GENOMICS AND PERSONALIZED MEDICINE TO IDENTIFY THOSE AT RISK FOR CARDIOTOXICITY

Dr Howard L. McLeod
Medical Director, DeBartolo Family Personalized Medicine Institute
Chair, Department of Individualized Cancer Medicine
Senior Member, Division of Population Sciences
State of Florida Endowed Chair
The clinical problem

- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

With choice comes decision
Probabalistic data is enough

Many clinical interventions are based on increased probability of a problem occurring

- Insulin/oral diabetes drugs
- Statins
- Antihypertensives
Increase risk = intervention  Colon cancer screening

[Graph showing the number of cases by age at diagnosis, with a focus on male and female cases.]
Pharmacogenomic examples-2018

- *bcr/abl* or 9:22 translocation—imatinib mesylate*
- HER2-*neu*—trastuzumab**
- C-kit mutations—imatinib mesylate**
- Epidermal growth factor receptor mutations—gefitinib
- BRAF-vemurafenib
- ALK-Crizotinib
- ROS-1_Crizotinib
- TPMT-mercaptopurine and azathio
- UGT1A1-irinotecan**
- CYP2C9/VKORC1-warfarin*
- HLA-B*5701-abacavir .
- HLA-B*1502-carbamazepine .
- IL28B-interferon
- CFTR-ivacaftor
- CYP2C19-clopidogrel, voriconazole
- CYP2D6-5-HT3 receptor antagonists

Pain control
Antiemetics
Antidepressants
ADHD drugs
Anticoagulants
Not just tumor markers!!
Translation to Cardiooncology?

• Family history/known syndromes

• Clonal hematopoiesis of unknown potential (CHIP)

• Polygenic propensity scores

• A lot more coming, lots to do
Those with pathogenic mutations in familial cardiomyopathy genes have a predisposition to heart disease.

Risk of anthracycline induced cardiotoxicity caused by asymptomatic familial cardiomyopathy likely similar to (or greater than) other conditions placing patients at risk of heart disease.

Table 2. Estimates in the Cox models both for risk of developing cardiotoxicity and for risk of death from all other causes among patients with metastatic breast cancer.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors for risk of developing cardiotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose of epirubicin (per 100 mg/m² increase)</td>
<td>0.334</td>
<td>1.40</td>
<td>1.21 to 1.61</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Predisposition to heart disease†</td>
<td>1.102</td>
<td>3.01</td>
<td>2.00 to 4.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous antihormonal† treatment for relapse</td>
<td>0.628</td>
<td>1.87</td>
<td>1.23 to 2.85</td>
<td>.003</td>
</tr>
<tr>
<td>Mediastinal irradiation</td>
<td>0.734</td>
<td>2.08</td>
<td>1.27 to 3.41</td>
<td>.004</td>
</tr>
<tr>
<td>Every additional year of age at epirubicin start§</td>
<td>0.025</td>
<td>1.03</td>
<td>1.01 to 1.05</td>
<td>.012</td>
</tr>
<tr>
<td>CMF at cumulative dose of epirubicin 500 mg/m²</td>
<td>−1.350</td>
<td>0.26</td>
<td>0.07 to 1.02</td>
<td>.053</td>
</tr>
<tr>
<td>CMF at cumulative dose of epirubicin (per 100 mg/m²)</td>
<td>0.316</td>
<td>1.37</td>
<td>1.08 to 1.74</td>
<td>.0092</td>
</tr>
</tbody>
</table>

† History of hypertension arterialis, diabetes mellitus, thyrotoxicosis, chronic obstructive lung disease, or obesity.

- Those with pathogenic mutations in familial cardiomyopathy genes have a predisposition to heart disease.
- Risk of anthracycline induced cardiotoxicity caused by asymptomatic familial cardiomyopathy likely similar to (or greater than) other conditions placing patients at risk of heart disease.

Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer

Mary C. Pinder, Zhigang Duan, James S. Goodwin, Gabriel N. Hortobagyi, and Sharon H. Giordano

- Age range 66 to 88 years
- 43,338 patients included
- Data-mined the SEER-Medicare-linked database
- HR for familial cardiomyopathy likely similar or higher that HR for pre-existing conditions

**Table 5.** Cox Proportional Hazards Model for Congestive Heart Failure by Pre-Existing Conditions

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>1.58</td>
<td>1.39 to 1.79</td>
</tr>
<tr>
<td>Chronic bronchitis/emphysema</td>
<td>1.68</td>
<td>1.54 to 1.84</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.74</td>
<td>1.66 to 1.83</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.45</td>
<td>1.39 to 1.52</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.31</td>
<td>1.22 to 1.41</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.94</td>
<td>0.75 to 1.19</td>
</tr>
</tbody>
</table>

NOTE. Adjusted for type of adjuvant chemotherapy, trastuzumab use, anthracycline received > 1 year after diagnosis, number of physician visits in the year prior to breast cancer diagnosis, year of diagnosis, age, race, stage, grade, and radiotherapy type.
# Familial Cardiomyopathy and Risk of Anthracycline-Induced Cardiotoxicity

<table>
<thead>
<tr>
<th>Major Findings</th>
<th>References</th>
</tr>
</thead>
</table>
| Autosomal dominant mutations (e.g., *MYH7, TNNT2, LMNA*) are associated with familial cardiomyopathy syndromes | • Morita et al. *N Engl J Med.* 358, 2008  
• Hougs et al. *Eur J Hum Genet.* 13, 2005  
• Long et al. *J Am Hear Assoc.* 9, 2015  
• Yang et al. *Gene.* 558, 2015  
• Coppini et al. *J Am Coll Cardiol.* 64, 2014  
• Marsiglia et al. *Am Heart J.* 166, 2013  
| ***Some phenotypes are mild, but can be exacerbated by environmental factors*** | • Van den Berg et al. *Eu J Heart Fail.* 12, 2010  
• Shipman et al. *JCO.* 29, 2011  
• Wasielewski et al. *Open Heart.* 18, 2014  
• Young et al. *Ann Oncol.* 22, 2011 |
| Inherited cardiomyopathy syndromes are a risk factor for anthracycline-induced cardiotoxicity | • Kalam et al. *Eur J Cancer.* 49, 2013  
• Conway et al. *BMC Cancer.* 366, 2015  
• Vejpongsa et al. *J Am Coll Cardiol.* 64, 2014 |
| Approaches for monitoring and preventing anthracycline-induced cardiotoxicity |                                                                 |
Translation to Cardiooncology?

- Family history/known syndromes
- Clonal hematopoiesis of unknown potential (CHIP)
- Polygenic propensity scores
- A lot more coming, lots to do
Clonal Expansion and Allelic Fractions.

CHIP found in ~20% of ‘healthy’ 60 year olds

Clonal hematopoiesis of unknown potential (CHIP) is a risk for primary and therapy-associated leukemia.
Association between Clonal Hematopoiesis of Indeterminate Potential (CHIP) and Coronary Heart Disease and Early-Onset Myocardial Infarction.

### A  CHIP and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants with Coronary Heart Disease/ No. at Risk</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biolmage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>94/326</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>19/44</td>
<td>1.8 (1.1–2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>MDC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>299/607</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>21/33</td>
<td>2.0 (1.2–3.1)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Fixed-effects meta-analysis</strong></td>
<td></td>
<td>1.9 (1.4–2.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### B  CHIP and Early-Onset Myocardial Infarction

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Participants with Myocardial Infarction/ No. at Risk</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATVB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>1716/3293</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>37/43</td>
<td>5.4 (2.3–13.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PROMIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mutation (reference)</td>
<td>2488/3844</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation</td>
<td>52/65</td>
<td>3.4 (1.8–6.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Fixed-effects meta-analysis</strong></td>
<td></td>
<td>4.0 (2.4–6.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Association between CHIP and Increased Coronary-Artery Calcification.

A Coronary-Artery Calcification (CAC) Scores, According to CHIP Status

B CHIP and CAC Score of ≥615 Agatston Units, According to Variant Allele Fraction

Translation to Cardiooncology?

• Family history/known syndromes

• Clonal hematopoiesis of unknown potential (CHIP)

• Polygenic propensity scores

• A lot more coming, lots to do
Genome-wide diseases identified to monogenic

Amit V. Khera, Mark C. Collins, Seung Hoan Choi, Pradeep L. N. Khatri, Patrick T. Ellinor, and S. B. Smith

Prevalence of coronary artery disease (%) vs. Percentile of polygenic score
Translation to Cardiooncology?

- Family history/known syndromes
- Clonal hematopoiesis of unknown potential (CHIP)
- Polygenic propensity scores
- A lot more coming, lots to do
Therapeutic Risk Mitigation plUs optiMized PharmacotHerapy (TRIUMPH)

• Quality Improvement Pilot

• The Primary goals are to:
  – Identify those genetically predisposed to adverse drug affects
  – Guide drug selection and dosing
  – Reduce untoward drug effects
  – Improve the quality of patient care

• Preemptive, initiated at first contact/first return visit
A Broader Strategy

- Neuropathy risk
- Cardiotoxicity risk
- Bone marrow ‘opathy’ risk
- Gastropathy risk
- Hereditary cancer risk
- Eligibility for PARP inhibitors
- Criteria for immunotherapy
- Drug selection and dosing
  - Pain control
  - Antiemetics
  - Antifungals
  - Anesthesia risks
  - Coagulation risks
Practical choices

Selection treatment from amongst ‘equals’
We have large cancer cohorts, so let’s look!
Quality improvement is needed to find the right fit for most health systems – don’t just copy the eggheads

‘acceptable’* levels of toxicity  We have to ask!
*to the patient, not prescriber

Preemptive assessment of benefit:risk, to AVOID risk and ASSURE the best change of benefit
Acknowledgements

**Personalized Medicine Clinical Service**
Howard McLeod, PharmD (Medical Director, Chair)
Heather Blanford (PMCS Admin Assistant)
Tim Block, MPA, HSA (Administrator)
J. Kevin Hicks, PharmD, PhD (Attending, Clinical Service)
Sapna Joshi (Executive Assistant)
Todd Knepper, PharmD (Attending, Clinical Service)
Neil Mason, MA, MBA, PSM (Strategist)
Daryoush Saeed-Vafa, MD (Fellow)
Christine Walko, PharmD, BCOP (Attending, CGAC Chair)
Pam Wilson, RN, MBA, MSN, CPHRM (Program Director)

**Clinical Service Consultants**
Terry Boyle, MD, PhD
Andy Brohl, MD
Mohammad Hussaini, MD
Eric Padron, MD
Teresa Vo, PharmD

**Genetics**
Xia Wang, MD, PhD, FACMG
Laura Barton, MA, MS, CGC
Christine Bruha, MS, CGC
Jennifer Brzosowicz, MS, CGC
Carolyn Haskin, MS, GCG
Kathleen Ray, MGC, CGC

**Bioinformatics**
Richard Lu, PhD
Jamie Teer, PhD
Guillermo Gonzalez-Calderon, PhD
Rodrigo Carvajal, PhD

**Outcomes Research**
Margaret Byrne, PhD
Deborah Cragun, MS, CGC, PhD
Kristine Donovan, PhD
Heather Jim, PhD
Susan Vadaparampil, PhD
Acknowledgements

EHR IT
Randa Perkins, MD (CMIO)
Alastair MacGregor, MD (Associate CMIO)
Jennifer Greenman (CIO)
Kerry Kelly, MT-ASCP
Joseph Markowitz, MD

Pathology
Anthony Magliocco, MD (Chair)
Lynn Moscinski, MD (Laboratory Medicine Chair)
Thomas Watson

Clinical Action Genomics Committee

Therapeutic Risk Mitigation Panel
Michael Fradley, MD (Physician Champion, Cardiooncology)
Sepideh Mokhtari, MD (Physician Champion, Neurology)
Sephalie Patel, MD (Physician Champion, Anesthesia)
Bijal Shah MD (Physician Champion, Lymphoma)
Mian Shahzad, MD, PhD (Physician Champion, Ovarian)
Hatem Soliman, MD (Physician Champion, Breast)

CYP2C19-Voriconazole Project
John Greene, MD
Rebecca Nelson, PharmD
Yanina Pasikhova, PharmD
Rod Quilitz, PharmD
Wonhee So, PharmD

PGx – Antidepressant Project
Margarita Bobonis, MD
Barbara Lubrano Di Ciccone, MD
Steven Sutton, PhD