Accession # 00216506
Female Sample Report
123 A Street
Sometown, CA 90266

Sex Hormones and Metabolites

Last Menstrual Period:
2015-10-12

Ordering Physician:
Dr. Dutch

DOB: 1976-01-01
Age: 39
Gender: Female

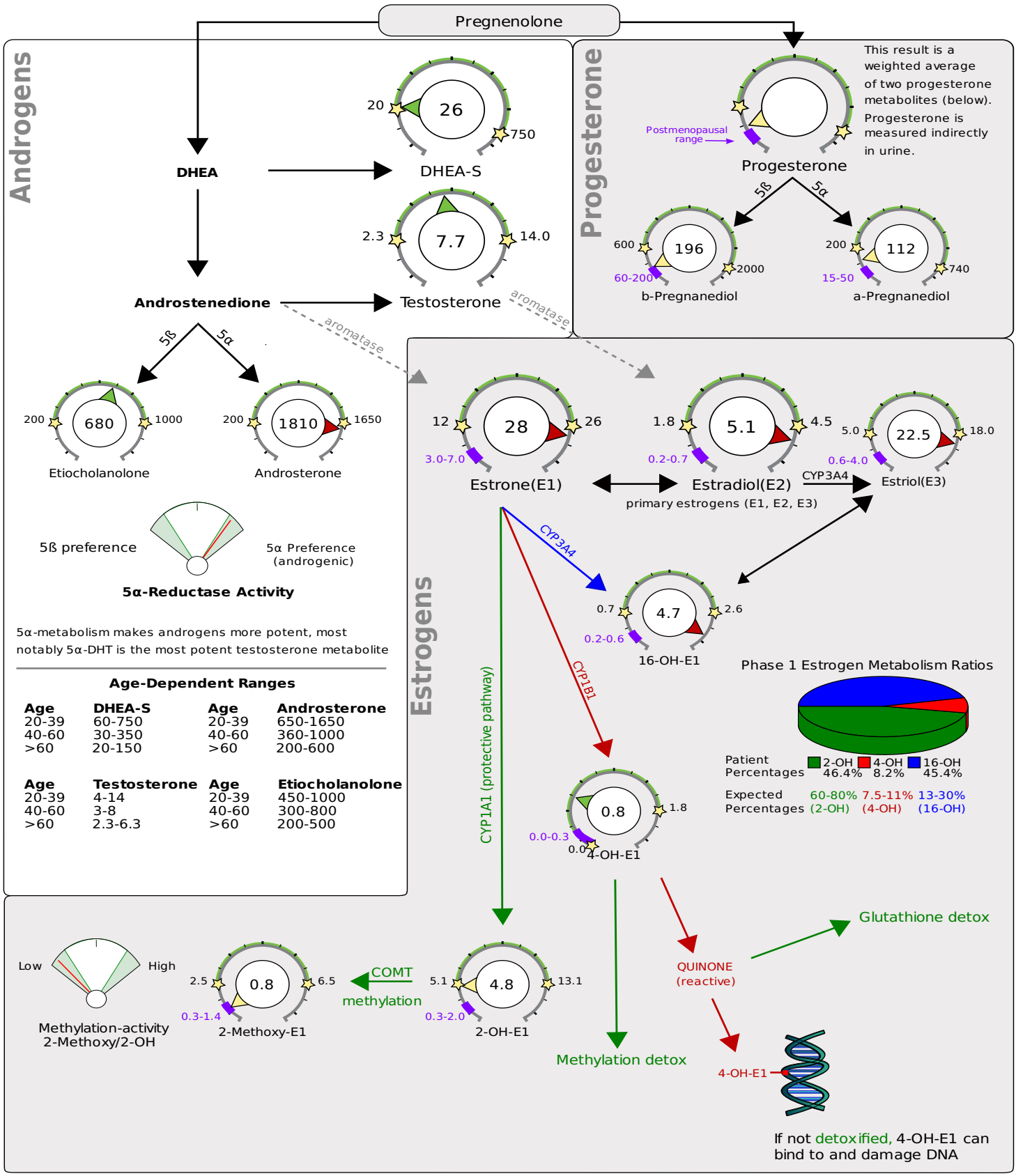
Collection Times:
2015-11-10 04:00AM
2015-11-10 06:00AM
2015-11-10 03:00PM
2015-11-10 09:00PM

Test		Result	Units	Luteal* Range	Postmenopausal Range
Progesterone Metabolites (Urine)					
b-Pregnanediol	Below luteal range	196.0	ng/mg	600 - 2000	60-200
a-Pregnanediol	Below luteal range	112.0	ng/mg	200 - 740	15-50
Estrogens and Metabolites (Urine)					
Estrone(E1)	Above luteal range	28.2	ng/mg	12 - 26	3.0-7.0
Estradiol(E2)	Above luteal range	5.1	ng/mg	1.8 - 4.5	0.2-0.7
Estriol(E3)	Above luteal range	22.5	ng/mg	5 - 18	0.6-4.0
2-OH-E1	Below luteal range	4.8	ng/mg	5.1 - 13.1	0.3-2.0
4-OH-E1	Within luteal range	0.8	ng/mg	0 - 1.8	0-0.3
16-OH-E1	Above luteal range	4.7	ng/mg	0.7 - 2.6	0.2-0.6
2-Methoxy-E1	Below luteal range	0.8	ng/mg	2.5 - 6.5	0.3-1.4
2-OH-E2	Low end of luteal range	0.19	ng/mg	0 - 1.2	0-0.3
4-OH-E2	Within luteal range	0.30	ng/mg	0 - 0.5	0-0.1
2-Methoxy-E2	Within luteal range	0.5	ng/mg	0 - 0.7	0-0.4
Androgens and Metabolites (Urine)					
DHEA-S	Low end of range	26.0	ng/mg	20 - 750	
Androsterone	Above range	1810.0	ng/mg	200 - 1650	
Etiocholanolone	Within range	680.0	ng/mg	200 - 1000	
Testosterone	Within range	7.7	ng/mg	2.3 - 14	
5a-DHT	Above range	7.2	ng/mg	0 - 6.6	
5a-Androstanediol	Above range	42.0	ng/mg	12 - 30	
5b-Androstanediol	Within range	32.0	ng/mg	20 - 75	
Epi-Testosterone	Within range	8.8	ng/mg	2.3 - 14	

*the Luteal Range is the premenopausal range. When patients are taking oral progesterone this range for progesterone metabolites is not luteal and reflects the higher levels expected when patients take oral progesterone. This test is intended to be taken in the luteal phase of the menstrual cycle (days 19-22 of a 28 day cycle) for premenopausal women. The ranges in the table below may be used when samples are taken during the first few days (follicular) of the cycle, during ovulation (days 11-14) or when patients are on oral progesterone. See the following pages for age-dependent ranges for androgen metabolites.

Additional Normal Ranges	Follicular	Ovulatory	Oral Pg (100mg)
b-Pregnanediol	100-300	100-300	2000-9000
a-Pregnanediol	25-100	25-100	580-3000
Estrone (E1)	4.0-12.0	22-68	N/A
Estradiol (E2)	1.0-2.0	4.0-12.0	N/A

Hormone metabolite results from the previous page are presented here as they are found in the steroid cascade. See the Provider Comments for more information on how to read the results.



Provider Notes

How to read the DUTCH report

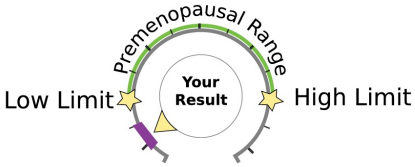
The graphic dutch dials in this report are intended for quick and easy evaluation of which hormones are out of range. Results below the left star are shaded yellow and are below range (left). Results between the stars and shaded green are within the reference range (middle). Results beyond the second star and shaded red are above the reference range (right). Some of these hormones also change with age, and the age-dependent ranges provided should also be considered.

Low Example

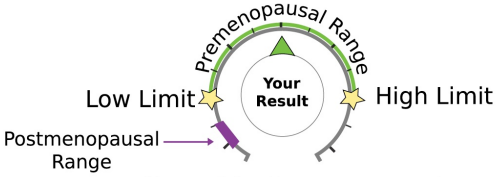
Normal Example

High Example

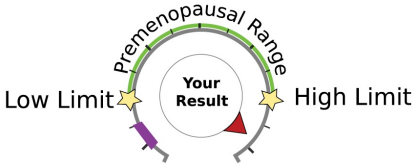
For female reproductive hormones, a purple band is present on the dutch dials. This band represents the expected levels (reference range) for postmenopausal (or non-cycling) women.



Low for Premenopausal
Normal for Postmenopausal

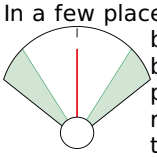


Normal for Premenopausal
High for Postmenopausal



High for Premenopausal
High for Postmenopausal

In a few places on the graphical pages, you will see fan-style gauges. For sex hormones, you will see one for the balance between 5a/5b metabolism as well as methylation. For adrenal hormones, you will see one to represent the balance between cortisol and cortisone metabolites. These indexes simply look at the ratio of hormones for a preference. An average or "normal" ratio between the two metabolites (or groups of metabolites) will give a result in the middle (as shown here). If the ratio between the metabolites measured is "low" the gauge will lean to the left and similarly to the right if the ratio is higher than normal.



Patient or Sample Comments

Throughout the provider comments you may find some comments specific to your situation or results. These comments will be found in this section or within another section as appropriate. Comments in other sections that are specific to your case will be in **bold**.

The following video link(s) may help those new to dutch testing to understand the results. If you only have a hardcopy of the results, the video names can be easily found in our video library at www.DutchTest.com. Be aware that our reporting format has recently undergone some cosmetic changes, so the results on the video may look slightly different. These results and videos are NOT intended to diagnose or treat specific disease states.

The following video may assist with the interpretation of the Progesterone and Estrogen results: Estrogen tutorial video

This video may assist with the interpretation of the Androgen results: Androgen tutorial video

The patient reports regular menstrual cycles.

The patient reported symptoms of excess estrogen. This can be caused by excess estrogen or progesterone deficiency. Results should be carefully reviewed. We do not report a progesterone to estrogen ratio. However, you can investigate this issue by looking at the relative level of these two hormones on their respective gauges.

The patient reported significant symptoms of excess androgen levels.

Progesterone Metabolism

The primary role of progesterone is to balance the strong effects of estrogen. Progesterone metabolites are measured and reflect progesterone levels well because very little progesterone is found in urine, so b-Pregnanediol is typically used as a surrogate marker because it is the most abundant metabolite, but we also test the corresponding a-pregnanediol. The average of the two metabolites is reported for progesterone. If levels are in the lower part of the reference range compared to estrogen levels, symptoms of too much estrogen may occur.
When ordering the DUTCH Complete, you will see Progesterone Serum Equivalent on the summary page 1. The urine metabolites of progesterone have been proven to correlate strongly enough to serum progesterone to provide this value. The correlation is the strongest for values within the premenopausal luteal range. Urine metabolites can at times result in somewhat higher serum equivalent results in the postmenopausal range. For this reason the postmenopausal Serum

Equivalent range is slightly higher than typical serum ranges. NOTE: If progesterone is taken orally (also with sublingual), these metabolites are elevated from gut metabolism and results do NOT accurately reflect serum levels.

Estrogen Metabolism

When evaluating estrogen levels, it is important to assess the following:

- **The status (low, normal or high?) of estrogen production:**

Levels of the primary ovarian product, estradiol (the strongest estrogen), as well as "total estrogens" may be considered. For women not on HRT, consider the appropriate range (premenopausal or postmenopausal).

- **Phase I Metabolism:**

Estrogen is metabolized (primarily by the liver) down three phase I pathways. The 2-OH pathway is considered the safest because of the anti-cancer properties of 2-OH metabolites. Conversely, the 4-OH pathway is considered the most genotoxic as its metabolites can create reactive products that damage DNA. The third pathway, 16-OH creates the most estrogenic of the metabolites (although still considerably less estrogenic than estradiol) - 16-OH-E1. If overall estrogen levels are high, production of 16-OH-E1 may exacerbate high estrogen symptoms. Similarly, a woman with very low levels of estrogens, may have less low estrogen symptoms if 16-OH metabolism is preferred. For example Armamento-Villareal showed that a higher 2-OH-E1/16-OH-E1 ratio correlated to bone loss (a low estrogen symptom). Estriol is thought of as a safer (weaker) estrogen metabolite, but it is important to remember that estriol is actually 16-OH-E2, so generally patients that make a lot of the potentially protective/weak estriol may also make a lot of the estrogenic 16-OH-E1.
When evaluating phase I metabolism, it may be important to look at the ratios of the three metabolites to see which pathways are preferred relative to one another. It may also be important to compare these metabolites to the levels of the parent hormones (E1, E2). If the ratios of the three metabolites are favorable but overall levels of metabolites are much lower than E1 and E2, this may imply sluggish phase I clearance of estrogens, which can contribute to high levels of E1 and E2. Similarly, patients with excessive phase I metabolism may have low E1 and E2 levels because of high rates of clearance (as opposed to simply not making a lot of estrogen).
The pie chart will assist you in comparing the three pathway options of phase I metabolism compared to what is "normal." 2-OH metabolism can be increased by using products containing D.I.M. or I-3-C. These compounds are found (or created from) in cruciferous vegetables and are known for promoting this pathway.

Patients typically metabolize a much higher percentage of their estrogens down the more protective 2-OH pathway in phase 1 detoxification. Diindolylmethane (DIM) or Indole-3-Carbinol containing products can help move estrogens more efficiently down this pathway. Be aware that this typically lowers most of the other estrogens, including E1 and E2 as well. If the patients are taking or considering hormone replacement therapy, these products may be considered but a higher dose of estrogen may be needed for the same clinical effect if taken at the same time.

- **Methylation (part of phase II metabolism) of estrogens:**

After phase I metabolism, both 4-OH and 2-OH (not 16-OH) estrogens can be deactivated and eliminated by methylation. The methylation-activity index shows the patient's ratio of 2-Methoxy-E1 / 2-OH-E1 compared to what is expected. Low methylation can be caused by low levels of nutrients needed for methylation and/or genetic abnormalities (COMT, MTHFR). The COMT enzyme responsible for methylation requires magnesium and methyl donors. Deficiencies in folate or vitamin B6 or B12 can cause low levels of methyl donors. MTHFR genetic defects can make it more difficult for patients to make sufficient methyl donors. Genetic defects in COMT can make methylation poor even in the presence of adequate methyl donors.

Androgen Metabolism

When evaluating androgen levels, it is important to assess the following:

- **The status (low, normal or high?) of DHEA:**

DHEA and androstenedione are made almost exclusively by the adrenal gland (although a smaller amount is made in the ovaries). These hormones appear in urine as DHEA-S (DHEA-Sulfate), androsterone and etiocholanolone. The best way to assess the total production of DHEA is to add up these three metabolites. This total can be seen on the first page of the DUTCH Complete (and DUTCH Plus). DHEA production decreases quite significantly with age. Age-dependent ranges can be seen on the graphical page of results.

The Total DHEA Production (page 1) was about 2,516ng/mg which is within the overall range and also within the age-dependent range for this patient. This implies that the adrenal glands are producing appropriate DHEA levels.

Because inflammation blocks DHEA being converted to DHEAS, consider inflammation as a potential part of the overall clinical picture when DHEAS is significantly lower than the downstream metabolites of DHEA (Androsterone, Etiocholanolone) as seen in this case. A sulfur deficiency can also lead to adequate androgens but deficient DHEA-S.

- **The status (low, normal or high?) of testosterone:**

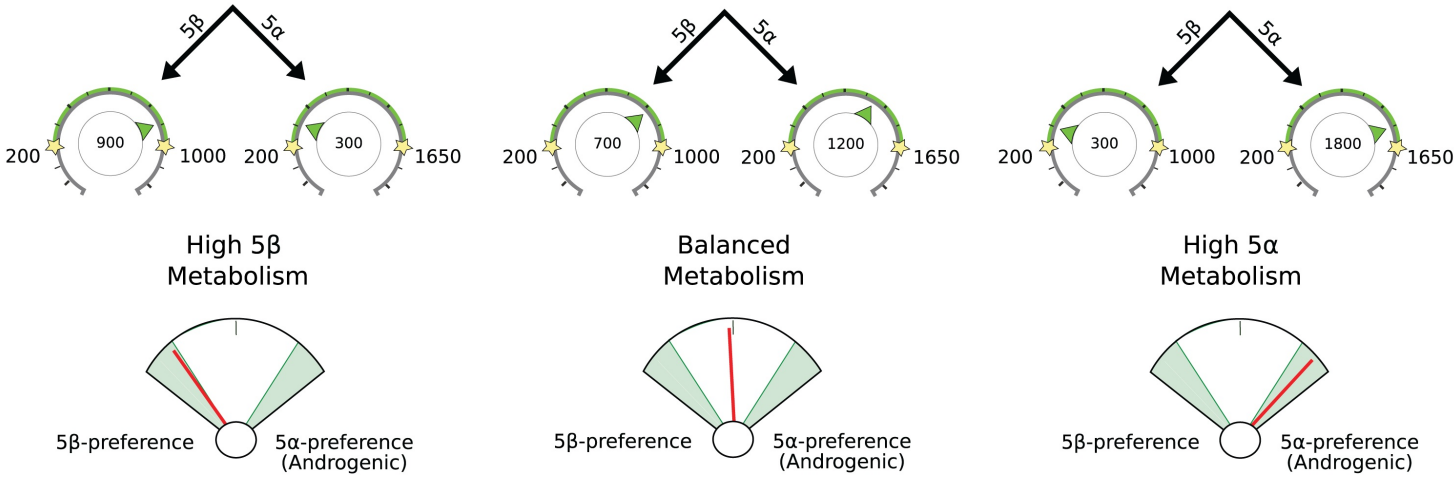
Females make most of their DHEA in the adrenal gland and a fraction of that DHEA trickles down metabolically to testosterone. For premenopausal women, some testosterone is also made by the ovaries. Levels of testosterone do drop somewhat with age, but not to the degree that DHEA decreases.

Testosterone levels for this patient were approximately 7.7ng/mg, which is within range. If symptoms potentially related to high or low testosterone exist, you may also want to carefully evaluate 5a-metabolism (see below). You may also want to evaluate testosterone's downstream metabolites, 5a-androstanediol and 5b-androstanediol. These two metabolites generally parallel testosterone production, although they can also be generated from DHEA without going through testosterone.

- **The metabolic preference for the 5a (5-alpha) or 5b (5-beta) pathway:**

5a-reductase converts testosterone into 5a-DHT (DHT), which is even more potent (~3x) than testosterone. High levels of DHT can lead to symptoms associated with too much testosterone. Metabolites created down the 5b-pathway are significantly less androgenic than their 5a counterparts. In the examples below, the example on the left shows a patient with 5b-metabolism preference. A patient with a pattern like the example on the right may have high androgen symptoms even though the hormones are in the normal range because of the likely preference for turning a lot of her testosterone into DHT. The fan-style gauge below the hormones shows the 5a or 5b preference based on etiocholanolone (5b) and androsterone (5a) results. Progesterone metabolites are also metabolized by 5a and 5b enzymes and the balance between its two metabolites can be useful to confirm a 5a or 5b preference.

Example of how to read fan-style gauge for 5a-reductase activity:



It is important to consider DHEA and testosterone production, 5a-metabolism patterns as well as the patient symptoms. For example, a woman with higher levels of DHEA and testosterone will often have high androgen symptoms (facial hair, thinning scalp hair, etc.) exacerbated by 5a-metabolism. If, on the other hand, she prefers 5b-metabolism she may not express high androgen symptoms in spite of higher levels of testosterone because 5b is the less androgenic pathway.
Testosterone levels may be better understood by also considering its downstream metabolites (5a-androstanediol, 5b-androstanediol). Technically, these metabolites can also be formed from DHEA metabolites without going through the testosterone pathway, but they generally tend to correlate with testosterone production.
You will also see levels of epi-testosterone, which is not androgenic like testosterone. It happens to be produced in about the same concentrations as testosterone (this is an approximate relationship). This can be helpful to assess testosterone therapy and rare cases where testosterone may have other complexities.

Urine Hormone Testing - General Information

What is actually measured in urine? In blood, most hormones are bound to binding proteins. A small fraction of the total hormone levels are "free" and unbound such that they are active hormones. These free hormones are not found readily in urine except for cortisol and cortisone (because they are much more water soluble than, for example, testosterone). As such, free cortisol and cortisone can be measured in urine and it is this measurement that nearly all urinary cortisol research is based upon. In the DUTCH Adrenal Profile the diurnal patterns of free cortisol and cortisone are measured by LC-MS/MS.

All other hormones measured (cortisol metabolites, DHEA, and all sex hormones) are excreted in urine predominately after the addition of a glucuronide or sulfate group (to increase water solubility for excretion). As an example, Tajic (Natural Sciences, 1968 publication) found that of the testosterone found in urine, 57-80% was testosterone-glucuronide, 14-42% was testosterone-sulfate, and negligible amounts (<1% for most) was free testosterone. The most likely source of free sex hormones in urine is from contamination from hormonal supplements. To eliminate this potential, we remove free hormones from conjugates (our testing can be used even if vaginal hormones have been given). The glucuronides and sulfates are then broken off of the parent hormones, and the measurement is made. These measurements reflect the bioavailable amount of hormone in most cases as it is only the free, nonprotein-bound fraction in blood/tissue that is available for phase II metabolism (glucuronidation and sulfation) and subsequent urine excretion.
Disclaimer: the filter paper used for sample collection is designed for blood collection, so it is technically considered "research only" for urine collection. Its proper use for urine collection has been thoroughly validated.

Reference Range Determination (last updated 06.20.2019)

We aim to make the reference ranges for our DUTCH tests as clinically appropriate and useful as possible. This includes the testing of thousands of healthy individuals and combing through the data to exclude those that are not considered "healthy" or "normal" with respect to a particular hormone. As an example, we only use a premenopausal woman's data for estrogen range determination if the associated progesterone result is within the luteal range (days 19-21 when progesterone should be at its peak). We exclude women on birth control or with any conditions that may be related to estrogen production. Over time the database of results for reference ranges has grown quite large. This has allowed us to refine some of the ranges to optimize for clinical utility. The manner in which a metabolite's range is determined can be different depending on the nature of the metabolite. For example, it would not make clinical sense to tell a patient they are deficient in the carcinogenic estrogen metabolite, 4-OH-E1 therefore the lower range limit for this metabolite is set to zero for both men and women. Modestly elevated testosterone is associated with unwanted symptoms in women more so than in men, so the high range limit is set at the 80th percentile in women and the 90th percentile for men. Note: the 90th percentile is defined as a result higher than 90% (9 out of 10) of a healthy population.

Classic reference ranges for disease determination are usually calculated by determining the average value and adding and subtracting two standard deviations from the average, which defines 95% of the population as being "normal." When testing cortisol, for example, these types of two standard deviation ranges are effective for determining if a patient might have Addison's (very low cortisol) or Cushing's (very high cortisol) Disease. Our ranges are set more tightly to be optimally used for Functional Medicine practices.

Below you will find a description of the range for each test:

Female Reference Ranges (Updated 06.20.2019)

	Low%	High%	Low	High		Low%	High%	Low	High
b-Pregnanediol	20%	90%	600	2000	Cortisol A (waking)	20%	90%	12	55
a-Pregnanediol	20%	90%	200	740	Cortisol B (morning)	20%	90%	38	155
Estrone (E1)	20%	80%	12	26	Cortisol C (~5pm)	20%	90%	7.3	30
Estradiol (E2)	20%	80%	1.8	4.5	Cortisol D (bed)	0	90%	0	14
Estriol (E3)	20%	80%	5	18	Cortisone A (waking)	20%	90%	40	120
2-OH-E1	20%	80%	5.1	13.1	Cortisone B (morning)	20%	90%	90	230
4-OH-E1	0	80%	0	1.8	Cortisone C (~5pm)	20%	90%	32	95
16-OH-E1	20%	80%	0.7	2.6	Cortisone D (bed)	0	90%	0	55
2-Methoxy-E1	20%	80%	2.5	6.5	Melatonin (6-OHMS)	20%	90%	10	85
2-OH-E2	0	80%	0	1.2	8-OHdG	0	90%	0	5.2
4-OH-E2	0	80%	0	0.5	Methylmalonate	0	90%	0	2.2
2-Methoxy-E2	0	80%	0	0.7	Xanthurenate	0	90%	0	1.4
DHEA-S	20%	90%	20	750	Kynurenate	0	90%	0	7.3
Androsterone	20%	80%	200	1650	Pyroglutamate	10%	90%	32	60
Etiocholanolone	20%	80%	200	1000	Homovanillate	10%	95%	4	13
Testosterone	20%	80%	2.3	14	Vanilmandelate	10%	95%	2.4	6.4
5a-DHT	20%	80%	0	6.6					
5a-Androstanediol	20%	80%	12	30	**Calculated Values**				
5b-Androstanediol	20%	80%	20	75	Total DHEA Production	20%	80%	500	3000
Epi-Testosterone	20%	80%	2.3	14	Total Estrogens	20%	80%	35	70
a-THF	20%	90%	75	370	Metabolized Cortisol	20%	90%	2750	6500
b-THF	20%	90%	1050	2500	24hr Free Cortisol	20%	90%	80	230
b-THE	20%	90%	1550	3800	24hr Free Cortisone	20%	90%	220	450

% = population percentile: Example - a high limit of 90% means results higher than 90% of the women tested for the reference range will be designated as "high."

Provider Notes:

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