Pharmacogenomics: Regulatory Considerations for the Next Generation of Medicines

Hobart Rogers, Pharm.D., Ph.D.,
Genomics and Targeted Therapies Group
Office of Clinical Pharmacology
FDA

The views expressed are those of the speakers and do not necessarily reflect the official policy of the FDA. No official endorsement is intended or should be inferred.
CPE Information and Disclosures

Hobart Rogers “declare(s) no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”
CPE Information

- Target Audience: Pharmacists and Pharmacy Technicians
- ACPE#: 0202-0000-18-226-L04-P/T
- Activity Type: Knowledge-based
Learning Objectives

1. State the regulatory perspectives of pharmacogenomics and targeted therapy in drug development.

2. Explain pharmacogenomic biomarkers and their impact on pharmacokinetics, safety, and efficacy.

3. Identify how synthetic nucleotides elicit their mechanism of action.
Self-Assessment Questions

1. Which of the following is not a type of genomic biomarker?
   a. Predictive
   b. Economic
   c. Prognostic
   d. Diagnostic

2. Approximately how many FDA-approved drugs now have pharmacogenomic biomarker information in their labeling?
   a. 15
   b. 45
   c. 140
   d. 280
Self-Assessment Questions Continued…

3. From a pharmacologic standpoint, how are oligonucleotides unique from small molecules and biologics?
   a. They are larger
   b. They are smaller
   c. They rely on RNA-centric pharmacology to elicit their mechanism-of-action
   d. They are only available by IV formulation
Agenda

• Overview of Pharmacogenomics
• Genomic Biomarkers in Drug Development and Product Labeling
• Precision Drug Approvals
  – Efficacy – Ivacaftor
  – Safety – Carbamazepine
  – Pharmacokinetic – Pimozide
• Oligonucleotide-Based Therapeutics
• Case Presentation - Pharmacogenomics in Action
• Q & A
Nuts and Bolts

- Genome contains ~3.2 billion nucleotide bases (A, C, T, G)
- Average gene consists of 3000 bases
- Total # of genes is ~ 22,000 (<2% of the genome codes for protein)
- Functions are unknown for over 50% of genes
- Almost all (>99%) nucleotides are the same in all people
3 billion DNA bases in the human genome
10 million single nucleotide polymorphisms (SNPs)
Many rare variants
Image source: Time magazine Feb 17, 2003
Our Ability to Generate Data Has Far Surpassed Our Ability to Interpret It

Image source: www.genome.gov/sequencingcosts
FDA has worked to respond to, anticipate and help drive scientific developments in personalized therapeutics and diagnostics.

The concept of personalized medicine is not new... What is new are technological advances in a wide range of fields from genomics to medical imaging... are allowing patients to be treated and monitored more precisely and effectively...

http://www.fda.gov/ScienceResearch/SpecialTopics/PersonalizedMedicine/ucm20041021.htm
“Personalized medicine is one patient at a time”

Stephen Spielberg
Former Deputy Commissioner, OMPT
Personalized Dosing and Patient Selection

Agenda

• Overview of Pharmacogenomics

• **Genomic Biomarkers in Drug Development and Product Labeling**

• Precision Drug Approvals
  – Efficacy – Ivacaftor
  – Safety – Carbamazepine
  – Pharmacokinetic – Pimozide

• Oligonucleotide-Based Therapeutics

• Case Presentation - Pharmacogenomics in Action

• Q & A
What Can Genomic Biomarkers Tell Us?

Susceptibility
Will I develop the disease?
BRCA → breast cancer

Safety
Am I having an adverse event?
ALT → Hepatotoxicity

Diagnosis
Do I have the disease?
CFTR → CF

Monitoring
Has the condition changed?
HIV RNA → HIV/AIDS

Prognosis
Will I live longer?
17p del → CLL

Response
Did treatment work?
INR → warfarin/stroke

Prediction
Will I respond to treatment?
BRAF → skin cancer

* Other types exist; functions are not mutually exclusive; see https://www.ncbi.nlm.nih.gov/books/NBK326791/
## Uses of Genomics in Drug Development

<table>
<thead>
<tr>
<th>Type</th>
<th>Uses</th>
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| Preemptive | • Validate targets for drug development  
             • Predict drug toxicities  
             • Define target population |
| Retrospective | • Explain variable responses to drug  
                        • Identify (non-)responders or patients with adverse reactions  
                        • Identify risk for serious drug interactions |
| Prospective | • Predict drug exposure  
                    • Minimize noise  
                    • Identify patients at risk for disease or event  
                    • Select patients likely to respond to drug |
Leveraging Genomics to Improve Benefit-Risk

Avoid Populations Likely to Experience Adverse Drug Reactions

Optimize Dose

Identify Likely Responders

Shifting Benefit-Risk Profile

Decreased Risk

Increased Benefit

Pharmacogenomic Labeling

INDICATIONS AND USAGE
  Patient selection

DOSAGE AND ADMINISTRATION
  Subgroup dosing

BOXED WARNING,
CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS,
USE IN SPECIFIC POPULATIONS
  Differential safety

CLINICAL PHARMACOLOGY
  Impact on PK/PD

CLINICAL STUDIES
  Substantial evidence of observed differences
Biomarkers and Genetic Factors in Labeling

284 biomarker-drug pairs
214 drugs, 64 biomarkers*
42% metabolism/transport
33% target/pathway
25% immunologic/other safety

139 actionable**
Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

* Includes some products with multiple drugs and families of biomarkers resulting in a phenotype (e.g., urea cycle disorders)
** Management recommendations excluding “use with caution”
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• Drug and Therapeutic Product Labeling
• Oligonucleotide Based Therapeutics
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• Q & A
Efficacy

High variability
Multimodal distribution
Race effects
Outliers

Clinical PK
Polymorphic metabolism/activation/transport

Exposure/response

Efficacy
Morbid disease
Genetic disease
Polymorphic drug target

Safety
Serious AEs
Poor tolerability

Idiosyncrasy
Ivacaftor: Targeted Therapy and Responder Subsets

- Initially targeted to specific CF “gating” mutation G551D
- CF gene – first discovered in 1989 by Collins

"Woe to the child who tastes salty from a kiss on the brow, for he is cursed and soon must die,"
-18th century Germany and Switzerland literature
Identifying (Non)Responders

Ivacaftor for Cystic Fibrosis

- Ivacaftor potentiates CFTR channel-open probability for “gating” mutations
- Targets the underlying molecular defect that causes disease

Identifying (Non)Responders

**Ivacaftor for Cystic Fibrosis**

- In vitro studies identify mutations that are responsive
- Two Phase 3 trials in G551D carriers (n=213) show benefit on lung function
- One Phase 2 trial in F508del (most common genotype) shows no benefit
- Efficacy in multiple rare mutations (informed by in vitro data) based on short-term clinical studies

Ivacaftor Labeling
KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 12 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data [see Clinical Pharmacology (12.1) and Clinical Studies (14)].
Safety

- High variability
- Multimodal distribution
- Race effects
- Outliers

Clinical PK
- Polymorphic metabolism/activation/transport

Efficacy
- Morbid disease
- Genetic disease
- Polymorphic drug target

Exposure/response

Safety
- Serious AEs
- Poor tolerability

Idiosyncrasy
Safety Pharmacogenomics

**Carbamazepine and Skin Reactions**

- Cutaneous reactions (maculopapular rash, hypersensitivity, SJS, and TEN) occur in 1/1,000 to 1/10,000 of carbamazepine-treated patients
- SJS/TEN – high case-fatality rates
- More common in patients of certain Asian ancestry

Safety Pharmacogenomics

Carbamazepine and Skin Reactions

Presence of HLA-B*1502 associated with Stevens Johnson Syndrome (SJS)

Meta-analysis of 205 cases and 692 controls

Safety Pharmacogenomics

Carbamazepine and Skin Reactions

WARNINGS

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE
SERIOUS AND SOMETIMES FATAL DERMATOLOGIC REACTIONS, INCLUDING TOXIC EPIDERMAL NECROLYSIS (TEN) AND STEVENS-JOHNSON SYNDROME (SJS), HAVE BEEN REPORTED DURING TREATMENT WITH CARBAMAZEPINE. THESE REACTIONS ARE ESTIMATED TO OCCUR IN 1 TO 6 PER 10,000 NEW USERS IN COUNTRIES WITH MAINLY CAUCASIAN POPULATIONS, BUT THE RISK IN SOME ASIAN COUNTRIES IS ESTIMATED TO BE ABOUT 10 TIMES HIGHER. STUDIES IN PATIENTS OF CHINESE ANCESTRY HAVE FOUND A STRONG ASSOCIATION BETWEEN THE RISK OF DEVELOPING SJS/TEN AND THE PRESENCE OF HLA-B*1502, AN INHERITED ALLELIC VARIANT OF THE HLA-B GENE. HLA-B*1502 IS FOUND ALMOST EXCLUSIVELY IN PATIENTS WITH ANCESTRY ACROSS BROAD AREAS OF ASIA. PATIENTS WITH ANCESTRY IN GENETICALLY AT-RISK POPULATIONS SHOULD BE SCREENED FOR THE PRESENCE OF HLA-B*1502 PRIOR TO INITIATING TREATMENT WITH CARBAMAZEPINE. PATIENTS TESTING POSITIVE FOR THE ALLELE SHOULD NOT BE TREATED WITH CARBAMAZEPINE UNLESS THE BENEFIT CLEARLY OUTWEIGHS THE RISK (SEE WARNINGS AND PRECAUTIONS, LABORATORY TESTS).
Safety Pharmacogenomics

Carbamazepine and Skin Reactions

Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D.,
Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D.,
Chih-Ta Tai, M.D., Shye-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D.,
Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D.,
Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D.,
Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S.,
Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S.,
Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D.,
Wen-Hung Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jery-Yuann Wu, Ph.D.,
Chi-Feng Chao, Ph.D., Luke Chen, Ph.D., Yuan-Tsiong Chen, M.D., Ph.D.

RESULTS
Mild, transient rash developed in 4.3% of subjects; more widespread rash developed in 0.1% of subjects, who were hospitalized. SJS–TEN did not develop in any of the HLA-B*1502–negative subjects receiving carbamazepine. In contrast, the estimated historical incidence of carbamazepine-induced SJS–TEN (0.23%) would translate into approximately 10 cases among study subjects (P<0.001).
Safety Pharmacogenomics

Carbamazepine and Skin Reactions

Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions

Zhibin Chan, MBiostat
Danny Liew, MD, PhD
Patrick Kwan, MD, PhD

ABSTRACT
Objective: To assess the effects of an active pharmacogenetic screening policy for antiepileptic drug (AED) therapy on everyday clinical practice and clinical outcomes.

Methods: We extracted data covering all public hospitals and clinics in Hong Kong for patients who were newly commenced on carbamazepine or other AEDs, or were tested for HLA-B*15:02 3 years before policy implementation (prepolicy: September 16, 2005 to September 15, 2008) and 3 years after (postpolicy: September 16, 2008 to September 15, 2011). We compared AED prescriptions and the incidence of SJS/TEN between the 2 periods and analyzed adherence to the policy.

Results: A total of 151,242 patients were included and 4,149 were tested for HLA-B*15:02. As a proportion of all new AED prescriptions, carbamazepine declined from 16.2% (108,725/677,225) to 13.9% (16,145/116,776; p = 0.001). The incidence of SJS/TEN induced by carbamazepine reduced from 0.24% (20/8,284) to 0% (0/1,076; p = 0.027), but SJS/TEN induced by phenytoin increased (0.15% [18/11,839] vs 0.26% [33/12,618], p = 0.058), and the overall incidence of AED-induced SJS/TEN remained unchanged (0.09% [42/45,832] vs 0.07% [39/55,326], p = 0.238). Test-prescription practice was adherent to the policy in only

Neurology® 2014;83:2077–2084

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Pharmacokinetics
Pimozide – Dosing based on PGx

• One of only two therapeutic modalities approved for the treatment of tics in Tourette’s syndrome
• Prolongs the QT interval
CYP2D6

- Approximately 5-10% of U.S. population are poor metabolizers (PMs)
- Carry two copies of null alleles (e.g. *3/*4)
- Limited or no functionality
Pimozide Plasma Concentration and CYP2D6 Genotype vs. Time

Rogers H et al., J Clin Psychiatry. 2012 Sep;73(9):1187-90
Pimozide: PGx based label changes

DOSAGE AND ADMINISTRATION

Adults
In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg/day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

At doses above 4 mg/day, CYP 2D6 genotyping should be performed. In poor CYP 2D6 metabolizers, ORAP doses should not exceed 4 mg/day, and doses should not be increased earlier than 14 days (see PRECAUTIONS – Pharmacogenomics).
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• Q & A
Synthetic Oligonucleotides: A New Therapeutic Modality

- Small molecule/protein based therapeutics – turn on/off light switches to modulate an effect

- Oligonucleotides – modulate the number of switches available; fix broken switch

- Gene Editing – install different types of switches

Courtesy: Bart Rogers
What are Synthetic Oligonucleotides?

- Modified nucleic acids typically designed to bind to complimentary DNA/RNA sequence and sometimes a protein (aptamers)
- Effects typically mediated by Watson-Crick base-pairing
- Modified to increase specificity and slow degradation
- Various means of synthetic modification: Backbone (e.g., phosphorothioate, morpholino); 2’ (e.g., Fluoro, MOE)
Types and Targets of Oligonucleotide-Based Therapies

- **Gene editing**
- **Antisense**: mipomersen, inotersen
  - Splice-altering: eteplirsen, nusinersen
  - siRNA: patisiran
  - microRNA
  - mRNA replacement
- **Aptamers**: pegatinib
  - CpG/TLR

FDA approved drugs in RED
Oligos – RNA Centric Pharmacology

- Most often work intracellularly
- Short plasma half-life, but long tissue half-life
- Distribute to certain organs (e.g. kidney, liver)
- Endosomal deposition and release
- Long PD half-life

Spinal Muscular Atrophy

- Spinal muscular atrophy (SMA) is one of the most common autosomal recessive diseases and is characterized by degeneration of spinal cord motor neurons, atrophy of skeletal muscles, and generalized weakness.
- The incidence of SMA is approximately 1/6,000 to 1/10,000 live births.
- SMA is caused by the dysfunction of the survival motor neuron (SMN) gene. The two versions of SMN, SMN1 and SMN2, differ by only five nucleotides. Typically, people have two copies of the SMN1 gene and up to two copies of the SMN2 gene in each cell.
Nusinersen

- Approved in Dec 2016 for the treatment of Spinal Muscular Atrophy (SMA)
- Targeted to specific sequence on SMN2 pre-mRNA
- 18-mer synthetic oligonucleotide with a 2’ MOE substitution and a phosphorothioate backbone
- MOA is to displace an intronic splicing silencer to increase the amount of full-length SMN2 transcripts to increase SMN protein
- Increase available SMN protein

Image Source: Sumner et al. Neuron Jan 4 2017
Nusinersen in action

Image Source: Chiriboga et al. PMID: 26865511
Nusinersen

**Figure 1.** Net Change from Baseline in Total Motor Milestone Score (HINE) by Percent of Subjects in the Interim Efficacy Set*

*Source: FDA product labeling*
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Pembrolizumab: Case Study of Targeted Therapy

- 73 year old female diagnosed with stage IV NSCLC in 04/14. 20 pack-year smoking history. Has not smoked in 20 years. Patient failed first chemotherapy regimen with carboplatin 09/14. Subsequent analysis found tumor to be expressing PD-L1 (> 50% TPS) and randomized to treatment with pembrolizumab vs. docetaxel.
Pembrolizumab: Targeted Immunotherapy in NSCLC

- MAB targeted to PD-1
- PD-1 inhibitory receptor for T-Cells
- T-Cell can again recognize and kill cancer cell expressing PD-L1

Targeting PD-L1 in NSCLC

- IHC used to measure PD-L1 expression
- Sub-group had a PD-L1 expression of ≥ 50% tumor cells
- 633 (28%) out of 2222 patients had high (≥50%) tumor proportion score (TPS)

Results of KEYNOTE-010

OS: PMB vs. DOC: 2mg/kg p< 0.0002; 10 mg/kg p<0.0001

PFS: PMB vs. DOC: 2mg/kg p< 0.0001; 10 mg/kg p<0.0001

PMID: 26712084
Other Results
Summary

Advanced tools, technology and research

Biomarker driven drug development

Gene-Centric Drug Development

Better patient outcomes
Key Points

- Pharmacists often play a major role in drug selection and dose adjustment in a traditional setting; pharmacogenomics is an extension of these basic clinical pharmacology concepts.
- The FDA is at the forefront of integrating pharmacogenomics into product labeling to better “personalize” treatment decisions.
- Numerous examples exist where genomic biomarkers have impacted product development.
- Oligonucleotide therapeutics represent a new “class” of drugs with great potential in targeting the underlying molecular cause of disease at the level of the RNA.
Answers to Self-Assessment Questions

1. Which of the following is not a type of genomic biomarker?
   a. Predictive
   b. Economic
   c. Prognostic
   d. Diagnostic

2. Approximately how many FDA-approved drugs now have pharmacogenomic biomarker information in their labels?
   a. 15
   b. 45
   c. 140
   d. 280
Self-Assessment Questions Continued…

3. From a pharmacologic standpoint, how are oligonucleotides unique from small molecules and biologics?
   
   a. They are larger 
   b. They are smaller 
   c. They rely on RNA-centric pharmacology to elicit their mechanism-of-action 
   d. They are only available by IV formulation
Questions?

“It is much more important to know which patient has the disease rather than which disease the patient has” – Sir William Osler