



New Paradigms in Understanding PCOS: Impact of the Microbiome

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Technical Issues & Clinical Questions

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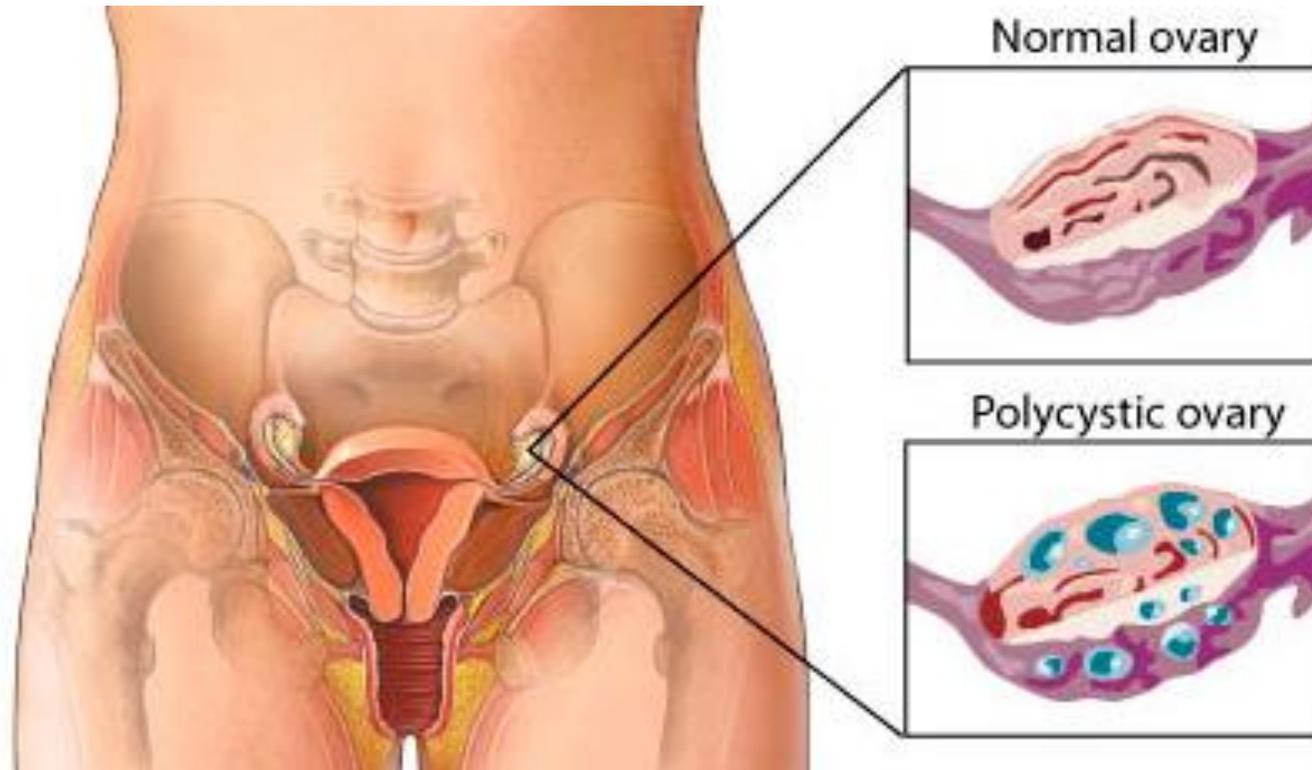
Lecture Objectives

- Review what the gut microbiome is, how it develops, and its significance for PCOS patients
- Discuss the “unhealthy gut microbiome” and its role in the development of systemic inflammation, insulin resistance, weight gain, hyperandrogenemia, and ovulatory dysfunction (creating the features of PCOS)
- Review the laboratory tests available to evaluate the gut microbiome
- Understand how to restore a healthy gut microbiome to re-establish metabolic homeostasis through dietary choices



Polycystic Ovary Syndrome (PCOS)

A hormonal disorder, becoming obvious after puberty, in women of reproductive age – named for the finding of small cysts developing in the outer edge of each ovary





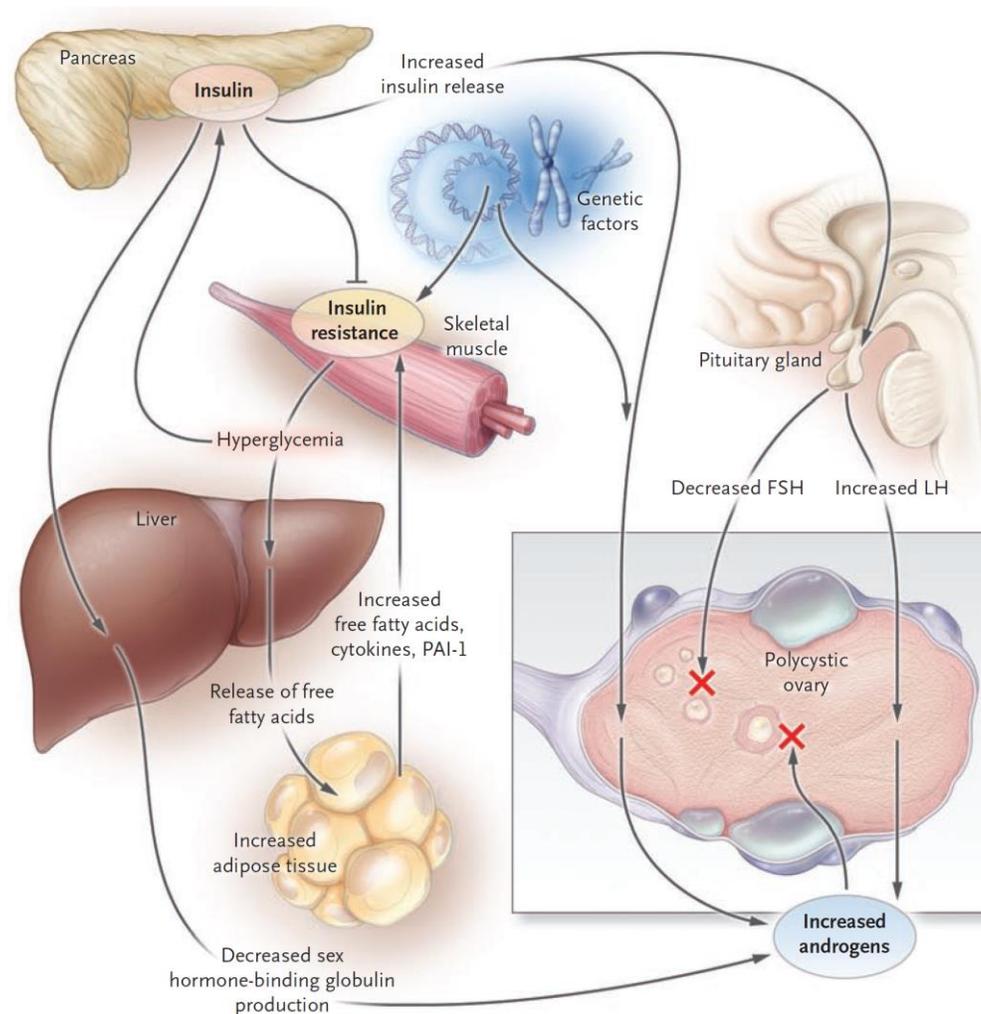
PCOS is a Global Epidemic

- A world-wide epidemic: now found EVERYWHERE!
- The most common endocrine dysfunction of women
- Affects 10-20% of women (some say up to 25%!)
- 88% are overweight/obese, 20% normal/lean
- Obese carry all the classic issues of PCOS, in addition to the metabolic burdens of obesity
- A LIFE-LONG disease with enormous medical, emotional, and financial consequences
- High risk for diabetes and metabolic syndrome in first degree relatives



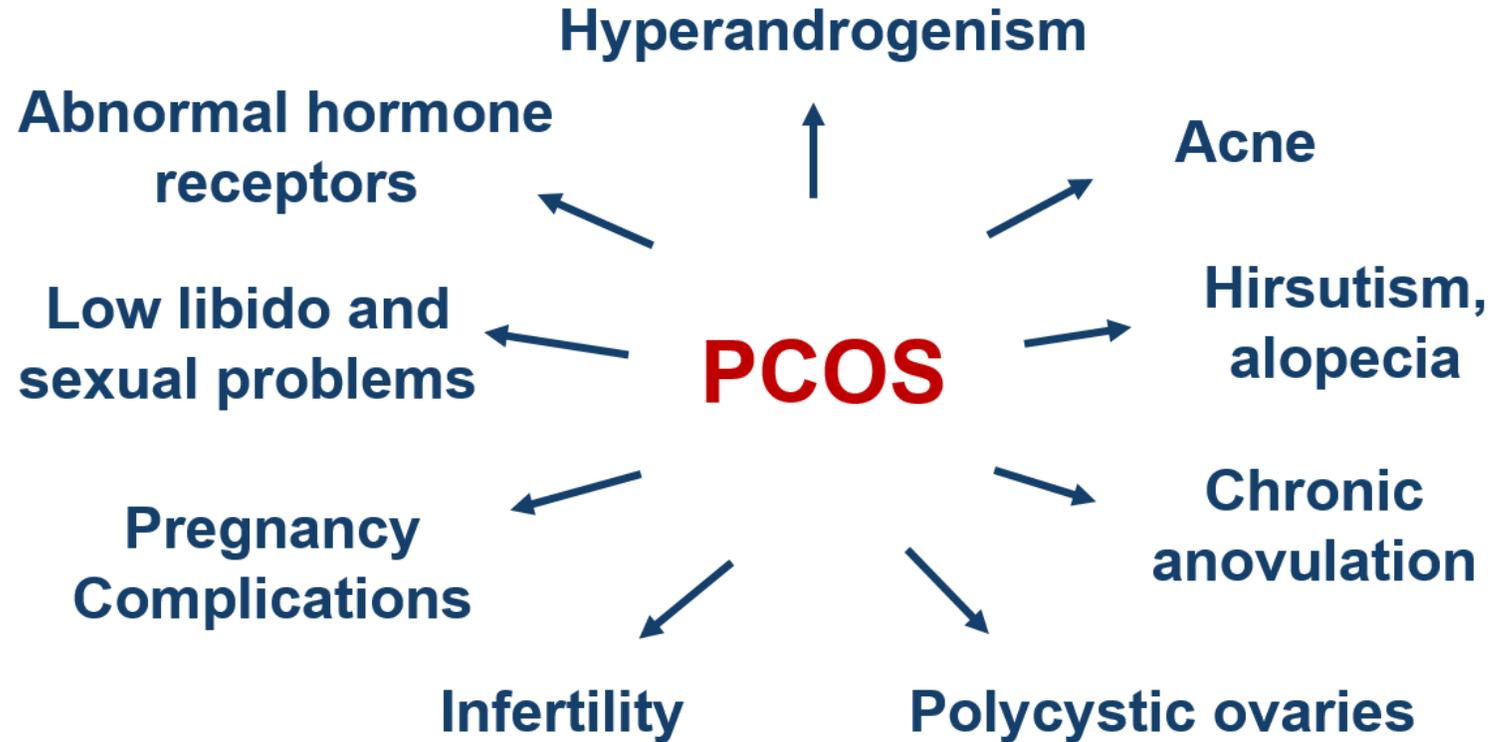
Complex Hormonal and Signaling Interactions are Involved

Dysregulation of various **hormonal** and **metabolic** processes



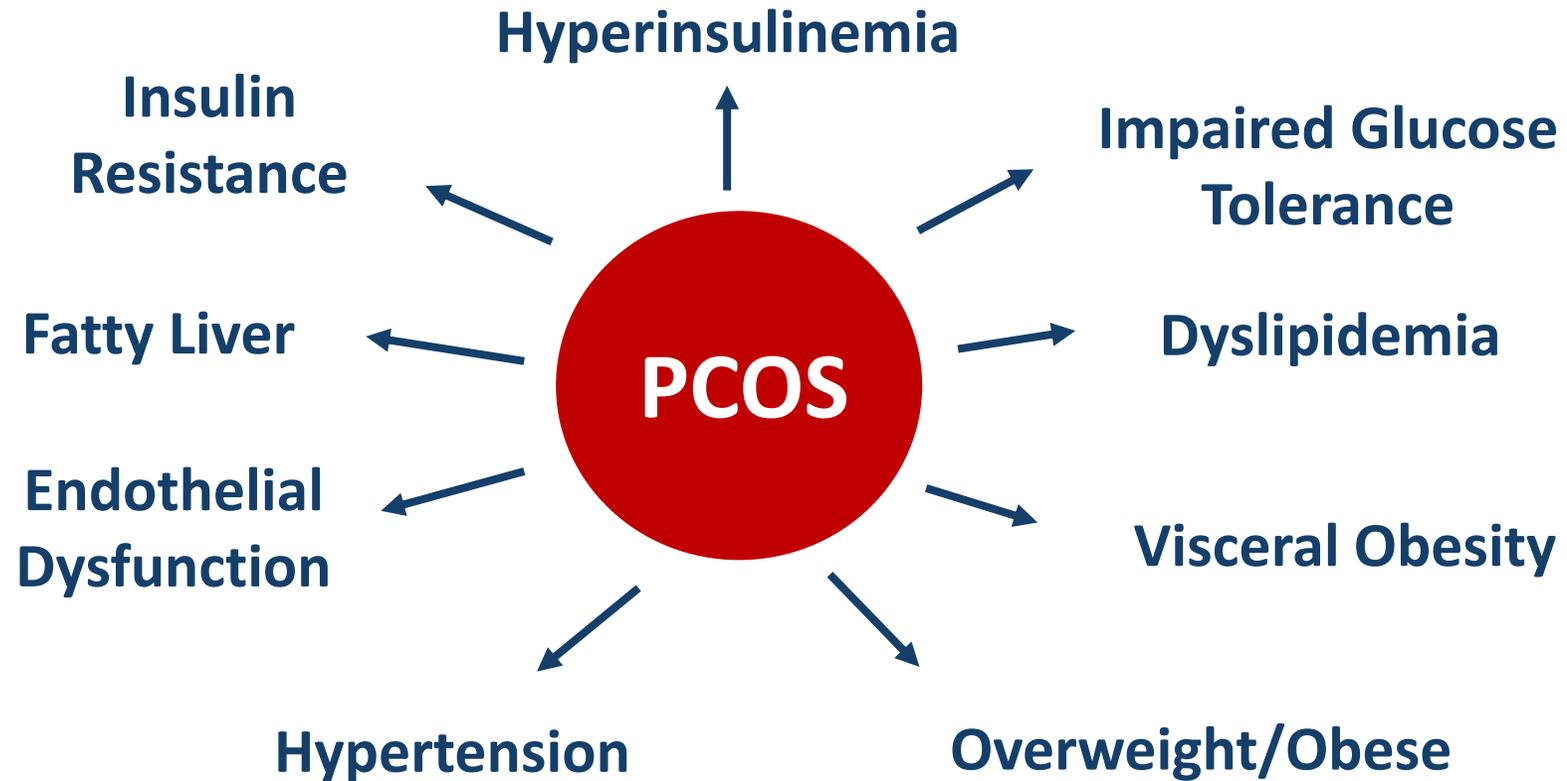


Hormonal/Reproductive Effects of PCOS





Metabolic Effects of PCOS





PCOS and Other Inflammatory-Related Conditions

- Autoimmune disease (especially thyroid)
- Skin tags and darkened skin (acanthosis nigricans)
- Gastrointestinal problems (IBS, leaky gut)
- Arthritis and tendinitis
- Depression, anxiety, stress
- Vaginal infections
- Sleep dysfunction and OSA
- Cancers
- Other GYN conditions: fibroids, endometriosis



Inflammation is The Driving Force

- Enhanced abdominal visceral fat
- Insulin resistance
- Abnormal adipose function with inappropriate adipokine release
- Inflammatory cytokines
- Abnormal glucose-regulation/gut hormones
- Ectopic lipid accumulation and lipotoxicity often occurs



Upregulated Macrophages: Set the Scene for Inflammation!

- Increased cytokine release from MNCs following lipopolysaccharide (LPS) exposure in the fasting state
- Pre-activation contributes to development of insulin resistance and hyperandrogenism in PCOS



Etiology of PCOS

- Complex interaction between genetics and the environment
 - genetic expression
- Prenatal hormonal fluctuations within the womb
- Exposure to endocrine disruptors, in-utero and subsequently – focus has been on BPA
- Abnormal hormone receptor functioning
- Oxidative stress beginning in-utero
- Gut inflammation: “leaky gut” and systemic inflammation, IR, elevated androgens

**The GI Tract:
An Exquisite Environment Which is Pivotal to
Maintain Local and Systemic Homeostasis**





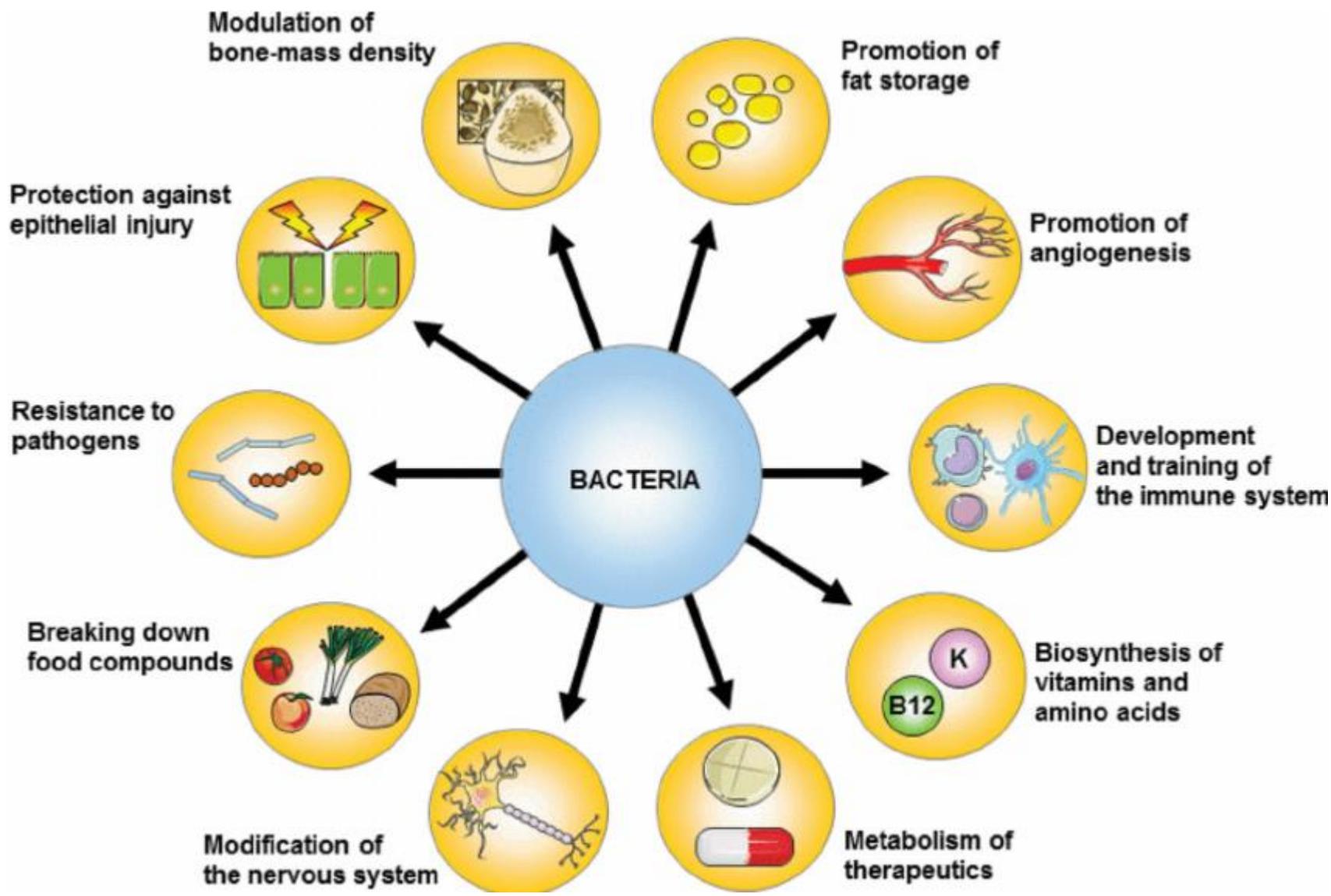
New Concepts - What is a Human?

- We are not quite what we seem!
- A microscopic civilization lives within and on us – controlling much more than we ever could have guessed!
- The gut microbiome impacts every aspect of our biological systems: digestion, metabolism, neurological, reproductive, cognitive, emotional, immune



Concept of The Super - Organism

- Our microbiome is the most complex ecological system ever discovered!
- Our incredible ecosystem consists of hundreds of bacterial species
- Controversial! The microbes may outnumber our own cells 10:1 ... or maybe they are equal in number!
- There is much yet to learn!





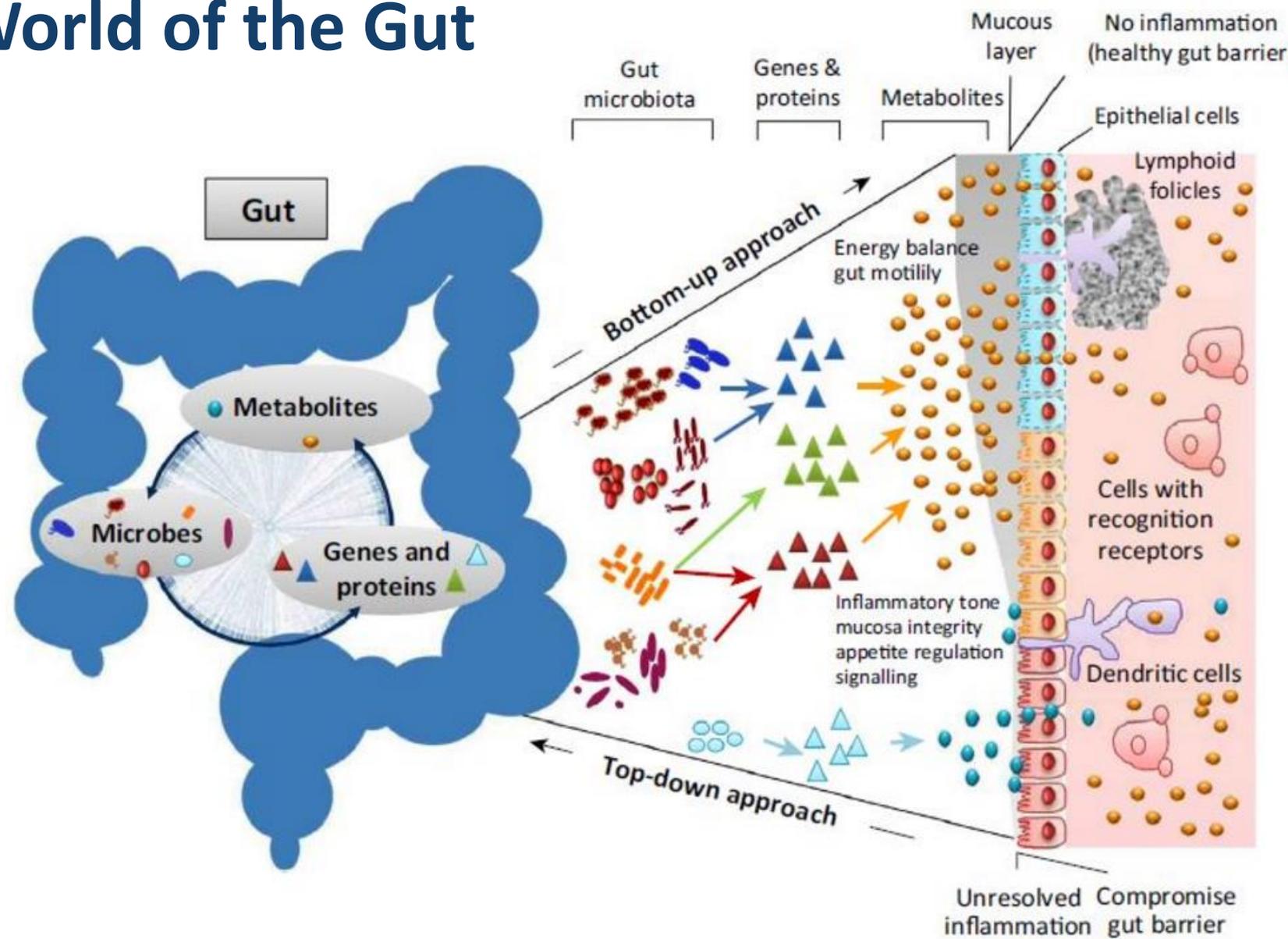
Role of Short-Chain Fatty Acids

- Can cause pathogen displacement
 - Secretes antimicrobials and competes for sites of nutrients (colonization resistance)
- Development of the immune system
- Important for development of regulatory T-cells, T-helper 1 and 2 cells, and T-helper 17 cells
- Exert strong immunomodulatory action—release of protective peptides, cytokines, chemokines, and phagocytes – “stuff” to aid our immune system!



The Complex World of the Gut

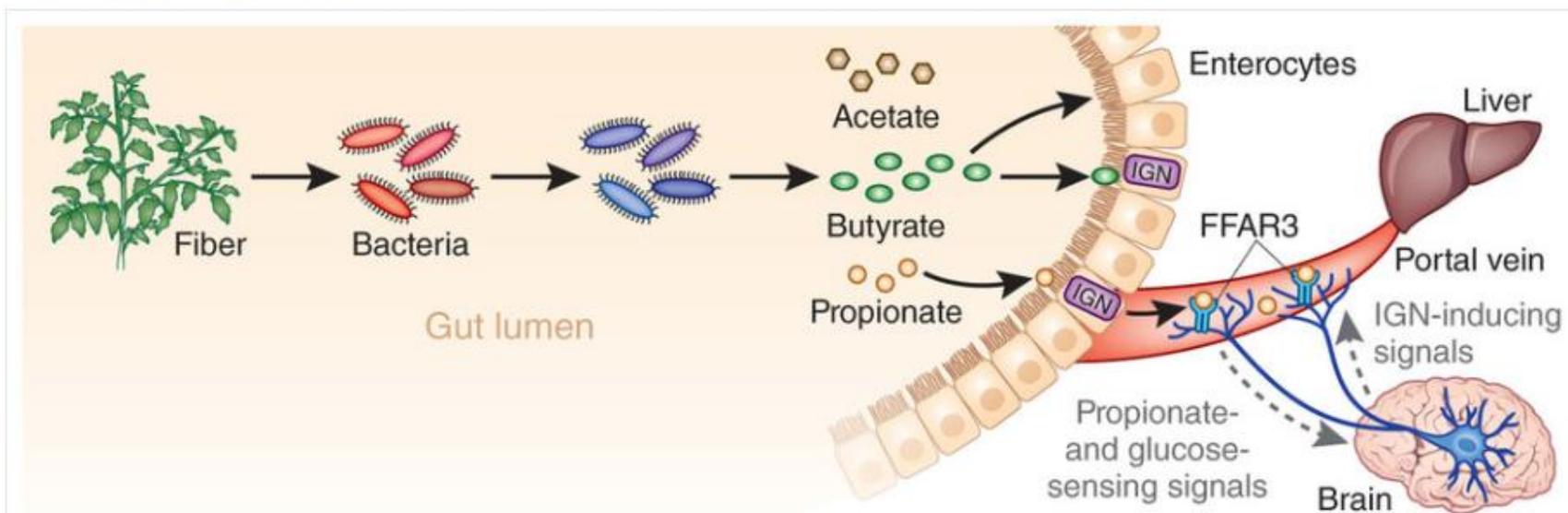
This figure shows how microbiota species are interchangeable in terms of functions by means of the metabolites produced by the action of gene products contained in the gut bacteria





Interactions: Microbiome and Short Chain Fatty Acids

Published online 10 March 2014



Fibers, specific oligosaccharides and resistant starch reach the colon intact, where they induce shifts in the composition and function of intestinal bacteria (shifts indicated by different colors). Intestinal bacteria use these compounds as substrates for the production of the short-chain fatty acids acetate, propionate and butyrate. These microbial metabolites are taken up by intestinal epithelial cells called enterocytes. Butyrate mainly feeds the enterocytes, whereas acetate and propionate reach the liver by the portal vein. Enterocytes can synthesize and release glucose to the portal vein. Propionate and butyrate promote intestinal gluconeogenesis (IGN) in different ways. Butyrate directly activates the expression of gluconeogenic genes in enterocytes by cAMP signaling whereas propionate stimulates gluconeogenesis by functioning as a gluconeogenic substrate and by FFAR3-dependent stimulation of peripheral nerves of the portal vein. The resulting gut-to-brain afferent nervous signal is required for activation of IGN, and nerves leaving the brain convey IGN-inducing signals back to the portal vein. It is not known how the efferent signals control IGN.



Major Influences on the Microbiome

- Type of birth and infant diet
- Diet, probiotics, and prebiotics
- Medications: antibiotics, NSAIDs, OCPs, PPIs, H2 blockers, laxatives, opioids
- Toxins in meal
- Frequency of meals
- Stress (emotional, social), sleep, hygiene

HORMONES – the forgotten piece



Alteration of Estrogen Receptor Function in Women with PCOS

- E2 Receptor Beta expression significantly higher than E2 Receptor Alpha
- E2 Receptor Beta is lower compared to levels of controls
- E2 Receptor Alpha is lower than levels found in controls



Old/New Views on Obesity, Insulin Resistance, and Metabolic Syndrome

- Formerly thought caused only by a positive caloric balance when caloric intake exceeds caloric expenditure and the excess of energy is stored in adipose tissue
- Studies show changes in the gut microbiota trigger the pathogenic mechanisms to promote obesity, T2DM, and metabolic syndrome
- Intestinal microbiota in T2DM patients exhibit dysbiosis

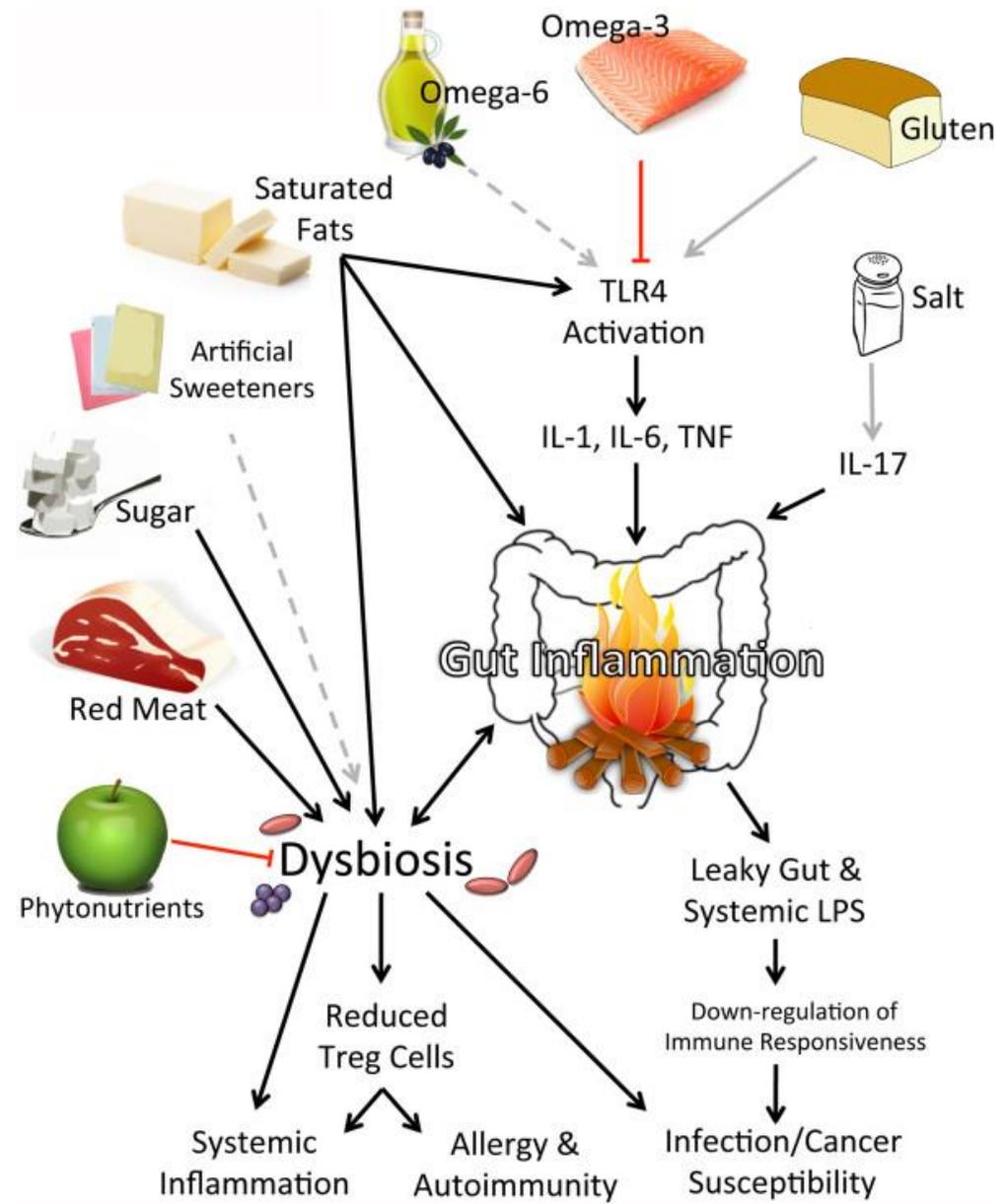


Western Diet and Endotoxemia

- Endotoxemia-stems from disruption of intestinal barrier & increase in Gram negative bacterial content of the microbiota
- High fat, high simple carbohydrate meal comprehensive endotoxemia and inflammation, increases expression of TLR-4 (specific receptor for endotoxin), and SOCS:- a protein - interferes with insulin signal transduction

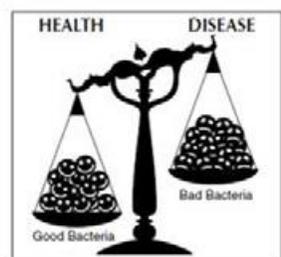


Dysbiosis and Inflammation





High fat/ sugar, low fibre diet causes an imbalance between "good" and bad" gut bacteria

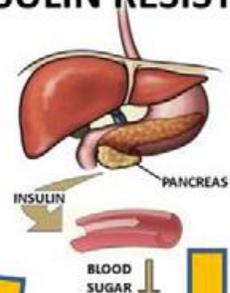


Obesity alters gut microbiota



Obesity directly increases gut permeability

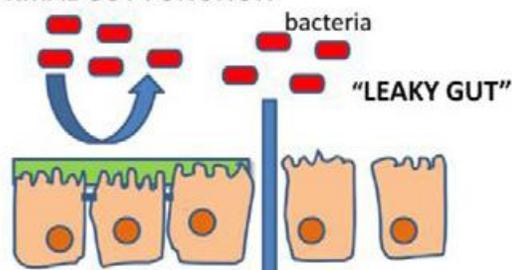
INSULIN RESISTANCE



Insulin drives Testosterone Production in ovary, while Impairing follicle development

Dysbiosis of colonic microbiota mucous production and epithelial integrity- resulting in a "leaky gut"

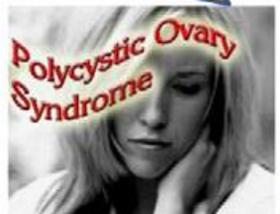
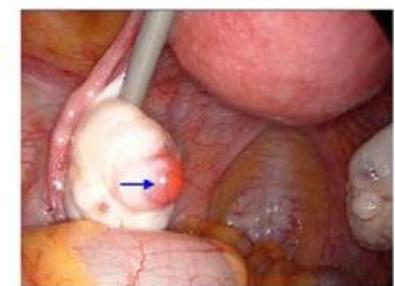
NORMAL GUT FUNCTION



Normal tight junction function and mucous barrier preventing the trans-epithelial passage LPS

Macrophages activated by bacterial LPS that passes through gut wall

Gut inflammation initiated State of Insulin resistance



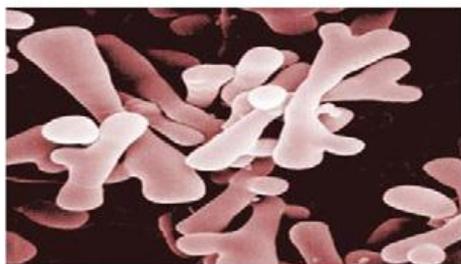
Polycystic morphology On ultrasound



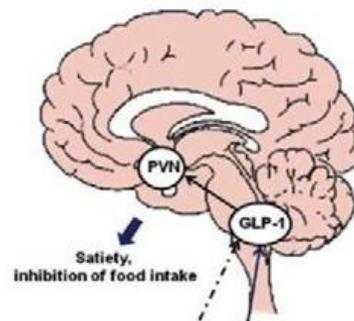
Acne/ hirsutism



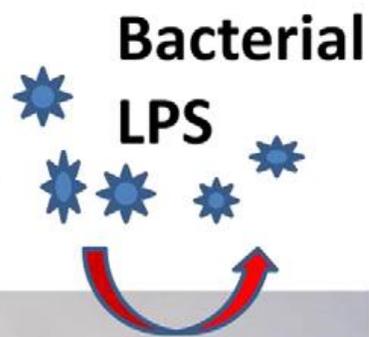
Impaired ovulation



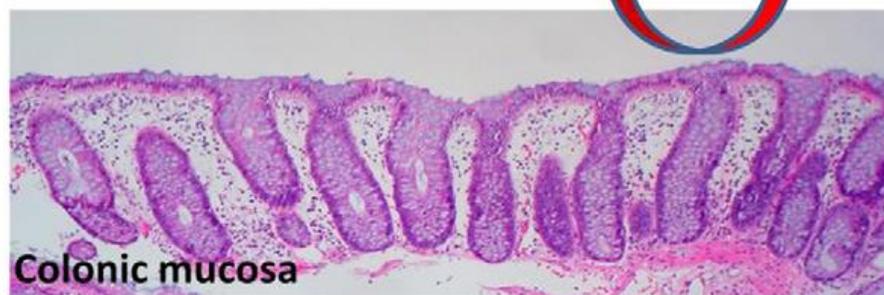
Probiotics and/or prebiotic treatment increases the number of beneficial "good" bacteria in the colon



Beneficial "good" bacteria produce Short Chain Fatty Acids (SCFA) that increase colonic mucous production and tight junction function- decreasing the passage of immuno-stimulatory LPS from the colonic lumen into the circulation



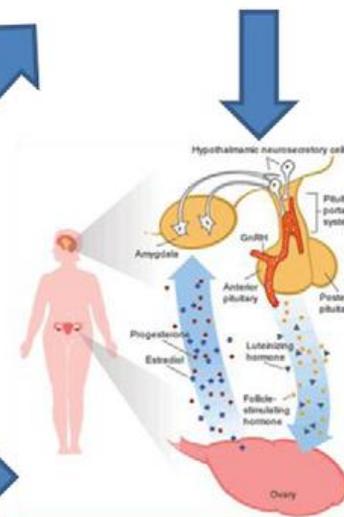
Increased production of the satiety hormone GLP-1 by the healthy colon mucosa reduces food intake and results in a Decrease in body fat content



Colonic mucosa



A reduction in inflammation due to reduced passage of LPS across the gut mucosa results in an improvement in insulin sensitivity, with a drop in serum insulin levels



RETURN TO NORMAL OVARIAN FUNCTION



Serum LBP Associated with Insulin Resistance in Women with PCOS

- Compared with controls, PCOS subjects had significantly higher LBP concentration
- Applied to both lean and obese PCOS women compared with controls
- Serum LBP levels significantly elevated in PCOS and independently associated with IR in PCOS



Dysbiosis of Gut Microbiota: Clinical Parameters

- Clear association of altered gut microbiome and PCOS disease phenotypes
- Reduced Akkermansia measured
- Plasma levels of serotonin, ghrelin, and peptide YY (PYY) were significantly decreased in PCOS patients and had a negative correlation with waist circumference
- Reduced gut microbiome diversity
- Serotonin made by spore forming gut bacteria – reduced in PCOS
- Increase in LPS producing bacteria in PCOS pts



Confirmation of Altered Gut Microbiome in PCOS Women

- Stool microbiome of PCOS patients showed a lower diversity and an altered phylogenetic composition compared to controls
- Alterations in some but not all markers of gut barrier function and endotoxemia
- In mouse model, dysbiosis of gut microbiota was associated with the pathogenesis of PCOS
- Fecal microbiota transplantation and *Lactobacillus* transplantation were beneficial as treatments of PCOS rats



New Ways to View Food

FOOD AS INFORMATION

FOOD AS MEDICINE

FOOD AS A HORMONE

**FOOD AS NOURISHMENT
FOR OUR GUT MICROBIOTA**





Food as Information

- Cannot just look at the macronutrient and micronutrient content of food to understand its actions
- Think of food differently-identify food and food metabolite-receptor interaction to understand the relationship between the food we eat and diseases, including diabetes
- Food components interact with gut flora to induce indirect signals



Food as a Hormone

- Food can be considered a cocktail of “hormones” ... food components travel through the blood and nutrient substrates can act as signaling molecules by activating cell-surface or nuclear receptors, to regulate metabolic health



Food to Feed our Microbiome

- New fields of bio-therapeutics-focus on diet to include nutrients that positively affect the microbiota: key role of probiotics and prebiotics to modulate the human intestinal ecosystem
- Diet rich in fiber, prebiotics and probiotics is useful for improving the composition of the gut microbiota



Diet Modulates the Microbiome

- Low fat/High complex carbohydrate diet improved Metabolic Syndrome by altering the gut microbiome
- Low fat/High complex carbohydrate diet-increase in *F. prausnitzii*
- This bacterial strain increases the SCFA - butyrate



Estrogens and the Gut Microbiota and Estrogen-like Foods for Health

- When all is “right,” there is a beautiful synergy of estrogen and the microbiome to influence and reduce obesity, cardiovascular disease, diabetes, cancer
- As an amazing “back-up,” the microbiota can even metabolize food containing estrogen-like compounds into biologically active forms
- Estrogen-like compounds (soy products, flax seeds, lignans) can promote the proliferation and growth of certain types of helpful bacteria

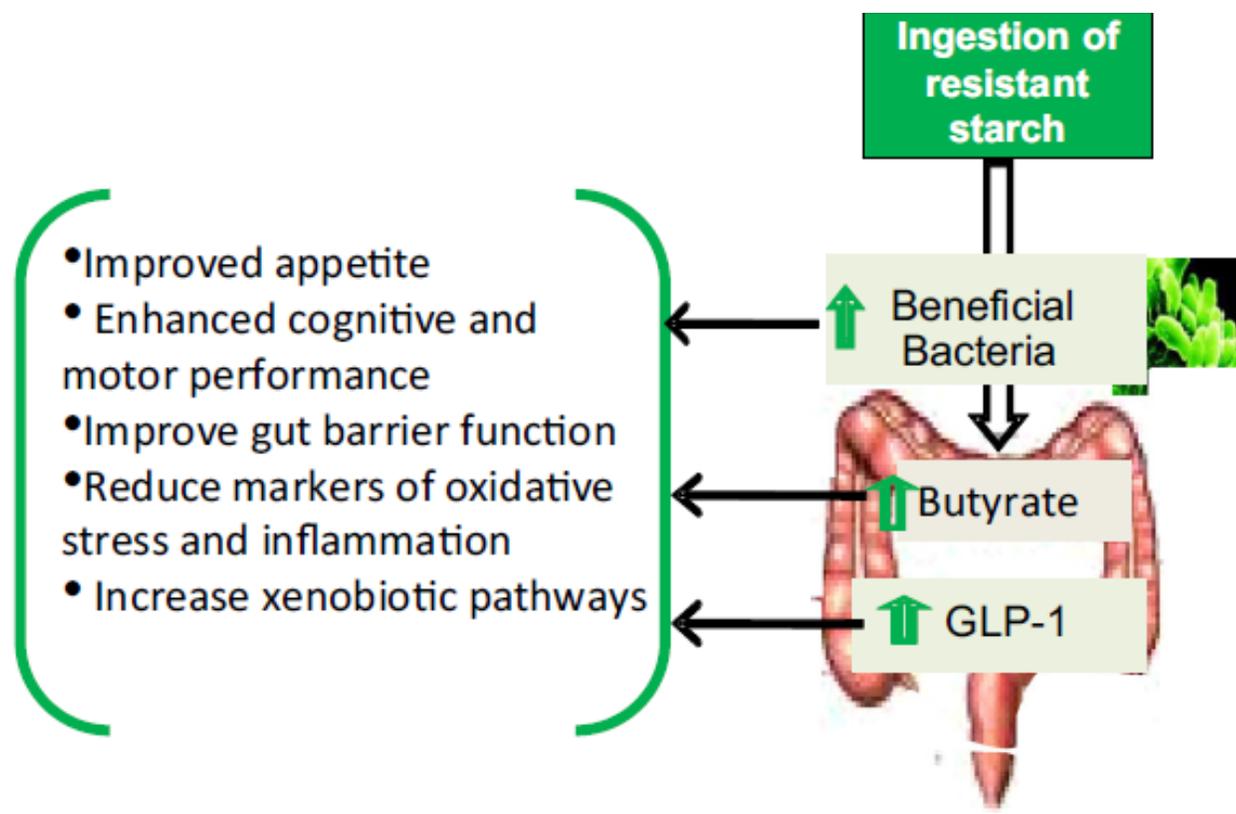


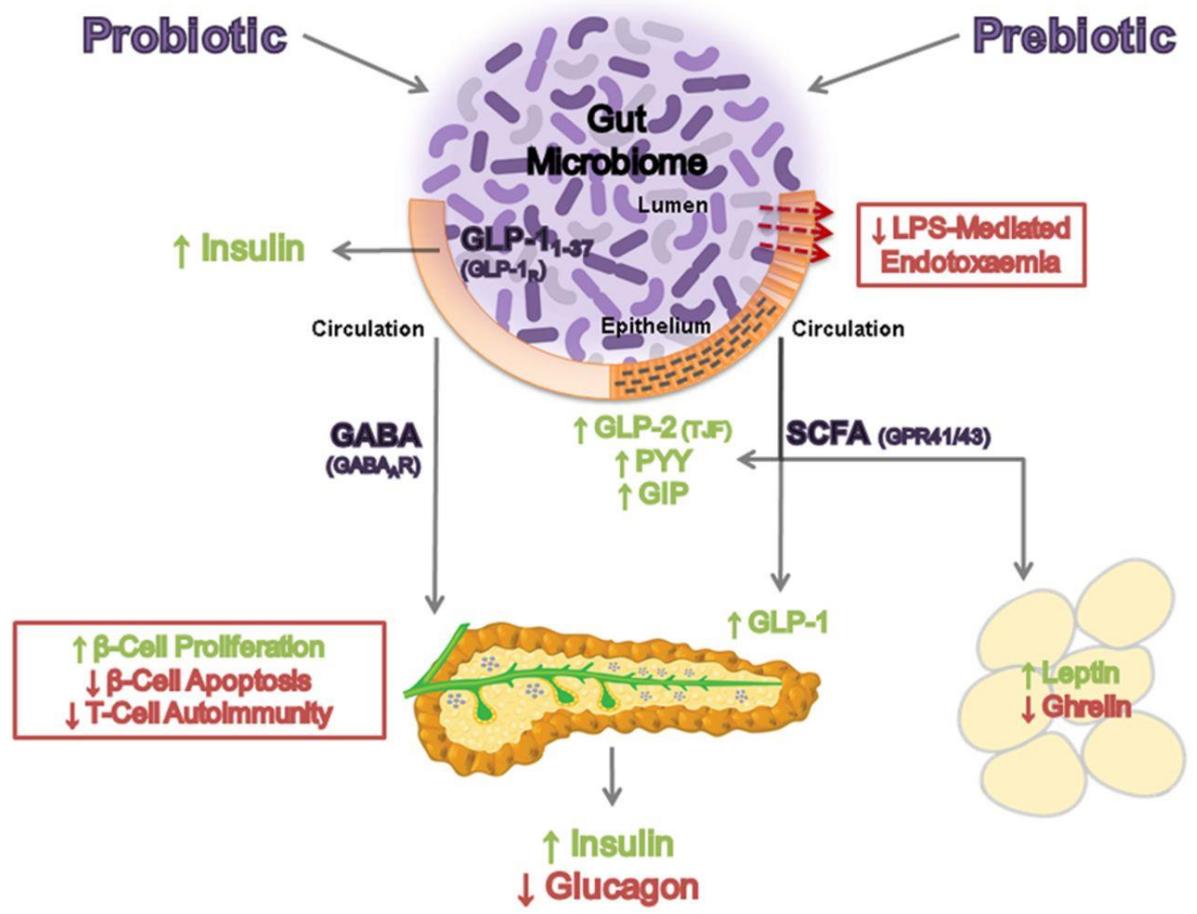
Probiotics and Prebiotics

- Probiotics: live microorganisms which when administered in adequate amounts confer a health benefit on the host
- Prebiotics: a non-digestible food ingredient that beneficially affect the host by selectively stimulating the growth and activity of one or a limited number of bacteria in the colon and improve host health



Fig. 1 Proposed mechanisms of HAS and Improved healthspan. Ingestion of high-amylose starches increases beneficial microbiota and stimulates the production of butyrate and increases GLP-1 release from the gut





“Putative mechanisms of action through which prebiotics and probiotic bacteria can impact on host metabolic health in type 1 and type 2 diabetes. Green and red texts indicate hormones, systems and actions that are upregulated and downregulated, respectively. LPS, lipopolysaccharide.”



How to Build a Better Microbiome

**Hormone balance is essential for a healthy microbiome...
though often difficult in women with PCOS**

- Dietary composition, modification, and interventions have a marked impact on gut microbiota diversity
- Plant based fiber is critical in influencing the composition and metabolic activity of the microbiome and determining levels of short chain fatty acids (SCFAs), improve colonic mucosal integrity, reduce gut apoptosis
- Agrarian diets high in fruit/legume fiber are associated with greater microbial diversity



Best to Start with: Vegan Diet for the Short Term

- Healthy fats-Omega 3 supplementation, Omega 6 and 9 from plants, Saturated fat from coconut oil
- Low protein (approximately 12%)
- High Complex carbohydrates (70%)
- Low fructose
- No animal protein-including no dairy or eggs
- No added sugars, No processed foods, Chemical free
- Rich in complex carbohydrates: whole-grain cereals, vegetables, legumes, organic/unprocessed soy
- Rich in natural fiber and prebiotic and probiotic products





A Safe Strategy to Reduce Markers of Insulin Resistance and Inflammation!

- Rapid improvements in all of the following:
- Fasting blood glucose
- Glycosylated hemoglobin
- Serum lipid profile
- Body mass index and percent fat
- Body weight
- Blood pressure
- Reduction in IGF-1





Diet Fat Content

- Low levels of saturated fat
- Moderate amounts of monounsaturated and polyunsaturated fats
- No trans-fats
- Omega 6: Omega 3 ratio of 5:1



Fat

- Types of fats consumed has a great impact on microbial diversity, composition, and state of overall inflammation
- Mice fed fish oil increased levels of Lactobacillus and Akkermansia
- Mice fed lard increased levels of Bilophila
- Lard-induced White Adipose Tissue (WAT) inflammation is mediated through gut microbial activation of TLR4



Benefits of Adding High Resistant Starch: High-Amylose Starch

Table 2 Summary of the effects of diet restriction and high-amylose starch

	Diet restriction	High-amylose starch	HAS references
Longevity	↑	?	
Inflammation	↓	↓	Zhou et al. 2012; Le Leu et al. 2013
Glucose clearance	Improved	Improved	Zhou et al. 2008; Shen et al. 2011
Insulin sensitivity	Improved	Improved	Robertson et al. 2005; Johnston et al. 2010; Robertson 2012
Blood lipids	↓	↓	Keenan et al. 2006, 2013; DeJonge et al. 2009
Oxidation of fatty acids	↑	↑	Higgins et al. 2004; Zhou et al. 2009
Lipogenesis	↓	↓	Higgins et al. 2006; Higgins and Brown 2013
Body fat	Reduced	Reduced	Keenan et al. 2006, 2013; Charrier et al. 2014
Cancer risk	↓	↓	Toden et al. 2007; Clarke et al. 2008
Oxidative Stress	↓	↓	Kwak et al. 2012



Diversity of Microbiome Requires Dietary Diversity

- The importance of microbiota diversity cannot be overstated!
- Microbiota produce an abundance of important molecules for host
- Each particular macronutrient has the potential to be metabolized into unique metabolic signals



Eat for Diversity-the Colors of the Rainbow for Microbiota Diversity

- With increased variation comes increased adaptability and increased range of physiological responses
- Elimination of one or more macronutrients results in selecting some microbiotic species over others



Hormetic Effects of Phytochemicals

- Small amounts have profound effects
- Hormone like action
- Metabolic performance
- Amplification of cell signaling pathways
- Enhancing growth of beneficial bacteria
- Competitively excluding specific pathogenic bacteria-some have bacterocidal/bacterostatic actions



Negative Effects of Different Diets on the Microbiome

- Ketogenic Diets: diminish total bacterial levels of the gut microbiota
- Long term adherence to high protein, low fermentable carbohydrate/fiber “weight-loss” diets increase Bacteroides-likely increasing risk of colonic disease





It's Not Just What You Eat, But Also When and How Often You Eat

- The benefits of periodic fasting:
Can increase gut bacterial diversity
- The benefits of timed eating

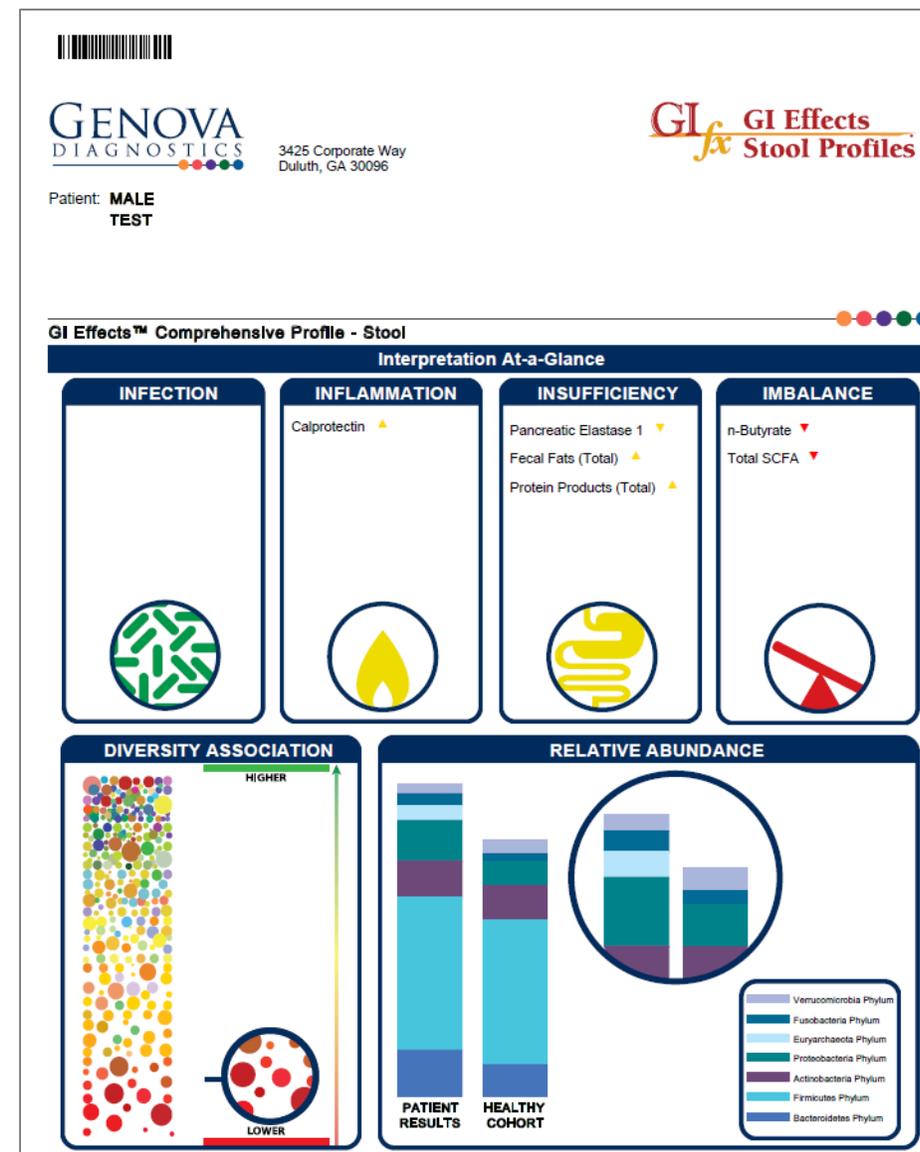


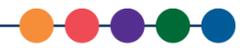


GI *fx* GI Effects Stool Profiles[®]

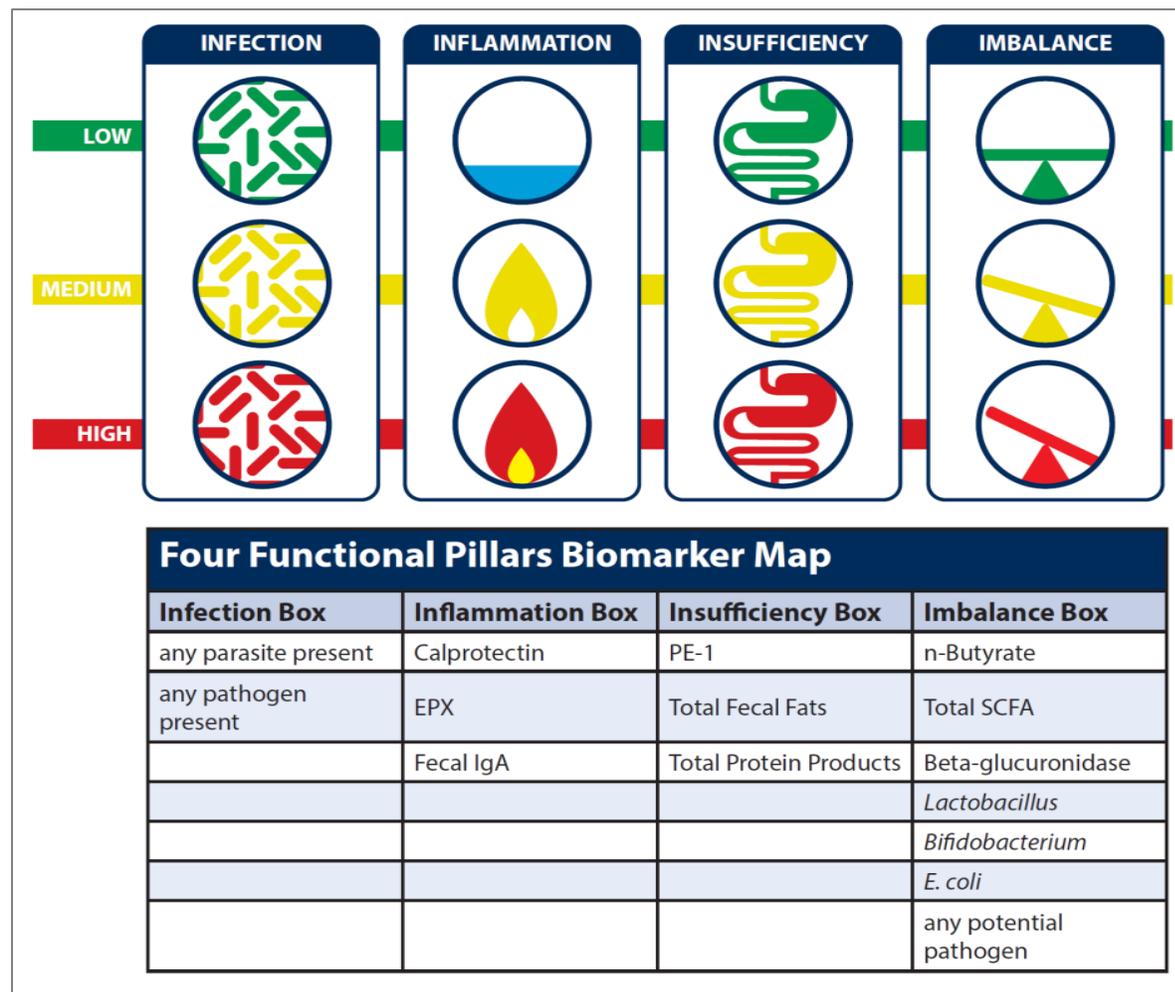


- **Four Functional Pillars**
 - Infection
 - Inflammation
 - Insufficiency (Digestive)
 - Imbalance (Metabolic)
- **Global Gut Health**



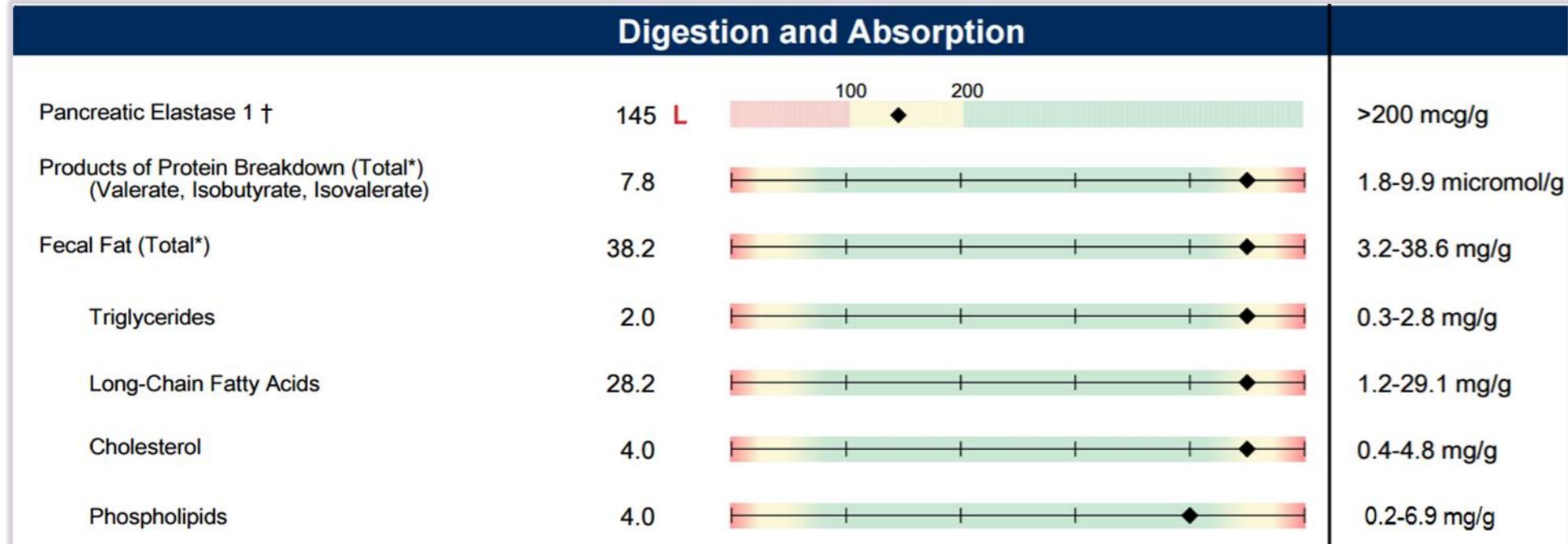


Interpretation-at-a-Glance: 4 Functional Pillars





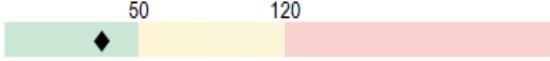
Digestion and Absorption



- Pancreatic Elastase 1
- Products of Protein Breakdown
- Fecal Fats



Inflammation & Immunology

Inflammation and Immunology			
Calprotectin †	37		<=50 mcg/g
Eosinophil Protein X (EPX) †	2.1		<=4.6 mcg/g
Fecal secretory IgA	2,427 H		<=885 mcg/g

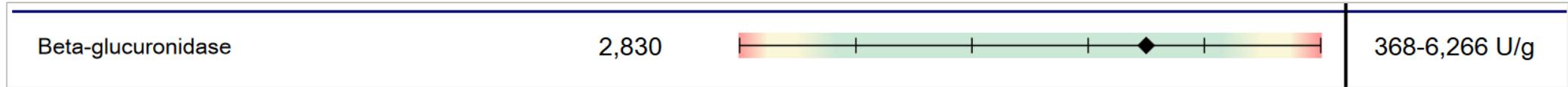
- Calprotectin
- Eosinophil Protein X (EPX)
- Fecal secretory IgA



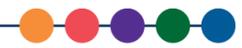
Tests Relating to Estrogen Detoxification



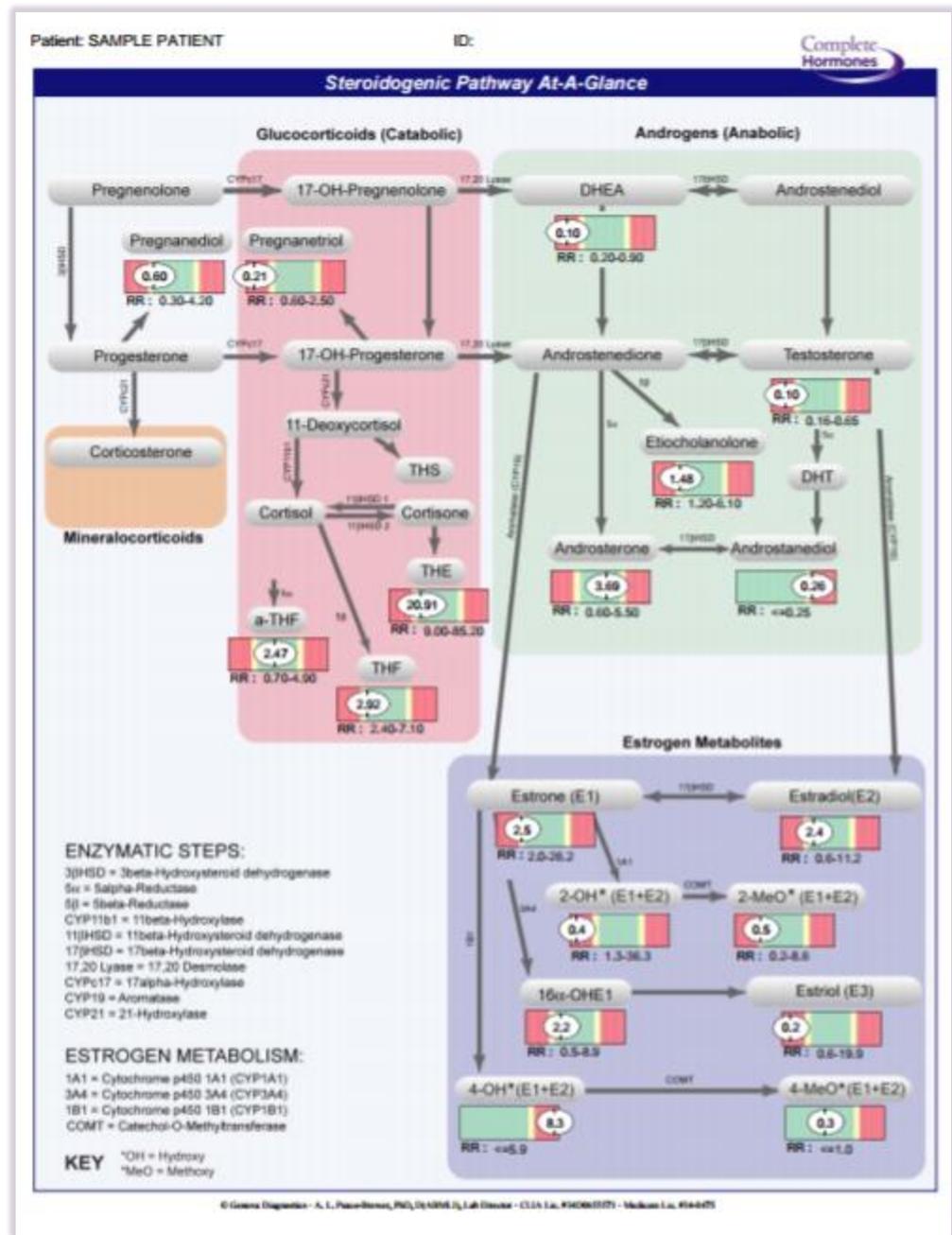
Beta - Glucuronidase



- Beta-Glucuronidase can effectively reverse detoxification that has taken place in the liver by uncoupling glucuronides
 - Promotes enterohepatic recirculation of toxins, hormones, and drugs
- A moderate level of Beta-Glucuronidase activity is preferred as activity appears to be important for normal enterohepatic recirculation of endogenous compounds and vitamins
- Limited human studies show a relationship to colon and hormone related cancers
 - Calcium-d-glucarate inhibits action of enzyme



Urine Detoxification Report: Estrogen Detoxification Pathways





Wrapping It Up!

**So What Does a Woman with PCOS
Actually Eat For A Healthy Microbiome
and to Maximize Hormonal Health?**



How to Eat: PCOS Guidelines

- Eat 2-3 meals a day and no snacks
- Periodic fasting
- Local and home grown
- Old/heritage seeds
- Home cooked
- Avoid refined oils/trans fats/alcohol
- Avoid food allergens and sensitivities - consider elimination diet
- Avoid toxic foods!
- Include phytoestrogens: organic, whole soy, flax seeds



How to Eat for PCOS

- 100% organic
- Sugar free, artificial sweetener free
- Gluten free and Dairy free/reduced
- High fiber/resistant starch
- Non-GMO (data on Roundup and Glyphosate)
- Real foods in natural state
- Variety of colorful fruits and veggies
- Limit processing



Thank You!

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Michael Chapman, ND
Moderator



Felice L. Gersh, MD
Presenter

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- Review a profile that has already been completed on one of your patients

We look forward to hearing from you!



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