Sex Hormone Essentials: Personalizing Hormone Therapy

Stephen L. Goldman, DC
Kathy O’Neil-Smith, MD
September 26, 2012
Kathy O’Neil-Smith, MD
Owner, Treat Wellness LLC
Clinical Questions

Clinical Questions will be answered during the final fifteen (15) minutes of the webinar.
Goals of Presentation

Review the components of the **Sex Hormone Pyramid** as they apply to clinical practice:

- Anabolic/ Catabolic Balance brief review
- Estrogen metabolism brief review
- Sex Hormones w/ clinical application and case study
What are the Symptoms of Hormonal Imbalance?

• Weight gain
• Anxiety
• Low libido
• Brain fog
• Vaginal dryness
• Hair loss
• Hot flashes
• Sleep disturbances
• Mood swings
• Breast tenderness…
Urine Test (FMV or 24 Hour) – provides comprehensive evaluation of hormone metabolism

- Unbound hormones and circulating metabolites
- Assess hormone metabolism
- Assess steroidal enzyme activity
- Hormone Therapy (HT), *use 24 hour collection* method

- “Adding up receipts”
Anabolic/Catabolic Balance
An Overview
Anabolic/Catabolic Balance

- If you don’t maintain an anabolic/catabolic balance, you will find overall sex hormone balance very difficult to achieve.
Cholesterol

Pregnenolone

Progesterone

Corticosterone

Aldosterone

(Mineralocorticoids)

17-OH-Pregnenolone

17-OH-Progesterone

DHEA

Androstenediol

Androstenedione

Testosterone

DHT

Estrone (E1)

Estradiol (E2)

Estriol (E3)

2-OHE1

2-MeOE1

16α-OHE1

Estriol (E3)

4-OHE1

4-MeOE1

(Estrogens)

Androgens)

Cortisol

(Glucocorticoids)
Cholesterol

Pregnenolone

DHEA

Androstenediol

Androstenedione

Testosterone

DHT

 Estrone (E1)  Estradiol (E2)

2-OHE1  2-MeOE1

16α-OHE1  Estriol (E3)

4-OHE1  4-MeOE1

Cortisol & DHEA derive from same precursors

Cortisol (Glucocorticoids)

Progesterone

17-OH-Progesterone

Androstenedione

Estradiol (E2)

2-OHE1  2-MeOE1

16α-OHE1  Estriol (E3)

4-OHE1  4-MeOE1

Androstenediol

(Aldosterone)

(Amrogens)

Estrone (E1)  Estradiol (E2)

2-OHE1  2-MeOE1

16α-OHE1  Estriol (E3)

4-OHE1  4-MeOE1

(Estrogens)
Estrogen Metabolism

Phase I and Phase II Detoxification
Assessing the Sex Hormones
Complete Hormones
24 hour collection
ENZYMATIC STEPS:
3\beta\text{HSD} = 3\text{beta}-\text{Hydroxysteroid dehydrogenase}
5\alpha = 5\alpha-\text{Reductase}
5\beta = 5\beta-\text{Reductase}
CYP11B1 = 11\text{beta}-\text{Hydroxylase}
11\beta\text{HSD} = 11\beta-\text{Hydroxysteroid dehydrogenase}
17\beta\text{HSD} = 17\beta-\text{Hydroxysteroid dehydrogenase}
17,20 \text{Lyase} = 17,20 \text{Desmolase}
CYP21 = 21-\text{Hydroxylase}
CYP21 = 21-\text{Hydroxylase}

ESTROGEN METABOLISM:
1A1 = Cytochrome p450 1A1 (CYP1A1)
3A4 = Cytochrome p450 3A4 (CYP3A4)
1B1 = Cytochrome p450 1B1 (CYP1B1)
COMT = Catechol-O-Methyltransferase
Progesterone
**Progesterone**

- “Hormone of pregnancy”, prepares the endometrium for implantation
- Precursor to numerous steroid hormones
- Balances estrogen, counters proliferative effects of estrogen on endometrium, downregulates estrogen receptors
- Metabolizes rapidly, thus measured via *Pregnanediol* in urine
**Steroidogenic Pathway At-A-Glance**

### Glucocorticoids (Catabolic)
- **Pregnenolone**
- **17-OH-Pregnenolone**
- **Pregnanediol**
- **Pregnanetriol**
- **Progesterone**
- **17-OH-Progesterone**
- **11-Deoxycorticisol**
- **Cortisol**
- **Cortisone**
- **11β-Hydroxylase**
- **Mineralocorticoids**
- **Corticosterone**
- **Aldosterone**

### Androgens (Anabolic)
- **DHEA**
- **Androstenediol**
- **Androstenedione**
- **Testosterone**
- **Etiocholanolone**
- **DHT**
- **Androstanediol**

### Estrogen Metabolites
- **Estrone (E1)**
- **Estradiol (E2)**
- **2-OHE1**
- **2-MeOE1**
- **16α-OHE1**
- **4-OHE1**
- **4-MeOE1**

**ENZYMATIC STEPS:**
- 3β-HSD = 3β-Hydroxysteroid dehydrogenase
- 5α = 5α-Reductase
- 5β = 5β-Reductase
- CYP11B1 = 11β-Hydroxylase
- CYP17 = 17α-Hydroxylase
- CYP19 = Aromatase
- CYP21 = 21-Hydroxylase

**ESTROGEN METABOLISM:**
- 1A1 = Cytochrome p450 1A1 (CYP1A1)
- 3A4 = Cytochrome p450 3A4 (CYP3A4)
- 1B1 = Cytochrome p450 1B1 (CYP1B1)
- COMT = Catechol-O-Methyltransferase
Symptoms of Progesterone Deficiency include:

- PMS
- Sleep disturbances
- Weight gain
- Arthritis
- Water retention
- Irregular periods/heavy periods
- Break-through bleeding
- Anxiety
- Fibrocytic breasts
- Headaches
- Fibroids
- Irritability
DHEA
DHEA

- Precursor to androgens and estrogens
- Plays a role in immune regulation, libido, lean muscle mass, insulin sensitivity and the body’s stress response
- Epidemiological studies show correlations between high DHEA and breast cancer in post-but not pre-menopausal women
- Supplementation in “low doses for short periods of time can relieve adrenal stress” Bethany Hays, MD, IFM
- Cannot be taken at face value in urine testing…must add-up receipts (metabolites)!
# Androgens

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<thead>
<tr>
<th>Substance</th>
<th>Value</th>
<th>Reference Range</th>
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<tr>
<td>DHEA (24hr urine)</td>
<td>0.16</td>
<td>0.20-0.90 micromol/24 hr</td>
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<tr>
<td>Androsterone (24hr urine)</td>
<td>1.69</td>
<td>0.60-5.50 micromol/24 hr</td>
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<td>Etiocholanolone (24hr urine)</td>
<td>1.60</td>
<td>1.20-6.10 micromol/24 hr</td>
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<tr>
<td>11-Keto-androsterone (24hr urine)</td>
<td>0.19</td>
<td>0.30-1.90 micromol/24 hr</td>
</tr>
<tr>
<td>11-Keto-etiocholanolone (24hr urine)</td>
<td>0.71</td>
<td>0.30-1.60 micromol/24 hr</td>
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<td>11-Hydroxy-androsterone (24hr urine)</td>
<td>0.59</td>
<td>1.30-4.10 micromol/24 hr</td>
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<td>11-Hydroxy-etiocholanolone (24hr urine)</td>
<td>0.98</td>
<td>0.50-2.60 micromol/24 hr</td>
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<td><strong>17-Ketosteroids, Total</strong> (24hr urine)</td>
<td>5.9</td>
<td>6.0-22.2 micromol/24 hr</td>
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# Glucocorticoids

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<th>Value</th>
<th>Reference Range</th>
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<tbody>
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<td>Pregnanetriol (24hr urine)</td>
<td>0.48</td>
<td>0.60-2.50 micromol/24 hr</td>
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<td>allo-Tetrahydrocortisol, a-THF (24hr urine)</td>
<td>2.55</td>
<td>0.70-4.90 micromol/24 hr</td>
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<td>Tetrahydrodeoxycortisol, THS (24hr urine)</td>
<td>0.34</td>
<td>&lt;= 1.00 micromol/24 hr</td>
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<td>Tetrahydrocortisone, THE (24hr urine)</td>
<td>22.50</td>
<td>3.80-11.20 micromol/24 hr</td>
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<td>Tetrahydrocortisol, THF (24hr urine)</td>
<td>7.78</td>
<td>2.40-7.10 micromol/24 hr</td>
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<td><strong>17-Hydroxysteroids, Total</strong> (24hr urine)</td>
<td>33.7</td>
<td>8.8-22.4 micromol/24 hr</td>
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* Total values equal the sum of all measurable parts

<table>
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<th>Substance</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol, Free (24hr urine)•</td>
<td>76</td>
<td>20-90 mcg/24 hr</td>
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</table>
Testosterone
Testosterone

• High levels related to hirsutism, PCOS, Metabolic Syndrome, acne, and increased risk of cardiovascular disease in women
• Low levels associated with reduced bone density and lean muscle mass and may influence libido
• Lowers SHBG allowing for lower levels of estradiol supplementation
• Urine is not the best way to assess the specific level of testosterone, the 17-ketosteroid total provides the best indication of overall androgen presence
Symptoms of Androgen Deficiency include:

- Low libido
- Vaginal dryness
- Fatigue
- Fibromyalgia
- Memory lapses
- Incontinence
- Heart palpitations
- Depression
- Sleep disturbances
- Bone loss
- Decreased muscle mass
Estrogens
ENZYMATIC STEPS:
3β-HSD = 3β-Hydroxysteroid dehydrogenase
5α = 5α-Reductase
5β = 5β-Reductase
CYP11B1 = 11β-Hydroxylase
11β-HSD = 11β-Hydroxysteroid dehydrogenase
17β-HSD = 17β-Hydroxysteroid dehydrogenase
17α,20 Lyase = 17α,20 Desmolase
CYP17 = 17α-Hydroxylase
CYP19 = Aromatase
CYP21 = 21-Hydroxylase

ESTROGEN METABOLISM:
1A1 = Cytochrome p450 1A1 (CYP1A1)
3A4 = Cytochrome p450 3A4 (CYP3A4)
1B1 = Cytochrome p450 1B1 (CYP1B1)
COMT = Catechol-O-Methyltransferase
Estrogens

- Assessment of Estradiol, Estriol and Estrone
- Metabolites allow for detoxification/risk assessment for Hormone Therapy (HT)
Symptoms of Estrogen Deficiency include:

- Night sweats
- Hot flashes
- Vaginal dryness
- Foggy thinking
- Memory lapses
- Depression

- Sleep disturbances
- Bone loss
- Dry skin/hair
- Headaches
Symptoms of Estrogen Excess Include:

- PMS
- Tender breasts
- Water retention
- Irritability
- Anxiety
- Sleep disturbances
- Fibrocystic breasts
- Uterine fibroids
- Weight gain in hips
- Bleeding changes
- Headaches
Dr. Kathy O’Neil-Smith

CASE STUDY

So Doctor, how does it really work in clinical practice?
Case Study: Patient History

• 52 yo Female
  – Complains of hot flashes (HF), insomnia and irritability
  – Was started on OCPs 12 months prior
  – Discontinued OCPs 5 months ago because periods were “weird and gloppy”
  – Since discontinuing OCPs has had increasing HFs, awakens every couple of hours and is irritable
  – Occasional need to change bed and pajamas due to night sweats
  – Overall, good health -> exercises regularly, no tobacco use reported
Case Study: Initial Lab Results

- Blood Work
Estrogen Metabolism

2-Hydroxyestrone/16α-Hydroxyestrone Ratio

16α-OHE1
Higher Risk of Breast/Prostate Cancer
RR = 1.7 - 2.8

2-OHE1
Lower Risk of Breast/Prostate Cancer

Methylation Activity

2-Methoxyestrone/2-Hydroxyestrone Ratio

Less Methylation
RR >= 0.09

More Methylation
## Androgens

<table>
<thead>
<tr>
<th>17-Ketosteroids</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>DHEA (FMV urine)</td>
<td>17.8</td>
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<tr>
<td>Androsterone (FMV urine)</td>
<td>323</td>
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<tr>
<td>Etiocholanolone (FMV urine)</td>
<td>488</td>
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<tr>
<td>11-Keto-androsterone (FMV urine)</td>
<td>24</td>
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<tr>
<td>11-Keto-etiocholanolone (FMV urine)</td>
<td>66</td>
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<tr>
<td>11-Hydroxy-androsterone (FMV urine)</td>
<td>206</td>
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<tr>
<td>11-Hydroxy-etiocholanolone (FMV urine)</td>
<td>66</td>
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<td>17-Ketosteroids, Total* (FMV urine)</td>
<td>1,191</td>
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<tr>
<td>17-Hydroxysteroids</td>
<td>Reference Range</td>
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<tr>
<td>----------------------------------------</td>
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<tr>
<td>Pregnanetriol (FMV urine)</td>
<td>23-176 nmol/dL (SG)</td>
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<tr>
<td>allo-Tetrahydrocortisol, a-THF (FMV urine)</td>
<td>38-331 nmol/dL (SG)</td>
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<td>Tetrahydrodeoxycortisol (FMV urine)</td>
<td>&lt;= 7.7 nmol/dL (SG)</td>
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<tr>
<td>Tetrahydrocortisone, THE (FMV urine)</td>
<td>126-730 nmol/dL (SG)</td>
</tr>
<tr>
<td>Tetrahydrocortisol, THF (FMV urine)</td>
<td>126-559 nmol/dL (SG)</td>
</tr>
<tr>
<td>17-Hydroxysteroids, Total*</td>
<td>166-1,751 nmol/dL (SG)</td>
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</table>
Anabolic/Catabolic Balance
17-Ketosteroids/17-Hydroxysteroids Ratio

**Anabolic/Catabolic Balance (FMV)**

- Catabolic (Wear & Tear) ≤ 1.0
- Anabolic (Growth & Healing) ≥ 1.0

**Anabolic/Catabolic Balance (FMV)**

- 0.48
- 1.00-3.86

**Catabolic**

- 17-Hydroxysteroids, Total* (FMV urine)
  - 2,487
  - 168-1,751 nmol/dL (SG)

**Anabolic**

- 17-Ketosteroids, Total* (FMV urine)
  - 1,191
  - 303-2,184 nmol/dL (SG)
**Additional Markers**

**Reference Range**

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<th>Additional Markers</th>
<th>0.64-2.57 mcg/g Creat.</th>
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<tr>
<td>Triiodothyronine, T3 (FMV urine)</td>
<td>0.82</td>
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**5α-Reductase Activity**
Ethiocholanolone/Androsterone (E/A) Ratio

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<tr>
<th>More 5α-Reductase</th>
<th>Less 5α-Reductase</th>
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<tr>
<td>1.51</td>
<td>RR = 0.55 - 2.45</td>
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**11β-HSD Index**
(α-THF + THF)/THE

<table>
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<tr>
<th>Less Cortisol</th>
<th>More Cortisol</th>
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<tbody>
<tr>
<td>0.54</td>
<td>RR = 0.59 - 1.42</td>
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**Therapeutic Interventions & Effects**

- Began TD BHT
  - Reduced HFs, but continued
  - Night sweats continued
  - Irritability continued

- ASP #2 showed increased catecholamines
  - Added Neuroendocrine/immune support
    - Botanicals = Boswellia, Rhodiola
    - Nutriceuticals = NAC, theanine, acetyl L carnitine, CoQ10, 5HTP
  - Hot flashes and night sweats resolved
  - Sleep improved to 1 awakening per night to urinate
  - Irritability decreased with increased focus, concentration, mood and energy
Remember ...

- The Sex Hormone Pyramid & Steroidogenic Pathway provide an important framework for understanding hormonal health.

- Metabolic pathways and clinical presentation guide us to personalize recommendations for treatment.
And ...

The components of the **Sex Hormone Pyramid** are easily applied to clinical practice:

- Anabolic/ Catabolic Balance brief review
- Estrogen metabolism brief review
- Sex Hormones with clinical application and case study.
Steroidogenic Pathways

Cholesterol
- Congenital adrenal hyperplasia (CAH), smoking, E2, progesterone, azole antifungals, spironolactone
- Hyperglycemia, azole antifungals, aging, smoking, dioxin toxicity, HIV, licorice, etomoxirate, ilerxole

Pregnenolone
- 17-hydroxylase
- 3β-HSD
- Pregnanolone, pregnanetriol
- Hyperglycemia, hyperinsulinemia, PCOS (ovary), stress, alcohol, antiepileptics
- CAH, late-onset adrenal hyperplasia, primary adrenal insufficiency, ankylosing spondylitis, increased salt cravings, retinol, soy isoflavonoids, DHEA, omeprazole

Progesterone
- 17-hydroxylase
- 17α-DHEA
- Sodium depletion, high prolactin
- CAH, DHEA, azole antifungals, etomoxirate, metyrapone

Cortisol
- 11β-HSD
- Aldosterone*
- Inactive
- Cortisone (active)
- 11β-HSD
- Licorice
- Insulin resistance, obesity, FCOS, androgenic alopecia, essential HT, high-calc diet, sodium restriction, DHEA
- Colic disease, 5α-reductase inhibitors (e.g., finasteride, saw palmetto, pygeum, stinging nettle, flaxseed soy isoflavones, EGCG, quercetin, progesterone, some progestins

Cortilol (active)
- Polycyclic aromatic hydrocarbons, PCIs
- Inactive
- Cortisone (active)
- Insulin resistance, obesity, fatty liver, nonalcoholic steatohepatitis

Thyroid (THF)
- 10α-HSD
- THF
- Colchicine, berberine, B6, calcium, B6, B12, folic acid, vitamin D, B12, B6, B12, B6, B12

Administered Cortisol (CTP)
- More cortisol: Obesity (esp. visceral), metabolic syndrome, hypothroid, inflammation, essential HT, cortisol resistance, cholestasis, hypoinsulin, cyclosporine, vitamin D, grapefruit, forsyolin
- Less cortisol: Good insulin sensitivity, hypothyroidism, reduced inflammation, Na restriction, hGH (via IGF-1), E2, coffee, ondansetron, ketocazole

DHEA
- CAH, chronic ETOH ingestion, PCB toxicity, progesterone, isoflavonoids, metformin, troglitazone, trilostane

Androstenediol
- Hyperadrenalism, hyperthyroidism, hyperinsulinemia, FCOS, IL-4 and IL-13, IGF-1, forsyolin

Testosterone
- Excess adipose, alcohol, zinc deficiency, stress, hyperinsulinemia, inflammation, licorice, vitamin D3 (in osteoblasts), forsyolin, solodronol

Etiocholanone
- DHT

Androsterone
- 17β-HSD

Estrone (E1)
- Crucifers, berries, BC, DIM, soy, flaxseed, caffeine, rosemary, exercise, thyroid

Estradiol (E2)
- 2-OHE1
- COMT
- 2-MeOE1
- Hypothyroidism, pesticides, arsenic, smoking, caffeine, various medications
- Grapefruit, peppermint oil, rosemary, wild yam, anti-fungals & other medications

Estriol (E3)
- 16α-OHE1
- 4-OHE1
- COMT
- 4-MeOE1
- CGMT support: Adequate methionine, Mg B vitamins, GSH; reduce stress, rule out Hg toxicity & oxidative stress
Questions & Answers

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The following LearnGDX modules are focused on giving clinicians insight into our newly redesigned and enhanced patient results.

Report Review

NutrEval
Optimal Nutritional Evaluation - ONE
Metabolic Analysis Profile - MAP
Essential & Metabolic Fatty Acids Analysis
Amino Acids

In-Depth Modules

Antioxidants, Interpretation At-A-Glance
B-Vitamins, Interpretation At-A-Glance
Minerals, Interpretation At-A-Glance
Digestive Support, Interpretation At-A-Glance
Functional Imbalances, Interpretation At-A-Glance

Case Studies

Fatigue - NutrEval
Depression - NutrEval
Optimal Health - ONE

Amino Acids Plasma - Biomarkers
Amino Acids Urine - Biomarkers
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We have your current email address as phanaway@gdx.net. A valid email address is vital to the operation of myGDX, so if that's no longer correct, please update your account.
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Upcoming LiveGDX Webinar Topics

• October 2012
  – Specialty Diagnostics & Breast Cancer Risk
• November 2012
  – Environmental Toxicants & Human Health
• December 2012
  – Nutritional Testing in Clinical Practice
Sex Hormone Essentials: Personalizing Hormone Therapy

Stephen L. Goldman, DC
Kathy O’Neil-Smith, MD
September 26, 2012