The Future of Drug Safety
Personalized Pharmacology: Pharmacogenetics

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Themes

• Genes and Genomes
• Molecular and Cellular Basis of Disease
• Infectious Disease and Host Defense
• Environmental Health Science
Research at Wadsworth

- Genes and Genomes

What do our genes have to do with drug safety?
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Central Tenet of Toxicology: “The dose makes the poison”
*Paracelsus 1493-1541*

Central Concept in Modern Pharmacology: Therapeutic Index (TI)

\[ TI = \frac{\text{Toxic Dose}}{\text{Therapeutic Dose}} \]

If \( TI >> 1 \), chemical = “medicine”
If \( TI \leq 1 \), chemical = “poison”
What do genes have to do with drug safety?

Central Tenet of Toxicology: “The dose makes the poison”
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Central Problem in Medicine: Patients differ in their responses to drugs

We have “personal TIs” that depend on many factors
- Age, weight, diet, general health status, etc.
- Genetic profile
  - i.e., variations in genes that affect drug uptake, metabolism, clearance...
Until recently, knowing our genetic profile was impractical ($, time)

Now, screening for hundreds and even thousands of genetic variants is becoming a reality

Coming soon: the “$1000 genome” (sequence all 3 billion bases in our DNA)

In principle someday: we’ll be able to predict individual disease susceptibilities, optimal lifestyle choices, and “personal TIs” for drugs (data → information)

**We are rapidly entering the *Era of Personalized Medicine***

Now: controversy over the value (clinical utility) of this data, since researchers are still establishing basic linkages:

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| GENOTYPE | PHENOTYPE |
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(Each gene has thousands of possible variant loci, each playing out against background of genetic and epigenetic variations in our other 30,000 genes)
Goal of research by Wadsworth scientists:

to explore actual associations between variations in genes and susceptibility of individuals to adverse side effects of clinically important drugs:

(1) Anti-cancer drugs ↔ ABC transport genes  E Schneider & J Finn (VA)
(2) L-dopa ↔ Multiple genes  H Payami & Consortium
(3) Warfarin ↔ POR gene  X Ding & L Kaminski (VA)
(4) Dilantin ↔ Multiple genes  X Ding & L Kan (LIJMC)
1. The Role of Single Nucleotide Polymorphisms in \textit{ABC TRANSPORT} Genes in the Susceptibility to Adverse Side Effects of \textit{ANTI-CANCER DRUGS}

Susan J. Wu*, Jaclyn A. Krolick*, JoAnn Finn+ and Erasmus Schneider*
*Wadsworth Center, NYDOH, Albany, NY
+Stratton VA Medical Center, Albany, NY

Goal of study

To identify single nucleotide polymorphisms (SNPs) in genes for the cell’s chemical “pumps” that may predispose patients to chemo-therapy related side effects
Goal of study:

To determine if L-dopa (Parkinsons drug) is associated with increased risk of hallucinations (possible under-diagnosed adverse side effect) and, if so, is this genotype specific.
3. Genetic Testing to Assure Safe Use of Warfarin

Xinxin Ding and colleagues*, Laurence Kaminsky and colleagues+

* Wadsworth Center, NYDOH, Albany, NY
+ Stratton VA Medical Center, Albany, NY

Goal of study:

To identify additional genetic factors that influence warfarin dosage requirements – to facilitate the safer administration of this widely used anti-coagulant (notorious for narrow TI and wide inter-individual variability)
4. Genetic Testing to Assure Safe Use of Dilantin

Xinxin Ding and colleagues*, Li Kan and colleagues+

* Wadsworth Center, NYDOH, Albany, NY
+ Schneider Children’s Hospital, LIJMC, New Hyde Park, NY

Goal of study:

To identify epileptic patients who have a genetic tendency to rare but severe neurological reactions to this widely used first-line anti-convulsant
Results from these 4 pilot grants have shown that genetic screening can help predict patient susceptibility to adverse side effects of drugs. Thus, **Pharmacogenetics** has tremendous potential to make drug use safer for individuals by, in effect, determining our “personal TIs” for drugs.