

Genetic Testing: Coming of Age

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Different people respond differently to the same drug. It is well known that this difference in drug response is because of genetic differences.

The study of these genetic differences to predict drug response is called Pharmacogenomics.

According to pharmacokinetics and genetics there are four types of people:

- 60 percent of the population will respond positively to a drug.
- 25 percent of the population is fast metabolisers of the drug and it means that the drug will get washed out of the body, before it can have any positive effect.
- 10 percent of the population is slow metabolisers. People in this population will have minor or major side effects because of accumulation of the drug, as the drug gets washed out very slowly.
- Five percent of the remainder population shows undetectable or no enzyme activity and so all the drug taken in by the person keep accumulating and this can cause severe side reactions.

In the U.S. alone, 20 million people need hospitalization to recover from these drug induced reactions and close to 1lakh people die every year.

It is alright if a mild drug for headache or fever does not work, but strong drugs like chemotherapy can cause severe damage, if they accumulate.

Doing a genetic test can give lots of information on how a patient is going to respond to drugs; so appropriate drugs and their dosage can be arrived at.

This subject is called Pharmacogenomics.

Tests Available Today!

Docetaxel (CYP3A4)

Docetaxel displays a broad spectrum of antitumor activity, and activity against breast, head and neck, lung, ovarian and prostate cancer. An important draw back with the use of docetaxel is

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Pharmacogenetics: A Case Study

Individuals respond differently to the anti-leukemia drug G-morcoploprine

The diversity in responses is due to variations in the gene for an enzyme called TPMT, or thiopurine methyltransferase

After a simple blood test individuals can be given doses of medication that one tailored to user genetic profile

Most people metabolize the drug quickly. Doses need to be high enough to treat leukemia and prevent relapses

Others metabolize the drug slowly and need lower doses to avoid toxic side effects of the drug

A small portion of people metabolize the drug so poorly that its effects can be fatal

Normal dose

Dose for an extra slow metabolisor (TPMT deficient)

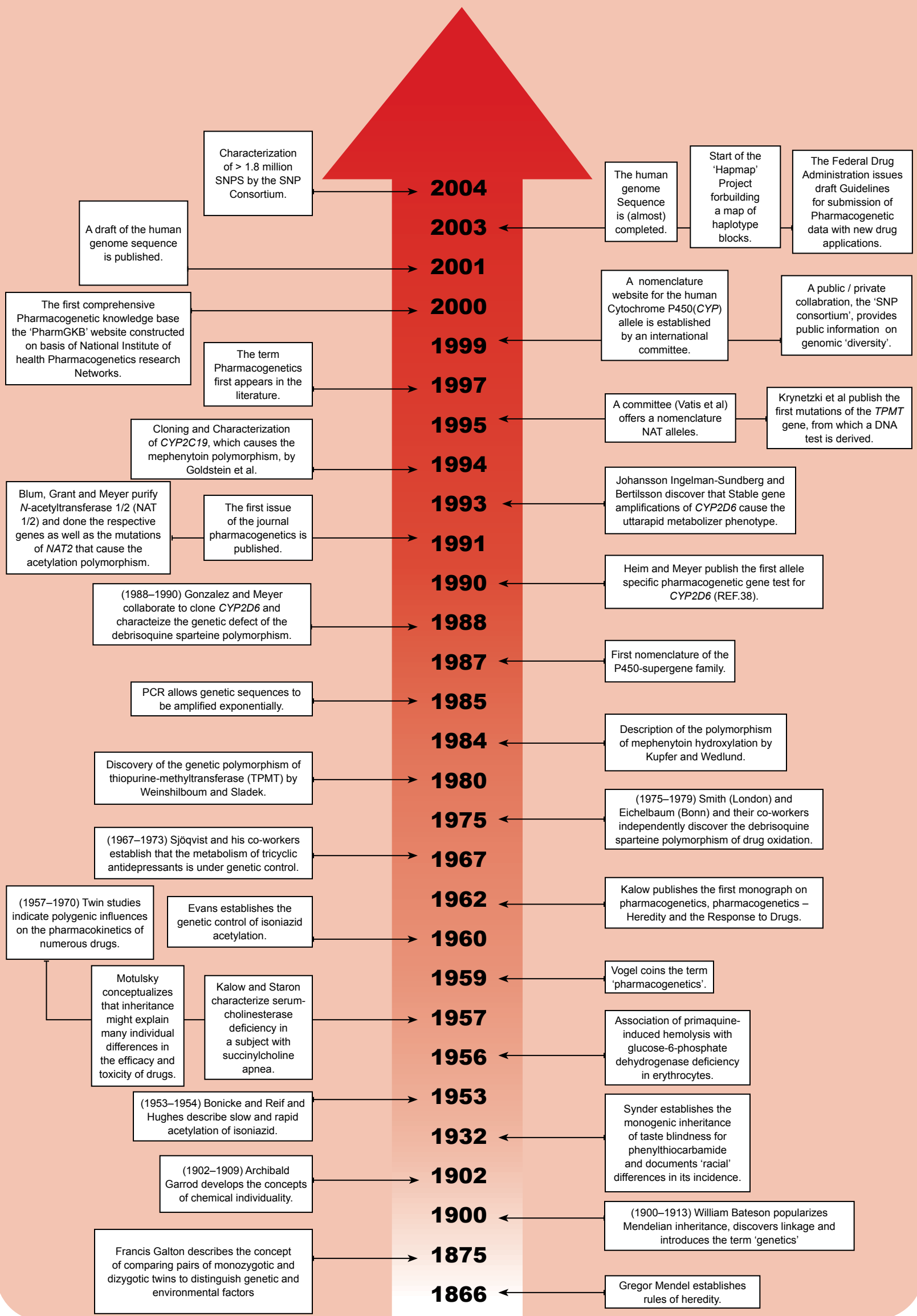
the large inter-individual variability in efficacy and toxicity. Adverse effects of Docetaxel include alopecia, asthenia, dermatological reactions, fluid retention, hypersensitivity reaction, motor and sensory neuropathies, stomatitis and diarrhoea. Docetaxel is extensively metabolized by cytochrome P450 3A4 to yield an inactive oxidation products. Variant alleles of CYP3A4 are common in our population, which results in decreased enzyme activity and increased toxicity. CYP3A4 is the most popular candidate for a genotyping test that would predict the potential for toxicity and allow individualized dose adjustments to be made.

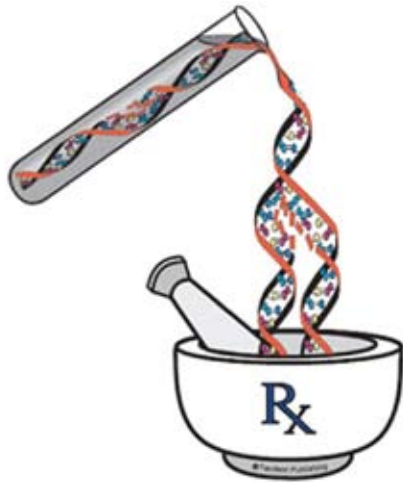
Warfarin (CYP2C9 and VKORC1)

Different patients need different doses of warfarin to attain the desired Prothrombin Time (PT) / INR. This difference can be attributed to diet, other co-administered drugs, age, sex, weight etc. But, sometimes two patients having very similar attributes might need very different doses of warfarin. This inter patient variation has been a hot topic of research in genetic laboratories and finally, US FDA has asked the pharma companies to modify the package insert and to mention that patient having mutations in CYP2C9 and VKORC1 are at



Timeline | A History of Pharmacogenetics





a greater risk of severe bleeding. These patients need much lower dose depending on the type of mutations they carry. Now, there are internationally accepted clinical guidelines to select the right dose for every patient and hence, avoid severe bleeding from Warfarin.

Irinotecan (UGT1A1)

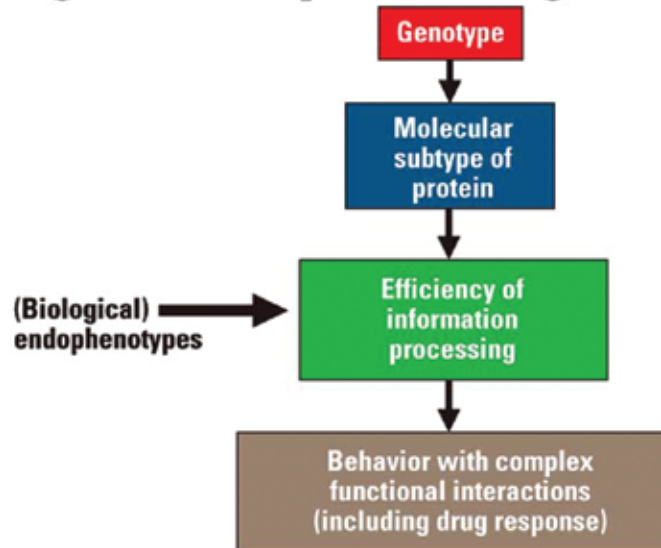
Irinotecan has been a valuable drug as first line therapy especially for gastrointestinal malignancies. Irinotecan is a prodrug and must be converted to SN-38 to have cytotoxic activity. Once a dose has done its job, the drug needs to be detoxified and cleared from the body. The enzyme responsible for this reaction is UGT1A1. Mutations in UGT1A1, lead to lower enzyme activity. There are retrospective studies, and prospective pilot studies with solid tumor treated with Irinotecan, where severe diarrhoea and neutropenia was observed only in patients with UGT1A1 *28 mutation. Severe toxicities are reported in homozygous mutants and the incidence of these patients in approximately 10 percent in Indian population. U.S. FDA has approved UGT1A1 testing before starting Irinotecan on a patient and have recommended “a reduced initial dose” to patients carrying UGT1A1*28 mutation.

Fluorouracil (DPD, MTHFR, TS)

5-FU (5-fluorouracil) has been a valuable drug against cancer. Dihydropyrimidine dehydrogenase (DPD), Thymidylate synthase (TS) and Methylene tetrahydrofolate reductase (MTHFR) are responsible for efficacy and toxicity from 5-FU. Hence, you can identify patients who will show severe toxicity to 5-FU. This is also mentioned in medical text books, international literature, and package insert of Xeloda. We are testing for the most common mutations in all these genes.

“Methotrexate is an antimetabolite drug and an analogue of folate. It interferes with folate metabolism by inhibiting dihydrofolate reductase, which leads to depletion of cellular folate.”

Pharmacogenetics: how relevant are your genes to your drug response?



Stahl SM. *Essential Psychopharmacology*. 3rd ed. New York, NY: Cambridge University Press. In press. Reproduced with permission. Copyright Neuroscience Education Institute.

Stahl SM. *CNS Spectr*. Vol 13, No 2. 2008.

Mercaptopurine (TPMT)

6-MP (6-Mercaptopurine) has been a valuable drug against Acute Lymphocytic Leukemia (ALL). However, 10 percent patients have shown severe side effects. Scientific research over the last 14 years in large hospital across the globe has demonstrated that these complications can be avoided by doing a TPMT genotyping test. Patients having mutations in TPMT gene will be at a much higher risk of developing toxicity from standard dosage of 6-MP. These patients should receive a reduced dose based on their genotype.

Methotrexate (MTHFR)

Methotrexate is a drug commonly used in treatment of Leukemia and solid tumors. Methotrexate is an antimetabolite drug and an analogue of folate. It interferes with folate metabolism by inhibiting dihydrofolate reductase, which leads to depletion of cellular folate. MTHFR is an important enzyme in maintaining cellular folate pools, and MTHFR gene variants associated with reduced enzyme function and hyperhomocysteinemia affect methotrexate sensitivity and contribute to toxicity. Commonly reported mutations in MTHFR gene are C677T and A1298C. These mutations cause reduction in enzyme activity. Patients having these mutations in MTHFR gene show severe side effects in cardiovascular, neurological, dermatologic, hematologic, hepatic, and gastrointestinal systems. These patients should receive a reduced dose based on their genotype.

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- “Drugs Don’t Work” by Dr Allen Roses, Worldwide Vice President of Genetics at GlaxoSmithKline
- U.S. FDA Guidance for Industry, Pharmacogenomic Data Submissions

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