Cardiovascular Phenotyping in Cooperative Clinical Trials – What and How to Measure?

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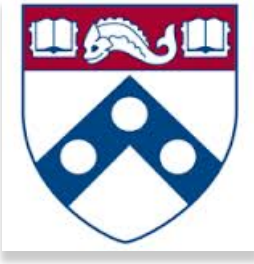
Cardiovascular Toxicity Assessment in Oncology Clinical Trials Workshop
September 22, 2016



Outline

- Key Considerations in Cardiovascular (CV) Phenotyping in Cooperative Clinical Trials
- Ongoing Work Focused on Robust Data Collection as it Relates to Exposures and Outcomes
  - ECOG Cardiotoxicity Working Group
  - RADCOMP
- Roadmap for Clinical Studies
- Needs and Opportunities

What and How to Measure? Key Considerations

- What is the overall objective of the study?

- What is the CV question of interest? What is the goal?
  - Deliver personalized and evidence-based medicine by determining therapeutic benefit and off-target toxicities of therapies

- How do we obtain high-quality data, as it relates to both exposures and outcomes?
  - What is the optimal strategy to characterize the disease?
  - When should we measure, and how often?
  - What is the most robust analytic platform? What are the test characteristics?
  - What is the feasibility, patient burden, and cost?

Califf, et al. JACC. 2016.

Cardiovascular Phenotyping Tools

- **Clinical parameters (exposures, outcomes)**
- Imaging measures (Weissman, Hundley)
- Biochemical Measures (Croce)
- Genetics
- Functional/physiologic measures

Cardiovascular Data Collection in Cooperative Clinical Trials – Exposures

- Robust data collection is critical to successful study execution
- Need for data harmonization with comprehensive and consistent collection of CV exposures in oncology studies
  - Risk factors (e.g. hypertension, diabetes, dyslipidemia, body mass index, blood pressure)
  - Medications
  - Disease (e.g. coronary artery disease, stroke, heart failure, cardiomyopathy)
- Allows for the opportunity to perform retrospective studies, meta-analyses, and build data repositories/registries

ECOG Efforts to Develop a Cardiotoxicity Case Report Form

- Objective – Develop a common case report form (CRF)/data repository of elements that can be used across trials

- Methods – Participants: ECOG Cardiotoxicity Working Group
  - Comprised of cardiologists, oncologists, biostatisticians, patient advocates
  - Held monthly conference calls over the course of 1 year to review data elements

- Processes – Modeled using established CRFs
  - Research into recent CRFs of cardiology and cardio-oncology studies performed
  - NCI PREDICT study (Lenihan, PI); E5103 (O'Neill, co-I); MESA, Framingham Heart Study
  - Iterative process of review and feedback incorporation

Cardiotoxicity CRF - Results

- Shared amongst multiple investigators across ECOG, RTOG, NRG, SWOG, NCI Community Oncology Task Force
- All terms mapped to MedDRA

Card Tox Version 0.2 (DEV): All Forms

Form: Baseline Cardiac Risk Factor and Diagnosis Assessment

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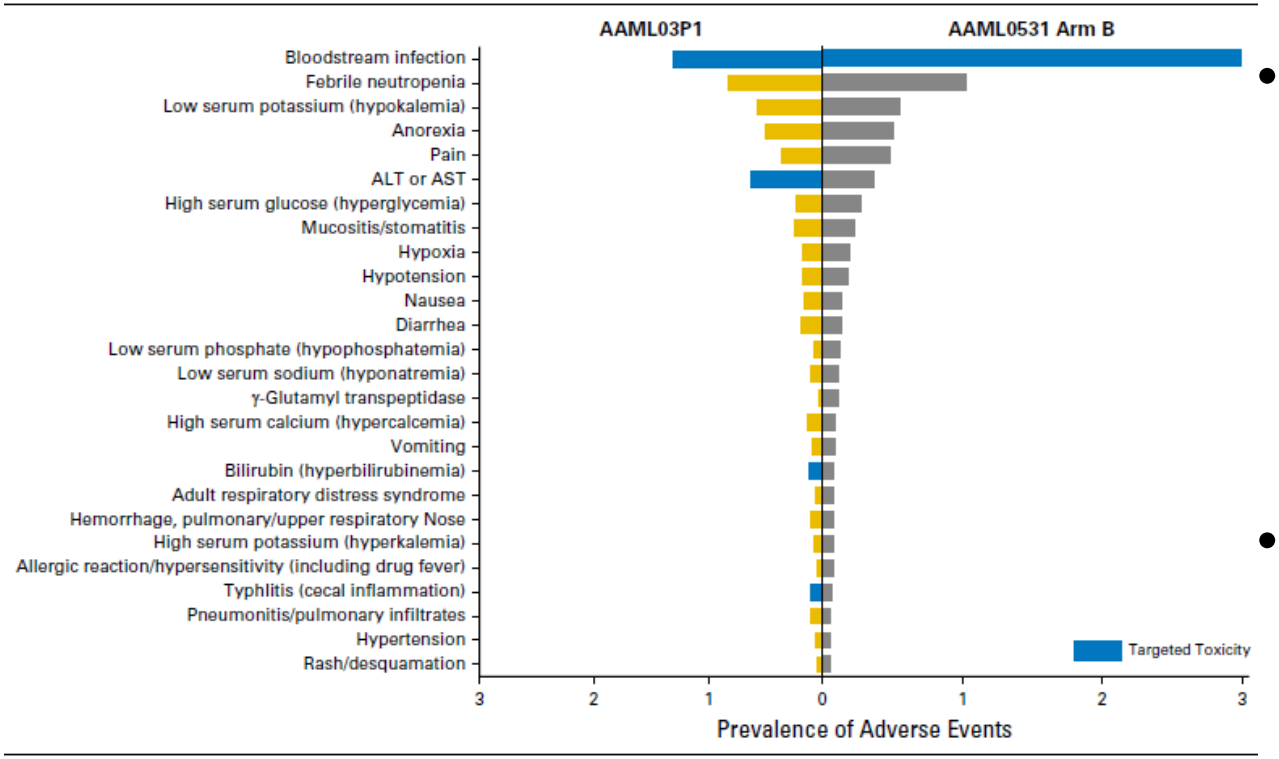
Diagnosis date	_____
Coronary artery bypass graft	No ☐ Yes ☐
Date of procedure	_____
Coronary artery disease	No ☐ Yes ☐
Diagnosis date	_____
Carotid disease	No ☐ Yes ☐
Diagnosis date	_____
Cardiomyopathy	No ☐ Yes ☐
Diagnosis date	_____
Coronary stent	No ☐ Yes ☐

Cardiovascular Data Collection in Oncology Clinical Trials – Adverse Events and Outcomes

Accuracy of Adverse Event Ascertainment in Clinical Trials for Pediatric Acute Myeloid Leukemia

Tamara P. Miller, Yimei Li, Marko Kavcic, Andrea B. Troxel, Yuan-Shun V. Huang, Lillian Sung, Todd A. Alonzo, Robert Gerbing, Matt Hall, Marla H. Daves, Terzah M. Horton, Michael A. Pulsipher, Jessica A. Pollard, Rochelle Bagatell, Alix E. Seif, Brian T. Fisher, Selina Luger, Alan S. Gamis, Peter C. Adamson, and Richard Aplenc



- 0531 and 03P1 evaluated same treatment
- 0531 used targeted toxicity (3 events) with enhanced infection monitoring (specific CRF)
- In contrast, 03P1 only used targeted toxicity (6 events)

Miller, et al. JCO. 2016.

Underestimation of Adverse Events in COG Study AAML0531

Table 2. Chart Abstraction Data Compared With Clinical Trial Adverse Event Report for Each of the 12 Grade 3 to 5 Toxicities

Toxicity	Chart Abstraction, No. (%)*	Adverse Event Report				
		No. (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Hypertension	28 (3.7)	9 (1.2)	21.4 (8.3 to 41.0)	99.6 (98.8 to 99.9)	66.7 (29.9 to 92.5)	97.1 (95.6 to 98.2)
Hypotension	46 (6.1)	35 (4.6)	56.5 (41.1 to 71.7)	98.7 (97.6 to 99.4)	74.3 (56.7 to 87.5)	97.2 (95.8 to 98.3)
Hypoxia	167 (22.0)	30 (4.0)	17.4 (12.0 to 24.0)	99.8 (99.1 to 100)	96.7 (82.8 to 99.9)	81.0 (78.0 to 83.8)
ARDS	13 (1.7)	11 (1.5)	38.5 (13.9 to 68.4)	99.2 (98.3 to 99.7)	45.5 (16.8 to 76.6)	98.9 (97.9 to 99.5)
Anorexia	307 (40.5)	100 (13.2)	30.6 (25.5 to 36.1)	98.7 (97.1 to 99.5)	94.0 (87.4 to 97.8)	67.6 (63.9 to 71.2)
Typhlitis	27 (3.6)	11 (1.5)	37.0 (19.4 to 57.6)	99.9 (99.2 to 100)	90.9 (58.7 to 99.8)	97.7 (96.4 to 98.7)
DIC	59 (7.8)	7 (0.9)	10.2 (3.8 to 20.8)	99.9 (99.2 to 100)	85.7 (42.1 to 99.6)	92.9 (90.9 to 94.7)
VGS	129 (17.0)	103 (13.6)	78.3 (70.2 to 85.1)	99.7 (98.9 to 100)	98.1 (93.2 to 99.8)	95.7 (93.9 to 97.1)
IFI	10 (1.3)	10 (1.3)	60.0 (26.2 to 87.8)	99.5 (98.6 to 99.9)	60.0 (26.2 to 87.8)	99.5 (98.6 to 99.9)
Pain	324 (42.7)	56 (7.4)	15.7 (12.0 to 20.2)	98.9 (97.3 to 99.6)	91.1 (80.4 to 97.0)	61.1 (57.4 to 64.7)
Seizure	5 (0.7)	2 (0.3)	0 (0.0 to 52.2)	99.7 (99.0 to 100)	0 (0.0 to 84.2)	99.3 (98.5 to 99.8)
Renal failure	6 (0.8)	4 (0.5)	50.0 (11.8 to 88.2)	99.9 (99.3 to 100)	75.0 (19.4 to 99.4)	99.6 (98.9 to 99.9)

NOTE. All data are for patients enrolled in clinical trial AAML0531 for whom chart abstraction was performed.
Abbreviations: ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation; IFI, invasive fungal infection; NPV, negative predictive value; PPV, positive predictive value; VGS, viridans group streptococcus.
*Chart abstraction data are the gold standard.

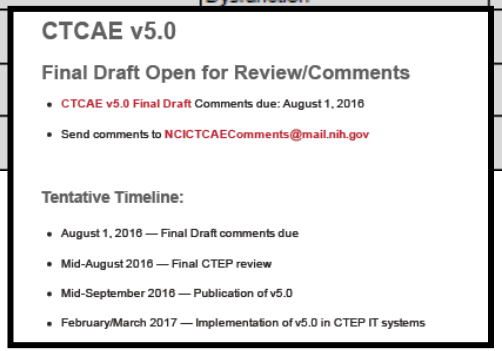
- Potential reasons: limited time and resources, complexity of CTCAE definitions and adverse events

Miller, et al. JCO. 2016.

ECOG Efforts to Harmonize CV Adverse Event Reporting in CTCAE

- ECOG Cardiotoxicity Working Group proposed modifications to the following in order to harmonize grading/definitions:
  - Heart Failure, Ejection Fraction Decreased, Restrictive Cardiomyopathy, Pericardial Effusion, Myocardial Infarction, Conduction Disorder, Arterial Thromboembolism, and others

Verstion 5 Draft 7-7-16						Proposed Edits to Version 5			
SOC	Event	MedDRA	Grade	Description	Action	SOC	Event	MedDRA	
Cardiac Disorders	Heart Failure	10019279	1	Asymptomatic with laboratory or cardiac	Modify Description; Move BNP and NT-proBNP to Investigations	Investigations	Brain natriuretic peptide (BNP) or N-terminal-pro BNP (NT-pro		
Investigations	Ejection Fraction Decreased	10050528			Eliminate and use Left Ventricular Systolic Dysfunction (grading	Cardiac Disorders	Left Ventricular Systolic Dysfunction	10069501	
Cardiac Disorders	Restrictive Cardiomyopathy	10038748			Eliminate; part of Heart Failure.				



CTCAE v5.0

Final Draft Open for Review/Comments

- CTCAE v5.0 Final Draft Comments due: August 1, 2016
- Send comments to NCICTCAEComments@mail.nih.gov

Tentative Timeline:

- August 1, 2016 — Final Draft comments due
- Mid-August 2016 — Final CTEP review
- Mid-September 2016 — Publication of v5.0
- February/March 2017 — Implementation of v5.0 in CTEP IT systems

Efforts to Collect Robust CV Exposures and Outcomes

RadComp
PATIENT POWERED

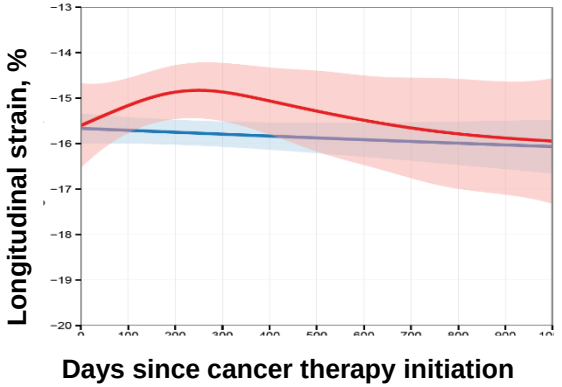
- Pragmatic randomized trial of proton versus photon therapy in patients with non-metastatic breast cancer receiving comprehensive nodal radiation
- Primary Objective: To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE)
- Sample size: 1,716 patients across 30 centers nationwide
- PI: Justin Bekelman, MD
- Multi-disciplinary team: Radiation oncologists, biostatisticians, cardiologists, symptom scientists, patients

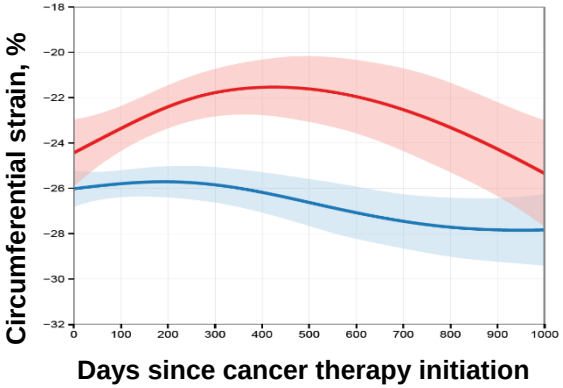
RADCOMP – An Example of One Approach to CV Phenotyping

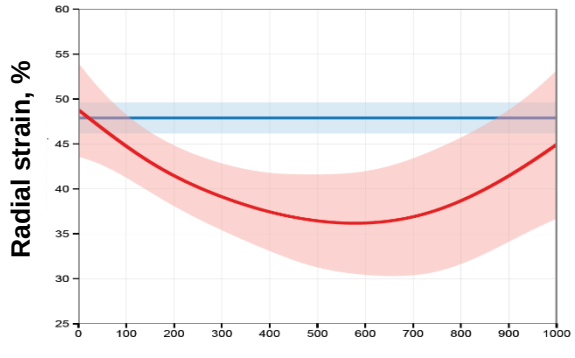
- Broad CV phenotyping approach: Detailed assessment of clinical exposures and outcomes
- Clinical events center (CEC): Detailed collection of CV outcomes, central adjudication of all CV events (Ky, CEC Chair)
- Detailed CV phenotyping approach: Ancillary studies, leveraging resources and infrastructure, utilize central core lab review of all data (Ky, R01 submission)
  - Specific questions of interest: Biologic mechanisms, intermediary markers, functional effects of radiation therapy

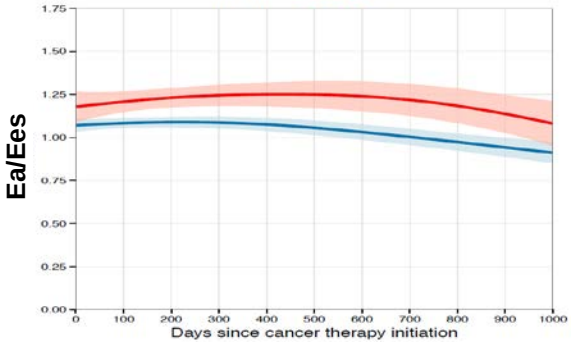
Which CV Phenotyping Tools?

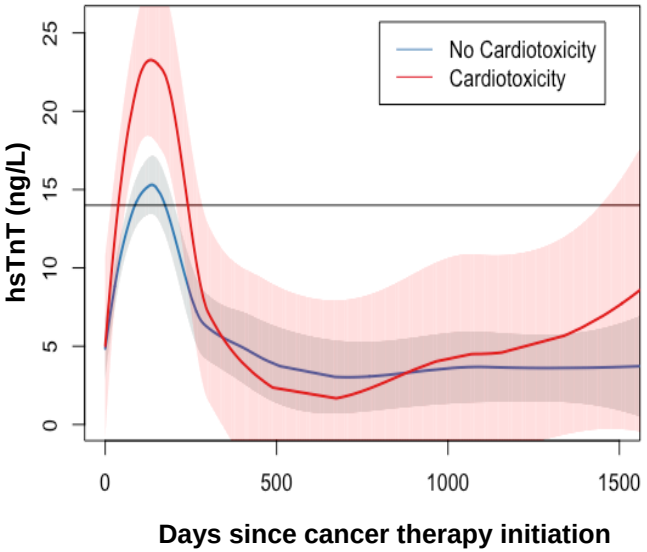
- Our longitudinal prospective cohort studies in cardio-oncology (breast, renal cell, radiation, lymphoma) are currently evaluating the utility of echocardiography and blood based measures in diagnosing and predicting cardiotoxicity











Narayan, et al. JACC Imaging. 2016.
Ky, Hubbard, Zhang, Liu. In Progress. 2016.

Which Adverse Events and Outcomes are Important to Report?

COMMENTARY

The Imperative for a New Approach to Toxicity Analysis in Oncology Clinical Trials

Gita Thanarajasingam, Joleen M. Hubbard, Jeff A. Sloan, Axel Grothey

Affiliations of authors: Department of Medical Oncology (GT, JH, AG) and Alliance Statistics and Data Center (JAS), Mayo Clinic, Rochester, MN.

Correspondence to: Gita Thanarajasingam, MD, Mayo Clinic Rochester, 200 First Street SW, Rochester, MN 55905 (e-mail: thanarajasingam.gita@mayo.edu).

- Important Needs:
  - Patient-based Reports of Outcomes over Time
  - Time Profile of Adverse Events
  - Comparison of Toxicity over Time
  - Focus on Longer-Lasting, Lower-Grade Toxicities
  - Implementation of Technology to Report Outcomes

Thanarajasingam, et al. JNCI. 2015.

One Potential Roadmap for CV Phenotyping in Cooperative Clinical Trials

- Goal: Comprehensive and harmonized phenotyping to inform the delivery of personalized and evidence-based medicine

- To use our “broad” phenotyping tools to understand adverse events and outcomes
  - Clinical variables, common CRF, adjudicated CV outcomes

- To then use our “deep” phenotyping tools to better understand the biologic/physiologic heterogeneity that occurs in response to cancer therapies
  - Repository of biomarkers (plasma, serum, DNA); imaging measures (echocardiography); functional measures ($V0_2$) Central, core lab review to reduce variability

Shah, et al. Circulation. 2016.
Delude, et al. Nature. 2015.

CV Phenotyping in Cooperative Clinical Trials: Needs and Opportunities

- Critical need to leverage cooperative group clinical trials to create necessary infrastructure to ask impactful questions

- Unique opportunities to understand mechanisms of disease; gain insight into the role of markers as intermediary measures; better understand cardiovascular outcomes

- Ongoing work to improve upon the robust collection of clinical exposures and adverse outcomes

- Focus collaborative resources on:
  - Harmonization and collection of robust data (management, accessibility, application of technology to improve reporting)
  - Development of biobanks (biomarker, genetics) and imaging banks

Needs and Opportunities

A national cancer data ecosystem for sharing and analysis. Create a National Cancer Data Ecosystem to collect, share, and interconnect a broad array of large datasets so that researchers, clinicians, and patients will be able to both contribute and analyze data, facilitating discovery that will ultimately improve patient care and outcomes.

Symptom management research. Support research necessary to accelerate the development of guidelines for routine monitoring and management of patient-reported symptoms in all care settings, throughout the cancer continuum (from diagnosis throughout survivorship and at end-of-life) and tailored to differing patient and survivor needs. Systematically gathered patient-reported outcomes data and evidence-based symptom management are needed to improve patients' quality of life and the likelihood that they will adhere to effective treatments that are effective rather than abandoning them because of intolerable side effects.

Needs and Opportunities

UNDERSTAND HUMAN BIOLOGY

To expand knowledge of the molecular, cellular, and physiological mechanisms governing the normal function of HLBS systems as essential elements for sustaining human health.

REDUCE HUMAN DISEASE

To extend our knowledge of the pathobiology of HLBS disorders and enable clinical investigations that advance the prediction, prevention, preemption, treatment, and cures of human diseases.

To enable and develop a diverse biomedical workforce equipped with the essential research resources to pursue emerging opportunities in science.

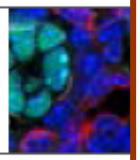
DEVELOP WORKFORCE AND RESOURCES

To facilitate innovation and accelerate research translation across the entire research spectrum, bridging basic to clinical, clinical to practice, and population to health impact.

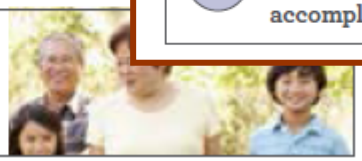
ADVANCE TRANSLATIONAL RESEARCH

1. Understand normal biological function and resilience

2. Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS diseases



3. Investigate factors that account for differences in health among populations



4. Identify factors that account for individual differences in pathobiology and in responses to treatments

5. Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases

6. Optimize clinical and implementation research to improve health and reduce disease

7. Leverage emerging opportunities in data science to open new frontiers in HLBS research

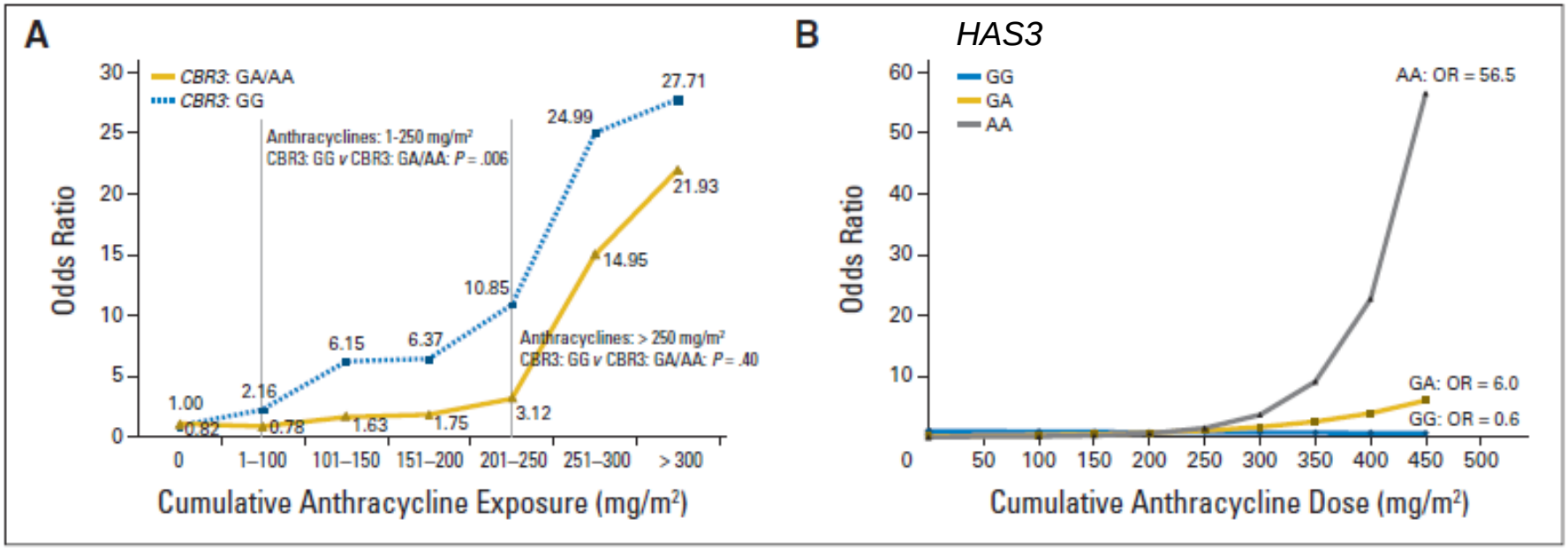
8. Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI's mission

THANK YOU

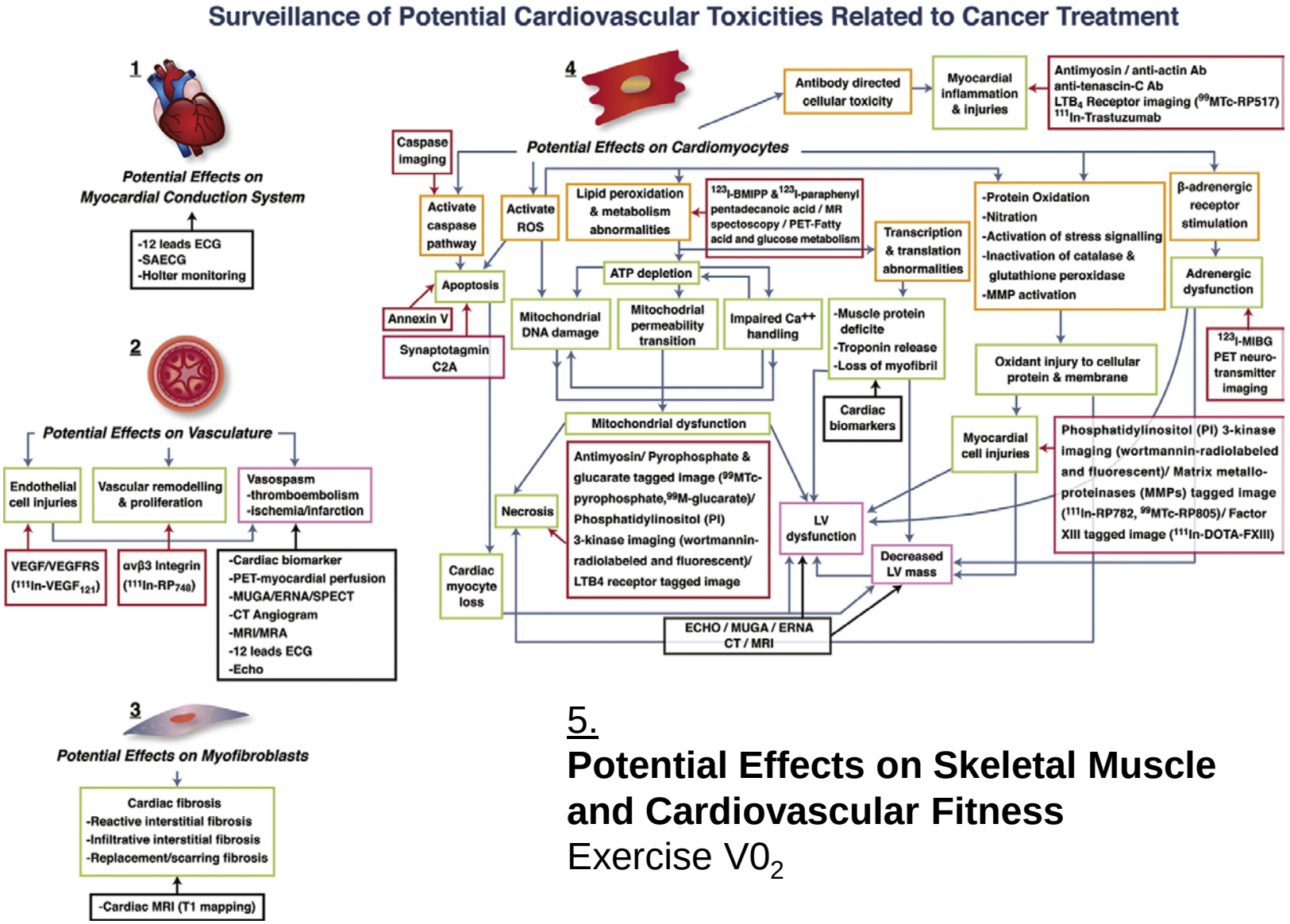
EXTRA SLIDES

Use of Genetics to Understand Anthracycline Cardiotoxicity

- Genetic variants in carbonic reductase 3 (CBR3) associated with cardiomyopathy with anthracyclines, modified by dose
- Hyaluronan synthase gene (HAS3) also exerts a modifying effect on cardiomyopathy in patients exposed to high dose



Bhatia, et al. JCO. 2015.



5.

Potential Effects on Skeletal Muscle and Cardiovascular Fitness

Exercise $V0_2$