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GENETIC TESTING LABORATORIES
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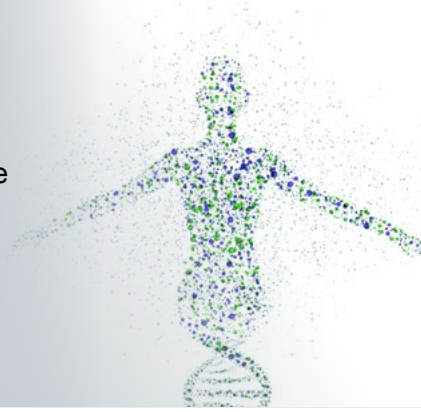
PERSONALISED MOLECULAR DIAGNOSTICS FOR YOU

Pharmacogenomics

Your genetic make-up determines how you respond to a number of drugs

Introduction

Pharmacogenomics (PGx) is the analysis of how genes affect a person's response to drugs. This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medications and doses that will be tailored to a person's genetic makeup. PGx is able to provide information about a patient's genetic likelihood to respond to a given medication or risk of an adverse drug response (ADR).



Multiple genes determine how drugs are metabolised in the body. The genetic makeup of every individual is unique, resulting in significant differences in the drug-metabolizing enzymes, drug transporters and drug targets.

Variations in the genes influence how quickly or how thoroughly individuals metabolize specific drugs. Individuals can be classified into poor, intermediate, normal, or ultra-rapid metabolizer for certain drugs. More than 75% of patients have significant variations in drug metabolism and fall outside of what is regarded as normal metabolizers.

Traditional approaches use "trial and error" to determine the optimum drug dose, however, this approach contributes to adverse drug reactions (side effects) and treatment failure and may take a period of time before an optimal dose is determined. The effect of drug therapy across all diseases is less than 100% because of these types of variations and only 25-80% of patients respond to medication depending on the type of drug being used.

In a patient classified as a "poor" metabolizer, drugs may be eliminated slowly and may accumulate, requiring a lower dose to avoid drug toxicity. For other drug classes, the poor metabolism may result in reduced drug efficacy, which may require the selection of alternative medication.

For patients who are classified as an "ultra-rapid" metabolizer, the drug is metabolized rapidly and this may mean that the drug is less effective at the standard dose, requiring a higher dose to be effective. For other classes of drugs, this may result in increased efficacy with a rapid onset of the drug's effect and increased side effects, requiring a reduction in the drug dosage to achieve the desired outcome.

In some cases, these differences can cause significant side effects or mean the medication is ineffective. In severe cases the effects may be life threatening.

Being aware of patients' genetic variations can help medical practitioners avoid drugs that may cause adverse reactions.

PGx testing is complex and involves multiple genes.

GTLDNA's Pharmacogenomics Panel uses next generation sequencing for genotyping single nucleotide polymorphisms (SNPs), as well as insertion/deletion (indel) and copy number variation (CNV) analysis in 40 known drug metabolizing enzymes (DMEs): ABCB1, ABCG2, ADRA2A, ANKK1, APOE, COMT, CYP1A2, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4, CYP3A5, DBH, DPYD, DRD1, DRD4, F2, F5, GABRA6, GABRP, GRIK4, HTR2A, HTR2C, ITGB3, KIF6, MTHFR, OPRD1, OPRK1, OPRM1, SLCO1B1, TPMT, UGT1A1, UGT2B15, UGT2B7, VKORC1, HLA-A*3101, HLA-B*5701, HLA-B*1502.

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Testing of these genes covers a wide range of drug metabolism including:

DISEASE	DRUG CLASS	EXAMPLES
Anticancer Agents	Antifolates	Methotrexate
Cardiovascular	Angiotensin II Receptor Antagonists	Irbesartan
	Antianginal Agents	Ranolazine*
	Antiarrhythmics	Flecainide
		Mexiletine*
		Propafenone*
	Anticoagulants	Apixaban
		Dabigatran Etexilate
		Edoxaban*
		Fondaparinux
		Rivaroxaban
		Warfarin
	Antiplatelets	Prasugrel
		Ticagrelor
		Vorapaxar*
		Clopidogrel
	Beta Blockers	Metoprolol
		Labetalol
		Propranolol
		Nebivolol
		Carvedilol
		Timolol
	Statins	Pitavastatin*
		Pravastatin
		Rosuvastatin
		Atorvastatin
		Fluvastatin
		Lovastatin*
		Simvastatin
Diabetes	Sulfonylureas	Glimepiride
		Glipizide
		Glyburide*
		Tolbutamide
Gastrointestinal	Antiemetics	Metoclopramide
		Dolasetron
		Ondansetron
		Palonosetron
	Proton Pump Inhibitors	Dexlansoprazole
		Esomeprazole
		Lansoprazole
		Omeprazole
		Pantoprazole
		Rabeprazole

DISEASE	DRUG CLASS	EXAMPLES
Infections	Antifungals	Voriconazole
	Reverse Transcriptase Inhibitor	Abacavir
Pain	Fibromyalgia Agents	Milnacipran*
	Muscle Relaxants	Carisoprodol*
		Cyclobenzaprine*
		Metaxalone*
		Methocarbamol*
		Tizanidine*
	NSAIDs	Ketoprofen
		Ketorolac
		Nabumetone*
		Naproxen
		Sulindac
		Celecoxib
		Diclofenac
		Flurbiprofen
		Ibuprofen
		Indomethacin
		Meloxicam
		Piroxicam
	Opioids	Alfentanil
		Buprenorphine
		Dihydrocodeine
		Hydromorphone
		Levorphanol*
		Meperidine
		Methadone
		Oxymorphone*
		Sufentanil*
		Tapentadol
		Fentanyl
		Hydrocodone*
		Morphine
		Oxycodone
		Codeine
		Tramadol
Psychotropic	Antiaddictives	Bupropion
		Naltrexone
	Anti-ADHD Agents	Amphetamine
		Clonidine
		Dextroamphetamine
		Guanfacine*
		Lisdexamfetamine

DISEASE	DRUG CLASS	EXAMPLES
		Atomoxetine
		Dexmethylphenidate*
		Methylphenidate
	Anticonvulsants	Carbamazepine
		Eslicarbazepine*
		Ethosuximide
		Ezogabine*
		Felbamate*
		Gabapentin
		Lacosamide
		Lamotrigine
		Levetiracetam
		Oxcarbazepine
		Perampanel
		Pregabalin
		Rufinamide*
		Tiagabine
		Topiramate
		Valproic Acid
		Vigabatrin
		Fosphenytoin*
		Phenobarbital
		Phenytoin
		Primidone
		Zonisamide
	Antidementia Agents	Memantine
		Donepezil
		Galantamine
	Antidepressants	Citalopram
		Desvenlafaxine
		Escitalopram
		Fluoxetine
		Levomilnacipran*
		Mirtazapine
		Sertraline
		Vilazodone*
		Duloxetine
		Fluvoxamine
		Maprotiline*
		Nefazodone*
		Vortioxetine
		Amoxapine*
		Amitriptyline
		Clomipramine
		Doxepin
		Imipramine
		Nortriptyline
		Paroxetine
		Protriptyline*
		Trimipramine
		Venlafaxine
	Antipsychotics	Asenapine

DISEASE	DRUG CLASS	EXAMPLES
		Clozapine
		Lurasidone
		Olanzapine
		Paliperidone
		Quetiapine
		Thiothixene*
		Trazodone*
		Trifluoperazine
		Ziprasidone
		Aripiprazole
		Chlorpromazine
		Fluphenazine
		Iloperidone*
		Perphenazine*
		Pimozide*
		Tetrabenazine
		Haloperidol
		Risperidone
		Thioridazine*
	Benzodiazepines	Alprazolam
		Clonazepam
		Diazepam
		Clobazam
		Lorazepam
		Oxazepam
Rheumatology	Immunomodulators	Apremilast
		Tofacitinib
		Leflunomide
Transplantation	Immunosupressants	Tacrolimus
Urologicals	5-Alpha Reductase Inhibitors for Benign Prostatic Hyperplasia	Dutasteride
		Finasteride
	Alpha-Blockers for Benign Prostatic Hyperplasia	Alfuzosin
		Doxazosin*
		Silodosin*
		Terazosin
	Antispasmodics for Overactive Bladder	Fesoterodine*
		Mirabegron
		Oxybutynin
		Solifenacin
		Trospium*
	Phosphodiesterase Inhibitors for Erectile Dysfunction	Avanafil*
		Sildenafil
		Tadalafil
		Vardenafil
Risk Management	Hyperlipidaemia/Atherosclerotic Cardiovascular Disease	Apolipoprotein E
	Thrombophilia	Factor V Leiden and Factor II
	Hyperhomocysteinaemia	MTHFR

*These drugs are not currently available in Australia but are included for completeness.

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Medication-related hospital admissions have been estimated to comprise 2% to 3% of all Australian hospital admissions.

In Australia between 8.5% and 12% of people attending general practice have experienced an adverse medication event in the previous six months. Eleven to twelve percent of these adverse events were considered severe and approximately 5% required hospitalisation.

In Australia, the Therapeutic Goods Administration received notification of 14,200 cases of severe adverse drug reactions in 2010.

Up to 80% of adverse reactions are of unknown origin, but are thought to be mostly due to genetic differences in either the targets of the drugs or in the enzymes involved in their metabolism.

Data from six surveys assessing the extent of side effects from consumers suggest that between 9% and 14% report experiencing side effects.

Currently more than 100 drugs mention specific markers that may change the way an individual responds to drug therapy.

PGx is particularly relevant in psychiatry where antipsychotics and antidepressants are essential components in treatment of most psychiatric disorders. Unfortunately, lengthy trials are often required before the optimum treatment dose and optimum drug is identified with significant symptom alleviation and minimal side effects. Unfortunately, 30-50% of patients with a major depressive disorder do not respond to their first antidepressant trial, however patients who had genetically guided prescribing based on PGx have more than a 2-fold greater chance of remission compared to patients without genetic prescribing.

ADVANTAGES

PGx can:

1. **Decrease the number of adverse drug reactions.**
2. **Save patients money on ineffective medications**
3. **Decrease the length of time patients are on medication.**
4. **Decrease and potentially eliminate the trial-and-error approach to find an effective therapy for patients.**
5. **Improve the quality of life for the patient.**

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