Presentation Outline

1. Translating pharmacogenomics into practice
2. Pharmacogenomic nomenclature
3. Example therapeutic area: infectious diseases
4. Ethical, legal, social (ELSI) & economic issues

Learning Objectives

• Upon completion of this program, participants will be able to:
  – Describe and define basic pharmacogenomic nomenclature
  – Describe polymorphism types and their impact on pharmacokinetics (PK) and pharmacodynamics (PD)
  – Summarize evidence-based recommendations for pharmacogenomic testing
  – Using patient case scenarios, formulate a plan for pharmacogenomics testing based upon available scientific evidence
  – Understand the ethical, legal, social issues (ELSI) & economic issues related to pharmacogenomic testing

Disclaimer

This presentation was supported by Grant Number IU38GD000070 from Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should seek the advice of their physicians, pharmacists, or other qualified health providers with any questions they may have regarding a medical condition or a medication.
Translating Pharmacogenomics into Practice

Current Drug Therapy

- Drug response rate
  - 30-60% response rate of drug therapies for Alzheimer’s, depression, rheumatoid arthritis, hypertension, osteoporosis (Physician’s Desk Reference, 2007)
- Adverse drug reactions (ADRs)
  - Many ADRs are reported from medical errors, which could potentially be minimized when pharmacogenomic information is integrated into practice
    - Up to 100,000 people/year die of medical errors in the U.S. (1999 IOM Report, To Err is Human)
  - ↑ Morbidity and Mortality
  - ↑ Cost
- Pharmacogenomics may improve drug response rate and minimize ADRs

Challenges of Pharmacogenomic Testing

- Access
  - Availability of test
  - Providers
  - Insurance coverage
- Feasibility
  - Turnaround time
  - Sensitivity/specificity of tests
  - Efficiency
- Cost
  - Genetic test
  - Disease management
  - Counseling
- Limited evidence
  - Few well done trials
  - Efficacy
  - Cost-effectiveness
  - Prospective vs retrospective studies
  - Long-term data lacking
  - Predictive value
  - Expertise
  - Quality and number of studies
  - Small sample sizes
  - Analytical and clinical validity
  - Phenotyping of clinical presentation
  - Clinical utility of testing

Patient/Consumer Demand

- Patients have high expectations
  - For their healthcare providers to explain and interpret pharmacogenomic test results
- Providers lack evidence-based resources
  - Reluctant to order pharmacogenomic tests due to limited utility information
  - There are logistic challenges of testing
- Both have concerns of privacy issues (Fargher EA et al 2007; Rogausch A et al 2006)
  - e.g., genetic testing vary from state to state
Knowledge Gap

- Lack of evidence of clinical utility for pharmacogenomic testing (EGAPP evidence reviews)
- Health informatics tools (e.g., Electronic Medical Records, Computerized Provider Order Entry) do not have pharmacogenomic information at the point of care for clinical decision support.
- Healthcare professionals need education (Frueh et al 2004)
- There is a need to educate future healthcare providers
  - Pharmacogenomics curriculum has increased in pharmacy schools (Latif et al 2005; Latif 2005; Murphy et al 2010)
  - Pharmacogenomics is not adequately taught in medical schools (Gurwitz 2005)

Competency in Pharmacogenetics/genomics

- General competency domains recommended include:
  1. Genetic basis of disease
  2. Drug discovery and disposition/drug targets
  3. Ethical applications, social & economic implications
- Open-access comprehensive web-based tutorials is recommended (Gurwitz et al 2005)

Practice Gap

- The field of pharmacogenetics/genomics is growing rapidly with new discoveries
- It is critical for clinicians to...
  - Appropriately interpret emerging data on pharmacogenomic tests
  - Become familiar with resources applicable to their practice

Pharmacogenetics/genomics Definitions

- Pharmacogenetics
  - “the study of genetic causes of individual variations in drug response” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)
- Pharmacogenomics
  - “more broadly involves genome-wide analysis of the genetic determinant of drug efficacy and toxicity” (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)
  - includes the use of genomics technologies (e.g. bioengineered proteins and gene therapy)
- Both terms are used interchangeably. The preferred term is pharmacogenomics.
Impact of Pharmacogenomics on Pharmacokinetics and Pharmacodynamics


Value of Pharmacogenomics

- Potential to optimize drug therapy
  - May maximize effectiveness and minimize toxicity
  - May minimize pharmacokinetic and pharmacodynamic variability of drug therapy
  - May avoid unnecessary treatment
- Personalize medicine using novel technologies
  - Using genetic tests and/or genotyping methods
  - Example: AmpliChip™ CYP450
- Optimize drug development

Molecular Biology 101

- What is a polymorphism?
  - Defined as a variation in DNA sequence
    - If present < 1% of population, known as a mutation
    - If present ≥ 1% of the population, known as a genetic polymorphism
  - Types of polymorphism
    - Single nucleotide polymorphism (SNP; pronounced ‘snip’)
    - Other types of polymorphisms include more than one nucleotide change, or an entire gene insertion or deletion, or ‘extra copies’ of a gene

Pharmacogenomic Nomenclature

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Systematic Approach to Understanding Polymorphisms

- Identify the polymorphism and what can be affected by the polymorphism?
  - Enzyme, transporter, receptor, disease
  - May have no functional effect
- Who is impacted?
  - Individual and population variation may exist
- Relevant to a drug?
  - May affect drug PK or PD resulting in changes in dosing, efficacy, or toxicity
  - May have no effect on a drug
- Relevant to a disease?
  - Increase or decrease disease susceptibility or condition
  - Utility as a screening or diagnostic tool

Definition of an Allele

- What is an allele?
  - The variant [and wild type] forms of a gene at a particular location on a chromosome. (National Human Genome Research Institute, http://www.genome.gov/10002096)
  - Humans are diploid organisms
    - Humans will generally have two copies of every chromosome; thus we will have 2 copies of the same gene
    - Each nucleotide base in the gene can be considered an allele
    - One allele is from your biological mother
    - One allele is from your biological father

Allele Numeric/Alphabetic Nomenclature

- Example: VKORC1 1173 C
- Example: VKORC1 1173 T
  - The first few letters/numbers identify the gene (e.g., VKORC1)
  - Numbers indicate the location of the nucleotide on the gene (e.g., 1173)
  - The letter C and T represent a nucleotide
    - Which is the wild type allele? Variant allele?

SNP Nomenclature

- Example: VKORC1 1173 C >T
- Example: ABCB1 3435 C >T
- The first few letters/numbers identify the gene (e.g., VKORC1, ABCB1)
  - Numbers following the gene indicate the nucleotide on the gene (e.g., 1173, 3435)
  - The first letter represents the original (or wild-type) nucleotide (e.g., C)
  - The second letter represents the nucleotide that has changed to result in the SNP (e.g., T)
Allele “Star” Nomenclature

• Allele nomenclature can also be…
  – Example: CYP2C19 *1 (CYP2C19)
  – Example: CYP2C19 *2 (CYP2C19 681 G > A)
  – Example: CYP2C19 *3 (CYP2C19 636 G > A)
    • The first few letters/numbers identify the gene (e.g., CYP2C19)
    • The * (star) and number after the gene designate the allele
  – Relevance
    • CYP2C19 function varies based on the allele (see next slide)

Allele “Star” Nomenclature

• Relevance
  – CYP2C19 function varies based on the allele
    – *1 allele = normal (wild-type) enzyme activity
    – *2 allele = no enzyme activity
    – *3 allele = no enzyme activity
  – But for another enzyme, CYP2C9
    – *1 allele = normal (wild-type) enzyme activity
    – *2 allele = decreased enzyme activity
    – *3 allele = decreased enzyme activity
  – Key point: Allele nomenclature can look exactly the same but have different functional effects based on the specific protein

Reference SNP (rs) Nomenclature

• The “rs” naming system is used in the SNP database (dbSNP)
  – dbSNP is the single database for all genetic variation information
  – Recommended by Human Genome Variation Society to be the standard nomenclature for SNPs
• Recall earlier example:
  – CYP2C19 *3 is the same as
  – CYP2C19 636 G > A
• Using the “rs” system, it is the same as
  – rs4986893

Genotype Nomenclature

• What is a genotype?
  – Each individual carries 2 alleles of each gene
  – The 2 alleles that any individual has represents his/her genotype
  – Example:
    • Allele of interest is the *2 allele for CYP2C19
    • Genotype = CYP2C19*2/*2
  – Consider your genotype in relation to drug metabolism
    – CYP2C19*1/*1 = normal (or wild type) enzyme activity
    – CYP2C19*2/*2 or *1/*3 = reduced enzyme activity
    – CYP2C19*2/*2, CYP2C19*2/*3, CYP2C19*3/*3 = no enzyme activity
Haplotype Nomenclature

• What is a haplotype?
  – A set of alleles at multiple loci or areas of a gene that co-exist on the same chromosome (Genetics Home Reference by the U.S. National Library of Medicine http://ghr.nlm.nih.gov/glossary)
  – When a higher frequency of the set of alleles co-exist than would be predicted by random chance = linkage disequilibrium (Genetics Home Reference by the U.S. National Library of Medicine http://ghr.nlm.nih.gov/glossary)
• VKORC1 example
  – There are at least 10 SNPs of VKORC1 that may have a functional effect
  – How would you simultaneously describe the multiple SNPs that may co-exist in an individual?
    • Haplotype A
    • Haplotype B

Polymorphism Types

• Single nucleotide polymorphism (SNP; pronounced ‘snip’)
  – A single base substitution occurs within a gene
  – Several million have been identified
  – SNPs may or may not alter protein synthesis
• Coding SNP types
  – Synonymous
  – Non-synonymous
  – Premature stop codon
• Other polymorphism types
  – Gene deletion
  – Copy number variant

Patient Case #1

• 35 year old Asian female complains of dyspepsia & epigastric pain. Denies N/V and blood in stools. Urea breath test is positive. She is diagnosed with H. pylori peptic ulcer disease.
• PMH:
  – No other significant past medical history
  – NKDA
• Medications: Begins 10-day course of omeprazole, amoxicillin, and clarithromycin
• Questions:
  – What is the primary enzyme responsible for omeprazole metabolism?
  – Does a polymorphism exist for this enzyme?
    • Anticipated effect on H. pylori cure rate (omeprazole pharmacodynamics)?
Synonymous SNP P-Glycoprotein (P-gp)

- **Nomenclature:** ABCB1 3435C > T (Hoffmeyer et al 2000)
  - Nucleotide change occurs (C > T), yet the resultant amino acid (Isoleucine) is unchanged from the reference DNA sequence
  - Functional effect: No clear consensus if there is an effect on P-gp function or expression
  - Affected drugs: Efavirenz, Cyclosporine

Reference or ‘wild type’ nucleotide sequence

\[
\begin{align*}
\text{GTG} & \quad \text{TCA} & \quad \text{CAG} & \quad \text{GAA} & \quad \text{GAG} & \quad \text{ATC} \\
\text{Val} & \quad \text{Ser} & \quad \text{Gln} & \quad \text{Glu} & \quad \text{Glu} & \quad \text{Ile}
\end{align*}
\]

Subsequent amino acid sequence

**P-glycoprotein polymorphism – nucleotide sequence**

\[
\begin{align*}
\text{GTG} & \quad \text{TCA} & \quad \text{CAG} & \quad \text{GAA} & \quad \text{GAG} & \quad \text{T}
\end{align*}
\]

Subsequent amino acid sequence

Val | Ser | Gln | Glu | Glu | Ile

**Non-Synonymous SNP TPMT**

- **Nomenclature:** TPMT*3A
  - TPMT = Thiopurine methyltransferase
  - Two nucleotide changes occur (Tai et al 1996; Weinshilboum et al 2001)
    1. **TPMT 615 G > A** results in an amino acid change (Alanine > Threonine)
    2. **TPMT 874 A > G** results in an amino acid change (Tyrosine > Cysteine)

Reference or ‘wild type’ nucleotide sequence

\[
\begin{align*}
\text{G} & \quad \text{CA} & \quad \text{TTA} & \quad \text{AAG} & \quad \text{T}
\end{align*}
\]

Subsequent amino acid sequence

Val | Ser | Gln | Glu | Glu | Ile

TPMT*3A polymorphism – nucleotide sequence

\[
\begin{align*}
\text{G} & \quad \text{CA} & \quad \text{TTA} & \quad \text{AAG} & \quad \text{T}
\end{align*}
\]

Subsequent amino acid sequence

Val | Ser | Gln | Glu | Glu | Ile

**Premature Stop Codon SNP CYP2C19**

- **Nomenclature:** CYP2C19*3
  - Nucleotide change occurs (G > A), the reference amino acid (Tryptophan) is no longer coded, and results in termination of protein synthesis (Demorais et al 1994)
  - Functional effect: CYP2C19*3 results in no enzyme activity
  - Affected drugs: Proton Pump Inhibitors (Omeprazole, Lansoprazole)

Reference or ‘wild type’ nucleotide sequence

\[
\begin{align*}
\text{ACC} & \quad \text{CCC} & \quad \text{TGG} & \quad \text{ATC} & \quad \text{CAG}
\end{align*}
\]

Subsequent amino acid sequence

Thr | Pro | Ile | Gln

CYP2C19*3 polymorphism – nucleotide sequence

\[
\begin{align*}
\text{ACC} & \quad \text{CCC} & \quad \text{TAG} & \quad \text{ATC} & \quad \text{CAG}
\end{align*}
\]

Subsequent amino acid sequence

Thr | Pro | STOP | - | -
CYP2C19 Genotype and Omeprazole Pharmacokinetics

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Omeprazole Exposure (Mean ± SD)</th>
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<tr>
<td>CYP2C19*1/*1</td>
<td>384 ± 64</td>
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<tr>
<td>CYP2C19*1/*2</td>
<td>1002 ± 532</td>
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<tr>
<td>CYP2C19*1/*3</td>
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</tr>
<tr>
<td>CYP2C19*2/*2</td>
<td></td>
</tr>
<tr>
<td>CYP2C19*2/*3</td>
<td>5590 ± 294</td>
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<tr>
<td>CYP2C19*3/*3</td>
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</table>

Omeprazole Pharmacodynamics & H. pylori Cure Rates

Gene Deletion CYP2D6

- Nomenclature: CYP2D6*5
  - Not just a single nucleotide polymorphism, but thousands of nucleotide base pairs that comprise the CYP2D6 gene are deleted (Gaedigk et al 1991)
  - Functional effect: Loss of function (or null activity) for CYP2D6
  - Results in a poor metabolizer (PM) phenotype
  - Affected drugs: SSRIs, tamoxifen, codeine, β-blockers

Other polymorphism types

Reference (or original) sequence of genes

CYP2D6*5 gene deletion
Copy Number Variant

**CYP2D6**

- Nomenclature: *CYP2D6*2XN
  - Extra copies of the CYP2D6 gene are present (N = 2,3,4,5,13) (Dahl et al 1995)
  - Results in an ultra rapid metabolizer (UM) phenotype
  - Affected drugs: SSRIs, tamoxifen, codeine, β-blockers

**Reference (or original) sequence of genes**

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**CYP2D6*2XN copy number variation**

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Systematic Approach to Understanding Polymorphisms

- Identify the polymorphism and what can be affected by the polymorphism?
  - CYP2C19 enzyme
  - CYP2C19*3 allele results in no CYP2C19 activity
- Who is impacted?
  - Frequency of the CYP2C19*3 allele higher in Asian populations
- Relevant to a drug?
  - Omeprazole plasma concentrations and exposure are higher in individuals with the CYP2C19*3 allele compared to those with the CYP2C19*1 allele
- Relevant to a disease?
  - *H. pylori* cure rates vary based on CYP2C19 genotype in patients who are on omeprazole-containing regimens

Patient Case #1 Summary

- Patient purchased a commercially available genotyping kit
  - Result: Patient’s genotype was CYP2C19*3/*3

- *H. pylori* cure rate anticipated to be 100% in patients with the CYP2C19*3/*3 genotype (Furuta et al 1998)

- Patient completed 10 day course of omeprazole, amoxicillin, and clarithromycin
  - Symptoms of dyspepsia and epigastric pain resolved
  - Patient was *H. pylori* negative and considered cured

Example Therapeutic Area: Infectious Diseases
**Therapeutic Area Discussion**

- **Format**
  - Patient case
  - Gene/Allele of interest
  - Functional effect
  - Population prevalence
  - Clinical relevance (dosing/selection, efficacy, and toxicity)
  - Genomic test and testing recommendation
  - Patient case summary

---

**Patient Case #2**

- 29-year old Caucasian male with HIV presents to clinic with fever, GI upset and skin rash on forearms and trunk
- Labs:
  - Viral load: 50,000 copies
  - CD4 count: 100/mm³
- Allergies: NKDA
- Medications (x 3 months): abacavir, zidovudine, efavirenz, sulfamethoxazole-trimethoprim
- Questions:
  - Cause of rash?
  - Testing recommended?
  - Intervention?

---

**Infectious Diseases: Abacavir**

- **Gene/Allele:** HLA-B*5701
- **Functional Effect**
  - Presence of allele confers high risk of abacavir-induced hypersensitivity reaction (HSR)
  - Symptoms of HSR may include fever, rash, GI and respiratory symptoms and general malaise
- **Population Prevalence**
  - Of those initiating therapy with abacavir:
    - Caucasians: 5-8% (Hetherington S et al 2001, Lucas A et al 2007)
    - Asians: 0-2%; Hispanics: 1%; African-Americans: 0.5% (Chui C 2007, Maiers M 2007)

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**Abacavir: Clinical Relevance**

- **Dosing/Selection**
  - Dosing is not affected by pharmacogenomic testing but drug selection may be affected
- **Efficacy**
  - No literature related to how pharmacogenomics impacts drug efficacy
- **Toxicity**
  - PREDICT-1 study showed that HLA-B*5701 screening can accurately predict patients who may be at risk for abacavir hypersensitivity (Mallal et al 2008)
  - Incidence of confirmed abacavir HSR was 2.7% vs 0% in the control vs screened patients (p<0.001) (Mallal et al 2008)
Abacavir: Clinical Relevance

• Toxicity (Cont.)
  – SHAPE study showed similar trend in Whites and Blacks
    • *HLA-B*5701 screening accurately predicted 100% of abacavir HSR cases (confirmed by skin patch testing) (Saag et al 2006)
  – ARIES study investigated *HLA-B*5701 negative patients
    • <1% had clinically suspected HSR and none had positive skin patch tests at 30 weeks (Young et al 2008)

Abacavir: Genomic Test

• Genomic Test
  – HLA typing: Positive test for *HLA-B*5701 confers ↑ risk for HSR
  – In *HLA-B*5701 negative: <1% HSR; in *HLA-B*5701 positive: >70% HSR (Mallal et al 2002, Hetherington et al 2002)

Abacavir: Genomic Test

• Genomic Testing Recommendations
  – Screening for *HLA-B*5701 prior to initiation of abacavir is recommended by the Department of Health and Human Services Guidelines (U.S. DHHS 2008)
  – Patients testing positive for the *HLA-B*5701 allele should not be prescribed abacavir
  – Screening for *HLA-B*5701 is included in the black box warning (Prescribing Information)

Patient Case #2

Summary

• Patient was screened for *HLA-B*5701
  – Result: positive for *HLA-B*5701 allele
• Concluded that symptoms were due to abacavir-induced HSR, not due to other medications in regimen
• Abacavir was discontinued; other medications were continued
• Symptoms resolved with discontinuation of abacavir
• Patient continued to be monitored for worsening hypersensitivity and other complications such as hepatomegaly, lactic acidosis, toxic epidermal necrolysis, Stevens-Johnson Syndrome
• Patient was not re-challenged with abacavir
Ethical, Legal, Social Issues (ELSI) & Economics

Ethical Issues

- Ethical
  - Loss of privacy
  - Whom do we test?
    - Genetic profiling
    - Discrimination/stigmatization
  - Distributive justice
    - Assess equitable distribution of benefits to patient populations
  - Prevention strategies (aimed at public health at large)
    - Genotypic versus phenotypic prevention
  - Clinical decisions
    - Should the test be ordered?
    - What should be done with test result?

Legal Issues

- Case Presentation
  - Equal Employment Opportunity Commission (EEOC) filed suit against the Burlington Northern Santa Fe (BNSF) Railroad for secretly testing its employees for predisposition to a rare genetic condition (carpal tunnel syndrome)
  - Genetic testing for other medical conditions (e.g. diabetes, alcoholism)
  - BNSF employees not informed of genetic testing and threatened with possible termination if they did not comply
  - EEOC argued that tests were unlawful under the Americans with Disabilities Act because tests were not job-related
  - BNSF settled lawsuit with EEOC and stopped testing in 2002

Legal Issues

- Legislature
  - Genetic Information Nondiscrimination Act (GINA) of 2008 protects Americans against discrimination based on genetic information when it comes to health insurance and employment
- Questions to consider:
  - If testing is recommended, are clinicians liable if they do not offer test or do not order test?
  - If adverse drug reaction occurs, who is responsible?
- Resource
  - National Human Genome Research Institute. Available at: www.genome.gov/24519851
  - University of Michigan Center for Public Health and Community Genomics. Available at: http://www.sph.umich.edu/genomics/
Social Issues

- Social
  - Health disparities
  - Limitation of race-based therapeutics
- Employment
- Insurance
  - Loss of coverage
  - Increase in premiums
  - Life, disability and long-term care insurance
- Access to test results and unfair risk assessment for coverage
- Societal benefits and burdens
  - Mandatory versus voluntary screening

Examples of Pharmacogenomics Tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test</th>
<th>Self-Pay Cost</th>
<th>Contract Cost</th>
<th>Specimen</th>
<th>Result In</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>AmPliChip CYP450</td>
<td>$750-1,470</td>
<td>$1,225</td>
<td>Whole blood</td>
<td>8-10 days</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B*1502</td>
<td>$489</td>
<td>$185</td>
<td>Whole blood, Buccal swab</td>
<td>5 days</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Tamoxifen CYP2D6</td>
<td>$589</td>
<td>$490</td>
<td>Whole blood</td>
<td>5 days</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2IHC</td>
<td>$333</td>
<td>$277</td>
<td>Formalin-fixed paraffin-embedded tumor tissue</td>
<td>3-7 days</td>
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<td></td>
<td>HER2/CEP17, FISH</td>
<td>$878</td>
<td>$731</td>
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<td>Azathioprine</td>
<td>PredicRx TPMT</td>
<td>$395</td>
<td>$395</td>
<td>Whole blood</td>
<td>2 days</td>
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<tr>
<td>Irinotecan</td>
<td>Invader</td>
<td>$75</td>
<td>NA</td>
<td>Whole blood, Buccal swab</td>
<td>5-7 days</td>
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<tr>
<td>Warfarin</td>
<td>CYP2C9 and VKORC1</td>
<td>$517</td>
<td>$517</td>
<td>Whole blood, Buccal swab</td>
<td>10 days</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA-B*5701</td>
<td>$157</td>
<td>$157</td>
<td>Whole blood, Buccal swab</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Reference: PharmGenEd™ team personal communication with select laboratories (Jan – Feb, 2009)

Health Economics & Cost Implications to Public Health

- Evidence needed to support cost-effectiveness of pharmacogenomic tests
  - Need good evidence-based rationales (Vegter et al 2008)
  - Willingness to pay from payers variable (Williams MS 2007)
- Unlikely to disrupt the current public health system
  - Gradual and incremental progression
  - Our system has flexibility to adapt (Garrison et al 2008)

Opportunities in Clinical Practice

- Develop clinical guidelines and standard of care
- Apply pharmacogenomics into clinical practice and research
- Provide informed consent and patient counseling
  - Confidentiality and privacy
- Evaluate impact of cost and coverage for patients and healthcare systems
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