Clinical Application of Pharmacogenomics Testing: A Tool for the Nurse Practitioner in the treatment Co-Occurring Disorders

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TheHuman Genome Project (1990-2003)

- Comprised of 20 Intuitions from 6 countries
- 13 years to complete
- Cost ~ $2.7 billion
- Identified ~ 3 billion base-pairs
- Identified ~ 20,500 human genes
- 3.7 million mapped human single nucleotide polymorphism (SNPs)

The Human Genome Project Advancements

- Fueled discovery of >1,800 disease genes
- Decreased time to screen genes suspected of causing an inherited disease to days rather than years
- >350 Biotech-based products are currently in clinical trial
- >2,000 genetic tests for human conditions available
- Provided the science for Pharmacogenomics & Pharmacogenetic (PGx) Testing

Why do some medications work for some patients, but not others?

On average, 40% of patients who take a given medication will not respond to treatment. Knowing a patient’s genetic profile can help.

Genomic variances in a patient’s metabolic pathway determine how a patient will respond to prescribed medications. Pharmacogenetic testing provides physicians with insight into individual genetic differences in their patients’ drug processing ability. Armed with this knowledge, physicians could predict the patient’s response to the majority of commonly prescribed medications allowing for precision prescription writing and better patient outcomes.

What is Pharmacogenetics?

Pharmacogenetics is the study of genetic variations that influence individual response to drugs.

Knowing whether a patient carries any of these genetic variations can help:
- Prescribes individualize drug therapy
- Decrease the chance for adverse drug events (ADEs)
- Increase the effectiveness of drugs

“One-Size-Fits-All” model

- Average patient wastes $800-$1,200/year on medications that do not work or they cannot tolerate. (Insurance Average)
- On average, a patient will take 3 or 4 different medications before reporting adequate symptom reduction (Mental Health)
- 33%-55% Rate of medication non-adherence (Mental Health)
- On average, 40% of patients who take a given medication will not respond to treatment (Mental Health)
Patient Safety

Adverse Drug Events (ADEs)
- ~850,000 ADEs annually
- >125,000 ADE deaths annually
- ~100,000 Emergency hospitalizations annually among >65 years old
- $289 Billion per year spent on ADEs

Medication Compliance
- 49% stopped at 16 weeks
- 59% stopped at 32 weeks
- “The Antidepressant wasn’t helping”
- “I was having side effects”

Personalized model

Goals of Personalized Model
- Reduction in ADEs
- Increase Therapeutic Response (Stabilization time)
- Increase Medication Compliance
- Reduce Overall Healthcare Cost (ie, RX, ER & office visits)

Personalized Medicine Approach

“Personalized medicine aims to streamline clinical decision making by using biological information available through a genetic test or biomarker, and then saying, ‘based on this profile, I think you’re more likely to respond to Drug A or Drug B, or less likely to have an adverse reaction with Drug C.’ The idea is to get patients on the right medication and to get them on it sooner.”

– Dr. Issam Zineh, Dir of Clinical Pharmacology, FDA

What Genes Are Analyzed?
- CYP450 - Responsible for drug metabolism
- COMT - Regulates Catecholamine Neurotransmitters
- SLC6A2 - Norepinephrine Transport Protein (NET)
- SLC6A4 - Serotonin Transport Protein (SERT)
- HTR2A - Serotonin Receptor Site
- HTR2C - Serotonin Receptor Site
- OPRM1 - Mu-Opioid Receptor
- MTHFR - Key regulatory enzyme in the metabolism of folate

Cytochrome P450 (CYP450)
- Family of liver enzymes responsible for metabolizing ~85% of prescribed medications
- 50+ Identified, but 6 are responsible for the majority of metabolism
- Variations in the CYP450 can cause the body to break down drugs more rapidly, or to break them down more slowly
  - Decreased drug concentration
  - Increased drug concentration
Clinical significance

Patient A: Ultra-Rapid Metabolizer - dose may have little to no therapeutic effect.
Patient B: Poor Metabolizer - dose may be toxic or cause ADEs.
Patient C: Extensive Metabolizer - fall within the drug's therapeutic window.

Serotonin (SERTs) & Norepinephrine (NETs) Transporter Proteins

- Help to regulate the effect of neurotransmitters in the CNS.
- Are the target for each major class of Antidepressants: SNRIs, SSRIs & TCAs.
- Mutations in the SERT and NET genes can alter the effectiveness of certain SSRIs & SNRIs, causing a reduced, slower or atypical response to the medication.

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Serotonin Receptors: HTR2A and HTR2C

- Work as part of a feedback loop that regulates Serotonin concentrations within the synaptic cleft.
- Involved in the response to various drugs used to treat Anxiety, Depression & Psychosis.
- Mutations in the HTR2A or HTR2C have been associated with lower response rate to and higher rate of side effects.

Retrieved from www.pharmgkb.com

Catechol-O-methyl transferase (COMT)

- Local metabolizing enzyme.
- Regulates extracellular neurotransmitter concentrations.
- Mutations in the COMT gene have been associated with decreased response to various ADHD & Antidepressants medication.
- Has been associated with schizophrenia, depression, anxiety, and bipolar disorder.

Retrieved from www.pharmgkb.com

Opioid Receptor Mu-1 (OPRM1)

- OPRM1 codes for the Mu-Opioid receptor.
- Main target of opioids such as Morphine & Fentanyl.
- Affects mechanisms related to pain, opioid efficacy, and opioid-related side effects, tolerance, dependence & reward.
- Mutations in the OPRM1 gene can decrease response to certain medications including Naltrexone and Buprenorphine.

Results of PGx Guided Treatment

- QIDS-C16 Score:
  - 7.2% reduction in the unguided group.
  - 31.2% reduction in the guided group.

- HAM-D17 ratings:
  - 18.2% reduction in the unguided group.
  - 30.8% reduction in the guided group.

- Economic Impact:
  - $1,036 in Rx savings.
  - $1,556 in office/ER visits.
  - $2,592 in total annual savings.

SUMMIT BEHAVIORAL HEALTH

- Offer a personalized addiction services continuum of care in PA, NJ and soon MA
- Co-occurring Disorders
- Adults and Adolescents
- Personalized client-centered care
  - meet the client ‘where they are’

CRITERIA FOR TESTING

- Co-occurring diagnosis failed treatment
- Multiple failed trials of psychotropic medication
- Chronic non-adherence to drug regimen
- Known adverse reactions
- Unresolved symptoms impacting quality of life
- Chronic relapse

Case Study 1

- Client is a 31 year old married female with Alcohol Use Disorder, Anxiolytic Use Disorder, MDD, GAD.
- Hx of outpatient tx for mental health
- Poor adherence due to adverse affects
- 4 prior suicide attempts (OD)
- Significant family history
- Completed 10 detox, stepped down to PHP
  - Recent SI, passive thoughts of OD "It would be ok if I didn’t wake -up"

Treatment Course

- Co-occurring disorders
- Medical Comorbidities: HTN, Renal
- Multiple failed trials SSRI
- Unable to work, executive
- Family history

ID Genetix Testing

- CYP1A2 UM
- CYP2C9 IM
- CYP3A5 IM
- HTR2A
- COMT

Application

- Stopped Lexapro
- Started Viibryd
- Discontinued Xanax
- Started Clonidine

Treatment Outcomes

- Sober 11 months
- Mood stabilized, rates depression as “2” and anxiety as “1”
- Reinstated drivers license
- Back to work
- Couples counseling, individual, aftercare group

Case Study 2

- The client is an 18 year old male graduated from HS in June.
  History of gambling, MDD, PTSD and GAD. Struggled through senior year
- Hx of outpatient tx
- Medical co-morbidity : musculoskeletal sports related injuries, surgery
- Due to injuries unable to golf (intended major in college)
- 14 days inpatient r/t SI with plan to OD. Transitioned to PHP, IOP
Case Study 3

- The client is a 49 year old married male with an Alcohol Use Disorder, MDD and GAD.
- No prior inpatient treatment
- Previous outpatient treatment for depression and anxiety
- Medical: HTN, congenital renal dysfunction
- Admitted to inpatient for detox and SI (passive)
- Transitioned to PHP - IOP

Treatment Course

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Application

- Started Deplin
- Stopped Wellbutrin
- Started Pristiq
- Added Abilify

Treatment Outcomes

- Several slips with gambling
- Depression stabilized, less anxiety, improved sleep
- Continued outpatient: individual and family
- 1st semester in college in Florida
- Increased physical activity, reconditioning
- Relationship with parents improved

Case Study 4

- The client is a 29 year old single male with a history of Opiate Use Disorder, MDD, Panic Disorder with agoraphobia
- No inpatient, Several episodes of outpatient treatment
- Medical co-morbidity: chronic severe testicular pain
- Isolated from family, unable to work

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Application

- Stopped Prozac
- Started Brintellix
- Increased Brintellix x2
- Added Abilify
- EMDR

Treatment Outcomes

- 2 slips over 1 year
- Kidney surgery
- Depression in remission
-Continues outpatient, increased engagement with anxiety
- Medication adjustments, group, EMDR
- Returned to work as bank vice president
- Anxiety “its manageable, feeling more like my old self”
- Increased physical activity, golf
Treatment Course

Co-Occurring Disorders
- Chronic severe pain
- Unable to work
- Impact quality of life, relationships, isolation

IDGenetix Testing
- CYP2C9 IM
- CYP2C19 UM
- CYP3A4 PM
- HTRA1
- OPRM1

Application
- Stopped benzosedepines
- Stopped Prozac
- Started Nortriptyline
- Suboxone low dose for pain

Treatment Outcomes

- Sober 14 months
- Effective use of low dose Suboxone
- Depression symptoms improved, sleeping "back to normal about 7 hours"
- Remains engaged in outpatient group, individual
  - Meditation, yoga
- Joined social group with guys in sober living
- Working part time

Conclusion, Next Steps

- A integral tool in our arsenal of strategies to support recovery for substance dependence and co-occurring disorders
- Pharmacogenomics as component of personalized treatment
  - Foster partnership with client, family and external providers
- Expanding use with focus on MAT
- Formalize research
- Reduce the long standing stigma of substance dependence and mental illness, empowering the client