Families Managing Kleefstra: Genetics beyond the EHMT1 gene variant

June, 30, 2018

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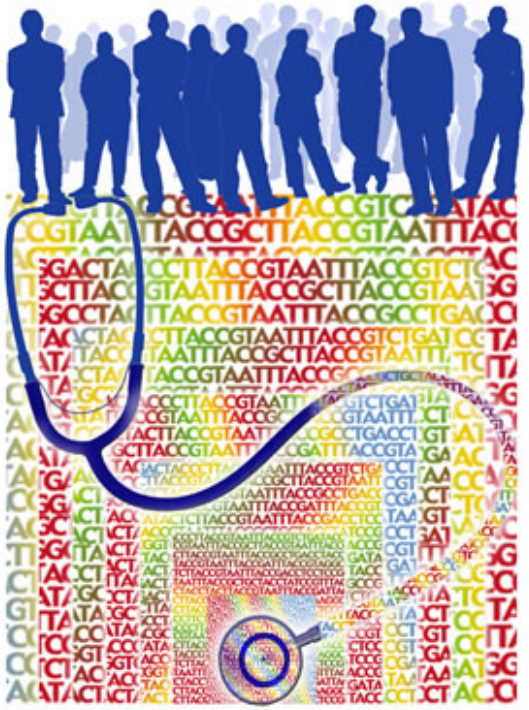


Background:

Professor, University of Minnesota

Research Laboratory in UMn Cancer Center

Focus on genetic variations leading to drug resistance in cancer

Step-parent to Andy, age 29

Autism
Scoliosis
Cognitive delays
Intellectual disability (functionally ~8 year old)
Physical: 6 ft, 205 lbs.
Low muscle tone
At age 25 identified EHMT1 mutation - Kleefstra

AJHG

Cell PRESS

Volume 79, Issue 2, August 2006, Pages 370–377

Report

Loss-of-Function Mutations in *Euchromatin Histone Methyl Transferase 1* (*EHMT1*) Cause the 9q34 Subtelomeric Deletion Syndrome

Tjitske Kleefstra[a], , , Han G. Brunner[a], Jeanne Amiel[b], As
M. Nillesen[a], Alex Magee[c], David Geneviève[b], Valérie Cormie
Jean-Pierre Fryns[d], Ben C.J. Hamel[a], Erik A. Sistermans[a], Be
van Bokhoven[a]

KLEEFSTRA SYNDROME

Therapeutic interventions to treat behaviors (including regression):

- Anxiety
- Obsessiveness
- Anger management
- Sleep disorder
- Catatonia
- Apathy
- Social interactions
- Focus / Attention

Our challenge:
Andy regression at age ~23

- Limb and whole-body jerking
- Decline in memory and auditory processing
- Dramatic insomnia - 4 hours tops
- Loss of daily living skills
- Non-communicative – eventually catatonic
- Dramatic weight loss
- Apathetic - no interest in any social engagement
- Life-altering separation anxiety

Can we identify variations in a genome that may contribute to how each person responds to drugs?

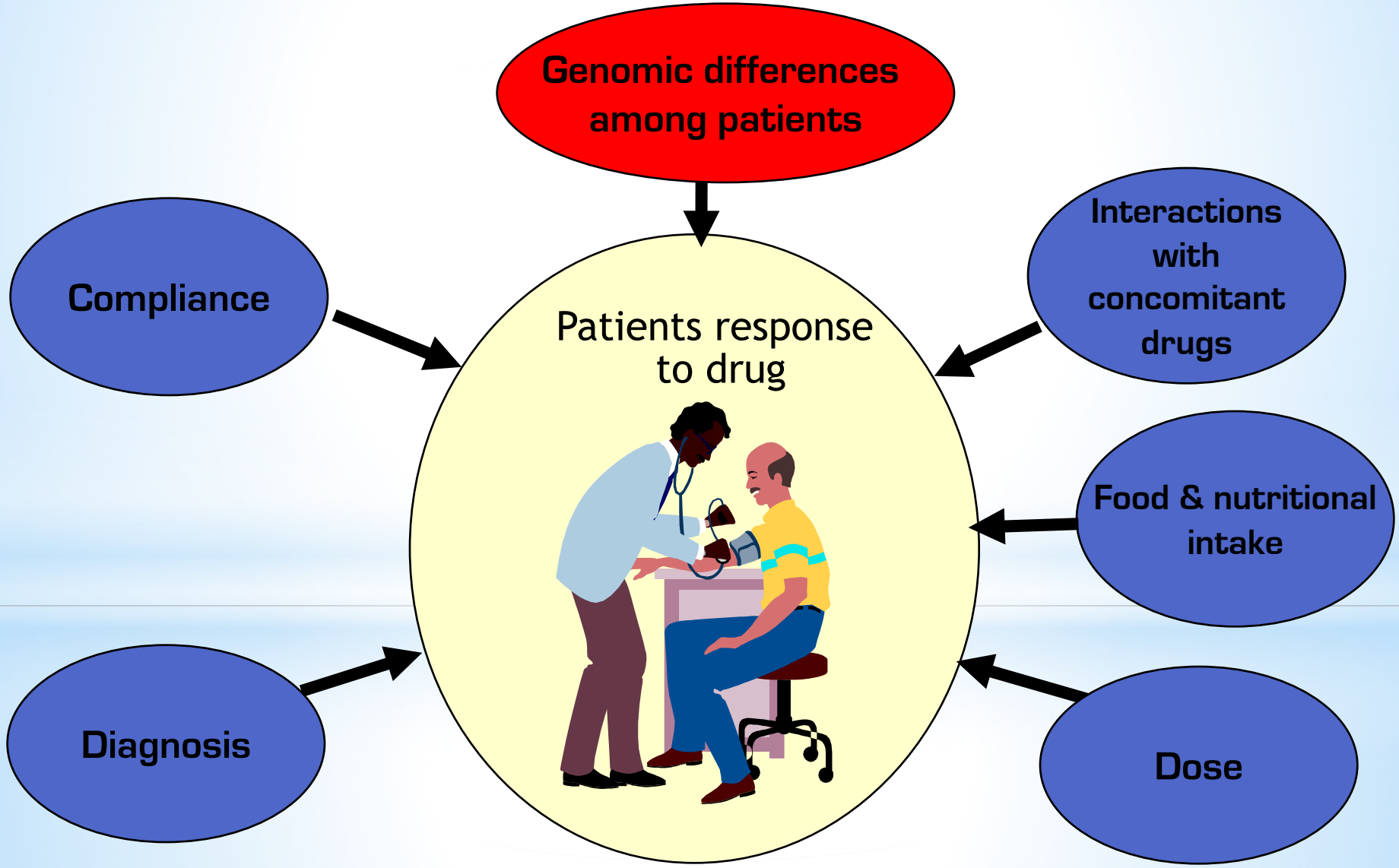
Consider issues in Personalized Medicine:

- The DNA codes for proteins that can activate, absorb, distribute, metabolize, and excrete drugs.

- There is a lot of population *variation* in the DNA coding of drug metabolizing genes.

- **PERSONALIZED MEDICINE** initiative is directed at identifying and understanding personal DNA variation impact on drugs, revealing:
  - ✧ Why some people do not benefit.
  - ✧ Why some people have bad side effects.
  - ✧ How choices for the right drug, for the right patient, at the right dose can be made based on **a DNA sequence**!

Many factors influence drug response



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A de novo splice site mutation in EHMT1 resulting in Kleefstra syndrome with pharmacogenomics screening and behavior therapy for regressive behaviors

Amit Kumar Mitra, Jessica Dodge, Jody Van Ness, Israel Sokeye, Brian Van Ness

First published: 26 December 2016 | https://doi.org/10.1002/mgg3.265 | Cited by: 1

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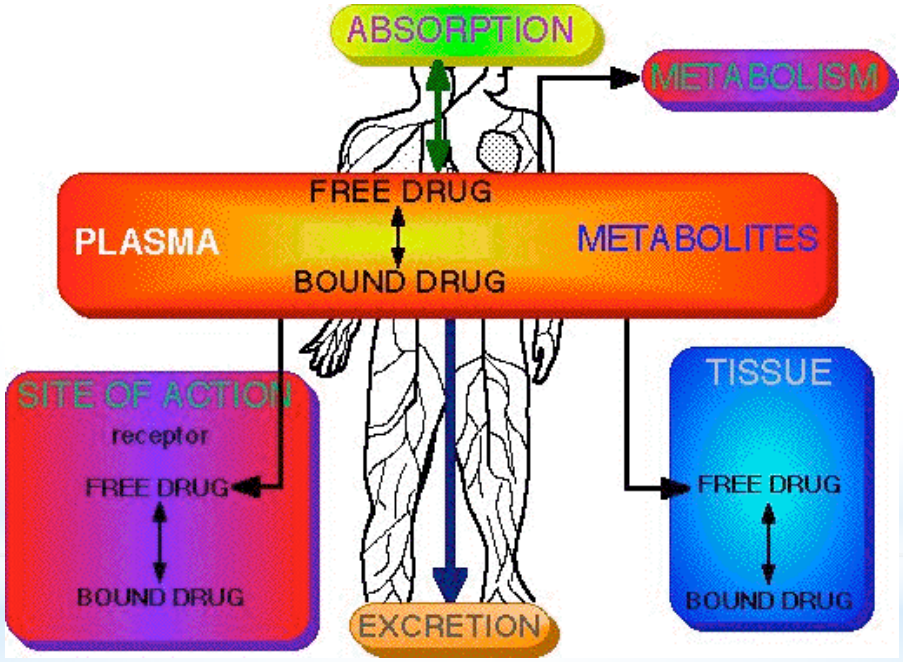
What happens to a drug after it enters the body?



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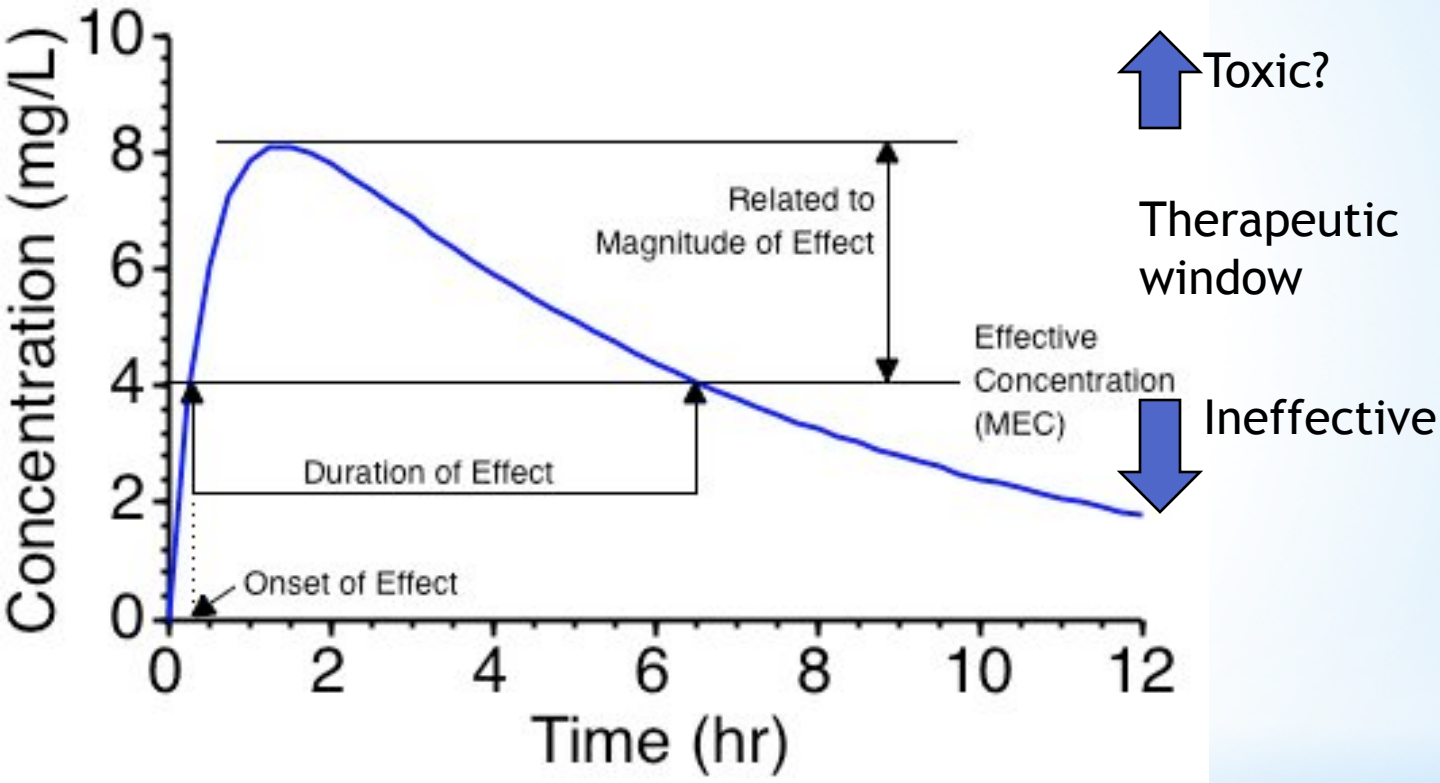
The ADME process

ADME PROCESSES

Absorption
Distribution
Metabolism
Excretion

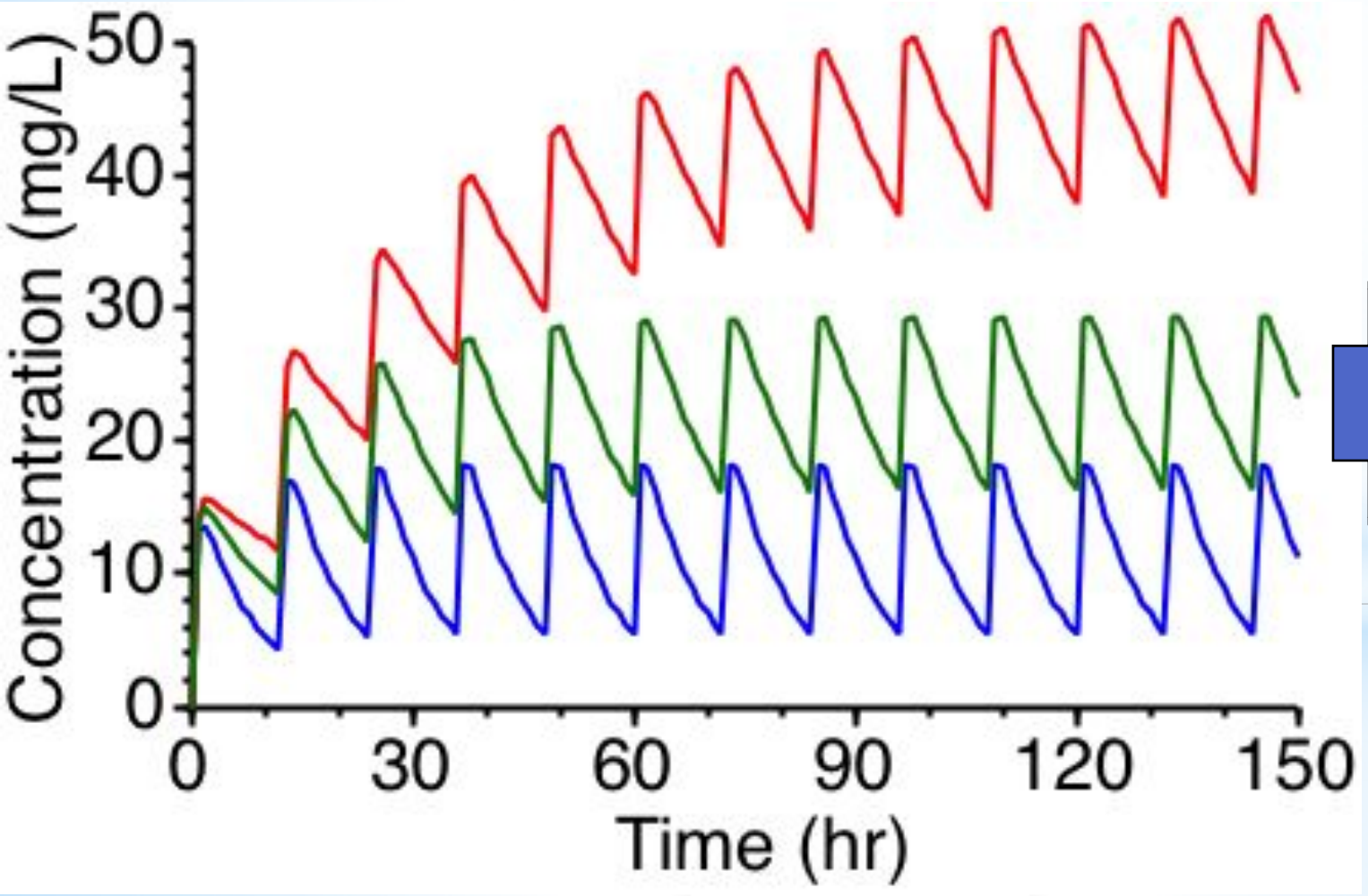
Drug dosing effects over time



Slide showing effect as a function of time. From a graph such as this we can see the relationship between drug concentration and drug effect. If a drug has to reach an effective concentration at a receptor site this will be reflected as a required blood concentration.

GENE VARIATION: DRUG METABLOLISM

Consider repeat doses in 3 scenarios



Toxic buildup

Effective dose

Ineffective dose

A medicine's absorption, distribution, metabolism, and elimination (ADME) depends on genetically programmed cellular functions, including:

- Receptors
- Ion channels
- Transport molecules
- Signaling pathways
- Metabolic pathways

All part of the GENETIC PROGRAM

(Does Andy have a different program?)

Genetic variation in the population

DNA sequence (Genotype) ⟷ Biological trait (Phenotype)

Environment

ATTCGCATGGACC (3 billion)

——C————

————A——

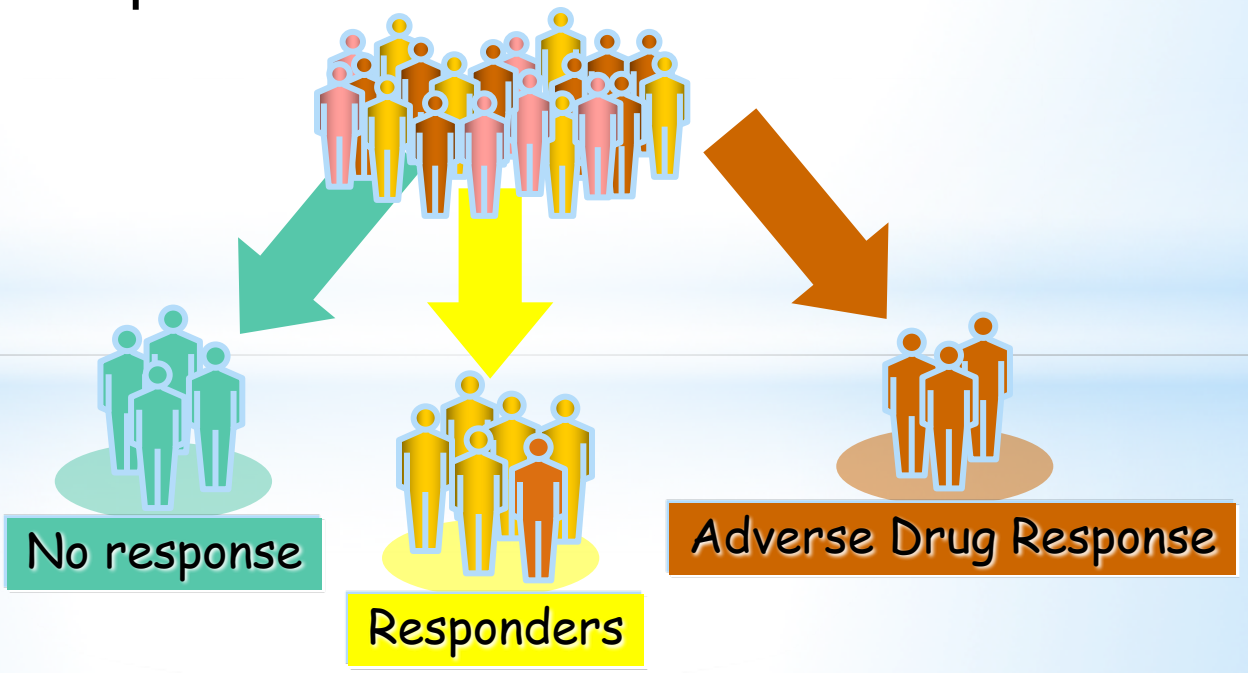
SNPs

Single Nucleotide Polymorphisms

~ 1/1000 bp

} Response to a drug is an individual trait that varies in a population

Pharmacogenomics is a science that examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or no response at all.



Adverse Drug Events (ADE's)

- Yearly: over 2.5 billion outpatient prescriptions (2/ 3 of office visits) and 2 million serious ADEs
- 4th leading cause of death, ahead of pulmonary disease, diabetes, AIDS, pneumonia--100,000 deaths yearly
- Costs USA $136 billion/ yr.
- ADE's are a big Public Health problem!

www.fda.gov/cder/drug/drugReactions/CERT%20Educational%20Module%201/sld001.htm

Most of the drug metabolism happens in the liver, by a group of enzymes encoded by the cytochrome p450 (CYP) genes.

A valuable resource

www.cpicpgx.org

CPIC provides peer-reviewed and published guidelines that enable the translation of genotypes into actionable prescribing decisions for specific drugs.

Journal
Clinical Pharmacology & Therapeutics

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors.

Hicks JK[1], Bishop JR[2], Sangkuhl K[3], Müller DJ[4], Ji Y[5], Leckband SG[6], Leeder JS[7], Graham RL[8], Chiulli DL[9], LLerena A[10], Skaar TC[11], Scott SA[12], Stingl JC[13], Klein TE[3], Caudle KE[14], Gaedigk A[7]; Clinical Pharmacogenetics Implementation Consortium.

Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. CYP2D6 and CYP2C19 polymorphisms can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. **We summarize evidence from the published literature supporting these associations and provide dosing recommendations for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline based on CYP2D6 and/or CYP2C19 genotype** (updates at www.pharmgkb.org).

Our journey continued with Andy's Personal Pharmacogenomics Profile

- Pharmacogenomic targeted gene panel done at AssureX (Cincinnatti, OH)

Assurex HEALTH

8 genes that can influence >80% drugs on the market

- Key result:

ANDY

CYP2D6 *4 / *4 genotype (a sequence variation in ~7%)

People with this genetics cannot metabolize a variety of drugs, including Luvox*.

May result in ***adverse events*** (behavior, physical)

* Andy was taking Luvox!

Andy's personalized management

- Medical:

  Recommendation from Dr. Kleefstra and colleagues:

  - An atypical anti-psychotic (Olanzapine), which also improves sleep

  Recommended by Andy's local psychiatrist:

  - Off Luvox – On a different SSRI not metabolized by CYP2D6

- Behavior and Cognitive:

  Fraser Institute (Minneapolis, MN autism center) behavior therapies
  Brain training with Fast Forward (from www.scilearn.com/products)

- Diet:

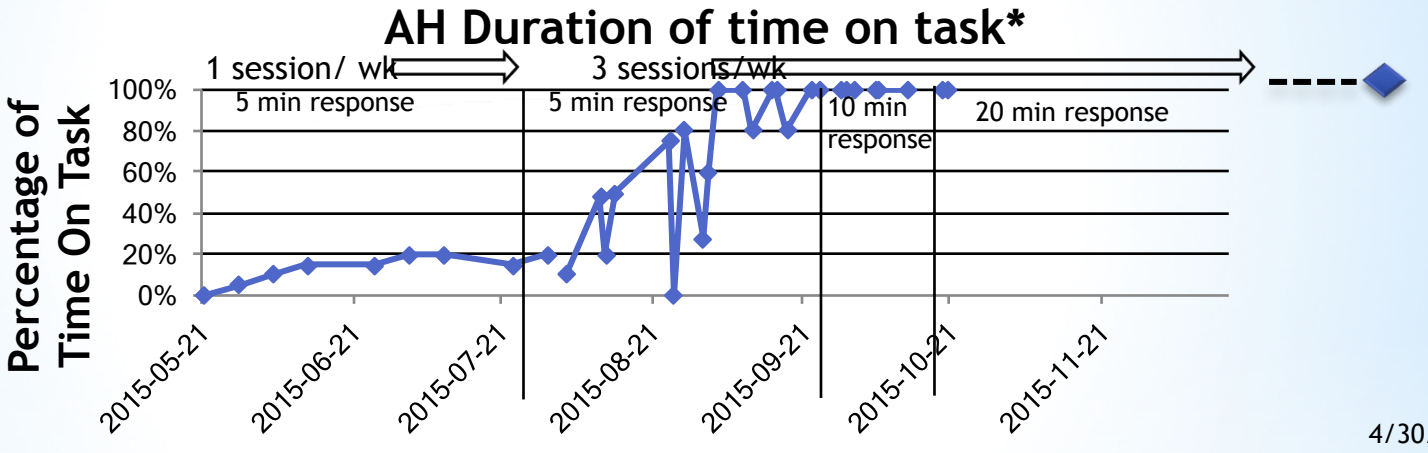
  Adjustments needed because drugs have risk of weight gain.

- Exercise:

  Minimal 3 times a week at the local YMCA gym and pool.

NOTE: This is a personalized recommendation based on Andy's genetics, individual features and behaviors, and still some experimentation in doses that are most effective for him. This is NOT generalizable to others.

Andy showed **major** improvements in behavior measures



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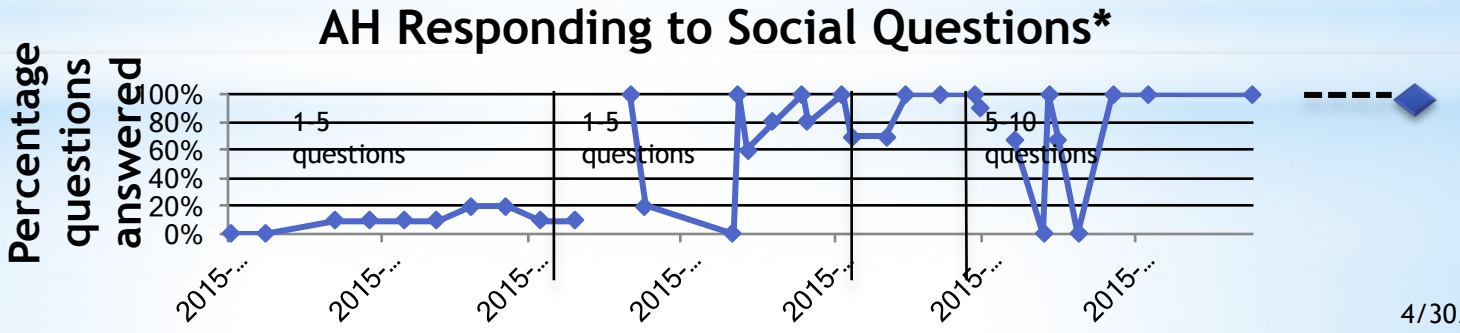

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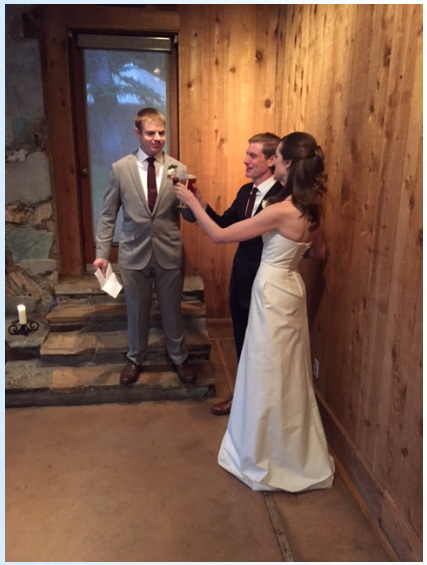
Quetiapine
Fluvoxamine
Desvenlafaxine
Olanzapine

*Study conducted by Dr. Jessica Dodge, clinical psychologist (Fraser Institute)

The impact of genetics on our journey



For Andy:

Autism still present
Sleep issues better
Anxieties reduced
Interactions greatly improved
Social engagement greatly improved
Cognitive function greatly improved
Employed 5 days a week
Living in a supported group home
Was an active best man at his brother's wedding
Employed, with new opportunities being explored
A happy guy with a bright future!

For the family:

Reduced anxiety and exhaustion
Pleasure of seeing independence grow, a new future Family planning
Andy's sister has a very healthy baby boy
Since parents do not carry the mutation, and siblings not affected, genetic risk is not increased relative to population.

Goals of pharmacogenomics

- ✧ Identify effective / ineffective treatments
- ✧ Reduce the time to achieve effective therapeutic window
- ✧ Identify proper dosage (i.e. SSRI's)
- ✧ Identify potential ADRs
- ✧ Reduce likelihood of harmful side effects
- ✧ Aid in new medication research and development

Pharmacogenomic PGx testing

Typically, the test is ordered by physician

Test cost $150-300 – currently not covered by all insurance (case by case)

CPIC guidelines continue to be issued – updates

Barriers:

- Many physicians unfamiliar with PGx testing results
- Not covered by all insurance providers
- Need to consider other factors
  - Drug-drug interactions
  - Environment (food)
- PGx guidelines not available for many drugs

Considerations of pharmacogenomic testing:

- Are there known genetic variations that impact medications being taken?
- Will insurance cover cost?
  Some do, some don't.
- Do you have genetic support professional to help interpret test results?
- Can you order the testing yourself, or only through physician?
  Some companies will do direct to customer.
- If you want more information:

Assurex HEALTH https://assurexhealth.com

ONEOME https://oneome.com

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