dnahormones®

Welcome

Exam ple2 Exam ple1

to your personalised DNA Hormones report

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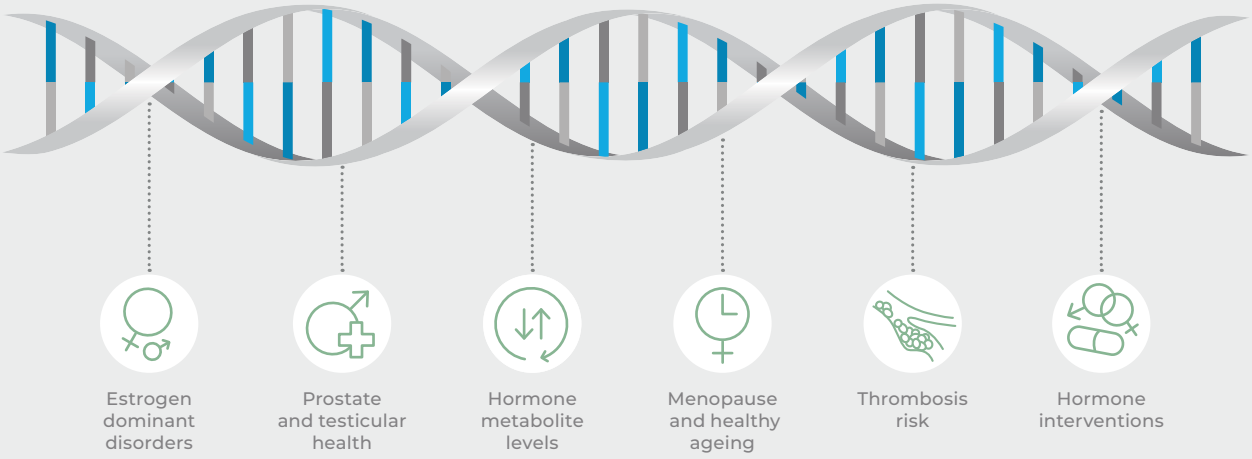
Referring practitioner: Private		

DNA Hormones is designed to identify variation in specific genes that affect metabolism and detoxification of sex hormones, potentially altering metabolite levels and impacting hormonal health. It offers personalised diet, lifestyle and hormone interventions to support relevant pathways and help you achieve and maintain optimal hormonal health and resilience.



Genetics and personalised medicine

Genes are segments of DNA that contain the instructions your body needs to make each of the many thousands of proteins required for life. Each gene is comprised of thousands of combinations of "letters" (called bases) which make up your genetic code. The code gives the instructions to make the proteins required for proper development and function.

Genetic variations (small differences in our DNA) can affect the expression of a gene, thereby affecting metabolic processes that are important for maintaining cellular health and how we respond to environmental interventions such as diet, lifestyle, supplements, and medication. Knowledge of these genetic variations offers unparalleled insight into your biological systems, allowing your healthcare practitioner to recommend precise interventions aimed at helping you reach your goals and achieve optimal health.

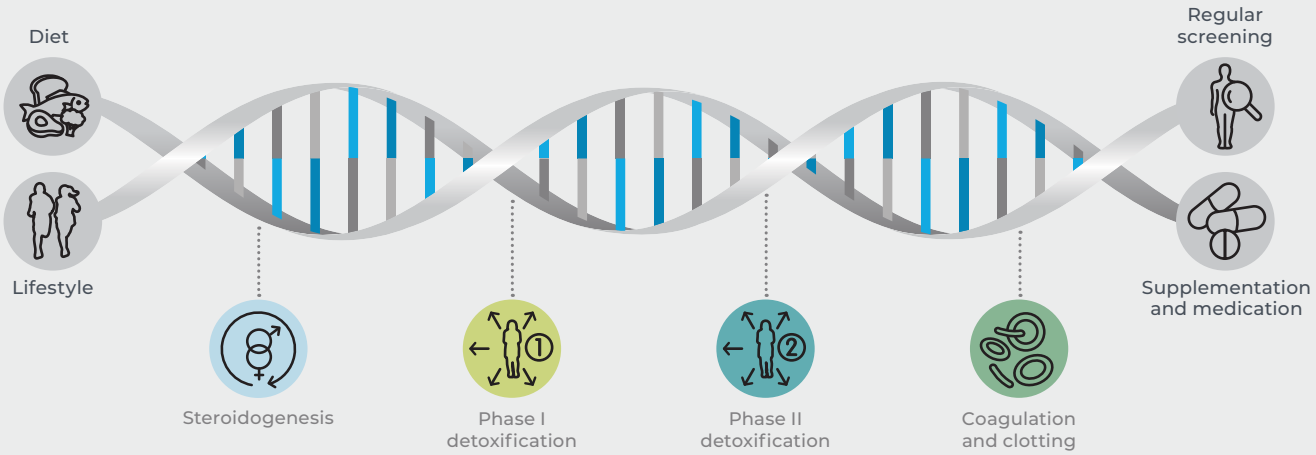
NORMAL GENE
Genotype resulting in baseline response to weight management interventions

VARIANT GENE
Genotype resulting in altered response to weight management intervention and need for personalisation

Personalised medicine and the effects of sex hormone metabolism and detoxification

Sex steroids, or steroid hormones are a group of organic compounds comprising estrogens, androgens and progestogens. They play an integral role in sexual differentiation, secondary sex characteristics, sexual behaviour, and reproduction, but are also important in skeletal, immune, muscular, and cardiovascular systems as well as cognitive function and mood regulation. Genetic variation is known to contribute to interindividual variability in the synthesis of these hormones as well as the binding and transport thereof and degradation to their respective metabolites. Genetic variation also influences how an individual will respond to environmental factors including diet and lifestyle, toxin exposure and hormone therapy, impacting risk for hormone related disorders. Thus gene-environment interactions are known to modulate susceptibility to hormone-related disorders.

This report tests for genetic variations that are associated with altered enzyme activity and function of key biological pathways involved in sex hormone synthesis (steroidogenesis), degradation and detoxification. This report provides valuable insights into individual priority areas that should be considered for successful optimisation of hormone pathways and to decrease risk for hormone related disorders. Hormonal balance is achieved through implementation of a personalised diet, nutraceutical, lifestyle and, when appropriate, hormone therapy program.

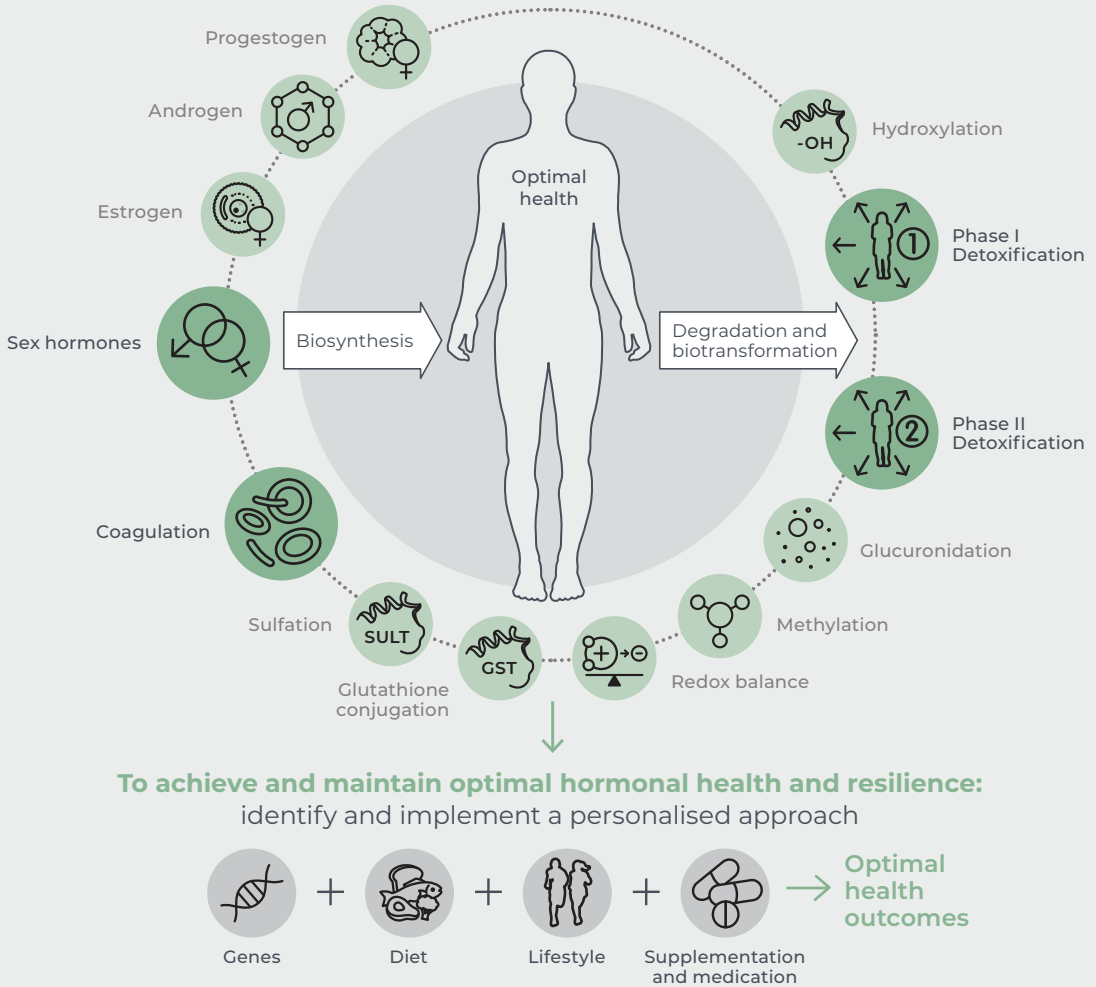


Understanding sex hormone metabolism and detoxification in the body

Sex hormones – progestogens (such as pregnenolone and progesterone), androgens and estrogens – are mainly synthesised in the adrenal gland, gonads (testes and ovaries), and placenta under the control of the hypothalamus-pituitary-gonadal (HPG) axis. Sex hormone synthesis also takes place, to a lesser extent, in other tissues including adipose tissues, the liver and bone. Sex hormone synthesis mainly involves biochemical processes of hydroxylation, lyase activity and dehydrogenation. They then bind to hormone related receptors or are transported to target tissues to perform respective functions from reproduction, to regulating bone and cardiovascular health and cognition.

These active sex steroid hormones and their metabolites are then degraded and undergo bio-transformation processes (phase I and II detoxification) mainly in the liver. Important biochemical processes involved include methylation, glutathione conjugation, glucuronidation, reduction, and sulfation. Depending on the stage in an individual's lifecycle, environmental exposures and genetic variants carried, certain biosynthesis, degradation and biotransformation pathways might be preferred. This increases risk for altered hormone metabolite ratios as well as imbalance in redox status. This has been linked to predisposition for hormone related disorders including endometriosis and polycystic ovarian syndrome (PCOS), earlier onset of, and heightened symptoms in menopause, bone health disorders, thrombosis, as well as breast, ovarian and prostate cancer.

DNA HORMONES PROVIDES INSIGHTS INTO KEY BIOLOGICAL PATHWAYS TO OPTIMISE HEALTH AND DECREASE RISK FOR RELATED DISORDERS THROUGH PERSONALISED SUPPORT



Result summary

Each biological area, influencing hormonal levels and related disorders, has been allocated a priority rating of low, moderate, or high priority, for you to understand where your focus areas should be. Based on the genes tested, a low priority biological area means that there is no need for increased support compared to standard health recommendations. A moderate or high priority biological area means that the particular area will require increased support with regards to appropriate diet, exercise, lifestyle and potentially hormone interventions to off-set the imbalances in that pathway caused by the genetic variants you carry. Detailed information on each biological area is provided in the body of this report.

	BIOLOGICAL AREA	PRIORITY
STEROIDOGENESIS	Progestogen synthesis	HIGH
	Androgen synthesis	MODERATE
	Estrogen synthesis	LOW
BINDING & TRANSPORT	Sex hormone binding	MODERATE
	Estrogen transport	LOW
PHASE I DETOXIFICATION	Hydroxylation	MODERATE
PHASE II DETOXIFICATION	Glucuronidation	HIGH
	Methylation	MODERATE
	Redox balance	MODERATE
	Glutathione conjugation	MODERATE
	Sulfation	LOW
CLOTTING RISK	Coagulation	HIGH

The combination of gene variants identified in this analysis indicates that you have efficient oestrogen detoxification and no additional support is required.

Summary recommendations

Based on your priority area outcomes, we have provided summary recommendations for the key area's you should be focusing on for successful and sustained hormone support. Personalised recommendations for diet, supplementation, exercise, and lifestyle, to support your priority areas, are summarised below.

Steroidogenesis

PRIORITY AREA	DIET	NUTRACEUTICAL	LIFESTYLE
Progestogen synthesis	Mediterranean diet, ↑ insoluble fibre & isoflavones. 3 Brazil nuts/day. Avoid refined CHO & acrylamide sources.	Vitamin D, vitamin K2, probiotic, sulforaphane.	Monitor vitamin D, PTH, sex hormone levels & BMD. Manage weight & blood glucose. Regular load-bearing exercise.
Androgen synthesis	Anti-inflammatory diet, ↑ insoluble fibre, isoflavones, flaxseed, cruciferous vegetables. Avoid acrylamide sources & processed meat.	Omega 3 FA, zinc, sulforaphane/DIM.	Manage stress, weight & blood glucose. Avoid toxin & xeno-estrogen exposure. Monitor hormone levels. Breast & prostate screening.

Estrogen availability: Binding & transport

PRIORITY AREA	DIET	NUTRACEUTICAL	LIFESTYLE
Sex hormone binding	Anti-inflammatory diet. ↑ MUFA, legumes, nuts, fruit & vegetables. Limit (refined) CHO.	Inositol, chromium.	Maintain a healthy weight & blood glucose level & regular exercise routine. Monitor Hs-CRP, insulin, SHBG & hormone levels.

Phase I detoxification

PRIORITY AREA	DIET	NUTRACEUTICAL	LIFESTYLE
Hydroxylation	Choose organic foods. ↑ berries & flavonoid rich foods (celery). Avoid smoked/ processed foods.	Sulforaphane &/DIM, genistein & daidzein, resveratrol.	Avoid procarcinogen exposure, do not smoke, limit alcohol & caffeine. Manage weight & inflammation.

Phase II detoxification

PRIORITY AREA	DIET	NUTRACEUTICAL	LIFESTYLE
Glucuronidation	Phytonutrient-rich ↑ fibre diet. Lycopene-rich foods, 3 Brazil nuts/day. Avoid processed meat.	Sulforaphane, zinc.	Maintain a healthy weight. Do not smoke. Vigilance in prostate health screening.
Methylation	Mediterranean diet. ↑ green leafy vegetables, fatty fish, pumpkin & flaxseed.	B-complex + methylated folate, Mg, nucleotides.	Limit alcohol. Do not smoke. Manage weight & stress. Monitor Hcy & estrogen metabolite levels.
Redox balance	Mediterranean diet. 3 Brazil nuts/day. Choose organic & avoid processed food. Intermittent fasting.	Sulforaphane, zinc, vitamin E, CoQ10.	Regular moderate intensity exercise. Avoid toxin exposure. Manage weight & stress. Monitor ox-LDL & 8-OHdG.
Glutathione conjugation	Mediterranean diet. ↑ cruciferous & allium vegetables. Choose organic & avoid processed food.	Sulforaphane/DIM, NAC.	Avoid procarcinogen exposure, do not smoke, limit alcohol & caffeine. Manage weight & stress. Monitor ox-LDL & 8-OHdG.

Coagulation

PRIORITY AREA	DIET	NUTRACEUTICAL	LIFESTYLE
Coagulation	Healthy dietary guidelines	No specific nutrients indicated.	No hormone therapy. Caution in pregnancy & frequent travel. Anti-clotting medication as indicated.

How to read your results

In the genotype results table on the page that follows, and throughout the report, you will find the gene name and description on the left. On the right, you will find your specific result, gene impact and enzyme activity level. On the following pages you will find the sex hormone metabolism and detoxification pathways highlighting enzyme activity based on genotype.

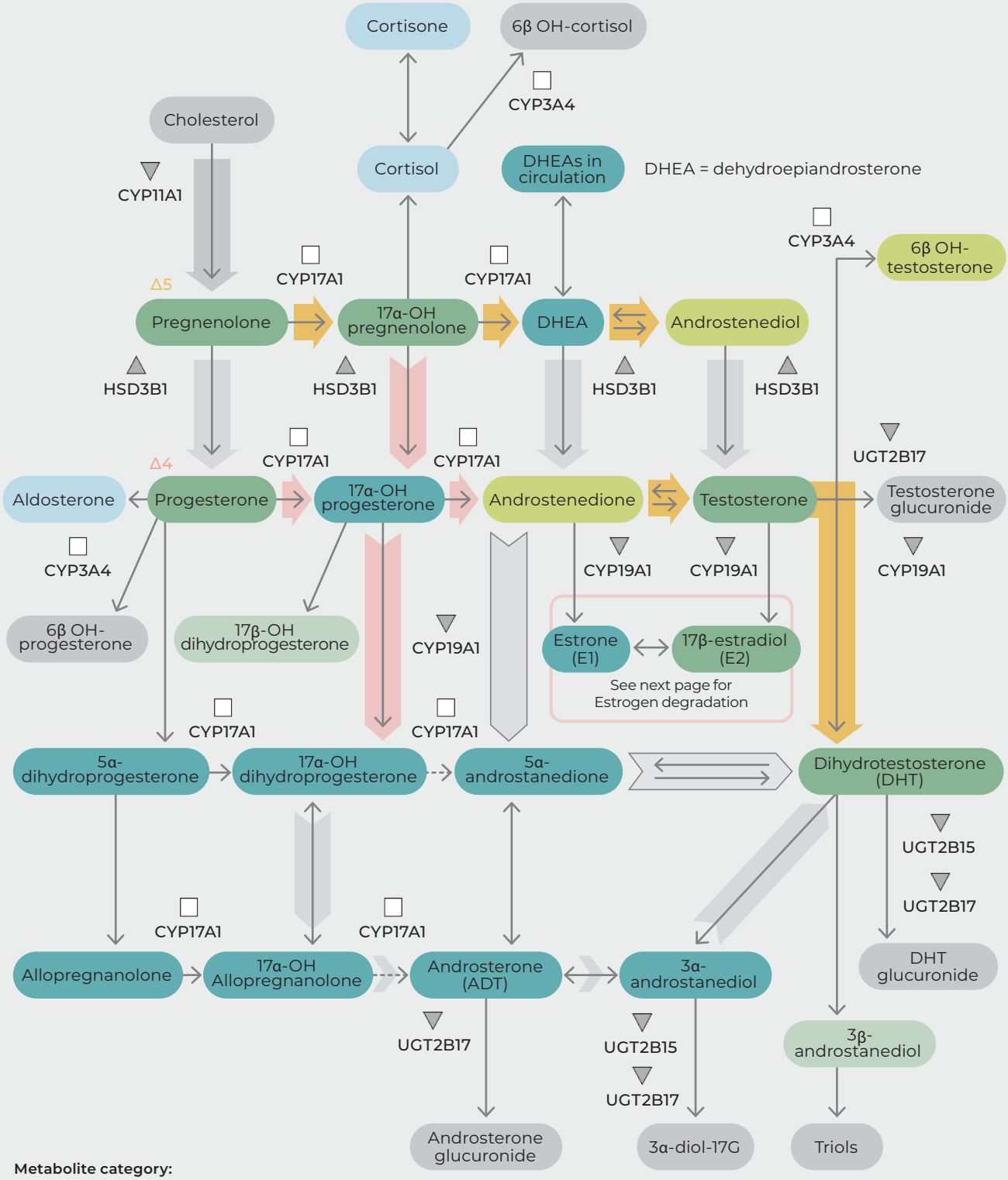
Genotype results table

Gene impact: ○ No Impact ✓ Benefical Impact ● Low Impact ●● Moderate Impact ●●● High Impact

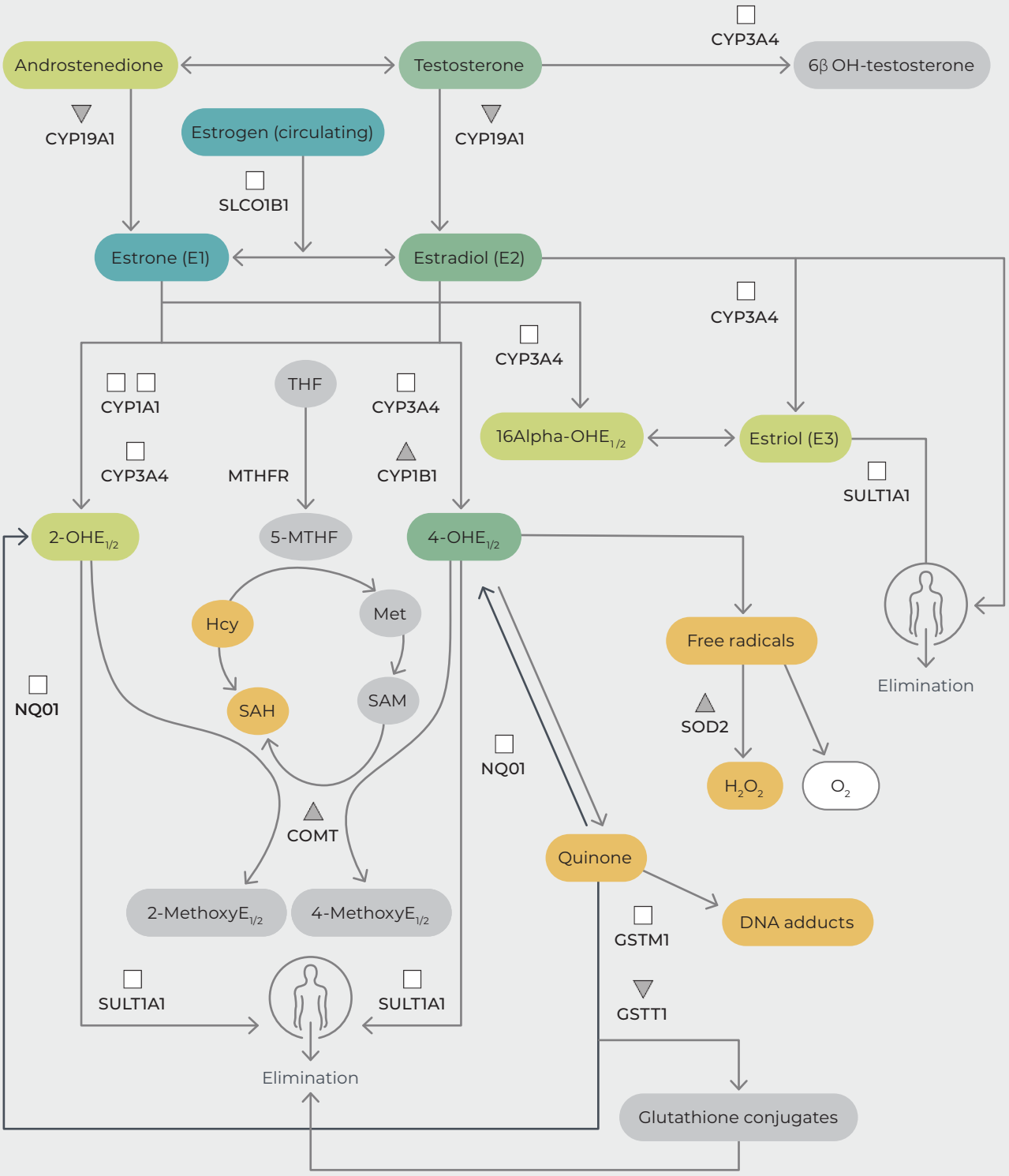
Enzyme activity level: △ Increased □ Neutral ▽ Decreased

	BIOLOGICAL AREA	GENE NAME	GENE VARIATION	RESULT	GENE IMPACT	ACTIVITY LEVEL
STEROIDOGENESIS	Progestogen synthesis	CYP11A1	A>G	GG	●●●	▽
	Androgen synthesis	CYP17A	34 T>C	TT	○	□
	Estrogen synthesis	CYP19A1	C>T	CT	●	▽
		HSD3B1	1245 C>A	CC	●●●	△
BINDING & TRANSPORT	Sex hormone binding	SHBG	T>C	TC	●●	▽
	Estrogen transport	SLCO1B1	Val174Ala 512 T>C	TT	●	□
PHASE I DETOXIFICATION	Hydroxylation	CYP1A1	Msp1 T>C	TT	○	□
			Ile462Val A>G	AA	○	□
		CYP1B1	Asn453Ser A>G	GG	●●●	△
		CYP3A4	-392 A>G	AA	○	□
PHASE II DETOXIFICATION	Glucuronidation	UGT2B15	Tyr85Asp T>G	TG	●●	▽
		UGT2B17	Insertion/Deletion	Deletion	●●●	▽
	Methylation	COMT	Val158Met 472 G>A	GG	○	△
		MTHFR	677 C>T	CT	●●	▽
	Redox balance	NQ01	609 C>T	CC	○	□
		MnSOD	Val16Ala 47 T>C	CC	●●	△
	Glutathione conjugation	GSTM1	Insertion/Deletion	Insertion	○	□
		GSTT1	Insertion/Deletion	Deletion	●●●	▽
	Sulfation	SULT1A1	638 G>A (Arg213His)	GG	○	□
CLOTTING RISK	Coagulation	FACTOR II	20210 G>A	AA	●●●	N/A
		FACTOR V	1691 G>A	GG	○	N/A

Your sex steroid metabolism and androgen detoxification pathway results



Your estrogen metabolism and detoxification pathway results



Metabolite category:

- High activity
- Medium activity
- Low activity
- Inactive/precursor
- Harmful

Enzyme activity level:

- Increased
- Neutral
- Decreased

Your results and recommendations

Steroidogenesis

Steroidogenesis is the process by which cholesterol is converted into steroids including the sex hormones progestogens, androgens and estrogens. The process of steroidogenesis is initiated when luteinizing hormone (LH) binds to target cells and increases expression of steroidogenic acute regulatory protein (StAR), which facilitates the transport of cholesterol to the inner mitochondrial membrane. Here, in the first rate limiting step, cholesterol is converted to pregnenolone via *CYP11A1*.

Progestogen synthesis

Pregnenolone is either converted to 17-hydroxypregnenolone (17α-OH pregnenolone) by *CYP17A1* or metabolised to progesterone by the enzyme 3β-hydroxysteroid dehydrogenase, encoded by *HSD3B1*. 17-OH pregnenolone is an important precursor that can produce dehydroepiandrosterone (DHEA) and, to a lesser extent, androstenedione by *CYP17A1* lyase. It can also be metabolised to cortisol by CYP21A2 and 11B1. Progesterone can be converted to 17α-hydroxyprogesterone (17α-OH progesterone) by *CYP17A1 hydroxylase*, or to 5α-dihydroprogesterone via steroid 5α-reductase (SRD5A1), which is then further hydroxylated to 17α-OH dihydroprogesterone or reduced to allopregnanolone by aldo/keto reductase (AKR1C2). Progesterone can also be metabolised to form aldosterone.

Androgen synthesis

In the classical Δ5 pathway, 17α-OH pregnenolone is converted to DHEA via CYP17A1 lyase activity. DHEA can be reversibly converted by *HSD17B*3 and *AKR1C3* to androstenediol, which produces testosterone using *HSD3B1* and *HSD3B2*. In males, cholesterol is preferentially converted into testosterone via this Δ5 pathway. Alternatively, in the minor Δ4 pathway DHEA is converted to androstenedione via *HSD3B1* and *HSD3B*2, which is further converted to testosterone by *HSD17B3* and *AKR1C3* as well as 5α-androstanedione or estrone (E1) by *CYP19A1*. Androstenedione can also derive from pregnenolone to progesterone by *HSD3B1* and *HSD3B2*, and then to 17α-OH progesterone by *CYP17A1*. Testosterone is then metabolised by *SRD5A1,2,3* and *CYP19A1* to the more active dihydrotestosterone (DHT). Beyond these pathways of steroidogenesis, a third back-door pathway, ends with the synthesis of DHT by bypassing testosterone. The backdoor pathway involves the (inter)conversion of 5α-androstanedione to DHT from 17α-OH dihydroprogesterone originating from either 17α-OH progesterone or 5α-dihydroprogesterone. The metabolite, 3α androstanediol, formed from 5α-dihydroprogesterone to allopregnanolone, can also be interconverted to DHT in this backdoor pathway.

Estrogen synthesis

Estrogen synthesis follows the same first steps in steroidogenesis as androgen synthesis; pregnenolone is converted to androstenedione via DHEA by *CYP19A1* and *HSD3B1* activity. Androstenedione is metabolised to the lesser active estrone (E1) and then to the active estradiol (E2) by HSD17B2 (17α-HSD). This conversion is reversible. The expression of *CYP19A1* and 17α-HSD is controlled by FSH stimulation. E2 can also be metabolised from testosterone by *CYP19A1*. DHEA (either from circulation or metabolised from pregnenolone) is converted to androstenediol, then testosterone by *HSD3B1*. In postmenopausal women, the primary source of E2 is from the conversion of androgens.

CYP11A1 A>G

Result: GG

CYP11A1 encodes a cholesterol side-chain cleavage enzyme, P450scc. This enzyme is localised to the inner membrane of mitochondria and is mainly expressed in the adrenal cortex, ovary, testis and placenta. It catalyses the conversion of cholesterol to pregnenolone. This is the first step in the synthesis of steroid hormones, which is a rate-limiting and hormonally regulated step. P450scc can also hydroxylate vitamin D3 and its precursors. CYP11A1 activity is stimulated directly by ACTH, LH, and FSH and indirectly by CRH, and proinflammatory cytokines such as IL-1, Il-6, and TNF-α. The SNP of interest is located in the promoter region of the gene, potentially altering CYP11A1 gene expression.

The GG genotype has been associated with increased risk of recurrent pregnancy loss potentially due to lower progesterone levels. The GG genotype also increases risk for BMD when there is reduced estrogen availability such as in postmenopausal women or in those using aromatase inhibitors. This suggests reduced steroidogenesis with this genotype. Regularly monitor vitamin D and parathyroid (PTH) levels and BMD, and consider other risk factors to assess the need for treatment including with anti-resorptive therapies. Monitor relative hormone levels. Hormone therapy may be indicated in certain high risk situations. Supplement with vitamin D where indicated and include a probiotic to support gut health.

CYP17A 34 T>C

Result: TT

CYP17 mediates both steroid 17α-hydroxylase and 17,20-lyase activities, and catalyses a rate-limiting step in ovarian and adrenal biosynthesis leading to the precursor, dehydroepiandrosterone. The C allele increases enzyme activity, thereby increasing the amount of bioavailable estrogen which in turn increases the risk of developing PCOS and prostate cancer.

The TT genotype does not alter enzyme function.

CYP19A1 C>T

Result: CT

CYP19A1 encodes the enzyme aromatase and is mainly expressed in the granulosa cells, placenta, fat and growing bones. It is responsible for the final step in estrogen biosynthesis where it converts the androgens, testosterone and androstenedione into estradiol (E2) and estrone (E1). The C>T polymorphism is located in the 3'-UTR of CYP19A1 gene, which likely affects the mRNA stability. The C allele is associated with decreased enzyme function. CC and CT genotype carriers thus tend to have lower levels of E1 and E2 compared to the TT genotype.

In females, the CT genotype is associated with a lower estradiol:testosterone and estrone:androstenedione ratio, as well as a lower estradiol:SHBG ratio. These women are at risk for a greater incidence of menopausal symptoms, specifically hot flashes/sweating. Follow an anti-inflammatory diet, manage stress and weight and control blood glucose levels. Consider inositol supplementation and hormone therapy as indicated. In males, serum PSA may be higher in T allele carriers compared to those with the CC genotype. Consider supplementation with sulforaphane and inositol. D-chiro-inositol promotes androgen synthesis in the theca layer and down-regulates aromatase and estrogen expression in granulosa cells, while myo-inositol strengthens aromatase and FSH receptor expression.

HSD3B1 1245 C>A

Result: CC

3β-hydroxysteroid dehydrogenase type 1 (3βHSD1), encoded by HSD3B1 is a rate-limiting enzyme that converts the adrenal-derived steroid DHEA to DHT. The HSD3B1 1245C allele is associated with stable enzyme activity and results in resistance to ubiquitination and deterioration and significantly increases the half-life of the enzyme, leading to higher levels of the 3βHSD1 enzyme. The C variant is referred to as being adrenal permissive, while the AA genotype leads to an adrenal restrictive phenotype.

Females with the CC genotype and a high intake of dietary acrylamide have an increased risk for ovarian cancer. The CC genotype is also associated with elevated circulating androstenedione levels in women and an increased risk of postmenopausal estrogen-driven breast cancer. In overweight women with PCOS, carrying the CC genotype significantly increased risk of female pattern hair loss compared to those of normal-weight. Manage weight, avoid acrylamide food sources and increase intake of isoflavones such as genistein and biochanin A, found in red clover, soy and fava beans, and alfalfa sprouts.
In males, the adrenal-permissive (CC) genotype leads to greater DHEA-sulfate conversion to testosterone and DHT, thereby generating higher downstream exposure of the prostate to potent androgens and stimulates local production of active androgens in the prostate. Men with the CC genotype, diagnosed with prostate cancer have a more rapid development and worse clinical outcomes and may benefit from therapeutic targeting of 3-hydroxysteroid dehydrogenase-1and the androgen-signaling axis.

Estrogen availability: Binding & transport

Bioavailability and action of sex steroids depend on several factors including whether they are bound or free in circulation, as well as whether they can enter target cells efficiently.

Sex hormone binding

Sex hormone-binding globulin, encoded by the gene SHBG, binds and transports sex hormones specifically testosterone and estradiol, to regulate plasma bioactive levels of these hormones. This affects their bioavailability and their potential to fulfil their vital functions.

Estrogen transport

The movement of estrogen into cells is facilitated by the membrane-bound, sodium-independent organic anion transporter protein (OATP1B1), which is encoded by SLCO1B1 and primarily expressed in the liver. OATP1B1 activity thus plays an important role in regulating the movement of estrogen into hepatocytes for metabolism and elimination, and regulating the availability of estrogen for sulfate conjugation, adding to or limiting the estrogen storage pool.

SHBG T>C

Sex hormone–binding globulin, encoded by the gene, SHBG, is produced by hepatocytes and, together with several other steroid-binding proteins, control the amounts of free steroids that passively diffuse into target cells. SHBG binds biologically active androgens and estrogens, regulating their bioavailability, and serving as a reservoir of sex steroids, protecting them from metabolic clearance. Of the androgens and estrogens, DHT has the highest affinity for SHBG, followed by testosterone and estradiol. Altered levels, particularly low levels of plasma SHBG have been related to an increased risk of various diseases including insulin resistance, type 2 diabetes, cancer and CHD. A regulatory T>C SNP within the SHBG gene is thought to influence the binding of transcription factors. This could have an impact on SHBG serum levels and disease susceptibility.

Result: TC

In females, the TC genotype may result in 12% reduction in SHBG levels compared to the CC genotype.
Males carrying the TT genotype may also exhibit a decrease in SHBG, total testosterone and DHT levels with an increased percentage of free testosterone. High levels of proinflammatory cytokines are known to further reduce SHBG levels, as do high refined carbohydrate diets. Monounsaturated fats, specifically extra virgin olive oil and regular physical activity increases SHBG. Maintaining a healthy weight and blood glucose levels is also important in supporting SHBG. Inositol or myo-inositol found in legumes, nuts and fruits, or supplemented, appears to have an insulin-sensitizing effect, thus potentially indirectly supporting SHBG levels.

SLCO1B1 Val174Ala 512 T>C

Result: TT

SLCO1B1 encodes the organic anion transporter protein (OATP1B1). OATP1B1 is membrane-bound and plays a critical role in hepatic uptake and clearance of numerous drug substrates and endogenous compounds, including transporting bilirubin and E1/E2 conjugates such as estrone sulfate, E1-3-sulfate and E2-17ß-D-glucuronide, from the blood into hepatocytes. Sulfated estrogens are considered to serve as a storage pool for estrogens. The SLCO1B1 T512C polymorphism results in decreased membrane expression of the transporter and thus reduced transport activity.

The TT genotype results in normal transporter function. Higher efficiency of OATP1B1-mediated estrogen transport may increase the estrogen movement into hepatocytes for metabolism and elimination. Females with the TT genotype are associated with having lower sulfated E1 and E2 levels and a lower E1-sulfate:E1 ratio. Menopausal symptoms might be heightened with this genotype. Personalise dose of HRT if/as indicated. Supplement with a suitable probiotic and support gut health. Monitor gut microbiome markers and sex hormone levels. EGCG, high in green tea, can inhibit OATP1B1 activity.

Phase I detoxification

Hormones and other endogenous compounds as well as exogenous products from our environment including toxins from pollutants and compounds from our diet need to be detoxified and work through our body's detoxification process. Phase I detoxification is generally governed by the cytochrome p450 family of enzymes, where the major sex steroids (and exogenous compounds) are hydroxylated, or 'activated' to form what are often deemed intermediate metabolites that can be potentially more reactive than their parent form. Some intermediate metabolites can also be more reactive and harmful compared to others.

Hydroxylation

In the case of testosterone, CYP3A4 is able to hydroxylate this steroid to an inactive metabolite 6βOH-testosterone. CYP3A4 can do the same to progesterone and cortisol, yielding 6βOH-progesterone and 6βOH-cortisol, respectively.

Estrone(E1) and estradiol (E2) can be interconverted via *HSD17B2*. E1 can be hydroxylated to 16-OH-estrone mainly by CYP3A4 (and to a lesser extent by CYP1A2). E2 is metabolised to its major metabolite, estriol (E3), by CYP3A4, which can also be converted to 16-OH estradiol, with this reaction being reversible. Alternatively, E1 and E2 can also be hydroxylated to the weak 2-$OHE_{1/2}$ by CYP1A1, CYP3A4 and CYP1A2, respectively, or to the proliferative 4-$OHE_{1/2}$ by CYP1B1 (and CYP3A4 and CYP1A2, to a lower degree).

CYP1A1 MspI T>C

Result: TT ○ □

The CYP1A1 gene encodes a phase I cytochrome P-450 enzyme that converts environmental procarcinogens such as PAHs and aromatic amines to reactive intermediates having carcinogenic effects. In addition, CYP1A1 is involved in the oxidative metabolism of estrogens, which may play a critical role in the aetiology of breast and prostate cancer.

The TT genotype does not alter enzyme function.

CYP1A1 Ile462Val A>G

Result: AA ○ □

The CYP1A1 gene encodes a phase I cytochrome P-450 enzyme that converts environmental procarcinogens such as PAHs and aromatic amines to reactive intermediates having carcinogenic effects. In addition, CYP1A1 is involved in the oxidative metabolism of estrogens, which may play a critical role in the aetiology of breast and prostate cancer.

The AA genotype does not alter enzyme function.

CYP1B1 Asn453Ser A>G

Result: GG ○○○ △

CYP1B1 enzymes catalyses the 4-hydroxylation of estrone and oestradiol, yielding the 4-OH E1/E2 metabolite that can be converted to reactive quinones, which can damage DNA. CYP1B1 also plays an important role in activation of procarcinogens such as PAHs, heterocyclic and aromatic amines, to reactive metabolites which have been found to be a direct source of DNA damage.

Compared to the AA genotype females carrying the GG genotype tended to have lower 2-OH and 16-OH E2 levels. The G allele has also been linked to earlier time to menopause as well as greater incidence and severity of hot flushes. Avoid procarcinogen exposure, do not smoke, and manage weight and inflammation. Increase intake of a variety of vegetables and fruit that contain flavonoids such as luteolin (celery and lemons). Genistein and daidzein have also shown CYP1B1 4-hydroxylation inhibitory activity. Consider supplementation with DIM and/or sulforaphane.

CYP3A4 -392 A>G

Result: AA ○ □

CYP3A4 is the most abundant cytochrome P450 enzyme in humans, accounting for up to 60% of total liver cytochrome P450 content and up to 80% of hepatic oestradiol oxidative metabolism. This enzyme is found to a lesser extent in extrahepatic tissues such as the intestines, lungs, kidneys, and prostate. It is responsible for the metabolism of exogenous and endogenous substances such as therapeutic drugs and the sex steroid hormones, estrogen and testosterone. Testosterone and estrogen are both catalysed by CYP3A4 to form various metabolites including the inactive 6β- hydroxy testosterone and multiple hydroxylated estrogen metabolites such as the inactive 2- OHE1/2 and genotoxic 4-OHE1/2 and 16-OHE1/2.

The AA genotype does not alter enzym e activity.

Phase II detoxification

Phase II detoxification is the essential step that generally follows phase I detoxification, whereby intermediate metabolites are made more water soluble, and thereby less reactive, so that they can be safely eliminated from the body. The biological processes involved in the phase II detoxification pathway for both hormone metabolites and products from our environment include glucuronidation, sulfation, methylation, reduction reactions and glutathione conjugation.

Glucuronidation

ANDROGEN DEGRADATION AND DETOXIFICATION

Rather than being metabolised to estradiol or DHT, testosterone can be glucuronidated by *UGT2B17* to the inactive testosterone glucuronide, which is then excreted. Androgens, produced via the backdoor pathway via dihydroprogesterone, or formed from DHT, are also glucuronidated to their water soluble forms to be excreted from the body. The DHT active metabolite 3α-androstanediol, if not converted back to DHT, can be glucuronidated by *UGT2B15* and *UGT2B17* to form 3α-diol-17G. Androsterone, formed from either 5α-androstanedione or allopregnanolone is glucuronidated by *UGT2B17* and *UGT2B7* to androsterone glucuronide.

ESTROGEN DETOXIFICATION

E2 can directly be glucuronidated by UGT enzymes to be eliminated, as can the 2-, 4-, and 16-OH estrogen metabolites, however no related SNPs are analysed in this report*.

*dnalife has not yet identified any clinically relevant gene variants based on our selection criteria.

UGT2B15 Tyr85Asp T>G

Result: TG

UGT2B15 plays a predominant role in glucuronidation of several important drugs and/or their metabolites and xenobiotic/ dietary substrates which include ethanol, phenolic compounds and flavonoids. It also plays a key role in the glucuronidation of androgens; testosterone and dihydrotestosterone and their metabolites; androstane-3α, 17β-diol, and catecholestrogens. The T allele causes the enzyme to have an increased Vmax activity compared to the G allele, resulting in a quicker androgen metabolite clearance while G allele is associated with slower clearance.

In males, the TG genotype is associated with having higher serum levels of 3-Diol-17G, DHT and SHBG than men with the TT genotype. They also have increased risk of developing prostate cancer. Maintain a healthy weight, ensure adequate fibre intake and phytonutrient-rich foods specifically with lycopene, and avoid processed meat. Supplement with sulforaphane.

UGT2B17 Insertion/Deletion

Result: Deletion

The UGT2B17 gene encodes the glucuronidation enzyme, UDP-glycosyltransferase B17. Besides therapeutic drugs and/or their metabolites and xenobiotic substrates, this enzyme displays high activity towards natural androgens (testosterone and dihydrotestosterone) and their metabolites (e.g., androsterone and androstane-3α,17-diol), causing their local inactivation, through glucuronidation. Glucuronidation of androgens is an irreversible event that renders them inactive as ligands for ARs. Androgen substrates of UGT2B17 in order of preference are DHT > 3α-diol > testosterone > androsterone. The UGT2B17 deletion is associated with a lower urinary testosterone to epitestosterone (T/E) ratio.

A deletion results in lower glucuronidation of androgens, increasing the likelihood of having higher systemic DHT and testosterone levels. Men with this genotype are at an increased risk of prostate cancer but generally have a lower BMI. Maintain a healthy weight, ensure adequate fibre intake and phytonutrient-rich foods specifically with lycopene, and avoid processed meat. Supplement with sulforaphane.
In females the deletion may play a beneficial role in protecting against low BMD and osteoporosis risk. Postmenopausal women with the UGT2B17 deletion who never used HRT, were found to have higher BMD, similar to premenopausal women.

Methylation

The 2-, and 4-OH estrogen metabolites can be further methylated by COMT to their methoxy forms, which are less reactive and more easily removed. COMT requires SAMe for this reaction. SAMe is produced from one-carbon metabolism (methylation pathway), where MTHFR plays a vital role in committing 5-methytetrahydrolfolate (5-MTHF) as a cofactor to remethylate homocysteine to methionine, which is metabolised to SAMe.

COMT Val158Met 472 G>A

Result: GG

Soluble catechol-O-methyltransferase (S-COMT) helps control the levels of certain hormones and is involved in methylation and inactivation of catechol estrogens. Accumulation of estrogen metabolites appears to confer increased risk of breast cancer via oxidative DNA damage.

No variant was detected at the 472 G>A locus.

MTHFR 677 C>T

Result: CT

Methylenetetrahydrofolate Reductase (MTHFR) is a key enzyme in the folate metabolic pathway, directing folate from the diet either to DNA synthesis or homocysteine remethylation. Reduced activity of this enzyme alone or in conjunction with folate insufficiency or alcohol consumption can influence the balance between DNA synthesis, repair and methylation processes.

The T allele lowers the activity of the MTHFR enzyme, which results in an increase in homocysteine levels, a decrease in DNA methylation and an increase in DNA adducts. Enzyme function is 70% of optimal in CT genotype individuals. Decreased MTHFR enzyme activity has been associated with increased premenopausal breast cancer risk with long duration of estrogen exposure, increased breast cancer risk amongst postmenopausal women with higher lifetime alcohol consumption and male infertility.
These individuals have increased folate, vitamin B2, B6 and B12 requirements. In addition to ensuring folate-rich foods, a general B vitamin or multi-vitamin supplement containing as much as 800ug folate may be recommended.

Redox balance

If the reactive 4-OH estrogen metabolite is left unchecked or levels rise beyond that where phase II detoxification processes can proceed efficiently, the 4-OH estrogen metabolite can go on to form reactive quinones and create DNA adducts. These quinones can be reduced back to either the 2- or 4-OH estrogen metabolites, reducing risk for DNA damage. Super oxide free radicals produced from high levels of 4-OH estrogen metabolites and other oxidative stressors can be mitigated by superoxide dismutase activity. In the mitochondria, SOD2 converts super oxide radicals into hydrogen peroxide and oxygen.

NQ01 609 C>T

Result: CC ○ □

NADP(H:) quinone oxidoreductase 1, encoded by NQO1, is primarily involved in the detoxification of potentially mutagenic and carcinogenic quinones derived from tobacco smoke, diet and estrogen metabolism. NQO1 also protects cells from oxidative stress by maintaining the antioxidant forms of ubiquinone and vitamin E. The variant is a C-to-T transition resulting in a proline to serine amino acid substitution at codon 187 in the protein. The variant T allele results in reduced enzymatic activity.

The analysis identified no genetic variation at the 209 C>T locus.

MnSOD Val16Ala 47 T>C

Result: CC ●● △

The MnSOD/SOD2 enzyme destroys the free radicals which are normally produced within cells and which are damaging to biological systems. The enzyme thus has important anti-oxidant activity within the cell, especially within the mitochondria.

Those with the CC genotype, with higher pollution exposure, tobacco use and a lower consumption of fruits and vegetables, may be at increased risk of developing disease, including breast cancer. Some evidence suggests women with the C allele who had ever used HRT or smoked were at a higher risk of breast cancer. Males with the CC genotype have increased risk of infertility and those who had ever-smoked were at almost 2-fold increased risk of male infertility. It is important for CC genotype individuals to ensure adequate fruit and vegetable intake, by preferably following a Mediterranean diet plan. Supplementation with antioxidant nutrients can reduce the oxidation of catechols and promote greater excretion of these metabolites through the methylation pathway. Monitor oxidative stress and hormone metabolite levels expecially if using HRT.

Glutathione conjugation

Quinones, formed from 4-OH estrogen metabolites can be conjugated with glutathione by the glutathione S-transferase family of enzymes including *GSTM1* and *GSTT1*, rendering them water soluble and allowing elimination from the body.

GSTM1 Insertion/Deletion

Result: Insertion

Glutathione S-transferase M1 is the most biologically active member of the GST super-family and is involved in Phase II detoxification in the liver. It is responsible for the removal of xenobiotics, carcinogens, and products of oxidative stress. These enzymes are involved in the phase 2 conjugation of estrogen quinones to glutathione.

The GSTM1 gene is present.

GSTT1 Insertion/Deletion

Result: Deletion

Glutathione S-transferases (GSTs) are a family of multifunctional enzymes involved in the metabolism of a variety of xenobiotic compounds, including mammary carcinogens. These enzymes are involved in the conjugation of estrogen quinones to glutathione.

A deletion results in an absence of the enzyme, leading to reduced capacity for hepatic detoxification & reduced metabolism of quinones. This can result in DNA adduct formation. In the presence of MetS, the GSTT deletion may serve as a predictor of prostate cancer.
GST enzyme activities are induced in part by the products of cruciferous and allium vegetables. These should be increased significantly in the diet to increase activity of other GST enzymes to compensate for decreased activity. Daily intake is recommended. When dietary intake is inadequate a high quality supplement containing DIM may be required. A diet rich in antioxidants is also recommended. Avoid exposure to dietary and environmental toxins.

Sulfation

The 2-, 4-, and 16-OH estrogen metabolites can also undergo sulfate conjugation via SULT1A1 enzyme activity. Take note, sulfate-conjugated estrogens may represent an inactive storage pool of precursor steroids that can be re-activated through deconjugation by sulfatases.

SULT1A1 638 G>A

Result: GG ○ □

Sulfotransferase 1A1 (SULT1A1) is involved in the inactivation of estrogens by forming sulfate compounds, which are rapidly excreted from cells, reducing the level of estrogen exposure in circulation and target tissues. This enzyme is also involved in the bio-activation of procarcinogens such as heterocyclic amines and polycyclic aromatic hydrocarbons.

No variant was detected at the 638 G>A locus.

Clotting risk: Coagulation

Thrombophilia is a blood coagulation disorder that increases the risk of developing venous thromboembolism (VTE) resulting in deep vein thrombosis (DVT) or pulmonary embolism (PE). Thrombophilic risk is multifactorial with both genetic and acquired risk factors. Acquired risk factors for VTE include oral contraceptive use, hormone replacement therapy, neoplasia, travel-related or prolonged immobility, and recent surgery. The most common genetic risk factor for inherited thrombophilia is the 1691 G>A mutation found in the Factor V gene, followed by the 20210 G>A mutation found in the Factor II gene. Genetic screening of thrombophilia in at-risk individuals can be useful in tailoring the management of the disorder and improve patient outcomes.

FACTOR II 20210 G>A

Result: AA ●●● N/A

The Factor II gene encodes the coagulation factor II, or prothrombin, which is a vitamin K–dependent proenzyme that functions in the area of blood coagulation. Factor II is a precursor to thrombin, which converts fibrinogen into fibrin, which in turn strengthens a protective clot.

The Factor II 20210 G>A gene variant results in increased levels of plasma prothrombin and thus an increased risk for thrombosis.

The Factor II AA genotype is associated with a 70% increase in plasma prothrombin levels and a significantly increased risk for venous thromboembolism (VTE).
Other factors that can increase the risk of thrombosis, together with the risk genotype include: travel, central venous catheter use, pregnancy, estrogen-based oral contraceptive use, hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), organ transplantation, injury, age, and surgery. The estrogen component of contraceptive pills and HRT is known to increase clotting risk by increasing plasma fibrinogen, a major coagulation factor, and decreasing antithrombin III which inhibits coagulation.

FACTOR V 1691 G>A

Result: GG ○ N/A

Factor V functions as a cofactor to allow factor Xa to activate the enzyme thrombin, and in turn cleaves fibrinogen to form fibrin, which polymerizes to form the dense meshwork that makes up the majority of a clot. Activated protein C (aPC) is a natural anticoagulant that acts to limit the extent of clotting by cleaving and degrading factor V. Factor V Leiden gene mutation is characterised by a poor anticoagulant response to APC and an increased risk for venous thromboembolism (VTE). Deep venous thrombosis (DVT) is the most common VTE, with the legs being the most common site however it VTE can also occur in other parts of the body including the brain, eyes, liver, and kidneys.

No variant was detected at the 1691G>A locus.

Glossary

ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
AMH	Anti mullerian hormone
ARs	Androgen receptors
BMD	Bone mineral density
BMI	Body mass index
CAT	Catalase
CHD	Coronary heart diseases
CHO	Carbohydrates
CRH	Corticotropin-releasing hormone
DHT	Dihydrotestosterone
E1	Estrone
E2:	Estradiol
EGCG	Epigallocatechin gallate
FSH	Follicle stimulating hormone
GPx	Glutathione peroxidase
H_2O_2	Hydrogen peroxide
Hcy	Homocysteine
Hs-CRP	High sensitivity C-reactive protein
HRt	Hormone replacement therapy
LH	Luteinizing hormone
IL-1	Interleukin-1
Il-6:	Interleukin-6
Mg	Magnesium
MUFA	Monounsaturated fatty acids
O_2^-	Superoxide radical
ox-LDL	Oxidised low-density lipoprotein
PAH	Polycyclic aromatic compounds
PCOS	Polycystic ovary syndrome
PTH	Parathyroid
RPL	Recurrent pregnancy loss
TNF-α	Tumour necrosis factor alpha
8-OHdG	8-hydroxydeoxyguanosine

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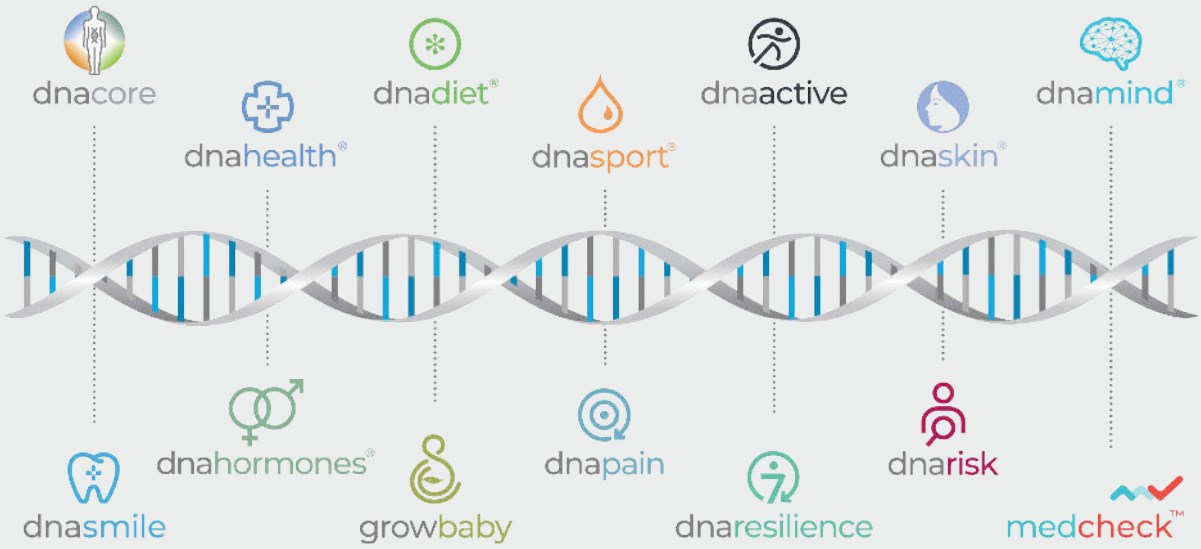

Requires finger prick blood spot sample collection

Our Commitment

DNAlysis Biotechnology is continuously developing new tests with the highest standards of scientific rigour. Our commitment to ensuring the ethical and appropriate use of genetic tests in practice means that gene variants are only included in panels once there is sound motivation for their clinical utility and their impact on health outcomes.

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