Pharmacogenetic Testing in Primary Care

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Objectives

► Discuss the foundational pharmacogenomics principles.

► Define basic genomic concepts and nomenclature.

► Review existing evidence and guidelines for use of pharmacogenomics in clinical decision making.

► Describe the considerations for selecting a pharmacogenomics test.

► Apply pharmacogenomic test results to make clinical recommendations.

I have no disclosure to report relevant to this presentation.
**DNA Organization**

- **Chromosome**
  - Composed of two longitudinal sister chromatids

- **Human genome contains >20,000 genes**

- **DNA Structure**
  - Composed of 3 billion DNA base pairs per cell
DNA

- Genetic information is stored in DNA and decoded by translation into a protein
- DNA Chemical Bases
  - A (Adenine)  T (Thymine)
  - G (Guanine)  C (Cytosine)
- 3 bases = 1 codon = 1 amino acid
- 2 or more amino acids = peptide
- ~50 or more amino acids = protein

Codon

- Codons are 3 nucleotides that code for an amino acid
Protein Formation

• 20 amino acids
• Proteins are chains of amino acids called polypeptides
• Polypeptide chains fold into a shape that is biologically active

Genomics versus Genetics

• Genomics - the study of the entire genome of an organism
• Genetics - the study of a particular gene

https://www.genome.gov/glossary/

Introduction to Genetics

Genotype = genetic constitution, alleles present at one locus
• Allele
• Locus

Phenotype = manifestation of the genotype
• Physical, biochemical, or physiological characteristics of an individual

Variable expressivity – phenotypic differences in same genotype
Genotype vs. Phenotype

**Genotype** is the name given to all the genes, even if they are not expressed.
- Instructions on how the body is supposed to be built and function

**Phenotype** is what you actually see expressed by the genotype
- Affected by environment (including illness and diet)
- Other unknown factors

Polymorphism

- Natural variation in a gene, DNA sequence, or chromosome that has no adverse effects on the individual
- Can be as small as a single change to any one of the 3 billion nucleotides,
  - e.g., from an A to a T or a G to a C
  - Or the change can be much larger
- A polymorphism is a genetic variant that appears in at least 1% of a population

Mutations (Pathogenic Variants)

Disease-associated (‘deleterious’) change in DNA – wrong or no protein

Mutations in DNA sequences generally occur through one of two processes:
- DNA damage from environmental agents such as tobacco, ultraviolet light, nuclear radiation or chemicals
- Mistakes that occur when a cell copies its DNA in preparation for cell division.
Gingerbread Recipe

Polymorphism
- 2 teaspoons ginger
- 2 eggs
- 2 cups flour
- 1 stick butter

Mutation
- 2 teaspoons ginger
- 2 eggs
- 2 cups flour
- 1 stick butter

Nucleotide
3 parts:
- Phosphate backbone
- 5 carbon sugar
- Base
  - Adenine
  - Cytosine
  - Guanine
  - Thymine

SNP ("snip"): Single nucleotide polymorphism
- Most common type of genetic variation among people
- Each SNP represents a difference in a single DNA building block (nucleotide)
- AAGCTTA to AAGCTTA
- occur normally throughout a person’s DNA
- occur once in every 300 nucleotides on average
- roughly 10 million SNPs in the human genome
SNPs

- Predict an individual’s response to certain drugs
- Susceptibility to environmental factors such as toxins
- Risk of developing particular diseases
  - Some SNPs increase risk of disease
  - Some SNPs protective against disease
- Direct to Consumer Testing e.g. 23andMe
- Gene discovery

Breast Cancer

- Persons may be at elevated risk for certain cancers based on their personal history, lifestyle, and family history.
- You are working in the High Risk Breast Clinic and need to calculate the lifetime risk of breast cancer for the new patient, Ms. Smith.
- Ms. Smith is a 39 year old white G3P2 premenopausal female with history of menarche age 12, use of OCPs for 7 years, left-sided breast biopsy was performed at age 37 and was negative for atypical cytology, and age of first live birth was 28.
- Ms. Smith’s family history is notable for the following; mother diagnosed with breast cancer at age 39 and maternal aunt was diagnosed and died with breast cancer at age 35.
Gail Model

Based on the information provided, apply the Gail Model risk estimation models to calculate the lifetime risk of breast cancer for Ms. Smith.

Gail Model (http://bcra.nci.nih.gov/brc/start.htm)

- 12%
- 37%
- 23%
- 15%

Breast Cancer Prevention

- Tamoxifen
- Raloxifene

Newborn screening

- State public health service – 4 million babies per year in US.
- Started in the 1960s- Robert Guthrie MD, PhD – blood test could detect metabolic disorder, phenylketonuria (PKU).
- Babies with PKU are missing an enzyme (phenylalanine hydroxylase) needed to break down an essential amino acid called phenylalanine– substance is found in foods that contain protein.
- Variability on each state’s newborn screening panel determined by state public health dept.
- Not a diagnostic test, need follow-up testing.
Newborn Genetic Screening

Amino Acid Disorders
- Diethylenetriamine

Congenital Adrenal Hyperplasia

Congenital Hypothyroidism

Critical Congenital Heart Disease (CCHD)

Cystic Fibrosis

Fabry

Fatty Acid Disorders

Gaucher

Hereditary fructose intolerance (Sickle Cell Anemia)

Krabbe

MPS I

Organic Acid Disorders

Phosphatidylsulfate (PSS)

Pompe

Severe Combined Immunodeficiency (SCID)

https://www.tn.gov/health/topic/MCH

Indications for Pediatric Genetics Consultation

• Developmental Delay
• Intellectual Disability
• Dysmorphic features
• Family History of...
• Failure to Thrive
• Atypical Growth

Genetic Evaluation of Individuals with Autism

• Clinical Genetics Evaluation in Identifying the etiology of Autism Spectrum Disorders
  * CMA- 10%
  * Fragile X- 1-5%
  * MECP2- 4% in females
  * PTEN- 5% with macrocephaly
  * Karyotype- 3%
  * "Other"- 10%
  * Total- 30-40%

**Percentages prior to large molecular panels ES
Genetic Testing Strategies

Chromosomal Analysis
Chromosomal Microarray
Single Gene Testing
Multi-gene Panel Testing
Methylation Studies
Exome Sequencing

Chromosomal Analysis (Karyotype)
Can detect large chromosomal changes
Trisomies
Duplications
Deletions
Inversions
Translocations
Structural abnormalities (rings)

"Looking at recipe books on a shelf"
FISH studies
- "Sending a probe to a specific book"
- Limited utility unless specific question or familial studies

Chromosomal Microarray (CMA)
Uses dosage to determine if there are any deletions or duplications
SNP arrays can detect Regions of Homozygosity (which can imply family relatedness or Uniparental Disomy)

"Flipping the pages of those recipe books looking for missing or extra pages"
Specific Gene Testing

Single Gene vs Panels

Sanger Sequencing vs Next Sequencing

“Reading a sentence(s) from the recipe book and running spell check”

Exome Sequencing (ES)

Sequencing of the exons (protein coding regions)

Take coverage into account

Primary Findings vs Secondary Findings

“Reading the parts of the recipe book that contain the recipes”
Cystic Fibrosis

Most common, deadly, inherited disorder affecting Caucasians in the US. Northern or Central European descent.

**CFTR gene**

- 1 in 29 Caucasian Americans have the defective CF gene.

**Autosomal Recessive**

Must inherit two defective CF genes - one from each parent.

[Link to CF gene inheritance]

CFTR Modulators

- In 2012, the first drug of this class was approved by FDA - historic breakthrough in how CF is treated – targeted the root cause.

  Cystic fibrosis transmembrane conductance regulator modulator therapies

  - correct the malfunctioning protein.

  - ivacaftor (Kalydeco®) - G551D gating mutation

  Expected to add decades of life


Case example of genetics care

2 do male infant identified as having Tetralogy of Fallot, abnormal ears, and cleft palate.

Genetics was consulted secondary to multiple congenital anomalies (MCAs) and concern for underlying genetic cause of his features.
Initial Resources and Examples: OMIM

http://omim.org/

Family Assessment

Comprehensive Family History
Important
Inexpensive
Underutilized genetic tool

“To fail to take a good family history is bad medicine”

-Barton Childs (1982)
Recognizing family risk

- Family history of known genetic disorder
- Multiple affected family members with same or related disorders
- Earlier age at onset of disease than expected for breast, ovarian, endometrial cancer < 50 yrs (premenopausal)
- Colon and prostate cancer < 50 yrs
- Stroke and noninsulin-dependent diabetes < 50 yrs
- Dementia < 60 yrs
- Coronary artery disease < 55 yrs males, < 65 yrs in females
- Sudden cardiac death in a person who seemed healthy
- Multifocal or bilateral occurrence in paired organs
- Ethnic predisposition to certain genetic disorders

My Family Health Portrait

Using My Family Health Portrait you can:
- Enter your family health history
- Share your family health history to share with family or your health care team
- Update your family health history so you can update it over time

Talking with your health care worker about your family health history can help you stay healthy.

Learn more about My Family Health Portrait.
Pedigrees & Patterns of Inheritance

• Gene
  • Hereditary unit
  • In molecular terms, a sequence of chromosomal DNA required for production of a protein

• Locus
  • Chromosomal location of a specific gene

• Alleles
  • Alternative forms of a gene at a given locus

Patterns of Inheritance

Autosomal Dominant inheritance
• Requires only one copy of a gene mutation to express the associated condition
• Phenotype is expressed in person heterozygous for a particular allele

Autosomal Recessive
• Requires two copies of a gene mutation (one from each parent) to manifest the condition
• Phenotype is expressed in person homozygous for a particular allele

![Pedigree diagram](image)
Case example for primary care

• Factor V Leiden

Factor V Leiden – Clinical Applications

• Identified in 1993 and genetic mutations have been found to cause a hereditary prothrombin condition associated with deep venous thrombosis (DVT).

• Mutations for Factor V Leiden occur in about 5% of Caucasians and are absent in Asians and Blacks.

• Heterozygotes have 4 to 10 times and homozygotes have 50 to 100 times the risk of DVT of the general population.


DVT

• Potential to cause pulmonary emboli and death.

• Incidence of DVT is increased with use of oral contraceptives.

• Two risk factors for DVT, oral contraceptives and Factor V Leiden mutation, interact.

• In women without the genetic mutation in Factor V Leiden, incidence of DVT rises from 0.8/10,000 women per year among those not on oral contraceptives to 3.0/10,000 women per year for those taking the pill.

• The baseline incidence of DVT in heterozygotes with a Factor V Leiden mutation is 5.7/10,000 women per year, rising to 28.5/10,000 women per year among those taking oral contraceptives.

Factor V Leiden

Calculate the following and enter the correct answer:

Absolute risk of DVT in women who neither have the Factor V Leiden mutation nor take oral contraceptives.
• 5.7/10,000/year
• 1.2/10,000/year
• 3.0/10,000/year
• 0.8/10,000/year

Factor V Leiden

Calculate the following and enter the correct answer:

Absolute risk of DVT in women who do not have the Factor V Leiden mutation but take oral contraceptives.
• 5.7/10,000/year
• 1.2/10,000/year
• 3.0/10,000/year
• 0.8/10,000/year

Factor V Leiden

Calculate the following and enter the correct answer:

Absolute risk of DVT in women who are heterozygous for the Factor V Leiden mutation but do not take oral contraceptives.
• 5.7/10,000/year
• 1.2/10,000/year
• 3.0/10,000/year
• 0.8/10,000/year
Factor V Leiden

To consider...

Would you prescribe oral contraceptives to a woman with a known Factor V Leiden mutation who is requesting birth control with OCPs and states she is aware of the risks discussed?

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Red Flags for Inherited Cancer

- Cancer diagnosed young
- Cancer in multiple family members across generations
- A person with multiple cancers
  - Same organs
  - Different organs
- Certain ethnic backgrounds
- Some tumor study results
Hereditary Breast and Ovarian Cancer

**BRCA1**: chromosome 17, cloned in 1994

**BRCA2**: chromosome 13, cloned in 1995

Lifetime risk of breast cancer is 45-87%

Lifetime risk of ovarian cancer:

- **BRCA1**: 40%
- **BRCA2**: 20%

Comparing Sequencing Technology

- **Sanger Sequencing**
  - Historical “gold standard”
  - 2 reads per base pair (forward and reverse)

- **Next Generation Sequencing**
  - Massively parallel sequencing
  - 100s – 10000s of reads per base pair

Why is inherited cancer important to identify?

- Using Inherited Breast Cancer as an example:
Multi-Gene Testing Options

Patients who are eligible for genetic testing can have all cancer related genes tested for initially.

Now this can be done upfront along with BRCA testing, with less cost, less time and more answers…

Next Generation Sequencing
sequence multiple genes simultaneously

Fanconi Anemia-BRCA DNA repair pathway

Multi-gene test examples:
- BRCApal
- BreastNext
- OvaNext
- ColoNext
- PancNext
- RenalNext
- PGLNext
- CancerNext
Hereditary Non-Polyposis Colorectal Cancer/Lynch Syndrome

Amsterdam Criteria 3-2-1 rule
3 relatives with colorectal cancer in family
2 or more generations
1 is a first-degree relative of the other 2
1 < 50 years

Amsterdam II
3 relatives with colorectal or other HNPCC cancer
• Colon
• Endometrium
• Small bowel
• Ureter
• Renal pelvis


Lynch Syndrome

Results from a mutation in one of the mismatch repair genes (MMR)
- MLH1, MSH2, MSH6, PMS2, EPCAM

- Autosomal dominant inheritance
- Microsatellite instability- in 80-90% of cases
- Can screen by testing colon cancer tumors –
- Test for microsatellite instability – if +, pt completes germline testing for MMR genes

NCCN Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Colorectal Cancer Screening, Version 1, 2018
Healthy People 2020 Genomics

- Goal - Improve health and prevent harm through valid and useful genomic tools in clinical and public health practices.

- All individuals newly diagnosed with colorectal cancer offered testing for a hereditary form of colorectal cancer - Lynch syndrome.

- Family members could benefit know they are at increased risk for colorectal cancer, screening interventions could reduce the risk of colorectal cancer in pts with Lynch syndrome by about 60%.

New Era

Era of genetic medicine has begun

Will challenge long held models of medical practice

Clinical care binary
- Diagnosis – Treatment
- Lack of prevention

Precision Cancer Care in the Genomic Era

- Requires genetic information for the most complete risk assessment and identification of best therapies/treatment.

PARP Inhibitor

- December 2015, a poly (ADP-ribose) polymerase (PARP) inhibitor class of medication was approved by FDA for women with ovarian cancer who were found to have a BRCA1 or BRCA2 mutation on genetic testing.

- PARP is one of the cellular mechanism for repairing single-strand DNA breaks. The use of PARP Inhibitors in women with ovarian cancer who have a BRCA mutation results in chromosomal instability, cell cycle arrest and apoptosis.

- PARP inhibition leads to cell death through a type of directed synthetic lethality, offering a targeted therapy treatment option compared to platinum-based chemotherapy.
Cisplatin & Immunotherapy

Pts with BRCA1/2 mutations more likely to respond to Cisplatin based chemotherapy. 


MSI


Precision Oncology – Emerging Model of Cancer Treatment

Tumor tissue routinely acquired for molecular diagnostics

All actionable mutations assessed

Therapy selected based on molecular characteristics

Somatic mutations
- Occur in nongermine tissues
- Cannot be inherited
- Mutation in tumor only (for example, breast)

Germline mutations
- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome
- Mutation in egg or sperm
- All cells affected in offspring

Parent

Child

Nonheritable

Heritable

Adapted from the National Cancer Institute and the American Society of Clinical Oncology
**Liquid Biopsy**

A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood.

**Cell free DNA**

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**Driver of Medical Genomics: Next Generation Sequencing**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Genomes</th>
<th>Turnaround Time</th>
<th>TEs</th>
<th>Cost per Genome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990-2003</td>
<td>1</td>
<td>~5 years</td>
<td>2,000</td>
<td>~$2.3 billion</td>
</tr>
<tr>
<td>2003-2009</td>
<td>~10 additional</td>
<td>~6 months</td>
<td>Dozens</td>
<td>$300,000–38,000</td>
</tr>
<tr>
<td>2010-2014</td>
<td>$10^{10}$</td>
<td>4-8 weeks</td>
<td>3.4</td>
<td>$6,000 exome $9,500 genome</td>
</tr>
<tr>
<td>2015-2020</td>
<td>Millions</td>
<td>15 minutes</td>
<td>&lt;&lt;1</td>
<td>$100-250</td>
</tr>
</tbody>
</table>

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**Pharmacogenetics**

- **Pharmacogenetics** is the study of inherited genetic differences in drug metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.

- Believed to account for inter-ethnic differences in adverse events and efficacy profiles of many widely used drugs.
  - Asian, Caucasian, African descent
Pharmacogenomics: PharmGKB

https://www.pharmgkb.org/

CPIC guidelines

Standardized system for grading levels of evidence
- linking genotypes to phenotypes,
- how to assign phenotypes to clinical genotypes,
- prescribing recommendations based on genotype/phenotype
- standard system for assigning strength to each prescribing recommendation.

https://cpicpgx.org/guidelines/
Case example- Codeine

- Healthy 2-year-old boy, wt of 13 kg, underwent elective adenotonsillectomy.
- Outpatient surgery uncomplicated
- Prescribed 10-12.5 mg of codeine and 120 mg of acetaminophen syrup po q4 to 6 h prn pain
- On post-op day 2, the child's vital signs were absent, and resuscitation efforts failed.
- Why?
  - He was prescribed and administered a dose of codeine within the recommended range 1 to 3 mg per kilogram of body weight per day.

Prescribing Considerations

- Dosage
- Formulation
- Schedule
- Body size and composition
- Age
- Disease states – liver, kidney dysfunction
- Interactions – drug/drug, drug/food
- Genetics?

CYP2D6

- Cytochrome P-450 2D6 (CYP2D6) genotyping revealed functional duplication of the CYP2D6 allele, resulting in the ultrarapid-metabolizer phenotype.
- Increased conversion of codeine to morphine due to ultrarapid metabolism resulted in toxic accumulation of morphine.
Preemptive Clinical Pharmacogenetics

Develop process to perform pharmacogenetic testing and use results in routine clinical care.

Codeine Metabolized by an enzyme that is genetically regulated called CYP2D6

\[ \text{Codeine} \rightarrow \text{CYP2D6} \rightarrow \text{Morphine (analgesic activity)} \]

Migrate pharmacogenetics tests from laboratory to routine patient care.

CYP2D6 - responsible for the metabolism of many commonly prescribed drugs -
Analgesics, antidepressants, beta-blockers, anti-psychotics

Striking population (ethno-graphic) differences - 30% of Asians and individuals of Asian descent are intermediate metabolizers.

CYP2D6

Nearly 90% of general population OK, but 10% has inactive copies = codeine has no analgesic effect

2-5% ultrarapid metabolizer

We have known this for greater than 25 years yet CYP2D6 is not considered when prescribing.

Could have dead prodrug or be dangerously activated; Inefficacy verses severe toxicity.
**Tamoxifen and CYP2D6**

- CYP2D6 enzyme metabolizes a quarter of all prescribed drugs.

- One of the main enzymes responsible for converting tamoxifen into its major active metabolite, endofixen.

- Variants in the CYP2D6 allele may lead to reduced ("intermediate metabolizer") or absent ("poor metabolizer") enzyme activity. Individuals who carry these variant alleles may have reduced plasma concentrations of endofixen = benefit less from tamoxifen therapy.

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**Metabolizer Status**

- **Ultra-rapid metabolizer (~1-2% of patients)**
  - Activity score > 2.0
  - An individual carrying more than two copies of functional alleles (*1/*1xN, *1/*2xN)
  - Increased formation of morphine following codeine administration, leading to higher risk of toxicity
  - Avoid codeine use due to potential for toxicity.
  - Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics.

- **Extensive metabolizer (~77-92% of patients)**
  - Activity score 1.0-2.0
  - An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele (*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10)
  - Normal morphine formation
  - Use label recommended age- or weight-specific dosing.

- **Intermediate metabolizer (~2-11% of patients)**
  - Activity score 0.5
  - An individual carrying one reduced and one nonfunctional allele (*4/*10, *5/*41)
  - Reduced morphine formation
  - Use label recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a non-opioid.
  - Monitor tramadol use for response.

- **Poor metabolizer (~5-10% of patients)**
  - Activity score 0
  - Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief
  - Avoid codeine use due to lack of efficacy.
  - Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics.
  - Tramadol, and to a lesser extent hydrocodone and oxycodone, are not good alternatives because their metabolism is affected by CYP2D6 activity; these will be less effective for patients who are poor metabolizers.

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### Pharmacogenetic implementation with available practice guidelines

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR</td>
<td>Ivacaftor</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Codeine</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
</tr>
<tr>
<td></td>
<td>SSRIs</td>
</tr>
<tr>
<td></td>
<td>TCAs</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Irinotecan</td>
</tr>
</tbody>
</table>

### Barriers to Integration

- Fragmentation of our health care system.

- Health care delivery systems and incentive structures are focused on sick care, not disease prevention or avoiding adverse effects.

- Complexity of the lab results.

- Lack of computational decision support.

### Primary Care genetic tests

- ADHD
- Analgesic
- MTHFR
- Psychotropic
Major Depression: Five or more for two weeks or longer

Treating Depression with Medication

- Treating depression with medication is a trial-and-error process.
  - (Arango, Kapur, & Kahn, 2015).

- 50% of those taking medication for depression will see no improvement
- Of those who do, 70% will have tried four or more medications (Bousman et al., 2017).

- Patients who require more medication trials are less likely to experience remission and more likely to relapse in the follow up period than those who do not (NIMH, 2001).

Pharmacogenetic Testing

- Pharmacogenetic considers how a patient’s genetics influence drug response or effect.
- Testing is expensive
- It is imperative to consider the cost and benefit to the patient as pharmacogenetic testing is integrated into clinical practice
Improve safety and efficacy

► can predict quite accurately which anti-depressant a patient will best respond to by simply looking into their genetic code

► previous practice of adjusting and experimenting with different medications to get the best response


Pharmacogenetic Test Results

<table>
<thead>
<tr>
<th>Green</th>
<th>Yellow</th>
<th>Red</th>
</tr>
</thead>
</table>
| • Not noted to have significant drug-gene interactions | • Some drug-gene interactions | • Significant drug-gene interactions
| | • May require a dose adjustment | • Increased Adverse Reactions |

Commonly used Drugs with Pharmacogenomic Biomarkers in Drug Labeling

- warfarin
- citalopram (Celexa)
- celecoxib (Celebrex)
- codeine
- carvedilol (Coreg)
- glipizide (Glucoptin)
FDA label for Citalopram

**Dosage and Administration**
20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation.

**Initial Treatment**
Citalopram should be administered at an initial dose of 20 mg once daily, with an increase to a maximum dose of 40 mg/day.

Citalopram Metabolism

- Metabolism pathway includes CYP2C19 gene
- CYP2C19 gene codes for CYP2C19 liver enzyme
- Genetic testing to find out if poor metabolizer

- Genetic testing report the alleles (aka variants or versions)
  - *1, *2, *4, *8, *18... and many more
  - All common alleles

Citalopram Metabolism

- CYP2C19*2/*2 means person inherited a copy of the mutation 681G>A from both parents
- Causes poor metabolism of citalopram
- Citalopram will not be effective at a normal dose

- Higher plasma concentrations may increase the probability of side effects

- "Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation."

File:///C:/Users/mcreynk/Downloads/Citalopram_10_17_13.pdf
**CYP2C19**

- Plavix/clopidogrel bisulfate
  - blocks platelet reception
  - One of the best selling prescription drug in the world
  - different responses among patients
- GWAS studies linked the gene **CYP2C19** to those who cannot normally metabolize Plavix.
- Plavix is given to pts s/p coronary artery stent to prevent clotting.
- Stent clots — heart attack or sudden death in 1-2% of the population — those with the CYP2C19 SNP.
- Scripps and **Vanderbilt University**, patients who are candidates for heart stents are screened for the CYP2C19 variants.

**PREDICT project**

- Dr. Dan Roden –
  - Senior VP for Personalized Medicine at VUMC, Professor of Medicine, Pharmacology and Biomedical Informatics
- Pharmacogenomic Resource for Enhanced Decisions in Care and Treatment, 2010
- Applies genomic testing to drug prescribing
- Goal - to incorporate genetic data with clinically useful guidance into the VUMC Electronic Medical Record.
- 32 common polymorphisms within 10 genes associated with drug absorption, distribution, metabolism, and excretion.
- Only results for genes that have been reviewed and approved as actionable by Vanderbilt will be released into the patient chart.

**PGEN4Kids**

- St Jude Children’s Research Hospital, Memphis TN
- Clinical implementation of pharmacogenetics
- Patients agree to be tested for 230 genes that encode proteins involved in drug responses

**Sources:**

- St Jude Children’s Research Hospital, Memphis TN
- Clinical implementation of pharmacogenetics
- Patients agree to be tested for 230 genes that encode proteins involved in drug responses
Clinical pre-emptively

Clinical Research
— Test if variants are r/t phenotypic variation.
— Are outcomes better if genetics is used to guide therapy?

Clinical Implementation
— Variants already validated/proven.
— Implement pathways to routinely perform pharmacogenetics testing and apply results to clinical care.

Personalized Medicine

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Pharmacogenetics</th>
<th>Risk Assessment, Risk Modification</th>
<th>New Targets, New Drugs</th>
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</thead>
</table>

Barriers to Integration

Fragmentation of our health care system.

Health care delivery systems and incentive structures are focused on sick care, not disease prevention or avoiding adverse effects.

Complexity of the lab results.

Lack of computational decision support.
10/15/2019

1. **Outcome of the assay**: 8 Jan 2014
2. **PGx Interpretation**: High Risk of SJS/TEN from Carbamazepine

**Suggestion**: According to update information, this person has HLA-B*1502 which has a high risk to develop a severe skin disorder (SJS/TEN), if he/she takes carbamazepine or drugs with similar structure.

**Need more information? Please contact our PGx laboratory Tel 02-200-4136-3...**

**Chung et al., Nature 2004;428:486.**

**ORIGINAL ARTICLE**

**CAUTION**: This patient carries the HLA-B*15:02 allele, a known risk factor for carbamazepine-induced SJS in persons of Asian ancestry...

**ANL cephar**

**YouScript**

**Sample Card**

**Name**

**Outcome of the assay**: 8 Jan 2014

**PGx Interpretation**: High Risk of SJS/TEN from Carbamazepine

**Pharmacogenetics and Personalised Medicine**
Faculty of Medicine, Chulalongkorn Hospital

**Update information**

**Original Article**

**CAUTION**: This patient carries the HLA-B*15:02 allele, a known risk factor for carbamazepine-induced SJS in persons of Asian ancestry...

**ORIGINAL ARTICLE**

**CAUTION**: This patient carries the HLA-B*15:02 allele, a known risk factor for carbamazepine-induced SJS in persons of Asian ancestry...
Ethical, Legal and Social Issues

Privacy: Disclosure of genetic testing to at-risk family members

GINA

Paradigm shift – “virtually all medical decisions will someday be informed at least, in part, by genomics, yet it will be impossible to have a medical geneticist involved in every decision”

(Medical Genetics in Pediatric Practice, 2013; Trotter and Saul)

Resources


International Society of Nurses in Genetics http://www.isong.org

National Society of Genetic Counselors: http://www.nsgc.org/