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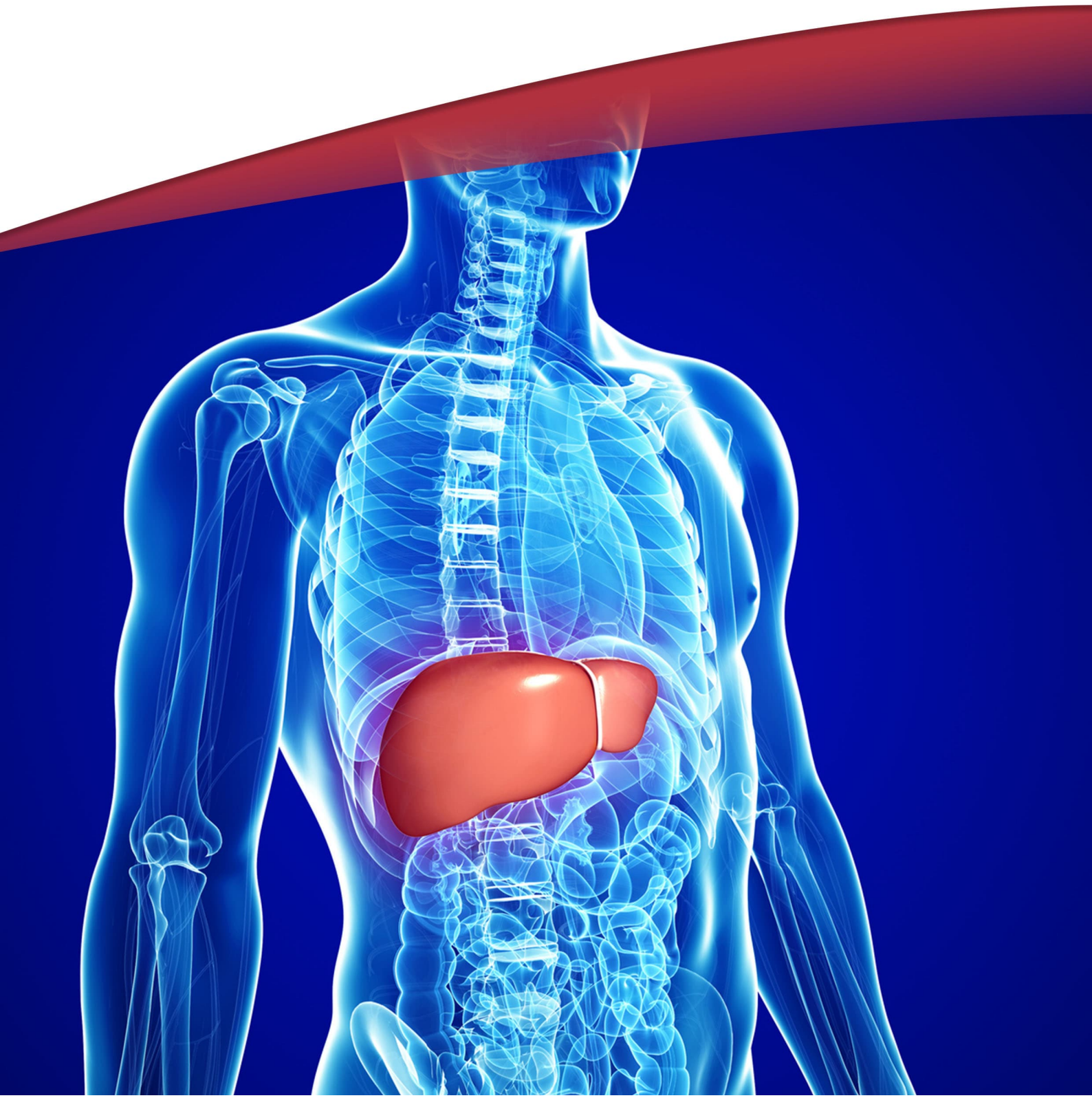
— Professional Genotype Analysis —

Detoxification Report



Report for Vaness Kimbell (CP00096235)

The human body is exposed to thousands of toxins every single day which need to be detoxified. Substances including environmental pollutants, food additives, pesticides, medication, alcohol and hormones are transformed from being fat-soluble to water-soluble, allowing them to be more easily excreted from the body via urine and bile.

Detoxification occurs predominantly in the liver in two major phases: Phase 1 Reactions and Phase 2 Conjugation, and a less well-known third phase: Phase 3 Antiporter Activity.

Poor detoxification can impact many systems, leading to various symptoms including:
• **Gastro-intestinal**: halitosis, bitter taste, bloating, fatty stools, constipation, diarrhoea, intolerance to fatty foods, swollen liver, gallbladder problems
• **Immune**: food allergies, skin issues (rashes, itchiness), asthma, recurrent infections
• **Endocrine**: infertility, PMS, weight gain, depression, anxiety, mood swings
• **Nervous**: headaches, dementia, poor memory and concentration, neuralgia
• **Musculo-skeletal**: muscle aches and weakness, arthritis
• **Other**: sensitivity to chemicals and odours, chronic fatigue, anaemia and premature ageing

Detoxification pathways are influenced significantly by genetic variance, as well as nutrition, age, sex, lifestyle habits such as drinking coffee or smoking.

The Detoxification report describes the genes, nutrients, and lifestyle and environmental factors that can impact detoxification. In addition to a detoxification overview diagram, it provides five personalised summary pathways and detailed results, followed by a detoxification guide. The pathways covered are:
• Alcohol
• Mould
• Non-steroidal anti-inflammatory drugs (NSAIDs)
• Paracetamol
• Polycyclic aromatic hydrocarbons (PAHs)

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Detoxification Summary

Phase 1 reactions

Cytochrome P450s

CYP1A1 🟢🟢
CYP1A2 🔴▲▲
CYP1B1 🟡🟡▲▲
CYP2A6 🟢
CYP2C19 🟡🟢▼
CYP2C9 🟢🟢
CYP2D6 🟡🟡🟢🟢▲▼
CYP2E1 🟢
CYP3A4 🟢

Alcohol

ADH1B 🟡🟢▲
ADH1C 🔴🔴▲▲▲▲
ALDH2 🟢

Pesticides, Lipids

PON1 🟡🟢▲▼

ROS detoxification

GPX1 🔴▼▼
NQO1 🟡▼
SOD2 🟡🟡▼▼

Phase 2 conjugation

Glucuronidation

UGT1A1 🟡▼
UGT1A6 🔴

Sulphonation

SULT1A1 🟢
SULT1E1 🟢
SULT2A1 🟡▼

Acetylation

NAT1 🟢
NAT2 🔴🟢▼▼

Glutathione conjugation

GSTM1 🔴▼▼
GSTP1 🟢🟢
GSTT1 🟢

Methylation

COMT 🟡🟡▼▼
TPMT 🟢🟢

Phase 3 antiporter

Antiporter

ABCB1 🔴▼▼

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Detoxification Summary
Inhibitors and Inducers

Phase 1 reactions

Cytochrome P450s

Caffeine
Smoking
Brussels sprouts
Carrots
Celery
Grapefruit
Green tea
Mustard
Parsley
Parsnips
Radish
St. John's Wort
Wasabi
Watercress

Alcohol

Magnesium
Molybdenum
Vitamin B2
Vitamin B3
Zinc

Pesticides

Calcium
Vitamin C
Vitamin E
Alcohol
Antibiotics
Heavy metals
Obesity
Smoking

ROS detoxification

Glutathione
Manganese
Selenium
Sulforaphane
Vitamin B2
Vitamin C

Phase 2 conjugation

Glucuronidation

Apples
Brussels sprouts
Broccoli
Cabbage
Calcium d-glucarate

Sulphonation

Sulphur foods

Acetylation

Acetyl-CoA
Vitamin B5

Glutathione conjugation

Glutathione

Methylation

B Vitamins
Choline
Magnesium
Zinc
Green tea

Phase 3 antiporter

Antiporter

Fasting
St. John's Wort
Black pepper
Flavonoids

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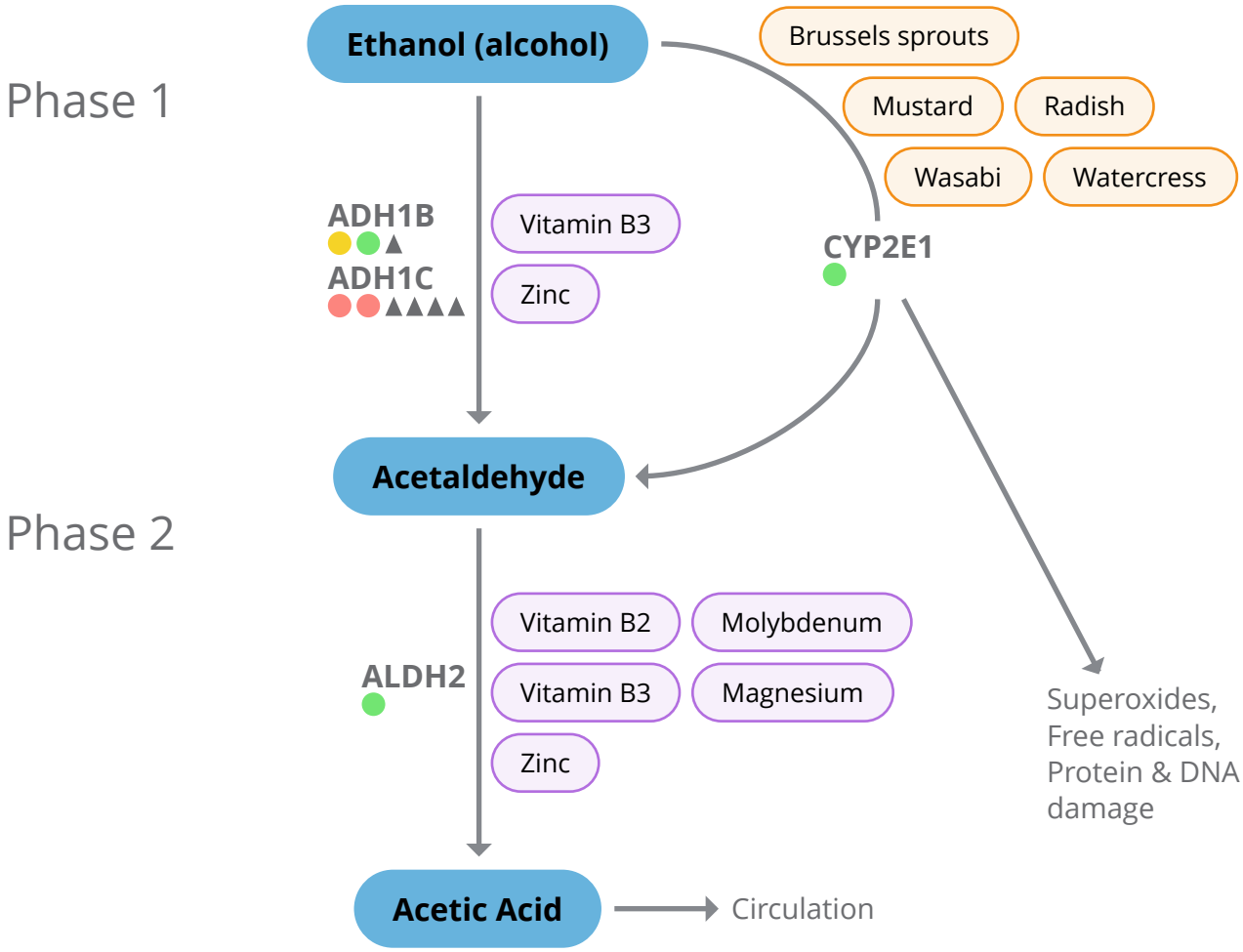
Alcohol Detoxification



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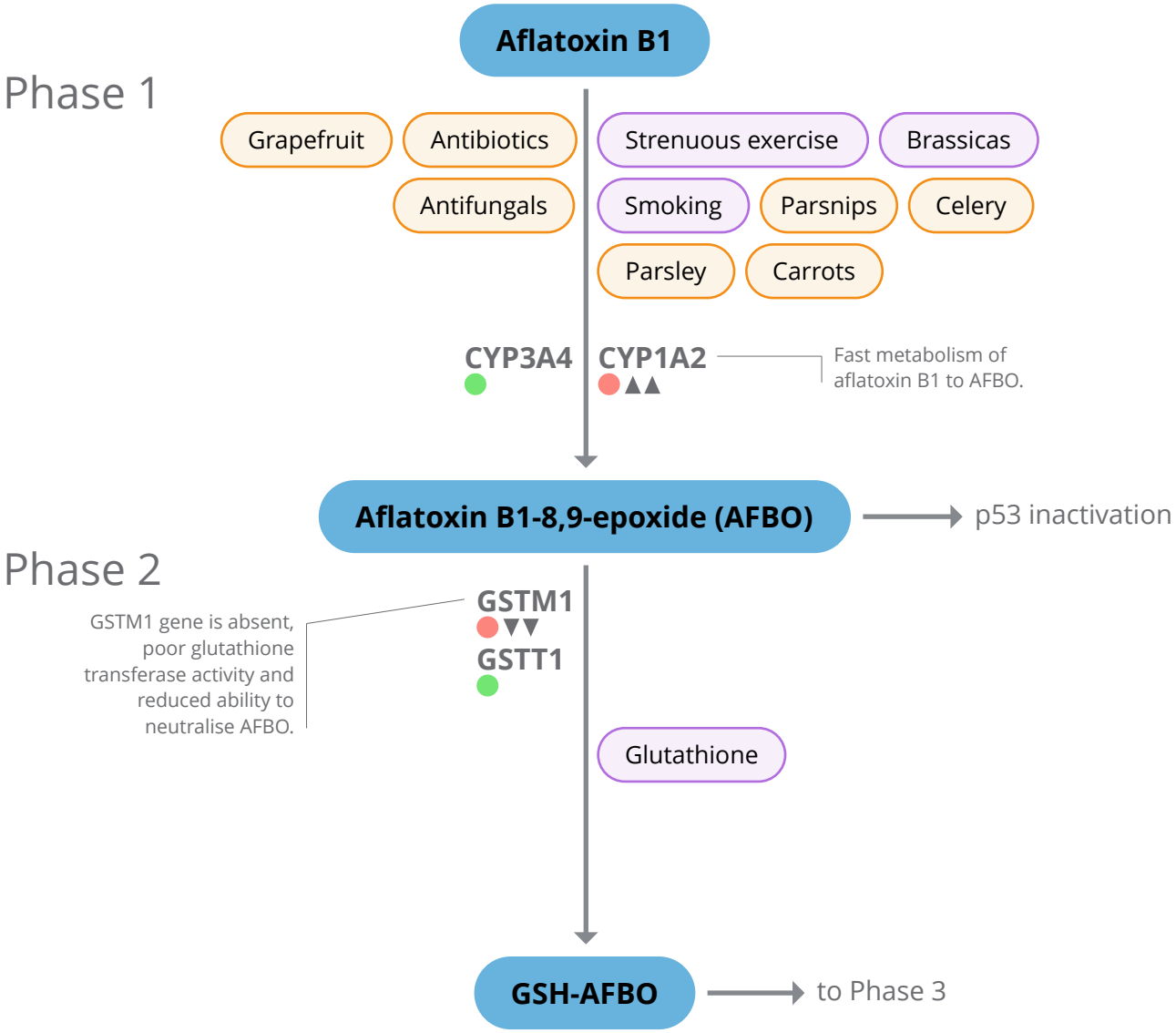
Mould Detoxification

This diagram specifically focuses on aflatoxin B1 but other types of moulds follow a similar detoxification pathway.



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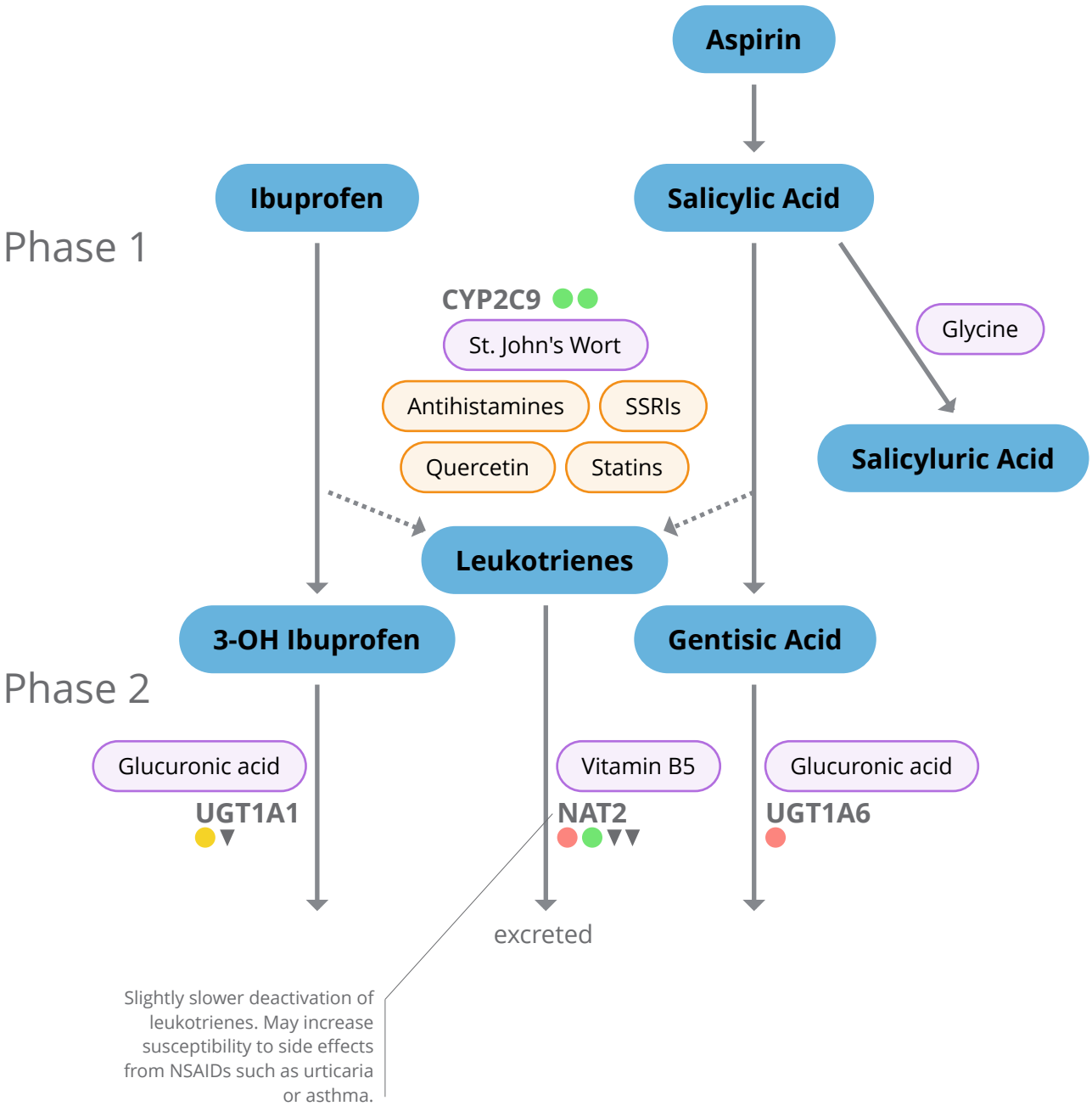
Non-steroidal anti-inflammatory drugs (NSAIDs) Detoxification



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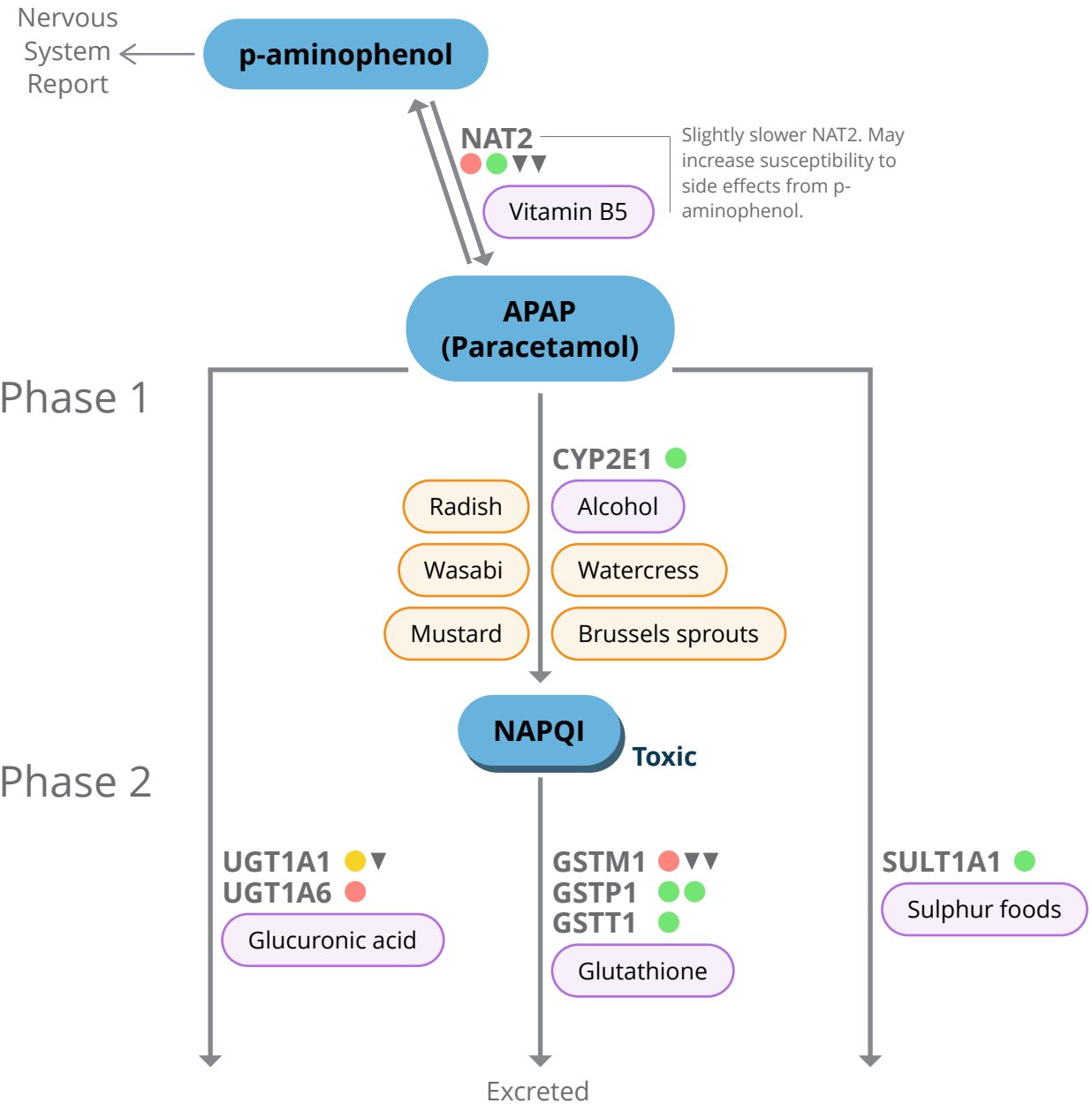
Paracetamol Detoxification



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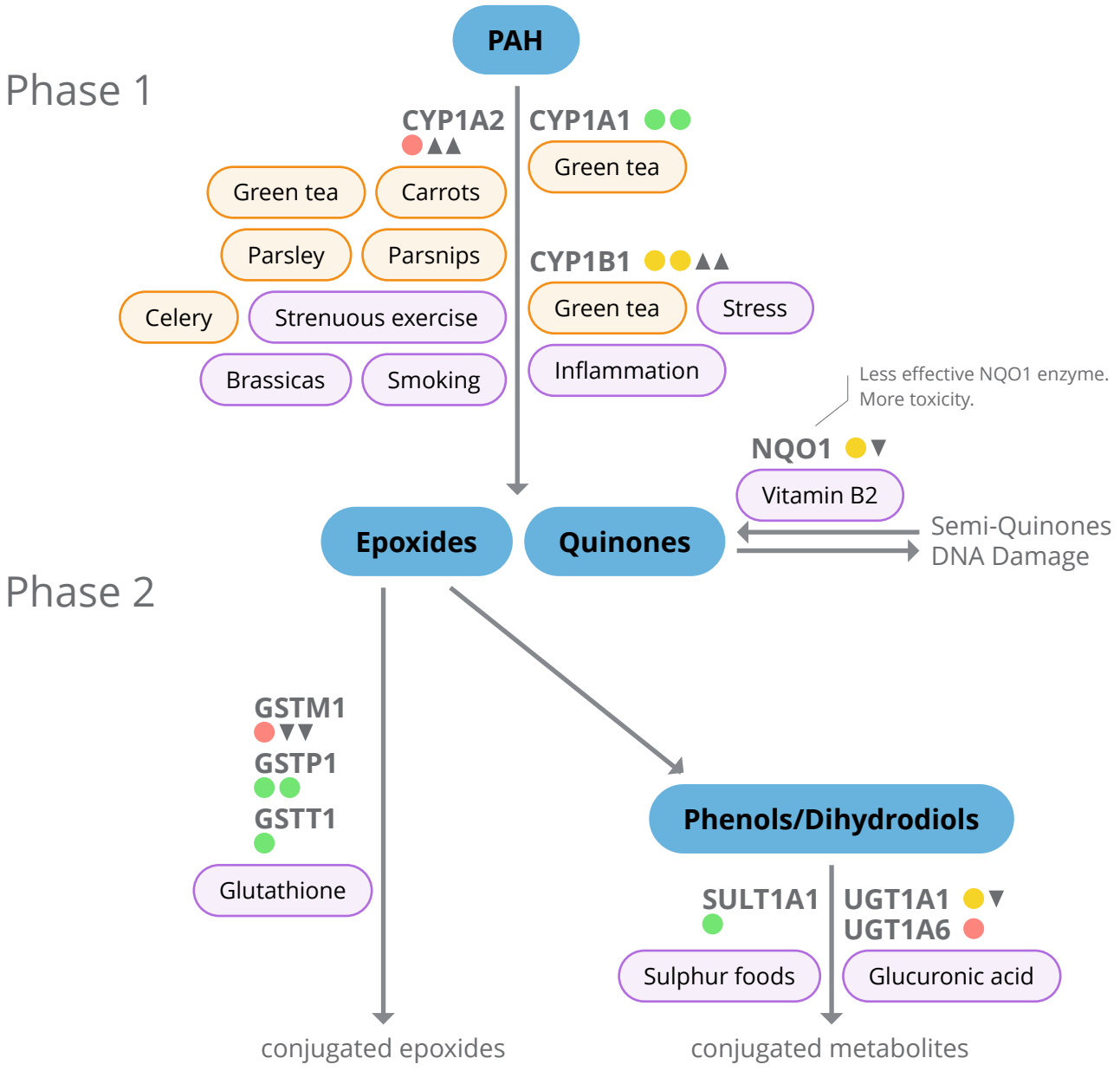
PAHs Detoxification

Polycyclic aromatic hydrocarbons (PAHs) are environmental pollutants formed during the incomplete combustion of fuels, diesel engine exhaust fumes, cigarette smoke, coal soot, smoke from high temperature cooking (grilling, roasting, frying), and forest & bush fires.



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Detailed Results for Phase 1

ADH1B
rs1229984

CT ▲

Faster metabolism of ethanol to acetaldehyde, due to the T allele. Increased risk of acetaldehyde toxicity or symptoms, but maybe protective against alcoholism. The T allele is common in Asian populations, but occurs at low frequency in European and African populations.

Replenish cofactors NAD+ (vitamin B3) and zinc, which may be depleted by alcohol metabolism.

ADH1B
rs2066702

GG

Relatively slower conversion of ethanol to acetaldehyde, compared to the A allele. No exceptional risk of acetaldehyde toxicity or symptoms. Most common genotype in all populations.

Replenish cofactors NAD+ (vitamin B3) and zinc, which may be depleted by alcohol metabolism.

ADH1C
rs1693482

CC ▲▲

Although this is the 'wild' type, it is reported as negative (red) due to higher enzyme activity and rate of conversion of ethanol to acetaldehyde. Increased risk of acetaldehyde toxicity after consuming alcohol which may cause unpleasant symptoms such as facial flushing, urticaria, dermatitis, rhinitis and asthma like reactions, more severe hangovers and protein and DNA damage. Most common genotype in Asians. May be protective against alcoholism.

Replenish cofactors NAD+ (vitamin B3) and zinc, which may be depleted by alcohol metabolism.

ADH1C
rs698

TT ▲▲

Although this is the 'wild' type, it is reported as negative (red) due to higher enzyme activity and rate of conversion of ethanol to acetaldehyde. Increased risk of acetaldehyde toxicity after consuming alcohol which may cause unpleasant symptoms such as facial flushing, urticaria, dermatitis, rhinitis and asthma like reactions, more severe hangovers and protein and DNA damage. Most common genotype in Asians. May be protective against alcoholism.

Replenish cofactors NAD+ (vitamin B3) and zinc, which may be depleted by alcohol metabolism.

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Detailed Results for Phase 1 (continued)

ALDH2 rs671	GG	Normal ability to detoxify acetaldehyde. No increase in risk of acetaldehyde toxicity. However detoxification may also be affected by other genetic variants, particularly on ADH and CYP2E1 genes, and by environmental factors including level of alcohol consumption, gender, body composition, nutritional status and liver health.
CYP1A1 rs1048943	TT	CYP1A1 catalyses many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. The CYP1A1 enzyme is induced by polycyclic aromatic hydrocarbons (PAHs) - chemicals released from burning coal, oil, tobacco, wood, or other organic substances such as chargrilled meat - which it may convert to carcinogenic intermediates. Normal enzyme activity leading to normal (not increased or decreased) metabolism of substrates. Lower risk of oxidative damage from reactive intermediate metabolites. Green tea, berries, turmeric and grapefruit can reduce CYP1A1 enzyme activity.
CYP1A1 rs4646903	AA	Normal CYP1A1 activity leading to normal (not increased or decreased) metabolism of substrates. Lower risk of oxidative damage from reactive intermediate metabolites. Green tea, berries, turmeric and grapefruit can reduce CYP1A1 enzyme activity.
CYP1A2 rs762551	AA ▲▲	CYP1A2's endogenous substrate is unknown; however it metabolises polycyclic aromatic hydrocarbons (PAHs) into carcinogenic intermediates. Other substrates for this enzyme include caffeine, aflatoxin B1, and paracetamol. Fast metabolism of substrates. We report this genotype as negative in the context of detoxification and fast synthesis of reactive intermediates, however it is positive in terms of caffeine tolerance. Smoking is a potent inducer of this pathway along with strenuous exercise and brassica foods. Green tea, grapefruit and apiaceous vegetables, such as carrots, parsnips, celery and parsley can help inhibit CYP1A2.

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Detailed Results for Phase 1 (continued)

CYP1B1
rs1056836

CG ▲

CYP1B1 is involved in oestrogen metabolism, particularly in the synthesis of 4-hydroxy (4OH) oestrogens, which are potentially harmful in the body. CYP1B1 is induced by polycyclic aromatic hydrocarbons (PAHs) causing increased synthesis of the undesirable 4OH oestrogens and other toxic intermediates. Increased CYP1B1 enzyme activity and risk of oxidative damage, particularly if Phase 2 pathways are slow.

CYP1B1 can be further induced by stress and inflammation, and its activity can be reduced with green tea, quercetin and olive oil.

CYP1B1
rs1800440

CT ▲

Increased CYP1B1 enzyme activity. Increased risk of oxidative damage, particularly if Phase 2 pathways are slow.

CYP1B1 can be further induced by stress and inflammation, and its activity can be reduced with green tea, quercetin and olive oil.

CYP2A6
rs1801272

AA

CYP2A6 is known to hydroxylate warfarin and other pharmaceutical drugs. It also metabolises nicotine, aflatoxin B1 and nitrosamines (from cigarette smoke). Normal (not increased or decreased) metabolism of substrates.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication. Nicotine and grapefruit inhibit CYP2A6 activity.

CYP2C19
rs12248560

CC

CYP2C19 metabolises a wide variety of pharmaceutical drugs including some NSAIDs, anticonvulsants, proton pump inhibitors, antidepressants, sedatives and antimalarials. Normal (not increased or decreased) metabolism of substrates. The other SNP has more impact on CYP2C19 than this one.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication.
St. John's Wort, acetylsalicylic acid (aspirin) and corticosteroids can increase CYP2C19 activity, while flavonoids and some SSRIs can reduce it.

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Detailed Results for Phase 1 (continued)

CYP2C19
rs4244285

AG▼

Decreased CYP2C19 enzyme activity and slower metabolism of substrates including anticoagulants and other pharmaceutical drugs which may alter their efficacy. This SNP has more impact on CYP2C19 activity than the other SNP.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication. St. John's Wort, acetylsalicylic acid (aspirin) and corticosteroids can increase CYP2C19 activity, while flavonoids and some SSRIs can reduce it.

CYP2C9
rs1057910

AA

CYP2C9 is metabolises a wide variety of pharmaceuticals, including certain anticonvulsants (phenytoin), blood sugar lowering drugs (tolbutamide), anti-inflammatories (ibuprofen) and anticoagulants (warfarin). Normal (not increased or decreased) enzyme activity and metabolism of substrates.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication.
St. John's Wort has been shown to induce CYP2C9 while antihistamines, statins, SSRIs and quercetin have been shown to inhibit this pathway.

CYP2C9
rs1799853

CC

Normal (not increased or decreased) enzyme activity and metabolism of substrates including anti-inflammatory and anticoagulant drugs.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication. St. John's Wort has been shown to induce CYP2C9 while antihistamines, statins, SSRIs and quercetin have been shown to inhibit this pathway.

CYP2D6
rs1135840

CG▲

CYP2D6 is known to metabolise as many as twenty five percent of commonly prescribed drugs as well as lipids, hormones and toxins. Its substrates include antidepressants, antipsychotics, analgesics and anti-tussives, beta adrenergic blocking agents, antiarrythmics and antiemetics. Fast metaboliser of substrates, such as conversion of codeine to morphine (which may increase risk of morphine toxicity).

Always refer to your GP or specialist before adjusting dosage of any prescribed medication.
Pregnancy and some medications can induce CYP2D6 while black pepper and valerian can inhibit it.

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Detailed Results for Phase 1 (continued)

CYP2D6 rs16947	GA▼	Possible slower metaboliser of substrates, such as tramadol, a pain relief drug, and conversion of codeine to morphine (which may reduce or delay efficacy). Always refer to your GP or specialist before adjusting dosage of any prescribed medication. Pregnancy and some medications can induce CYP2D6 while black pepper and valerian can inhibit it.
CYP2D6 rs35742686	II	Normal (not increased or decreased) enzyme activity and metabolism of substrates, such as conversion of codeine to morphine, and of lipids and hormones. Always refer to your GP or specialist before adjusting dosage of any prescribed medication. Pregnancy and some medications can induce CYP2D6 while black pepper and valerian can inhibit it.
CYP2D6 rs3892097	CC	Normal (not increased or decreased) enzyme activity and metabolism of substrates, including conversion of codeine to morphine, and of lipids and hormones. Always refer to your GP or specialist before adjusting dosage of any prescribed medication. Pregnancy and some medications can induce CYP2D6 while black pepper and valerian can inhibit it.
CYP2E1 rs2031920	CC	CYP2E1 metabolises endogenous substrates (ethanol, acetone, acetal) and exogenous substrates such as benzene, carbon tetrachloride, ethylene glycol, and nitrosamines (in cigarette smoke). It is accountable for up to 10% of ethanol oxidation in the liver. In the absence of NADPH (vitamin B3), oxidation of ethanol to aldehyde by CYP2E1 results in superoxides. Normal CYP2E1 activity and alcohol metabolism (conversion of ethanol to acetaldehyde). High alcohol consumption, starvation and diabetic state will increase CYP2E1 activity regardless of genotype and should be avoided since increased activity of this pathway generates free radicals including increased acetaldehyde.

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Detailed Results for Phase 1 (continued)

CYP3A4
rs2740574

TT

The CYP3A4 enzyme is involved in the metabolism of approximately half the drugs in use today, including acetaminophen, codeine, cyclosporin A, diazepam and erythromycin. It also metabolises some steroids and hormones, as well as aflatoxin B1. Normal CYP3A4 activity and metabolism of pharmaceutical drugs and aflatoxin B1. Lower risk of oxidative damage.

Always refer to your GP or specialist before adjusting dosage of any prescribed medication.
CYP3A4 expression is induced by glucocorticoids and some pharmacological agents and is strongly inhibited by grapefruit, antifungals and antibiotics.

GPX1
rs1050450

AA ▼▼

GPX1 supports the removal of hydrogen peroxide (H2O2) with cofactor glutathione, which protects cells from oxidative damage. Lower GPX activity. The A allele indicates more potential for H202 accumulation.

Support GPX1 with selenium and glutathione.

NQO1
rs1800566

AG ▼

NQO1 reduces quinones to hydroquinones, preventing the production of radical species. Less effective conversion (reduction) from quinones to hydroquinones. This can result in more toxicity.

As NQO1 is a flavoprotein, supporting flavin levels with vitamin B2 can be helpful. THF (folate) can also act as a reducing agent. Glucosinolate derived compounds, such as sulforaphane, found in cruciferous vegetables (and mustard, cabbage and horseradish) are known to effectively induce NQO1.

PON1
rs662

CT ▲

PON1 is responsible for the detoxification of organophosphates (the base of many insecticides, herbicides and nerve agents), oxidised lipids and aromatic esters. Intermediate enzyme activity, although somewhat substrate dependent. Associated with slightly faster hydrolysation of organophosphate pesticides but slightly slower hydrolisation of nerve gases such as sarin (than the TT wild genotype).

The C allele occurs much more frequently in East Asian, Sub-Saharan African and USA African American populations than in Caucasian populations. Calcium and vitamins C & E can help support PON1 activity.

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Detailed Results for Phase 1 (continued)

PON1 rs854560	TA ▼	High levels of PON1 and ability to metabolise pesticides and oxidised fats (but lower than wild type). Decreased risk of development of atherosclerosis. Calcium and vitamins C & E can help support PON1 activity.
SOD2 rs2758331	AC ▼	Reduced SOD activity and potential for higher superoxides and free radical damage. Ensure adequate intake of manganese to support SOD activity and increase antioxidant levels to reduce free radical damage.
SOD2 rs4880	GA ▼	Reduced SOD activity and potential for higher superoxides and free radical damage. Ensure adequate intake of manganese to support SOD activity and increase antioxidant levels to reduce free radical damage.

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Detailed Results for Phase 2

COMT rs4633	TC ▼	Reduced COMT activity and slower metabolism of catecholamines (dopamine and adrenaline), which can be helpful or not depending on the context. Be aware of other factors that may raise catecholamines, such as stress, caffeine and other stimulants. Support steady (but not excessive) methylation to provide SAMe (cofactor), and limit SAH (inhibitor) - excess homocysteine may indicate imbalance.
COMT rs4680	AG ▼	Reduced COMT activity and slower metabolism of catecholamines (dopamine and adrenaline), which can be helpful or not depending on the context. Be aware of other factors that may raise catecholamines, such as stress, caffeine and other stimulants. Support steady (but not excessive) methylation to provide SAMe (cofactor), and limit SAH (inhibitor) - excess homocysteine may indicate imbalance.
GSTM1 GSTM1	DD ▼▼	The GSTM1 gene is absent (null). Loss of function of the GSTM1 gene, poor glutathione transferase activity and inability to neutralise semi-quinones. Increase antioxidants including glutathione and address inflammation and oxidative stress which deplete glutathione levels further. Consider all GST genotypes together.
GSTP1 rs1138272	CC	Normal glutathione transferase activity. High levels of oxidative stress and low glutathione levels will slow GST activity regardless of genotype. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended.
GSTP1 rs1695	AA	Normal glutathione transferase activity. High levels of oxidative stress and low glutathione levels will slow GST activity regardless of genotype. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended.

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Detailed Results for Phase 2 (continued)

GSTT1 GSTT1	II	GSTT1 present. Normal GSTT1 glutathione transferase activity. High levels of oxidative stress and low glutathione levels will slow GSTT1 activity regardless of genotype. Reducing stress and inflammation and increasing antioxidants including glutathione is recommended.
NAT1 rs4986782	GG	NAT1 metabolises various drugs and environmental toxins including aromatic amines in hair dyes and cigarette smoke. Normal acetylator. Not associated with increased risk of DNA damage. Increase vitamin B5 to support this pathway.
NAT2 rs1041983	CC	Wild genotype - fast NAT2 acetylation activity. Not associated with susceptibility to side effects from particular chemicals. Increase acetyl-CoA and vitamin B5 to support this pathway.
NAT2 rs1801280	CC ▼▼	Slow NAT2 activity. Increased susceptibility to side effects from many chemicals including those produced by caffeine and cigarettes as well as aromatic amine and hydrazine drugs used medicinally. Increase acetyl-CoA and vitamin B5 to support this pathway.
SULT1A1 rs9282861	CC	Wild genotype - normal sulphate conjugation activity. A diet low in sulphur will impede this pathway regardless of genotype - ensure adequate sulphur-containing nutrients in the diet to support this pathway.
SULT1E1 rs3736599	CC	Normal sulphoconjugation (detoxification) of substrates including oestrogen, DHEA and pregnenolone. A diet low in sulphur will impede this pathway regardless of genotype - ensure adequate sulphur-containing nutrients in the diet to support this pathway.
SULT2A1 rs182420	TC ▼	Reduced SULT2A1 enzyme activity and sulphoconjugation of DHEA. Associated with higher circulating androgens and increased risk of PCOS if unmanaged. Ensure adequate sulphur-containing nutrients in the diet to support this pathway.

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Detailed Results for Phase 2 (continued)

TPMT rs1142345	TT	Normal TPMT enzyme activity and metabolism of thiopurine drugs. Ensure adequate methylation. Always consult a medical professional before altering dosage of prescription drugs.
TPMT rs1800460	CC	Normal TPMT enzyme activity and metabolism of thiopurine drugs. Ensure adequate methylation. Always consult a medical professional before altering dosage of prescription drugs.
UGT1A1 rs4148324	TG ▼	Possible impaired glucuronidation and inactivation of steroids (including sex steroid hormones) bilirubin, and medications (including paracetamol and aspirin). Avoid carbohydrate-free diets since glucose is needed for this pathway to function optimally. Calcium d-glucarate has been shown to improve glucuronidation by inhibiting beta-glucuronidase produced by unhealthy gut bacteria.
UGT1A6 rs17863783	GG	Wild genotype - associated with low UGT1A6 enzyme activity. Calcium d-glucarate has been shown to improve glucuronidation by inhibiting beta-glucuronidase produced by unhealthy gut bacteria.

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Detailed Results for Phase 3

ABCB1
rs1045642

AA ▼▼

Low ABCB1 enzyme activity. Less effective transport of substrates across cellular membranes - slower detoxification of drugs, xenobiotics, lipids and steroids.

Increased risk of toxicity. St. John's Wort and fasting are inducers of ABCB1 while black pepper and flavonoids are inhibitors.

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A Guide to Detoxification

This guide provides detailed explanations of the genes and gene products involved in detoxification.

Toxins

Toxins are exogenous and endogenous substances that are harmful to the body and are capable of causing disease.

Exogenous toxins include alcohol, cigarette smoke, diet (sugar, trans-fats, food additives), environmental pollutants (smoke, pesticides and herbicides), household detergents, cosmetics, radiation, water (chlorine and fluorine), mould, pollen, heavy metals (aluminium, lead, mercury etc.), and pharmaceutical drugs.

The majority of endogenous toxins are products and by-products of digestion, but also result from stress, oxidative stress, dysbiosis, bacterial, fungal or viral infection, hormones and inflammatory chemicals, such as histamine.

The rate at which the liver, and other organs, can eliminate toxins determines individual susceptibility to increased toxic load. High toxic load can cause a wide range of symptoms affecting gastro-intestinal, immune, endocrine, nervous and musculo-skeletal systems.

The detoxification pathways are influenced by nutrition, age, sex, lifestyle habits such as drinking coffee or smoking, as well as genetic variance. In this report we will focus on five detoxification pathways: alcohol, mould, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and polycyclic aromatic hydrocarbons (PAHs).

Phase 1 Reactions

During Phase 1, substrates are primed for conjugation by the addition or exposure of a binding site via oxidation, reduction or hydrolysis reactions. A significant side effect of Phase 1 detoxification is the production of free radicals as the toxins are transformed, making them more reactive and potentially damaging.

Increased Phase 1 enzyme activity may be helpful and/or unhelpful since it increases the metabolism of environmental toxins but can also alter the efficacy or toxicity of certain prescription medications, and can lead to higher circulating free radicals. For this reason, we report increased Phase 1 enzyme activity due to genetic variance as negative.

The CYP450 enzymes

The cytochrome P450 (CYP450) enzymes are a large superfamily of enzymes, requiring heme and NADPH as cofactors, responsible for metabolising thousands of endogenous and exogenous substances. They are expressed in the membranes of mitochondria and the endoplasmic reticulum of cells - primarily the liver, but also in other organs and systems. CYP enzymes function as monooxygenases and effect oxidation by transfer of one oxygen atom through a number of steps.

Some CYPs metabolise only one or very few substrates while others are responsible for metabolising multiple substrates. Many genetic polymorphisms have been discovered for the CYP450s which can explain the differences in metabolism of steroids, fatty acids, and xenobiotics between individuals.

Inducers increase the activity of CYPs and accelerate the metabolism of the substrates handled by the respective enzymes. Some substrates are also inducers. In general, cigarette smoke, charred food, caffeine, alcohol, cruciferous vegetables and St. John's Wort are all potent inducers of Phase 1 enzymes. On the contrary, inhibitors of CYPs reduce the metabolism of the substrates and may lead to altered efficacy (of prescription medications, for example) or toxicity of any substrate or metabolite.

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The table below shows the CYP enzymes present in the Detoxification report with their inducers and inhibitors (non-exhaustive list).

Enzyme	Inducers	Inhibitors
CYP1A1	Poly aromatic hydrocarbons (PAHs) (inc. in chargrilled meat, cigarette smoke), oestrone, cruciferous vegetables containing indole 3 carbinol (I3C), diindolylmethane (DIM), insulin, omeprazole (PPI)	Hesperetin (in citrus fruits), resveratrol (purple grapes), ellagic acid (berries), green tea catechins (EGCG), kava, naringenin (in grapefruit), cumin, turmeric, peppermint, St. John's Wort, DHEA. Fluoroquinolones (antibiotics)
CYP1A2	Poly aromatic hydrocarbons (PAHs) (inc. in chargrilled meat, cigarette smoke), caffeine, aflatoxin B1, cruciferous vegetables, strenuous exercise	Resveratrol (purple grapes), ellagic acid (berries), green tea catechins (EGCG), kava, apiaceous vegetables, naringenin (in grapefruit). DHEA. Some pharmaceutical medications - fluoroquinolones (antibiotics), fluvoxamine (SSRI), and oral contraceptive pills (OCP)
CYP1B1	Poly aromatic hydrocarbons (PAHs), stress, inflammation (via TNF cytokine)	Green tea catechins (EGCG), DHEA, diindolylmethane (DIM), St. John's Wort, grapefruit, quercetin, olive oil, kaempferol (in kale, beans, tea, spinach, and broccoli)
CYP2A6	Coumarin, nicotine, cotinine, barbiturates	Flavonoids (naringenin - in grapefruit. Nicotine. Many pharmaceutical medications
CYP2C9	Alcohol, ibuprofen, St. John's Wort	Flavonoids (naringenin - in grapefruit), alkaloids, quercetin, some pharmaceutical medications - antihistamines, statins and (some) SSRIs
CYP2C19	St. John's Wort, acetylsalicylic acid (aspirin), corticosteroids	Flavonoids (naringenin - in grapefruit). Some SSRIs
CYP2D6	Pregnancy, some medications - haloperidol (antipsychotic), rifampicin (bactericidal) and dexamethasone (glucocorticoid)	Black pepper, goldenseal, valerian, black cohosh, berberine, some SSRIs, cannabidiol, niacin (Vitamin B3)
CYP2E1	Alcohol, fasting, acetaminophen (paracetamol)	Grape seed extract, resveratrol, tannic acid, garlic, liquorice root, watercress, isothiocyanates (radish, watercress, mustard and wasabi), niacin (Vitamin B3)
CYP3A4	Many pharmaceutical medications - check with a reliable source. St. John's Wort, capsaicin, valerian, echinacea purpurea, Poly aromatic hydrocarbons (PAHs) (inc. in chargrilled meat, cigarette smoke)	Many pharmaceutical medications - check with a reliable source. Grapefruit juice (bergamottin, naringenin) and noni juice, St. John's Wort, sage, ginkgo biloba, green tea catechins (ECGC), milk thistle, resveratrol

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Other Phase 1 enzymes

Other major Phase 1 enzymes include alcohol and aldehyde dehydrogenases and PON1:

• Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) are responsible for the two-part break-down, by oxidative dehydrogenation, of alcohol in the body. This is discussed in detail later in the guide.

• Paraoxonase 1 (PON1) - breaks down, by hydrolysis, pesticides and oxidised lipids

PON1 encodes an enzyme responsible for the detoxification of organophosphates (the base of many insecticides, herbicides and nerve agents), oxidised lipids and also aromatic esters, particularly those of acetic acid. Human PON1 is synthesised in the liver and secreted into the blood, where it is associated exclusively with high density lipoproteins (HDLs) and may protect against development of atherosclerosis. Variants on PON1 decrease enzyme activity and plasma levels increasing risk of exposure to harmful chemicals, oxidised lipids and development of atherosclerosis. Inhibitors of PON1 include obesity, antibiotics, heavy metals, alcohol and smoking. Calcium and vitamins C & E can help support PON1 activity.

Free Radicals

Free radicals produced by Phase 1, also known as Reactive Oxygen Species (ROS), are extremely reactive, and should be detoxified (neutralised) as soon as possible, to prevent inflammation and tissue damage.

Manganese superoxide dismutase (MnSOD), coded by the SOD2 gene, is activated in mitochondria to detoxify the free radical superoxide into hydrogen peroxide (H2O2) and molecular oxygen. The H2O2 is largely removed by glutathione peroxidases and catalase. A SNP on SOD2 can reduce its activity increasing risk of free radical damage. Manganese, found in whole grains, nuts, leafy vegetables and teas, can help support SOD2 activity. The glutathione peroxidase GPX1, requires selenium (it is a selenoprotein), and glutathione as cofactor. A SNP can result in lower GPX1 activity, which indicates more potential for oxidative stress.

NADPH quinone oxidoreductases (NQOs) are involved in converting quinones to corresponding hydroquinones, preventing the production of radical species. SNPs on the NQO1 gene result in lower activity and less DNA protection.

Phase 2 Conjugation

During Phase 2, substrates are deactivated and made more water-soluble, a process that prepares them for excretion via the bile to the small intestine or via the kidneys to urine. Decreased Phase 2 activity is unhelpful as it can lead to higher levels of toxic intermediates (products of Phase 1). For this reason we report decreased Phase 2 enzyme activity due to genetic variance as negative.

Conjugation occurs via one of six reactions:

Glucuronidation
substrates are conjugated with glucuronic acid by UDP-glucuronosyltransferase (UGT) enzymes, coded by UGT genes. The UGTs metabolise small lipophilic molecules, such as steroids, bilirubin, hormones and 40–70% of pharmaceutical drugs, including aspirin and paracetamol. UGT1A1 variants lead to lower enzyme activity, however a UGT1A6 variant can increase enzyme activity and confer better protection. Good sources of glucuronic acid include apples, Brussels sprouts, broccoli and cabbage. Additionally, calcium d-glucarate can help to reduce excess beta-glucuronidase, produced by certain types of gut bacteria, which can otherwise de-conjugate toxins.

Sulphonation
substrates are conjugated with sulphate by sulphotransferase (SULT) enzymes. They catalyse the conjugation of many substrates including steroid hormones, neurotransmitters, iodothyronines, eicosanoids, retinol, vitamin D, pharmaceutical drugs, and xenobiotic compounds reducing their reactivity and preparing them for excretion. Variants on SULT genes cause decreased enzyme activity and impaired sulpho-conjugation. Sulphur-containing nutrients, in garlic, onion, Brussels sprouts and kale, can help to support this pathway.

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Glutathione conjugation
substrates are conjugated with glutathione by glutathione transferase (GST) enzymes. GSTM1, GSTP1 and GSTT1 are vital for the detoxification of compounds including pharmaceutical drugs, environmental toxins and endogenous toxins, including products of oxidative stress. Whole gene deletions of GSTM1 and GSTP1 (known as 'null' genotypes) confer higher risk of toxicity. To support this pathway, increase antioxidants including glutathione, vitamins C and E, and reduce inflammation and oxidative stress which deplete glutathione levels.

Amino acid conjugation
substrates are conjugated with glycine via glycine N-acyltransferase (GLYAT) in the mitochondria of liver and kidney cells. This process affects mitochondrial ATP production. GLYAT is thought to be important in the detoxification of endogenous and xenobiotic acyl-CoAs (which metabolise fatty acids) and salicylates (in aspirin, and in a wide array of foods). There are no meaningful SNPs to report for this gene.

Acetylation
substrates are conjugated by the addition of an acetyl group by N-terminal acetyltransferases (NAT) enzymes. NATs metabolise compounds found in many prescription drugs, caffeine, cigarette smoke and other xenobiotics. The variant on NAT1 is the most common and is associated with slow acetylation. Homozygous variants on NAT2 are associated with slow acetylator phenotypes and higher incidence of some cancers, and drug toxicity. The two NAT2 SNP genotype panel enables assessment of rapid vs slow acetylation. The cofactor acetyl-CoA and its precursor vitamin B5 are needed to support acetylation.

Methylation
substrates are conjugated by the addition of a methyl group via methyltransferases (MT) enzymes. The COMT enzyme inactivates neurotransmitters (dopamine, adrenaline, and noradrenaline) and hormones (including oestrogens) by applying a methyl group from SAMe to methylate the catechol molecule. Variants on the COMT gene are associated with lower activity. B vitamins including folate (B9), B2, and B12, and choline and betaine support SAMe synthesis. However, excess methyl groups may cause irritability, heightened stress response, hyperactivity, heightened pain sensitivity. The TPMT gene metabolises thiopurine chemotherapeutic and immunosuppressive drugs.

Phase 3 Antiporter Activity

Phase 3 involves the transport of a broad range of substrates including drugs, chemotherapeutic agents, lipids, steroids, peptides, bilirubin and glucocorticoid conjugates within and out of cells into urine, bile, the intestinal lumen and across the blood-brain barrier into capillaries for elimination.

Multidrug resistance protein 1 (MDR1), also known as P-glycoprotein 1 (P-gp or Pgp), coded by the ABCB1 (ATP-binding cassette sub-family member 1) gene, is an ATP-dependent efflux pump with broad substrate specificity. While decreased efflux activity may promote disease susceptibility (for example, in Alzheimer's disease) and drug toxicity, increased efflux activity may confer resistance to therapeutic drugs, for example, in IBD (inflammatory bowel disease) and multidrug-resistant cancers. As this report relates to detoxification, we report lower ABCB1 activity due to genetic variance as negative. St. John's Wort and calorie restriction are inducers of ABCB1 while black pepper and flavonoids are inhibitors.

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Alcohol

After alcohol is consumed, it is absorbed mainly from the small intestine into the bloodstream and then to the liver, where it is exposed to enzymes and metabolized.

Alcohol is detoxified in two steps. The first step (Phase 1) is the conversion of ethanol to, more toxic, acetaldehyde, by ADH genes. If alcohol intake is high, and ADH capacity is exceeded, more ethanol is metabolized to acetaldehyde, by the CYP2E1 gene. In the second step (Phase 2), acetaldehyde is metabolized to the inert metabolite acetic acid, by ALDH, which may be converted to acetyl CoA and enter the Krebs cycle.

Faster metabolism of ethanol to acetaldehyde and/ or slower metabolism of acetaldehyde to acetic acid can significantly raise acetaldehyde levels which, in turn, can stimulate histamine release. Acetaldehyde is also found in indoor air, tobacco smoke, and as a product of candida overgrowth. Acetaldehyde toxicity can cause unpleasant symptoms such as facial flushing, urticaria, dermatitis, rhinitis and asthma-like reactions (broncho-constriction), nausea, tachycardia, headaches, and protein and DNA damage.

ADH genes play a major role in ethanol metabolism to acetaldehyde. SNPs on ADH1B can lead to significantly increased enzyme activity and high levels of acetaldehyde, whereas the rate of ethanol conversion to acetaldehyde is reported to be up to 70% higher for the ADH1C wild type than for the variant genotype. Individuals with SNPs on ADH genes may experience increased toxicity (from alcohol consumption) and depletion of cofactors NAD+ (vitamin B3) and zinc, which should be replenished.

Along with ADH1B and ADH1C, CYP2E1 is one of the most important enzymes for phase 1 alcohol metabolism - accounting for up to 10% of ethanol oxidation in the liver. In the absence or insufficiency of NAD+ (cofactor of ADH), increased oxidation of ethanol to aldehyde by CYP2E1 generates reactive oxygen species (ROS).

Variants on the CYP2E1 gene are associated with up-regulated enzyme activity. Isothiocyanates, found in foods such as radish, Brussels sprouts, watercress, mustard and wasabi, have been found to reduce CYP2E1 activity.

ALDH2 is the major enzyme involved in the second stage (phase 2) of alcohol metabolism. Polymorphisms on ALDH2 can result in an inactive ALDH2 enzyme and a high risk of acetaldehyde toxicity after consumption of alcohol. As with ADH genes, cofactors for ALDH2 may be depleted during alcohol (acetaldehyde) metabolism, and requirements for NAD+, magnesium and molybdenum should be considered.

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Mould (Mycotoxins)

A mould is a fungus that grows in the form of multicellular filaments called hyphae. Some diseases can be caused by certain moulds: disease may result from allergic sensitivity to mould spores, from growth of pathogenic moulds within the body, or from the effects of ingested or inhaled toxic compounds (mycotoxins) produced by moulds.

There are numerous types of mould that produce different mycotoxins that are carcinogenic and/or toxic - such as acremonion, aflatoxin, alternaria, fusarium, penicillium or stachybotrys (black mould). The major foodborne mycotoxins of public health interest are aflatoxins.

Aflatoxin B1 (AFB1) is an aflatoxin produced by Aspergillus flavus and A. parasiticus. Aflatoxin B1 is a common contaminant in a variety of foods including peanuts, cottonseed meal, corn, and other grains; as well as animal feeds. It is considered the most toxic aflatoxin and it is highly implicated in hepatocellular carcinoma (HCC), which is the most well-known primary liver malignancy worldwide.

AFB1 is metabolised by cytochrome-P450 enzymes to the reactive intermediate AFB1-8,9-epoxide (AFBO), which can increase the risk of liver damage such as cirrhosis and, which binds to liver cell DNA, resulting in DNA adducts. DNA adducts interact with the guanine bases of liver cell DNA and cause a mutational effect in the P53 tumor suppressor gene, which may lead to HCC.

The main cytochrome P450 enzyme involved in mould detoxification is CYP1A2. As CYP1A2 SNPs are associated with fast activity they are considered detrimental. Smoking is a potent inducer of CYP1A2 along with strenuous exercise and brassica foods. Apiaceous vegetables, such as carrots, parsnips, celery and parsley can help inhibit CYP1A2. CYP3A4 is also involved in the first phase of detoxification. Grapefruit is a potent inhibitor of CYP3A4 activity. Consult your GP if you are on any medication since grapefruit has been shown to interact with many medications.

Phase 2 detoxification of the highly genotoxic AFBO intermediate is an essential pathway in order to prevent the formation of DNA adducts. Glutathione conjugation is involved in the elimination of AFBO, and AFB1-glutathione conjugate by GST is then degraded. Variance on GSTM1 and GSTT1 genes, which may be null (absent), can negatively impact ability to detoxify AFBO.

Alcohol and Hepatitis B & C have a synergistic effect with Aflatoxin B1 exposure by increasing the risk of liver damage and HCC, by favouring the persistence of mutations, and uncontrolled cell cycling when p53 is non-functional.

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NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature. Common NSAIDs include aspirin, ibuprofen, naproxen and diclofenac. Worldwide, over 73 million prescriptions of NSAIDs are written yearly, and approximately 30 million people take NSAIDs daily.

Side effects depend on the specific drug but largely include an increased risk of gastrointestinal ulcers and bleeds, heart attack, and kidney disease. Risk of experiencing side effects can be increased or decreased by genetic polymorphisms and nutrition and lifestyle factors.

Aspirin, or acetylsalicylic acid (ASA), is a natural chemical found in plants that is used to treat pain, fever, inflammation, migraines, and reduce the risk of major adverse cardiovascular events. After entering the body, aspirin is quickly deacetylated into salicylic acid, which is the active form. It is classified as a non-selective cyclooxygenase (COX) inhibitor. Ibuprofen is also a non-selective COX inhibitor used for treating pain, fever, and inflammation associated, for example, with painful menstrual periods, migraines, and rheumatoid arthritis.

In the first phase of detoxification, the clearance of NSAIDs is mediated by CYP2C9 to inactive hydroxy-NSAIDs. CYP2C9 genetic variants result in lower enzymatic activity and increased potency (analgesic effects) and side effects, including gastrointestinal bleeding. Therefore, a lower dose may be required.

St. John's Wort induces CYP2C9, which may reduce efficacy, whereas antihistamines, statins, SSRIs and quercetin can inhibit it, which may increase efficacy but also side effects.

As NSAIDs inhibit COX activity, the switch towards the alternative pathway 5-lipoxygenase (5-LOX) increased production of leukotrienes (proinflammatory mediators). As leukotrienes are inactivated by acetyl coenzyme A-dependent N-acetyltransferase (NAT). SNPs on the NAT2 gene can increase the risk of NSAID hypersensitivity symptoms such as urticaria or asthma.

Hydroxy-NSAIDs are conjugated mainly by glucuronidation via UGT1A1 and UGT1A6 enzymes. Decreased UGT activity leads to less efficient inactivation of NSAIDs, and their reactive metabolites.

It is worth mentioning that salicylic acid is mainly (about 65%) conjugated by glycine in phase 2 by ACSM2B although there are no significant SNPs to report.

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Paracetamol

Paracetamol, also known as acetaminophen (or APAP), is one of the most used fever and pain-relieving drugs worldwide, and its consumption is increasing every day.

The medication exerts its analgesic effect when p-aminophenol is converted to AM404 (N-arachidonoylphenolamine) by FAAH in the brain. A SNP on FAAH resulting in decreased enzyme activity could alter the therapeutic effects of paracetamol. As this happens in the brain, we test for this gene in our Nervous System Report.

As too much p-aminophenol is toxic, it needs to be deacetylated by N-deacetylase enzymes. It is conjugated via the addition of an acetyl group by the N-terminal acetyltransferases (NAT) enzymes. A slow NAT2 activity increases the susceptibility to side effects from paracetamol by having too much of p-aminophenol. The two-SNP genotype panel enables assessment of rapid vs slow acetylation.

Paracetamol is degraded via a minor pathway (about 5%) by CYP450s mainly by CYP2E1 to the liver-toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI). This is toxic even at therapeutic doses, causing hepatotoxicity, making paracetamol the first cause of acute liver failure in the Western world. NAPQI can be eliminated with the help of glutathione (via GST enzymes), hence high levels of paracetamol can deplete glutathione status. SNPs on GST genes can compromise the ability to neutralise NAPQI.

As alcohol is also degraded by CYP2E1, into acetaldehyde, it will also deplete glutathione, and can cause liver damage. Hence, drinking alcohol is not recommended while taking paracetamol (and vice-versa). Starvation and diabetic state increase CYP2E1 activity, further increasing the risk of NAPQI toxicity and free radical damage. Isothiocyanates, found in radish, Brussels sprouts, watercress, mustard and wasabi, can help to slow down CYP2E1 activity.

The majority of paracetamol (just over 50%) is metabolised by glucuronidation. SNPs on UGT1A1 may result in impaired glucuronidation of paracetamol. SNPs on UGT1A6 that increase its activity may be beneficial in detoxifying paracetamol more quickly. Approximately 30–44% of paracetamol is sulphonated. Polymorphisms on SULT1A1 can impair detoxification of paracetamol via this route.

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Polycyclic Aromatic Hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons (PAHs) are environmental pollutants formed during the incomplete combustion of fuels, diesel engine exhaust fumes, cigarette smoke, coal soot, smoke from high temperature cooking (grilling, roasting, frying), and forest & bush fires. Humans are exposed by inhalation, ingestion and skin contact.

Exposure to PAHs can cause symptoms such as eye and skin irritation, nausea, vomiting, diarrhoea and confusion in the short term, and increase the risk of developing atherosclerosis, cardiovascular diseases and cancers. Indeed, many PAHs have toxic properties. Approximately 90% of lung cancer cases are related to tobacco smoking and 1–2% are accounted for by outdoor air pollution and secondhand smoke.

Once absorbed, PAHs enter the lymph, circulate in the blood, and induce and are metabolized predominantly by CYP1A1, CYP1A2 and CYP1B1 enzymes in the liver. Pulmonary CYP1A1 is highly inducible by PAHs and the induction may last months, even after exposure to PAHs is discontinued.

These reactions lead to the formation of the active diol-epoxides, radical cations, and o-quinones which produce DNA adducts. PAH metabolites also trigger synthesis of reactive oxygen species (ROS), which can directly damage DNA, lipids, or proteins.

NADPH quinone oxidoreductases (NQOs) are involved in converting quinones to corresponding hydroquinones, preventing the production of radical species. SNPs on the NQO1 gene result in lower activity and less DNA protection.

The hydroxylated metabolites of the PAHs are excreted in urine both as free hydroxylated metabolites and as hydroxylated metabolites conjugated to glucuronic acid and sulfate. Phase 2 enzymes in the liver are responsible for the clearance of PAHs - including glutathione transferase (GST), UDP-glucuronosyltransferase (UGT), and sulfotransferase (SULT). SNPs on these genes alter their biological functions and affect the susceptibility to symptoms by long term PAH exposure (especially GSTM1 and GSTT1 polymorphisms).

Urinary 1- Hydroxypyrene (1-HP) is a commonly measured urine metabolite to assess PAH exposure.

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How to Read the Report

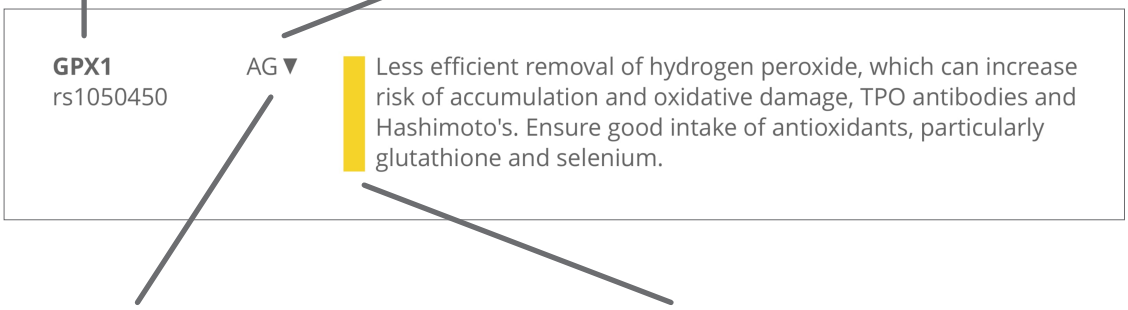
Genes

Results are listed in order of the gene short name. The 'rs' number is the reference sequence number that identifies a specific location on the genome. It is also known as a SNP (Single Nucleotide Polymorphism) pronounced 'snip', polymorphism or mutation.

Personalised Result

Your genotype result is shown as two letters (A,G,T or C) which represent the DNA bases present at that location.

Multiple attempts are made to achieve the required level of statistical confidence, but if that cannot be met it is reported as **'No result'**.



Arrow Direction

The direction of the arrow indicates the potential effect of the SNP on gene expression, where applicable - it can increase or decrease activity, or neither.

▲ up-regulates or increases the activity and effect on the gene

▼ down-regulates or decreases the activity and effect on the gene

No arrow - no effect on the activity of the gene

Highlight Colour

The genotype result highlight indicates the potential effect of the SNP on gene function in a particular context.

RED the effect of the variant is negative

AMBER the effect of the variant is somewhat negative

GREEN no variation, or the effect of the variant is positive

Pathway Diagram Key

Cofactor Inhibitor

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CYP3A4 Cytochrome P450, Family 3, Subfamily A, Polypeptide 4

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GPX1 glutathione peroxidase 1

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NQO1 NAD(P)H Quinone Dehydrogenase 1

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PON1 Paraoxonase 1

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SOD2 Superoxide Dismutase 2, Mitochondrial

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TPMT Thiopurine S-Methyltransferase

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UGT1A1 UDP Glucuronosyltransferase Family 1, Member A1

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