Specialty Diagnostics for Men's Health:
Going beyond the PSA

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Technical Issues & Clinical Questions

Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.

We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.

DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

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Specialty Diagnostics for Men's Health:
Going beyond the PSA

Warren Brown, ND

OVERVIEW

- Discuss testing considerations for all men, including those on hormone therapy
- Highlight key pathways and patterns in androgen and estrogen metabolism that are involved in disease risk
- Provide an overview of therapeutic strategies that influence hormone metabolism

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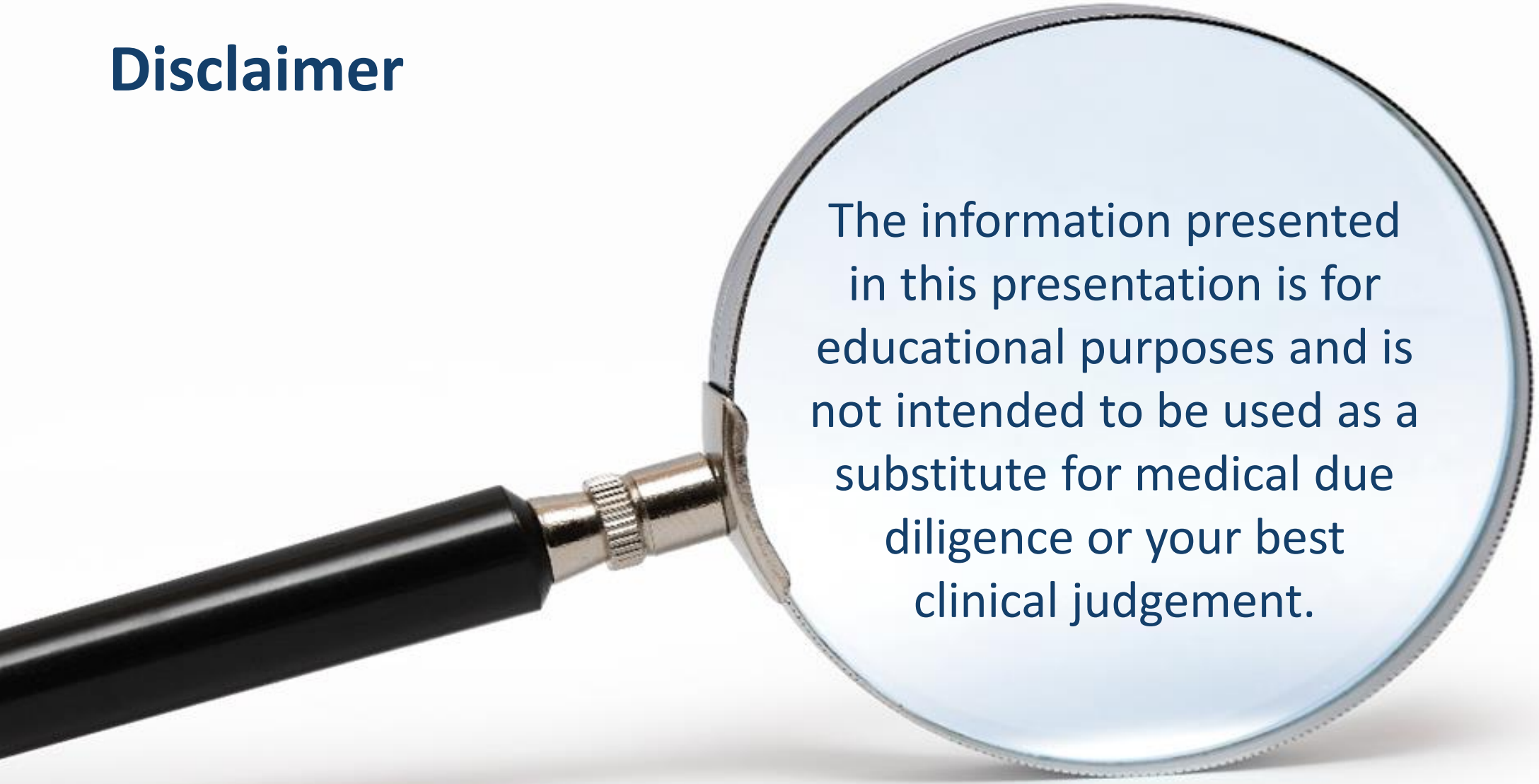
Disclaimer



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Statistics on Prostate Cancer

- Currently, 1 in 6 men in the United States are at risk of developing prostate cancer
- Aside from non-melanoma skin cancer, prostate cancer is the most common cancer among men in the United States
- In 2013, in the US there were:
  - 176,450 men in the United States were diagnosed with prostate cancer
  - 27,681 men in the United States died from prostate cancer
- Worldwide, there are 13 million new cases of prostate cancer annually

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CDC. Prostate Cancer Statistics. Accessed online, 2017. https://www.cdc.gov/cancer/prostate/basic_info/screening.htm
Adjakly, M., et al. " In *Annales d'endocrinologie*, vol. 76, no. 1, pp. 25-41. Elsevier Masson, 2015.

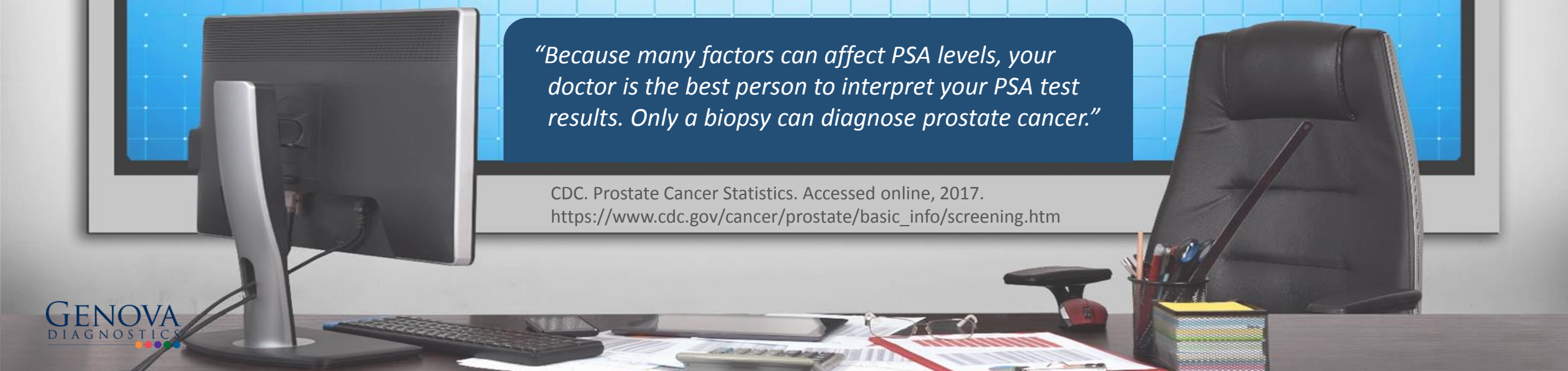
Screening for Prostate Cancer

Two tests are commonly used to screen for prostate cancer:

- Prostate Specific Antigen (PSA)
- Digital Rectal Exam (DRE)

"Because many factors can affect PSA levels, your doctor is the best person to interpret your PSA test results. Only a biopsy can diagnose prostate cancer."

CDC. Prostate Cancer Statistics. Accessed online, 2017. https://www.cdc.gov/cancer/prostate/basic_info/screening.htm



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Pros & Cons of the PSA & DRE

	Potential Pros	Potential Cons
PSA	• Reductions in prostate cancer mortality • High specificity rate (at certain values)	• Overdiagnosis and overtreatment, leading to negative impacts to quality of life
DRE	• Detection of nodules from prostate cancer or enlargement from benign prostatic hyperplasia (BPH)	• Invasive/uncomfortable • Dependent on efficiency and skill of clinician • 10% of prostate cancers are undetected

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Quality-of-life effects of prostate-specific antigen screening. N Engl J Med. 2012 Aug 16;367(7):595-605.
Lowry, F. Time to abandon the digital rectal exam? Medscape. September, 2016
Rodic, Stefan, and Ariel Gershon. "Questioning the benefits of current screening protocols for common cancers." Arch Ital Urol Androl, 2006; 78:125-9.

Limitations of the PSA

"PSA screening for prostate cancer has long been controversial. Although the PSA test is simple, safe and has an acceptable sensitivity and specificity, estimates of the costs, risk of overdiagnosis and side effects of unnecessary treatment are unfavourable."

BJC British Journal of Cancer

Search

Journal home > Archive > Clinical Studies > Full text

Clinical Study

British Journal of Cancer (2009) **101**, 1833–1838. doi:10.1038/sj.bjc.6605422
www.bjcancer.com
Published online 10 November 2009

BJC OPEN

Overdetection, overtreatment and costs in prostate-specific antigen screening for prostate cancer

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Advance online publication 10 November 2009

Abstract

Top

• Background: • Methods: • Results: • Conclusion: • Materials and methods • Results • Discussion • References • Figures and Tables

BACKGROUND: Prostate cancer screening with prostate-specific antigen (PSA) has shown to reduce prostate cancer mortality in the European Randomised study of Screening for Prostate Cancer (ERSPC) trial. Overdetection and overtreatment are substantial unfavourable side effects with consequent healthcare costs. In this study the effects of introducing widespread PSA screening is evaluated.

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Recent Developments in the Landscape of Prostate Cancer Screening

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"Pumping the Brakes" on Aggressive Prostate Cancer Management

"Active surveillance" involves reserving treatments for intermediate-to-high-risk cancers

- Not all prostate cancers are created equal – Emerging strategies suggest that they're best categorized into risk and dealt with accordingly:
  - **Low-risk**
    - Indolent and slow growing
    - 50% of prostate cancers
    - PSA < 10, Gleason score < 7
    - In 2002, 94% of men with low-risk prostate cancer received radical treatment
  - **Intermediate-risk**
  - **High-risk**

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Klotz, L. "Active surveillance for prostate cancer: for whom?." *Journal of Clinical Oncology* 23, no. 32 (2005): 8165-8169.
Cooperberg, M. R., et al. "The contemporary management of prostate cancer in the United States: lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry." *The Journal of urology* 171, no. 4 (2004): 1393-1401.

Prostate Specific Antigen (PSA)

- US Preventive Services Task Force
  - Since May of 2012, the US Preventive Services Task Force had recommended *against* PSA-based screening for prostate cancer, citing the balance of evidence for both benefit and harms
  - Until very recently, the USPFTF gave the PSA a "D" in terms of evidence grades. However, they seem to be in the process of moving towards 2-tiered, age-based approach *(see USPFTF "Draft Recommendation Statement" on prostate cancer screening)*
    - For men ages 55-69: "Grade C" recommendation
    - For men age 70 and older: "Grade D" recommendation

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men	The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)–based screening for prostate cancer.	D

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Men ages 55 to 69 years	The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA) –based screening for prostate cancer. The decision about whether to be screened for prostate cancer should be an individual one. Screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and impotence. The USPSTF recommends individualized decisionmaking about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. Please refer to the Clinical Considerations sections on screening in African American men and men with a family history of prostate cancer for more information on these higher-risk populations.	C
Men age 70 years and older	The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older.	D

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USPFTF. Final Recommendation Statement: Prostate Cancer Screening. Accessed online, 2017.
https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening
https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/prostate-cancer-screening1

Prostate Specific Antigen (PSA)

- American Urological Association
  - Recommends against PSA screening in men under age 40 years
  - Does not recommend routine screening in men between ages 40 to 54 years at average risk
  - Men ages 55 to 69: the decision to undergo PSA screening involves weighing the benefits and risks
  - Recommends shared decision-making (patient and provider) for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences
  - Does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy

"Average risk" is defined as a man *without* risk factors, such as:

- A family history of prostate cancer in multiple generations and/or family history of early onset below age 55 years
- African American race

"High risk"

- Men with a family history or PrCA
- African-American race

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American Urological Association. Patient Access to PSA Testing (USPFTF Reform). Accessed online, 2017. http://www.auanet.org/advocacy/advocacy-by-topic/patient-access-to-psa-testing-(uspstf-reform)

Prostate Specific Antigen (PSA)

- NIH National Cancer Institute

  "Until recently, many doctors and professional organizations encouraged yearly PSA screening for men beginning at age 50. Some organizations recommended that men who are at higher risk of prostate cancer, including African American men and men whose father or brother had prostate cancer, begin screening at age 40 or 45. However, as more has been learned about both the benefits and harms of prostate cancer screening, a number of organizations have begun to caution against routine population screening. Although some organizations continue to recommend PSA screening, there is widespread agreement that any man who is considering getting tested should first be informed in detail about the potential harms and benefits."

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NIH National Cancer Institute. Prostate Specific Antigen Test. Accessed online, 2017. https://www.cancer.gov/types/prostate/psa-fact-sheet

Prostate Specific Antigen (PSA)

- American Academy of Family Physicians
  - "The AAFP *recommends against* prostate-specific antigen (PSA)-based screening for prostate cancer. (2012)"
  - "Grade D" recommendation

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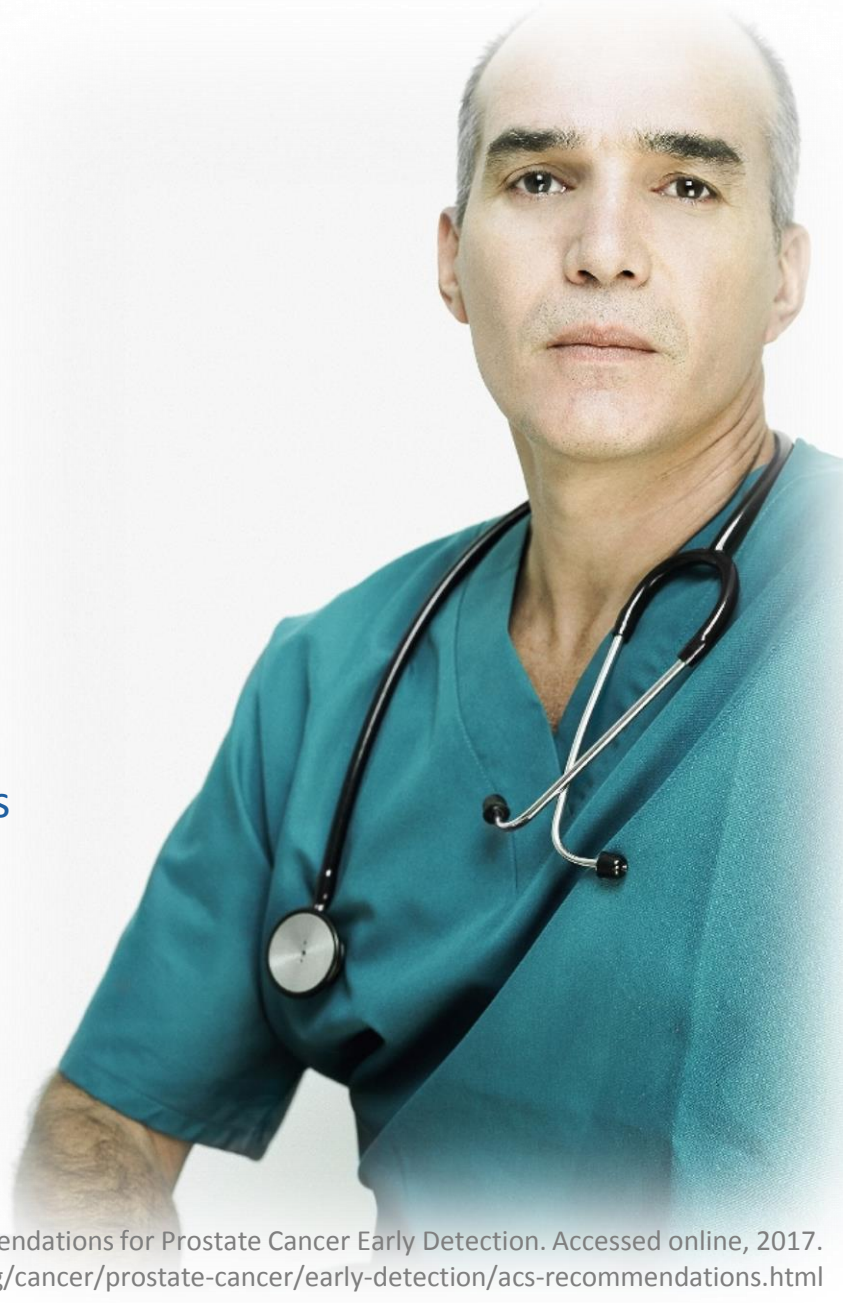
American Academy of Family Physicians. Prostate Cancer. Accessed online, 2017. http://www.aafp.org/patient-care/clinical-recommendations/all/prostate-cancer.html

Prostate Specific Antigen (PSA)

- American Cancer Society
  - *"…decision should be made after getting information about the uncertainties, risks, and potential benefits of prostate cancer screening. Men should not be screened unless they have received this information."*
    - Age 50 for men who are at average risk of prostate cancer and are expected to live at least 10 more years
    - Age 45 for men at high risk of developing prostate cancer. This includes African Americans and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65)
    - Age 40 for men at even higher risk (those with more than one first-degree relative who had prostate cancer at an early age)



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American Cancer Society. Recommendations for Prostate Cancer Early Detection. Accessed online, 2017. https://www.cancer.org/cancer/prostate-cancer/early-detection/acs-recommendations.html

Other Clinical Tools to Consider

Patient Symptom Questionnaires

- International Prostate Symptom Score (I-PSS)
- American Urological Association Symptom Index

"Novel" Ways to Use PSA

- PSA Density
- PSA Velocity
- PSA Doubling Time
- Free PSA

Imaging Techniques

- Endorectal MRI
- Color Doppler Ultrasound

Functional Laboratory Testing

- Sex Hormone Metabolites
  - 4-OH estrogens can generate quinones that can damage DNA
  - DHT is a potent androgen and a product of 5-alpha reductase activity
  - Androstenedione and testosterone can be aromatized into the estrogens

- **Genetic SNPs**
  - Cytochrome P450 1B1
  - Catechol-O-methyltransferase (COMT)

Important Concepts for Testing Hormones in Men

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Reminder: S/Sx of Prostate Cancer

Generally 'silent' until reaching advanced stages, but symptoms may include:

- Difficulty starting urination
- Weak urine stream
- Dribbling
- Increased urinary frequency, especially at night
- Pain during urination
- Blood in the urine or ejaculate
- Difficulty having or maintaining an erection
- Pain with ejaculation
- Pain or stiffness in the lower back, hips, pelvis, and upper thighs
- Unexplained weight loss and/or loss of appetite
- Anemia
- Nodules on the prostate

These findings could be ominous, so a conventional medical workup is advisable.

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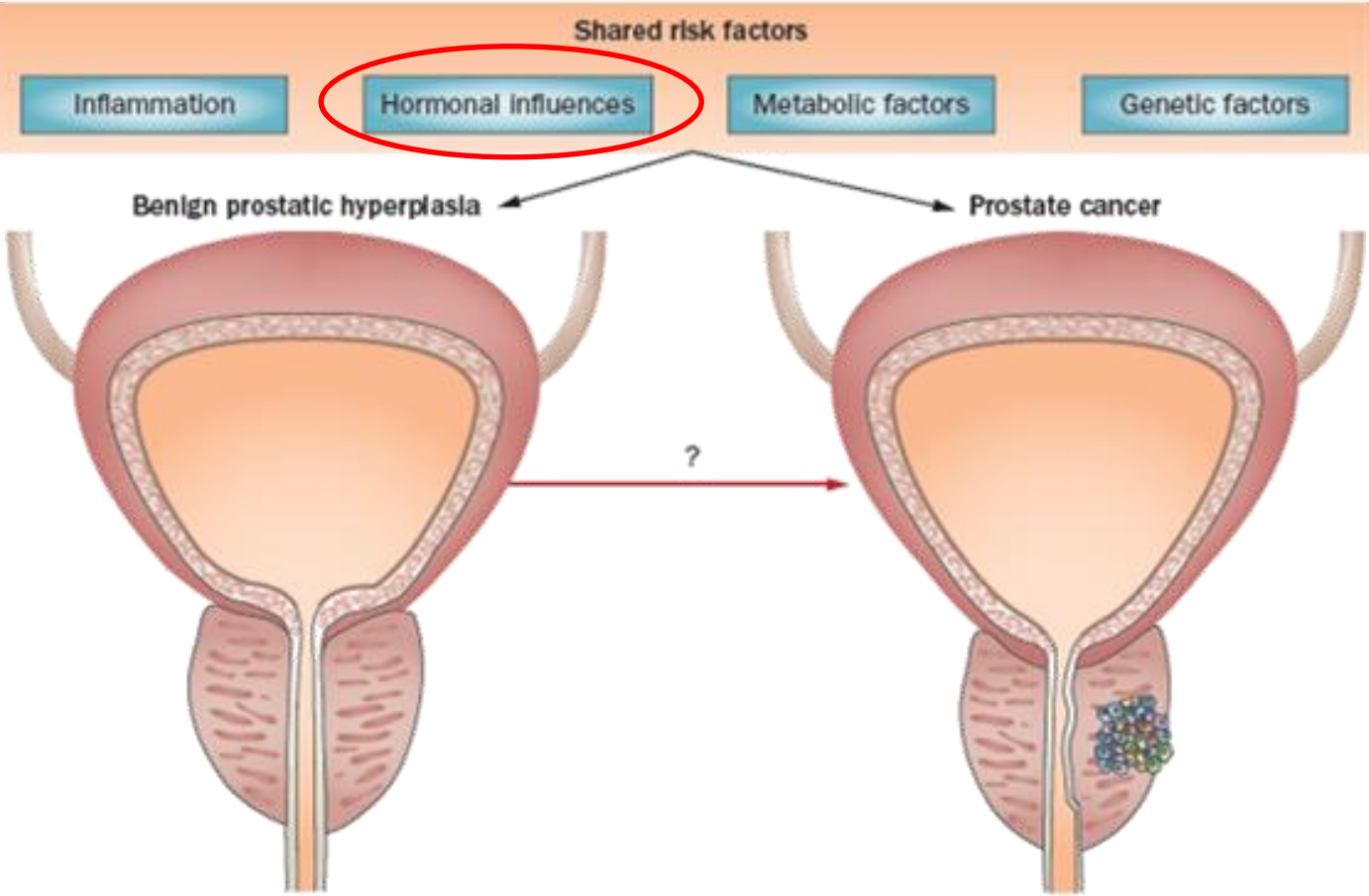
FamilyDoctor.org
Feri, F. Ferri's Clinical Advisor, 2012

Reminder: Benign Prostatic Hyperplasia (BPH) & Prostate Cancer



nature REVIEWS UROLOGY

Ørsted, D. D. & Bojesen, S. E. (2012) The link between benign prostatic hyperplasia and prostate cancer *Nat. Rev. Urol.* doi:10.1038/nrurol.2012.192

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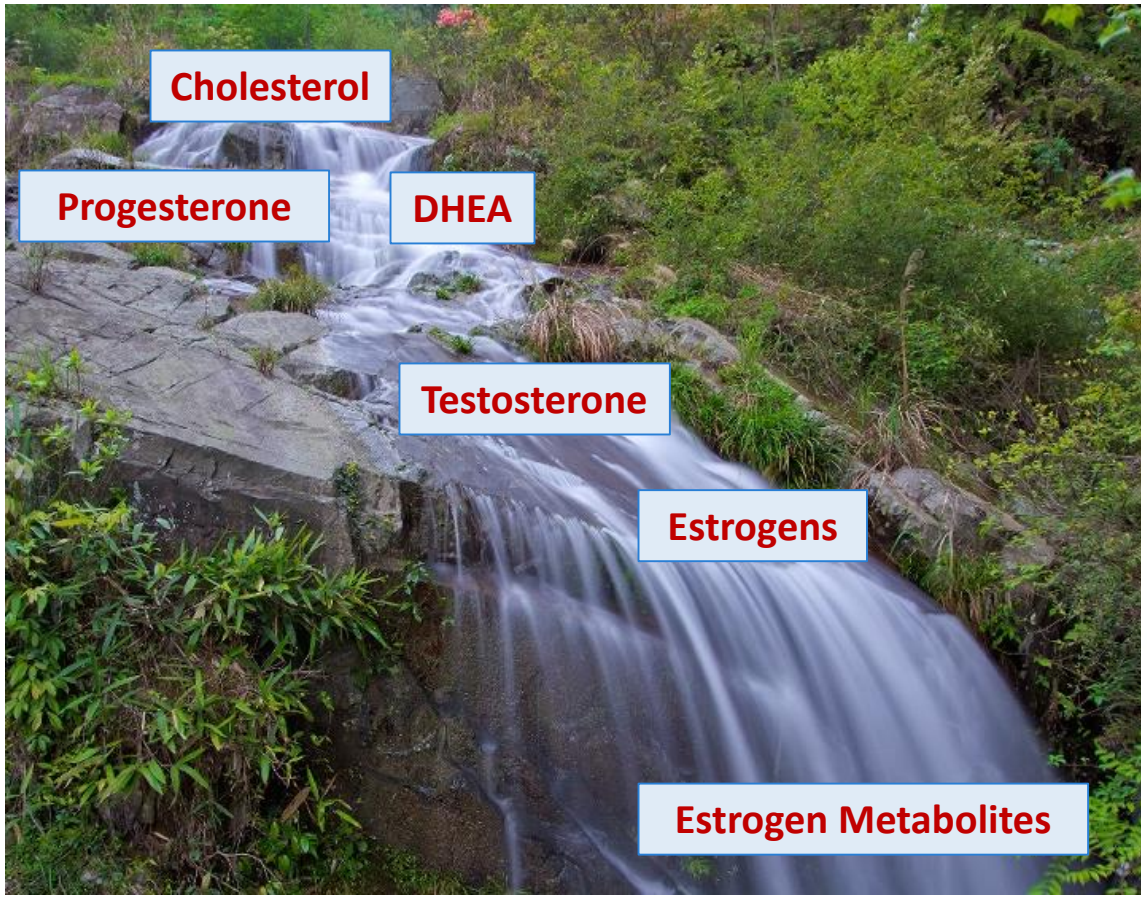
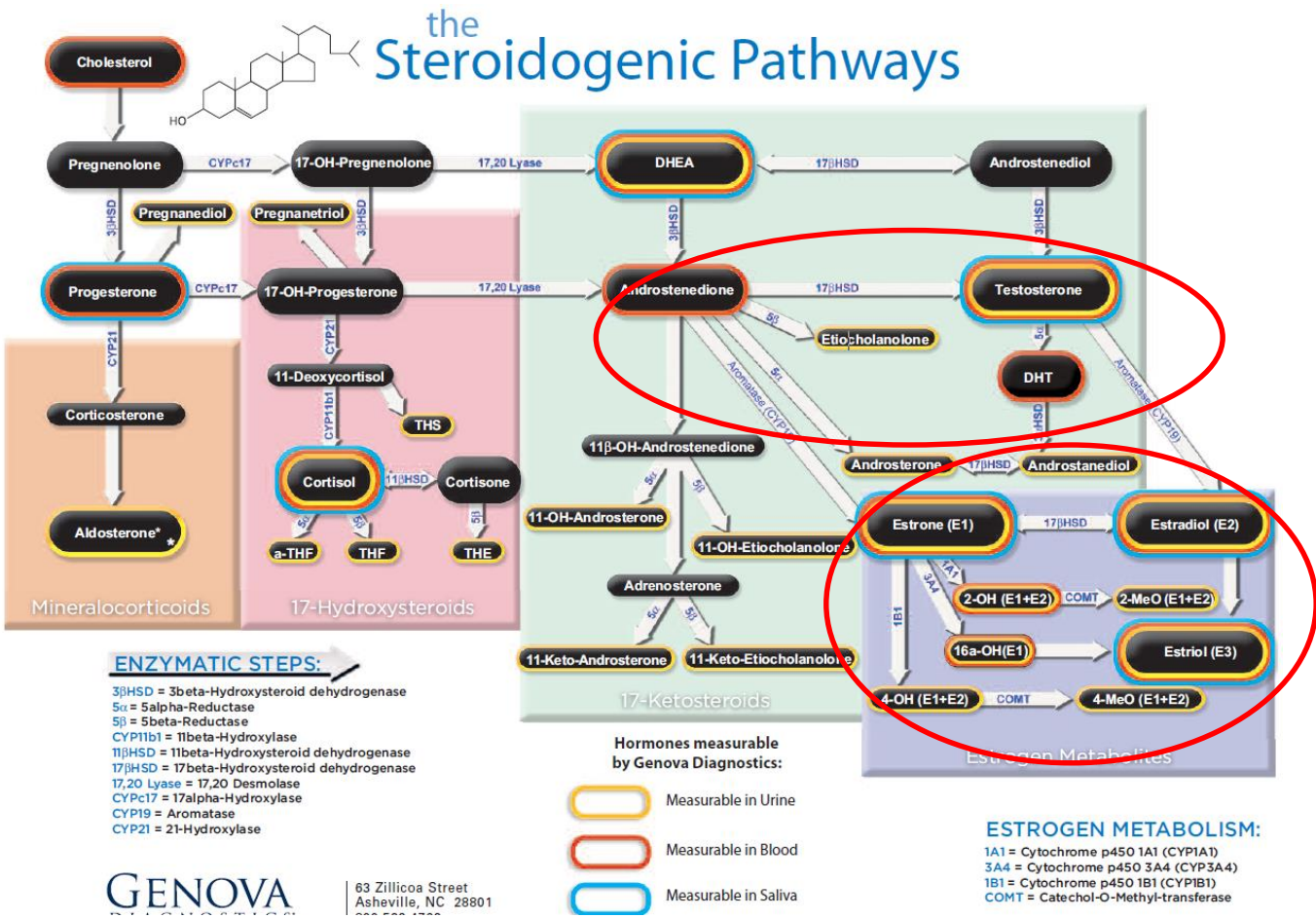
Steroidogenic Pathways





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Sex Hormone Metabolites

	Urine	Saliva	Serum
Where to look for hormone metabolites?	Estrogen metabolites measurable in urine: • 2-OH (E1+E2) • 16α-OHE1 • 4-OH (E1+E2) • 2-MeO (E1+E2) • 4-MeO (E1+E2) • 2/16 Ratio • 2-OH/2-MeO Ratio	Appropriate for determining free/bioavailable fraction of hormones, but not metabolites.	Some estrogen metabolites can be measured in serum: • 2-OHE1 • 16-OHE1 • 2/16 Ratio

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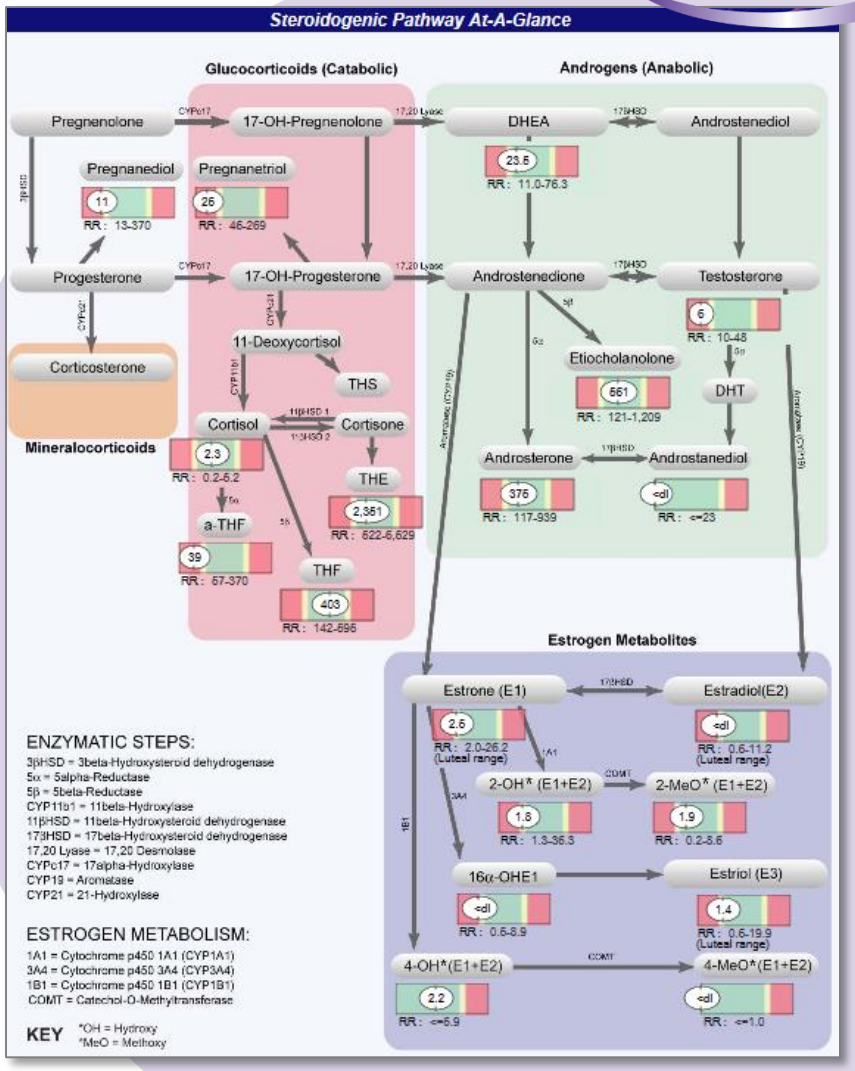
Sex Hormone Metabolites

Complete Hormones™

- Urinary hormone testing provides a comprehensive look at hormone metabolism
- Emerging research reinforces the potential relationship of disease risk with downstream metabolites, especially those of the CYP1B1 pathway, which are not routinely measured in blood or salivary testing
- Evaluation of stress-hormone metabolic pathways provides an indicator of balance between anabolic and catabolic metabolism
- Offers convenient, at-home collection of a first-morning (FMV) or 24-hour specimen



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Complete Hormones™

- Urine shows unbound hormones and circulating metabolites
- Assess hormone metabolism; provides average of hormone fluctuations; assess steroidal enzyme activity
- Representative of the last 48 hours of hormones fluctuations

Genova's most comprehensive urinary hormone test, designed to assist in the clinical management of hormone-related conditions. This hormone profile assesses parent hormones, their metabolites, and key metabolic pathways.

This test is not intended to be used as a screening tool for prostate cancer. However, some of the analytes have been associated with prostate cancer in the literature.

Complete Hormones™ – FMV or 24hr?

Complete Hormones™ FMV

A good choice for patients who are ***not*** on hormone therapy

FMV (First Morning Void)

Complete Hormones™ 24hr

For patients on hormone therapy, the 24hr collection is recommended

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"Top 5" Hormone Pathways to Know for Men:

- CYP 1B1
- CYP 1A1 (CYP 3A4)
- Aromatase
- 5-α Reductase
- COMT

Description of the Pathway → Example of the Pathway → Treatment Considerations

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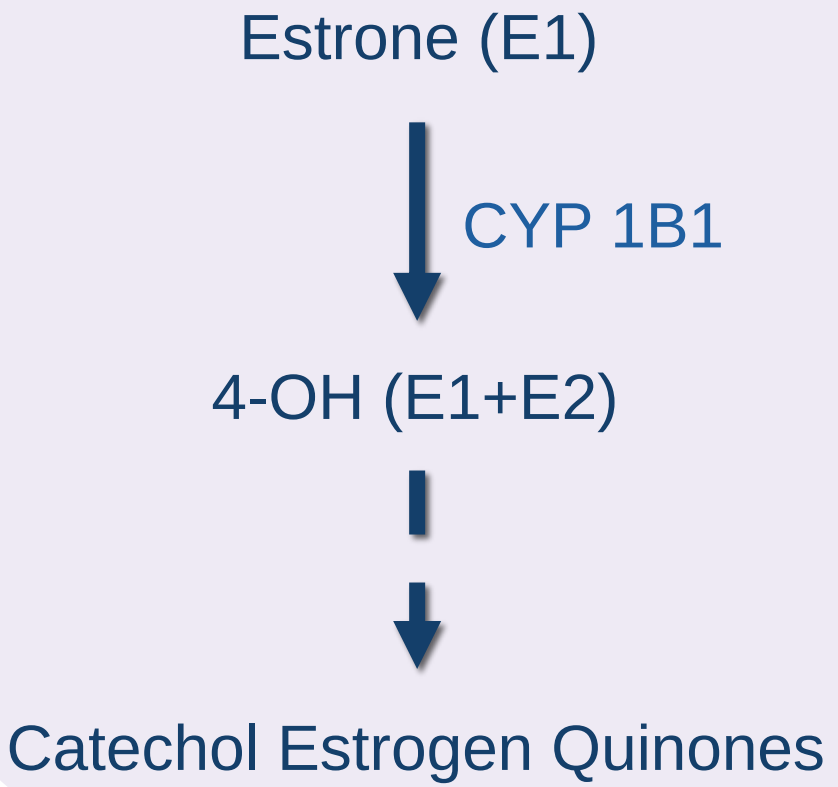
CYP 1B1 Pathway



- 4-OH (E1+E2) is thought to have greater estrogenic and genotoxic potential than either 2-hydroxyestrone or 16α-hydroxyestrone
- Metabolites of 4-hydroxyestrone may induce DNA damage through redox cycling which generates reactive oxygen species

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Cavalieri and Rogan. Molecular Etiology and Prevention of Estrogen-Iniated Cancers. Mol Aspects Med. 2014

CYP 1B1: Catechol Estrogens & Prostate Cells

Toxicol Lett. 2013 Jul 18;220(3):247-58. doi: 10.1016/j.toxlet.2013.05.002. Epub 2013 May 15.

Catechol estrogens induce proliferation and malignant transformation in prostate epithelial cells.

Mosli HA[1], Tolba MF, Al-Abd AM, Abdel-Naim AB.

Author information

Abstract

In the current study, the non-transformed prostatic epithel ... tradiol (2-OHE2) or 4-hydroxyestradiol (4-OHE2), or the parent h ... d of 6 weeks. It was found that both 2-OHE2 and 4-OHE2 have ... -OHE2 or E2 resulted in a significant increase in the protein abunda ... proliferative phase as indicated by FACScan. BPH-1 cells ... (ERα) and its downstream IGF-1R. Reduced abundance of estro ... observed in cells exposed to E2, 2-OHE2 and, to a greate ... ed significant genotoxic effects as compared to E2. 4-OHE2 ... by increased colony forming capacity in soft agar and matrix ... rm human prostatic epithelial cells. Further, 4-OHE2 is more

PMID: 23685341 DOI: 10.1016/j.toxlet.2013.05.002

"In vitro exposure to [catechol estrogens] could neoplastically transform human prostatic epithelial cells."

"4-OHE2 is more carcinogenic to prostate epithelial cells than the parent hormone E2."

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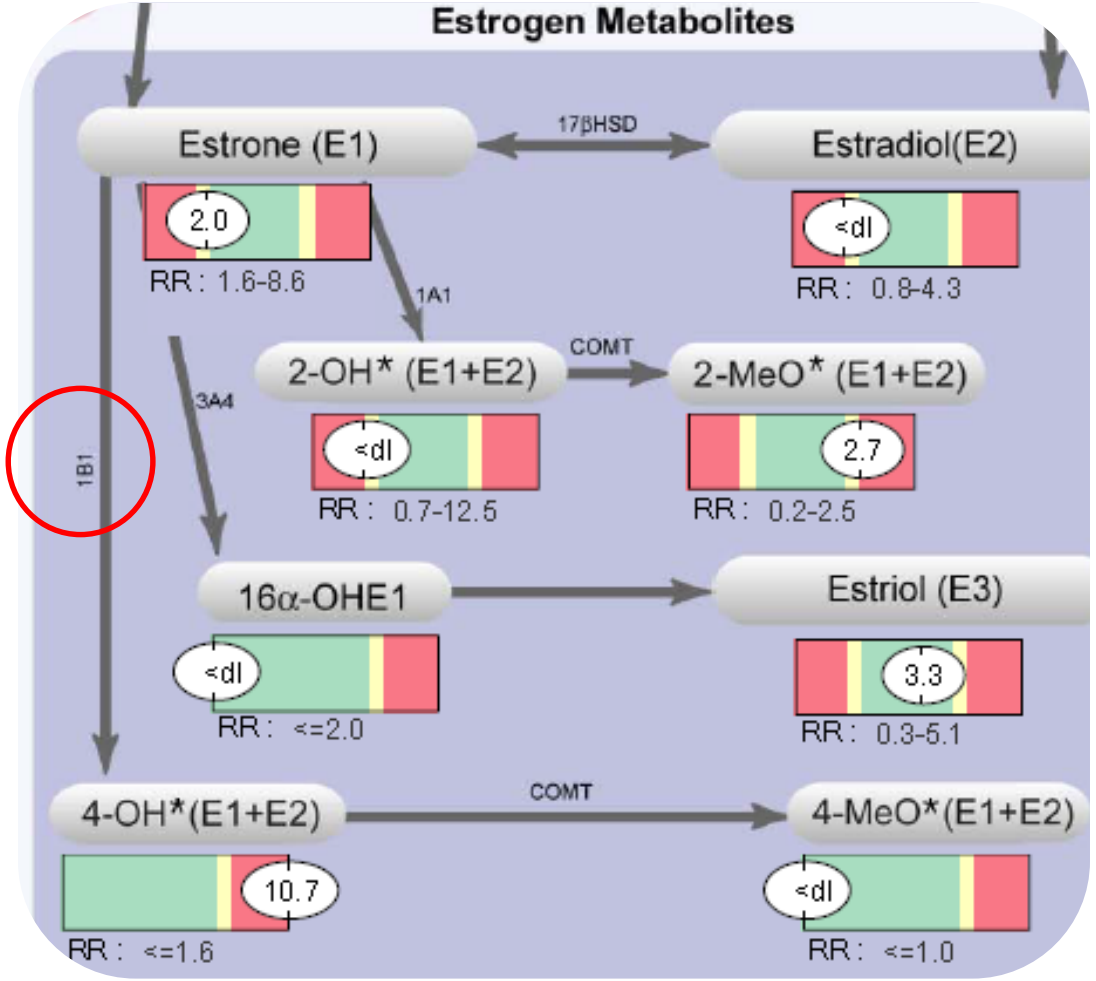
CYP 1B1 Pathway: Pattern Recognition



Example of excessive 4-OH production

- High 4-OH (E1+E2)
- Possible excessive conversion from Estrone (E1)

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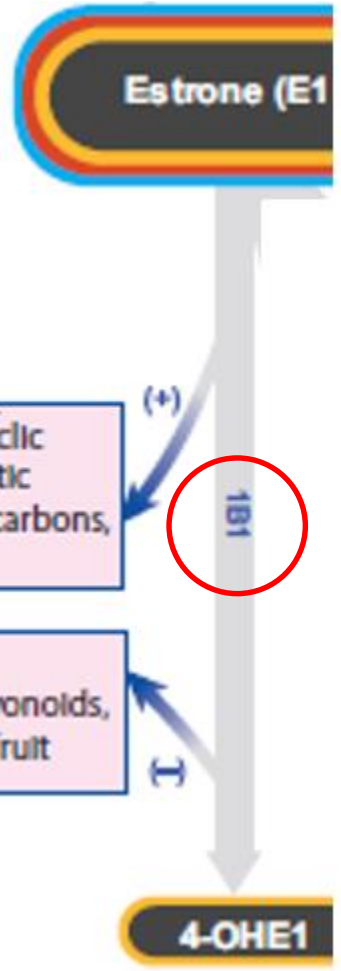
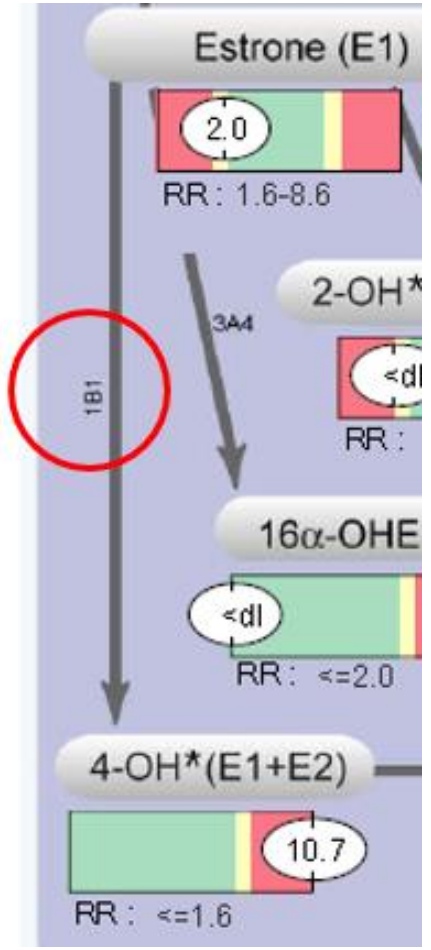
CYP 1B1 Pathway: Tx Considerations

These things should be avoided b/c they upregulate the 1B1 pathway

These are potential treatments that inhibit the 1B1 pathway.
Also, consider supporting the 1A1 pathway





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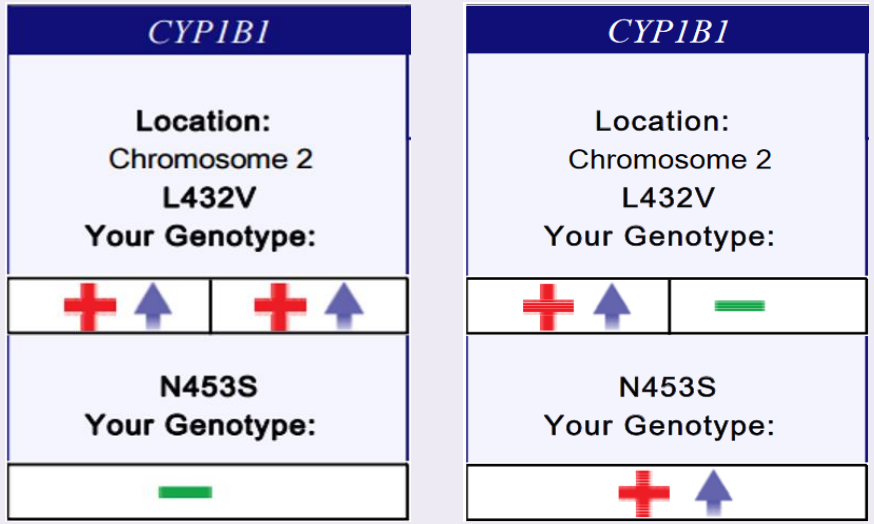
CYP 1B1 Pathway: 1B1 SNP Add-On to Complete Hormones™

- Cytochrome P450 1B1 (CYP1B1) is a phase I detoxification enzyme responsible for the oxidative metabolism of numerous compounds, including estradiol (e.g., 4-hydroxylation of estrogen) and testosterone

- CYP 1B1 variants have been clinically associated with increased risk for cancers in specific patient populations and exposure-specific cancers (breast, cervical, endometrial, prostate, hepatocellular, head and neck, lung).

Complete Hormones™ GENOMICS



Kasimsetty, S. et al. "Effects of pomegranate chemical constituents/intestinal microbial metabolites on CYP1B1 in 22Rv1 prostate cancer cells." *Journal of Agricultural and Food Chemistry* 57, no. 22 (2009): 10636-10644.

Lingling, et al. "Association of the CYP1B1 Leu432Val polymorphism with the risk of prostate cancer: a meta-analysis." *Molecular biology reports* 39, no. 7 (2012): 7465-7471.

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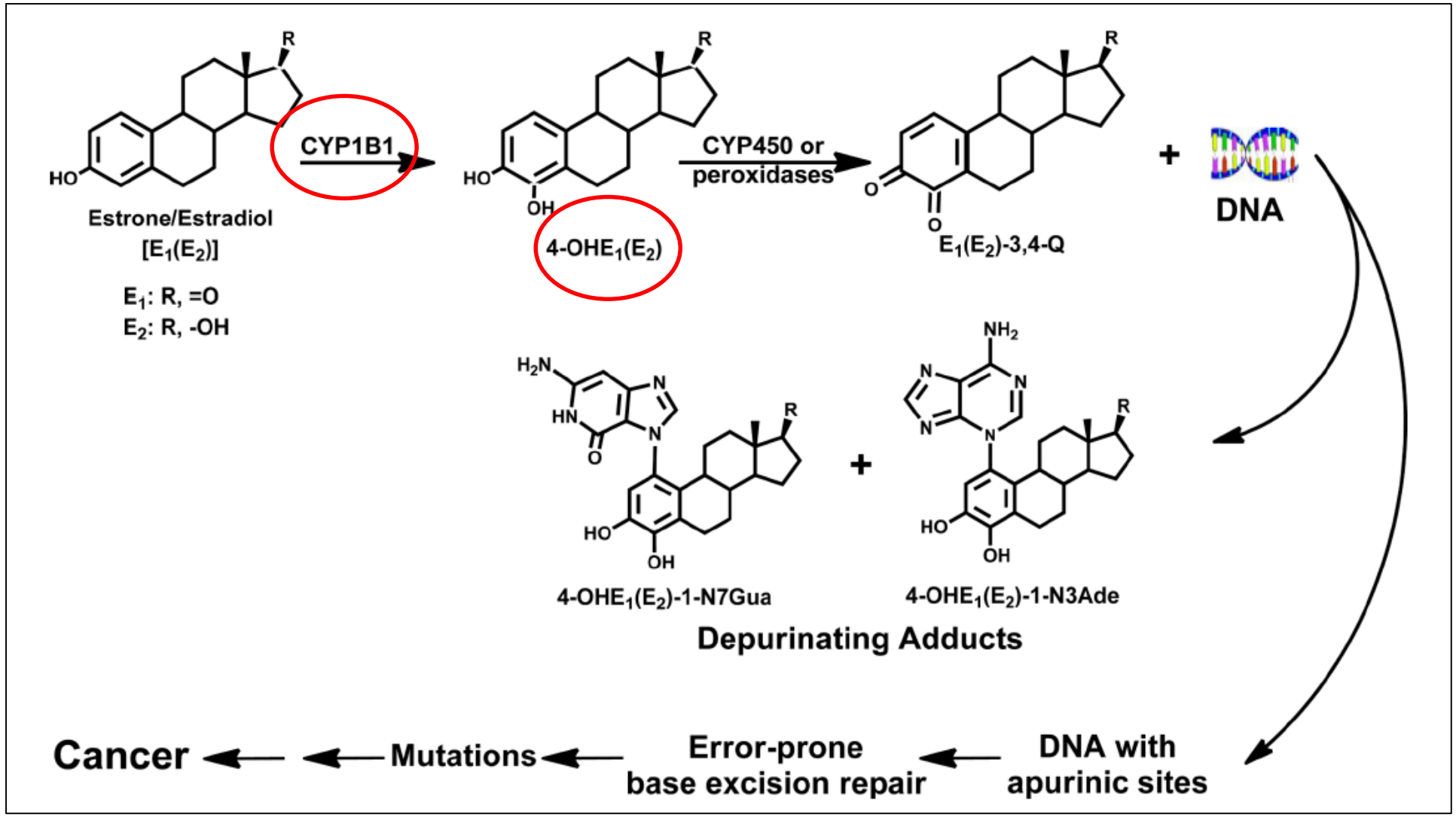
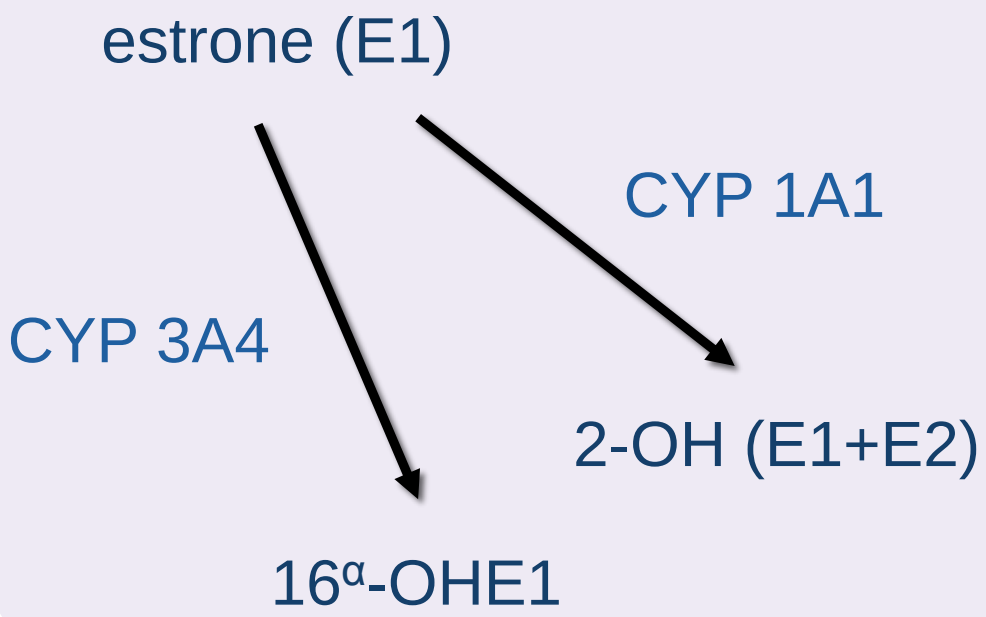
Proposed Mechanism for CA Initiation by Estrogens



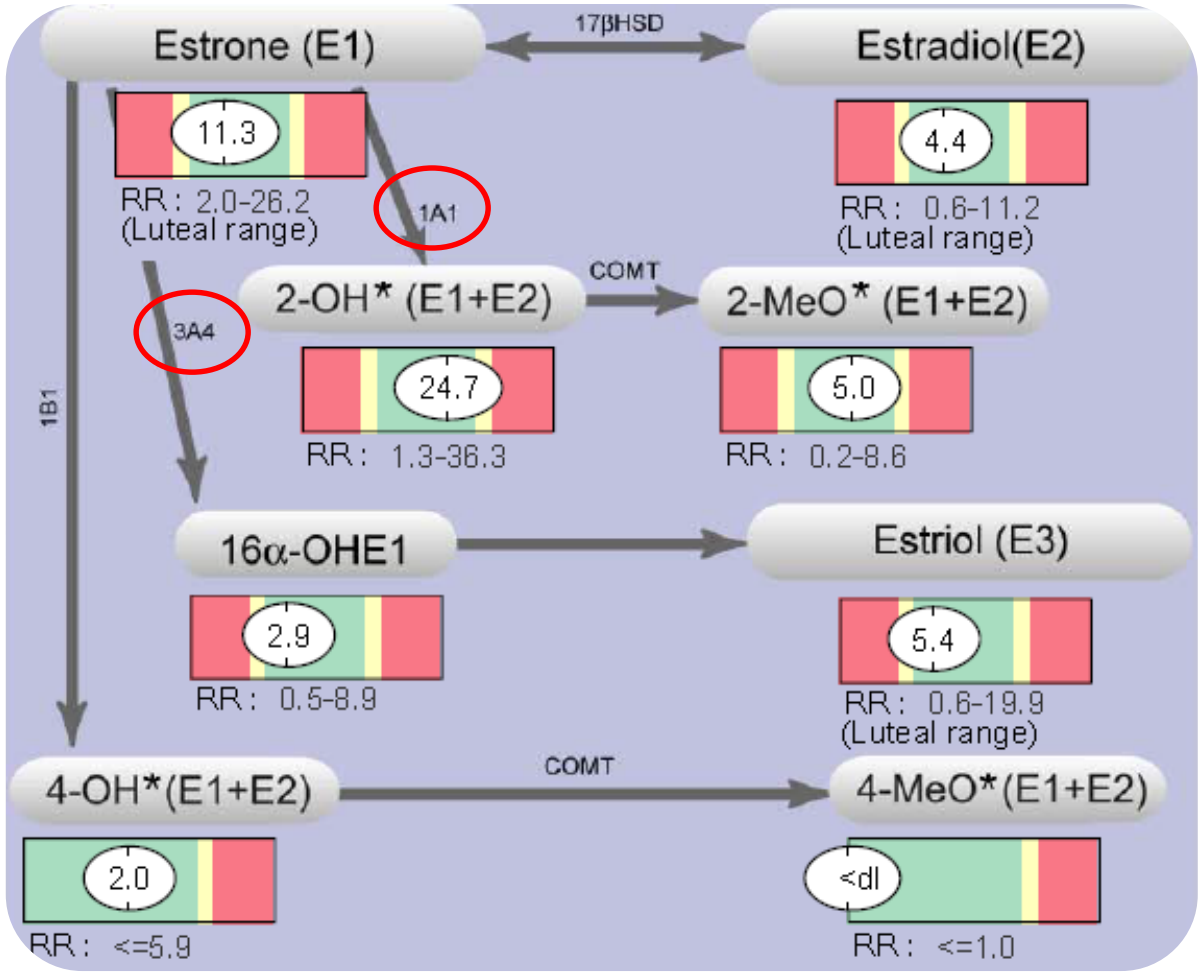
Cavalieri and Rogan. Molecular Etiology and Prevention of Estrogen-Iniated Cancers. Mol Aspects Med. 2014

CYP 1A1 & 3A4 Pathways



- Higher 2-OH (E1+E2)/16α-OH ratios in males have been associated with reduced risk of prostate cancer
- Upregulation of these pathways may be a therapeutic target if 4-OH (E1+E2) levels are high

CYP 1A1 & 3A4 Pathways: Pattern Recognition



Example of normal pattern

- Normal levels of 2-OH (E1+E2)
- Normal levels of 16-α (E1+E2)
- Normal (not high) levels of 4-OH (E1+E2)

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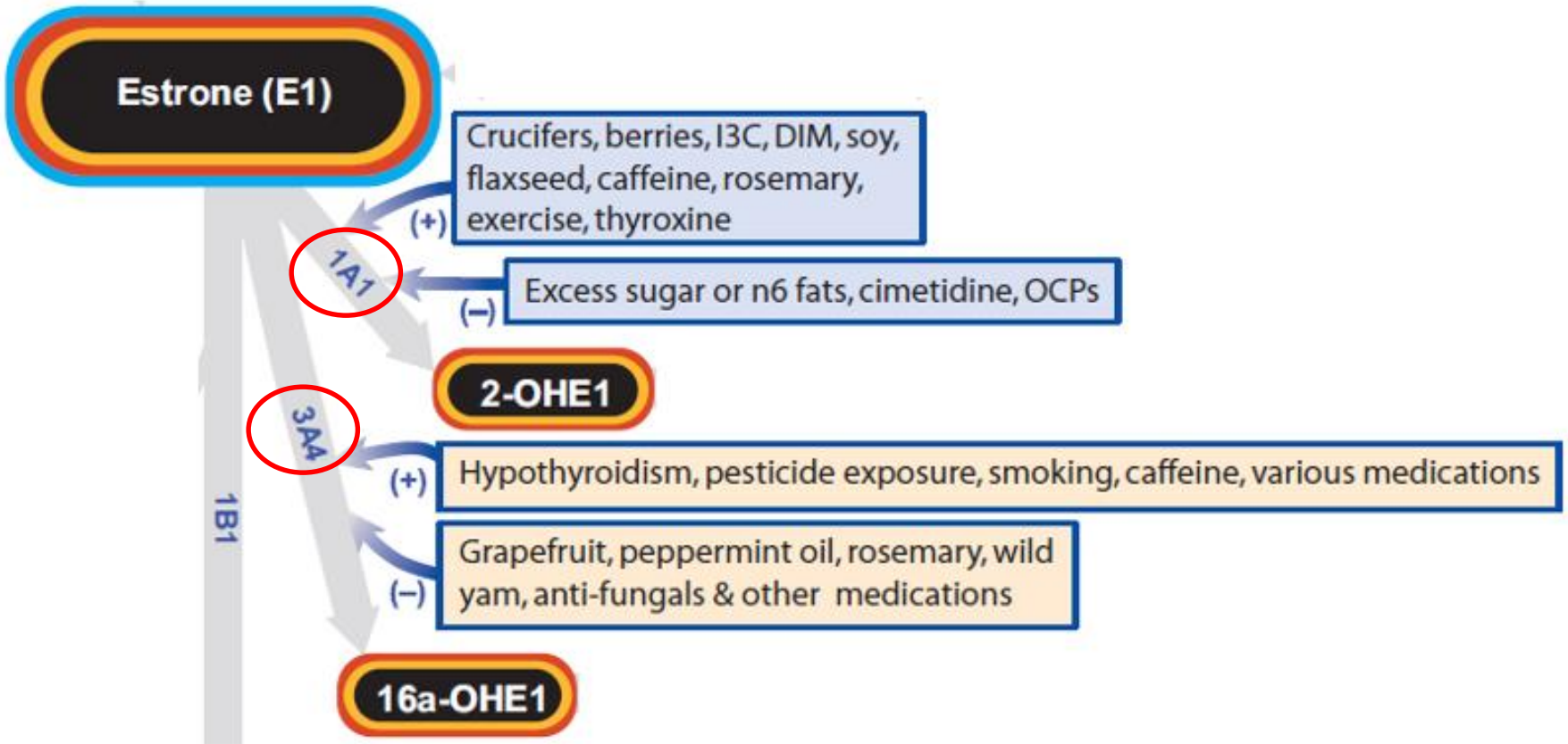
CYP 1A1 & 3A4 Pathways: Tx Considerations



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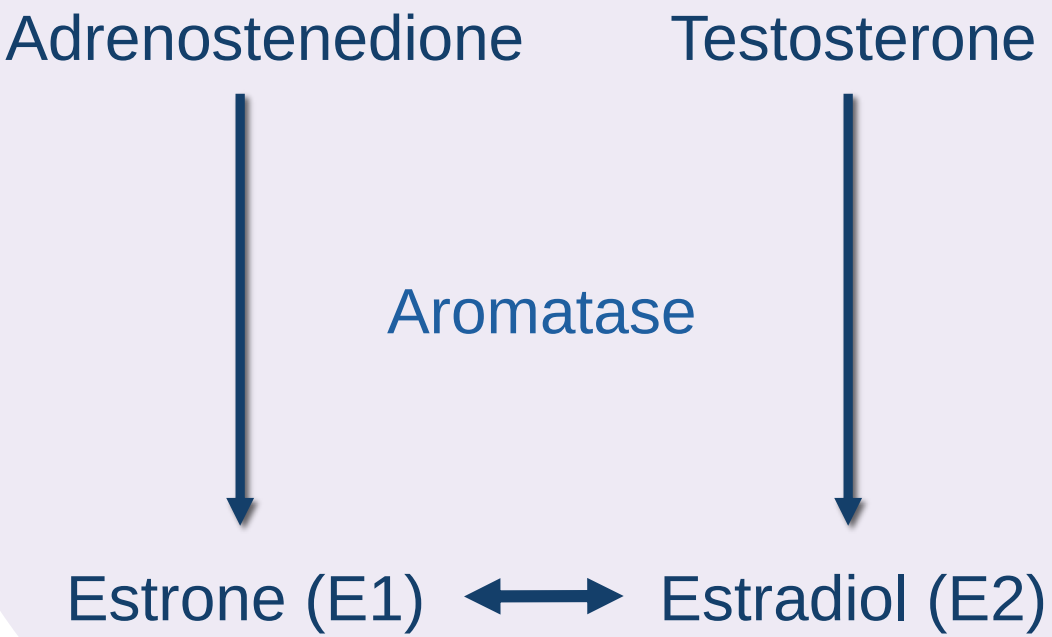
Aromatase Pathway



- Involves conversion of androgens into estrogens
- Found in many tissue types, but high concentrations found in **adipose tissue**, muscle tissue, and testis

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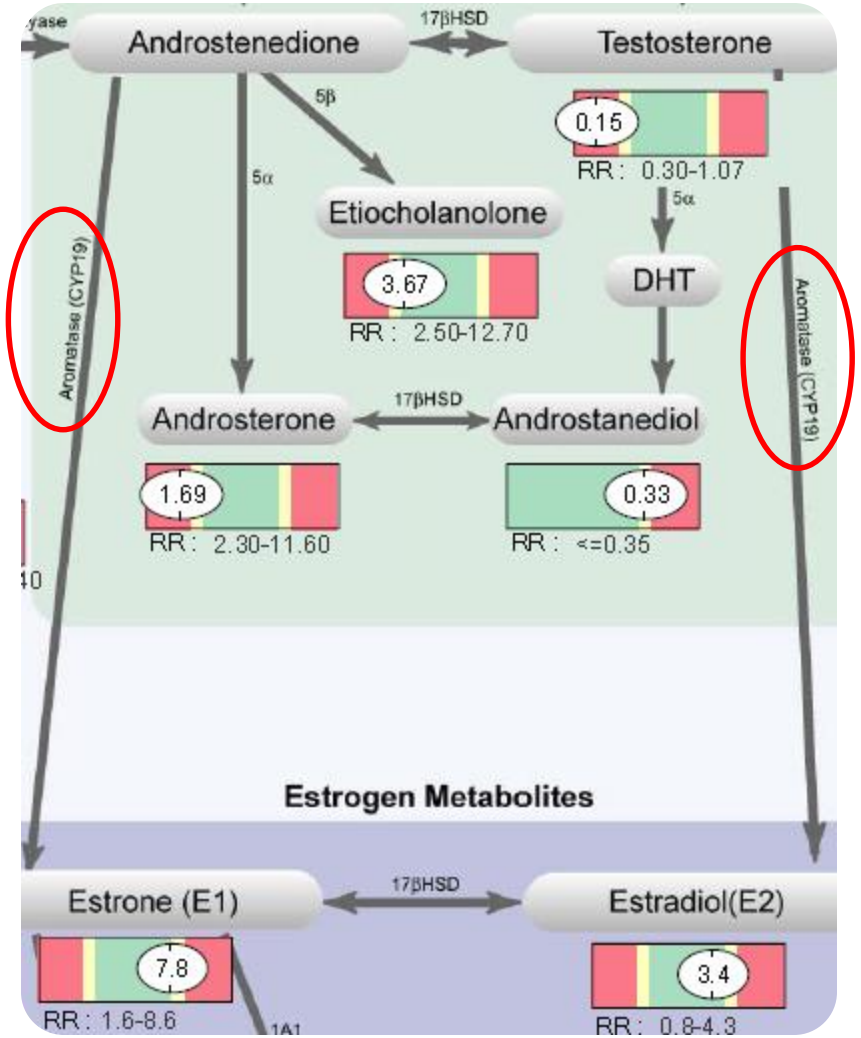
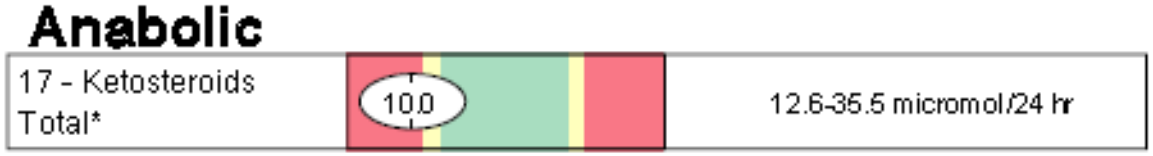
Aromatase Pathway: Pattern Recognition



Example of excessive conversion

- Androgens (17-ketosteroids total) appear to be low, while estrogens (E1 and E2) are robust



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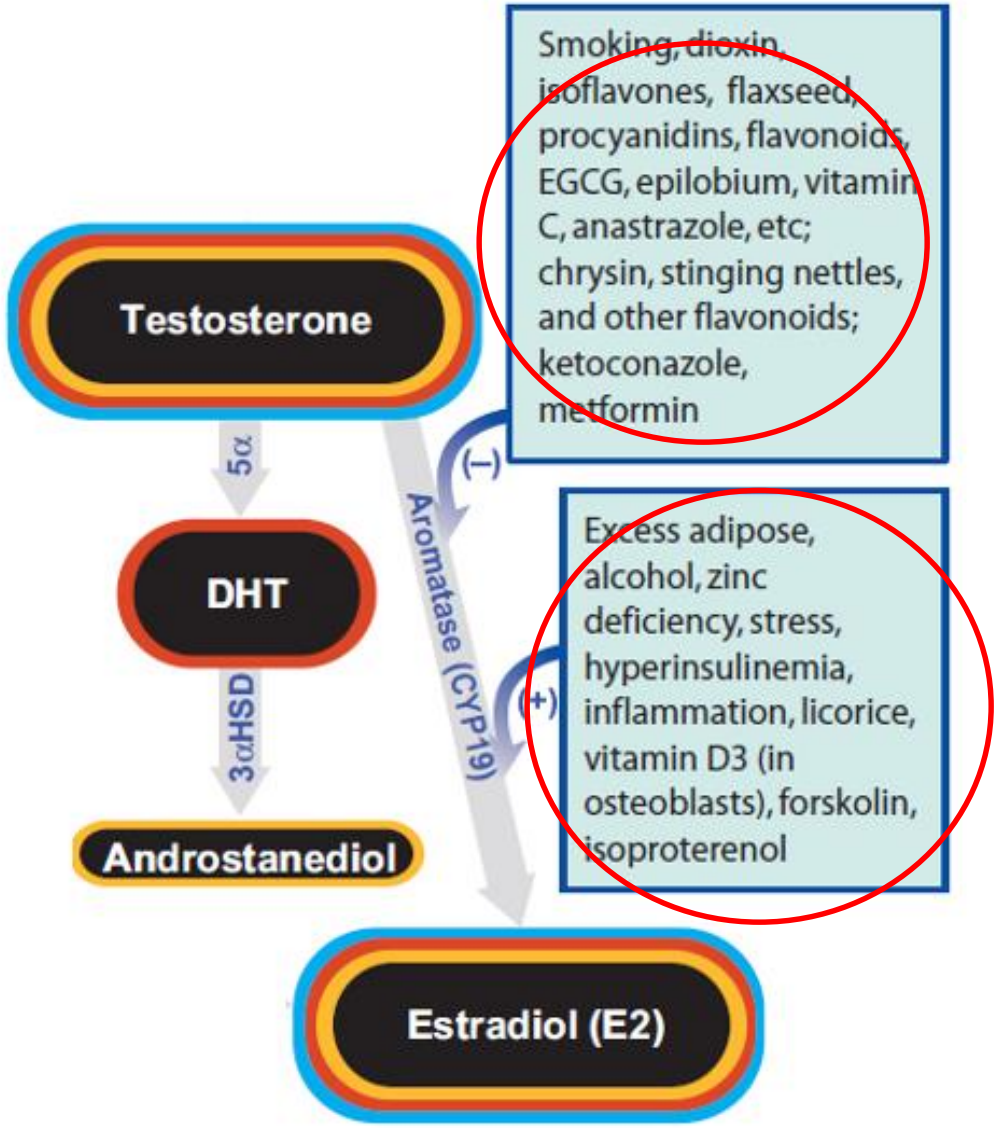
Aromatase Pathway: Tx Considerations



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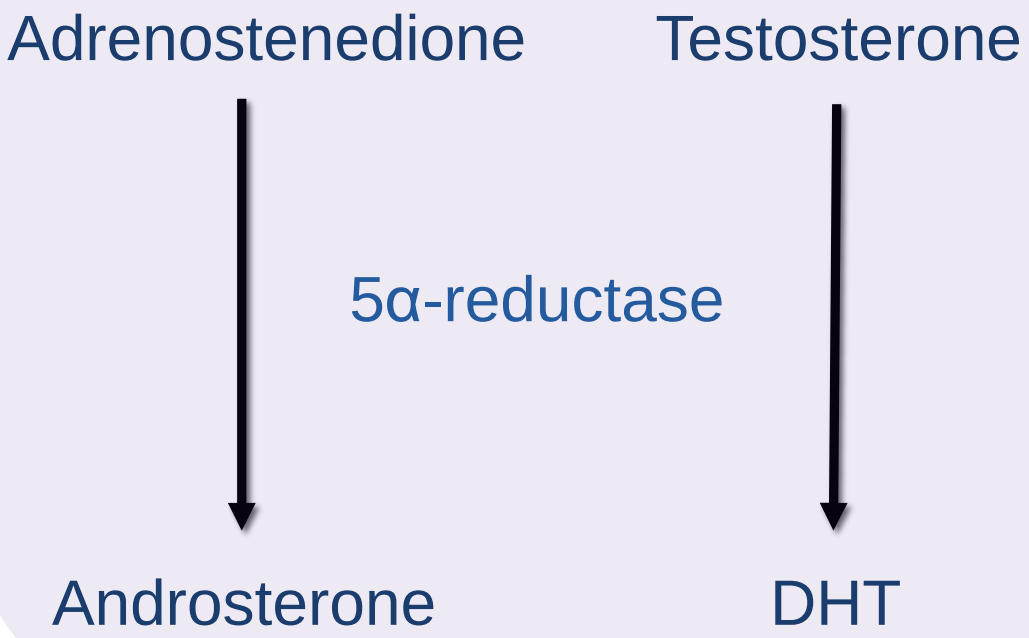
5α-Reductase Pathways



- Strong expression of 5a-reductase as a local androgen amplification mechanism
- DHT is 5x more potent than testosterone
- DHT is found in prostate tissues
- DHT has known associations with:
  - Male pattern baldness
  - Benign Prostatic Hypertrophy (BPH)
- When pathways are upregulated, more DHT is produced

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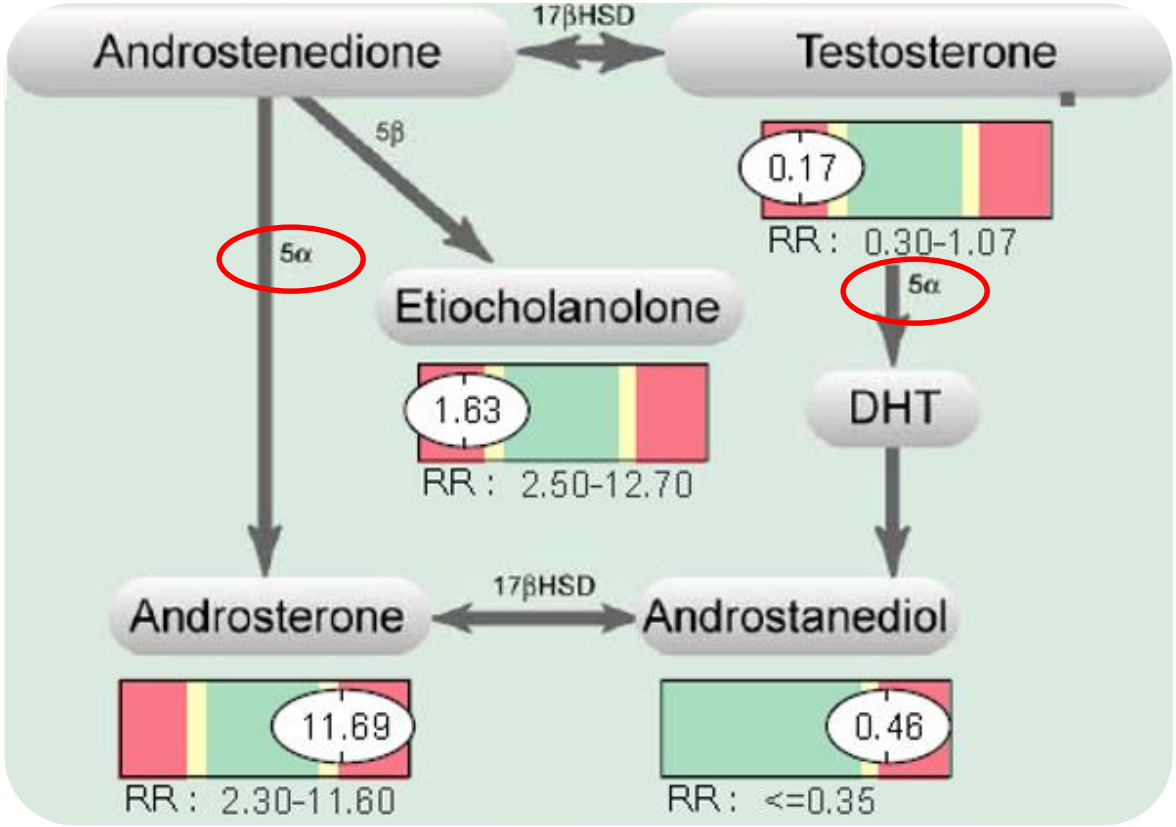
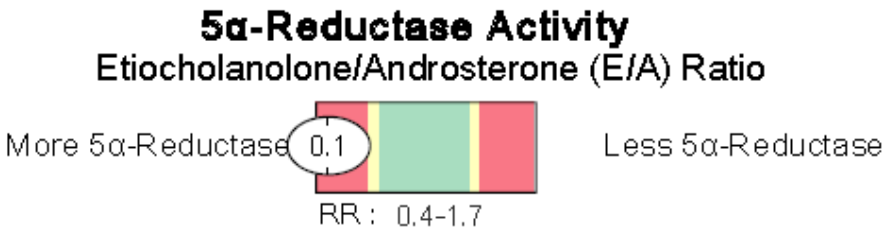
Handelsman, D. Androgen Physiology and Abuse. Endotext, 2016

5α-Reductase Pathways: Pattern Recognition



Example of excessive 5α-reductase activity

- 5α-reductase activity assessment is provided by the etiocholanolone/androsterone (E/A) ratio



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5α-Reductase Pathways: Tx Considerations

Potential reasons for increased enzyme activity:

- High insulin levels / Type II Diabetes
- Obesity

To inhibit enzyme activity:

- Saw palmetto (*Serenoa repens*)
- Finasteride or Dutasteride

To complement a 5α-reductase inhibiting therapy:

- Nettles (*Urtica dioica*)
- EGCG (epigallocatechin gallate)
- Progesterone
- Zinc
- Metformin for androgen receptor targeting (Wang, et al)
- Spironolactone for blocking conversion of potent androgens to weaker ones in peripheral tissues (Medscape, 2017)

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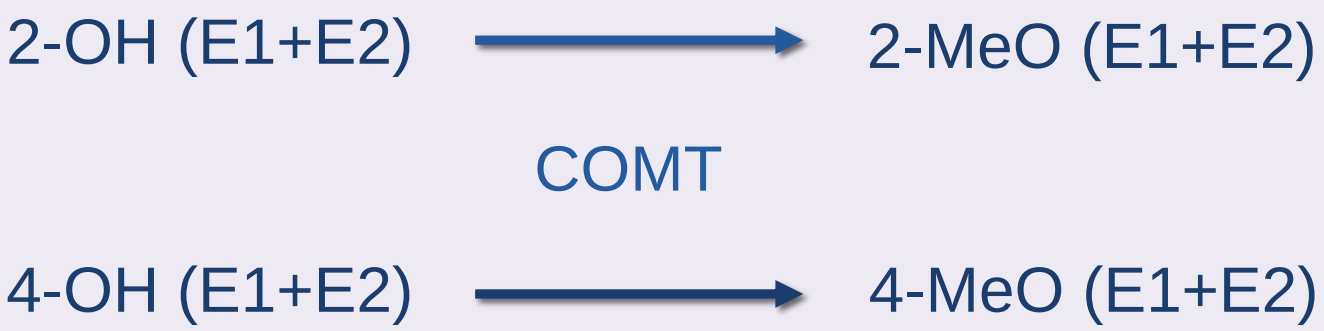
Wang, Y. et al. "Metformin represses androgen-dependent and androgen-independent prostate cancers by targeting androgen receptor." *The Prostate* 75, no. 11 (2015): 1187-1196.

COMT Pathways



- Important conjugation pathways for hydroxylated estrogens
  - Conversion of the “OH” groups to the “MeO” allows for proper detoxification of these estrogen metabolites
- Pathway may be compromised in a patient with a COMT SNP

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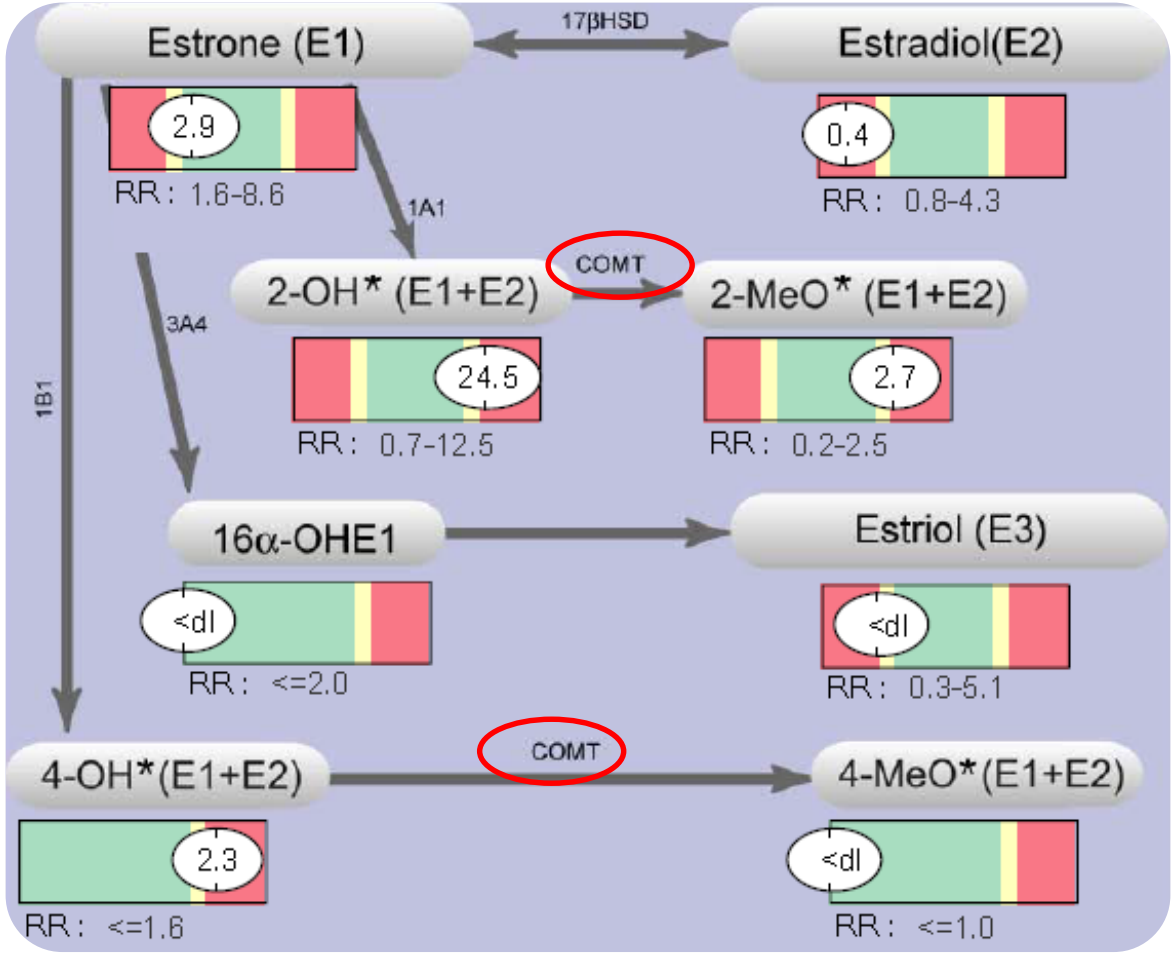
Cavalieri, Ercole, Dhubajyoti Chakravarti, Joseph Guttenplan, Elizabeth Hart, James Ingle, Ryszard Jankowiak, Paola Muti et al. "Catechol estrogen quinones as initiators of breast and other human cancers: implications for biomarkers of susceptibility and cancer prevention." *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer* 1766, no. 1 (2006): 63-78.

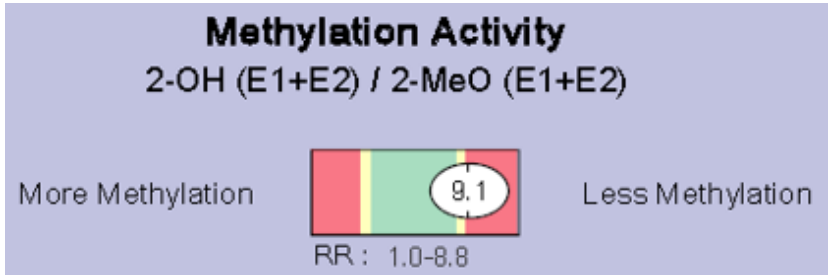
COMT Pathways: Pattern Recognition

Example 1 of 2



Example of poor methylation

- Poor conversion from 2-OH (E1+E2) to 2-MeO (E1+E2)
- Consider COMT SNP (available as add-on)
- A **high** 2-OH (E1+E2) / 2-MeO (E1+E2) ratio may indicate **less** methylation activity



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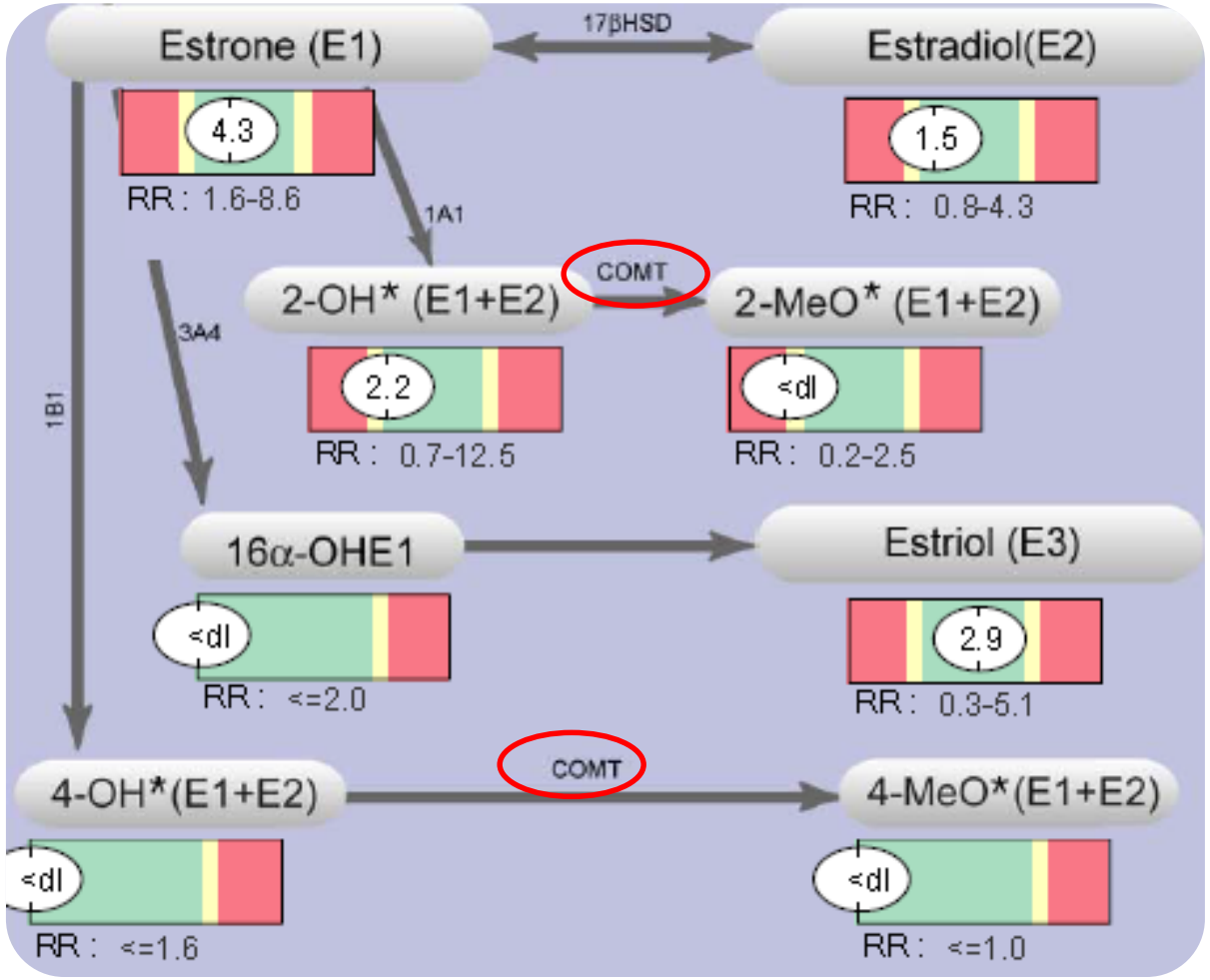
COMT Pathways: Pattern Recognition

Example 2 of 2



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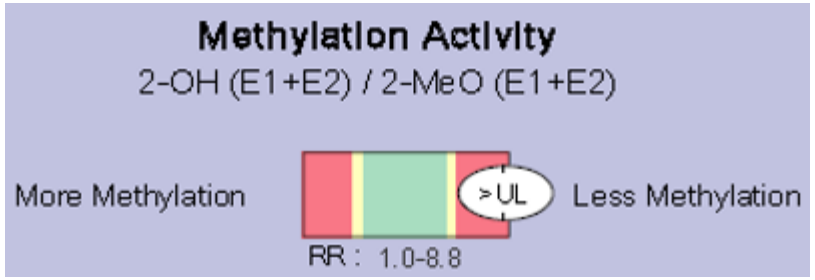

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COMT Pathways: COMT SNP Add-On to Complete Hormones™

A key enzyme involved in the deactivation of catechol compounds

May have increased relevance in:

- Mood imbalances
- Chronic pain syndromes
- Elevated stress levels

Complete Hormones™ GENOMICS

AAs	Patient Result	Impact on enzyme activity
158 V/V		Baseline “normal” COMT activity
158 V/M		Moderately Decreased COMT activity
158 M/M		Substantially decreased COMT activity (3-4 fold reduction)

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Xiao, L. et al. “The l58Val/Met polymorphism of catechol-O-methyl transferase gene and prostate cancer risk: a meta-analysis.” Mol Biol Rep. 2013 Feb;40(2):1835-41.

COMT Pathways: Tx Considerations

Methylation Support

- Magnesium
- B-vitamins (B2, B6, B12)
- Folic acid (also as folinic acid or 5-methy THF)
- Trimethylglycine (also known as TMG or betaine)
- SAMe
- Methionine
- Stress management practices

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Other Clinical Considerations & Resources

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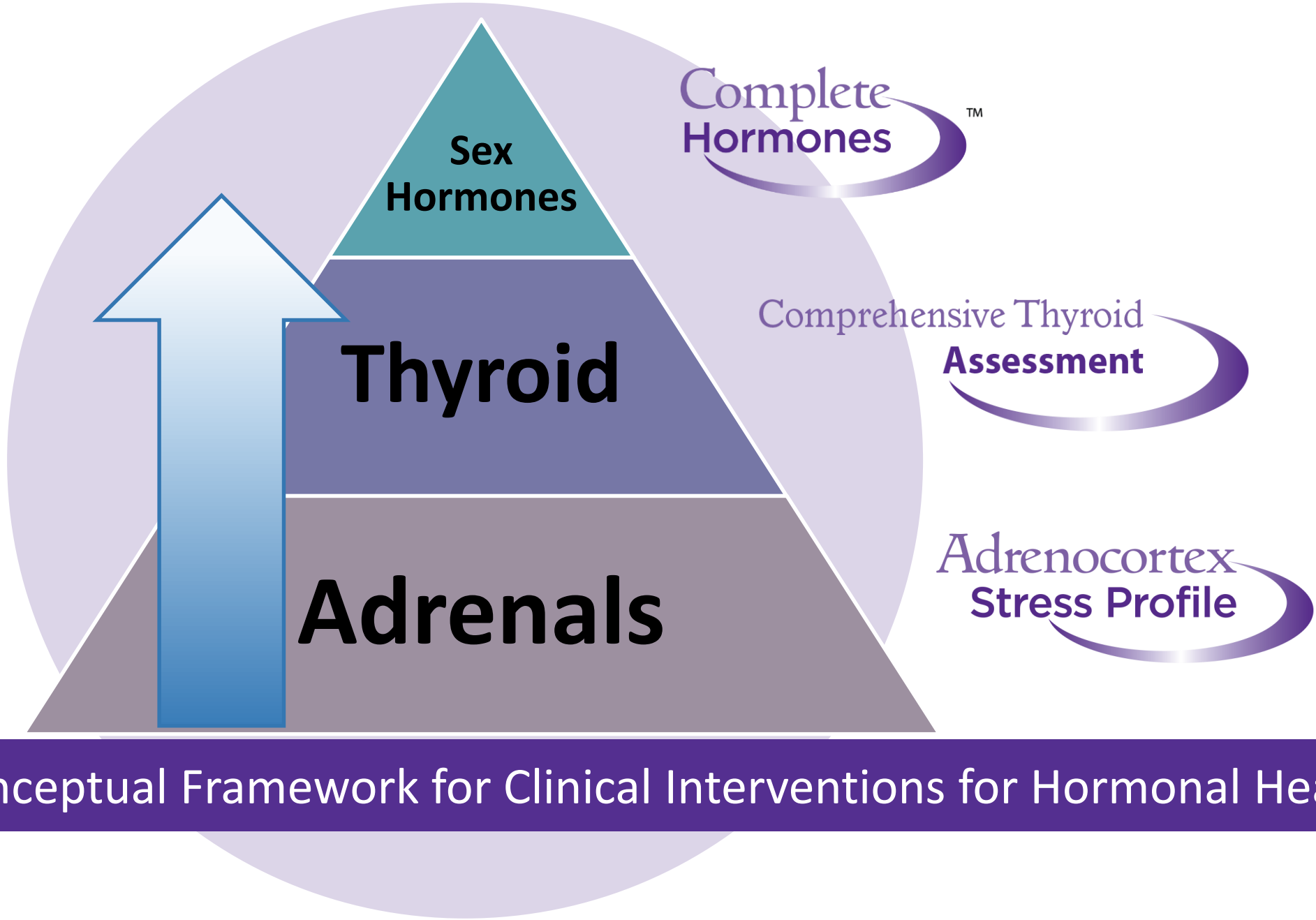
Other Genomic Add-Ons to the Complete Hormones™

MTHFR

- Methylenetetrahydrofolate reductase is one of the key regulatory enzymes in folate and homocysteine metabolism
- Clinical indications for assessing MTHFR include hyperhomocysteinemia and low levels of B vitamins (especially folate), and concerns related to increased risk for cardiovascular disease and stroke, low bone mineral density and/or fracture, and risk of all cancers

VDR

- Vitamin D Receptor intracellular hormone receptor that specifically binds the active form of vitamin D and interacts with target-cell nuclei to produce effects
- Polymorphisms of this receptor impact the body's ability to utilize bioavailable vitamin D, and low levels of vitamin D have been linked to an expanding list of health concerns including osteopenia/osteoporosis and overall musculoskeletal health, autoimmune diseases, obesity (adipogenesis, adipocyte-generated inflammation and adipocyte secretion), metabolic syndrome, and cancer risk and progression (breast, prostate, lung, thyroid, colorectal)



A Conceptual Framework for Clinical Interventions for Hormonal Health

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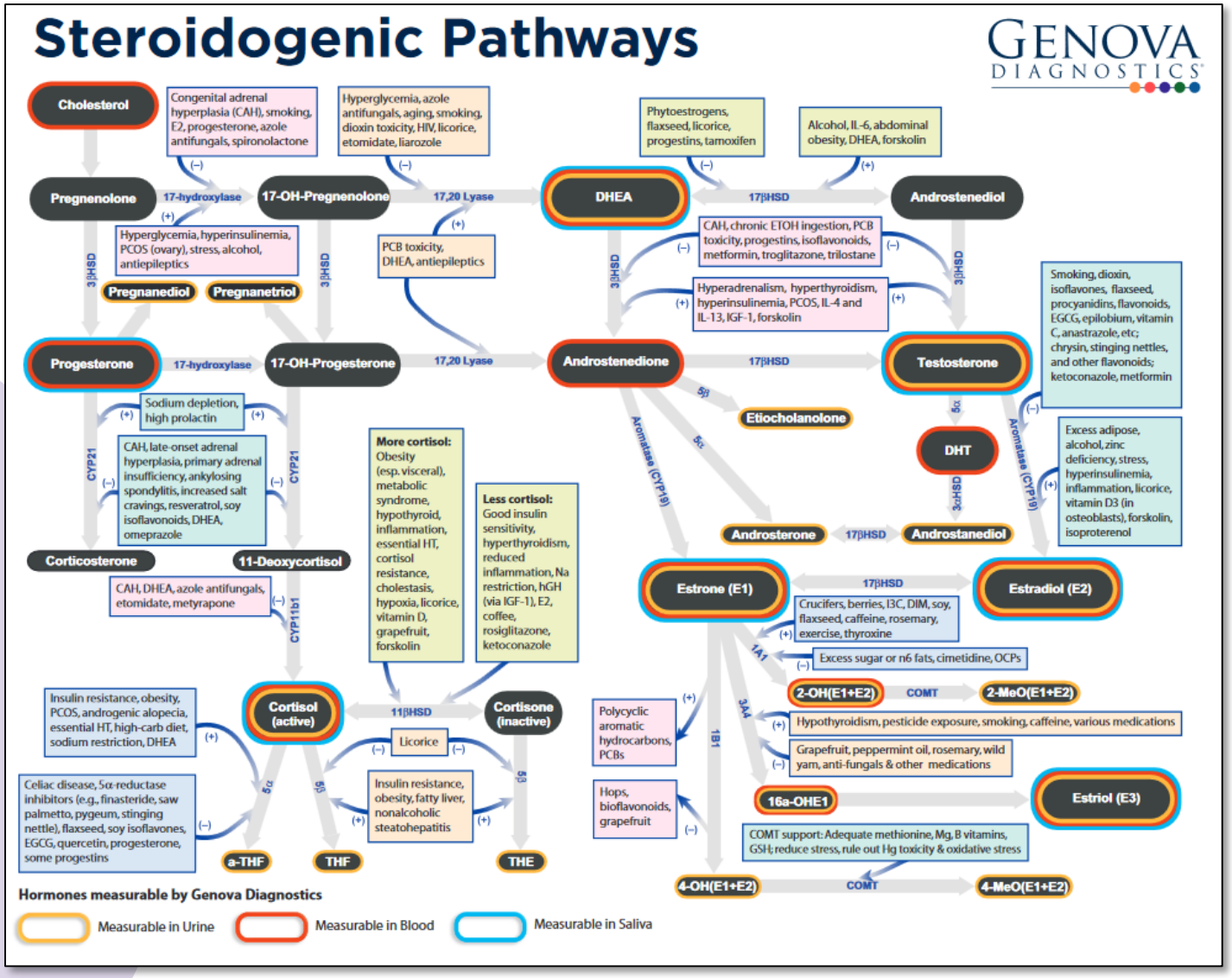
Genova Diagnostics Resources

Steroidogenic Pathways Chart

This document, available for download at www.gdx.net/files/Steroidogenic-Pathways-Chart.pdf

Or, look for us at your next conference and pick up a color copy from the Genova Diagnostics booth.



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Christine Stubbe, ND
Moderator

Warren Brown, ND
Presenter

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- How Genova's profiles might support patients in your clinical practice
- Review a profile that has already been completed on one of your patients

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Going beyond the PSA

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