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Please refer to PDF report attached

Practitioner:	RACHEAL LEE (NPINS) SHOP 6/115 SHINGLEY DRIVE AIRLIE BEACH QLD QLD 4802
Request id:	4039837
Patient:	KATE JARVIE 14 STONEHAVEN COURT AIRLIE BEACH QLD QLD 4802
Date of Birth:	08-Nov-1987
Sex:	F

TEST REPORT

 # 2024 11 05 205 U

Ordering Provider:
NutriPath

Samples Received
11/05/2024

Report Date
11/11/2024

Samples Collected
Urine - 10/29/24 05:20
Urine - 10/29/24 07:50
Urine - 10/29/24 16:15
Urine - 10/29/24 20:30

Patient Name: Kate Jarvie
Patient Phone Number:

Gender	Last Menses	Height	Waist
Female	Unspecified	156 cm	Unspecified
DOB	**Menses Status**	**Weight**	**BMI**
11/8/1987 (36 yrs)	Pre-Menopausal - Irregular	56 kg	23.0

TEST NAME	RESULTS | 10/29/24	RANGE
Urinary Estrogens		
Estradiol	53.35 H	0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	186.10 H	2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	4.91 H	0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	0.02 L	>0.3 (> median value)
2-OH Estradiol	3.31 H	0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	8.63 H	0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.86 H	0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	3.89 H	0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	5.12 H	0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	2.33	1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.29 H	0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	3.36 H	0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.39 H	0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	0.15 H	<0.04 µg/g Cr
4-MeO Estrone	0.03	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.01 L	0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.17	0.10-0.29 Premeno-luteal or ERT
Bisphenol A	<dl L	1.11-3.74 µg/g Cr Premeno-luteal

TEST NAME	RESULTS | 10/29/24	RANGE
Urinary Progestogens		
Pregnanediol	427 L	465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	1.33 L	2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	6.15 L	14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	2.21 H	0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	0.92 L	3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	1.49	0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	10.14 H	3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	8.00 L	1000-1500 (Optimal Luteal Only)
Urinary Androgens		
DHEA	70.99	15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	8.50	3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	610	248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	1662 H	330-960 µg/g Cr Premeno-luteal or ART
Testosterone	3.18	1.22-3.97 µg/g Cr Premeno-luteal or ART
Epi-Testosterone	1.61 L	2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	1.98	0.5-3.0
5α-DHT	1.44	0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	7.12	2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids		
Total Cortisol	37.95 H	12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	68.94 H	23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.55	0.5-0.7
Tetrahydrocortisol	423	214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	908	437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol		
Free Cortisol	26.58	7.8-29.5 µg/g Cr (1st Morning)
Free Cortisol	36.26	23.4-68.9 µg/g Cr (2nd Morning)
Free Cortisol	14.36	6.0-19.2 µg/g Cr (Evening)

TEST NAME	RESULTS | 10/29/24	RANGE
Urinary Free Diurnal Cortisol		
Free Cortisol	3.92	2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone		
Free Cortisone	104.81 H	31.6-91.6 µg/g Cr (1st Morning)
Free Cortisone	91.46	63.3-175.8 µg/g Cr (2nd Morning)
Free Cortisone	80.12	30.6-88.5 µg/g Cr (Evening)
Free Cortisone	21.81	15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s		
Melatonin	45.92 H	18.0 - 40.9 µg/g Cr (1st Morning)
Melatonin	21.50	7.3 - 31.9 µg/g Cr (2nd Morning)
Melatonin	2.42 H	0.7 - 2.2 µg/g Cr (Evening)
Melatonin	19.46 H	1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine		
Creatinine (pooled)	1.15	0.3-2.0 mg/mL
Creatinine	0.57	0.3-2.0 mg/mL (1st morning)
Creatinine	1.77	0.3-2.0 mg/mL (2nd morning)
Creatinine	0.86	0.3-2.0 mg/mL (Evening)
Creatinine	1.19	0.3-2.0 mg/mL (Night)

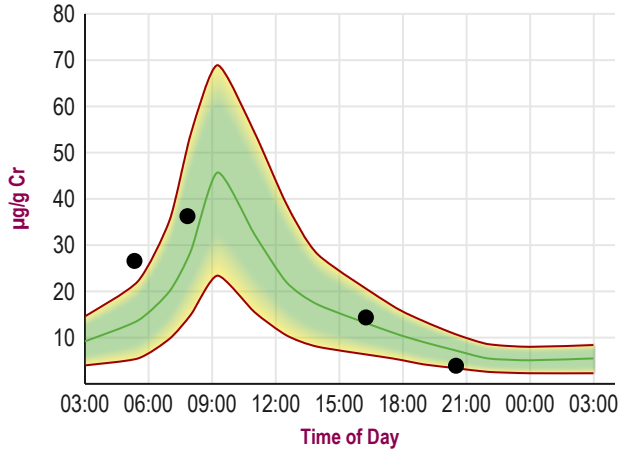
<dl *= Less than the detectable limit of the lab.* ***N/A*** *= Not applicable; 1 or more values used in this calculation is less than the detectable limit.* ***H*** *= High.* ***L*** *= Low.*

Therapies

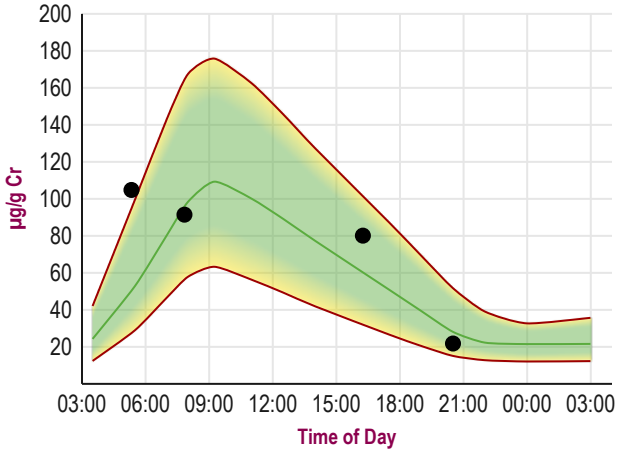
None Indicated

Graphs

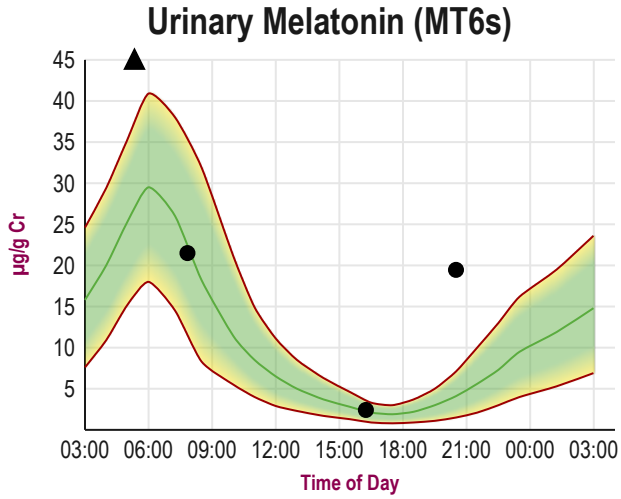
Urinary Free Cortisol



Urinary Free Cortisone



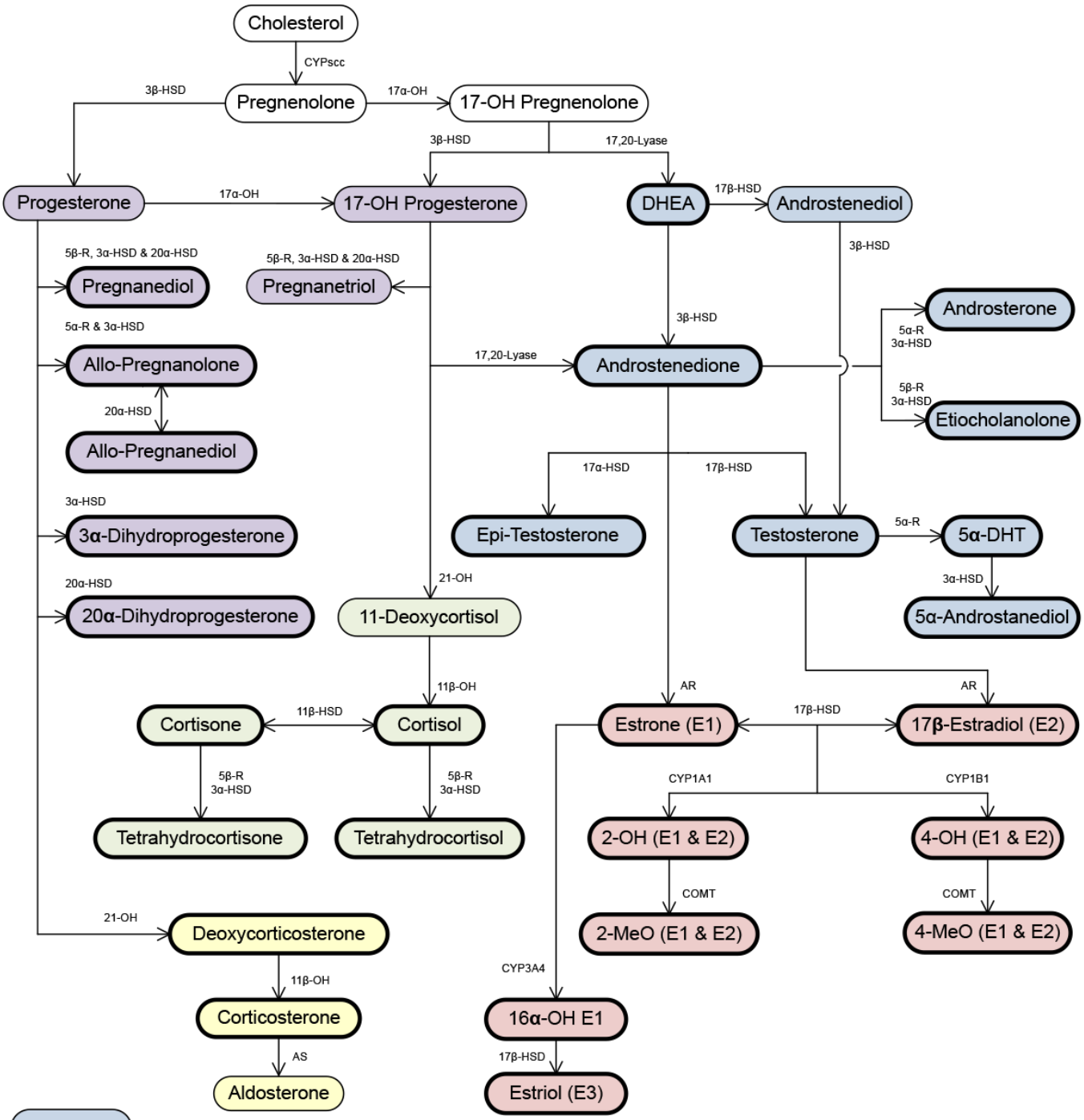
Urinary Melatonin (MT6s)



TEST NAME	WOMEN
Urinary Estrogens	
Estradiol	0.15-0.75 µg/g Cr Postmenopausal; 0.78-1.79 µg/g Cr Premeno-luteal or ERT
Estrone	0.64-2.56 µg/g Cr Postmenopausal; 2.27-5.22 µg/g Cr Premeno-luteal or ERT
Estriol	0.28-1.17 µg/g Cr Postmenopausal; 0.78-1.98 µg/g Cr Premeno-luteal or ERT
E3/(E1+E2)	>0.3 (> median value)
2-OH Estradiol	0.08-0.31 µg/g Cr Postmenopausal; 0.17-0.70 µg/g Cr Premeno-luteal or ERT
2-OH Estrone	0.25-1.00 µg/g Cr Postmenopausal; 0.70-2.54 µg/g Cr Premeno-luteal or ERT
4-OH Estradiol	0.03-0.12 µg/g Cr Postmenopausal; 0.10-0.18 µg/g Cr Premeno-luteal or ERT
4-OH Estrone	0.06-0.22 µg/g Cr Postmenopausal; 0.17-0.47 µg/g Cr Premeno-luteal or ERT
16α-OH Estrone	0.10-0.41 µg/g Cr Postmenopausal; 0.35-1.07 µg/g Cr Premeno-luteal or ERT
2-OH (E1 + E2)/16-α-OH E1	1.47-8.17 Postmenopausal; 1.29-5.49 Premeno-luteal or ERT
2-MeO Estradiol	0.02-0.07 µg/g Cr Postmenopausal; 0.03-0.08 µg/g Cr Premeno-luteal or ERT
2-MeO Estrone	0.06-0.29 µg/g Cr Postmenopausal; 0.26-0.68 µg/g Cr Premeno-luteal or ERT
2-MeO E1/2-OH E1	0.19-0.36 Postmenopausal; 0.21-0.38 Premeno-luteal or ERT
4-MeO Estradiol	<0.04 µg/g Cr
4-MeO Estrone	<0.04 µg/g Cr
4-MeO E1/4-OH E1	0.03-0.38 Postmenopausal; 0.05-0.13 Premeno-luteal or ERT
4-MeO E2/4-OH E2	0.14-0.73 Postmenopausal; 0.10-0.29 Premeno-luteal or ERT
Bisphenol A	1.5-4.5 µg/g Cr Postmenopausal; 1.11-3.74 µg/g Cr Premeno-luteal
Urinary Progestogens	
Pregnanediol	56-220 µg/g Cr Postmenopausal; 465-1609 µg/g Cr Premeno-luteal or PgRT
Allopregnanolone	0.3-1.31 µg/g Cr Postmenopausal; 2.23-14.87 µg/g Cr Premeno-luteal or PgRT
Allopregnanediol	1.38-6.75 µg/g Cr Postmenopausal; 14.65-76.71 µg/g Cr Premeno-luteal or PgRT
3α-Dihydroprogesterone	0.19-0.77 µg/g Cr Postmenopausal; 0.67-2.03 µg/g Cr Premeno-luteal or PgRT
20α-Dihydroprogesterone	0.60-5.53 µg/g Cr Postmenopausal; 3.93-11.62 µg/g Cr Premeno-luteal or PgRT
Deoxycorticosterone	0.37-1.97 µg/g Cr Postmenopausal; 0.69-2.23 µg/g Cr Premeno-luteal or PgRT
Corticosterone	2.32-9.88 µg/g Cr Postmenopausal; 3.19-9.59 µg/g Cr Premeno-luteal or PgRT
Pgdiol/E2	1000-1500 (Optimal Luteal Only)
Urinary Androgens	
DHEA	8.63-37.28 µg/g Cr Postmenopausal; 15.82-129.17 µg/g Cr Premeno-luteal or DHEAT
Androstenedione	2.07-7.94 µg/g Cr Postmenopausal; 3.93-13.53 µg/g Cr Premeno-luteal or ART
Androsterone	152-482 µg/g Cr Postmenopausal; 248-937 µg/g Cr Premeno-luteal or ART
Etiocholanolone	239-777 µg/g Cr Postmenopausal; 330-960 µg/g Cr Premeno-luteal or ART
Testosterone	0.66-2.89 µg/g Cr Postmenopausal; 1.22-3.97 µg/g Cr Premeno-luteal or ART

TEST NAME	WOMEN
Urinary Androgens	
Epi-Testosterone	0.39-1.32 µg/g Cr Postmenopausal; 2.01-4.66 µg/g Cr Premeno-luteal
T/Epi-T	0.5-3.0
5α-DHT	0.26-0.98 µg/g Cr Postmenopausal; 0.28-1.52 µg/g Cr Premeno-luteal or ART
5α,3α-Androstanediol	2.32-8.17 µg/g Cr Postmenopausal; 2.98-13.10 µg/g Cr Premeno-luteal or ART
Urinary Glucocorticoids	
Total Cortisol	13.23-39.26 µg/g Cr Postmenopausal; 12.26-33.12 µg/g Cr Premeno-luteal
Total Cortisone	23.32-59.61 µg/g Cr Postmenopausal; 23.27-50.88 µg/g Cr Premeno-luteal
Cortisol/Cortisone	0.5-0.7
Tetrahydrocortisol	281-711 µg/g Cr Postmenopausal; 214-546 µg/g Cr Premeno-luteal
Tetrahydrocortisone	551-1474 µg/g Cr Postmenopausal; 437-1184 µg/g Cr Premeno-luteal
Urinary Free Diurnal Cortisol	
Free Cortisol	7.8-29.5 µg/g Cr (1st Morning); 23.4-68.9 µg/g Cr (2nd Morning); 6.0-19.2 µg/g Cr (Evening); 2.6-8.4 µg/g Cr (Night)
Urinary Free Diurnal Cortisone	
Free Cortisone	31.6-91.6 µg/g Cr (1st Morning); 63.3-175.8 µg/g Cr (2nd Morning); 30.6-88.5 µg/g Cr (Evening); 15.5-44.7 µg/g Cr (Night)
Urinary Diurnal Melatonin MT6s	
Melatonin	18.0 - 40.9 µg/g Cr (1st Morning); 7.3 - 31.9 µg/g Cr (2nd Morning); 0.7 - 2.2 µg/g Cr (Evening); 1.7 - 11.1 µg/g Cr (Night)
Urinary Creatinine	
Creatinine (pooled)	0.3-2.0 mg/mL
Creatinine	0.3-2.0 mg/mL (1st morning); 0.3-2.0 mg/mL (2nd morning); 0.3-2.0 mg/mL (Evening); 0.3-2.0 mg/mL (Night)

The Steroid Hormone Cascade



Enzyme Abbreviations

(5α-R) 5α-Reductase
(5β-R) 5β-Reductase
(11β-OH) 11β-Hydroxylase
(17α-OH) 17α-Hydroxylase
17,20-Lyase (same enzyme as 17α-OH)
(21-OH) 21-Hydroxylase
(3α-HSD) 3α-Hydroxysteroid dehydrogenase
(3β-HSD) 3β-Hydroxysteroid dehydrogenase
(11β-HSD) 11β-Hydroxysteroid dehydrogenase
(17α-HSD) 17α-Hydroxysteroid dehydrogenase
(17β-HSD) 17β-Hydroxysteroid dehydrogenase
(20α-HSD) 20α-Hydroxysteroid dehydrogenase
(AR) Aromatase
(AS) Aldosterone Synthase
(CYP) Cytochrome p450 (scc, 1A1, 1B1 & 3A4)
(COMT) Catechol-O-Methyl-Transferase

Lab Comments

HYDROXYLATED (CATECHOL) ESTROGENS (2-OH E2 & E1, 4-OH E2 & E1, 16-OH E1) and 2-OH/16-OH RATIO

The hydroxylated estrogens (2-OH-E2, 2-OH-E1, 4-OH-E2, 4-OH-E1), referred to as catechol estrogens, are all within the upper quadrant of the reference ranges, or higher.

The hydroxylation of estradiol and estrone represent the first phase of metabolism and elimination of these estrogens via urine. Following hydroxylation at the 2-, 4-, or -16 positions, the estrogens undergo further modification (methylation, sulfation, glucuronidation) that increases their solubility and excretion in urine. The sulfate and glucuronide groups are removed by enzyme hydrolysis, which allows for measurement of the different types of hydroxylated estrogens that formed elsewhere in the body but were excreted in urine.

Research and clinical studies show that the 2-hydroxylated estrogens (2-OH E2 and 2-OH E1) are a safer pathway of hydroxylation than the 4-hydroxyestrogens (4-OH E2 and 4-OH E1), which are considered more toxic as they bind to DNA causing mutations that are associated with increased breast cancer risk. For reviews see: Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010; and Lee, JR, Zava DT What Your Doctor May Not Tell You About BREAST CANCER: How Hormone Balance Can Help Save Your Life: Chapter 7.

The safer 2-hydroxylated estrogen metabolism is increased, relative to the 4-hydroxylation pathways, with cruciferous vegetables and extracts of them. The most commonly used are indole-3-carbinol (I3C) and its metabolite diindolylmethane (DIM). Eating a healthy diet of plants with beneficial phytochemicals (e.g. leafy vegetables with color, soy foods, flax, foods high in antioxidants such as turmeric) also helps prevent toxic estrogen metabolism. Iodine also increases the 2-hydroxylation of estrogens, with a slight increase in 4-hydroxylation (Stoddard FR et.al. Int J Med Sci 5: 189-196, 2008).

The more dangerous 4-hydroxylated estrogen metabolism is enhanced by exposure to environmental toxins, mostly petrochemical-based products but also heavy metals that induce 4-hydroxylation pathway enzymes (1B1), and cause formation of Reactive Oxygen Species (ROS) that co-oxidize the catechol estrogens to much more reactive quinone estrogens. The 4-quinone estrogens, if not inactivated by glutathione, can potentially bind to and damage DNA leading to mutations that increase lifetime risk for cancer.

16-hydroxyestrone is another pathway of estrone metabolism and is a precursor to estriol (see Steroid Hormone Cascade). Early clinical research in humans suggested that a high urinary level of 16-hydroxyestrone relative to 2-hydroxylated estrogens (i.e. a low 2-OH E1 + 2-OH E2/16-OH E1 ratio), was associated with an increased risk of breast cancer in premenopausal women, but not in postmenopausal women. This has remained controversial and newer research suggests that while higher levels of 16-hydroxy estrone may indeed be slightly associated with increased breast cancer risk in premenopausal women, higher levels are associated with a decreased risk in postmenopausal women (Huang J et.al. Analytica Chimica Acta 711: 60-68, 2012). A meta-analysis of nine studies investigating the relationship of the urinary 2/16 ratio have NOT shown it to be useful for predicting breast cancer risk (Obi N et.al. Int J Women's Health 3: 37-51, 2011).

METHYLATION OF HYDROXYESTROGENS

The methylated forms of the 2-hydroxyestrogens (2-MeO-E2 and 2-MeO-E1) are higher than reference ranges and the ratio of the methoxyestrogens to the catechol estrogens (2-MeO-E2/2-OH-E2 and 2-MeO-E1/2-OH-E1) is high (beneficial). While the more toxic 4-OH-E2 is well methylated and the ratio of 4-MeO-E2/4-OH-E2 is within range (beneficial), 4-OH-E1 is not well methylated and the ratio of 4-MeO-E1/4-OH-E1 is lower than reference ranges. Adequate methylation of the hydroxyestrogens, and an associated high ratio of 4-hydroxylated estrogens to 4-methoxyestrogens (i.e. 4 MeO-E2/4-OH-E2 and 4-MeO-E1/4-OH-E1) is considered beneficial as this indicates the 4-hydroxyestrogens are rendered inert preventing them from oxidizing further to more dangerous 4-estrogen quinones that can form adducts with DNA, causing mutations that can lead to increased cancer risk.

The 2- and 4- hydroxyl estrogens are methylated by the enzyme Catechol-o-Methyl Transferase (COMT), which renders these catechol estrogens inert and harmless (Cavalieri EL, Rogan EG Future Oncol 6(1): 75-79, 2010). In this form the methylated catechol estrogens are rapidly excreted in urine. However, if methylation pathways are inadequate due to low levels of COMT, or lack of precursors of methylation (i.e. vitamins B6, B12, folate, betaine), the 2- and 4-hydroxyl estrogens can take a more insidious and dangerous pathway of metabolism, which is oxidation of the hydroxyl (catechol) groups to quinones. Estrogen quinones, especially the 4-quinone of estradiol (4-Quinone-E2) and estrone (4-Quinone-E1) are highly electrophilic and bind to DNA, forming adducts that lead to permanent mutations. Many studies have shown that high urinary levels of these 4-quinones of estradiol and/or estrone are associated with increased breast cancer risk if the 4-hydroxylated estrogens are notinactivated by methylation, or the 4-quine estrogens are inactivated by glutathione sulfation. The 2- and 4-hydroxy estrogens are converted to their more dangerous oxidized quinone forms under oxidizing conditions in the cell, and this occurs more efficiently in the presence of oxidized lipids, especially those from trans-hydrogenated fats. These estrogen quinones, like all oxidized and electron-hungry molecules in the body are inactivated when bound to glutathione, the most ubiquitous antioxidant in the body. However, if glutathione is low, due to insufficient levels of minerals (selenium, iodine) and vitamins (C and E), the quinone estrogens are less likely to be detoxified (inactivated) and have potential to damage cells/DNA in close proximity to their formation (i.e. the breast cell/DNA). Neither the quinone estrogens nor their interaction with DNA is measured-only the precursor hydroxyl-estrogens and their methylated metabolites. Nevertheless, clinical studies investigating estrogen metabolites have shown that high levels of 4-hydroxylated estrogens (4-OH-E2 and 4-OH-E1) and/or low levels of their methylated forms are associated with increased breast cancer risk.

BISPHENOL A (BPA)

Bisphenol A (BPA) is within reference range. BPA is an endocrine disrupting chemical (EDC) derived from plastics used for making bottles, wraps for foods, and linings for food cans. BPA is not retained in the body for a prolonged period of time and is rapidly excreted into urine. High urinary levels of BPA indicate recent exposure to plastics that released excessive amounts of BPA into food or beverages consumed in the past 24-48 hr.

BPA acts as an EDC by binding to a activating both membrane and nuclear estrogen receptors in a manner similar to estradiol. Thus by mimicking the actions of endogenous estrogens, high levels of BPA can contribute to symptoms of estrogen dominance. High BPA levels have been associated with increased risks for many different health issues, including diabetes, breast cancer, and prostate cancer. When BPA levels are elevated, identification of its source and reducing exposure is worth considering.

PROGESTERONE METABOLITES (PREGNANEDIOL-PgDiol, ALLOPREGNANOLONE-AlloP)

The urinary levels of the progesterone metabolites pregnanediol (PgDiol) and allopregnanolone (AlloP), a neuroactive steroid, are within the low-normal luteal reference ranges. PgDiol serves as a good surrogate marker metabolite of the progesterone as levels increase in parallel with endogenous progesterone production by the ovaries. Lower levels of these progesterone metabolites could result from luteal phase deficiency (more common in premenopausal women with Polycystic Ovarian Syndrome-PCOS and in peri-menopausal women transitioning to menopause) or collection of urine outside the peak of progesterone that occurs mid-luteal phase (days 19-25 in women with normal 28 day cycles).

AlloP is a neuroactive steroid that freely enters the brain from the bloodstream, where it binds to GABA receptors and induces a calming effect (anxiolytic). This contributes to AlloPs calming and sleep-inducing effects. Insufficient amounts of AlloP can have a paradoxical effect and cause an anxiogenic effect, increasing symptoms such as anxiety and premenstrual dysphoric disorder (PMDD) and premenstrual syndrome (PMS). Only high levels of AlloP, achieved at peak of an optimal luteal phase, during pregnancy, and with progesterone therapy, have the anxiolytic effects on GABAa receptors in the brain.

Consider progesterone replacement therapy if symptoms of estrogen dominance are problematic. Estradiol should be balance with progesterone (pregnanediol when testing urine) at a PgDiol/E2 ratio of about 1000-1500. Lower values are usually associated with symptoms of estrogen dominance when estradiol is within or higher than luteal range.

ANDROGEN PRECURSOR (DHEA/S)

Total urinary DHEA(S) and its downstream hormone androstenedione are within normal reference ranges. DHEA is synthesized in the adrenal glands and is rapidly sulfated to DHEA-sulfate (DHEAS) to extend its half-life in blood. DHEA is converted to androstenedione and then to testosterone and Epi-testosterone in near equal amounts in most individuals, or into estrone. More conversion to the estrogen, estrone, occurs in individuals with higher amounts of adipose (fat) tissue.

DHEA is considered a universal precursor to both androgens (androstenedione, testosterone, DHT), and estrogens (estradiol and estrone). DHEA is commonly used as a supplement to raise both DHEA and testosterone levels in women. Much less DHEA is converted to T and DHT in men.

DHEA itself has very little androgenic activity and serves mostly as a precursor to other downstream more potent metabolites (androgens and estrogens). In the sulfated form DHEA sulfate (DHEAS) plays an important role in the integrity of the immune system via binding to specific DHEAS binding sites on lymphocytes. In the brain DHEAS acts as a neuroactive steroid where it modifies dopaminergic pathways responsible for uplifting mood and increasing feeling of wellbeing.

DHEA/ANDROSTEINE METABOLITES: (ANDROSTERONE-ANDROS, ETIOCHOLANOLONE-ETIO)

Etiocholanolone is higher than reference range, whereas, androsterone is within range. Androsterone and etiocholanolone are downstream metabolites of androstenedione, which is a metabolite of DHEA (see Steroid Hormone Cascade). DHEA is converted to androstenedione via 3 beta-HSD and then into etiocholanolone by 5-beta-reductase or androsterone by 5-alpha-reductase (see Hormone Cascade). Lower relative amounts of androsterone is usually associated with lower 5-alpha DHT as well as it's neuroactive metabolite 5-alpha, 3-alpha DHT.

A higher etiocholanolone is reported to be protective against cancer by inhibiting glucose utilization, essential for tumor growth. Therefore, higher etiocholanolone, as a result of higher androstenedione conversion via 5 beta reductase, is associated with a lower cancer risk. In contrast, higher androsterone indicates higher 5 alpha reductase activity, which increases conversion of T to 5-alpha-DHT and progesterone to 5-alpha-dihydroxyprogesterone (DHP). High DHP is associated with a higher risk of stimulating hormone sensitive breast cancers through membrane-associated progesterone metabolite receptors, which are induced by estrogens (Wiebe JP, Cancer Res 60: 936-943, 2000).

TESTOSTERONE, EPI-TESTOSTERONE, AND 5-ALPHA-DIHYDROTESTOSTERONE)

Testosterone (T) is within the normal reference range for a premenopausal woman. In contrast, the inert epimer of T, Epi-testosterone (Epi-T), is lower than reference range. DHT, the downstream and more potent metabolite of T, is within reference range.

Higher T relative to Epi-T (ratio > 3) usually indicates exposure to exogenous T, or some precursor of T (e.g. DHEA). Epi-T and T usually are synthesized endogenously in about equal amounts from androstenedione, a down-stream metabolite of DHEA, and the T/Epi-T ratio is about 1, but ranges from about 0.5-2. When testosterone is supplemented the T rises in proportion to dosage, but Epi-T remains the same, reflecting endogenous production. This individual has not indicated supplementation with any androgen, therefore, the slightly higher T/Epi-T may be normal, or caused by medications that differentially affect the enzyme activities of 17-alpha-hydroxysteroid dehydrogenase (converts androstenedione to Epi-T) or 17-beta-hydroxysteroid dehydrogenase (converts androstenedione to T).

Androgens (T and DHT) are important for strengthening structural tissues such as muscles, bone, connective tissue, and skin. They also play an important role in the brain to increase the level of neurotransmitters such as dopamine, which are important for mood elevation and sex drive. T is also precursors to the estrogens, estradiol and estrone. The most potent of the androgens is dihydrotestosterone (DHT), which is created from testosterone via 5a reductase. Testosterone itself is derived mostly from androstenedione and DHEA. In premenopausal women about half of the testosterone is derived from androstenedione produced by the ovaries, and the other half from peripheral conversion of DHEA manufactured in the adrenals. More recent studies have shown that testosterone, and likely DHT, have a protective effect as regards breast cancer risk (Glaser RL, Maturitas 76: 342-349, 2013).

5-ALPHA 3-ALPHA ANDROSTANEDIOL (ADIOL)

The downstream metabolite of DHT, 5-alpha 3-alpha androstanediol (Adiol), is within expected reference range. Adiol is considered a neuroactive steroid that can passively enter the brain from the bloodstream through the blood brain barrier.

Adiol binds to GABAa receptors in the brain and has a similar anxiolytic (calming) effect, albeit weaker than allopregnanolone. It also interacts with the dopaminergic pathways in the brain and is associated with the dopamine pleasure and reward pathway. Thus, low levels of Adiol are more likely to be associated with conditions/symptoms common to low dopamine, and high levels with high dopamine. Fibromyalgia and chronic fatigue syndrome (CFS) are common in individuals with low dopamine, as are symptoms of brain fog, achy muscles, and excessive fatigue.

TOTAL GLUCOCORTICOIDS

Total cortisol (F) and cortisone (E) are higher than the expected reference ranges, suggesting some type of adrenal stressor. The down-stream metabolites of cortisol and cortisone, tetrahydrocortisol (THF) and tetrahydrocortisone (THE) are within normal levels, indicating some strain on the adrenal glands to keep up with cortisol/cortisone synthesis. The total levels of these glucocorticoids are determined from the average of four urine collections throughout the day and are very similar to the 24 hour urine values. While 24 hr and 4-spot total cortisol urine tests provide useful information about the adrenal glands average capacity to synthesize cortisol and down stream metabolites in a day, they provide no information about the dirurnal synthesis of cortisol throughout the day. In healthy individuals cortisol/cortisone synthesis should be high in the morning, drop progressively throughout the day, and be at the lowest level during the night while sleeping. Deviations from this pattern are associated with poor health and disease. Thus, total glucocorticoid production, while important, should be viewed in light of the diurnal cortisol pattern, which can be determined by testing cortisol 4x throughout the day in saliva, or urine (referred to as UFC-Urinary Free Cortisol).

While a high cortisol is a normal and healthy response to an acute stressor, a persistent stressor and chronic high cortisol can lead to multiple dysfunctions and disease. Elevated cortisol is usually caused by different types of stressors (emotional, physical-(e.g. excessive exercise, injury, surgery), chemical-(e.g. environmental pollutants, medications), inflammations-(e.g. cancer, metabolic syndrome), pathogens-(e.g. bacterial, fungal, viral infections).

Typical acute symptoms/signs of high cortisol can include anxiety, nervous-irritability, self-perceived stress, sleep disturbances. More chronic elevated cortisol is commonly associated with the same symptoms seen with acutely high cortisol but also include memory problems, depression, loss of muscle mass, and weight gain in the waist. Insulin resistance and metabolic syndrome are also a consequence and cause of elevated cortisol, as are the diseases of aging such as diabetes, cardiovascular disease, cancer, and bone loss. When cortisol remains high these symptoms/conditions/syndromes/diseases progressively become more problematic over time.

For additional information about strategies for supporting adrenal health and reducing stress(ors), the following books are worth reading: "Adrenal Fatigue", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "Awakening Athena" by Kenna Stephenson, MD.

URINARY FREE CORTISOL (F) AND CORTISONE (E)

Urinary free cortisol (F) and cortisone (E) are within/near expected reference ranges throughout the day and are following a normal circadian rhythm. A normal daily output of cortisol is essential to maintain normal metabolic activity, help regulate steady-state glucose levels (important for brain function and energy production), and optimize immune function. When cortisol levels are within normal range under situations of excessive stress this usually indicates that the adrenal glands are overworking to keep up with the demands of the stress(ors). These conditions are most commonly caused by one or more of the following: psychological stress (emotional), physical insults (surgery, injury), diseases (cancer, diabetes), chemical exposure (environmental pollutants, excessive medications), and/or pathogenic infections (bacteria, viruses and fungi).

When these stressors persist, or become worse, over a period of time this can lead to adrenal exhaustion, low cortisol levels, and symptoms which often overlap with those of high cortisol (e.g. fatigue, sleep disturbances, low thyroid symptoms) or are more characteristic only of low cortisol (e.g. allergies-immune dysfunction, chemical sensitivity, and sugar craving due to hypoglycemia). For additional information about

strategies to support adrenal health and reduce stress(ors) that can lead to high or low cortisol, the following books are worth reading: "Adrenal Fatigue; The 21st Century Stress Syndrome", by James L. Wilson, N.D., D.C., Ph.D.; "The Cortisol Connection", by Shawn Talbott, Ph.D.; "The End of Stress As We Know It" by Bruce McEwen; "The Role of Stress and the HPA Axis in Chronic Disease Management" by Thomas Guilliams, PhD.

MELATONIN METABOLITE 6-SULFATOXYMELATONIN (MT6s)

The melatonin metabolite MT6s is following a normal circadian rhythm in the first and second morning voids, but is slightly higher than reference ranges in the afternoon, and evening collections. MT6s should be at its highest level in the in the first morning void, which is reflective of the dark period, progressively fall throughout the daylight hours and then begin to rise again with darkness and more subdued lighting. During the darkness of night melatonin synthesis should peak around 2 am. The first morning void, which represents the sum of melatonin produced during the night, should have the highest MT6s level. Evening and night melatonin levels are slightly above range, which may be normal for this individual if exposed to less light, or may represent melatonin supplementation (none indicated).

In a healthy individual the circadian rhythm of melatonin is inversely related to cortisol, i.e. melatonin rises with darkness and peaks about 2-3 am, while cortisol falls to its lowest level at this time of day. With morning and onset of light exposure, melatonin drops rapidly and cortisol rises, peaking to its highest level about 30 min to 1 hr after waking. By mid-afternoon melatonin reaches a nadir. With lower lighting as darkness approaches melatonin then gradually begins to rise again. Cortisol continues to fall as melatonin rises during the dark hours of the night, when both hormones reach their nadir and peak, respectively, about 2-3 am. Melatonin synthesis by the pineal gland is controlled by light exposure, while cortisol synthesis is controlled by the hypothalamic-pituitary axis in response to stressors. Melatonin and cortisol have opposing circadian rhythms; however, neither hormone directly controls the synthesis of the other.

The circadian patterns of melatonin are easily tracked with collections of urine timed throughout the day and measurement of 6-sulfatoxymelatonin (MT6s), a stable metabolite of melatonin and surrogate marker of melatonin synthesis. MT6s levels in urine lag several hours behind active circulating levels of melatonin found in blood and saliva, which makes early morning first void MT6s measurements convenient for determining melatonin's average synthesis during the dark hours of sleep at night.

Melatonin, produced by the pineal gland in the brain and released into the circulation, rapidly enters tissues throughout the body where it carries out its restorative properties. Melatonin synthesis decreases with aging and calcification of the pineal gland, the latter of which can result in very low production of melatonin.

Melatonin is known to have many different beneficial effects in the body. It helps slow the aging process, is a potent anti-oxidant, inhibits formation and growth of tumors such as breast and prostate cancers, and helps regulate the synthesis of the sex-hormones estradiol and progesterone (melatonin increases progesterone and decreases estrogens). Melatonin also down-regulates cellular estrogen receptors, further inhibiting response of estrogen target tissues (e.g. breast, uterine, and prostate) to estrogens. Pineal calcification, which is accelerated with aging and diseases, including breast cancer, is associated with very low melatonin production at night. Low melatonin has been associated with many different dysfunctions and diseases such as immune dysfunction, neurodegenerative disorders (Alzheimer's disease, senile dementia), pain disorders, cardiovascular disease, cancers of the breast and prostate, and type 2 diabetes (Hardeland R. Aging and Disease 3 (2): 194-225, 2012).

Low melatonin is also thought to contribute to obesity in people with insomnia or those who do night shift work. Low night time melatonin levels are seen commonly in breast and prostate cancer patients. The WHO's International Agency for Research on Cancer has concluded that "shift work that involves circadian disruption is probably carcinogenic to humans", because of the suppression of melatonin production by exposure to light during the night.

Because of its established role in the regulation of the circadian rhythm, treatment with exogenous melatonin has been found useful in people with circadian rhythm sleep disorders, such as delayed sleep phase disorder, jet lag, shift worker disorder, and the non-24-hour sleep-wake disorder most commonly found in totally blind individuals; however, its utility for the treatment of insomnia is not established and remains controversial.

If melatonin is taken as a supplement (available OTC) to correct low levels or treat a condition, the timing and dosage are important to its effectiveness, especially as a sleep aid. Response to supplemental melatonin can be very individual. For optimal benefit it is best to work with a health care provider familiar with melatonin dosage and timing. Excessive dosing can result in spillover of melatonin into daylight hours, excessive sleepiness during the day, and disruption of the normal melatonin-cortisol circadian rhythms. This will be seen as very high levels of MT6s in the first and second urine voids, and often carry-over into the evening when levels should be low. Consider dosage reduction if MT6s levels are excessive throughout the daylight hours and this is associated with persistent sleepiness during the day. While MT6s is an excellent surrogate marker for melatonin levels in the circulation, oral melatonin supplementation results in much higher MT6s levels in urine that are NOT reflective of active circulating levels of melatonin, since most of the exogenous oral melatonin is rapidly metabolized by the liver and kidney and excreted into urine.

For more general information about melatonin please see: http://www.nlm.nih.gov/medlineplus/druginfo/natural/940.html

Urinary creatinine is within normal reference ranges throughout the day, based on testing diurnal 2x, 4x, or 6x urine collections. Creatinine values slightly lower than range usually indicate overly dilute urine from excessive water intake shortly before collection, or not

spacing collection of multiple urine samples by at least 2 hr (most problematic in second morning urine collection). Creatinine slightly higher than range is usually due to inadequate hydration.
Extreme low or high values may be caused by kidney or other metabolic disorders (e.g. metabolic syndrome and diabetes).