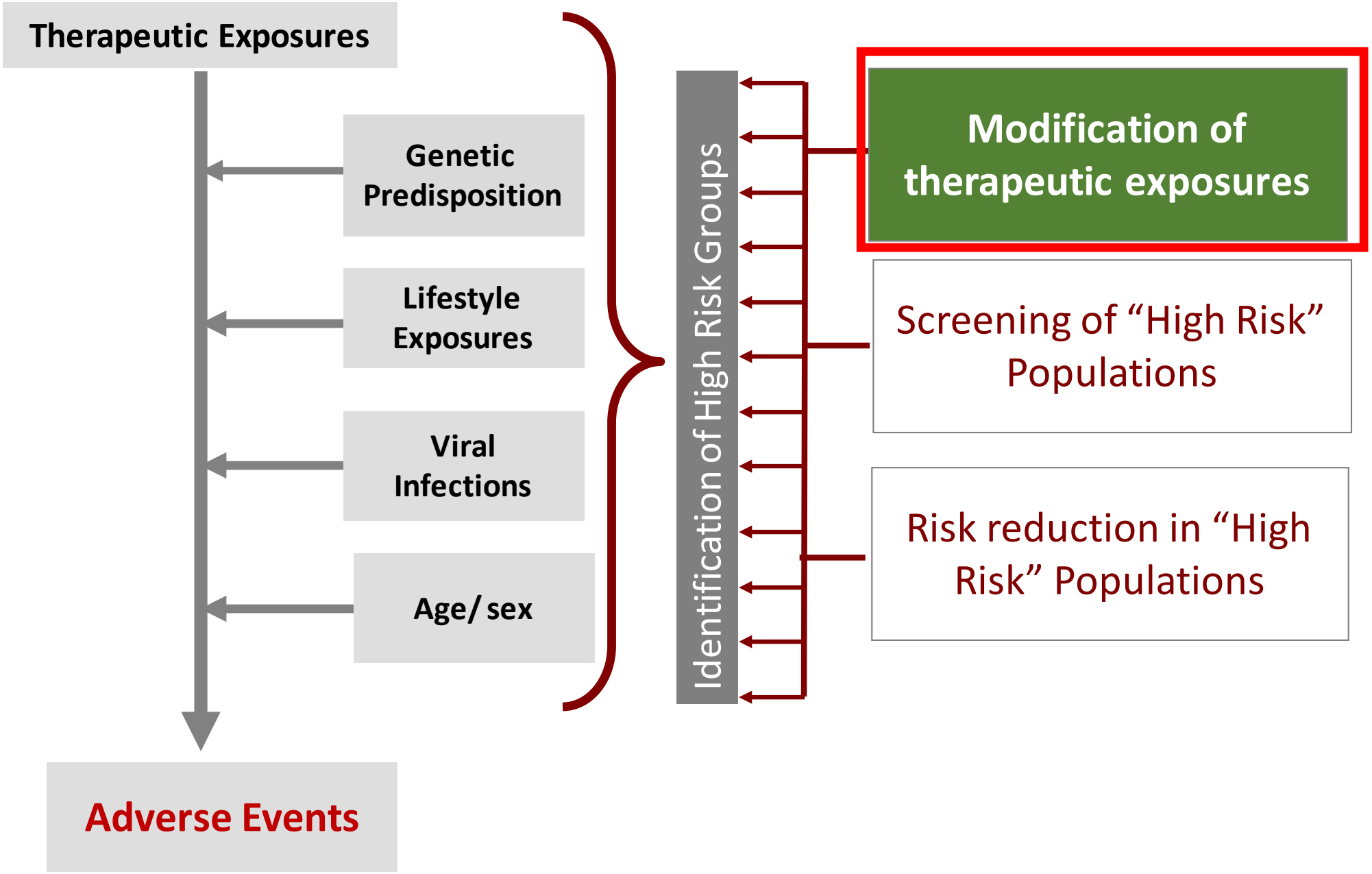



Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations



COG Long-term Follow-up Guidelines for survivors of Childhood, Adolescent, and Young Adult Cancers

www.survivirshipguidelines.org


Therapeutic Exposures
Genetic Predisposition
Lifestyle Exposures
Viral Infections
Age/ sex
Adverse Events
Identification of High Risk Groups
Modification of therapeutic exposures
Screening of "High Risk" Populations
Risk reduction in "High Risk" Populations

Modification of Therapeutic Exposures

- Elimination of **cranial radiation** therapy for children with standard/ low risk acute lymphoblastic leukemia
  - Reduction in risk of secondary brain tumors and cognitive impairment
- Reduction in dose of radiation and field of **chest radiation**
  - Reduction in risk of secondary breast cancer, pulmonary toxicity, coronary artery disease
- Reduction in **anthracycline dose**
  - Reduction in risk of cardiomyopathy
- Reduction of **dose and type of alkylators**
  - Reduction in risk of secondary leukemia

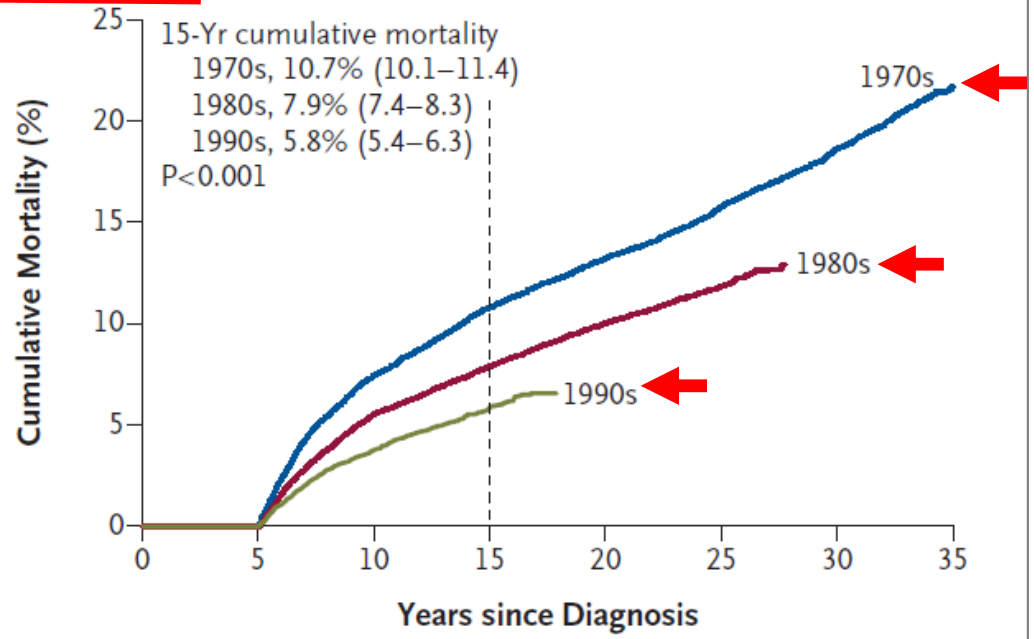
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer

N ENGL J MED 374;9 NEJM.ORG MARCH 3, 2016

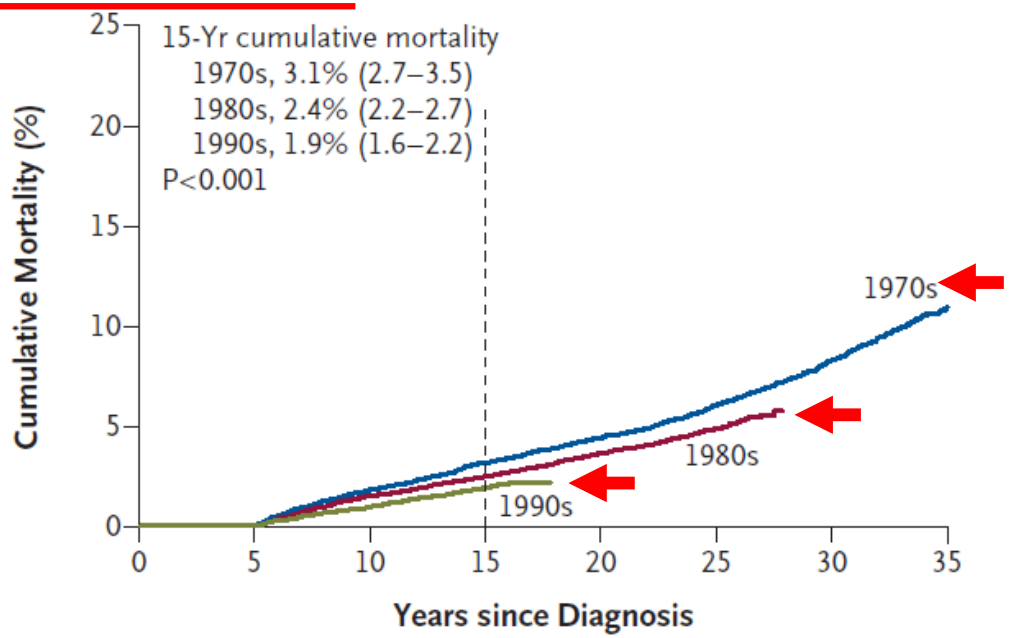
A Death from Any Cause



No. at Risk

1970s	9,416	8,722	8,406	8,182	7942	5556	1506
1980s	13,181	13,443	13,105	10,389	3583		
1990s	11,436	11,411	3,924				

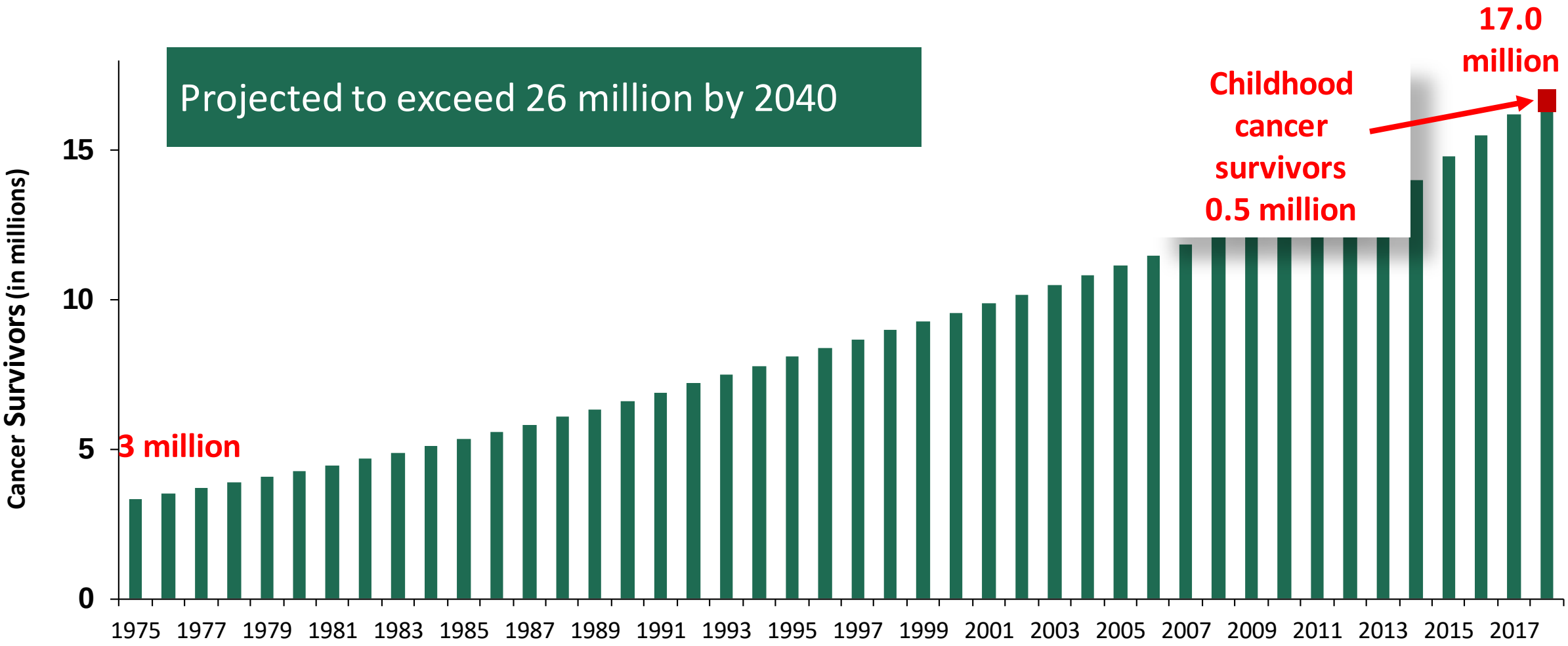
C Death from Health-Related Cause



No. at Risk

1970s	9,416	8,722	8,406	8,182	7942	5556	1506
1980s	13,181	13,443	13,105	10,389	3583		
1990s	11,436	11,411	3,924				

Estimated number of cancer survivors in the US (1975 to 2016)



Burden of Morbidity in Adults with Acute Myeloid Leukemia

The burden of morbidity in adults is substantial and needs to be addressed urgently


Not yet…
…But we are solidly on the right path
Are We There Yet?
SHUTTERSTOCK

Acknowledgements

NIH NATIONAL CANCER INSTITUTE

R01 CA096670

R01 CA174683

R01 CA139633

R01 CA140245

RC4 CA156499

U10 CA098543

R35 CA220502

V FOUNDATION®
Victory Over Cancer

St. Baldrick's FOUNDATION
Conquer Childhood Cancers

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Scholar Award for Clinical Research 2191-02

Translational Research Program 6093-08

Translational Research Program 6563-19

Patients and their families