PharmGenEd™: Bridging the Gap Between Science & Practice

Concepts and Clinical Applications

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UNIVERSITY of CALIFORNIA, SAN DIEGO
SKAGGS SCHOOL of PHARMACY
and PHARMACEUTICAL SCIENCES

Disclaimer

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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

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)

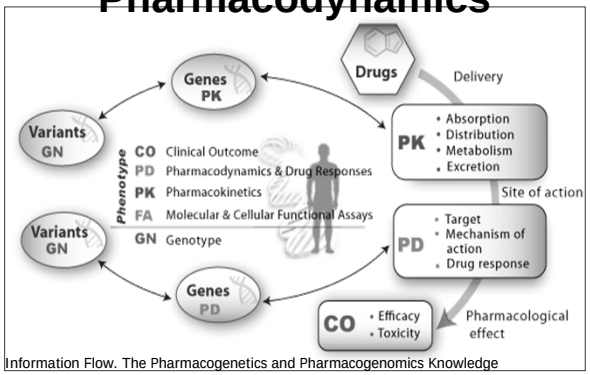
Practice Gap

- 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

- Pharmaco***genetics***
  - "the study of genetic causes of individual variations in drug response" (American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group)
- Pharmaco***genomics***
  - "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



PGx Information Flow. The Pharmacogenetics and Pharmacogenomics Knowledge Base, https://www.pharmgkb.org/index.jsp. Use of image granted permission from PharmGKB and the Dept. of Genetics, Stanford U-School of Medicine.

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

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Pharmacogenomic Nomenclature

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

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*1/*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)?

Coding SNP Types

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

GTG	TCA	CAG	GAA	GAG	AT**C**

Subsequent amino acid sequence

Val	Ser	Gln	Glu	Glu	**Ile**

P-glycoprotein polymorphism – nucleotide sequence

GTG	TCA	CAG	GAA	GAG	AT**T**

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)
  - Functional effect: Decreased *TPMT* enzyme activity
  - Affected drugs: Azathioprine, 6-mercaptopurine

Reference or 'wild type' nucleotide sequence

GCA	TTA	AAG	TTA	T**A**T	CTA

Subsequent amino acid sequence

Ala	Leu	Lys	Leu	**Tyr**	Leu

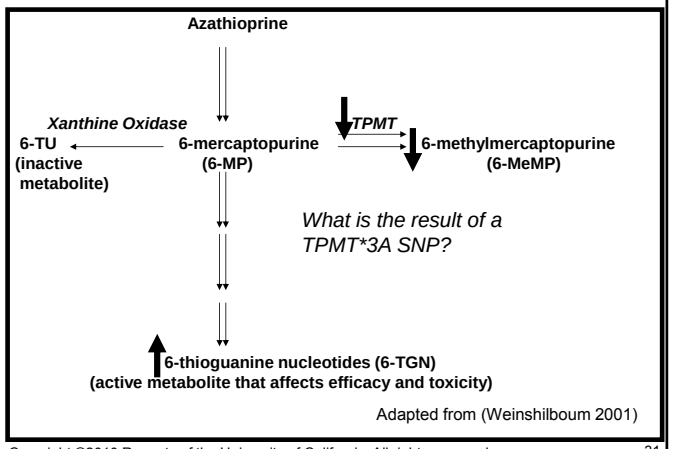
TPMT*3A polymorphism – nucleotide sequence

ACA	TTA	AAG	TTA	T**G**T	CTA

Subsequent amino acid sequence

Thr	Leu	Lys	Leu	**Cys**	Leu

Non-Synonymous SNP *TPMT*



Adapted from (Weinshilboum 2001)

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

ACC	CCC	T**G**G	ATC	CAG

Subsequent amino acid sequence

Thr	Pro	**Trp**	Ile	Gln

CYP2C19*3 polymorphism – nucleotide sequence

ACC	CCC	T**A**G	ATC	CAG

Subsequent amino acid sequence

Thr	Pro	**STOP**	-	-

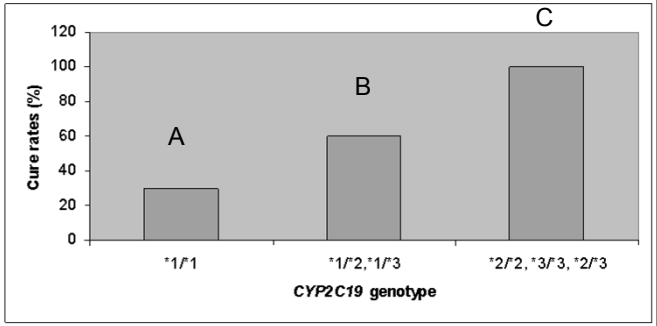
CYP2C19 Genotype and Omeprazole Pharmacokinetics

Genotype	Omeprazole Exposure (Mean + SD)	
*CYP2C19*1/*1*	384	64
*CYP2C19*1/*2*	1002	532
*CYP2C19*1/*3*		
*CYP2C19*2/*2*		
*CYP2C19*2/*3*	5590	294
*CYP2C19*3/*3*		

Drug X —*CYP2C19*3/*3*→ *Metabolite Y*

(Furuta et al 1999)

Omeprazole Pharmacodynamics & *H. pylori* Cure Rates



p < 0.05 for A vs B and A vs C (Adapted from Furuta et al 1998)

Other polymorphism types

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

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

*CYP2D6*2XN copy number variation*

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

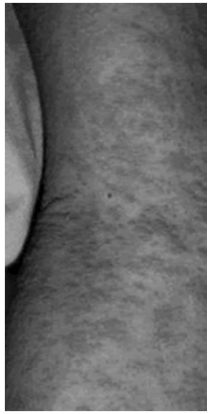
Example Therapeutic Area: Infectious Diseases

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/mm^3
- Allergies: NKDA
- Medications (x 3 months): abacavir, zidovudine, efavirenz, sulfamethoxazole-trimethoprim
- Questions:
  - Cause of rash?
  - Testing recommended?
  - Intervention?



Highleyman L, 2008. www.hivandhepatitis.com/recent/2008/101008_c.html. Use of image granted permission from HIV and Hepatitis.com. For educational use only, not for commercial reproduction

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)

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 2008)
  - 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

Drug	Test	Self-Pay Cost	Contract Cost	Specimen	Result In
SSRI	AmPliChip CYP450	$750-1,470	$1,225	Whole blood	8-10 days
Carbamazepine	HLA-B*1502	$489	$185	Whole blood Buccal swab	5 days
Tamoxifen	Tamoxifen CYP2D6	$589	$490	Whole blood Buccal swab	5 days
Trastuzumab	HER2IHC	$333	$277	Formalin-fixed paraffin-embedded tumor tissue	3-7 days
	HER2/CEP17, FISH	$878	$731		
Azathioprine	PredictRx TPMT	$395	$395	Whole blood	2 days
Irinotecan	Invader	$75	N/A	Whole blood Buccal swab	5-7 days
	UGT1A1	$441	$368		
Warfarin	CYP2C9 and VKORC1	$517	$517	Whole blood Buccal swab	10 days
Abacavir	HLA-B*5701	$157	$157	Whole blood Buccal swab	5 days

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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