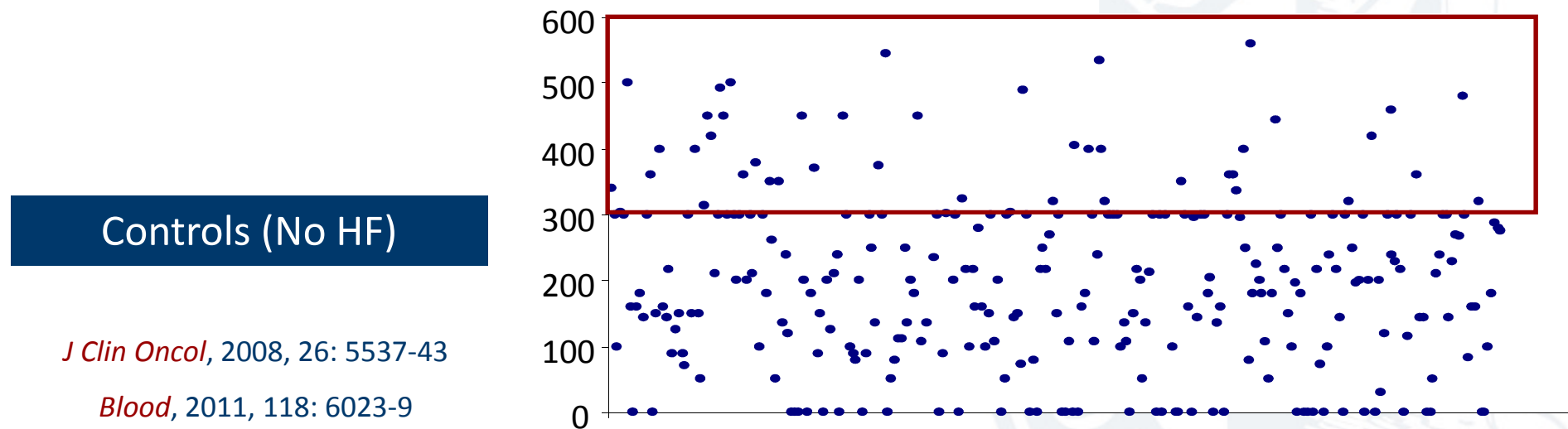
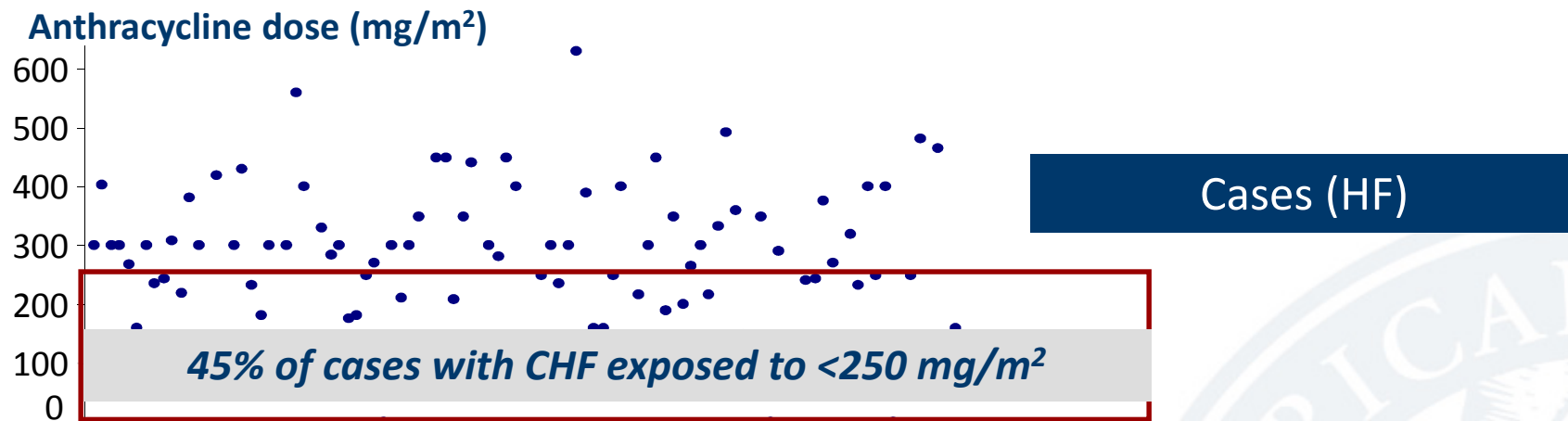


Genetics and CVD in Cancer Patients

Saro Armenian DO, MPH



AMERICAN
COLLEGE of
CARDIOLOGY



J Clin Oncol, 2008, 26: 5537-43

Blood, 2011, 118: 6023-9

Risk Profile: Therapy-Related HF

For a given exposure, there is marked variation in prevalence and severity of heart failure that is not explained exclusively by clinical risk factors

Clinical risk factors

Age at exposure
Female gender
Anthracycline dose
Comorbidities

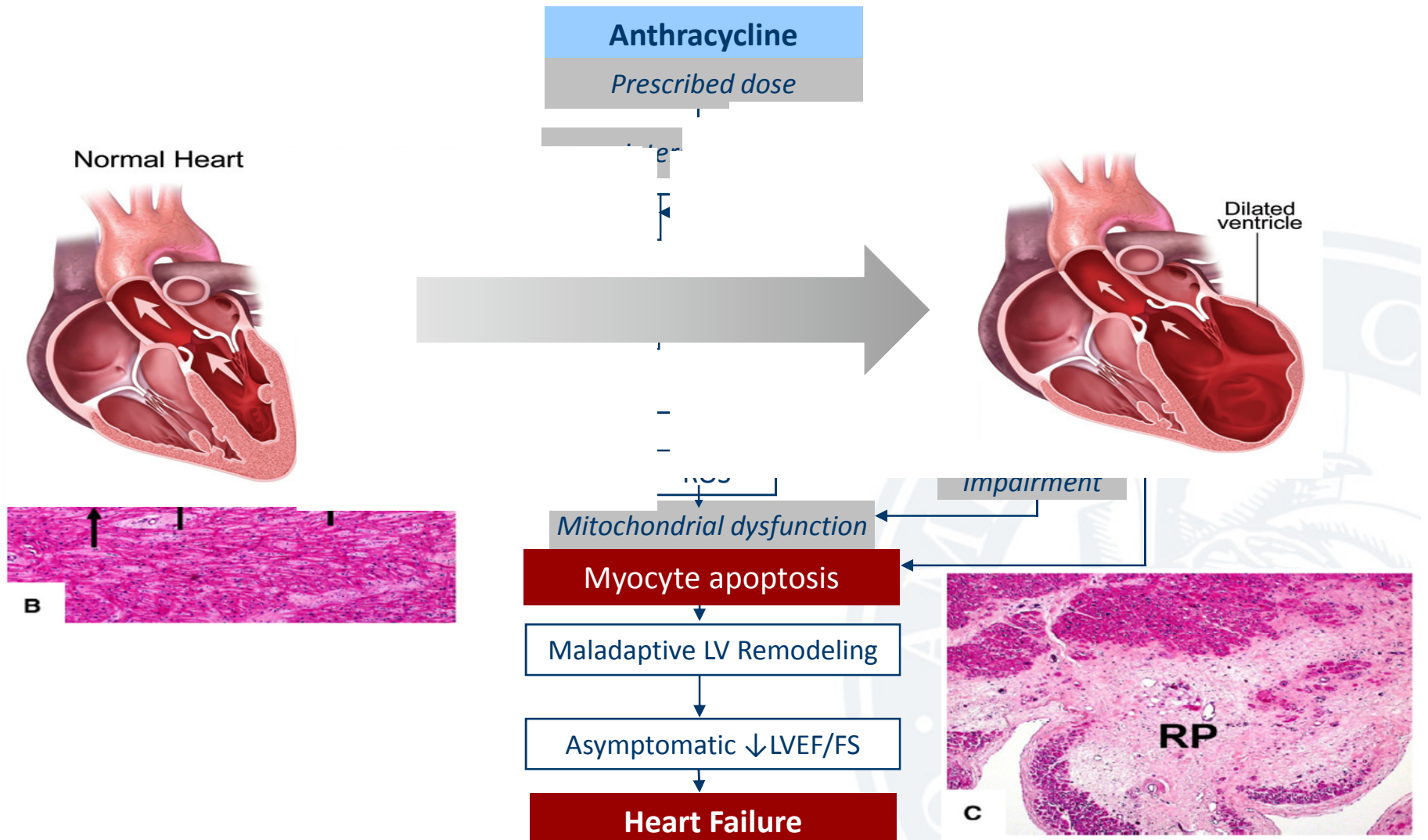
Genetic risk factors

Drug metabolism and Transport
Generation of reactive oxygen species
Anti-oxidant defense
DNA repair pathways
Renin-angiotensin system

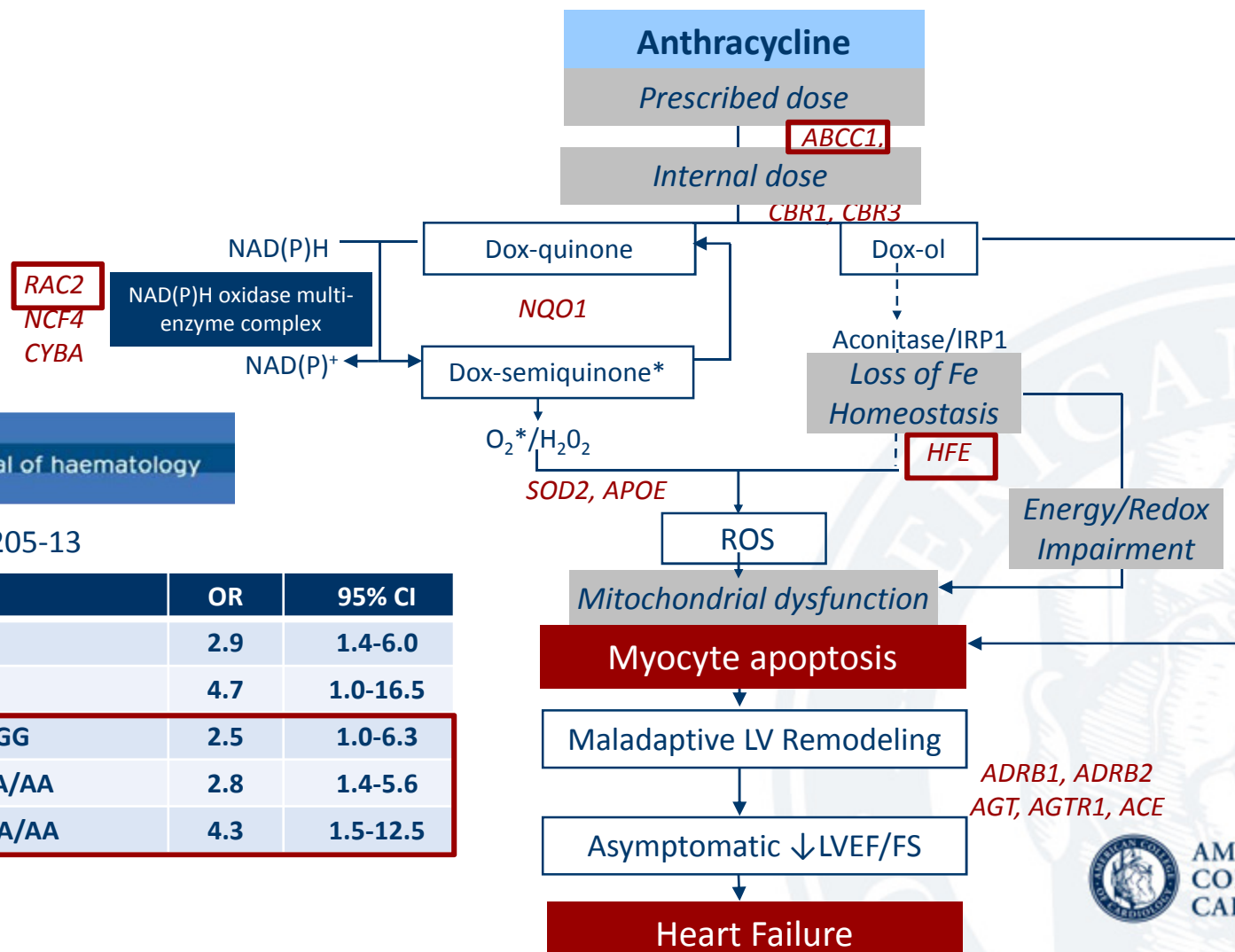
Therapy-Related Heart Failure



AMERICAN
COLLEGE of
CARDIOLOGY



	OR	95% CI
Female	2.9	1.4-6.0
Chest XRT	4.7	1.0-16.5
<i>HFE</i> (rs1799945), GC/GG	2.5	1.0-6.3
<i>RAC2</i> (rs13058338), TA/AA	2.8	1.4-5.6
<i>ABCC2</i> (rs818710), GA/AA	4.3	1.5-12.5



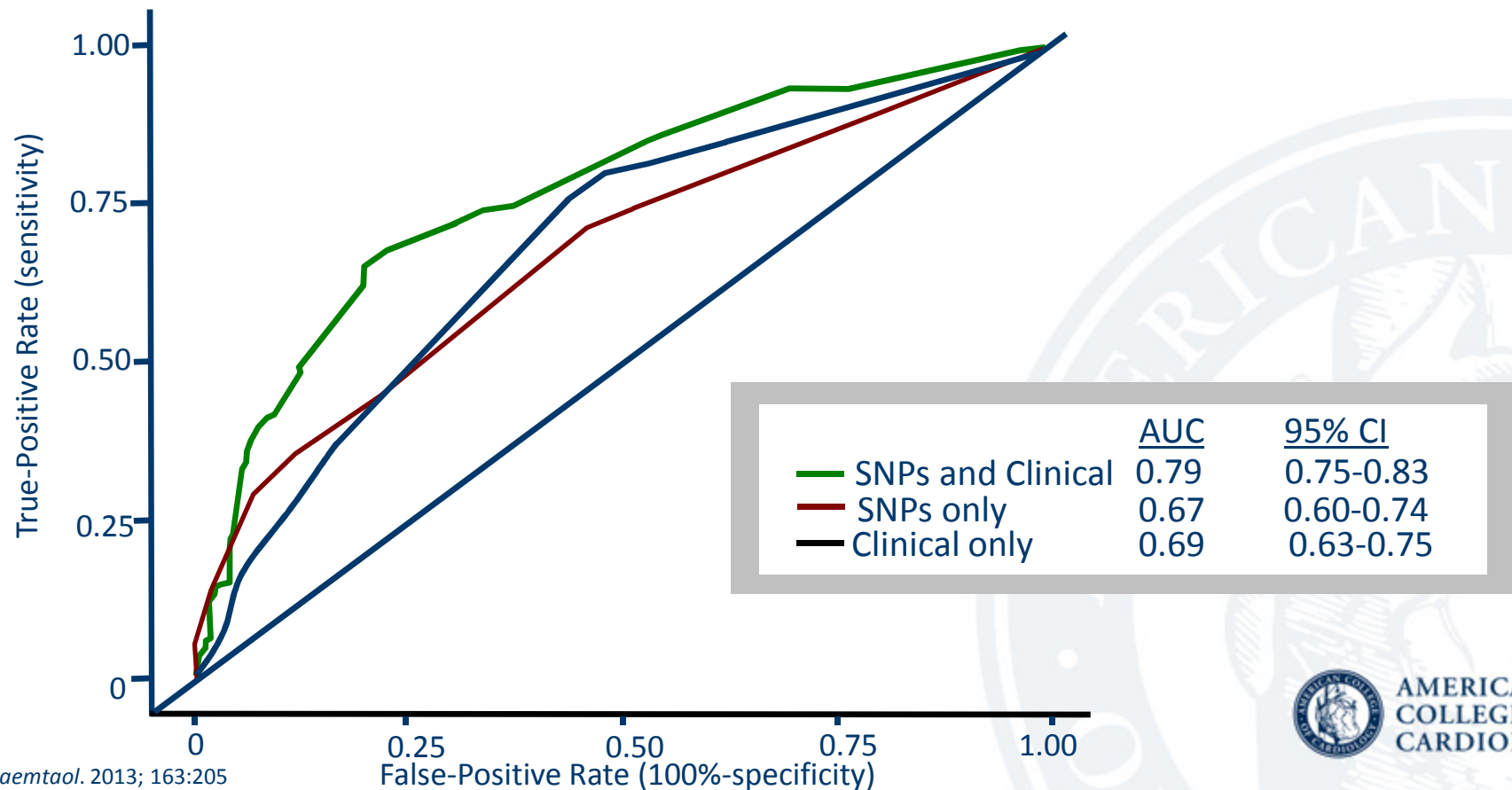
Functional genomics

- **Multidrug resistant protein (MRP2) - rs8187710**
 - MRP2 protein expression liver, kidney
 - Anthracycline clearance via biliary system
 - Inhibition of MRP2 expression, decreased anthracycline clearance
 - CHF risk – OR 2.3; 95%CI 1.0-5.4. *Circulation*, 2005, 112:3754-3762
- **NAD(P)H oxidase subunit (RAC2) - rs13058338**
 - NAD(P)H oxidase multi-enzyme complex, electron donor Dox-quinone
 - RAC2: GTPase regulator of NAD(P)H oxidase activity
 - CHF risk – OR 2.6; 95%CI 1.3-5.1 *Circulation*, 2005, 112:3754-3762
- **Hemochromatosis (HFE2) - rs1799945**
 - Iron homeostasis
 - *HFE* knock-out murine model vs. wild-type
 - *Higher myocardial iron burden*
 - *Greater anthracycline cardiotoxicity in HFE knock-out*



AMERICAN
COLLEGE of
CARDIOLOGY

Receiver operating characteristic (ROC) curves



Br J Haematol. 2013; 163:205



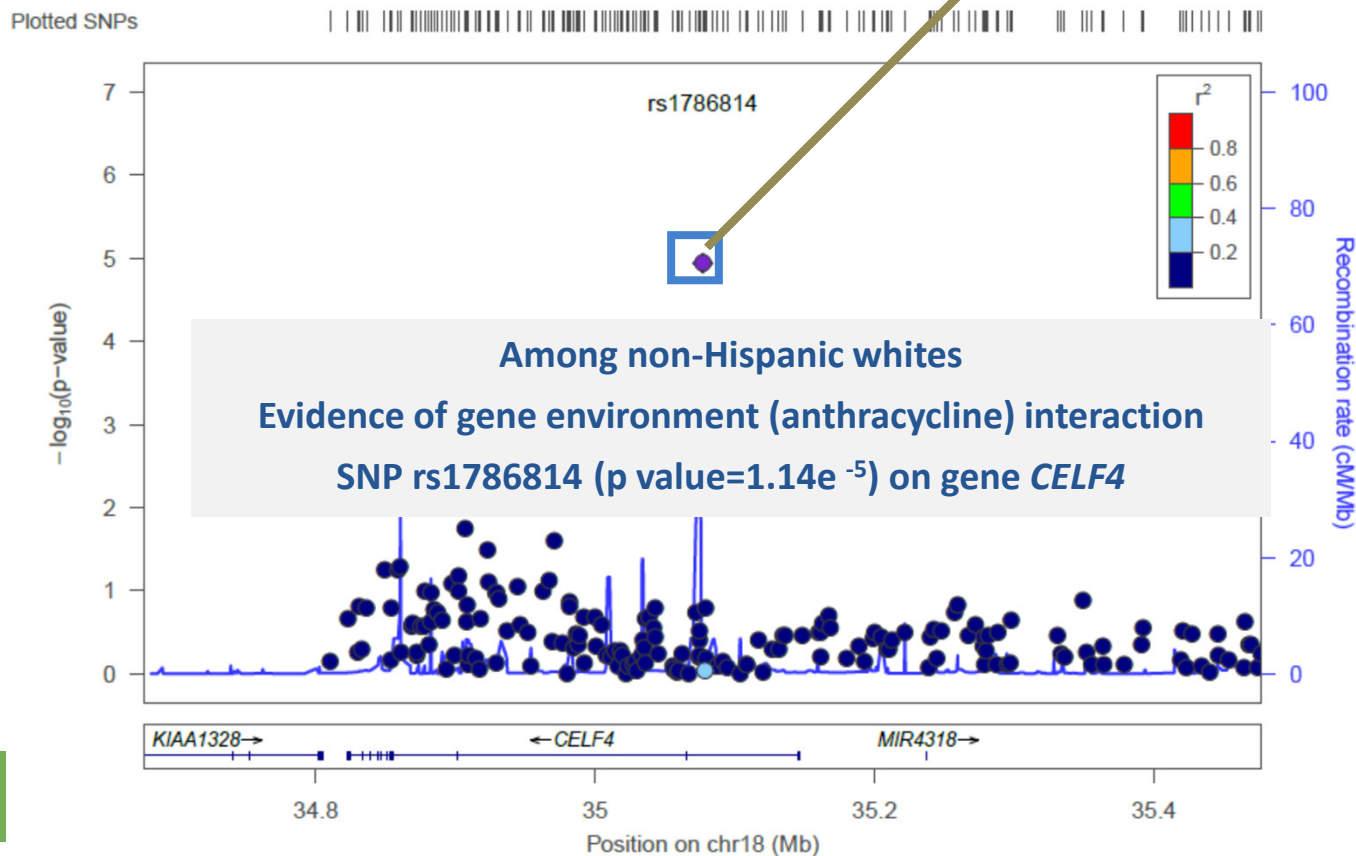
AMERICAN
COLLEGE of
CARDIOLOGY

Genome-wide Association Study

[*J Clin Oncol.* 2016 Mar 10;34\(8\):863-70.](#)

rs1786814*anthracycline, $p=1.14 \times 10^{-5}$

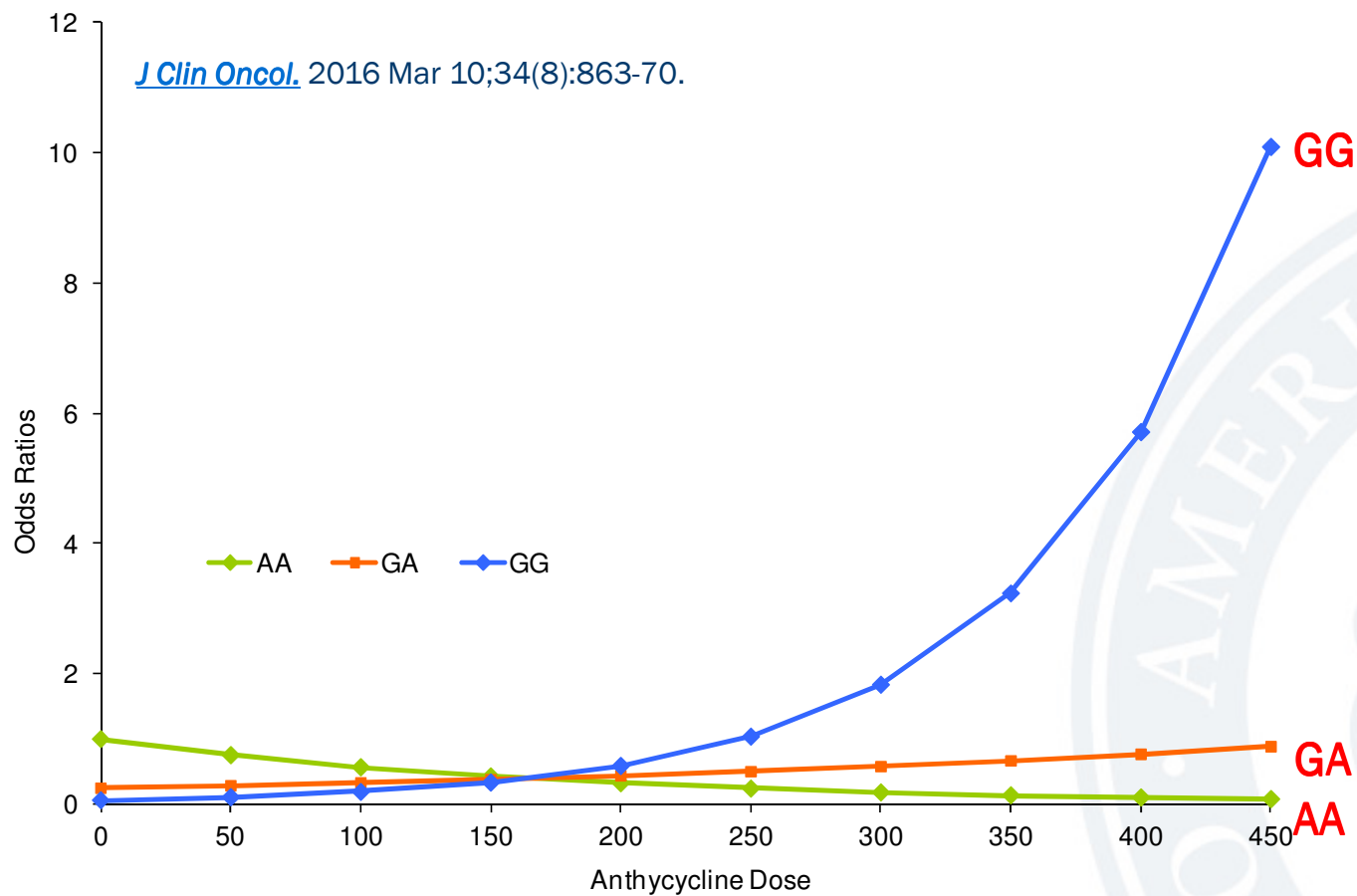
CELF4 Gene



CHILDREN'S
ONCOLOGY
GROUP

AMERICAN
COLLEGE of
CARDIOLOGY

Anthracycline exposure and risk of cardiomyopathy by CELF4 genotype



AMERICAN
COLLEGE of
CARDIOLOGY

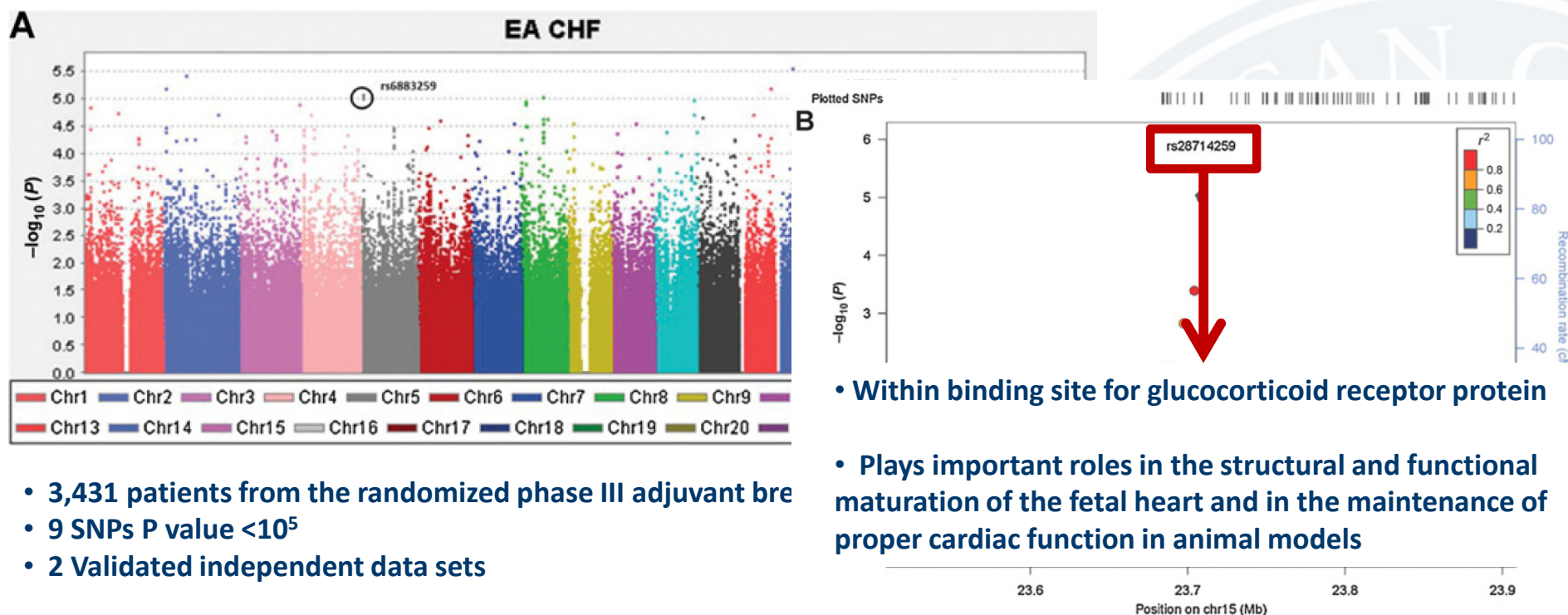
***CELF4* gene**

- CELF4 is a protein that in humans is encoded by the ***CELF4* gene** on chromosome 18
- CELF family of RNA-binding proteins is implicated in the **alternative splicing** of *TNNT2* gene during development.
- *TNNT2* encodes for **cardiac troponin T (cTnT)**
- During development, splicing of *TNNT2* leads to inclusion of alternative exon 5 with insertion of 10 additional amino acids into protein
 - *TNNT2* splicing variants carrying exon 5 are expressed in embryonic hearts, and are mostly absent from mRNAs found in adult hearts
- Persistent expression of embryonic *TNNT2* variant in adult cardiac muscle can result in coexistence of embryonic + adult variants.
 - results in a temporally split in myofilament response to increasing Ca^{2+} concentrations
 - decreased myocardial contractility and ventricular pumping efficiency

Genome-Wide Association Study for Anthracycline-Induced Congestive Heart Failure

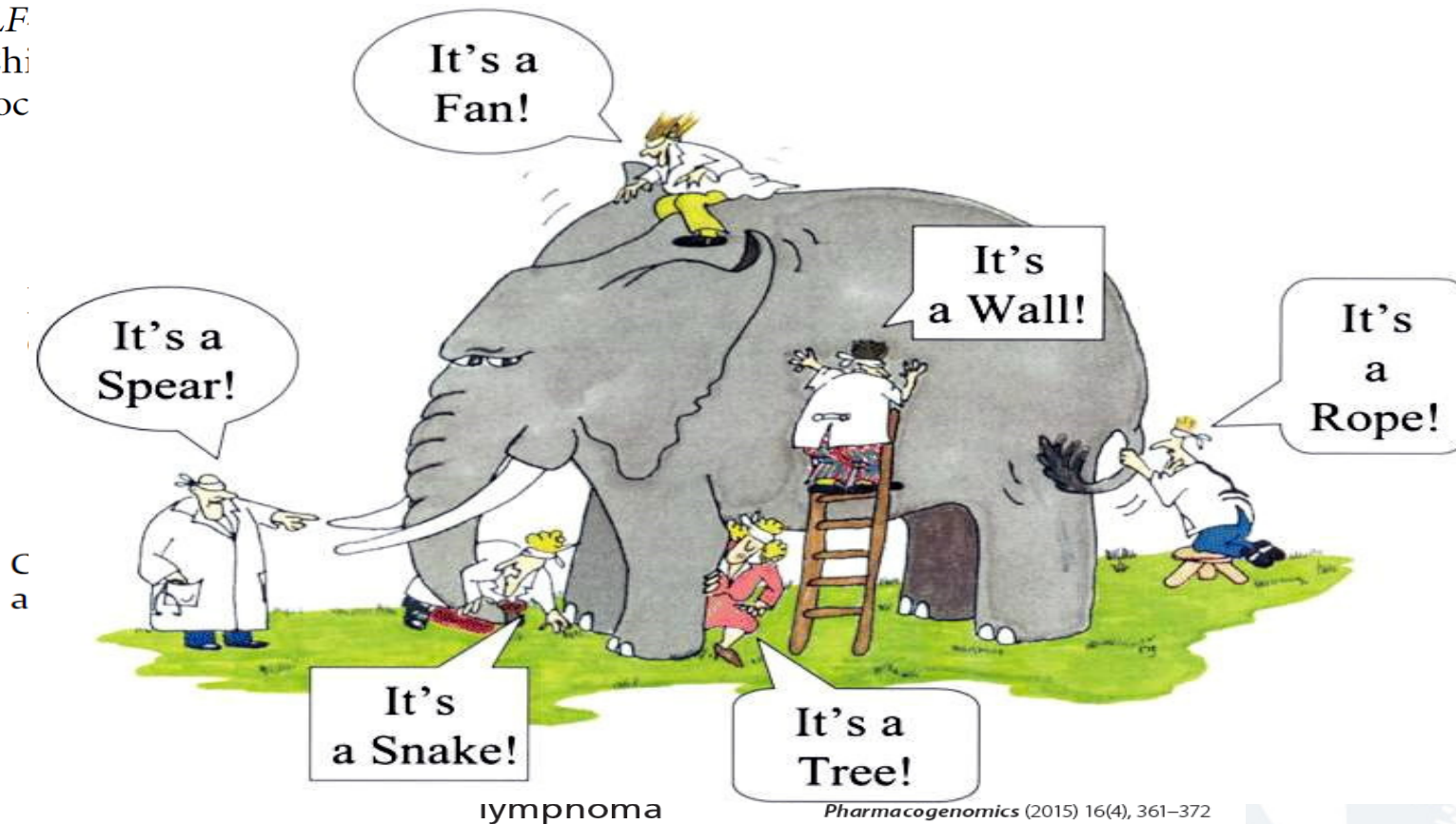
Bryan P. Schneider¹, Fei Shen¹, Laura Gardner¹, Milan Radovich¹, Lang Li¹, Kathy D. Miller¹, Guanglong Jiang¹, Dongbing Lai¹, Anne O'Neill², Joseph A. Sparano³, Nancy E. Davidson⁴, David Cameron⁵, Irmina Gradus-Pizlo¹, Ronald A. Mastouri¹, Thomas M. Suter⁶, Tatiana Foroud¹, and George W. Sledge Jr⁷

Clin Cancer Res; 23(1) January 1, 2017



Germline genomics and risk prediction

CELF
A Chi
Assoc



lymphoma

Pharmacogenomics (2015) 16(4), 361–372

ood
se
ap
'29. © 2011

e-Related
Oncology

01

AMERICAN
COLLEGE of
CARDIOLOGY

Germline genomics and heart failure risk

- Inter-individual variability in therapy-associated HF may be due to genetic modifiers of risk
- Limitations
 - Small sample sizes
 - Heterogeneous outcomes across studies
 - Lack of replication of findings across studies
 - Context relative to existing known clinical risk factors (age, CV risk factors)
- Future directions
 - Primary and secondary prevention critical to risk reduction



AMERICAN
COLLEGE of
CARDIOLOGY



AMERICAN
COLLEGE *of*
CARDIOLOGY