Comprehensive Hormone Insights™

COMPREHENSIVE HORMONE INSIGHTS™
TEST REPORT

Rocky Mountain Analytical

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Rocky Mountain Analytical®
Changing lives, one test at a time

Date of Collection: 2019/02/03
Time of Collection: 11:00AM
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Reported On: 2019/09/11

CHI

Healthcare Professional

Rocky Mountain Analytical
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105 - 32 Royal Vista Drive NW
Calgary, AB T3R0H9

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Patient

Age: 60
Date of Birth:
Gender: Male

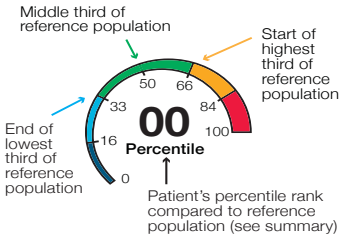
Relevant Medications	Biometrics
	Height (in) : 0
	Weight (lb) : 0
	BMI : 0
	Waist (in) : 0
	Hip (in) : 0

CHI

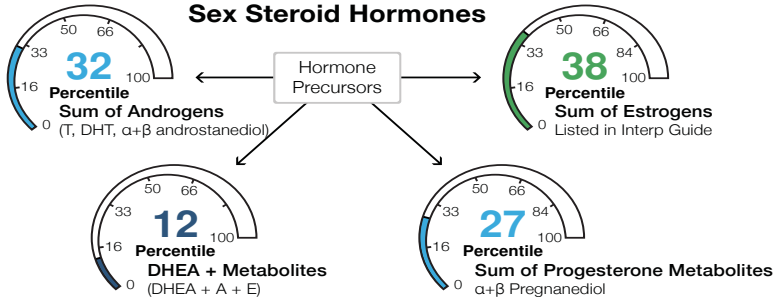
Comprehensive Hormone Insights™

SUMMARY
HMUS01

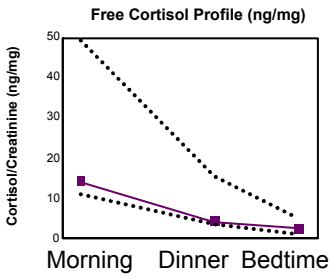
LEGEND: How to read the graphs



Sex Steroid Hormones

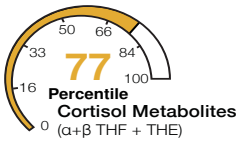


Cortisol

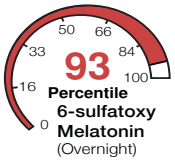


Free cortisol profile is used to assess diurnal cortisol rhythm

Cortisol Metabolites provides a general assessment of adrenal cortisol production

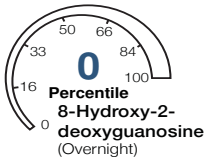


Melatonin

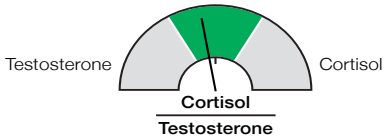


6-sulfatoxymelatonin provides insight into melatonin levels.

Oxidative Stress



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



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

DISPLAYING OF RESULTS AND RATIOS BELOW LIMIT OF REPORTING

When a result is below the reportable limit it will be displayed on the heatmap with grey endcaps. On the bar graphs, in the Result column, the result will be "<XX" where XX is the reportable limit. The percentile will show as "<DET" and the marker will be located at 0. When a result is below its reportable limit it is generally at or below the 10th percentile, i.e. quite low.

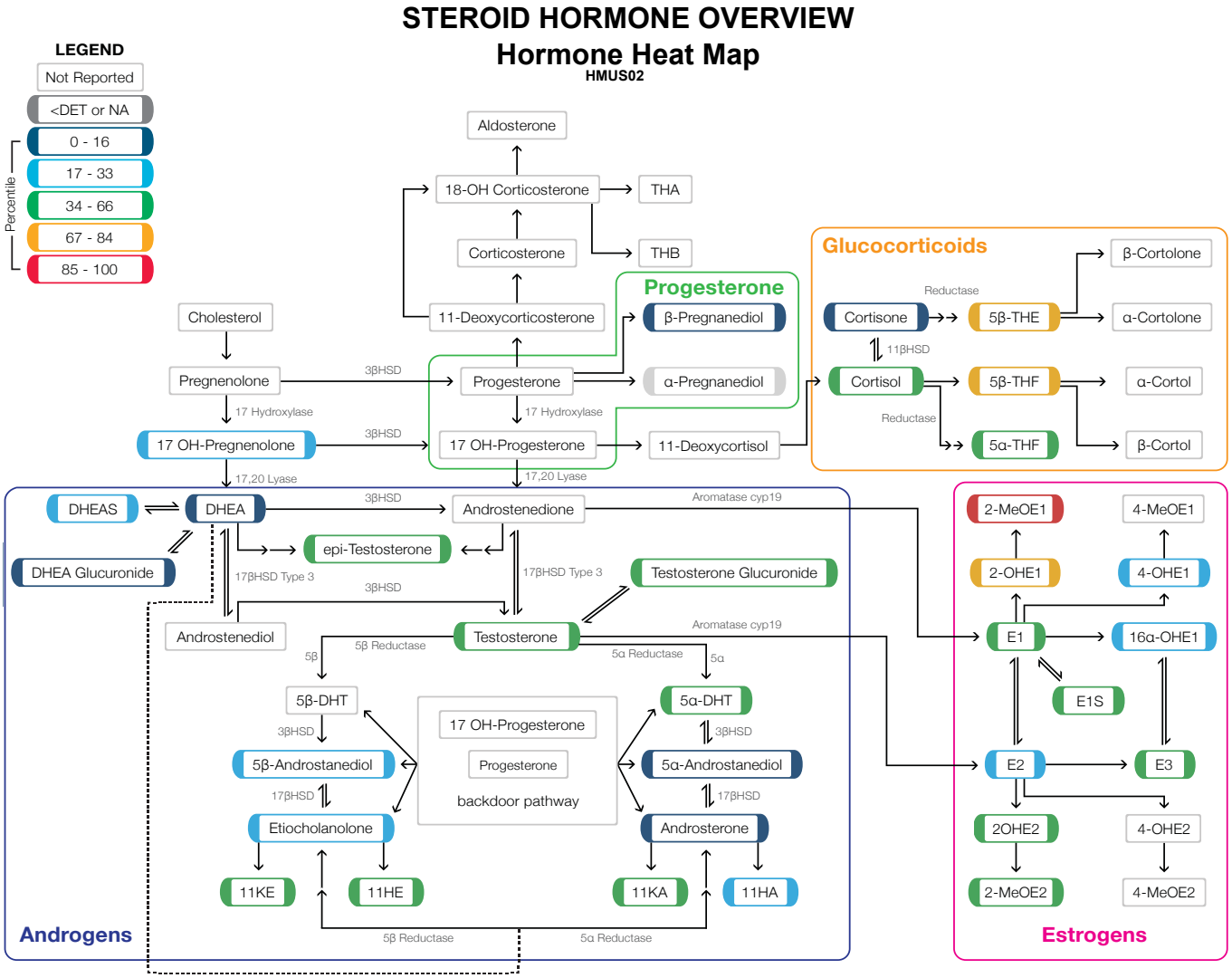
When either the numerator, denominator or both components of a ratio are less than or equal to the reporting limit, the ratio will not be displayed. On heat maps, the small bar graphs will be missing. On larger bar graphs, the markers will be set to zero, no range will be displayed, and the result and the percentile will not be displayed.

COMMENTARY WHEN ANY RESULT IS AVERAGE

When a result lies between the 33rd and 66th percentiles (> 33% and <= 66%) its oval will have green endcaps on the heat maps and the marker will be in the middle green section on bar graphs. In most of these cases, no commentary is offered as the result is more or less average and there is nothing to add.

SYMPTOM INVENTORY WAS LEFT BLANK

The symptom inventory was left blank. In some cases, this may limit the commentary for various of the test results. Collection of symptom information assists in the refinement of future interpretations, as it allows the discovery of correlations between symptoms and metabolite levels.



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

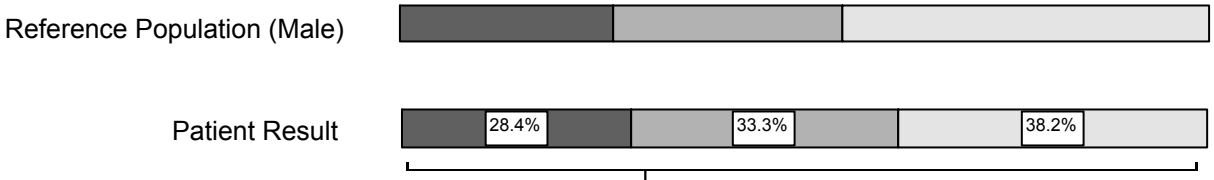
2OHE2: 2-hydroxyestradiol
4OHE2: 4-hydroxyestradiol
16α-OHE1: 16α-hydroxyestrone

CORTISOL & CORTISOL METABOLITES
Hormone Heat Map

HMUS03

CORTISOL CONJUGATION PATTERN

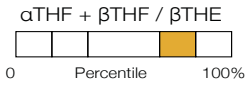
Cortisol (free)	Cortisol sulfate	Cortisol glucuronide
18.2 - 32.8 %	20.7 - 34.7 %	40 - 53.1 %



Cortisol-Cortisone Metabolite Balance

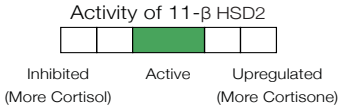
Ratio of αTHF + βTHF / βTHE

The ratio of aTHF+ βTHF over βTHE provides insight into the relative balance of cortisol metabolites over cortisone metabolites.



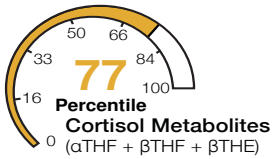
Activity of 11-β HSD2

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.

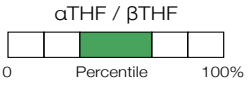


Cortisol Metabolites

Insight into adrenal production of cortisol metabolites.



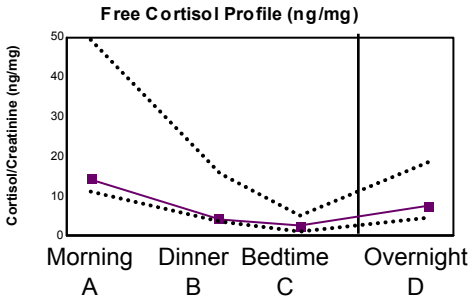
Alpha Reductase Preference



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.

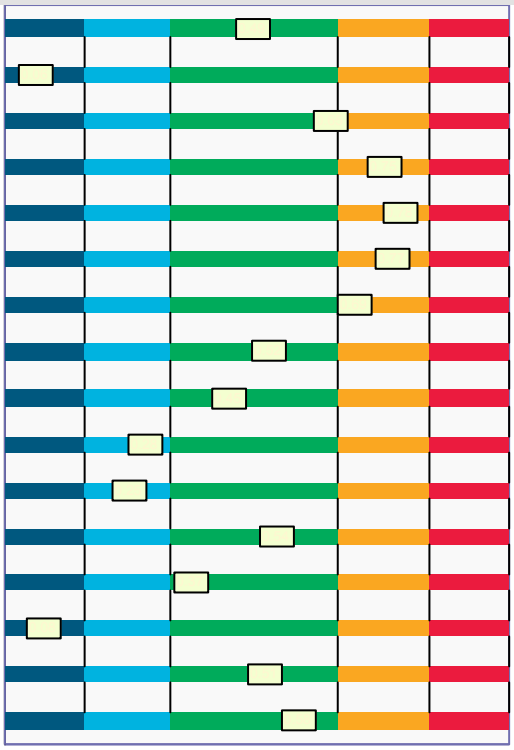
Two ratios are calculated:
- Overnight Cortisol Response (D/C)
- Morning Cortisol Response (A/D)

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)	60	40 - 78	ng/mg		49%	Male
Cortisone (GCMSMS)	44	63 - 120	ng/mg		6.2%	Male
a-Tetrahydrocortisol (aTHF)	360	170 - 430	ng/mg		65%	Male
ß-Tetrahydrocortisol (ßTHF)	1,500	860 - 1,500	ng/mg		75%	Male
ß-Tetrahydrocortisone (ßTHE)	2,300	1,500 - 2,500	ng/mg		78%	Male
aTHF+ßTHF+ßTHE	4,200	2,700 - 4,400	ng/mg		77%	Male
(a-THF + ß-THF)/ß-THE	0.79	0.65 - 0.84			69%	Male
a-THF/ß-THF	0.25	0.16 - 0.36			52%	Male
Cortisol/Testosterone	0.36	0.20 - 0.85			45%	Male
Morning Free Cortisol (Specimen A)	14	11 - 49	ng/mg		28%	Male
Dinnertime Free Cortisol (Specimen B)	4.3	3.6 - 16	ng/mg		25%	Male
Bedtime Free Cortisol (Specimen C)	2.5	1.2 - 5.2	ng/mg		54%	Male
Overnight Free Cortisol (specimen D)	7.6	4.5 - 19	ng/mg		37%	Male
Free Cortisol (pooled specimen)	8.6	10 - 28	ng/mL		7.7%	Male
Free Cortisone (pooled specimen)	45	34 - 58	ng/mL		51%	Male
11-beta HSD2 Activity Ratio	1.2	0.42 - 1.8				All



CORTISOL PREAMBLE

The regulation of cortisol is exceedingly complex, involving multiple deactivation strategies (reduction, conjugation, conversion to cortisone), regeneration via conversion of cortisone back to cortisol in the liver as well as in body fat and muscle, and multiple feedback avenues. Feedback mechanisms include inflammatory markers impinging on the brain and adrenals, ambient light sensing, information gathered by the splanchnic organs and intestines fed back to the brain via the vagus nerve and sensing of blood levels in the hypothalamus and pituitary.

We make our best attempt to rationalize the findings of these cortisol markers and to offer possible interventions that might be helpful. But as always, the clinician must be guided by the clinical presentation, i.e. signs and symptoms of too much or too little cortisol acting in target tissues. Levels measured in blood, saliva and urine must take second place to the clinical picture.

(aTHF + THF + THE) RESULT ELEVATED
The result for the sum: aTHF + THF + THE lies above the 66th percentile, or the result for each metabolite individually lies above the 66th percentile. Collectively, these markers are thought to make up more than half of the metabolites of cortisol and give a good measure of cortisol secretion. Note that the clinical presentation doesn't ride solely on the total amount of cortisol secreted, but on how much free cortisol is "left on the table" to talk to receptors in target tissues. Some patients with elevated cortisol metabolites may feel fine and not complain of high cortisol symptoms nor display signs of high cortisol.

Symptoms of increased activity of cortisol at the tissue receptor level may include weight gain, high blood pressure, insulin-glucose axis imbalance, irritability, sleep disturbances as well as symptoms of antagonism of other hormones, i.e. low testosterone, low progesterone, low estrogen symptoms. At the same time, bear in mind that excess cortisol can drive conversion of androgens to estrogens by upregulating aromatase. Symptoms depend heavily on how much secreted cortisol is left in the form of cortisol. If cortisol secretion is high but most of it is deactivated to cortisone and tetrahydro-cortisone, there will be less adverse impact.

Elevated glucocorticoid metabolites may be seen in a wide range of conditions of cortisol overproduction, including Cushing's Disease, adrenal hyperplasias, adrenal adenomas, pituitary tumors, acute stress, acute illness, depression and hyperthyroidism.

Note also, that elevated glucocorticoids may be a result of supplementation with adrenal extracts or herbs intended to increase the output of the adrenals. Supplementation with progesterone and pregnenolone may elevate cortisol, especially if these hormones are administered orally or sublingually.

Interventions will depend on the clinical presentation, as always.

PREAMBLE: BETA-REDUCTASE VS ALPHA-REDUCTASE

The 5-reductase enzymes are involved in the metabolism of many steroid hormones including cortisol, testosterone, progesterone and androstenedione. 5-alpha reductases are in the SRD enzyme family (SRD5) and 5-beta reductase is in the AKR family (AKR1D1). The main difference between the two enzymes is that AKR1D1 mediates a key step in the synthesis of chenodeoxycholic acid (CDCA), a principal bile acid, whereas the SRD5 enzymes are not active in this domain: both types of reductase are important for cortisol deactivation. Inhibition of both these enzyme systems, especially beta-reductase, cripples the liver's ability to deactivate cortisol.

These reductases are both activated in generalized obesity where urinary excretion of alpha-THF, beta-THF and beta-THE is increased; however, increased secretion of the beta metabolites can also be associated with insulin resistance and high triglycerides (Westerbacka 2003). Increased beta i.e. AKR1D1 activity is associated with increased CDCA. CDCA is inflammatory and left unchecked, eventually manifests with fatty liver (Gong 2016). Elevated CDCA is also associated with cholestasis and biliary obstruction.

Bile acids are structurally similar to cortisol, so if their levels increase enough, they can act as competitive inhibitors of cortisol clearance, further magnifying hepatic fat accumulation and inflammation. AKR1D1 can also be inhibited by Finasteride, a commonly-used 5-alpha inhibitor (Drury 2009). Loss-of-function mutations for AKR1D1 also occur although they are rare and usually present with neonatal jaundice (Chen 2019).

Methylsulfonylmethane or MSM is produced naturally in humans by colonic flora when foods high in sulfur are consumed. MSM is also a well-documented hepatoprotective supplement known to inhibit the inflammasome pathway (Ahn 2015). The unsaturated Omega-3 fatty acids, EPA and DHA, have also been studied in the context of hepatic inflammation (Tillman 2012). Both these approaches might be effective in addressing inflammation induced by elevated CDCA.

Both AKR1D1 and the alpha-reductases are regulated by T3. The activity of both the alpha- and beta-reductase enzymes decreases in hypothyroidism with alpha activity falling off more sharply than beta (Hoshiro 2006). This results in a reduced aTHF/THF ratio in hypothyroidism. (THF should more accurately be written as beta-THF.) Similarly, Hoshiro also saw increases in both alpha- and beta-reductases in hyperthyroidism, with alpha activity increasing more than beta, resulting in an elevated aTHF/THF ratio. He also noted an increase in the ratio of androsterone (alpha reductase product) to etiocholanolone (beta reductase product) in hyperthyroid women compared to euthyroid controls. Skovsted had previously also found that the ratio Androsterone/(Androsterone + Etiocholanolone) increased in hyperthyroidism and diminished in hypothyroidism (Skovsted 1966).

If both of the aTHF/THF and Androsterone/(Androsterone + Etiocholanolone) ratios align in the same direction consideration should be given to reviewing the patient for signs and symptoms of altered thyroid hormone status. If the patient is taking supplemental thyroid hormones (T4 and/or T3) a dose adjustment may be indicated, depending on the clinical picture.

It is difficult to attribute elevated or diminished beta-reductase activity to just one factor; cortisol clearance (11beta-HSD and reduction), thyroid hormone activity, pattern of bile acids, and colonic flora are inextricably intertwined.

RATIO: aTHF/THF RESULT IS NORMAL

This result for this patient's aTHF/THF ratio lies between the 33rd and 66th percentiles. This ratio is more or less normal. There are no significant implications regarding 5-alpha and 5-beta reductases.

(aTHF + bTHF)/THE RESULT IS ELEVATED
The result for this ratio lies above the 66th percentile.

In the past this ratio has been studied as a window into the activity of 11-beta HSD enzymes, particularly in relation to obesity and more extensively in females. However, this ratio is sensitive to various factors including 11-beta HSD type 1 activity (regenerating cortisol from cortisone), 5-alpha reductase activity, 5-beta reductase activity, Phase II hepatic conjugation and conversion to other metabolites such as hydroxycortisol. It can be difficult to correlate this ratio to any single factor. As a research tool it tends to give inconsistent results across the literature for the most part.

An elevated ratio may be seen in obesity and generally means that 11-beta HSD1 is busily converting cortisone to cortisol at a higher than average rate in peripheral adipose tissue, skeletal muscle and in the liver. This may be driven by local inflammation in peripheral adipose tissue.

This ratio has also been seen to correlate to thyroid status, being elevated in hypothyroid patients (Hoshiro 2006).

GLUCURONIDATED CORTISOL FRACTION OF TOTAL CORTISOL IS LOW
The total cortisol result (measured by GC-MSMS 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 within the middle 60% of the respective reference ranges, between the 20th and 80th percentiles. The percentage of total which is cortisol glucuronide lies at or below the 33rd percentile.

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.

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 LOW
The cortisone result lies at or below the 33rd percentile. Circulating cortisone can be depleted by increased conversion to cortisol through upregulation of 11-beta HSD1in the periphery (skeletal muscle/adipose) and in the liver. Factors upregulating this enzyme include supplementation with cortisol (Dube 2015), testosterone (Gambineri 2014), metformin supplementation, and increased peripheral adiposity (Baudrand) as well as inflammatory mediators such as TNF-alpha (Walker 2001, Chapman 2013). 11-beta HSD1 activity is also higher in normal-weight postmenopausal females (Andersson 2009).

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

FLATTENED FREE CORTISOL DAY CURVE
The day curve is flattened. The slope is -0.74 ng/mg creatinine-hour which is low. Flattened curves typically arise due to a blunting of cortisol production overnight and blunting of the rise in cortisol which takes place after waking. The extreme example of this would be adrenal failure. In general, disruption of diurnal rhythm can also occur with an erratic sleep-wake schedule (e.g.shiftwork), poor sleep hygiene and chronic illness.

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 AUC is at or below the 25th percentile, reflecting low or low normal free cortisol output.

The result for the ratio of overnight free cortisol to bedtime cortisol is in the middle tertile indicating that the rise in cortisol overnight is more or less average. This ratio and the ratio of morning cortisol to overnight cortisol will be discussed in a separate comment.

OVERNIGHT CORTISOL RESPONSE IS AVERAGE
The Overnight Cortisol Response or ratio of free cortisol in the overnight (D sample) to free cortisol in the bedtime (C sample) is 3.0 and this result lies between the 33rd and 66th percentiles i.e. quite normal. 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.

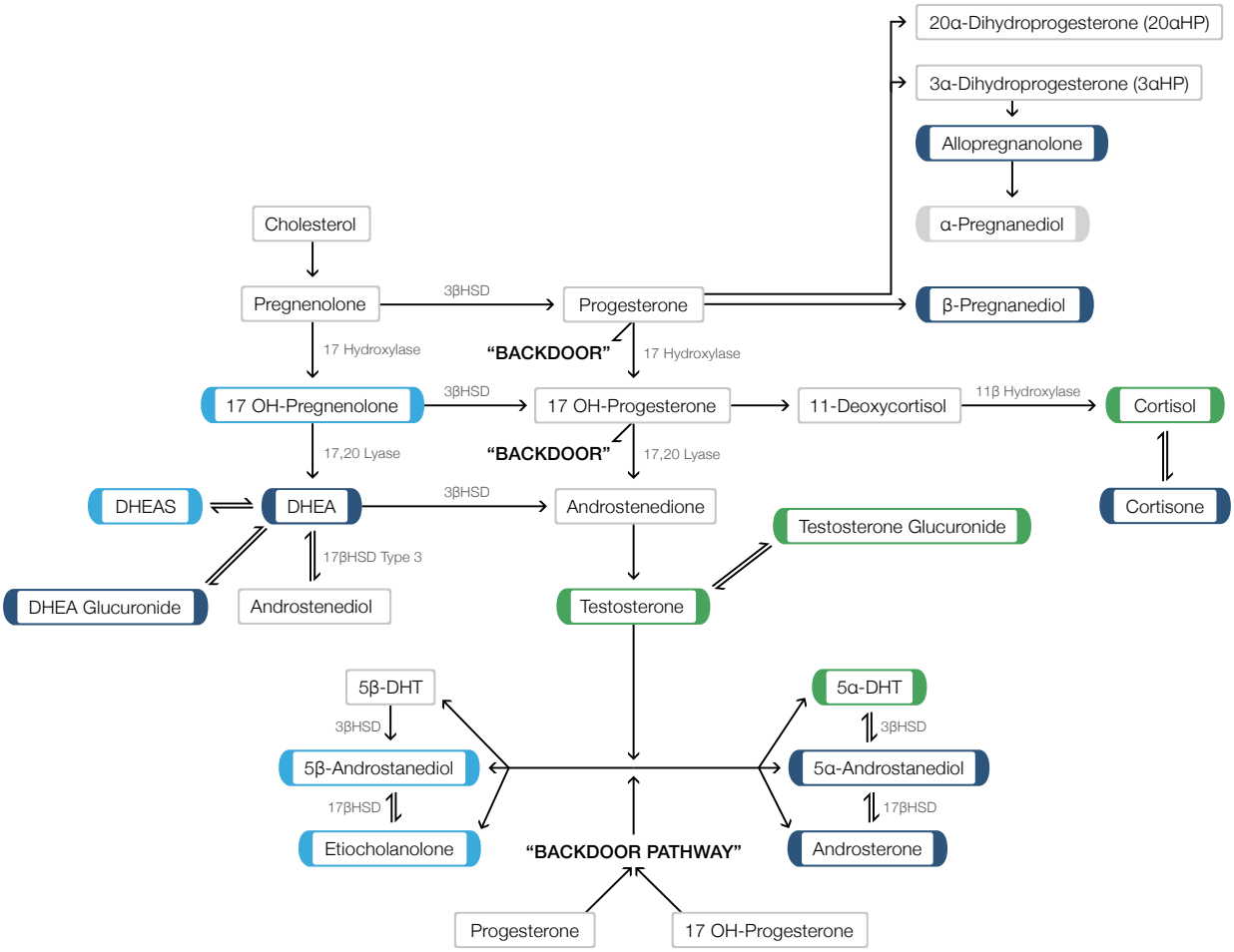
MORNING CORTISOL RESPONSE IS NORMAL
The Morning Cortisol Response (MCR) is defined by RMA as the ratio of free cortisol in the Morning or (A) specimen to free cortisol in the Overnight (D) specimen. The ratio is 1.9 for this patient. This result lies between the 33rd and 66th percentiles for the reference population and is more or less average. 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). The urine MCR discussed here MAY be a surrogate for saliva CAR measurements but additional research is needed.

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		32%	Male
a-Pregnanediol + ß-Pregnanediol	150	110 - 380	ng/mL		27%	Male
ß-Pregnanediol	100	110 - 370	ng/mL		11%	Male
a-Pregnanediol	< 100	0 - 0	ng/mL		<DET	Male
ß-Pregnanediol/a-Pregnanediol	< 0.010	0 - 0	ng/mL		<DET	Male
Allopregnanolone	0.88	11 - 39	ng/mL		3.1%	Male
Total Progesterone (via GCMSMS)	0.39	0.30 - 0.39	ng/mL		86%	Male

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.

17-HYDROXYPREGNENOLONE RESULT IS LOW
The result for 17-hydroxypregnenolone (17HPE) lies at or below the 33rd percentile. Low 17HPE together with a pattern of multiple low levels of hormones across all other classes may be seen when cholesterol is very low. This might occur in an individual on aggressive statin therapy. 17-hydroxypregnenolone also decreases with age.

Note that steroidogenesis in general depends on an adequate amount of T3 in mitochondria, an adequate supply of cholesterol, and adequate glutathione stores, as well as an absence of barriers to hormone synthesis. All these factors should be considered in the face of low levels of multiple steroid hormones.

17-hydroxypregnenolone declines with age and it is higher in males compared to females. For reference, in men the average result as a function of age is as follows:
<30 years: 5.2 ng/mL
31-50 years: 3.0 ng/mL
>50 years: 1.4 ng/mL

BETA-PREGNANEDIOL RESULT IS LOW
The result for beta-pregnanediol, the major metabolite of progesterone, ranks equal to or below the 33rd percentile. In males progesterone comes from the adrenal glands. Low beta-pregnanediol in males is associated with reduced adrenal output of progesterone.

ALLOPREGNANOLONE RESULT IS LOW
The result for allopregnanolone lies at or below the 33rd percentile.

Allopregnanolone arises from progesterone. In our database, allopregnanolone was readily detected in males, cycling women in the follicular phase and postmenopausal women. It may be secreted directly by the adrenal glands to some extent or may arise from progesterone of adrenal origin. Either way, low allopregnanolone may therefore reflect an adrenal issue.

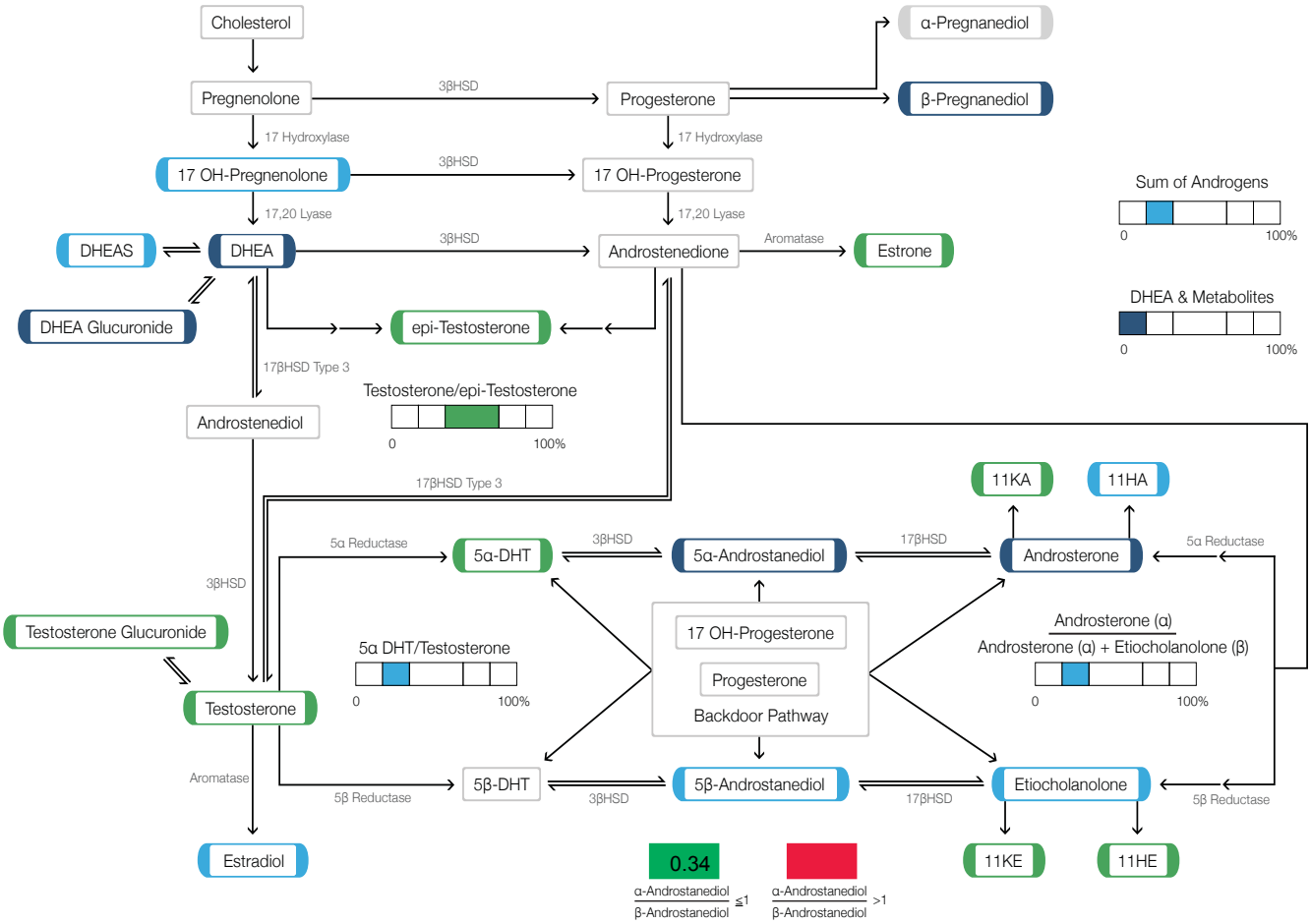
Individuals with low allopregnanolone might have difficulty sleeping and may struggle with depression (Eser 2007, Slopein 2018). Low allopregnanolone in women may be seen when endogenous ovarian progesterone is diminished but also when 5-alpha reductase activity is impaired.

In general, 5-alpha reductase impairment is seen in low-T3 states, PCOS, diabetes. Impairment can arise via agents which inhibit 5-alpha reductase including pharmaceuticals, nutrients and natural products. Loss-of-function reductase enzyme SNPs are also noted, but not common.

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.

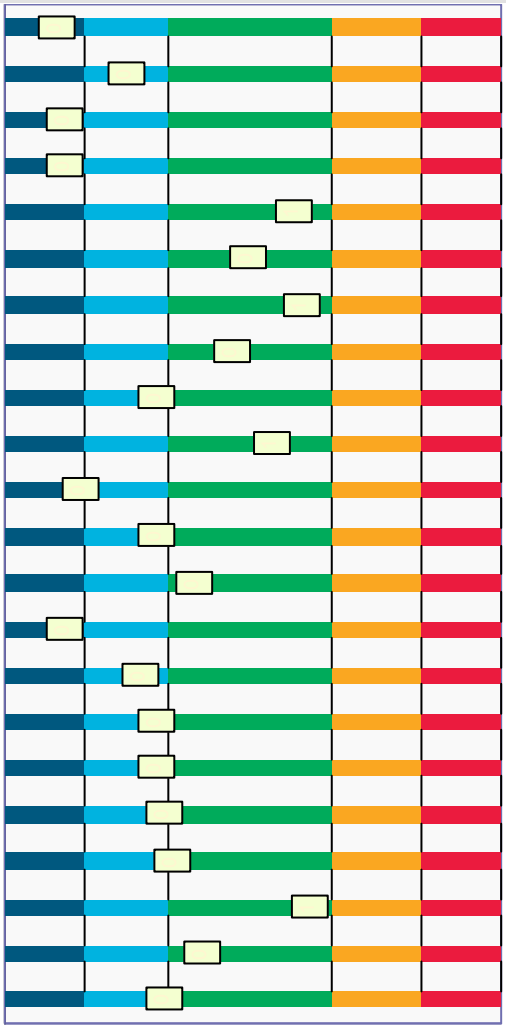
ANDROGENS/17-KETOSTEROIDS
Hormone Heat Map
HMUS05



ANDROGENS / 17 KETOSTEROIDS

ANDROGEN RATIOS AND SUMS

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%ile	Range Applied
DHEA (free and conjugated)	190	250 - 1,300	ng/mL		11%	Male
DHEA sulphate (DHEAS) via LCMSMS	130	110 - 1,500	ng/mL		25%	Male
DHEA glucuronide via LCMSMS	150	170 - 390	ng/mL		12%	Male
DHEA&metabolites (DHEA+AND+ETIO)	1,800	2,300 - 5,000	ng/mL		12%	Male
Testosterone (T)	33	6.7 - 60	ng/mL		58%	Male
Epi-testosterone (Epi-T)	41	26 - 93	ng/mL		49%	Male
Testosterone/Epi-Testosterone (T/Epi-T)	0.82	0.12 - 1.5			60%	Male
a-Dihydrotestosterone (aDHT)	5.6	3.3 - 11	ng/mL		46%	Male
a-DHT/Testosterone	0.17	0.14 - 0.55			31%	Male
Testosterone glucuronide via LCMSMS	20	3.0 - 45	ng/mL		54%	Male
a-Androstanediol	22	30 - 69	ng/mL		15%	Male
ß-Androstanediol	64	41 - 200	ng/mL		31%	Male
a-Androstanediol/ß-Androstanediol	0.34	0.24 - 0.94			39%	Male
Androsterone (AND)	720	800 - 2,100	ng/mL		12%	Male
Etiocholanolone (ETIO)	880	830 - 1,800	ng/mL		28%	Male
Androsterone Excretion Ratio	0.45	0.42 - 0.64			31%	Male
AND/ETIO	0.81	0.72 - 1.8			31%	Male
Androgen sum (T,DHT,androstanediols)	120	98 - 310	ng/mL		32%	Male
11-Ketoetiocholanolone (11KE)	110	69 - 330	ng/mL		34%	Male
11-Hydroxyetiocholanolone (11HE)	220	34 - 350	ng/mL		62%	Male
11-Ketoandrosterone (11KA)	12	9.3 - 23	ng/mL		40%	Male
11-Hydroxyandrosterone (11HA)	380	320 - 650	ng/mL		32%	Male



TOTAL DHEA RESULT IS LOW

The resultfor hydrolyzed DHEA lies at or below the 33rd percentile and this patient is not supplementing with DHEA, 7-keto DHEA or pregnenolone. This finding may imply reduced production of DHEA from the adrenal glands especially if it is coupled with low cortisol production.

Low or low normal levels of total DHEA in men may be associated with chronic stress and chronic illness. Both rheumatoid arthritis and hypothyroidism are also associated with low total DHEA. Note that the oldest patients in our reference population were approximately 70 years old. Total DHEA declines with age; patients older than 70 years may very well have a "low" reading when they are normal for age.

Symptoms and conditions associated with low total DHEA may include decreased stamina and libido, feeling "burned out", dry skin, thinning skin, thinning pubic hair, muscle and bone loss, declining cognitive performance (slower processing speed and memory problems), insulin resistance and low Growth Hormone.

RESULT FOR SUM OF ANDROGENS IS LOW
The results for testosterone and its direct metabolites DHT, alpha- and beta-androstanediol lie at or below the 33rd percentile, or their sum lies at or below the 33rd percentile.

These findings may be associated with various symptoms including fatigue, low sex drive, prostate complaints (frequent urination, urgency), diminished erections, shrinkage of genitalia, depression, "grumpiness", loss of sense of humor and lack of enthusiasm for trying new things. Not all these symptoms are present in every individual with low testosterone, and this list of symptoms is by no means exhaustive.

Low DHEA may give rise to low testosterone. Testosterone declines with age at a rate of approximately 1% per year after the age of 35 to 40. A wide range of organic environmental pollutants have been implicated in low testosterone due to inhibition of the 3-beta hydroxysteroid dehydrogenase enzyme which converts DHEA into testosterone and alpha-DHT into alpha-androstanendiol.

Low DHT may arise from impairment of 5-alpha reductase. In general, 5-alpha reductase impairment is seen in low-T3 states, PCOS, diabetes. Impairment can arise via agents which inhibit 5-alpha reductase including pharmaceuticals, nutrients and natural products. Loss-of-function reductase enzyme SNPs are also noted, but not common.

RESULT FOR DHEA AND PRINCIPAL METABOLITES IS LOW
The result for DHEA and its chief metabolites (androsterone, etiocholanolone) lies at or below the 33rd percentile. This supports the notion that overall DHEA production is actually low, despite what is left on the table as DHEA, DHEAS and DHEA glucuronide.

This is particularly important for older men and women. As levels of estrogens and testosterone decline with age, DHEA can serve as a modest backup system, as it can be converted into both these hormone classes.

ALPHA-DIHYDROTESTOSTERONE RESULT IS NORMAL
The result for 5-alpha DHT lies between the 33rd and 66th percentiles. An average level of testosterone tends to yield average 5-alpha DHT when the activity of 5-alpha reductase is more or less average.

COMMENT REGARDING (ALPHA DHT)/TESTOSTERONE
The ratio alpha DHT/Testosterone doesn't necessarily track the component hormones i.e. the results for alpha-DHT and testosterone can both be low or both be high yet their ratio may still be normal. The ratio simply looks at the relative amounts of the two hormones. It would be redundant to comment on a low or high ratio when comments have already been made regarding low or high alpha DHT and low or high testosterone. It would also add unnecessary length to the interpretation. The reader should be able to work through the implications of low or high aDHT/T ratios by considering aDHT and testosterone results individually.

RATIO alpha-ANDROSTANEDIOL/beta-ANDROSTANEDIOL LESS THAN/EQUAL TO 1
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; hence, this is a normal finding.

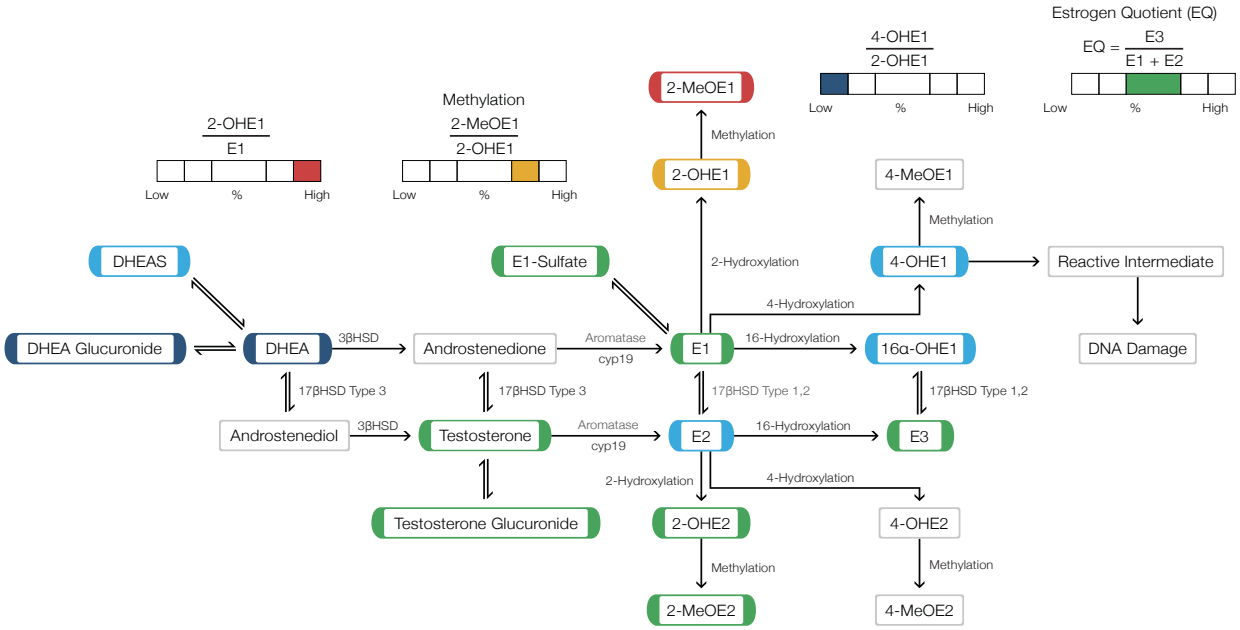
ANDROSTERONE EXCRETION RATIO IS LOW

The Androsterone excretion ratio is Androsterone/(Androsterone + Etiocholanolone). The result for this ratio lies at or below the 33rd percentile. Skovsted noted that this ratio is low in hypothyroid patients (Skovsted 1966). If the ratio is well below the 33rd percentile 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.

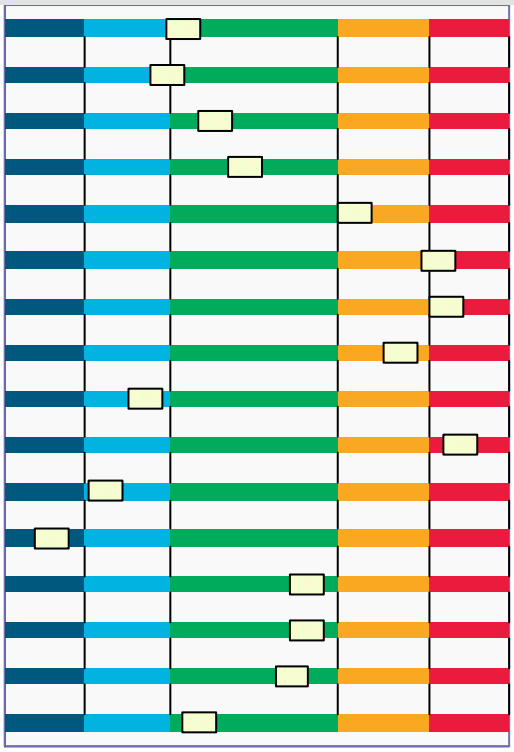
Anything which elevates etiocholanolone, including testosterone, DHEA or progesterone supplementation, may result in a lower ratio without necessarily indicting tissue activity of thyroid hormones. This metabolite may be elevated due to upregulation of the activity of AKR1D1: the beta-reductase enzyme. 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 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)	3.1	2.6 - 5.4	ng/mL	35%	Male
Estradiol (E2)	0.83	0.70 - 2.0	ng/mL	32%	Male
Estriol (E3)	3.6	2.1 - 8.5	ng/mL	42%	Male
E3/(E1 + E2)	0.91	0.51 - 1.6		47%	Male
2-Hydroxyestrone (2-OHE1)	2.7	0.82 - 3.5	ng/mL	69%	Male
2-OHE1/E1	0.86	0.25 - 0.72	ng/mL	86%	Male
2-Methoxyestrone (2-MeOE1)	1.6	0.36 - 1.4	ng/mL	88%	Male
2-MeOE1/2-OHE1	0.59	0.23 - 0.60		78%	Male
16a-Hydroxyestrone (16a-OHE1)	0.71	0.58 - 2.6	ng/mL	28%	Male
2-OHE1/16a-OHE1	3.7	0.66 - 3.2		90%	Male
4-Hydroxyestrone (4-OHE1)	0.37	0.37 - 0.94	ng/mL	20%	Male
4-OHE1/2-OHE1	0.14	0.21 - 0.52		9.2%	Male
2-Hydroxyestradiol (2-OHE2)	0.39	0.075 - 0.67	ng/mL	60%	Male
2-Methoxyestradiol (2-MeOE2)	1.5	0.21 - 3.7	ng/mL	60%	Male
Estrone sulphate (E1-Sulphate or E1S)	0.64	0.43 - 1.2	ng/mL	57%	Male
Sum of Estrogens	13	10 - 26	ng/mL	38%	Male



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

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%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	0% 16% 33% 66% 84% 100%	%ile	Range Applied
6-Sulfatoxymelatonin	340	4.4 - 14	ng/mg		93%	Male

CREATININE

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%ile	Range Applied
Pooled Creatinine	0.93	1.1 - 2.2	mg/mL		12%	Male
Overnight Creatinine (D)	0.38	0.96 - 2.6	mg/mL		4.6%	Male
Morning Creatinine (A)	1.5	0.98 - 2.1	mg/mL		48%	Male
Dinnertime Creatinine (B)	0.76	0.59 - 2.0	mg/mL		29%	Male
Bedtime Creatinine (C)	1.1	0.81 - 2.4	mg/mL		29%	Male

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

Analyte	Result	Range	Units	0% 16% 33% 66% 84% 100%	%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)	1.00	0.89 - 1.0	ng/mL		69%	Male
Total Progesterone (via GCMSMS)	0.39	0.30 - 0.39	ng/mL		86%	Male

RESULT FOR SUM OF ESTROGENS IS AVERAGE
The result for the sum of estrogens lies between the 33rd and 66th percentiles. This doesn't preclude the possibility that results for some of the individual estrogens are outside of the middle tertile.

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.

The role of 2OHE1 in men's health has not been explored so this ratio is offered for information and research purposes only

Interventions generally seen to be beneficial for breast health in women include: exercise, progesterone, T3, cruciferous vegetables, iodine and high fibre intake. These interventions push estrogens down the 2-hydroxylation pathway.

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.
to 16-hydroxyestrone ratio predictive for breast cancer? Int J Womens Health 2011;3:37-51.

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.

RATIO: 4OHE1/2OHE1 IN MALES
Just as the ratio 2OHE1/16OHE1 has been considered as a possible marker informing on future risk of breast cancer in women, various researchers have postulated that the 4OHE1/2OHE1 ratio might also inform on the risk of estrogen-sensitive cancer, since 4OHE1 is known to be much more genotoxic than 16 OHE1. 4OHE1 has been studied in the context of breast cancer and there is some literature pertaining to males and prostate disease but as of 2019, the utility of the ratio 4OHE1/2OHE1 for males is not known and remains speculative at best.

RATIO: 4OHE1/2OHE1 RESULT IS LOW
Here the result for the ratio lies at or below the 33rd percentile, indicating that there is less formation of 4OHE1 relative to 2OHE1. Even so, if the two estrone metabolites making up the ratio are somewhat elevated (consistent with high overall estrogen production) consideration should be given to decreasing overall estrogens by attention to fibre intake, enterohepatic recirculation and factors which may be upregulating aromatase and also driving high androgens.

ESTRADIOL-DERIVED METHYLATION RATIO
We don't report the ratio 2-methoxyestradiol/2-hydroxyestradiol because this ratio is less reliable for the estradiol metabolites due to sensitivity considerations. Nevertheless, the same pattern seen for the estrone metabolites may also be seen for the estradiol metabolites. Use caution in trying to correlate the estrone and estradiol methylation ratios.

COMMENT ON RATIO 2-METHOXYESTROGENS / 2-HYDROXYESTROGENS
Some 2-hydroxyestrogen is cleared by conversion to the methoxylated product, 2-methoxyestrogen. Here, it’s possible to consider ratios for both methoxyestrone and methoxyestradiol as all components are within detection range. The methoxyestradiol/hydroxyestradiol ratio is not tabulated.

The estrone-derived ratio is valid. An average ratio probably doesn’t warrant action. The meaning of an elevated ratio is unclear.

A low methylation ratio may indicate a need for support of methylation pathways, since there is relatively less of the methylated product, relative to the precursors. A proportion of these patients 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.

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 MARKEDLY ELEVATED
The principal metabolite of melatonin (6-sulfatoxymelatonin) is elevated into the range seen when melatonin is supplemented. (If the patient is supplementing with melatonin, the result may very well be in the hundreds or thousands of ng/mg.) This reflects immediate conversion of oral /sublingual melatonin to 6-sulfatoxymelatonin. It does NOT reflect excessive melatonin dosing.

Melatonin is instrumental in maintaining proper diurnal rhythm/sleep wake cycling. There is evidence that melatonin has profound influence on immune function in general and specifically may be protective against estrogen-sensitive cancers. Melatonin is also a neuroprotective brain antioxidant.

ONE OR MORE CREATININE RESULTS IN A, B, C, D SAMPLES IS/AREMARKEDLY LOW
Here one or more of the results for creatinine in the four samples A,B,C,D is/are at or below the 16th percentile. Since creatinine is a byproduct of muscle breakdown/turnover, low urine creatinine can reflect a lower than average muscle mass. This would generally show in more than one specimen. Low urine creatinine may also be indicative of water loading, as this would dilute the attendant specimen(s) accordingly.

POOLED CREATININE RESULT IS LOW
The result for pooled creatinine lies at or below the 33rd percentile.

Since creatinine is a byproduct of muscle breakdown/turnover, low urine creatinine can reflect low muscle mass. Low muscle mass, in turn, can be due to low androgens, hypothyroidism, low protein intake and deconditioning. Low urine creatinine may also be indicative of excessive water intake. Finally, kidney disease may also result in low urine creatinine.

Clinical correlation is advised when interpreting this finding.

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.

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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