



Stanford - South Africa

Biomedical Informatics Program



Clinical setting of pharmacogenomics

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The typical clinical flow

In order to understand the opportunity for pharmacogenomics, one must understand the clinical setting and the flow of activities for physician-prescribers.

Doctors learn these classes, and typically memorize information and use one or a few members of each class in practice.



Drug classes

Most physicians think about drugs as grouped together by the disease that they treat, e.g.

Antibiotics--treat bacterial infections

Antivirals--treat viral infections

Cholesterol medicines--lower 'bad' cholesterol to avoid heart attacks

Blood pressure medicines--lower blood pressure to avoid strokes & heart attacks

Diabetes medicines--lower blood sugar

And many others...



Making the prescribing decision

- Patient comes to clinic with a problem.
- Physician takes history, examines patient, orders tests, and attempts to make a diagnosis.
- Physician may then evaluate the options for treatment with medications



What does doctor consider?

- Efficacy of drug for this condition: is a drug likely to help the patient? Has it worked in the past?
- Side effects of the drug: is there a high rate of adverse reactions to the drug? Has this patient taken it before with problems or success?



What does doctor consider?

- Compliance with drug dosing: Is the patient likely to take the drug?
 - 10% to 90% noncompliance to all drug prescriptions. Noncompliance can be due to:
 - Cost (expensive?)
 - Perceived benefit by patient (symptom relief vs. not, e.g. hypertension meds)
 - Dosing complexity (1/day vs. 4/day)
 - Side effects (tolerable or not)



What does doctor consider?

- Patient lifestyle: special elements of patient environment (based on their job, e.g.), use of over-the-counter medications, use of herbal medications, unusual diet, travel.
- Interactions with other drugs or diseases relevant to this patient



Doctor makes a decision

- Gives patient a prescription for a drug
- Patient fills the prescription?
- Patient takes the medication on correct schedule, with/without food?
- Patient takes the medication for the time prescribed?
- Patient has special genetic background that changes expected response?



Key pharmacogenomics assumptions:

Assuming that the (1) patient fills the prescription, (2) follows the dosing recommendations, (3) does not have an unusual diet, then

Variation in response to the drug may be due to genetic factors (PD and/or PK).



What is opportunity?

- High individual risk prescriptions, e.g.
 - Serious infections: HIV, malaria, TB all potentially life threatening
 - Cancer: because of resistance developing, would like to get prescription right on the first try.
 - Depression: failure to adequately treat can be deadly (suicide)
 - Major pain: major suffering of patient must be avoided



What's the opportunity?

- Low individual risk, common disease, e.g.
 - Diabetes, increases long term risks for cardiovascular disease, kidney disease, blindness
 - High blood pressure, increases risks for stroke and cardiovascular disease
 - Minor pain, can be disabling over long term



What could we test for PGx?

- Genotype (ONLY DO ONCE)
 - The whole genome? (Too expensive currently)
 - Focused genetic tests
- Phenotype (MAY NEED MULTIPLE)
 - Molecular
 - Cellular
 - Clinical

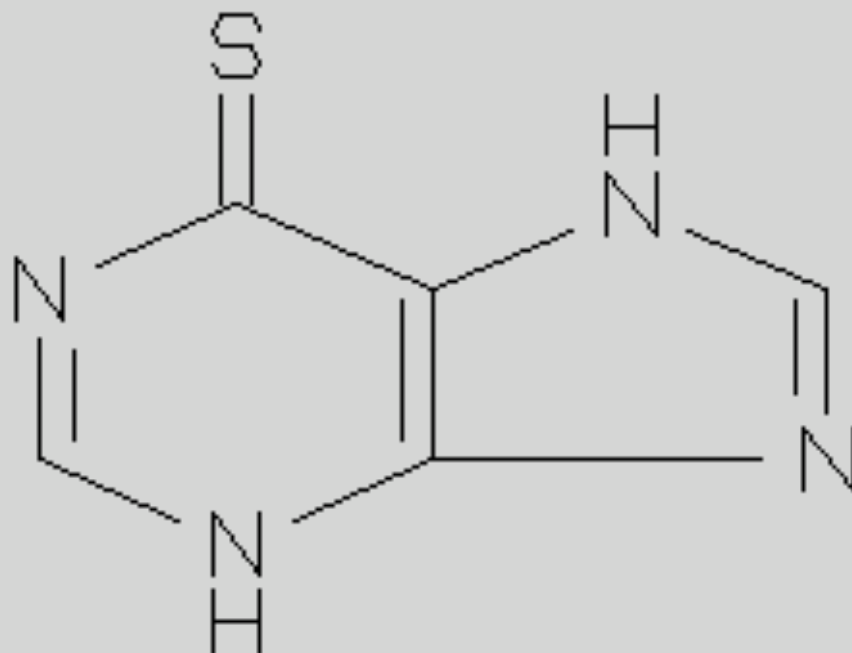
NOTE: downstream phenotype measurements may be more accurate, since more functional



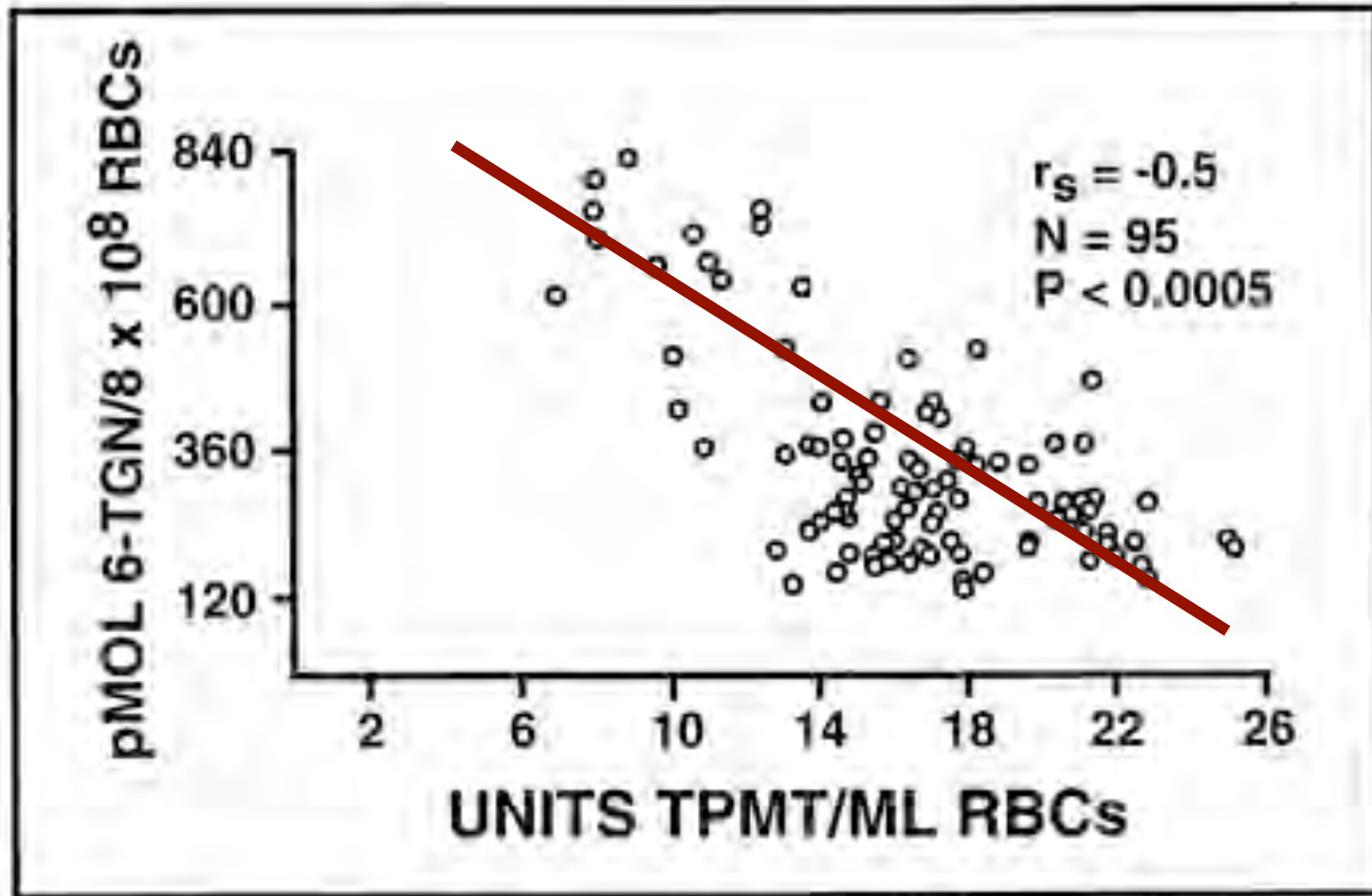
EXAMPLE: TPMT testing

- TPMT is an enzyme that metabolizes a drug called 6-mercaptopurine (6-mp). Variation in TPMT can lead to increased 6-mp side effects.
- Can measure the genotype of TPMT
- Can measure the activity of TPMT enzyme in red blood cells.





More TPMT, less TGN



Genotyping issues

- When to genotype?
 - At birth (or establishment of care with doctor)?
 - At time of prescribing?
- Where should genotype be stored?
 - Measure and throw away
 - Store in medical record
 - Store in centralized database



Where should we store genotypes?

- Give to patient
- Store in local healthcare facility
- Store in central healthcare database
- With the government
- With a trusted third party
- Other?

These choices have implications for privacy/security and patient comfort with information.



How do we deliver genotype information?

Doctor needs genotype information to inform prescription decision in a timely manner. Too late = useless.

- Fax
- Phone
- Email
- Mail

How do we explain the results to an MD who does not understand recommendation?



Who pays for genetic tests?

- Individual
- Health care system
- Government

Does this affect who has the right to see the information?

