698814

Comprehensive Hormone Insights™

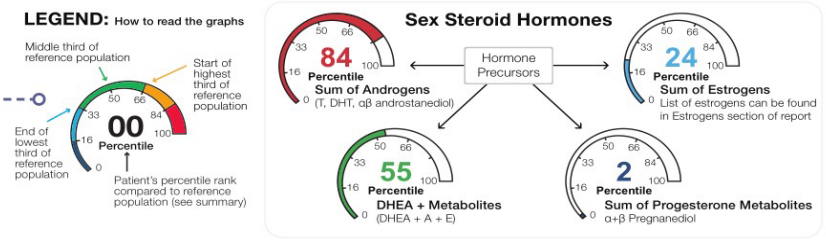
COMPREHENSIVE HORMONE INSIGHTS™
TEST REPORT

Dr. Maximus, N.D.

How to read a CHI report

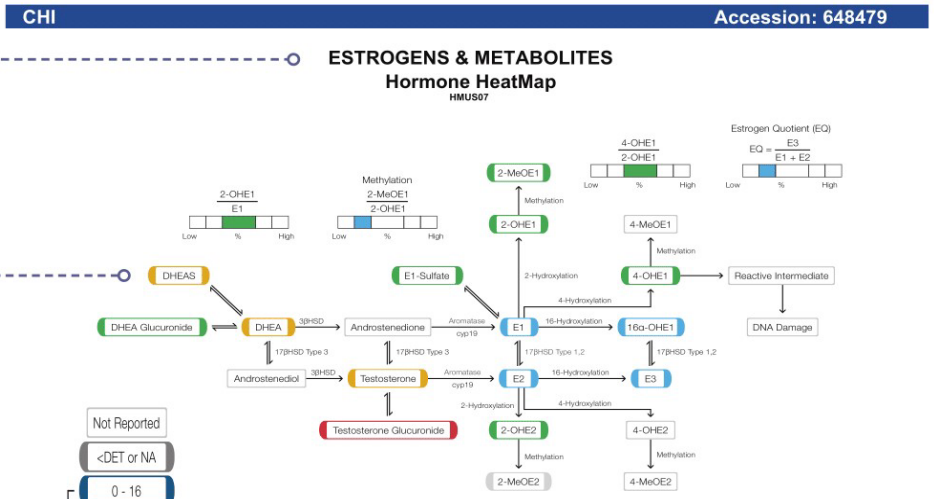
SUMMARY DIALS

The first page of the report summarizes key hormone measures including: androgens, estrogens, progesterone metabolites, DHEA & metabolites, 8OH2dG, 6-sulfatoxymelatonin and the ratio of cortisol to testosterone.



HORMONE CATEGORY

Each hormone category has its own heatmap and corresponding bar graphs for individual analytes.



HEATMAP

Hormone endcap colour immediately identifies which hormone levels are high, high normal, normal, low normal and low.

LEGEND

Identifies by colour what the patient percentile "zone" is for each reported analyte or ratio.

RESULTS & RANGES

This section reports the results, ranges and graphs for the percentiles of individual analytes and sums/ratios. Range applied is specific to patient: male, female and whether luteal, follicular or post-menopausal.

Reference range low is 20th percentile, and high is 80th percentile.

ESTROGENS

Analyte	Result	Range	Units	%ile	Range Applied
Estrone (E1)	6.7	5.3 - 15	ng/mL	31%	d21
Estradiol (E2)	2.4	2.3 - 5.5	ng/mL	25%	d21
Estriol (E3)	7.2	6.7 - 39	ng/mL	24%	d21
E3/(E1 + E2)	0.79	0.65 - 2.7		26%	d21
2-Hydroxyestrone (2-OHE1)	6.0	3.0 - 12	ng/mL	41%	d21
2-OHE1/E1	0.89	0.38 - 0.99	ng/mL	66%	d21
2-Methoxyestrone (2-MeOE1)	1.5	0.79 - 4.5	ng/mL	39%	d21
2-MeOE1/2-OHE1	0.25	0.21 - 0.55		29%	d21
16a-Hydroxyestrone (16a-OHE1)	2.7	2.3 - 10	ng/mL	25%	d21
2-OHE1/16a-OHE1	2.2	0.43 - 2.6		69%	d21
4-Hydroxyestrone (4-OHE1)	0.98	0.53 - 2.1	ng/mL	41%	d21
4-OHE1/2-OHE1	0.16	0.13 - 0.26		40%	d21
2-Hydroxyestradiol (2-OHE2)	0.94	0.42 - 2.8	ng/mL	48%	d21
2-Methoxyestradiol (2-MeOE2)	< 0.30	0.085 - 4.1	ng/mL	<DET	d21
Estrone sulphate (E1-Sulphate or E1S)	0.95	0.45 - 2.0	ng/mL	55%	d21
Sum of Estrogens	28	27 - 87	ng/mL	24%	d21

COMMENTARY

Custom interpretation comments appear after each hormone category.

INTERPRETATION WHEN MULTIPLE ESTROGENS AND ESTROGEN METABOLITES ARE LOW
Many estrogenic hormones and hormone metabolites measured here are low. This pattern may still be quite clinically meaningful; however, prudence should be used when attempting to correlate and compare results via ratios. The clinician has to always bear in mind that the ratio may be less significant when the results making up the numerator and denominator are low compared to ratios constructed from results that are normal or elevated.

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Date of Collection:
Time of Collection:
Date of Receipt:
Reported On:

CHI — Accession: 698814

Healthcare Professional
Dr. Maximus, N.D.

Patient

Age:
Date of Birth:
Gender: Male

F:

Relevant Medications	Biometrics
Curcumin	**Height (in) :** 73 **Weight (lb) :** 180 **BMI :** 24 **Waist (in) :** 35 **Hip (in) :** 41

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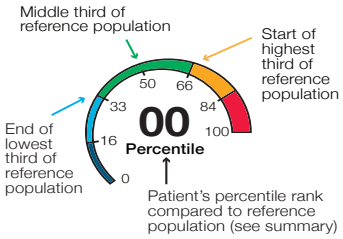
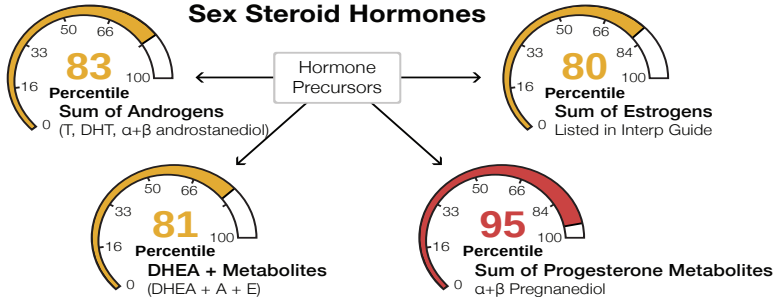
Comprehensive Hormone Insights™

SUMMARY
HMUS01

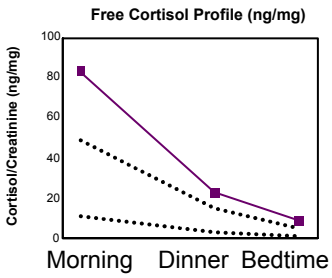
LEGEND: How to read the graphs



Sex Steroid Hormones

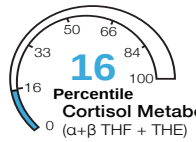


Cortisol

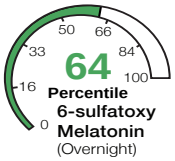


Free cortisol profile is used to assess diurnal cortisol rhythm

Cortisol Metabolites provides a general assessment of adrenal cortisol production

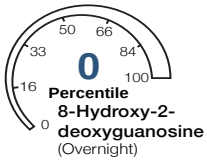


Melatonin

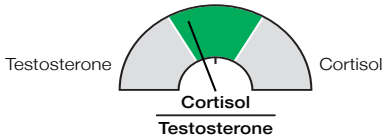


6-sulfatoxymelatonin provides insight into melatonin levels.

Oxidative Stress



8-hydroxy-2-deoxyguanosine is a marker of oxidative stress



Cortisol/Testosterone provides insight into relative catabolic (cortisol) and anabolic (testosterone) states.

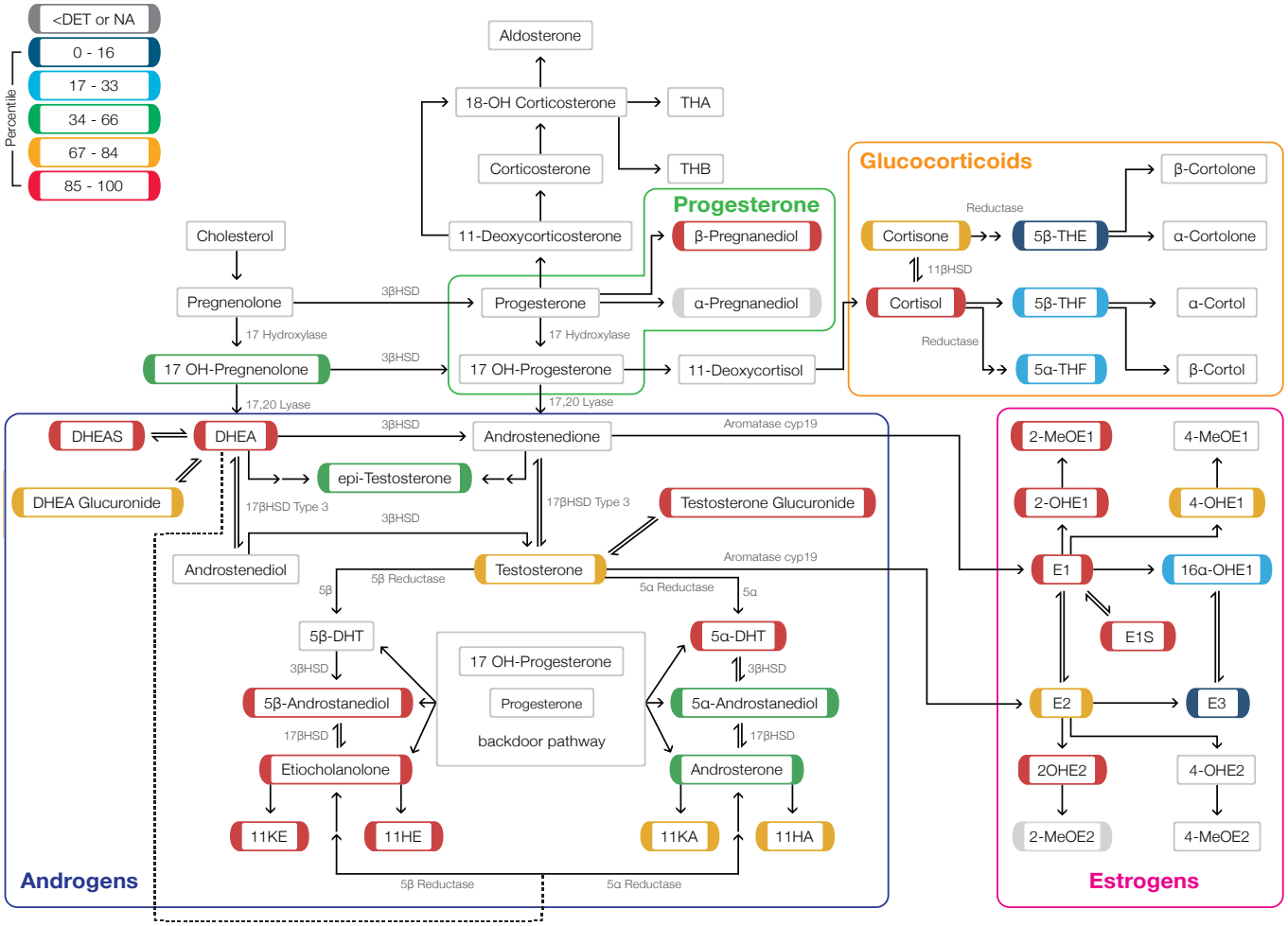
MARKERS REFLECTING THYROID HORMONE ACTIVITY

There are multiple ratios and patterns measured in this test that can potentially inform on the overall activity of thyroid hormones. The interpretation is “tuned” to comment on thyroid hormone activity only when there is sufficient alignment amongst all the various indicators. If alignment is not sufficient, various individual comments about thyroid hormone activity may appear but there will be no overall “verdict” regarding thyroid hormone activity. When multiple indicators are measured simultaneously, chance variations can decrease the likelihood that all of the indicators will align perfectly, even in the face of a bona fide thyroid hormone issue.

STEROID HORMONE OVERVIEW

Hormone Heat Map

HMUS02



The Rocky Mountain Analytical Hormone HeatMap provides an overview of sex steroid hormone and hormone metabolite results. For each of the Hormone HeatMap pathways, the colour that frames the named hormone or metabolite corresponds to the percentile found in the Legend (top left). This makes deficiencies or excesses in the major hormone groups easy to identify and patterns easier to discern.

Note: Hormones bordered in gray are either not tested or not reported. They are included for completeness.

HORMONE ABBREVIATIONS

5ß-THE: 5ß-tetrahydrocortisone
5α-THF: 5α-tetrahydrocortisol
5ß-THF: 5ß-tetrahydrocortisol
11HA: 11-hydroxyandrosterone
11HE: 11-hydroxyetiocholanolone
11KA: 11-ketoandrosterone
11KE: 11-ketoetiocholanolone
DHEAS: dehydroepiandrosterone sulfate
DHEA: dehydroepiandrosterone

E1: estrone
E2: estradiol
E3: estriol
2-MeOE1: 2- methoxyestrone
2-MeOE2: 2-methoxyestradiol
2-OHE1: 2-hydroxyestrone
4OHE1: 4-hydroxyestrone

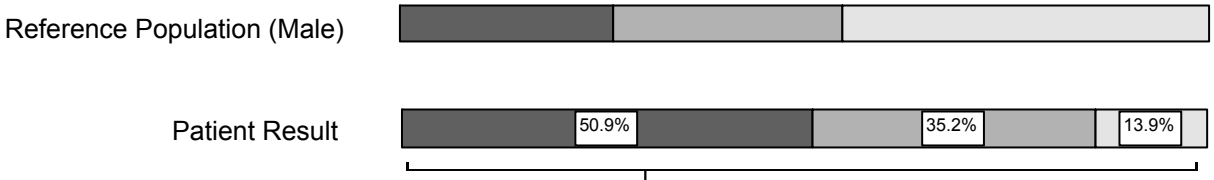
2OHE2: 2-hydroxyestradiol
4OHE2: 4-hydroxyestradiol
16α-OHE1: 16α-hydroxyestrone

CORTISOL & CORTISOL METABOLITES
Hormone Heat Map

HMUS03

CORTISOL CONJUGATION PATTERN

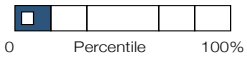
Cortisol (free)	Cortisol sulfate	Cortisol glucuronide
18.2 - 32.8 %	20.7 - 34.7 %	40 - 53.1 %



Cortisol-Cortisone Metabolite Balance

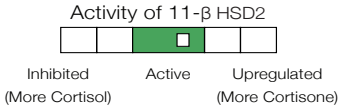
Cortisol Clearance Ratio

The ratio (αTHF+ βTHF + βTHE) / (Cortisol + Cortisone) provides insight into the overall "speed" of reduction or hydrogenation of cortisol and cortisone.



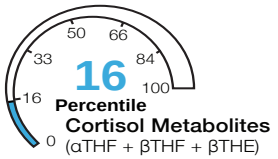
Activity of 11-β HSD2

This marker informs on the nature of the activity of 11-β HSD2 enzyme. 11-β HSD2 converts cortisol to inactive cortisone in kidneys, distal colon and saliva glands. When this enzyme is markedly inhibited free cortisol will be much greater than free cortisone. When the enzyme is upregulated free cortisone will typically be much greater than free cortisol.

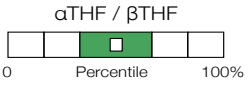


Cortisol Metabolites

Insight into adrenal production of cortisol metabolites.



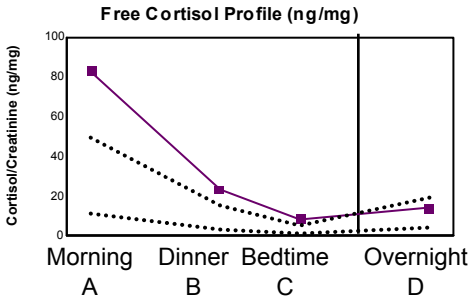
Alpha Reductase Preference



Alpha reductase preference may be influenced by thyroid status.

Free Cortisol Profile

The dotted lines represent the 20th and 80th percentiles for each cortisol point.



The Free Cortisol Profile provides insight into the diurnal rhythm of cortisol.

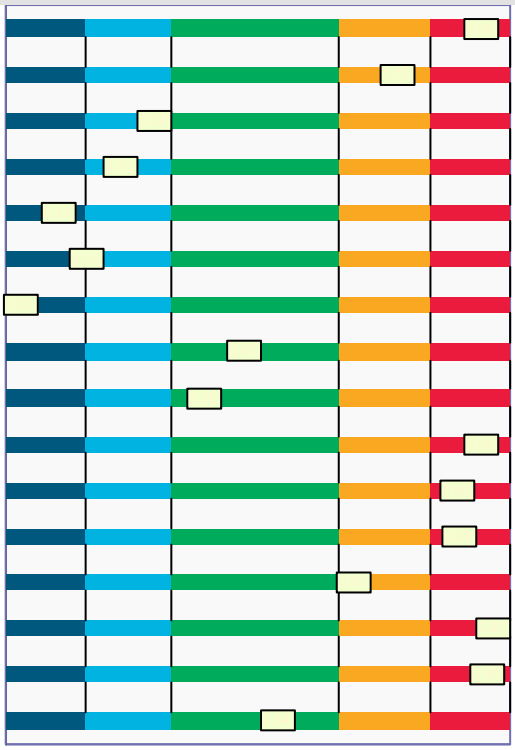
Two ratios are calculated:
- Overnight Cortisol Response (D/C)
- Morning Cortisol Response (A/D)

Neither ratio is graphed, but both are commented on in the interpretation.

CORTISOL RATIOS AND SUMS

CORTISOL & METABOLITES

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%ile	Range Applied
Cortisol (GCMSMS)	100	40 - 78	ng/mg		94%	Male
Cortisone (GCMSMS)	110	63 - 120	ng/mg		78%	Male
a-Tetrahydrocortisol (aTHF)	200	170 - 430	ng/mg		29%	Male
ß-Tetrahydrocortisol (ßTHF)	890	860 - 1,500	ng/mg		23%	Male
ß-Tetrahydrocortisone (ßTHE)	1,400	1,500 - 2,500	ng/mg		11%	Male
aTHF+ßTHF+ßTHE	2,500	2,700 - 4,400	ng/mg		16%	Male
Cortisol Clearance Ratio	12	18 - 31			3.1%	Male
a-THF/ß-THF	0.23	0.16 - 0.36			47%	Male
Cortisol/Testosterone	0.31	0.20 - 0.85			39%	Male
Morning Free Cortisol (Specimen A)	83	11 - 49	ng/mg		94%	Male
Dinnertime Free Cortisol (Specimen B)	23	3.6 - 16	ng/mg		90%	Male
Bedtime Free Cortisol (Specimen C)	8.7	1.2 - 5.2	ng/mg		90%	Male
Overnight Free Cortisol (specimen D)	14	4.5 - 19	ng/mg		69%	Male
Free Cortisol (pooled specimen)	53	10 - 28	ng/mL		97%	Male
Free Cortisone (pooled specimen)	90	34 - 58	ng/mL		95%	Male
11-beta HSD2 Activity Ratio	1.0	0.42 - 1.8				All



DETERMINANTS OF FREE CORTISOL

The amount of free cortisol relative to overall cortisol production is determined by five main factors:

1. The overall extent of production of cortisol, influenced by various factors including sleep (quantity, quality, OSA), allostatic load (stress), inflammation, thyroid hormone activity, body fat burden, calorie intake.
2. The combined rates at which alpha- and beta-reductase irreversibly convert cortisol and cortisone to hydrogenated metabolites-influenced by presence or absence of biliary stasis, hepatic inflammation, thyroid hormone activity, intake of lipotrophic nutrients and foods.
3. The tendency to preserve cortisol as cortisol or shift it to cortisone-which is subject to bile acids, insulin, exercise, % body fat, supplements
4. The extent to which conjugation (Phase II) enzymes are active-which is subject to genetics, exposure to external toxins, diet, hormones and supplements taken.
5. General nutrient intake including nutrients relevant for adrenal health (e.g. Vitamin C, B Vitamins, Mg, K, adequate Na intake).

It is difficult to identify any one factor that will be dominant: thyroid support, liver support, identification and removal/mitigation of sources of inflammation, and normalization of the insulin-glucose axis all play some role.

Here the result for free cortisol (ng/mg) in the pooled specimen lies at 95 % in the reference population.

***NOTE: The percentile for the pooled free cortisol cannot be estimated by taking the average of the percentiles for each of the four point free cortisols !!

RESULT FOR SUM OF MAJOR CORTISOL METABOLITES IS LOW; LOW CORTISOL SYMPTOMS ARE NOT PROMINENT OR NOT LISTED

The result for the sum of the major cortisol metabolites, reflective of overall cortisol production, lies at or below the 33rd percentile; however, symptoms of low cortisol are not prominent or the symptom inventory was not filled out. Symptoms of low cortisol secretion can include anxiety, increased tendency to allergies, morning sluggishness, low blood pressure, low blood sugar between meals, irritability, muscle aches and pains as well as problems with memory.

It's possible that the patient has many of these symptoms but may be downplaying their severity. Note that individuals using inhaled or topical glucocorticoids can exhibit low glucocorticoid output but do not display low cortisol symptoms.

Symptoms usually reflect the activity of free or active cortisol. In this case, there is ample free cortisol output, as demonstrated by the day curve where the area under the curve is in the upper tertile.

CORTISOL CLEARANCE RATIO IS LOW NORMAL OR LOW

The Cortisol Clearance Ratio (CCR) is calculated as follows: (aTHF + bTHF + bTHE)/ (Cortisol + Cortisone). The ratio assesses the overall “speed” of the irreversible reduction of cortisol and cortisone. The two drivers of reduction are bile acids, regulating beta-reduction (AKR1D1) and androgens/androgen precursors, regulating alpha-reduction (SRD5A1).

The result for this patient's ratio is 12 and lies close to or below the 33rd percentile.

Overall, alpha-reductase activity appears low when we look at the “androgenic” chain of hormones extending from 17-hydroxypregnenolone through to androsterone, and this reduced alpha- tendency also manifests with reduced clearance of cortisol though alpha-THF formation. This is often seen when overall cortisol production is low and both alpha- and beta-reduction of cortisol are throttled back to conserve cortisol.

Downregulation of both alpha- and beta-reductase can reflect low thyroid hormone activity. Beta-reductase downregulation can also reflect elevated levels of chenodeoxycholic acid (CDCA) due to biliary stasis/obstruction or hepatic inflammation. Rarely, supplementation with CDCA will suppress beta-reductase. Use of a prescription 5-alpha reductase inhibiting drug or use of a natural product which can inhibit 5-alpha reductase may also inhibit beta reductase, but one would see low 5-alpha reduced androgens if that were the case.

Note that severe elevation of bile acids, such as that seen in cirrhosis, can lead to HPA axis suppression with adrenal atrophy. This mechanism may be playing out to a lesser extent when liver handling of bile is impaired but not drastically so, and may explain some cases of low cortisol production.

Clinical correlation is required to better understand which factor or factors might be relevant here.

FREE CORTISOL & CORTISOL SULFATE FRACTIONS HIGH: CORTISOL GLUCURONIDE FRACTION LOW
The total cortisol result (measured by GCMSMS after sample hydrolysis) is comprised of three major fractions measured by LC-MSMS without hydrolysis: non-conjugated or free cortisol, cortisol glucuronide and cortisol sulfate.

The free cortisol and cortisol sulfate fractions are markedly high. The fraction of total cortisol which is made up of cortisol glucuronide is low.

The free cortisol fraction may be elevated when 11-beta HSD2 is saturated and is deactivating cortisol to cortisone at a fixed rate. This might occur in a patient taking oral cortisol or oral progesterone. Note that there is a direct path from progesterone to cortisol as shown on the second heat map at the front of this report. If the patient is supplementing progesterone a dose reduction might be indicated depending on the clinical presentation: signs and symptoms of elevated cortisol. Free cortisol may also be elevated when reduction of cortisol via the 5-alpha and 5-beta reductase enzymes is impaired. Note that 5-alpha reductase inhibitors can impair both alpha and beta reduction.

The amount of cortisol sulfate is determined by the balance between the activity of sulfotransferase (sulfate conjugate-forming) and sulfatase (hydrolysis of sulfate conjugates).

Sulfation is a Phase II detoxification mechanism. In general, a wide range of organic pollutants and other xenobiotics acting on at least five different nuclear receptors act to both up- and down-regulate sulfation. Medications such as oral estrogens, progesterone and melatonin are known to increase sulfation of estrogens and DHEA via increased SULT1 activity. The regulation of the cortisol-sulfating enzyme (SULT2) is not well studied. It is possible that cortisol sulfation is upregulated by some of the same influences that estrogen and DHEA sulfation are subject to. Identification and removal of suspected upregulators may be helpful.

A high level of cortisol sulfate could arise by inhibition of sulfatase. Genetic sulfatase deficiency is well recognized. Synthetic sulfatase inhibitors have been identified but are in use only for estrogen-sensitive cancers. Some natural substances known to promote sulfation (e.g. progesterone, melatonin) also inhibit sulfatase.

When the proportion of cortisol glucuronide is markedly below the low end of its respective range this may be indicative of downregulation of hepatic Phase II glucuronidation. Liver disease, including cirrhosis and hepatitis can result in downregulation as can hypothyroidism and malnutrition (Lu 2005). Loss-of-function glucuronidation SNPs are also well-recognized, e.g. Gilbert's Syndrome. This would presumably result in low levels of multiple glucuronides.

Note that females tend to have lower glucuronidation activity compared to males, and older individuals in general tend to form glucuronides less readily.

Low glucuronidation may also reflect a lack of cofactors for the enzyme. A list of supplements and foods that promote glucuronidation can be found in the following article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4488002/

A long list of medications including azepams, NSAIDs, codeine, amitryptyline, ethinyl estradiol, and anti-seizure medications may inhibit glucuronidation.

Normalization of conjugation patterns may involve liver support, identification and removal of offending agents including other medications, as well as dietary changes (organic produce, measures to ensure normal bowel habit).

Besides conjugation, the other mechanisms to deactivate cortisol include conversion to cortisone and reduction of cortisol to tetrahydro metabolites (alpha- and beta-THF). Not all aspects of the regulation of reduction to tetrahydro metabolites are well understood. Conversion to cortisone is governed by the 11-beta HSD2 enzyme. The interplay of these factors determines how much free cortisol is "left on the table." This will be discussed in subsequent commentary.

CORTISOL GLUCURONIDE FRACTION IS LOW NORMAL OR LOW
The proportion of hydrolyzed cortisol (total cortisol by GC-MSMS) lies close to or below the 33rd percentile. The following summarizes supplements which might increase cortisol glucuronide (and decrease free cortisol). From Hodges 2015:

Resveratrol
Dandelion
Rooibos
Rosemary
Soy
Ellagic acid
Curcumin

Again, from Hodges, the following factors may lower cortisol glucuronide, thereby causing the low percent cortisol glucuronide issue to arise in the first place:

High fat diet
Green or black tea
Quercetin (red onions)
Rutin
Naringenin
Peppermint oil
Cacao
Silymarin
Lithocholic acid, chenodeoxycholic acid (Lu 2005)
Astaxanthin
Calcium glucarate
Oligomeric Proanthocyanins (OPC)

11-BETA HSD2 ACTIVITY RATIO IS IN THE NORMAL OR ACTIVE ZONE
The marker for the activity of the 11-beta HSD2 enzyme is in the active zone which simply means that the enzyme is actively converting cortisol to cortisone. Free cortisone is typically somewhat greater than free cortisol but not excessively so. This is quite normal. The interpretation is that 11-beta HSD2 is neither markedly inhibited nor markedly upregulated/overactive. The derivation of this marker and the rationale for its use is outlined in the Interpretive Guide.

TOTAL CORTISONE RESULT IS ELEVATED
The cortisone result lies above the 66th percentile. Cortisone is consumed /converted to cortisol in the periphery (skeletal muscle/adipose) and in the liver through the activity of the 11-betaHSD1 enzyme. Elevated cortisone may therefore indicate inhibition of 11-betaHSD1. Keeping cortisone as cortisone prevents clinical manifestations of glucocorticoid excess.

Inhibitors of 11-betaHSD1 include: natural compounds e.g. apigenin and quercetin found in a wide variety of vegetables, fruits and spices (Zhu 2018). as well as estradiol and Growth Hormone (Walker 2001), testosterone (Gambineri 2014) and certain bile acids (Diederich 2000).

There is a dose-dependent effect of the bile acid CDCA on the activity of the 11beta-HSD enzymes (both type 1 and type 2 can be affected) (Morris 2004). The activity of AKR1D1 is also influenced by CDCA as mentioned in the Preamble. Bile acids, in turn, are entangled with thyroid hormone activity.

The clinician has to give careful consideration to the thyroid axis along with the capacity of the liver to form and secrete bile when attempting to understand disturbances in the cortisol-cortisone balance.

STEEP CORTISOL DAY CURVE
The day curve slopes steeply down to the right and its slope is -4.6 ng/mg creatinine-hour. A curve of this nature was seen in fewer than 1 in 5 people in our reference population.

A central aspect of the day curve is the area under the curve or AUC. The sum of the free cortisol concentrations in the three samples is proportional but not identical to the area under the curve-reflecting free cortisol output. Here the result for the AUC lies in the upper tertile possibly reflecting overall higher free cortisol output and/or a point which is higher than usual.

The rise in cortisol overnight is attenuated; the degree of increase is in the bottom tertile of the reference population. More detailed commentary on the attenuated overnight rise in cortisol will follow.

Treatment will depend on the clinical correlation and whether the patient is exhibiting signs and symptoms of excess tissue exposure to cortisol.

BEDTIME CORTISOL AND SLEEP
Recognize that there is an optimum range for bedtime cortisol. If bedtime cortisol is too low, there is some evidence that normal sleep architecture is not established (insufficient REM sleep) (Garcia-Borreguero 2000). Conversely, high bedtime cortisol is suppressive for melatonin, and may result in difficulty initiating and sustaining sleep.

Here the result for free cortisol measured at bedtime is high, lying above the 66th percentile so it may be worthwhile considering whether the free cortisol level before retiring is playing a role in sleep problems for this patient. No complaints about sleep were noted on the requisition but it is still worth questioning the patient about this possibility.

OVERNIGHT CORTISOL RESPONSE IS LOW
The result for the Overnight Cortisol Response or ratio of free cortisol in the overnight (D sample) to free cortisol in the bedtime (C sample) is 1.6 and this lies at or below the 33rd percentile. Note that this result is not displayed graphically on the Cortisol & Cortisol Metabolites Heat Map page but can be appreciated by looking at the relevant bar graphs preceding this block of comments.

A low ratio is typically seen when cortisol secretion is static throughout 24 hours-indicating loss of diurnal variation. Cortisol may be either statically high or statically low and the management depends on which of these two situations applies. A low ratio could also arise if there was a transient, acute emotional or physical stressor in the hours before retiring, which would elevate bedtime cortisol.

Melatonin and cortisol enjoy a reciprocal relationship. Melatonin supplementation may act to suppress the overnight rise in cortisol. Elevated testosterone can also suppress cortisol by enhancing hypothalamic sensitivity to negative feedback inhibition of CRH release.

Note that if the overnight and or bedtime creatinines differ significantly from each other this can distort the appearance of the free cortisol curve. The underlying trends are still valid in most cases.

MORNING CORTISOL RESPONSE IS ELEVATED
The Morning Cortisol Response (MCR) is defined by RMA as the ratio of free cortisol in the Morning or (A) specimen to free cortisol in the Overnight (D) specimen. The ratio is 5.8 for this patient. This result lies above the 66th percentile for the reference population. Note that this result is not displayed graphically on the Cortisol & Cortisol Metabolites Heat Map page but can be appreciated by looking at the relevant bar graphs preceding this block of comments.

The surge in free cortisol measuring in saliva in the first hour after waking is known as the Cortisol Awakening Response (CAR). An elevated saliva CAR has been associated with stress anticipating the upcoming day/week, anxiety and panic disorder, an acute stressor unique to the day of collection, untreated anorexia nervosa, insulin-glucose axis dysregulation, as well as deficiency of omega-3 fatty acids.

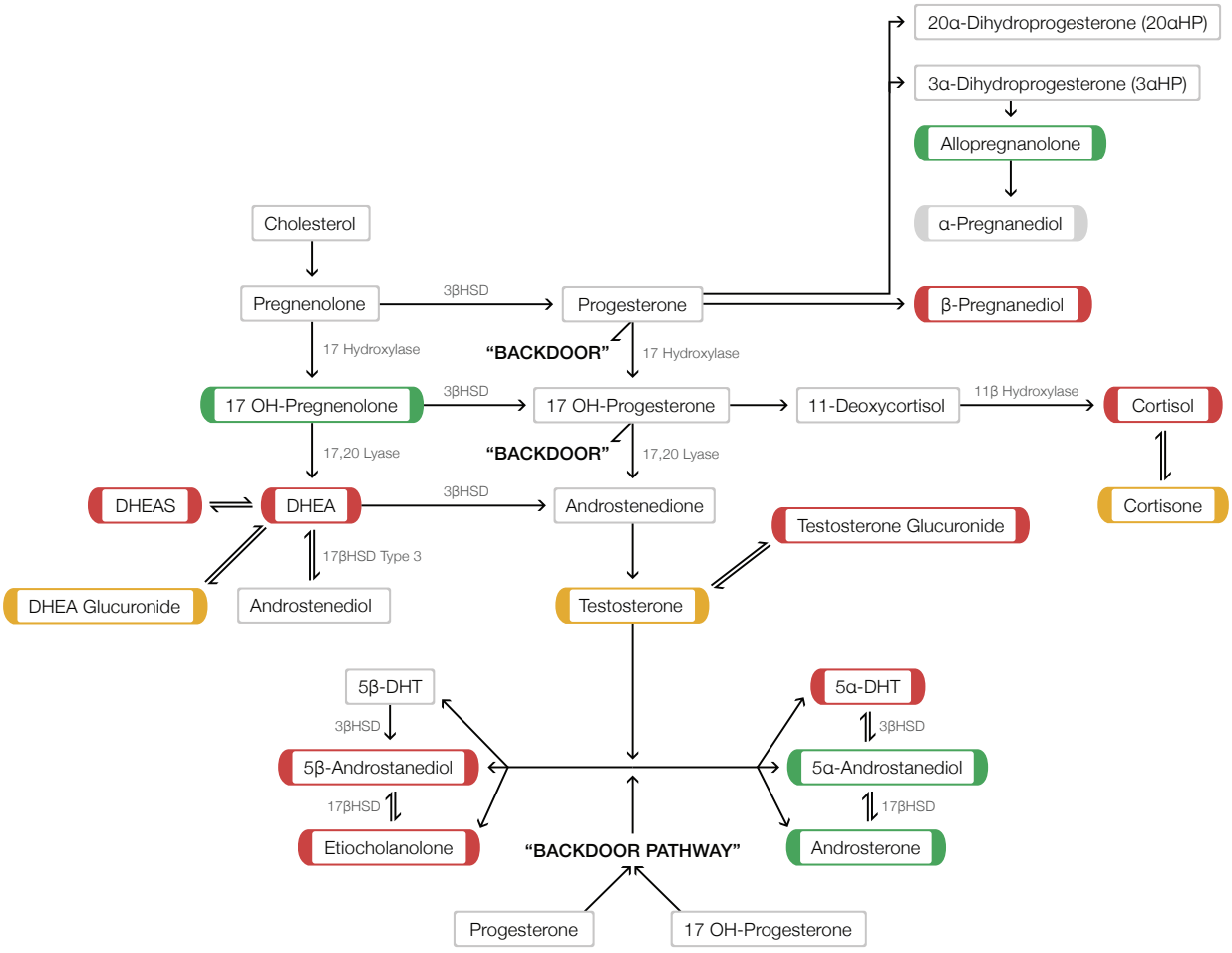
The urine MCR discussed here MAY be a surrogate for saliva CAR measurements but additional research is needed. An elevated urine MCR needs to be interpreted in light of a good history surrounding acute and longer term stressors.

Note that if the overnight and or morning creatinines differ significantly from each other this can distort the appearance of the free cortisol curve. The underlying trends are still valid in most cases.

BALANCED RATIO: CORTISOL/TESTOSTERONE
We consider that the ratio of cortisol to testosterone might be reflective of the balance between anabolic and catabolic steroid hormones. This result is displayed in the bar graph section and also on the first page of the report. When the indicator points within the middle 1/3 of the semicircular gauge (between the 33rd and 66th percentiles) this may reflect a reasonable balance between tissue breakdown (catabolism) and tissue growth/repair (anabolism).

The ratio is constructed from molar concentrations (nmol/mL):
Cortisol * / (Testosterone + DHT + alpha-Androstanediol + beta-Androstanediol)
* total Cortisol via GCMSMS after hydrolysis

PROGESTERONE & 17OH PRECURSOR STEROIDS
Hormone Heat Map
HMUS04



PROGESTERONE METABOLITES

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%ile	Range Applied
17-Hydroxypregnenolone	2.0	1.1 - 4.0	ng/mL		33%	Male
a-Pregnanediol + ß-Pregnanediol	710	110 - 380	ng/mL		95%	Male
ß-Pregnanediol	660	110 - 370	ng/mL		95%	Male
a-Pregnanediol	< 100	0 - 0	ng/mL		<DET	Male
ß-Pregnanediol/a-Pregnanediol	< 0.010	0 - 0	ng/mL		<DET	Male
Allopregnanolone	28	11 - 39	ng/mL		63%	Male
Free Progesterone (via GCMSMS)	< 0.95	0.30 - 0.39	ng/mL		<DET	Male

SUM OF ALPHA- AND BETA-PREGNANEDIOL: ALPHA P2 BELOW REPORTING LIMIT
The result for alpha-pregnanediol is below the reporting limit of 100 ng/mL. In order to report a result for the sum of alpha- and beta-pregnanediols, a value of 50 ng/mL is arbitrarily assigned for alpha-pregnanediol when it is below the reporting limit.

Here the beta-pregnanediol result is 660 and the alpha-pregnanediol result is below the reporting limit but we still know that the result for the sum lies somewhere between 660 and 760 ng/mL so we split the difference and report the sum as 710 ng/mL.

This is a rather arbitrary decision and has the effect of making the sum of alpha- and beta-pregnanediol appear higher than the picture gleaned from beta-pregnendiol in isolation.

PROGESTERONE IN MALES
Both men and women make a modest baseline amount of progesterone in the adrenal glands. The metabolites of progesterone include alpha- and beta-pregnanediol as well as allopregnanolone. In men these metabolites tend to be quite low, especially alpha-pregnanediol and allopregnanolone. Although we report both the sum of the pregnanediols as well as the individual results, the sum and the beta-pregnanediol result are usually identical. Commentary therefore focuses on the beta-pregnanediol result.

BETA-PREGNANEDIOL RESULT IS HIGH NORMAL OR HIGH
The result for beta-pregnanediol lies close to or above the 66th percentile. In males, excess progesterone activity might lead to depression and "brain fog".

This finding could be due to supplementation with progesterone or pregnenolone (particularly oral or sublingual). It may also be due to Clomid and/or HCG often used to stimulate testosterone production in males. Exposure to progesterone itself may be gained by intercourse with a person who is supplementing with vaginal or labial progesterone. Some older males supplement with progesterone as it is thought to be beneficial for the prostate by some authorities. Elevated progesterone may also accompany elevations in glucocorticoid metabolites, as they all arise from a common precursor.

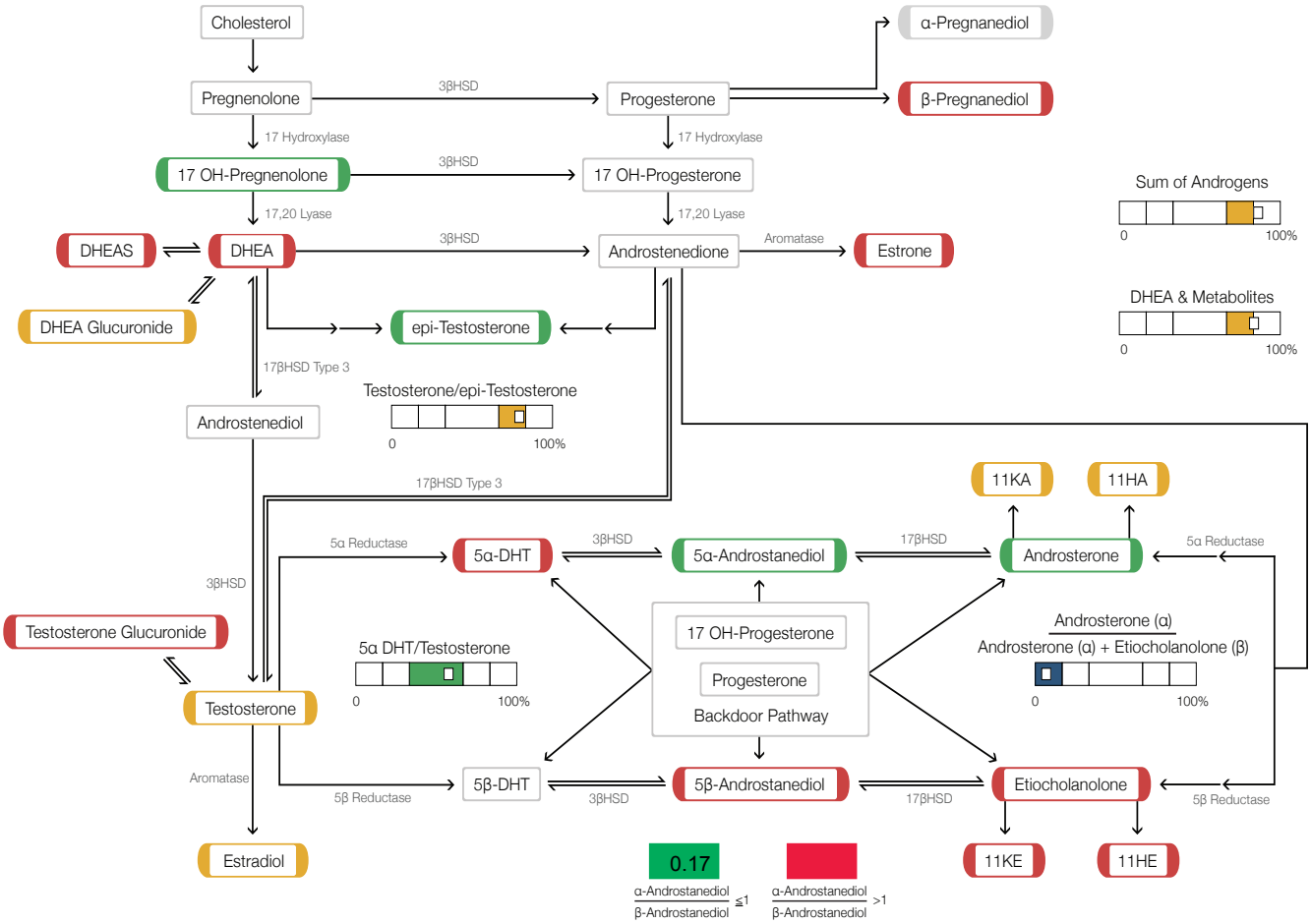
Otherwise, this level of pregnanediol may reflect ample formation of progesterone in the adrenal glands.

ALLOPREGNANOLONE RESULT IS NORMAL
The result lies between the 33rd and 66th percentiles. Apart from women in the luteal phase, and women supplementing with something that can metabolize to progesterone, allopregnanolone arises from progesterone of adrenal origin. This patient likely has adequate adrenal progesterone secretion.

ALPHA-PREGNANEDIOL RESULT IS LOW
The result for alpha-pregnanediol is below the limit of reporting (i.e. very low).
There is very little in the literature regarding alpha-pregnanediol. The clinical significance of this result is unknown beyond that it is reflective of overall low progesterone production. Low alpha-pregnanediol is a completely normal finding in men, postmenopausal women and cycling women who are not in the luteal phase of the menstrual cycle.

RATIO beta-PREGNANEDIOL/alpha-PREGNANEDIOL CAN'T BE CALCULATED
The ratio of beta- to alpha-pregnanediol isn't calculated because the result for alpha-pregnanediol is below the limit of reporting.

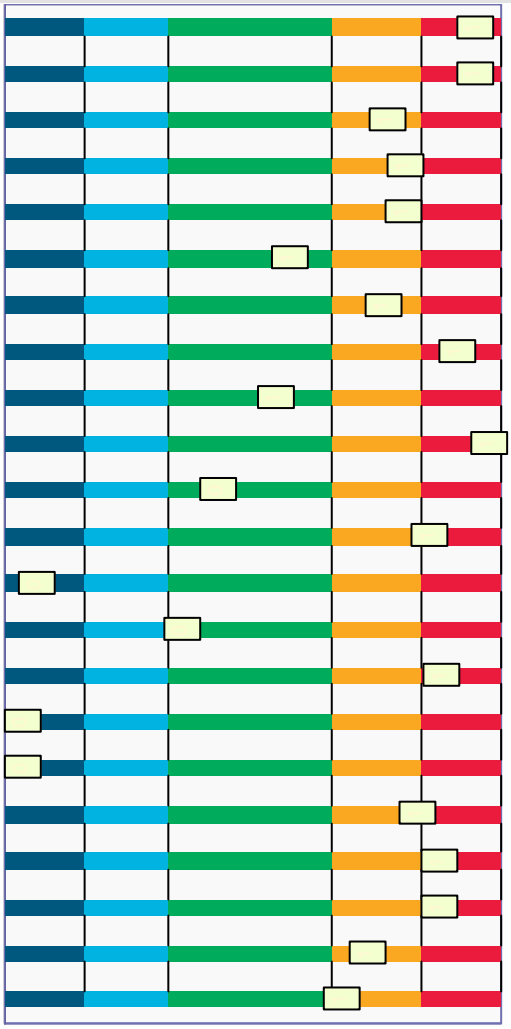
ANDROGENS/17-KETOSTEROIDS
Hormone Heat Map
HMUS05



ANDROGENS / 17 KETOSTEROIDS

ANDROGEN RATIOS AND SUMS

Analyte	Result	Range	Units	%ile	Range Applied
DHEA (free and conjugated)	2,100	250 - 1,300	ng/mL	95%	Male
DHEA sulphate (DHEAS) via LCMSMS	2,400	110 - 1,500	ng/mL	95%	Male
DHEA glucuronide via LCMSMS	370	170 - 390	ng/mL	77%	Male
DHEA&metabolites (DHEA+AND+ETIO)	5,300	2,300 - 5,000	ng/mL	81%	Male
Testosterone (T)	63	6.7 - 60	ng/mL	81%	Male
Epi-testosterone (Epi-T)	45	26 - 93	ng/mL	58%	Male
Testosterone/Epi-Testosterone (T/Epi-T)	1.4	0.12 - 1.5		77%	Male
a-Dihydrotestosterone (aDHT)	16	3.3 - 11	ng/mL	91%	Male
a-DHT/Testosterone	0.26	0.14 - 0.55		55%	Male
Testosterone glucuronide via LCMSMS	100	3.0 - 45	ng/mL	98%	Male
a-Androstanediol	43	30 - 69	ng/mL	43%	Male
ß-Androstanediol	250	41 - 200	ng/mL	86%	Male
a-Androstanediol/ß-Androstanediol	0.17	0.24 - 0.94		6.7%	Male
Androsterone (AND)	1,100	800 - 2,100	ng/mL	36%	Male
Etiocholanolone (ETIO)	2,100	830 - 1,800	ng/mL	88%	Male
Androsterone Excretion Ratio	0.34	0.42 - 0.64		4.0%	Male
AND/ETIO	0.52	0.72 - 1.8		4.0%	Male
Androgen sum (T,DHT,androstanediols)	370	98 - 310	ng/mL	83%	Male
11-Ketoetiocholanolone (11KE)	400	69 - 330	ng/mL	88%	Male
11-Hydroxyetiocholanolone (11HE)	410	34 - 350	ng/mL	88%	Male
11-Ketoandrosterone (11KA)	20	9.3 - 23	ng/mL	73%	Male
11-Hydroxyandrosterone (11HA)	560	320 - 650	ng/mL	68%	Male



DHEA RESULT IS ELEVATED

The result for DHEA lies above the 66th percentile. Symptoms of high DHEA in males are primarily those of high testosterone/high DHT and include acne, oily skin, irritability and a "short fuse". Complaints of breast enlargement or tender breasts in association with elevated DHEA indicate that it is being converted to estrogen via the aromatase enzyme.

DHEA declines naturally with age. This patient's age is less than 35 years. Although our reference population did include patients in their 20's and early 30's, the average age was 42 years. If a reference range had been constructed using only patients in their early 30's, this result would likely not be high, when compared to that range. In other words, this DHEA result could be normal for age.

DHEA could be elevated at any age if the patient is taking supplemental DHEA, 7-keto DHEA, Growth Hormone, Growth Hormone secretagogues or GHRH peptide analogs. Various adrenal pathologies may give rise to elevated DHEA. This is beyond the scope of this discussion.

DHEA is associated with fat-burning as it is closely tied to Growth Hormone (GH). DHEA also helps maintain bone density, muscle mass and may help dispose glucose into muscle by a non-insulin dependent mechanism. It is thought to be neuroprotective; hence, elevated DHEA may confer significant health benefits in the right patient.

RESULT FOR SUM OF ANDROGENS IS ELEVATED
The mass balance for testosterone is best reflected by consideration of testosterone, DHT, alpha- and beta-androstanediol, and possibly androsterone, according to Labrie (Labrie 1997). Here the results for testosterone, DHT, alpha-androstanediol and beta-androstanediol individually or in summation lie above the 66th percentile for the chosen reference range.

Whether any action is indicated here depends in part, on the clinical presentation: presence or absence of symptoms and signs of androgen excess. Note that DHT exhibits the most activity at the androgen receptor, followed by testosterone. The other metabolites may have activity at hair follicles. It is therefore difficult to attribute symptoms to one hormone in isolation.

Elevated androgens may be seen in the context of insulin resistance and/or Metabolic Syndrome, as well as PCOS. This is especially true in the face of elevated body mass index. Further investigation of the insulin-glucose axis may be warranted. This is less likely to be an issue if the body mass index is below circa 22.

TESTOSTERONE RESULT IS ELEVATED
The testosterone result lies above the 66th percentile. This can be due to supplementation with testosterone or its precursors including DHEA and pregnenolone. Neither was listed on the requisition. Growth Homone supplementation may also elevate testosterone as will resistance training.

Casodex is also known to raise testosterone.

Elevated testosterone might present with symptoms of androgen excess including acne, oily skin, irritability and aggressiveness; however, the actual clinical picture will also depend on the level of estrogens. Note that high estrogens may oppose the action of androgens at the gene promoter level in target tissues such as the penis and prostate.

RESULT FOR DHEA AND METABOLITES IS ELEVATED
The approximate mass balance for DHEA can be assessed by looking at the sum of the results for both DHEA and its metabolites: androsterone (5-alpha reduced metabolite) and etiocholanolone (5-beta reduced metabolite). Here the sum lies above the 66th percentile. This reinforces the notion that overall production of DHEA is elevated even if DHEA itself is not elevated.

TESTOSTERONE GLUCURONIDE RESULT IS ELEVATED
Intact testosterone glucuronide is measured directly by LC-MSMS. When the sample is hydrolyzed for GC-MSMS analysis all testosterone glucuronide should be converted to free testosterone. The GC result should represent the total of free testosterone naturally present, free testosterone generated from hydrolysis of testosterone glucuronide, and free testosterone generated by hydrolysis of testosterone sulfate. The GC and LC results are not additive. Typically the testosterone result should be about 0.6 to 0.8 times the testosterone glucuronide result, if free testosterone and testosterone sulfate levels are minimal.

Here, an elevated testosterone glucuronide result is a simple reflection of increased total testosterone production.

ALPHA DIHYDROTESTOSTERONE RESULT IS ELEVATED
The result for 5-alpha DHT lies above the 66th percentile. This may simply be due to an excessive level of testosterone precursor, combined with average conversion of testosterone to 5-alpha DHT.

Elevated DHT can also arise from elevated androsterone, via androstanediol, even when testosterone is normal.

Since 5-alpha DHT is the most potent ligand for the androgen receptor, symptoms of elevated testosterone might be noted, although this depends on the levels of other competing steroids including estrogens and cortisol.

Note that zinc supplementation can raise the levels of testosterone and/or DHT (Netter 1981).

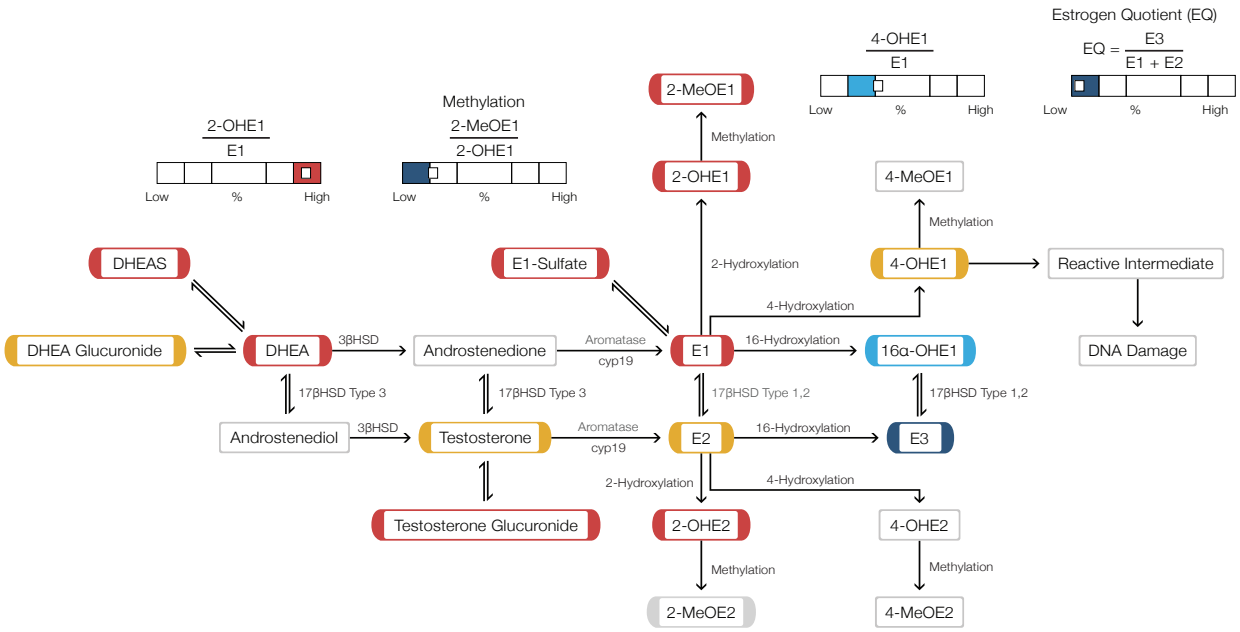
RATIO alpha-ANDROSTANEDIOL/beta-ANDROSTANEDIOL MARKEDLY LOW
The androstanediols can be formed either from 5-alpha and 5-beta DHT or from androsterone and etiocholanolone. We measure the ratio of 3-alpha-5-alpha androstanediol to 3-alpha-5-beta androstanediol. In our database, these analytes correlate most closely to androsterone and etiocholanolone. The result for this ratio is less than 1 in most males but here the result for the ratio is markedly low, at or below the 16th percentile. This may be an indicator of reduced tissue activity of T3 (triiodothyronine).

ANDROSTERONE EXCRETION RATIO IS LOW NORMAL OR LOW
The Androsterone excretion ratio is Androsterone/(Androsterone + Etiocholanolone). The result for this ratio lies close to or below the 33rd percentile. Skovsted noted that this ratio is low in hypothyroid patients (Skovsted 1close 966). If the ratio is low the clinician should review the patient with an eye toward signs and symptoms of decreased tissue activity of T3. If the patient is supplementing thyroid hormones the dose may be suboptimal.

A low ratio may also be seen in low body weight including anorexia nervosa(Wassif 2011). Presumably reduced thyroid hormone activity is at play here as well, in the face of reduced calorie intake. Impairment in the ability to form the 5-alpha-reduced product androsterone due to 5-alpha reductase inhibition by pharmaceutical or natural inhibitors can also result in a low excretion ratio.

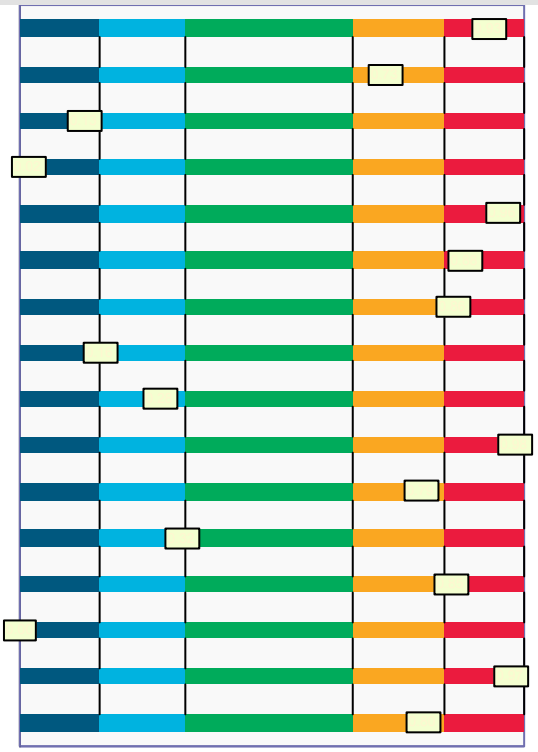
Anything which elevates etiocholanolone, including testosterone, DHEA or progesterone supplementation, may result in a lower ratio without necessarily indicting tissue activity of thyroid hormones. This metabolite may be elevated due to upregulation of the activity of AKR1D1: the beta-reductase enzyme. As of 2019, the AKR family of enzymes has not been extensively studied and its regulation is complex. Increased thyroid hormone activity (whether endogenous or via dosing of supplemental thyroid hormones) should be considered. Early-stage obesity, insulin resistance, Metabolic Syndrome, fatty liver and impairment of bile production and secretion can be involved. As these conditions become more severe, AKR1D1 can eventually shut down due to negative feedback from CDCA.

ESTROGENS & METABOLITES
Hormone HeatMap
HMUS07



ESTROGENS

Analyte	Result	Range	Units	%ile	Range Applied
Estrone (E1)	7.6	2.6 - 5.4	ng/mL	93%	Male
Estradiol (E2)	1.6	0.70 - 2.0	ng/mL	73%	Male
Estriol (E3)	1.4	2.1 - 8.5	ng/mL	13%	Male
E3/(E1 + E2)	0.15	0.51 - 1.6		2.0%	Male
2-Hydroxyestrone (2-OHE1)	7.0	0.82 - 3.5	ng/mL	96%	Male
2-OHE1/E1	0.93	0.25 - 0.72	ng/mL	88%	Male
2-Methoxyestrone (2-MeOE1)	1.5	0.36 - 1.4	ng/mL	86%	Male
2-MeOE1/2-OHE1	0.22	0.23 - 0.60		16%	Male
16a-Hydroxyestrone (16a-OHE1)	0.73	0.58 - 2.6	ng/mL	28%	Male
2-OHE1/16a-OHE1	9.6	0.66 - 3.2		98%	Male
4-Hydroxyestrone (4-OHE1)	0.90	0.37 - 0.94	ng/mL	79%	Male
4-OHE1/E1	0.12	0.099 - 0.23		32%	Male
2-Hydroxyestradiol (2-OHE2)	1.1	0.075 - 0.67	ng/mL	85%	Male
2-Methoxyestradiol (2-MeOE2)		0 - 0	ng/mL	<DET	No data
Estrone sulphate (E1-Sulphate or E1S)	3.1	0.43 - 1.2	ng/mL	97%	Male
Sum of Estrogens	22	9.3 - 22	ng/mL	80%	Male



8-HYDROXY-2-DEOXYGUANOSINE (8OH2dG) - OVERNIGHT COLLECTION

NOTE: The upper end of the listed range is the 67th percentile which is at the green-yellow border.

Analyte	Result	Range	Units	%ile	Range Applied
8-Hydroxy-2-deoxyguanosine (8-OH2dG)	< 0.010	0 - 0.90	ng/mg	<DET	Male

6-SULFATOXY MELATONIN (OVERNIGHT COLLECTION)

Analyte	Result	Range	Units	%ile	Range Applied
6-Sulfatoxymelatonin	8.8	4.4 - 14	ng/mg	64%	Male

CREATININE

Analyte	Result	Range	Units	%ile	Range Applied
Pooled Creatinine	1.4	1.1 - 2.2	mg/mL	46%	Male
Overnight Creatinine (D)	1.6	0.96 - 2.6	mg/mL	48%	Male
Morning Creatinine (A)	1.6	0.98 - 2.1	mg/mL	56%	Male
Dinnertime Creatinine (B)	0.62	0.59 - 2.0	mg/mL	21%	Male
Bedtime Creatinine (C)	1.7	0.81 - 2.4	mg/mL	67%	Male

Free steroids : USEFUL FOR DETECTION OF CONTAMINATION OF URINE BY SUPPLEMENTAL HORMONES

Analyte	Result	Range	Units	%ile	Range Applied
Free Estrone (via LCMSMS)	< 0.50	0.028 - 0.82	ng/mL	<DET	Male
Free Estradiol (via LCMSMS)	< 0.60	0 - 0.65	ng/mL	<DET	Male
Free Estriol (via LCMSMS)	< 0.50	0 - 0.60	ng/mL	<DET	Male
Free Testosterone (via LCMSMS)	< 0.90	0.89 - 1.0	ng/mL	<DET	Male
Free Progesterone (via GCMSMS)	< 0.95	0.30 - 0.39	ng/mL	<DET	Male

FINDINGS ARE CONSISTENT WITH INCREASED AROMATASE ENZYME ACTIVITY

Cortisol induces increased synthesis of the aromatase enzyme which converts androgens to estrogens. Note also that since cortisone may be converted back to cortisol in adipose tissue, both cortisol and cortisone may be drivers of increased aromatase activity.

The results for cortisol, cortisone, testosterone, estradiol and estrone are all elevated above the 66th percentile. This pattern is consistent with increased aromatase activity.

Measures to mitigate increased conversion of androgens to estrogens include zinc supplementation, lowering of cortisol and cortisone levels, melatonin supplementation and weight loss.

RESULT FOR THE SUM OF ESTROGENS IS ELEVATED

The result for the sum of the estrogens lies above the 66th percentile. High or high normal estrogens can be seen with DHEA supplementation, especially oral DHEA, as well as pregnenolone supplementation. Neither was listed on the requisition. Commercially raised beef and poultry may be high in estrone/estrone sulphate, so excess consumption of these foods may occasionally be a factor. Excessive alcohol intake is also known to elevate estrogens.

Other factors affecting estrogen levels include constipation, elevated percent body fat, and elevated cortisol. Estrogens are excreted in the stool so prolonged retention of stool can result in increased reabsorption of estrogens from the colon. Estrogens can be made from androgens via aromatase enzymes in adipose tissue, so obesity may contribute to excess estrogens. Elevated endogenous cortisol secretion or exogenous corticosteroid use may increase the expression of

aromatase enzymes. Zinc deficiency also leads to increased expression of aromatase.

Testosterone supplementation may result in elevated estrogens through conversion of testosterone to estradiol and estrone via the aromatase enzyme system. High endogenous testosterone may result in high estrogens for the same reason. The patient did not indicate that they were supplementing with testosterone.

Measures to reduce estrogens include decreasing alcohol consumption, weight loss, zinc supplementation, ensuring regular bowel movements, increasing fibre intake. Fibre traps estrogens preventing enterohepatic recirculation, and also modifies intestinal flora to minimize deconjugation and reuptake of estrogens. Supplementation with calcium-D-glucarate may also prevent deconjugation of estrogens and facilitates their excretion. Many practitioners supplement with DIM or I3C thinking that this increases overall estrogen excretion. These compounds may act to shift metabolism of estrogens down the 2-hydroxylation pathways but may not increase overall excretion.

ESTRONE RESULT ELEVATED
The estrone result lies above the 75th percentile. This might be expected to be accompanied by elevations in some of the other estrone metabolites such as 2, 4 and 16-hydroxyestrone. Note that estrone is a relatively weak estrogen. In target tissues, it may be converted to estradiol, which is a much more potent estrogen. Elevated estrone is more worrisome in the setting of increased waist circumference (>= 40 inches), and clinical manifestations of elevated estrogens including breast enlargement and penis shrinkage. Elevated estrone is also seen in the context of excessive alcohol consumption. Supplementation with testosterone and/or DHEA may also elevate estrogens without elevating androgens.

SUM OF ESTROGENS AND TOTAL DHEA IS ELEVATED
Here, the result for the total of all estrogens measured along with total DHEA ranks at or above the 80th percentile. In general, estrogens can arise peripherally from testosterone and androstenedione, respectively, via the aromatase enzyme expressed in adipose tissue as well as the liver. High DHEA can therefore lead to elevated estrogens, as may be the case here.

Factors which may increase aromatase activity include obesity, especially visceral obesity. If an inflammatory milieu exists within adipose tissue, the cytokine mixture produced tends to increase aromatase activity.

Zinc deficiency can also play a role. Zinc (and progesterone) are often cited as "aromatase inhibitiors", but both zinc and progesterone do not inhibit the activity of the aromatase enzyme. They do decrease the transcription of the gene coding for aromatase, resulting in a net decrease in the number of copies of the enzyme produced in any given tissue. Insufficent zinc (and progesterone) takes the "brakes" off the espression of aromatase enzyme copies. Similarly, melatonin acts as a brake on aromatase expression. Low melatonin was promote higher estrogens.

The patient did not list the use of estrogens, testosterone, DHEA, 7-keto DHEA or pregnenolone. It's quite possible that her estrogens are high because she is using one or more of these hormones, but didn't list this on the requisition.

ESTRIOL RESULT IS LOW
The result for estriol lies at or below the 33rd percentile. The significance of low estriol in males is not known.

Note that increased thyroid hormone activity can push parent estrogens away from estriol and 16-hydroxyestrone.

EFFECT OF METHYLATION ON INTERPRETATION OF 2OHE1/E1 RATIO
Here the estrone methylation ratio (2-methoxyestrone/2-hydroxyestrone) is lower than average. This makes the apparent ratio 2OHE1/E1 appear higher than it might otherwise be. The ratio 2OHE1/E1 can only reflect "pure" 2-hydroxylation activity when methylation activity is within normal limits.

2-HYDROXYESTRONE RESULT HIGH NORMAL OR HIGH
The 2-hydroxyestrone metabolite level is elevated close to or above the 66th percentile. This estrogen is usually the most abundant estrogen in urine, in other words it makes up the highest percentage of the total. Elevated 2-hydroxyestrone may be due to interventions including I3C, DIM, T3 and progesterone. High normal or high 2-hydroxyestrone may also reflect an elevated level of the parent estrone. This in turn may be seen in a variety of settings including obesity, elevated DHEA or testosterone, and excessive alcohol intake.

A study by Wellejus looked at risk of breast cancer as a function of the 2-16 ratio in women supplementing with estrogens and found that risk increased with the ratio, and that this risk increase was actually due to the absolute level of

2-hydroxyestrogens and was unrelated to the level of 16-hydroxyestrone (Wellejus 2005).

There is no information on a potential connection between elevated 2-hydroxyestrone and prostate cancer risk.

Note that when the methylation ratio is low, this can lead to high 2-hydroxyestrone without invoking other explanations.

RATIO: 2OHE1/E1
The 2-hydroxylation pathway for estrogens is considered to be the most favorable pathway in women and in many cases 2OHE1 is found to be the most abundant estrogen via GSMSMS. Interventions generally seen to be beneficial for breast health in women include: exercise, progesterone, T3, cruciferous vegetables, DIM, I3C, iodine and high fibre intake. These interventions push estrogens along the 2-hydroxylation pathway.

The role of 2OHE1 in men's health has not been explored in detail.

An elevated ratio may indicate increased tissue activity of T3 (Doufas 2000) but correlation with the aTHF/THF ratio and the Androsterone Excretion Ratio is advised, along with correlation to the clinical presentation. If methylation activity is low, alteration in thyroid activity can't necessarily be deduced from a high level of 2-hydroxyestrone.

Note that when testosterone (or DHEA) is supplemented, correlation to thyroid hormone activity may be lost. Note also that a male exposed to progesterone through intercourse with a partner using vaginal progesterone can exhibit a ratio 2OHE1/E1 which "looks like" elevated thyroid activity due to the effect of progesterone on 2-hydroxylation.

BOTH 2OHE1 AND 2OHE2 ARE HIGH NORMAL OR HIGH
The results for 2-hydroxyestrone (2OHE1) and 2-hydroxyestradiol (2OHE2) are close to or above the 66th percentile. The same comments made above for 2OHE1 may also apply for 2OHE2.

RATIO: 2-HYDROXYESTROGENS/16-HYDROXYESTRONE
The ratio of these catechol estrogens has long been studied as a predictor informing on the future risk of for estrogen-sensitive cancers. The association between breast cancer and the 2-16 ratio is at best weak as shown by numerous studies. This is discussed in a meta-analysis by Obi (Obi 2011).

The body of literature on catechol estrogens (measured via ELISA) and the risk of prostate cancer is quite small in comparison to the literature on catechol estrogens and breast cancer risk (Barba 2009).

The original research on the 2-16 ratio was performed with the Estramet ELISA kit which was not able to distinguish between various 2-hydroxylated estrogens. The ratio 2-hydroxyestrone/16-hydroxyestrone measured by mass spectrometric techniques is not the same as the 2-hydroxyestrogen/16-hydroxyestrone ratio measured by ELISA. Any prostate cancer risk threshold arrived at with ELISA cannot be "translated" into a risk threshold arrived at via mass spectrometry. Prospective studies would have to be undertaken, to determine what relationship, if any, exists between prostate cancer and 2- and 16-oxidized estrones measured by GC-MS or LC-MS.

SIGNIFICANCE OF ESTROGEN QUOTIENT IN MALES
In general, the clinical significance of the Estrogen Quotient E3 / (E1 + E2) in males is not known. In females, ratios >1 have been tentatively associated with a decreased risk of breast cancer but this has never been explored prospectively. The ratio is presented here for information and research purposes.

4-HYDROXYESTRONE RESULT IS ELEVATED
The result for this metabolite lies above the 66th percentile. There is some evidence that 4-hydroxyestrone may play a role in promoting the development of breast cancer by forming adducts with DNA. Higher levels of DNA adducts have also been found in the urine of men with prostate cancer (Markushin 2006). The significance of an elevated level of the 4-hydroxyestrone conjugate measured here (which is not to be confused with the adduct) is unknown. The literature pertaining to males is scanty.

RESULT FOR 4OHE1/E1: MALE PATIENT
The significance of 4OHE1 In males is not known; therefore, commentary on the ratio 4OHE1/E1 is not given.

2-METHOXYESTRADIOL NOT REPORTED
The estrogen metabolite 2-methoxyestradiol is not currently being reported due to a technical issue with the analyte. None

of the other estrogens and estrogen metabolites are affected.

RATIO: 2-METHOXYESTRONE / 2-HYDROXYESTRONE IS LOW
Some 2-hydroxyestrone (2OHE1) is cleared by conversion to the methoxylated product, 2-methoxyestrone (2meOE1) via the COMT enzyme. This can be assessed by looking at the ratio 2-meOE1/2OHE1. Here the result for that ratio lies close to or within the bottom tertile, so methylation is slowed down or blocked, depending on how low the ratio is.

NOTE: An elevated 2OHE1/E1 ratio can be indicative of increased thyroid hormone activity; however, low methylation can cause 2-hydroxyestrone to “pile up” and thereby increase the ratio 2OHE1/E1. Use caution in trying to infer anything about thyroid hormone activity when methylation is slowed or blocked.

A low methylation ratio may indicate a need for support of methylation pathways. A proportion of patients with poor estrogen methylation may benefit from supplementation with any or all of betaine, methylated tetrahydrofolate, folate, B-12, SAMe, magnesium, B6 and MSM.

The methylation ratios are also a function of the activity of the relevant methyltransferase enzyme, COMT. Polymorphisms which result in a loss of COMT function may therefore result in a lower ratio. Supplementation may or may not be helpful in these cases. Betaine and MSM exert other beneficial effects on the liver apart from supporting methylation.

Catecholamines are also a substrate for COMT. Excessive catecholamines may compete with estrogens for COMT catalytic "space". Measures to normalize catecholamine output may free up COMT to form more methoxylated estrogen metabolites.

Note that supplementation with estrogens may increase the demand for methylation cofactors, and in time, deplete them, leading to decreased "yield" of methoxyestrone relative to the parent hydroxyestrone.

OXIDATIVE STRESS MARKER 8-HYDROXY-2-DEOXYGUANOSINE RESULT IS UNDETECTABLE
8-hydroxy-2-deoxyguanosine (8-OHdG) is a recognized marker of oxidative stress. The level should be as low as possible. Many individuals have a result that is undetectable which is perfectly normal. In this case the dial gauge reads "1" and the bar graph marker sits at zero. The result will be "<0.001".

MELATONIN METABOLITE RESULT NORMAL
The result for the principal melatonin metabolite measured here between the 33rd and 66th percentiles. Melatonin declines with age and is instrumental in maintaining proper diurnal rhythm and sleep-wake cycling. Low melatonin may be associated with failure to suppress cortisol production overnight. Low melatonin has also been shown to be associated with chronic migraine and supplementation with melatonin may be beneficial in chronic migraine sufferers (Bougea 2016). Overnight melatonin output is also adversely affected by exposure to bright lighting in the evening, including “screen time” from electronic devices (Perrault 2019).

There is evidence that melatonin has a profound influence on immune function in general and specifically may be protective against breast cancer. Consideration might be given to supplementation with melatonin 0.5 to 2 mg at bedtime.

GENERAL COMMENT: FREE SEX STEROIDS
Most of the hormones circulate in blood as conjugates which are more soluble than non-conjugated steroids. Under normal circumstances, there are only minute amounts of free or non-conjugated steroids in blood, with free cortisol being an exception. The same pattern is seen in urine.

In most cases these urine levels can generally be disregarded for men and also for women not using hormones.

If women are applying sex hormones in the vicinity of the urethral meatus (the opening from which urine comes) or on the labia minora, it's possible that these hormones will directly contaminate the urine leading to falsely elevated results. To a lesser extent, this might also happen with vaginal application of hormones. This situation is analogous to using sublingual hormones and then attempting to measure those hormone levels via a saliva sample: direct contamination of the sample may occur.

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George Gillson MD, PhD
Medical Director

Note: The College of Physicians and Surgeons of Alberta considers urine steroid hormone testing and some forms of bio-identical hormone replacement to be complementary medicine. The interpretation comments have not been evaluated or approved by any regulatory body. Commentary is provided to clinicians for educational purposes and should not be interpreted as diagnostic or treatment recommendations. *General treatment suggestions can be found in the Rocky Mountain Analytical Resource Binder.

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