YOUR HORMONE PULSE REPORT

PROVIDES KEY GENOMIC INSIGHTS INTO THE BIOSYNTHESIS, METABOLISM AND ELIMINATION OF YOUR ANDROGENS AND ESTROGENS

THE DNA COMPANY

PERSONAL **DETAILS**

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GENDER:

REPORT DATE:

DISCLAIMER

This test and its report are meant strictly for research use only (RUO) purposes. This report is solely intended as an educational/recreational tool, and is not intended for use in medical decision-making without the consultation of a licensed health care professional. This test is not intended for Direct to Consumer (OTC) use, and any and all healthcare decisions ultimately return entirely to the healthcare provider. This test has not been cleared or approved by the U.S. Food and Drug Administration nor Health Canada (or affiliated regulatory agencies) as it is meant strictly as a recreational/educational tool and can only be dispensed through a medical professional.

UNDERSTANDING YOUR **HORMONE PULSE REPORT**

Sex hormones (androgens and estrogens), also known as gonadal steroids, are potent, biologically active steroid hormones that mediate growth, development and sexual maturity. While necessary for normative growth and development, lifetime exposure to estrogens, and their metabolites, is a well-established and significant risk factor in developing hormone related diseases in women (and to a lesser extent, in men as well).

In women, estrogen exposure is reflective of time of menarche, parity, term of breastfeeding, and age of menopause[1]. Additionally, lifestyle choices and environment contribute to estrogen levels throughout the life of a woman.

A woman's sex hormone health is reflective of her individual ability to maintain the delicate balance between the necessary biologic functions of estrogens versus the potential of these very estrogens, and their metabolites, to be instigators of aberrant cellular behavior.

The production, metabolism, and elimination of estrogens are controlled via a complex network of tightly regulated enzymatic steps. The enzymes and respective genes, responsible for the biosynthesis, metabolism, and elimination of estrogens are well studied and characterized. Several genetic polymorphisms identified within these genes have been and have been shown to alter discrete steps in estrogen biosynthesis, metabolism, and elimination. These genetic polymorphisms are significant contributors to a woman's individual estrogen / estrogen metabolite exposure and ultimately, to her sex hormone health[2].

This report is comprised of three sections and evaluates genetic polymorphisms related to the biosynthesis, metabolism, and elimination of sex hormones and is a powerful tool in uncovering potential areas of hormone imbalances.

IMPORTANT. PLEASE READ FIRST:
INTERPRETING YOUR RESULTS

Your Hormone Pulse Report is only intended for use by healthcare practitioners and is meant solely for research and educational purposes. It is not intended for use in disease diagnostics nor for healthcare management. This report It is not intended for direct-to-consumer use. Production of your reproductive hormones, followed by their metabolism and eventual elimination, is one of the best examples of the stepwise, biochemical cascades that occur in your body. Importantly, the incremental steps that define this cascade are well-studied, and the genes involved in them, well validated.

Your Hormone Pulse Report has been designed to show these genes in an innovative 'Traffic Light' manner. The Traffic Light depiction of your results portrays the relative efficiency of each step in your hormone metabolic cascade. It is important to understand that beyond your innate genetics, factors such as diet, lifestyle and environment can all significantly impact the efficiency of the various steps involved in your hormone production, metabolism, and eventual elimination.

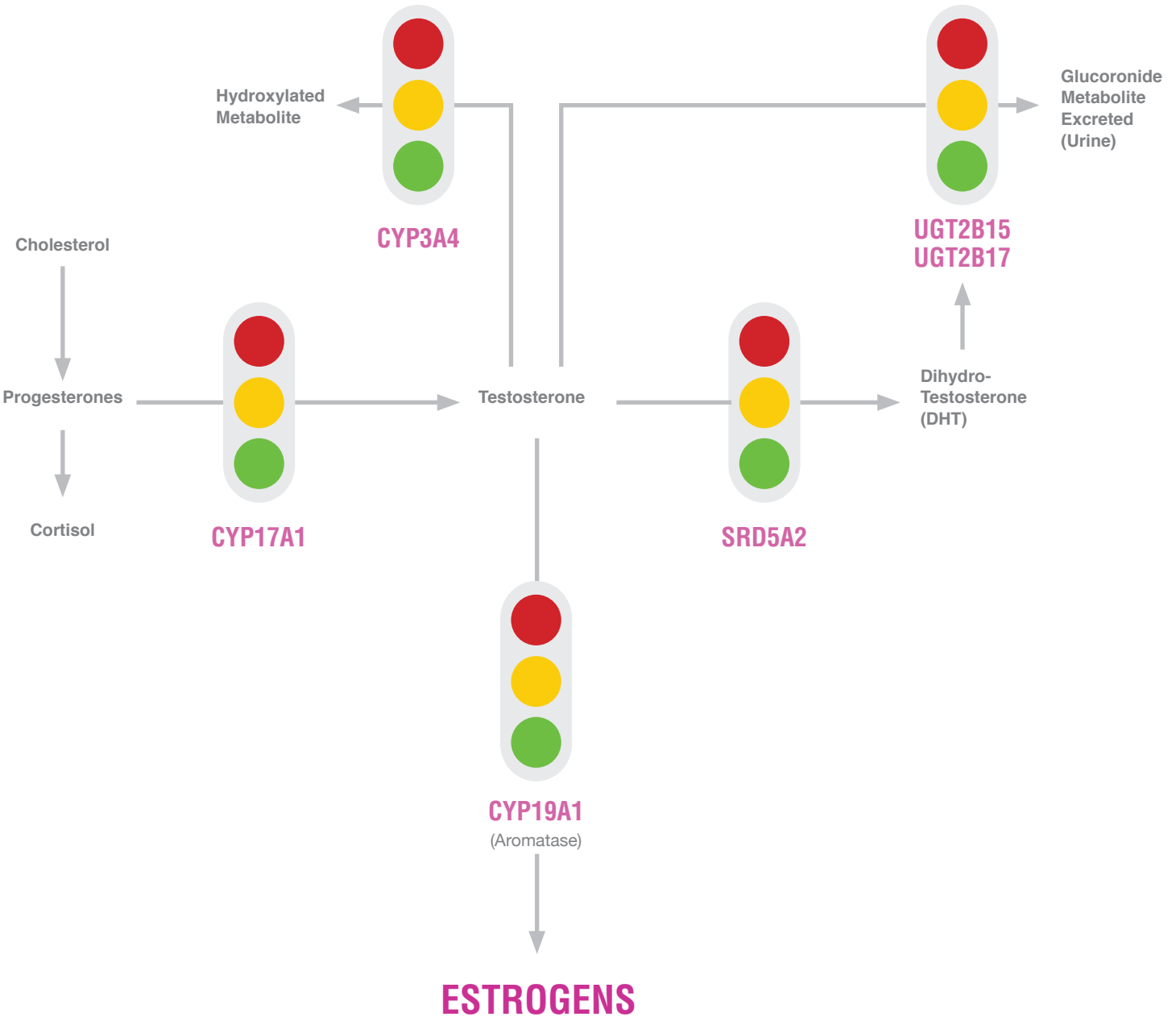
A **'GREEN LIGHT'** indicates that your genotype (the version of your gene) is generally associated with the most efficient conduction (compared to other genotypes of the same gene) of the relevant step in your report. Please note that a **'GREEN LIGHT'** is not necessarily the most optimal or desirable result. For example, a **'GREEN LIGHT'** for the UGT2B17 gene (section ONE of report) can mean that you are overefficiently clearing/eliminating your testosterone and other androgens. The implication of this in men is obvious. However, as androgens can act as precursors to the production of estrogens in women, the overly rapid clearance of androgens in women can also present important health considerations. Likewise, a **'GREEN LIGHT'** result for CYP1B1 (section TWO of report) can mean that your body will tend to overproduce the undesirable estrogen metabolite, 4-hydroxy-estrogen.

An **'ORANGE LIGHT'** indicates that your genotype is generally associated with a moderate conduction (compared to other genotypes of the same gene) of the relevant step in your report.

A **'RED LIGHT'** result indicates that your genotype is generally associated with a slow or inefficient conduction (compared to other genotypes of the same gene) of the relevant step in your report. Please note that a **'RED LIGHT'** result does not mean that the relevant step is not occurring. Rather, it is only meant to symbolize that this step is likely occurring at a lower rate of efficiency when compared to the other genotypes of the gene. Importantly, a **'RED LIGHT'** result may be considered the most desirable result for a given gene. A **'RED LIGHT'** result for the CYP1B1 gene (section TWO of report) is generally considered advantageous as it is associated with lower production levels of the undesirable 4-hydroxy-estrogen metabolite. Similarly, in men, a **'RED LIGHT'** result for the CYP19A1 (aromatase) gene (section ONE of report) may be considered desirable as it reduces the conversion of androgens into estrogens.

SECTION 1

STEROIDOGENESIS (BIOSYNTHESIS OF ANDROGENS AND ESTROGENS) AND ANDROGEN METABOLISM



The production of sex steroids, steroidogenesis, stems from a single parent molecule, cholesterol. Through the multi-step metabolism of cholesterol, progesterones, androgens and estrogens are sequentially synthesized (and androgens are metabolized).

Key genes, and the enzymes they encode, play critical roles in this multi-step biosynthesis and metabolism:

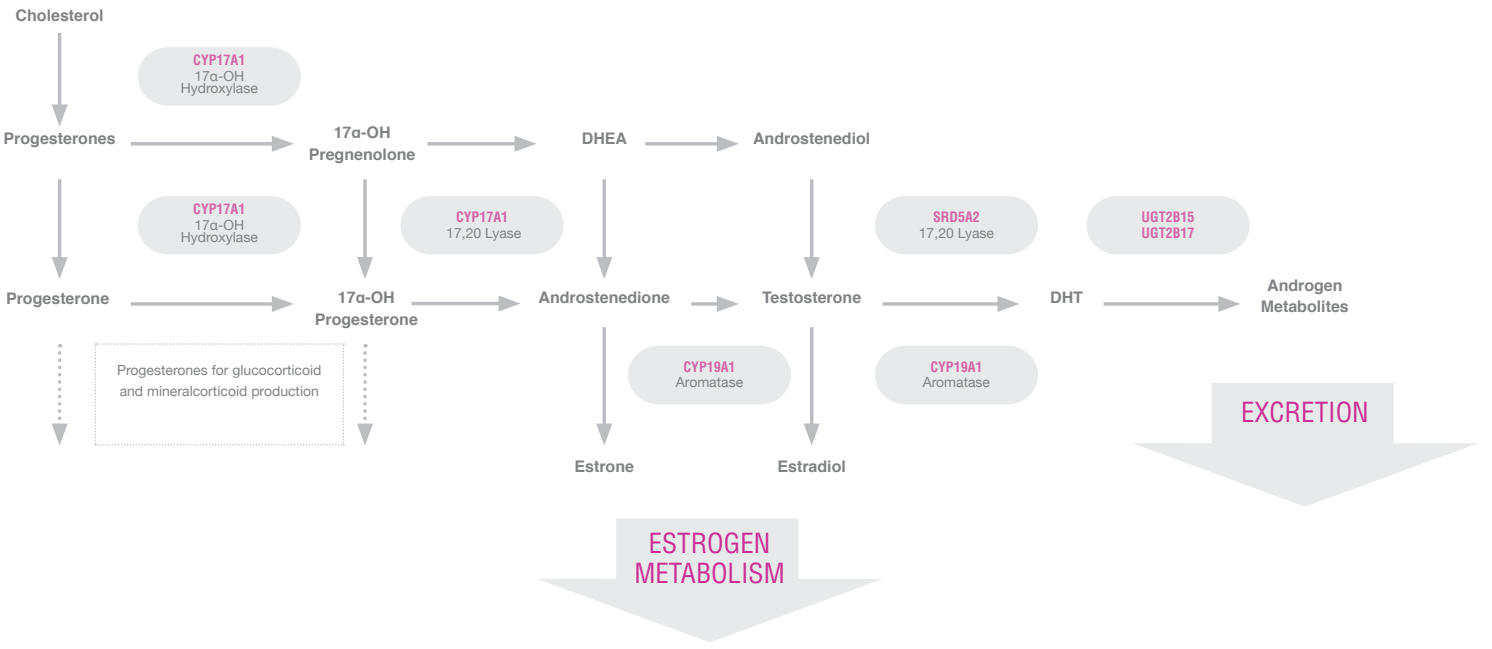
PROGESTERONES **CYP17A1:** Responsible for catalyzing the sequential 17α-hydroxylase and 17,20-lyase activities, which convert cholesterol into progesterones and androgens, respectively

ANDROGENS **SRD5A2:** Also known as 5α-reductase, converts testosterone into dihydrotestosterone (DHT)

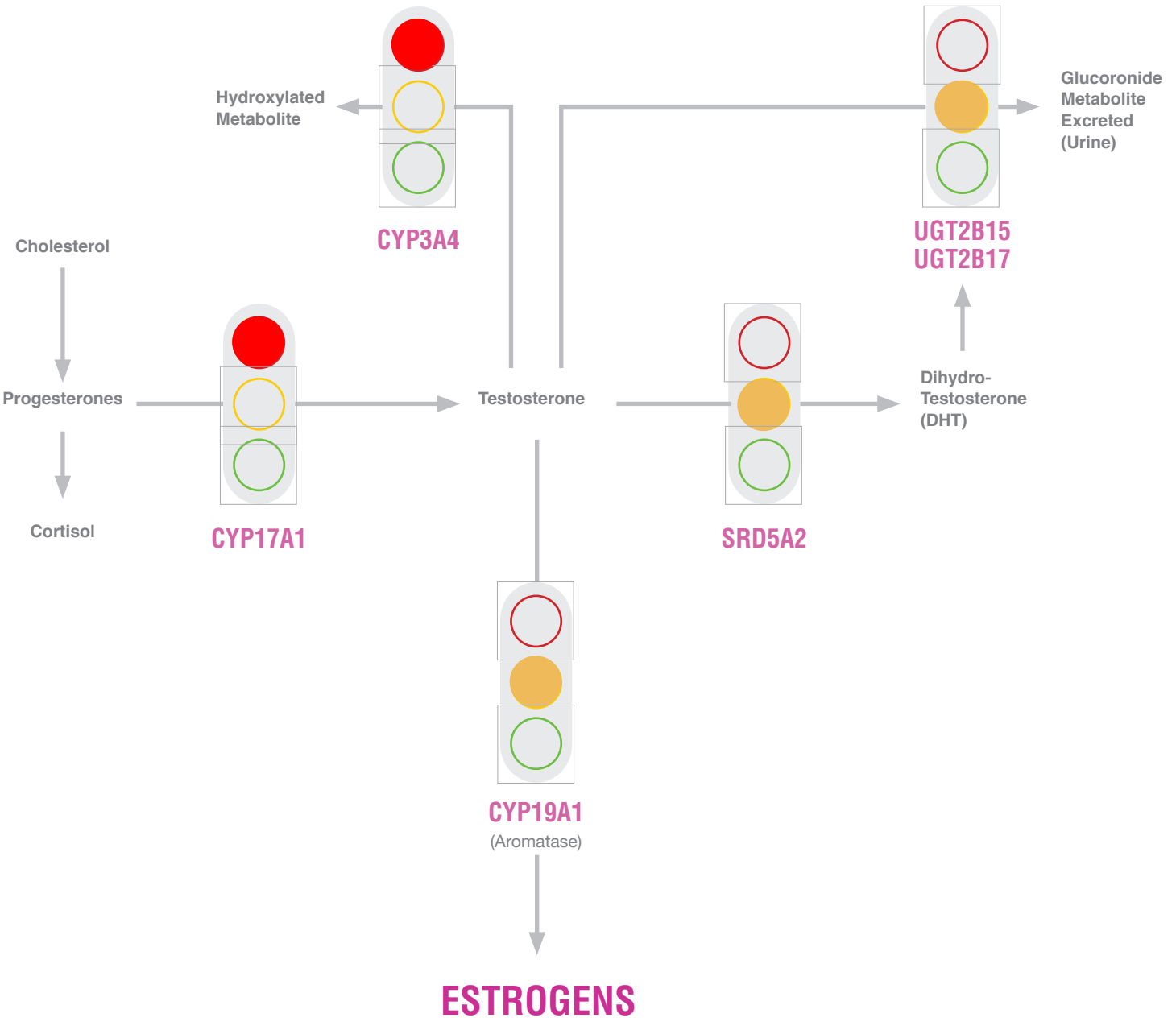
UGT2B17 (and to a lesser extent UGT2B15): Responsible for the catabolism of androgens, androgen metabolites, and catechol estrogens

ESTROGENS **CYP19A1:** Also known as aromatase, is the rate-limiting step in the conversion of androgens into estrogens

Note: Glucocorticoids and mineralcorticoids are also produced from cholesterol. However, for the purpose of this report only the three classes of hormones mentioned above will be discussed

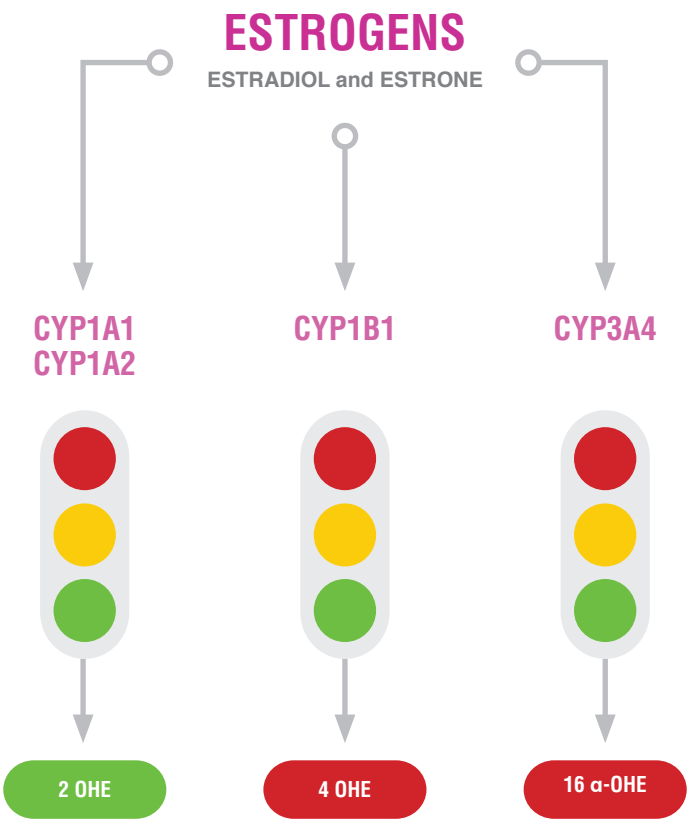


YOUR **RESULTS**



SECTION 2

METABOLISM OF ESTROGENS



Protective

Potentially Harmful

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The metabolism of estrogens begins with Phase I hydroxylation, catalyzed by specific members of the cytochrome P450 family of enzymes.

Both estradiol and estrone are hydroxylated.

Hydroxylated estrogens are collectively known as catechol estrogens (CEs) and can retain biologic activity. The bioactivity of the hydroxylated estrogens is dependent on the position of the added hydroxyl group.

The primary enzymes involved in the hydroxylation of estrogens (and the resulting metabolites) include:

CYP1A1 › produces **2-hydroxy-estrogen (2-OHE)** – estrogen antagonist and generally considered protective

CYP1B1 › produces **4-hydroxy-estrogen (4-OHE)** – estrogen agonist and generally considered deleterious

CYP3A4 › produces **16α-hydroxy-estrogen (16α-OHE)** – estrogen agonist and generally considered deleterious

NOTE: CYP3A4 also plays a major role in the catabolism of testosterone through 16α-hydroxylatio

The hydroxylation of estrogens exhibits tissue and estrogen-type specific patterns.

CYP1B1 exhibits higher catalytic efficiency (in breast tissue, when compared to CYP1A1) for the metabolism of estradiol.

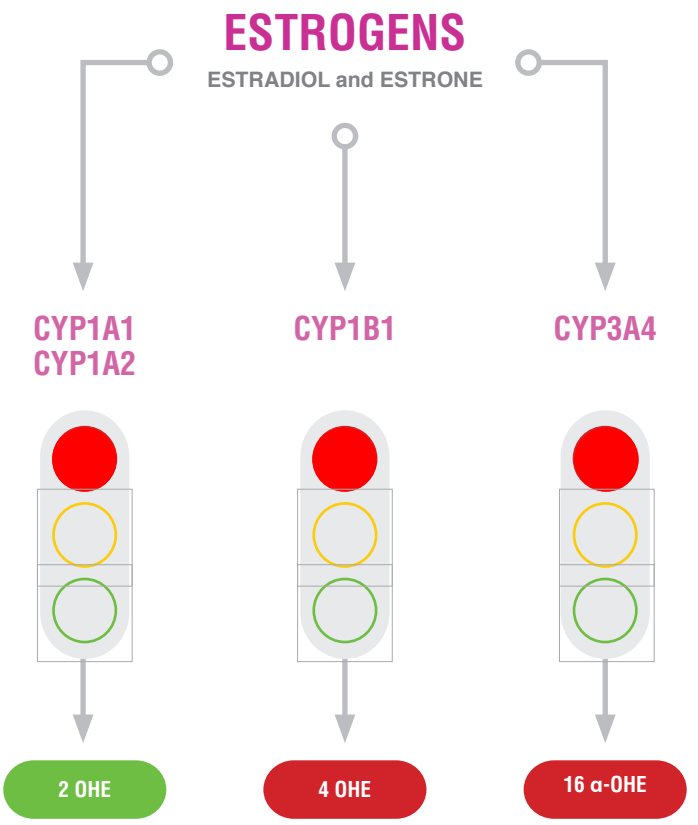
Polymorphisms that increase the expression of CYP1B1 (and environment/lifestyle factors that increase estradiol analogues within breast tissue) increase the levels of **4-OHE2** metabolite of estradiol within breast tissue.[46]

4-OHE2 induces DNA single-stranded breaks and significantly increases 8-hydroxy-2'-deoxyguanosine levels (a marker of DNA oxidative damage) with concomitant increased risk for tissue damage and hormone-related disease.

The **2-OHE** : **16α-OHE** ratio has been commonly assessed in clinical practice to determine risk of hormone related cancers associated with premenopausal women.[45]

This ratio may be modified by genetic polymorphisms and environmental factors including BMI and alcohol use. Obesity has been linked to preferential estrogen metabolism via the **16α-hydroxylation** pathway (thereby reducing the **2-OHE** : **16α-OHE** ratio) and increased hormone related diseases.[45]

YOUR **RESULTS**



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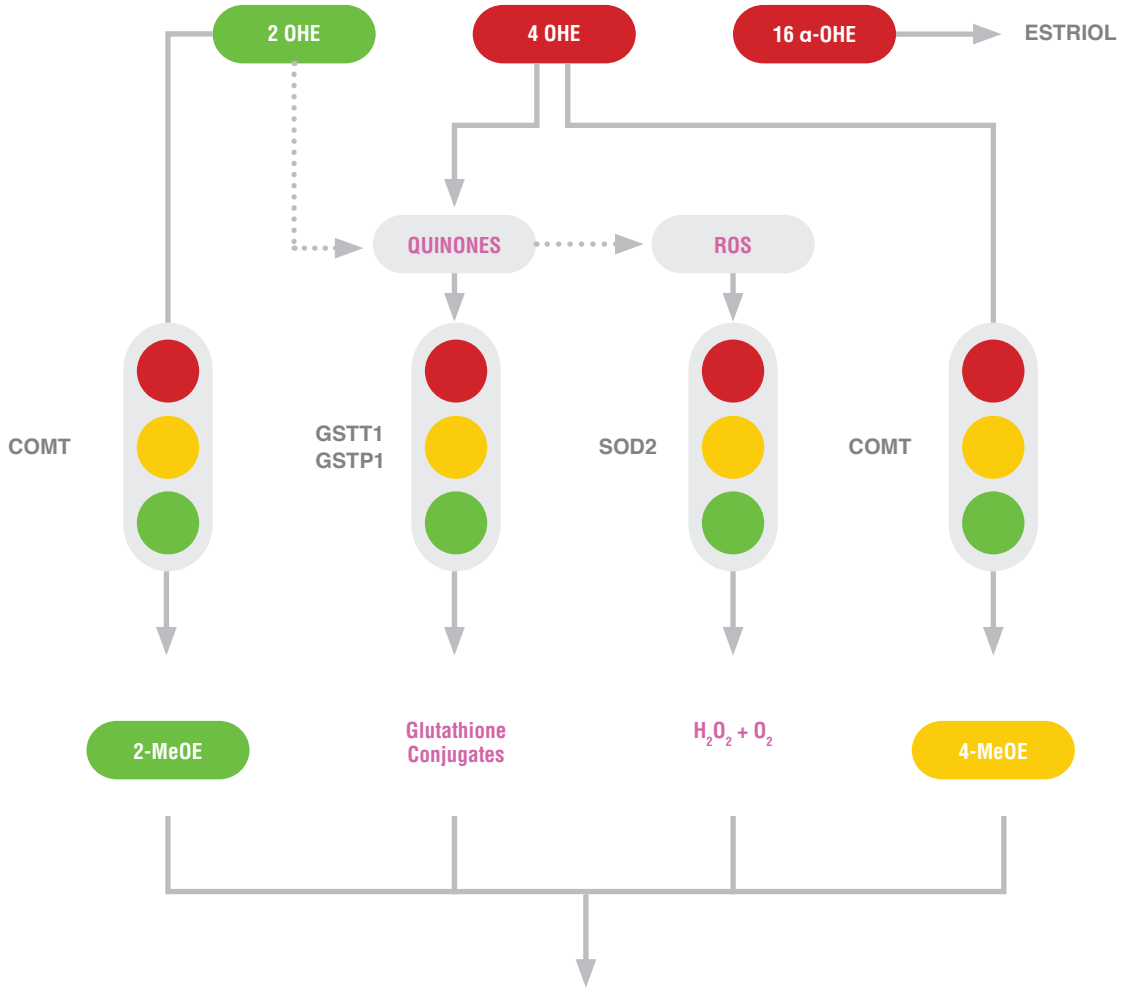
SECTION 3 ELIMINATION OF ESTROGEN & ESTROGEN METABOLITES



ELIMINATION

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In the last section of this report we query genomic polymorphisms capable of moderating the body's ability to effectively eliminate estrogens and their metabolites.

PHASE II: ESTROGEN ELIMINATION THROUGH CONJUGATION ENZYMES

After catechol estrogens (CEs) are formed through phase I cytochrome P450 metabolism, they are subject to deactivation by phase II conjugation enzymes.[70] Conjugation enzymes attach different chemical groups onto the CEs and estrogen metabolites, increasing their solubility and facilitating renal and biliary excretion.

These processes and their respective enzymes include:
Methylation › Catechol-O-methyltransferase (COMT)
Glucuronidation › UDP-glucuronosyltransferase (UGT)
Glutathionization › Glutathione S-transferase (GST)

METHYLATION AND COMT

COMT is the major metabolizer of CEs in extrahepatic tissue, forming methyoxy-estrogen (MeOE) metabolites. Similar to their hydroxylated precursors, the 2-MeOE are usually anti-estrogenic and considered protective.[70]

A high ratio of 2-OHE1 : 2-MeOE1 may indicate an imbalance in estrogen metabolism and low activity of COMT

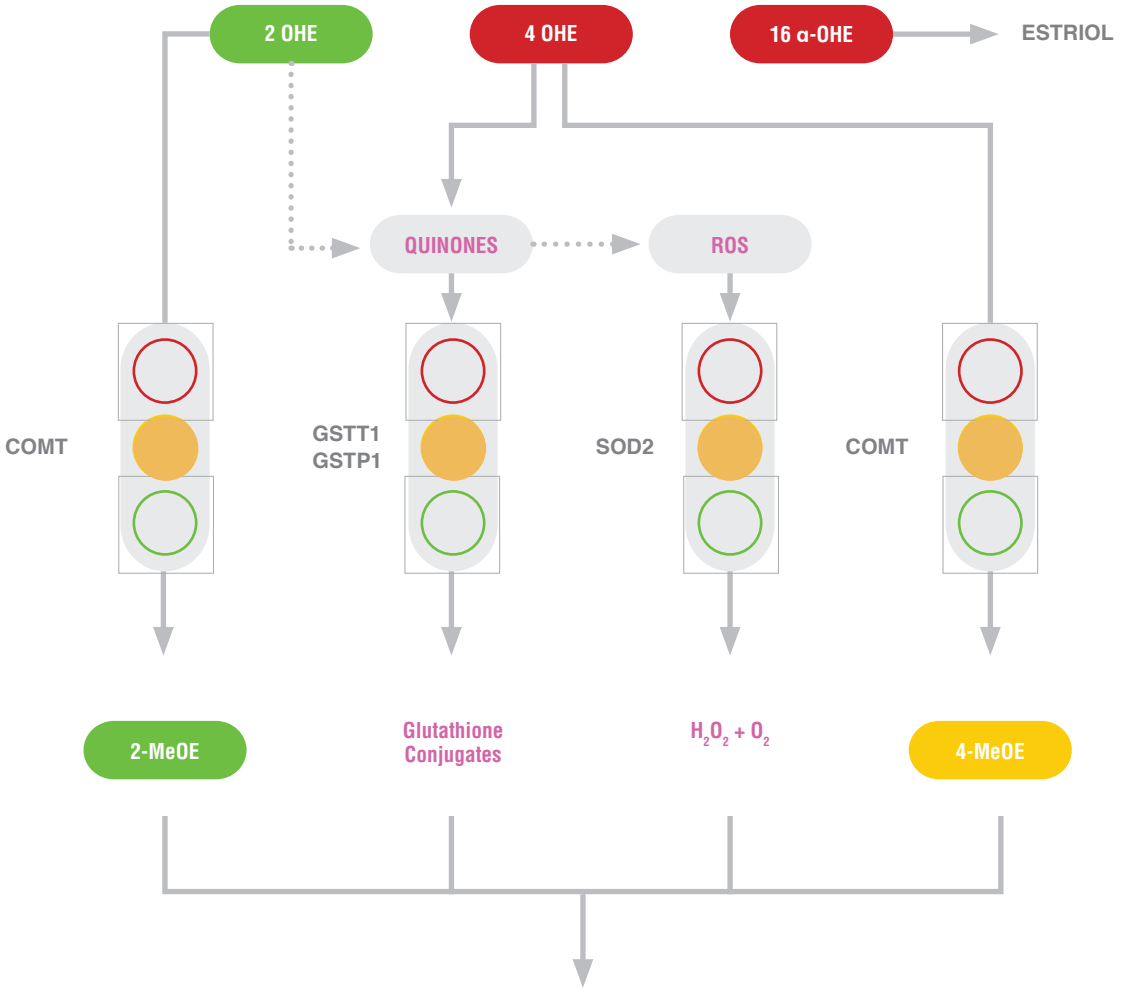
GLUCURONIDATION AND UGTS

As an alternative to methylation, glucuronic acid may be conjugated to CEs by the UGT enzymes. Without effective conjugation, CEs are oxidized to semiquinone and quinone by-products. Both semiquinones and quinones are highly reactive electrophilic metabolites capable of forming DNA adducts and ROS[46,70], which may exert adverse biological effects in estrogen-dependent tissues.

GLUTATHIONIZATION AND ANTI-OXIDATION (VIA SUPEROXIDE DISMUTASE)

Three classes of glutathione S-transferases (GSTs) – theta, mu and pi – are associated with estrogen metabolism. In breast and endometrial tissue, GST pi (GSTP1) is the predominant form.[70,71] GSTs conjugate glutathione to quinones to neutralize and eliminate these highly reactive electrophilic metabolites. Finally, GSTs and superoxide dismutase (SOD2) work in concert to eliminate ROS generated as end stage metabolites. ROS are capable of mediating DNA damage, protein oxidation, and lipid peroxidation, processes known to trigger genetic instability and cellular damage.[72]

YOUR **RESULTS**



Protective

Potentially Harmful

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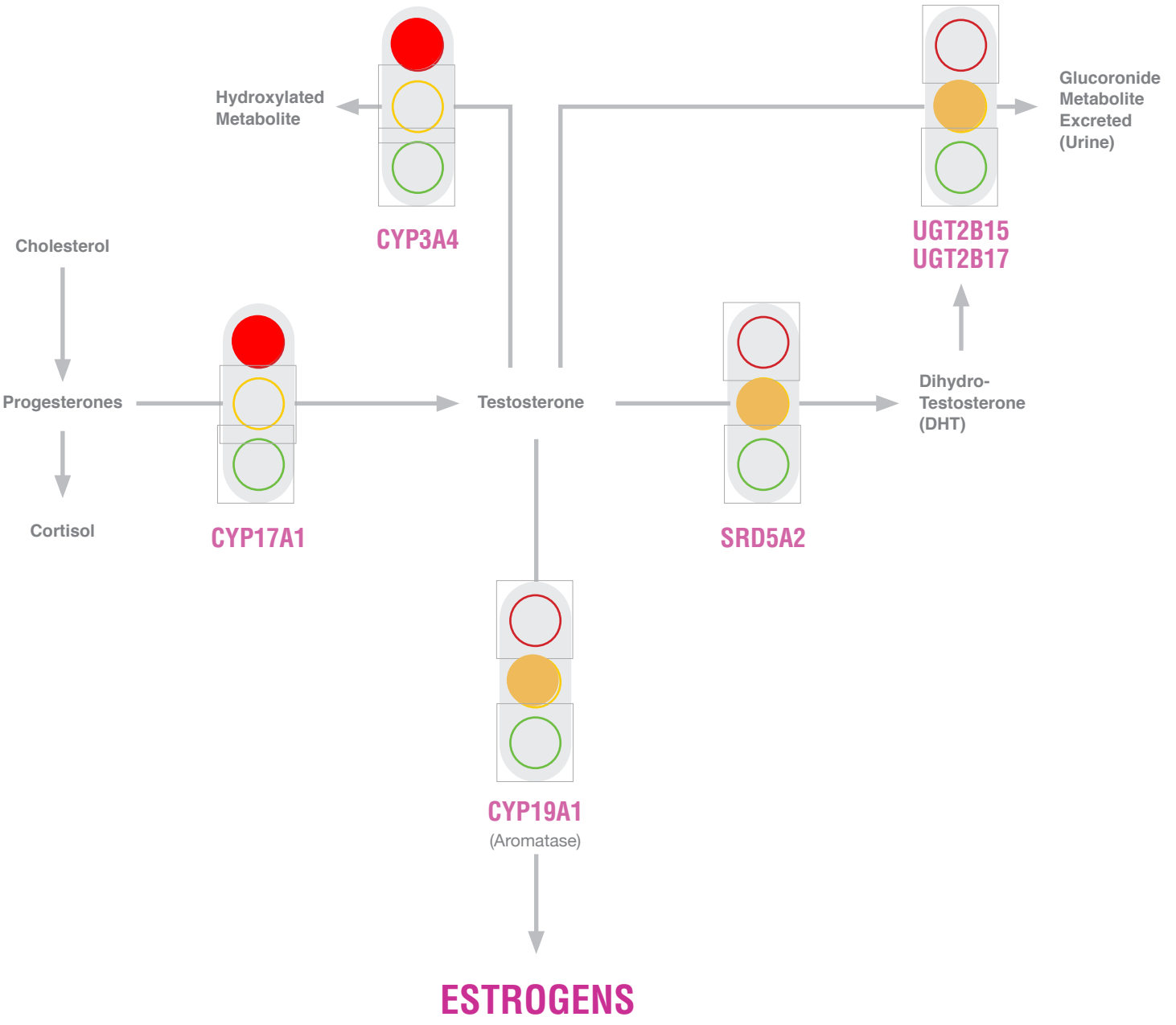
SECTION 1

STEROIDOGENESIS (BIOSYNTHESIS OF ANDROGENS AND ESTROGENS) AND ANDROGEN METABOLISM



CYP17A1
Rs743572

	A/A	Associated with low CYP17A1 expression and activity. No association to elevated estradiol levels or risk of hormone related diseases, especially in premenopausal women
	A/G	Associated with increased CYP17A1 expression and activity. Increased circulating estradiol levels and potentially increased risk of hormone related diseases, especially in premenopausal women
	G/G	Associated with increased CYP17A1 expression and activity. Increased circulating estradiol levels and potentially increased risk of hormone related diseases, especially in premenopausal women

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

SRD5A2
Rs523349

	C/C	Associated with reduced enzyme activity and reduced conversion of testosterone to DHT, minimizing risk associated with high DHT levels
	C/G	Associated with moderate enzyme activity and moderate conversion of testosterone to DHT, with potential risk associated with high DHT levels
	G/G	Associated with increased enzyme activity and moderate conversion of testosterone to DHT, with potential risk associated with high DHT levels

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

UGT2B15
Rs1902023

	T/T	Associated with increased glucuronidation of androgens and androgen metabolites, including DHT
	T/G	Associated with moderate glucuronidation of androgens and androgen metabolites, including DHT
	G/G	Associated with reduced glucuronidation of androgens and androgen metabolites, including DHT

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

UGT2B17
CNV

	2 COPIES	Associated with increased enzyme activity and decreased concentrations of circulating testosterone and estradiol levels. Associated with low BMD and increased risk for osteoporosis
	1 COPY	Associated with moderate enzyme activity and moderate concentrations of circulating testosterone and estradiol levels
	NO COPIES	Associated with absent enzyme activity and increased concentrations of circulating testosterone and estradiol levels

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

CYP19A1
Rs 10046

	C/C	Associated with reduced CYP19A1 expression and enzyme activity with reduced levels of estrogens and estrogen to androgen ratios, especially in postmenopausal women
	C/T	Associated with moderate CYP19A1 expression and enzyme activity with moderately reduced levels of estrogens and estrogen to androgen ratios, especially in postmenopausal women
	T/T	Associated with increased CYP19A1 expression and enzyme activity with increased levels of estrogens and estrogen to androgen ratios, especially in postmenopausal women

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

CYP17A1
Rs743572

A/A

Cytochrome 17A1 (CYP17A1) is essential in the production of glucocorticoids and sex steroids. A member of the cytochrome P450 family, this enzyme catalyzes 17α-hydroxylase and 17, 20-lyase activities in two sequential reactions to convert pregnenolone and progesterone to DHEA and androstenedione, respectively.

The CYP17A1 enzyme is encoded by the gene CYP17A1. The CYP17A1 enzyme is found in the adrenal glands and gonads. It catalyzes key steps in steroidogenesis to regulate the levels of mineralocorticoids, glucocorticoids, androgens and estrogens. While CYP17A1 catalyzes the biotransformation of both pregnenolone and progesterone, it exhibits a greater affinity for pregnenolone. Progesterone is preserved for glucocorticoid synthesis and thus susceptible to depletion during high cortisol demand and production (such as during prolonged periods of stress) [4]

GENETIC VARIATION TESTED

The CYP17A1 gene is located on chromosome 10 at 10q24.32. The rs743572 SNP corresponds to an A>G substitution [5]

IMPLICATIONS OF THE GENETIC VARIATION

The rs743572 polymorphism is found in the 5'-promoter region of the CYP17A1 gene. The 'G' allele of this SNP is associated with increased CYP17A1 transcription and enzyme activity compared to the 'A' allele [5,6]

CYP17A1
Rs743572

A/A

G GENOTYPES

- The G allele (G/G and A/G genotypes) is associated with increased enzyme expression, enzyme activity and circulating levels of estradiol in premenopausal women compared to A/A genotypes [5,6,7]
- The G allele is associated with earlier menarche compared to A/A genotypes and thus a potential increase in total lifetime estrogen exposure [7]
- The G allele is associated with an increased risk for PCOS and infertility in those with stage I-II endometriosis, and breast cancer in women who have been treated with HRT for longer than 10 years [4,5,8,9]
- In men, the G allele is associated with an increased risk of prostate cancer in African Americans. This was not seen in Caucasian or Asian populations [10]
- The G allele significantly interacts with phthalate exposure to increase the risk of leiomyoma [11]
- The G allele interacts with soy isoflavones to reduce the risk of breast cancer in premenopausal Asian women [12]

A GENOTYPES

- The A/A genotype is associated with a decrease in enzyme expression and enzyme activity [7]
- The A/A genotype is associated with a later onset of menarche compared to A/G and G/G genotypes [7]

SRD5A2
Rs523349

C/G

Steroid 5α-reductase (SRD5A2) enzyme is involved in the metabolism of androgens. The enzyme catalyzes the NADPH dependent conversion of testosterone into the more potent and biologically active dihydrotestosterone (DHT)

The 5α-reductase type 2 isozyme (SRD5A2) is encoded by the SRD5A2 gene and is expressed during various stages of development to influence sex development. There are three isoforms of the enzyme. Type 2 isoforms reside mainly in reproductive tissue of both males and females, including the reproductive tract, ovaries, testes, prostate, and other organs such as the liver and skin.[17,18] Obesity is shown to influence the activity of SRD5A2, causing an increase in catalytic activity and production of biologically active androgens that influence hormonal homeostasis.

GENETIC VARIATION TESTED

The SRD5A2 gene is located on chromosome 2 at 2q23.1. The rs523349 SNP corresponds to a C>G conversion.

IMPLICATIONS OF THE GENETIC VARIATION

The ‘G’ (Val) allele is associated with increased enzyme activity, while the ‘C’ (Leu) allele is associated with a 10-40% reduction in SRD5A2 activity.[13,17,1]

SRD5A2
Rs523349

C/G

G GENOTYPES

- The G/G genotype is associated with a 30% increase in enzyme activity, compared to C homozygotes. This results in an increased turnover rate of testosterone to DHT [13]
- The G allele (G/G and C/G genotypes) is most common in African American populations while Asians have the lowest frequency. This association has been related to relative risks of prostate cancer [19]
- A 1000-fold increase in SRD5A2 activity is seen in the ovarian follicle of women with PCOS [17]
- SRD5A2 metabolites act as inhibitors of aromatase (CYP19A1) activity and facilitate the pathogenesis of PCOS [20,21]

C GENOTYPES

- The C/C genotype is associated with reduced enzyme activity and decreased levels of circulating DHT[13,22.] Interestingly, the C allele is associated with a 30% reduction in testosterone production, highlighting the complexity of feedback regulation in hormone metabolism [13]
- The C/C genotype is associated with a decreased frequency of PCOS [21]

UGT2B15
Rs1902023

G/T

UDP-glucuronosyltranferase 2B15 (UGT2B15) contributes to the phase II deactivation of sex steroids. This enzyme contributes to estrogen and steroid signalling through targeted inactivation and elimination of catechol estrogens and androgens, including testosterone, dihydrotestosterone (DHT), and 3α-diol (5α-androstane-3α,17β-diol) [31]

The UGT2B15 enzyme is encoded by the UGT2B15 gene, which is widely expressed in the liver, esophagus, intestine, breast, prostate, testis, placenta, adipose tissue and uterus. It is unregulated by estrogen, genistein, and DHT[31]. In addition, the UGT2B enzymes are also involved in the metabolism of drugs and xenobiotics, including benzodiazepines, acetaminophen[32], tamoxifen metabolites, and BPA.[23,33,34]

GENETIC VARIATION TESTED

The UGT2B15 gene is located on chromosome 4 at 4q13.2. The rs1902023 SNP corresponds to a G>T conversion

IMPLICATIONS OF THE GENETIC VARIATION

The functional rs1902023 SNP corresponds to an Asp85Tyr amino acid substitution, which affects the substrate binding domain and catalytic activity of the enzyme (depending on the substrate being metabolized).[35]

UGT2B15
Rs1902023

G/T

T GENOTYPES

- The T allele (T/T and G/T genotypes) is associated with increased enzyme activity and metabolism of androgenic steroids (androstane-3α,17b-diol and DHT), resulting in a 33% reduction in DHT levels [36,37]
- The T allele (T/T and G/T genotypes) is associated with a 40-50% decrease in oxazepam, lorazepam and sipoglitazar clearance compared to the G/G genotype [34,35,37,38.] The difference in clearance rate between substrates shows that the effect of the polymorphism on this enzyme is substrate dependent
- In a multi-ethnic study, the T allele is associated with a significant reduction in BPA glucuronidation, an endocrine disrupting plasticizer commonly found in dentistry, food packaging and lacquers[34]. This is shown to potentially increase susceptibility for BPA toxicity [39]

G GENOTYPES

- The G/G genotype is associated with a decrease in DHT glucuronidation, higher intraprostatic DHT concentration and increased subsequent risk for prostate cancer [41-43]
- The G allele is associated with decreased enzyme activity and slower glucuronidation and secretion of active tamoxifen metabolites, correlating to an increase in survival in patients with breast cancer [40]
- The G/G genotype is associated with an increased risk of colorectal cancer, which is further increased with the use of aspirin compared to non-users carrying the T allele [44]

UGT2B17
CNV

1 COPIES

UDP-glucuronosyltranferase 2B17 (UGT2B17) is an important phase II enzyme in the deactivation of sex steroids. This enzyme catalyzes the transfer of glucuronic acid to androgens, including testosterone, dihydrotestosterone (DHT), 17β-diol, and androsterone.[23]

The UGT2B17 enzyme is encoded by the UGT2B17 gene. Interestingly, UGT2B17 and UGT2B15 share more than 95% sequence homology yet catalyze distinct reactions.[23,24] The UGT2B17 enzyme is not limited in its role in androgen inactivation. It also metabolizes exogenous xenobiotic compounds such as ibuprofen, coumarins, anthraquinones and flavonoids.[23] As part of the 2B family of UGT enzymes, its classic role in detoxification is supported by its expression in the gastrointestinal tract, liver, and kidneys.

GENETIC VARIATION TESTED

The UGT2B17 gene is located on chromosome 4 at 4q13.2.

IMPLICATIONS OF THE GENETIC VARIATION

The UGT2B17 gene is susceptible to copy number variations and is one of the most commonly deleted genes.[26] This type of variation affects the entire gene and can determine if the gene (and hence its product) is literally **absent** from a person's genomic make-up (the null genotype), or **present** in 1 or more copies. The number of gene copies directly influences the amount of enzyme expressed and subsequent activity, with amplification (more than 1 copy in the case of UGT2B17) resulting with the highest catalytic activity.

UGT2B17
CNV

1 COPIES

ABSENT GENOTYPES

- Null genotypes (homozygous deletion) are associated with a significant reduction in the rate of testosterone glucuronide excretion compared to those carrying 1 and 2 copies of the UGT2B17 gene. This relates to a decreased rate of steroid deactivation and elimination [25]
- Null genotypes are associated with significantly higher plasma concentrations of testosterone and estradiol [25]
- Null genotypes are found in 27% of Caucasians, while 43% have two copies [26]
- Null genotypes are associated with a decrease in colorectal cancer (CRC) risk in Caucasian men [27]
- UGT2B17 metabolizes certain flavonoids with anti-oxidative properties, null genotypes may therefore have higher circulating levels of protective dietary flavonoid components [27]
- Those with the null variant of UGT2B17 show elevated levels of UGT2B15 activity in the liver (increase in mRNA), an enzyme that is strongly involved in testosterone and DHT deactivation [28,29]

PRESENT GENOTYPES

- The presence of the UGT2B17 gene (1 or 2 copies) is associated with an increase in androgen urinary metabolite excretion and testosterone to epitestosterone (T/E) ratio compared to UGT2B17 null genotypes [29]
- Amplification of UGT2B17 (2 copies) is associated with a lower bone-mineral density (BMD) and increased risk for osteoporosis and osteroporotic hip fracture. As a result of rapid inactivation of the androgen-signalling pathway, bone resorption is favoured over bone formation, impairing proper bone formation [30]

CYP19A1
Rs10046

C/T

Cytochrome 19A1 (CYP19A1), or aromatase, is responsible for the rate-limiting step in estrogen biosynthesis. A member of the cytochrome P450 family, this enzyme catalyzes the conversion of androgens to estrogens

The CYP19A1 enzyme is encoded by the CYP19A1 gene, which may be induced by follicular stimulating hormone (FSH) to increase estrogen production. Aromatase is present in a variety of tissues beyond the reproductive organs: skin, muscle, nerve, liver, hair follicles, adipose tissue and brain. Aromatase functions in sex steroid hormone synthesis as well as growth and differentiation, influencing such differences as male and female fat distribution

GENETIC VARIATION TESTED

The CYP19A1 gene is located on chromosome 15 at 15q21.2. The rs10046 SNP corresponds to a C>T conversion

IMPLICATIONS OF THE GENETIC VARIATION

The ‘T’ allele is associated with an increase in CYP19A1 transcription and enzyme activity compared to the ‘C’ allele

CYP19A1
Rs 10046

C/T

T GENOTYPES

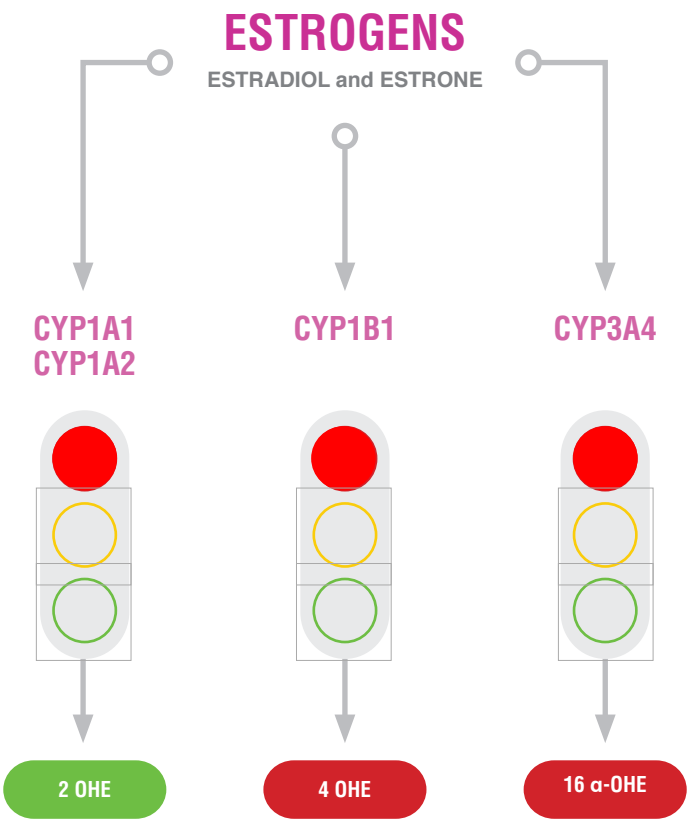
- The T allele (T/T and C/T genotype) is associated with increased CYP19A1 mRNA levels and enzyme activity [1,13]
- The T allele is associated with elevated estradiol levels and increased estrogen to androgen ratios [14,15]
- The T allele is significantly associated with Premature Ovarian Failure (POF) [16]

C GENOTYPES

- The C/C genotype is associated with lower levels of CYP19A1 mRNA and reduced enzyme activity compared to the T allele [13]
- The C allele is associated with reduced levels of estradiol, estrone, and ratios of estradiol to testosterone and estrone to androstenedione. This association is more significant in postmenopausal women [13,15]

SECTION 2

METABOLISM OF ESTROGENS



Protective

Potentially Harmful

Potentially Harmful

CYP1A1
Rs1048943

	A/A	Associated with decreased enzyme activity and decreased production of 2-OH-estrogen metabolites. Also associated with low enzyme inducibility upon exposure to toxins with reduced risk of toxic intermediate and ROS accumulation
	A/G	Associated with increased enzyme activity and increased production of 2-OH-estrogen metabolites. However, also associated with increased enzyme inducibility upon exposure to toxins with increased risk of toxic intermediate and ROS accumulation
	G/G	Associated with increased enzyme activity and increased production of 2-OH-estrogen metabolites. However, also associated with increased enzyme inducibility upon exposure to toxins with increased risk of toxic intermediate and ROS accumulation

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

CYP1B1
Rs1056836

	C/C	Associated with decreased enzyme activity, decreased production of 4-OH-estrogen metabolites, and potentially decreased DNA damaging events (with inducing environmental factors).
	C/G	Associated with increased enzyme activity, increased production of 4-OH-estrogen metabolites, and potentially increased DNA damaging events (with inducing environmental factors).
	G/G	Associated with increased enzyme activity, increased production of 4-OH-estrogen metabolites, and potentially increased DNA damaging events (with inducing environmental factors).

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

CYP3A4
Rs2740574

	A/A	Associated with decreased enzyme activity and decreased production of 16α-OH-estrogen metabolites. Also associated with decreased catabolism of testosterone.
	A/G	Associated with increased enzyme activity and increased production of 16α-OH-estrogen metabolites. Also associated with increased catabolism of testosterone.
	G/G	Associated with increased enzyme activity and increased production of 16α-OH-estrogen metabolites. Also associated with increased catabolism of testosterone.

NB: While all possible results are shown, your specific result is highlighted with the appropriate 'traffic light'
IMPORTANT: CYP3A4 is one of the most abundant phase I metabolizers. It is also BOTH highly *inducible* and *suppressible*

CYP1A1
Rs1048943

A/A

Cytochrome 1A1 (CYP1A1) is the major enzyme responsible for the conversion of estrogens into 2-hydroxy-estrogen (2-OHE) metabolites. 2-OHE catechols are generally considered protective, reflective of their inert hormone activity.[47]

CYP1A1 is encoded by the CYP1A1 gene. In high concentrations, 2-OHEs inhibit CYP1A1 and CYP1B1 activity to limit catechol estrogen production. [48]

Importantly, CYP1A1 also metabolizes a wide variety of environmental genotoxic compounds, such as polyaromatic hydrocarbons (PAHs) (typically produced from combustion of organic materials, tobacco smoke and charbroiled meats). An increase in activation of CYP1A1 not only increases 2-OHE production, which may be beneficial from a hormonal perspective, but it also activates environmental toxins (the hydroxylation of compounds such as PAHs often produces intermediates more toxic than the original PAH) – revealing the complex interconnectivity of enzyme function (driven by functional polymorphisms), environment, lifestyle, and the risk of disease development.[49]

GENETIC VARIATION TESTED

The CYP1A1 gene is located on chromosome 15 at 15q22-24. The rs1048943 SNP results in a A>G conversion and is the most common functional variant found in the CYP1A1 gene.[48]

IMPLICATIONS OF THE GENETIC VARIATION

The ‘G’ (Val) allele is associated with an increase in enzyme activity compared to the ‘A’ (Ile) allele with concomitant implications to substrate exposure and metabolism.[50]

CYP1A1
Rs1048943

A/A

G GENOTYPES

- The G allele (G/G and A/G genotypes) is associated with increased gene expression and catalytic activity [47,48]
- The G allele interacts significantly with environmental toxins, including polychlorinated biphenyls, AHH (aryl hydrocarbon hydroxylase), and PAHs, and increases the risk of certain types of cancer (breast, prostate, ovarian) [51]
- The G allele is found in 18-33% of Asians, 2-10% of Caucasians and 81-100% in Amerindian populations living in South America.[48] The homozygous G/G genotype is rare in Caucasian or African populations [52]
- In vitro studies suggest that compounds such as hypercin, pseudohypercin and quercetin inhibit CYP1A1 expression [48]

PRESENT GENOTYPES

- The A/A genotype is associated with decreased enzyme activity compared to G allele carriers

CYP1B1
Rs1056836

C/C

Cytochrome 1B1 (CYP1B1) is the major enzyme responsible for the conversion of estrogens into 4-hydroxy-estrogen (4-OHE) metabolites. The 4-OHE estrogens are considered proliferative and carcinogenic as a result of their retained estrogenic activity and quinone by-products.[31,47,53]

The CYP1B1 enzyme is encoded by the CYP1B1 gene, which is expressed in the presence of steroids and many environmental toxins, including those found in cigarettes such as PAHs, nitrosamines, and heterocyclic amines.[54] CYP1B1 is the predominant enzyme within the breast tissue responsible for 4-hydroxylation of estrone (E1) and estradiol (E2).[46] Enhanced CYP1B1 activity, as seen with exposure to environmental toxins, shifts estrogen metabolism towards 4-hydroxylation, diverted from the protective 2-hydroxylation pathway.[55] The 4-OHE metabolites, and their respective quinone by-products, are recognized as the most potent carcinogenic metabolites, capable of significantly inducing oxidative DNA damage [46,56]

GENETIC VARIATION TESTED

The CYP1B1 gene is located on chromosome 2 at 2p21. The rs1056836 corresponds to C>G SNP. This is the most noted functional polymorphism[47] and is in linkage disequilibrium with other functionally relevant SNPs such as rs1800440.[57]

IMPLICATIONS OF THE GENETIC VARIATION

The ‘G’ allele is associated with higher enzyme activity towards estrogens, resulting in increased formation of 4-OHE.[57] However, the ‘C’ allele (though associated with decreased production of 4-OHE) potentiates procarcinogen activation – again revealing the complex interconnectivity of enzyme function (driven by functional polymorphisms), environment, lifestyle, and the risk of disease development.[56]

CYP1B1
Rs1056836

C/C

G GENOTYPES

- The G allele (G/G and C/G genotypes) is associated with higher enzyme activity [58]
- The G allele is associated with a threefold increase in 4-hydroxylase activity compared to the C allele, resulting in a higher ratio of 4- to 2-hydroxy estrogen metabolites [47,59]
- In postmenopausal women the G allele did not produce a measurable influence on estrogen metabolites [2]
- C/G genotypes are associated with a decrease in VMS (vasomotor symptoms) related to menopause (hot flashes, night sweats, and /or cold sweats) in African women [53]

C GENOTYPES

- The C/C genotype is associated with higher concentrations of luteal estradiol compared to G/G genotypes, consistent with the lower enzyme activity of the C/C genotype [2,60]
- The C allele is the major allele found in Asian, Caucasian, Chinese and Japanese women (but not in African American women) [52,59]
- Like many of the cytochrome P450 enzymes, the risk associated with CYP1B1 genotype/activity is highly variable depending on environmental exposures. C/C genotypes may be protected from high levels of 4-OHE, BUT if they smoke there is increased CYP1B1 activation of environmental toxins, including benzopyrene.
- Importantly, and reflecting on the point above, genistein, raspberries, blueberries and ellagic acid reduce xenobiotic-induced CYP1A1 and CYP1B1 expression and inhibit their catalytic activity [47,61]

CYP3A4

Rs2740574

A/A

Cytochrome 3A4 (CYP3A4) is one of the most abundant cytochrome P450 enzymes found within the liver and small intestines. It is responsible for the metabolism of approximately 50- 60% of available pharmaceuticals, including oral contraceptives.[62] In addition, CYP3A4 is a major catalyst in the hydroxylation of steroid hormones, including estradiol, estrone and testosterone.

CYP3A4 is expressed in the prostate, breast, stomach, colon, small intestine and liver.[63] CYP3A4 metabolizes a large number of environmental chemicals, therapeutic drugs and steroid hormones, including testosterone, progesterone, cortisol and vitamin D.

CYP3A4 enzyme activity is significantly modifiable. St. John's Wort, glucocorticoids, smoking, alcohol and oral contraceptives all induce CYP3A4 expression, while grapefruit juice strongly inhibits it. Inhibition is shown to increase circulating levels of estrogen and the bioavailability of many drugs.[62]

The CYP3A4 metabolite of estrone, 16α-OHE1, maintains its estrogenic properties and can lead to unregulated cellular proliferation.[64,65] A low ratio of 2-OHE1: 16-OHE1 is implicated in breast and endometrial cancer. [45]

GENETIC VARIATION TESTED

The CYP3A4 gene is located on chromosome 7 at 7q22.1. The rs2740574 SNP corresponds to an A>G conversion within the 5' promoter region of the gene.

IMPLICATIONS OF THE GENETIC VARIATION

The 'G' allele is associated with an increase in expression and enzyme activity compared to the 'A' allele.

CYP3A4
Rs2740574

A/A

G GENOTYPES

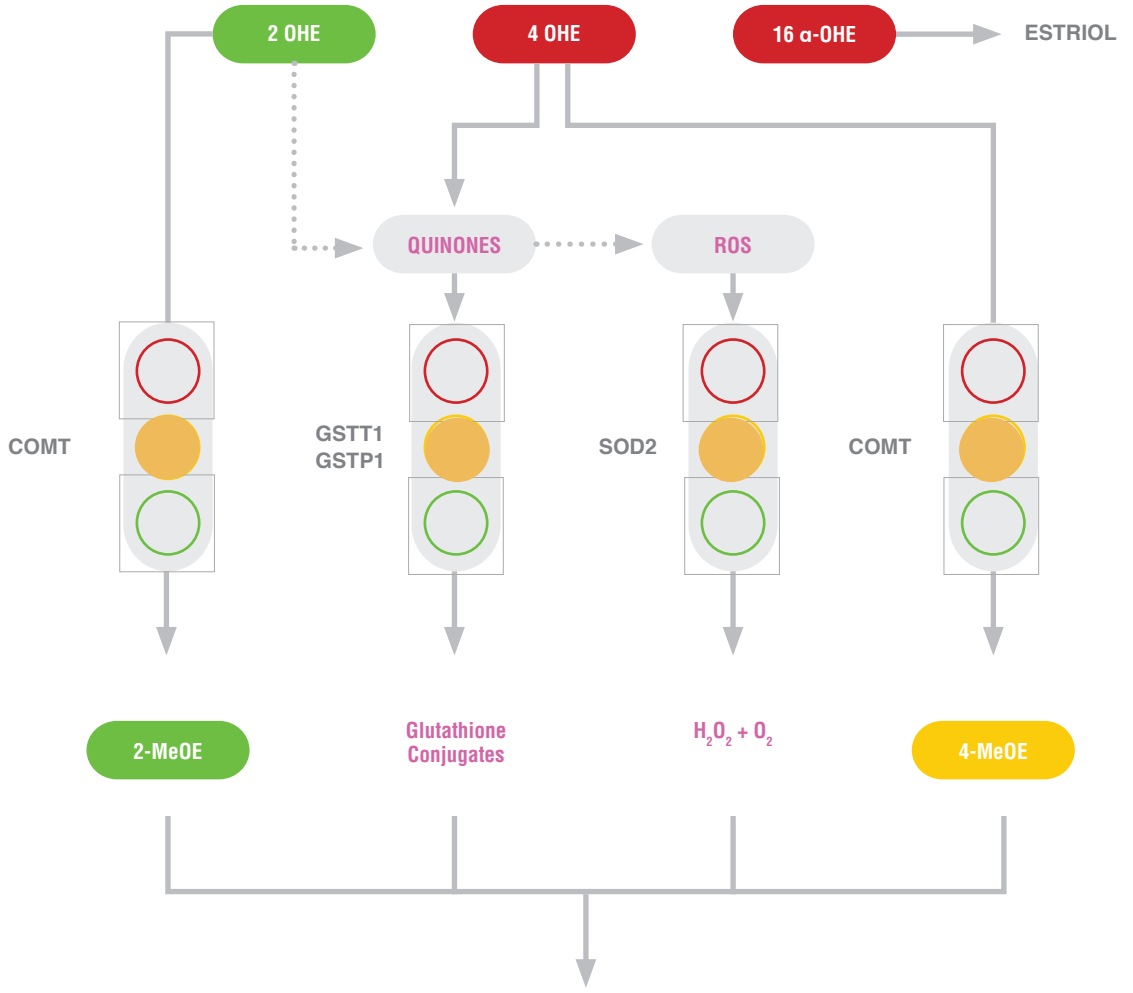
- The G allele (G/G and A/G genotypes) is associated with moderately increased gene expression and enzyme activity when compared to the A/A genotype [67]
- The G allele is associated with early-onset-menarche in African American, Hispanic and Caucasian girls [68]
- The G allele frequency is much higher in African populations (59.7-80% in African American, 69% in Ghanaians) than other ethnicities (3.6-9.6% in Caucasians, 9.3-10.7% in Hispanics, 8.9% in Saudis) [62,68,69]
- The G allele is associated with a decrease in the oxidation of testosterone (deactivation) and with concomitant higher Gleason grade and TNM stage prostate cancer in men over the age of 65 [69]
- The prevalence of the G allele in African American men may contribute to the increased risk of prostate cancer in this population
- The G/G genotype is associated with an increased risk of invasive ovarian cancer in African Americans, but not in Caucasian or Asian populations [62,68]

A GENOTYPES

- The A/A genotype is associated with a decrease in expression and enzyme activity compared to G allele carriers
- The A/A genotype is associated with preferential response to several pharmaceuticals that are metabolized via CYP3A4 (due to slower metabolic clearance)
- A/A genotypes with ovarian cancer are associated with increased survival when treated with platinum and taxane chemotherapeutics (due to the reduced clearance of these drugs in A/A genotypes) [66]

SECTION 3

ELIMINATION OF ESTROGEN & ESTROGEN METABOLITES



Protective

Potentially Harmful

Potentially Harmful

COMT
Rs4680

	G/G	Associated with optimal enzyme activity and increased methylation of catechol estrogens with decreased risk of estrogen-DNA adduct formation and associated tissue damage
	G/A	Associated with moderate enzyme activity and methylation of catechol estrogens with possible risk of estrogen-DNA adduct formation and associated tissue damage
	A/A	Associated with reduced enzyme activity and methylation of catechol estrogens with increased risk of estrogen-DNA adduct formation and associated tissue damage

NB: While all possible results are shown, your specific result is highlighted with the appropriate 'traffic light'

GSTT1
CNV

	2 COPIES	Associated with increased enzyme activity and increased clearance of estrogen quinone by-products and ROS, with reduced risk of associated tissue and DNA damage seen with ROS accumulation
	1 COPY	Associated with average enzyme activity and average clearance of estrogen quinone by-products and ROS, with moderate risk of associated tissue and DNA damage seen with ROS accumulation
	NO COPIES	Associated with absent enzyme activity and low clearance of estrogen quinone by-products and ROS, with increased risk of associated tissue and DNA damage seen with ROS accumulation

NB: While all possible results are shown, your specific result is highlighted with the appropriate 'traffic light'

GSTP1
Rs1695

	A/A	Associated with optimal enzyme activity and increased clearance of estrogen quinone by-products, with reduced risk of associated tissue and DNA damage seen with ROS accumulation
	A/G	Associated with moderate enzyme activity and moderate clearance of estrogen quinone by-products, with moderate risk of associated tissue and DNA damage seen with ROS accumulation
	G/G	Associated with reduced enzyme activity and decreased clearance of estrogen quinone by-products, with increased risk of associated tissue and DNA damage seen with ROS accumulation

NB: While all possible results are shown, your specific result is highlighted with the appropriate ‘traffic light’

GSTM1
CNV

	2 COPIES	Associated with increased enzyme activity and increased clearance of estrogen quinone by-products and ROS, with reduced risk of associated tissue and DNA damage seen with ROS accumulation
	1 COPY	Associated with average enzyme activity and average clearance of estrogen quinone by-products and ROS, with moderate risk of associated tissue and DNA damage seen with ROS accumulation
	NO COPIES	Associated with absent enzyme activity and low clearance of estrogen quinone by-products and ROS, with increased risk of associated tissue and DNA damage seen with ROS accumulation

NB: While all possible results are shown, your specific result is highlighted with the appropriate 'traffic light'

SOD2
Rs4880

	C/C	Associated with optimal enzyme activity and low risk of oxidative damage associated with ROS production
	C/T	Associated with up to 35% reduction in enzyme activity and low risk of oxidative damage associated with ROS production
	T/T	Associated with up to 70% reduction in enzyme activity and high risk of oxidative damage associated with ROS production

NB: While all possible results are shown, your specific result is highlighted with the appropriate 'traffic light'

COMT
Rs4680

G/A

Catechol-O-methyltransferase (COMT) is a pleiotropic enzyme that facilitates the S-adenosylmethionine (SAMe) dependent methylation of catechol containing substances, including the estrogen metabolites, 2- and 4-hydroxy catechol estrogens. This enzyme also supports the biotransformation of catecholamine neurotransmitters, xenobiotics, steroids and drugs.

The COMT enzyme is encoded by the COMT gene. O-methylation catalyzed by the COMT enzyme is the primary route for phase II detoxification of catechol estrogens.[58] Both 2-hydroxyestrogen (2-OHE) and its COMT derivative, 2-methyoxy-estrogen, are typically anti-proliferative and protective to hormone sensitive tissues.[47,48] Conversely, 4-hydroxy-estrogen (4-OHE) and its COMT derivative, 4-methyoxy-estrogen, retain their hormonal activity and are known to cause oxidative damage that can contribute to carcinogenesis.

GENETIC VARIATION TESTED

The COMT gene is located on chromosome 22 at 22q11.21. The rs4680 SNP is a well-studied functional polymorphism that corresponds to a G1947A conversion (also known as a Val to Met amino acid substitution at position 158).

IMPLICATIONS OF THE GENETIC VARIATION

The ‘A’ (Met) allele is associated with a significantly lower enzyme activity when compared to the ‘G’ (Val) allele.[73]

COMT
Rs4680

G/A

A GENOTYPES

- The A/A genotype is associated with reduced enzyme activity and decreased methylation of catechol estrogens
- The A/A genotype is associated with increased urinary hydroxylated estrogen metabolites –28% increase in 2-OHE1 and 31% increase in 16α-OHE1 – consistent with reduced methylation of catechol estrogens[2]
- The A allele (A/A and G/A genotypes) is associated with elevated levels of estrogen-DNA adducts [73]
- The A/A genotype interacts significantly with lifestyle factors and increases the risk of breast cancer.[2,74] When combined with the at-risk G allele for the methionine synthase gene (MTR), A/A genotype women with BMIs greater than 30kg/m^2, who consume a diet low in dietary folate, are at an increased risk for high plasma levels of 8-hydroxy-2'-deoxyguanosine (8-OH-2DG). High plasma 8-OH-2DG is a potent marker for DNA damage [73]

G GENOTYPES

- The G/G genotype is associated with higher enzyme activity (when compared to A allele carriers) and increased/more optimal methylation of catechol estrogens

GSTT1
CNV

1 COPIES

Glutathione-S-transferase theta 1 (GSTT1) is the dominant member of the GST family of enzymes involved in phase II detoxification. The GST family conjugates reduced glutathione to quinones and semiquinone by-products of catechol estrogens. In addition, GSTT1 catalyzes glutathione conjugation of electrophilic xenobiotics, carcinogens, drugs and ROS, thereby facilitating their deactivation and elimination from the body.[48]

The theta isozyme of the glutathione S-transferase GSTT1, is encoded by the GSTT1 gene. The GSTT1 enzyme is constitutively expressed in the liver, However, it is also expressed in the gastrointestinal tract, red blood cells, kidneys and lungs.

GENETIC VARIATION TESTED

The GSTT1 gene is located on chromosome 22 at 22q11.23. One important distinction regarding the genomic variation of the GSTT1 gene is that it is not actually a SNP, but rather a copy number variation (CNV). This type of variation affects the entire gene and can determine if the gene (and hence its product) is literally absent from a person's genomic make-up (the null genotype), or present in one or more than (the normal) 2 copies.

IMPLICATIONS OF THE GENETIC VARIATION

As a function of the key role GSTT1 enzyme plays in Phase II detoxification, both deletion and amplification (greater than 2 copies) of the gene can dramatically affect the efficacy of detoxification and clearance rate of reactive estrogen metabolites. It is important to note that growing genotype data for this gene indicates that a single copy is most common and that even 2 copies (otherwise considered the norm) would result in higher than normal gene expression and enzyme activity.

GSTT1
CNV

1 COPIES

ABSENT GENOTYPES

- Redox cycling of quinones leads to the generation of ROS and adduct formation with DNA, contributing to tumerogenesis.[73] Null genotypes are associated with poor detoxification/conjugation of methoxy derived quinones.

- Substrate clearance is not completely absent in null genotypes due to compensatory induction of other GST members and overlapping substrate specificity. However, as GSTT1 is the dominant member of the GST family of enzymes, its null genotype is considered the most deleterious variation amongst the GST genes.

- A higher frequency of GSTM1/GSTT1 null genotypes are found in preterm delivery (PTD) (1.47-6.55, OR = 3.10) [82]

- Because of the common concern of heavy metal poisoning, particularly mercury (Hg) poisoning, it should be noted that Hg is cleared via the GSTT1 pathway [83]

PRESENT GENOTYPES

- Copy gain of this gene results in increased production of the GSTT1 enzyme with concomitant increased clearance of its targeted substrates.

- The presence of multiple copies of GSTT1 is a poor predictive marker for chronic myeloid leukemia (CML) treatment, due to its escalated clearance rate of imatinib (which has become a first-line choice for treatment of CML and other blood cancers) [84]

- The presence of multiple copies of GSTT1 is also associated with generally poor long-term response with the host of pharmaceutics that are cleared via this pathway (due to overly rapid clearance of the drug in question)

GSTP1
Rs1695

A/A

Glutathione-S-transferase theta 1 (GSTT1) is the dominant member of the GST family of enzymes involved in phase II detoxification. The GST family conjugates reduced glutathione to quinones and semiquinone by-products of catechol estrogens. In addition, GSTT1 catalyzes glutathione conjugation of electrophilic xenobiotics, carcinogens, drugs and ROS, thereby facilitating their deactivation and elimination from the body.[48]

The GSTP1 enzyme is encoded by the GSTP1 gene. GSTP1 is widely expressed in all cells, except erythroid cells, and catalyzes the conjugation of reduced glutathione to hydrophobic and electrophilic compounds. GSTP1 metabolizes an array of exogenous and endogenous substrates, and is one of the main enzymes, including GSTM1, to detoxify carcinogenic polyaromatic hydrocarbon (PAH) intermediates produced by CYP P450 enzymes.87 In addition to conjugation reactions, GSTP1 expression modulates estrogen receptor activity, thereby promoting estrogen metabolism.[91]

GENETIC VARIATION TESTED

The GSTP1 gene is located on chromosome 11 at 11q13.2. The **rs1695** SNP corresponds to a **A**313**G** conversion (also referred to as a Ile to Val amino acid substitution at position 105).

IMPLICATIONS OF THE GENETIC VARIATION

The **'G' (Val)** allele of the **rs1695** SNP results in an amino acid change within the active electrophile-binding site of the enzyme, reducing its catalytic activity and substrate specificity when compared to A/A genotypes.[89]

Glutathione S-transferase P1 (GSTP1)

Rs1695

A/A

The GSTP1 gene encodes glutathione-S-transferase pi 1 (GSTP1), a member of the GST family of enzymes involved in phase II detoxification. The GST family catalyzes the glutathione conjugation of electrophilic xenobiotics, carcinogens, drugs and reactive oxygen species/oxidants (ROS), thereby facilitating their deactivation and elimination from the body.

GSTP1 is widely expressed in all cells, except erythroid cells, and catalyzes the conjugation of reduced glutathione to hydrophobic and electrophilic compounds. GSTP1 metabolizes an array of exogenous and found in the gastrointestinal tract, red blood cells, kidneys and lungs. endogenous substrates, and is one of the main enzymes, including GSTM1, to detoxify carcinogenic polyaromatic hydrocarbon (PAH) intermediates produced by CYPP450 enzymes. In addition to conjugation reactions, GSTP1 expression modulates estrogen receptor activity, thereby promoting estrogen metabolism. Moreover, GSTP1 plays an important role in the glutathionization of the estrogen by-products, quinone and semiquinone.

GENETIC VARIATION TESTED

The GSTP1 gene is located on chromosome 11 at 11q13.2. An A>G (rs1695) SNP (also referred to as a Ile to Val amino acid substitution) has been well-studied and exerts a functional change to the efficacy of the encoded enzyme.

IMPLICATIONS OF THE GENETIC VARIATION

The G (Val) allele of the rs1695 SNP results in an amino acid change within the active electrophile-binding site of the enzyme, reducing its catalytic activity and substrate specificity when compared to A/A genotypes.

GSTP1
Rs1695

A/A

G GENOTYPES

- The G/G genotype is associated with a reduction in GSTP1 activity, and increased susceptibility of cell damage from increased exposure to electrophiles [89]
- When combined, GSTP1 G allele carriers (A/G or G/G genotypes) and GSTM1 null genotypes show significantly higher levels of DNA adducts when exposed to carcinogenic compounds, including those found in tobacco smoke [92,93]
- The G/G genotype is associated with an increased risk of breast cancer in premenopausal women, especially when combined with a diet low in cruciferous vegetables. The upshot though is that the G/G genotype is associated with increased anti-oxidation and protection with the consumption of cruciferous vegetables. The latter is likely due to higher circulating concentrations of isothiocyanates, which are spared rapid metabolism in G/G genotypes. Isothiocyanates are known to induce phase II detoxifying enzymes and promote anti-oxidation and detoxification [50,94]
- The G/G genotype is associated with a more adventitious response to α-tocopherol supplementation[95]

A GENOTYPES

- The A/A genotype is associated with a decreased susceptibility to DNA damage with exposure to electrophiles.
- Paradoxically, the A allele (A/A and A/G genotypes) is associated with an increase in IL-6 following supplementation with α-tocopherol (when compared to the G/G genotype), diminishing one of the key benefits associated with α-tocopherols (i.e. reduction in expression of the pro-inflammatory IL-6) [87]

GSTM1
CNV

0 COPIES

Glutathione-S-transferase mu 1 (GSTM1) is a member of the GST family of phase II detoxification enzymes. Similar to GSTT1, GSTM1 catalyzes the conjugation of reduced glutathione to quinone by-products formed during estrogen metabolism, as well as to other electrophilic compounds, including xenobiotics, carcinogens, drugs and ROS.[85]

The mu isozyme of glutathione S-transferase (GST) family of enzymes, GSTM1, is encoded by the GSTM1 gene. GSTs are responsible for detoxification of many endogenous ROS and play a key role in protecting cells against oxidative stress. The GSTM1 enzymes are highly expressed in cells of the liver, heart, lung, and brain.

GENETIC VARIATION TESTED

The GSTM1 gene is located on chromosome 1 at 1p13.3. As with the GSTT1 gene, the GSTM1 gene is susceptible to copy number variations (CNV). As a consequence, this gene (and hence its product) may be absent from a person's genomic make-up (the null genotype), or present in more than (the normal) 2 copies.

IMPLICATIONS OF THE GENETIC VARIATION

As a member of Phase II detoxification, both **deletion** and **amplification** (greater than 2 copies) of the gene can dramatically affect the efficacy of detoxification and the clearance rate of several xenobiotics and endogenous metabolites (such as those from the metabolism of estrogens). The null genotype is found in as many as 50% of the Asian population, while a double deletion of GSTT1 and GSTM1 is found in approximately 10% of the population.[71]

GSTM1
CNV

0 COPIES

ABSENT GENOTYPES

- In general, the null genotype of the GSTM1 gene is associated with poorer clearance of its target substrates, which may be observed as a significant increase in ROS and DNA-adducts, with concomitant increased susceptibility to cellular dysfunction [86]
- The null genotype is associated with an increase in DNA adduct levels with exposure to carcinogens such as PAHs, and with increased risks of toxicity [82,87]
- Substrate clearance is not completely absent in GSTM1 null genotypes due to compensatory induction of other GST members and overlapping substrate specificity [71]
- The null genotype is associated with higher IGF-1 levels with oral contraceptive use. High IGF-1 levels are associated with increased risk of premenopausal breast cancer [71]
- Interestingly, there are noteworthy positive aspects to null GSTM1 genotypes. Isothiocyanates, metabolized by GSTM1, are found abundantly in cruciferous vegetables, and are shown to have strong chemopreventative properties against certain cancers. Accordingly, those with absent GSTM1 genotypes stand to benefit more from the protective advantage of consuming cruciferous vegetables, by virtue of the reduced elimination of isothiocyanates [88]

PRESENT GENOTYPES

- Conversely, copy gain of this gene results in increased production of the GSTM1 enzyme with concomitant increased clearance of its targeted substrates

SOD2
Rs4880

C/T

Mitochondrial Superoxide Dismutase (SOD2) is a mitochondrial enzyme responsible for the manganese dependent conversion of reactive oxygen species (ROS) into hydrogen peroxide ($H2O_2$) and diatomic oxygen (O_2). ROS are generated from estrogen metabolism through catechol estrogen redox cycling. ROS contribute to oxidative stress, lipid peroxidation, and DNA damage, which in turn can lead to unregulated cellular proliferation and tumor promotion [9]

Mitochondrial SOD, alternatively known as manganese SOD (MnSOD), is encoded by the SOD2 gene. In addition to its role in estrogen metabolism, the SOD2 protein metabolizes superoxide by-products of cellular respiration to protect the cell from oxidative damage. High levels of ROS lead to oxidative stress and is linked to genetic instability and carcinogenesis. Interestingly, SOD2 function may be modulated by estrogen, signifying the importance of SOD2 in hormonal regulation.

GENETIC VARIATION TESTED

A number of polymorphisms in the SOD2 gene, found on chromosome 6 at 6q25, have been described. The **rs4880** SNP results in a **C**47**T** conversion and is of particular functional significance. The 'T' (or Val) allele of the gene disrupts the alpha-helical structure of the protein and reduces its enzymatic activity.

IMPLICATIONS OF THE GENETIC VARIATION

The 'T' allele is considered the deleterious allele, and is associated with 30-40% lower activity (per T allele). 'T' allele carriers are associated with increased susceptibility to oxidative stress compared to C/C genotypes.

SOD2
Rs4880

C/T

T GENOTYPES

- The T allele (T/T and C/T genotypes) is associated with a reduced capacity to handle oxidative stress. The risk of oxidative damage among T allele carriers is increased among premenopausal women with a diet low in fruits and other antioxidants, such as selenium[96], and in women exposed to environmental carcinogens, including alcohol or tobacco smoke [54,97]

- High quinone concentration, as a product of estrogen metabolism, is related to **SOD2 inactivation** with consequent oxidative stress leading to mitochondrial dysfunction [98]

- In general, as a function of the important role SOD2 plays in the clearance of ROS, and the deleterious effects of the latter, a thorough evaluation of ROS stress is recommended in T allele carriers, including markers of lipid peroxidation and oxidation of DNA (such as testing for 8-hydroxy-2'-deoxyguanosine)

C GENOTYPES

- The C/C genotype is associated with optimal function of the SOD2 enzyme; individuals with this genotype are expected to exhibit normal SOD2 function with a healthy lifestyle

- Contrary to expectations, the C allele (C/C and C/T genotypes) is associated with an increase in breast cancer with long-term (>5 years) use of HRT (combined estrogen plus progestin). Proposed mechanisms include the increased production of H2O2 by SOD2 from high estrogen quinone production, which yields other ROS such as hydroxy radicals (OH-) that cause damage to DNA. In addition, high H2O2 reduces TNFα-mediated apoptosis, allowing perpetuation of genetic mutations, which can potentiate carcinogenesis [99]

- The C allele (C/C and C/T genotypes) is associated with a poorer progression-free survival in breast cancer patients treated with cyclophosphamide without hormonal regimens compared to T/T genotypes [9]

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