Learning Objectives

• Upon completion of this program, participants will be able to:
  – Identify specific drug therapies used in cardiology in which pharmacogenomic testing can be applied in the clinical setting
  – Summarize evidence-based recommendations for pharmacogenomic testing
  – Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence

Presentation Outline

• Irinotecan and UGT1A1
  – Role in UGT1A1 in metabolism of irinotecan
  – Association of UGT1A1 genotype and irinotecan toxicity
  – Practice recommendations
• EGFR Therapy and KRAS
  – Overview of EGFR pharmacology and role of KRAS
  – Impact of KRAS on response to EFG therapy
  – Practice recommendations
• Tamoxifen and CYP2D6
  – Role of CYP2D6 in metabolism of tamoxifen
  – Overview of clinical data evaluating the impact of CYP2D6 on tamoxifen clinical outcomes
  – Practice recommendations
Case Study #1

• SK is a 55-year-old male with newly diagnosed stage IV colorectal cancer
• His oncologist orders a UGT1A1 genotype and finds the SK is homozygous for the UGT1A1*28 polymorphism
• How would this information change your recommendation for irinotecan dosing?

Irinotecan (Camptosar®)

• Camptothecin class of topoisomerase inhibitors
• Activity against a variety of malignancies
  – Colorectal cancer
  – Small cell lung cancer
• Significant side effects including diarrhea, neutropenia, and vascular syndromes

Irinotecan Metabolism & UGT1A1 polymorphism


UGT1A1 Polymorphism and Functional Effect

• Gene/Allele of interest: UGT1A1*28
  – Result of 7 TA repeats in the promoter region instead of 6 repeats
• Functional effect: reduced UGT1A1 transcription & enzyme (or glucuronidation) activity
• Associated with reduced clearance of SN-38 (active and toxic metabolite)
• Associated with hyperbilirubinemia (Gilbert’s Syndrome)

Hahn et al 2006
Population Prevalence of UGT1A1 Genotype

<table>
<thead>
<tr>
<th>Race</th>
<th>UGT1A1 Genotype</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
<td>*1/*28</td>
<td>*28/*28</td>
</tr>
<tr>
<td>Caucasian</td>
<td>46%</td>
<td>39%</td>
<td>13%</td>
</tr>
<tr>
<td>Asian</td>
<td>76%</td>
<td>20%</td>
<td>5%</td>
</tr>
<tr>
<td>African American</td>
<td>26%</td>
<td>37%</td>
<td>19%</td>
</tr>
</tbody>
</table>

Liu et al 2007; Beutler et al 1998

Clinical Relevance: Toxicity & Efficacy

Rates by UGT 1A1 Genotype (%) (95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>*1/*1</th>
<th>*1/*28</th>
<th>*28/*28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Neutropenia</td>
<td>9.8 (6.8-14)</td>
<td>18 (14-23)</td>
<td>38 (22-57)</td>
</tr>
<tr>
<td>Severe Diarrhea</td>
<td>18 (11-28)</td>
<td>27 (20-36)</td>
<td>27 (12-48)</td>
</tr>
<tr>
<td>Tumor Response</td>
<td>41 (33-40)</td>
<td>45 (33-63)</td>
<td>70 (40-84)</td>
</tr>
</tbody>
</table>

Adapted from: EGAPP Working Group 2009

Clinical Relevance: Dosing

In July 2005, product labeling change to include initial dose reduction by one dosing level for patients homozygous for UGT1A1*28 polymorphism

DOSAGE AND ADMINISTRATION
Dosage in Patients with Reduced UGT1A1 Activity
When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (see CLINICAL PHARMACOLOGY and WARNINGS). However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 10-13).

Camptosar Product Information 2008

Pharmacogenomic Test

- Invader UGT1A1 Molecular Assay
  Manufactured by Third Wave Molecular Diagnostics
- FDA approval August 2005
- 100% accuracy compared to DNA sequencing
- Processing time of 4-5 hours
- Several commercial tests are available
**UGT1A1 Genotyping Debate**

**Pro**
- Strong association with dose limiting toxicities
- Commercially available assay
- Common polymorphism in general population
- FDA recommendation included in PI

**Con**
- Only 30-40% of UGT1A1*28 homozygous patients suffer severe toxicities
- Dose reduction may result in decrease efficacy
- 20% dose reduction not prospectively studied
- Current common dose used (100-125mg/m^2) is lower than in previous studies (200-350mg/m^2)

*EGAPP Working Group 2009; Hoskins et al 2007*

**Testing Recommendations**

- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group
  - "Evidence is currently insufficient to recommend for or against the routine use of UGT1A1 genotyping in patients with metastatic colorectal cancer who are to be treated with irinotecan."
  - "Found no intervention trials showing that targeted dosing of irinotecan based on UGT1A1 genotyping could reduce the rates of two specific adverse drug events, severe (Grade 3–4) neutropenia or diarrhea."

*EGAPP Working Group 2009*

---

**Could the UGT1A1*28 polymorphism impact dose finding studies?**

- Standard dose of irinotecan in FOLFIRI determined to be 180mg/m^2
- Presumption that early dose finding studies included patients with UGT1A1*28 polymorphism
- If UGT1A1*28 homozygous patients excluded from previous dose finding studies, would maximum tolerated dose (MTD) differ?

*Toffoli et al 2010*

**UGT1A1 and MTD**

- Patients screened for genotype and excluded all UGT1A1*28 homozygous patients
- Starting dose of irinotecan 215mg/m^2 with FOLFIRI regimen
- MTD for UGT1A1*1/*1: 370mg/m^2
- MTD for UGT1A1*1/*28: 310mg/m^2
- Currently recommended dose of 180mg/m2 considerably lower than tolerated dose when UGT1A1*28 homozygous patients excluded
**UGT1A1*28 Summary**

- *UGT1A1* genotype associated with irinotecan toxicities
- Prospective genotype-guided dosing trials with irinotecan are needed to confirm or deny the benefit of *UGT1A1* genotyping

---

**Case #1 Summary**

- SK was homozygous for the *UGT1A1*28 polymorphism
- This puts SK at significantly higher risk of severe neutropenia and possibly higher risk of diarrhea
- Although empiric dose reductions may reduce this risk, it may also compromise the efficacy of therapy

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**Case Study #2**

- KG is a 58 year-old female with a recent diagnosis of metastatic colorectal cancer (mCRC)
- She is told that her tumor will be tested for KRAS to help determine the best chemotherapy regimen for her
- The results return that she has a KRAS mutation in codon 12
- How should this influence the selection of therapy for this patient?

**EGFR Inhibitors and KRAS**
EGFR Inhibitors

- Two monoclonal antibodies currently approved to treat mCRC
  - Cetuximab
  - Panitumumab
- Bind to extracellular EGFR domain leading to inhibition of downstream signaling
- Only 10-20% of patients with mCRC benefit from anti-EGFR therapy
- EGFR expression does not correlate with clinical benefit

Bardelli et al 2010

EGFR Mechanism of Action

KRAS

- Gene of interest: KRAS
  - Kirsten (K) RAS is a downstream effector of EGFR
  - KRAS belongs to the gene family of oncogenes encoding guanosine di-/triphosphate-binding proteins
  - The KRAS signaling pathway is thought to control cell growth, differentiation, and apoptosis

Bardelli et al 2010

KRAS

- Functional effect: Activating mutations in KRAS result in activation of downstream signaling pathways and confers resistance to inhibition of cell surface receptor tyrosine kinases such as EGFR
- Population Prevalence: The prevalence of mutated KRAS ranges between 27-43% in tumor samples collected from colorectal cancer patients across 7 trials

Siddiqui et al 2010
Clinical Relevance: Efficacy

- Tumors from 30 mCRC patients evaluated for KRAS
- KRAS mutation found in 43% of all mCRC tumor samples
- 37% (11 of 30) of patients responded to cetuximab
- No responders had KRAS mutation (0 of 11)
- 68% of non-responders had KRAS mutation (13 of 19)

Lievre et al 2006

Clinical Relevance: Efficacy of anti-EGFR monotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Intervention</th>
<th>Outcomes in KRAS-mutated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002048</td>
<td>469</td>
<td>BSC + Panitumumab</td>
<td>No difference in PFS, OS, ORR</td>
</tr>
<tr>
<td>NCIC-017</td>
<td>572</td>
<td>BSC + Cetuximab</td>
<td>No difference in PFS, OS, ORR</td>
</tr>
</tbody>
</table>

BSC-Best supportive care; PFS-Progression free survival; OS-Overall survival; ORR-Overall response rate

Adapted from Bardelli et al 2010

Efficacy of Combination Chemotherapy with anti-EGFR

<table>
<thead>
<tr>
<th>Trial</th>
<th># Patients</th>
<th>Intervention</th>
<th>Primary endpoint in KRAS-mutated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME</td>
<td>1,183</td>
<td>FOLFOX4 + Panitumumab</td>
<td>Worse PFS</td>
</tr>
<tr>
<td>CRYSTAL</td>
<td>1,198</td>
<td>FOLFIRI + Cetuximab</td>
<td>No difference PFS</td>
</tr>
<tr>
<td>OPUS</td>
<td>337</td>
<td>FOLFOX4 + Cetuximab</td>
<td>Worse ORR</td>
</tr>
<tr>
<td>PACCE</td>
<td>1,053</td>
<td>Chemo + Bev + Panitumumab</td>
<td>Worse PFS</td>
</tr>
<tr>
<td>CAIRO2</td>
<td>736</td>
<td>CapOx + Bev + Cetuximab</td>
<td>Worse PFS</td>
</tr>
<tr>
<td>EPIC</td>
<td>1,298</td>
<td>Irinotecan + cetuximab</td>
<td>Worse OS</td>
</tr>
<tr>
<td>181 Trial</td>
<td>1,186</td>
<td>FOLFIRI + panitumumab</td>
<td>No difference PFS, OS</td>
</tr>
</tbody>
</table>

Adapted from Bardelli et al 2010

Clinical Relevance

- Efficacy: In summary, colorectal cancer patients whose tumor has a mutated KRAS, have a low likelihood of responding to anti-EGFR monoclonal antibody therapy
- Toxicity: No literature related to KRAS mutational status impacting anti-EGFR toxicity
- Dosing: No literature related to KRAS mutational status impacting anti-EGFR dosing

Clinical Relevance
Pharmacogenomic Test

- FDA updated prescribing information to recommend against use of EGFR inhibitors in KRAS mutated tumors
- Tumor DNA extracted from tissue sample
- Multiple commercials KRAS test kits available

Testing Recommendations

- American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion
  - “All patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations.”
  - “If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.”

KRAS Summary

- Only 10-20% of patients with mCRC respond to anti-EGFR therapy
- KRAS mutational status predicts responsiveness and clinical benefit with anti-EGFR monoclonal antibodies in mCRC
- Mutations for KRAS should be evaluated for all mCRC patients considered for anti-EGFR monoclonal antibody therapy

Case #2 Summary

- KG’s tumor is positive for a KRAS mutation
- She is unlikely to benefit from EGFR therapy and possibly may do worse if an EGFR inhibitor is used
- KG should not receive therapy which contains cetuximab or panitumumab
Case Study #3

• JB is a 45 year-old female with breast cancer who has recently completed adjuvant chemotherapy and is scheduled to begin tamoxifen
• She has recently read that her genetics could help identify if she would respond to tamoxifen
• Upon asking her pharmacist, he states that this has not been proven yet
• Could this patient’s genetics predict the efficacy of tamoxifen for breast cancer?

Tamoxifen

• Tamoxifen is considered the gold standard endocrine therapy for patients with estrogen receptor positive (ER+) or progesterone receptor positive (PR+) breast cancer
• Considered a selective estrogen receptor modulator
• Approved for a variety of indications including metastatic and adjuvant therapy as well as breast cancer risk reduction

Tamoxifen Biotransformation

Chemical structure of tamoxifen and major biotransformation pathways.

**CYP2D6 and Endoxifen**

- Endoxifen is the metabolite most responsible for the in vivo pharmacologic activity of tamoxifen.
- The formation of endoxifen is dependent on the hepatic CYP2D6 pathway.
- The CYP2D6 enzyme is highly polymorphic.

Hoskins et al 2009

**CYP2D6 Polymorphisms**

- Gene of interest: CYP2D6
  - At least 74 CYP2D6 allele variants have been identified.
    - Different polymorphisms exist based on the allele subtype.
- Functional effect: (Broly et al 1993, Zhou et al 2010)
  - Wild type allele (normal enzyme activity): CYP2D6*1
  - Alleles associated with decreased enzyme activity: CYP2D6*10, *17, and *41
  - Alleles associated with a loss (null) of enzyme activity: CYP2D6*3, *4, *5, and *6
  - Alleles associated with increased enzyme activity: CYP2D6*17x2 and *41x2
  - Polymorphisms in CYP2D6 can have as much as a 200-fold effect on drug metabolism.

**CYP2D6 Phenotype-Genotype Association**

- Phenotype classification
  - Definition of phenotype: The clinical presentation of an individual with a particular genotype.
  - In general:
    - Extensive metabolizers (EM) will possess 2 wild type alleles (e.g., CYP2D6*1/*1).
    - Intermediate metabolizers (IM) will have 1 wild type allele and 1 variant allele (e.g., CYP2D6*1/*4).
    - Poor metabolizers (PM) will have 2 variant alleles (e.g., CYP2D6*4/*4).

**Population Prevalence of Common CYP2D6 Variant Alleles**

<table>
<thead>
<tr>
<th>Race</th>
<th>CYP2D6 Variant Allele</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*4</td>
</tr>
<tr>
<td>Caucasian</td>
<td>20-25%</td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
</tr>
<tr>
<td>African American</td>
<td>6-7%</td>
</tr>
</tbody>
</table>

Impact of CYP2D6 Genotype on Endoxifen Concentrations

<table>
<thead>
<tr>
<th>CYP2D6 Genotype</th>
<th># Patients</th>
<th>Mean Endoxifen Concentration nM (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>48</td>
<td>78.0 (65.9 to 90.1)</td>
</tr>
<tr>
<td>*1 plus 1 variant allele</td>
<td>29</td>
<td>43.1 (33.3 to 52.9)</td>
</tr>
<tr>
<td>2 variant alleles</td>
<td>3</td>
<td>20.0 (11.1 to 28.9)</td>
</tr>
</tbody>
</table>

P<0.001
Jin et al 2005

Clinical Relevance: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Extensive Metabolizer</th>
<th>Intermediate Metabolizer</th>
<th>Poor Metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Recurrence Rate</td>
<td>12.4%</td>
<td>17.7%</td>
<td>24.1%</td>
</tr>
<tr>
<td>Event-free survival event</td>
<td>22.2</td>
<td>27.6</td>
<td>32.9</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>16.7%</td>
<td>18.0%</td>
<td>22.8%</td>
</tr>
</tbody>
</table>

Schroth et al 2009

Supportive Clinical Trial Data

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Data Collection</th>
<th>TAM Dose</th>
<th>CYP2D6 Variants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goetz 2005</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>20mg QD x 5y</td>
<td>*4</td>
<td>*4/4 DFS HR 1.85</td>
</tr>
<tr>
<td>Goetz 2007</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>20mg QD x 5y</td>
<td>*4</td>
<td>*4/4 TTR HR 1.91</td>
</tr>
<tr>
<td>Schroth 2007</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>Not provided</td>
<td>*4, *5, *10</td>
<td>PMs RFS HR 2.24</td>
</tr>
<tr>
<td>Lim 2007</td>
<td>Adjuvant / Metastatic</td>
<td>Not provided</td>
<td>20mg QD</td>
<td>*5, *10</td>
<td>*10/10</td>
</tr>
<tr>
<td>Xu 2008</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>20mg QD</td>
<td>*10</td>
<td>*10/10 DFS HR 4.7</td>
</tr>
<tr>
<td>Newman 2008</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>20mg QD x 4y</td>
<td>*4, *5, *41</td>
<td>CYP2D6 Activity RFS HR 1.9</td>
</tr>
<tr>
<td>Bonnani 2006</td>
<td>Prevention</td>
<td>Retro</td>
<td>20mg QD x 5y</td>
<td>32 alleles</td>
<td>PMs 1 breast cancer, p ≥ 0.4</td>
</tr>
</tbody>
</table>

DFS = disease free survived, HR = hazard ratio, TTR = time to relapse, RFS = relapse free survived, OR = odds ratio

Adapted by permission from Oxford University Press: [J Natl Cancer Inst] 97(1):30-9, copyright 2005
Schroth et al 2009
Contradictory Results

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Data Collection</th>
<th>TAM Dose</th>
<th>CYP2D6 Variants</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wegmen 2005</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>40mg QD x 2y</td>
<td>*4</td>
<td>*4 carrier ↓ recurrence risk (RR 0.28, p = 0.009)</td>
</tr>
<tr>
<td>Wegmen 2007</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>20-40mg QD x 2-5y</td>
<td>*4</td>
<td>*4/*4 vs *1/*1 ↑ DFS (p = 0.05)</td>
</tr>
<tr>
<td>Nowell 2005</td>
<td>Adjuvant</td>
<td>Retro</td>
<td>Not included</td>
<td>*4</td>
<td>HR+ *4 carrier: HR 0.77 (95% CI 0.32-1.81)</td>
</tr>
</tbody>
</table>

DFS = disease free survival, HR = hazard ratio

Tamoxifen: Clinical Relevance

- Efficacy
  - Overall Survival
    - No effect or association of CYP2D6*4 with overall survival (Goetz et al 2005, Schroth et al 2007, Nowell, et al 2005)
  - Disease recurrence (measured as either relapsed free time or relapsed free survival)
    - Increased risk (Goetz et al 2005, Schroth et al 2007, Goetz et al 2007)
    - Decreased risk (Wegman et al 2005)
    - No risk associated (Wegman et al 2007)
  - Disease Free Survival
    - Decreased disease free survival (Goetz et al. 2007, Schroth et al 2007)

- Toxicity
  - Incidence of hot flashes
    - Decreased incidence in CYP2D6*4/*4 patients (Goetz et al 2005)
    - Variable incidence reported elsewhere in CYP2D6*4/*4 patients (Bonanni et al 2006)

Pharmacogenomic Test & Testing Recommendations

- Genomic Test
- Pharmacogenomic Test Recommendations
  - No formal recommendation (FDA, PI)
  - FDA Advisory Committee recommended label update to reflect increased risk; no formal consensus on genetic testing (10/18/06)
**What are the therapeutic alternatives to tamoxifen?**

- **Post-Menopausal women**
  - Could switch to aromatase inhibitor
  - Possible dose increase but unproven benefit
- **Pre-Menopausal women**
  - No proven alternatives to tamoxifen
  - Possible dose increase

**Study LCCC 0801: Dosage Increase in IM/PM**

- **Objective**: Evaluate changes in endoxifen concentration following tamoxifen dose increase in patients with IM and PM phenotypes.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N (%)</th>
<th>Baseline (ng/mL)</th>
<th>4-Month (ng/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM</td>
<td>29 (33%)</td>
<td>34.33</td>
<td>29.23</td>
<td>0.42</td>
</tr>
<tr>
<td>IM</td>
<td>51 (57%)</td>
<td>18.45</td>
<td>21.84</td>
<td>0.0008</td>
</tr>
<tr>
<td>PM</td>
<td>9 (10%)</td>
<td>4.18</td>
<td>12.89</td>
<td>0.0195</td>
</tr>
</tbody>
</table>

**Case #3 Summary**

- JB inquired if her genetics could predict response to tamoxifen
- Several trials have demonstrated a correlation between CYP2D6 genotype and outcomes with tamoxifen
- No trials have demonstrated clinical benefit to screening CYP2D6 in breast cancer patients taking tamoxifen
Acknowledgements

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• **Project Coordinator**
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References


Table of valid genomic biomarkers in the context of approved drug labels. Available at: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm