What is Pharmacogenomics?

When a patient has their DNA sequenced in the Personalised Breast cancer Program (PBCP), we look for changes to genes that give us information about breast cancer in the tumour cells (somatic DNA) and the patients familial (germline) DNA. The germline DNA can also give us information about how individuals process drugs in their body. This is why people can experience a range of different side effects from the same drugs.

How does the body process drugs?

We have evolved to be very good at removing chemicals from our body. When someone is given a drug, it will be chemically altered in the liver before exiting the body via urine, faeces or sweat.

An important part of clinical trials of a drug is to understand how a drug is absorbed, distributed, metabolised and excreted. This is called the pharmacokinetics of the drug.

Enzymes are a protein which facilitate chemical reactions. The instructions to make enzymes are contained within DNA. There are a lot of enzymes in the liver which are able to process different chemicals that enter the body as food and drink or from the environment. Understanding the genetic code for these enzymes and how they process chemicals is called Pharmacogenomics.

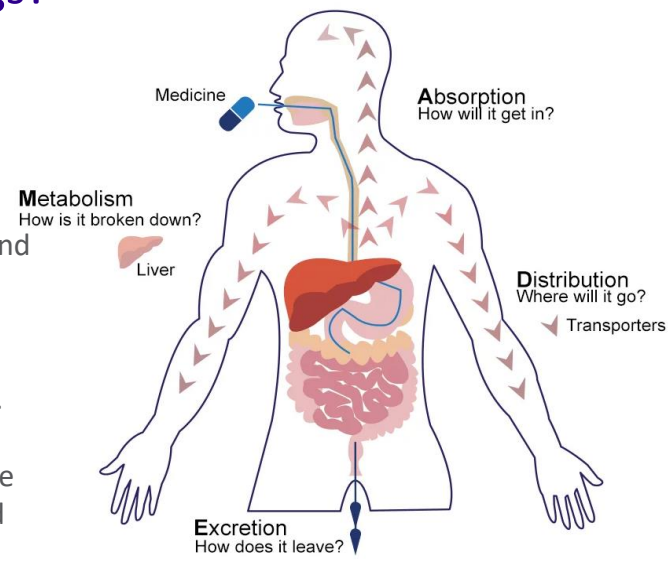

Image from EUPATI Pharmacokinetics toolkit

DPYD and Chemotherapy

The gene called DPYD codes for an enzyme called dihydropyrimidine dehydrohenase (DPD) which is a key enzyme for breaking down certain chemotherapy drugs called fluoropyrimidines.

Alterations in the DPYD gene can make DPD less efficient at breaking down these chemotherapy drugs. This changes the pharmacokinetics of the chemotherapy so that it is circulating in the body for longer and at higher concentrations. This can result in a higher chance of experiencing side effects.

It is now routine in the NHS to check for DPYD alterations before prescribing these chemotherapy drugs. If the alterations are present, the dose can be lowered to balance the reduced enzyme activity.

CYP2D6 and Tamoxifen

Tamoxifen is a drug commonly taken by patients with Oestrogen Receptor (ER) positive breast cancer. Tamoxifen itself is not an active drug. It requires a chemical conversion to Endoxifen to have it's desired effect of blocking oestrogen receptors. This happens in the liver by an enzyme called CYP2D6.

A change in the sequence for CYP2D6 that slows down its ability to convert Tamoxifen to Endoxifen will result in a lower level of active drug in the body, meaning that it might be less effective. If these changes are identified in PBCP, the patients consultant may discuss an alternative anti-oestrogen drug with the patient.

We will be able to analyse the germline DNA sequences collected in PBCP and compare it to the clinical information that is collected on the treatment and side effects experienced by the patients. This information will help us personalise breast cancer treatment in the future, helping consultants select the drugs that will be the most effective and at the right dose for each patient.