



GHAPP

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NASH in IBD: A Grown Problem An Additional Phenotype

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Disclosures

Amanda Chaney, DNP, APRN

Author: Springer Publishing, Clinical Area – Liver disease

Advisory Board: Salix, Clinical Area – Hepatic Encephalopathy

Speaker Bureau: Mallinckrodt, Clinical Area – Hepatorenal Syndrome

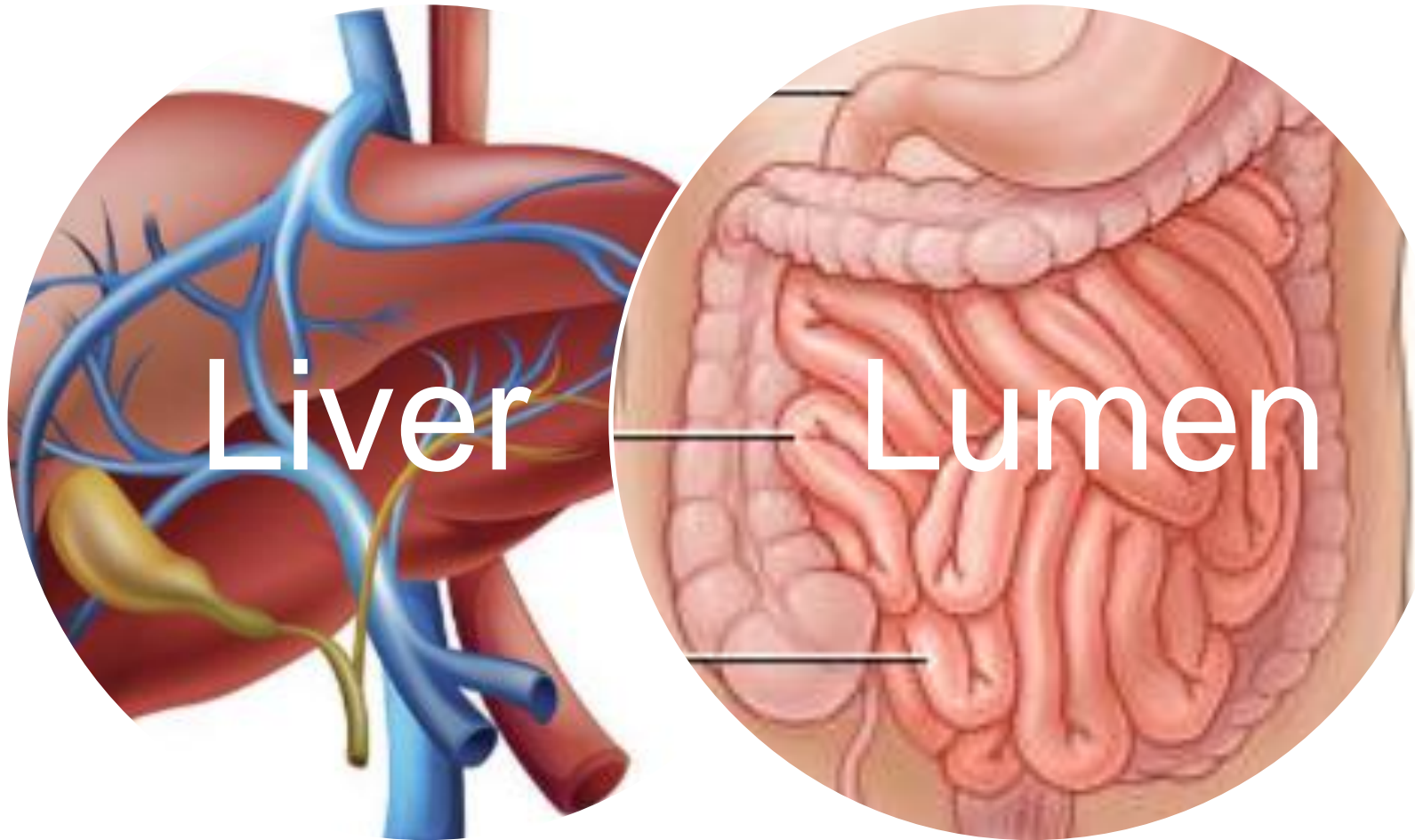
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NASH in IBD: A Growing Problem

An Additional Phenotype

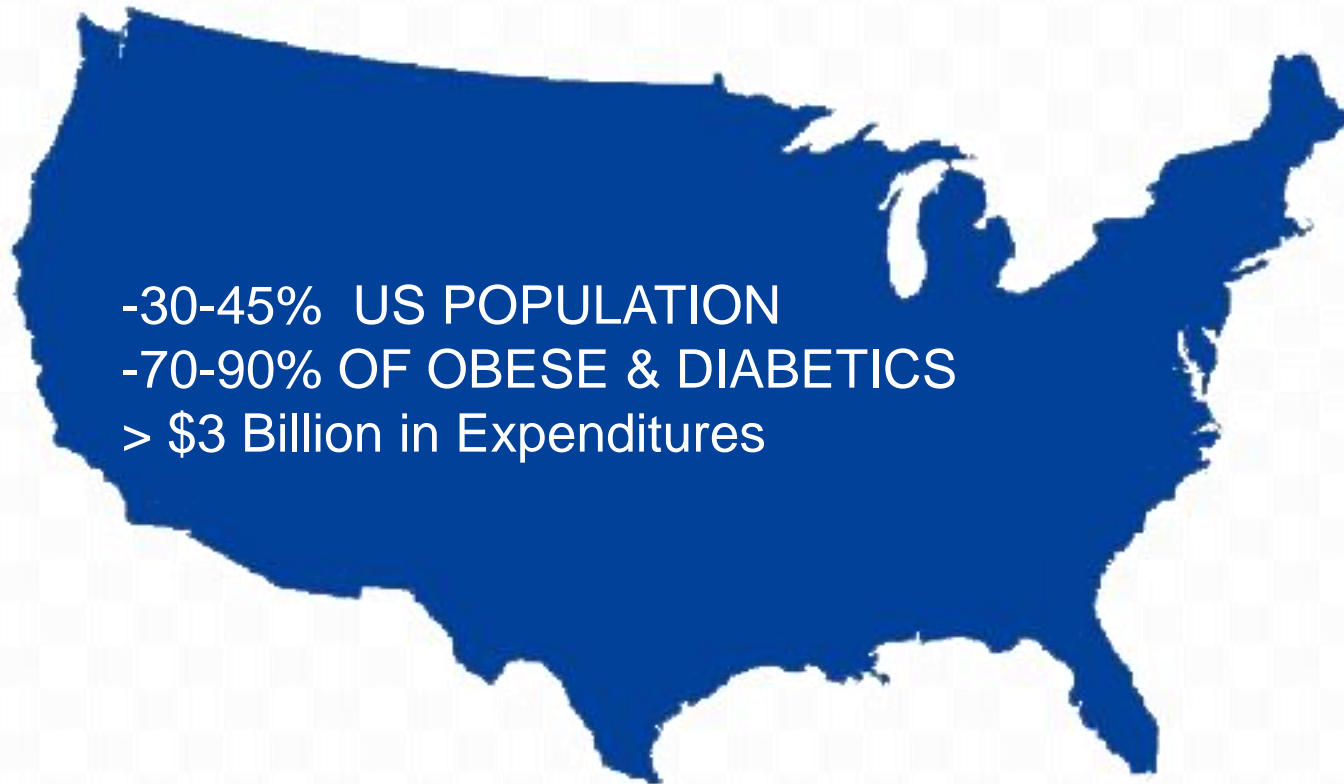


Cross Talk!

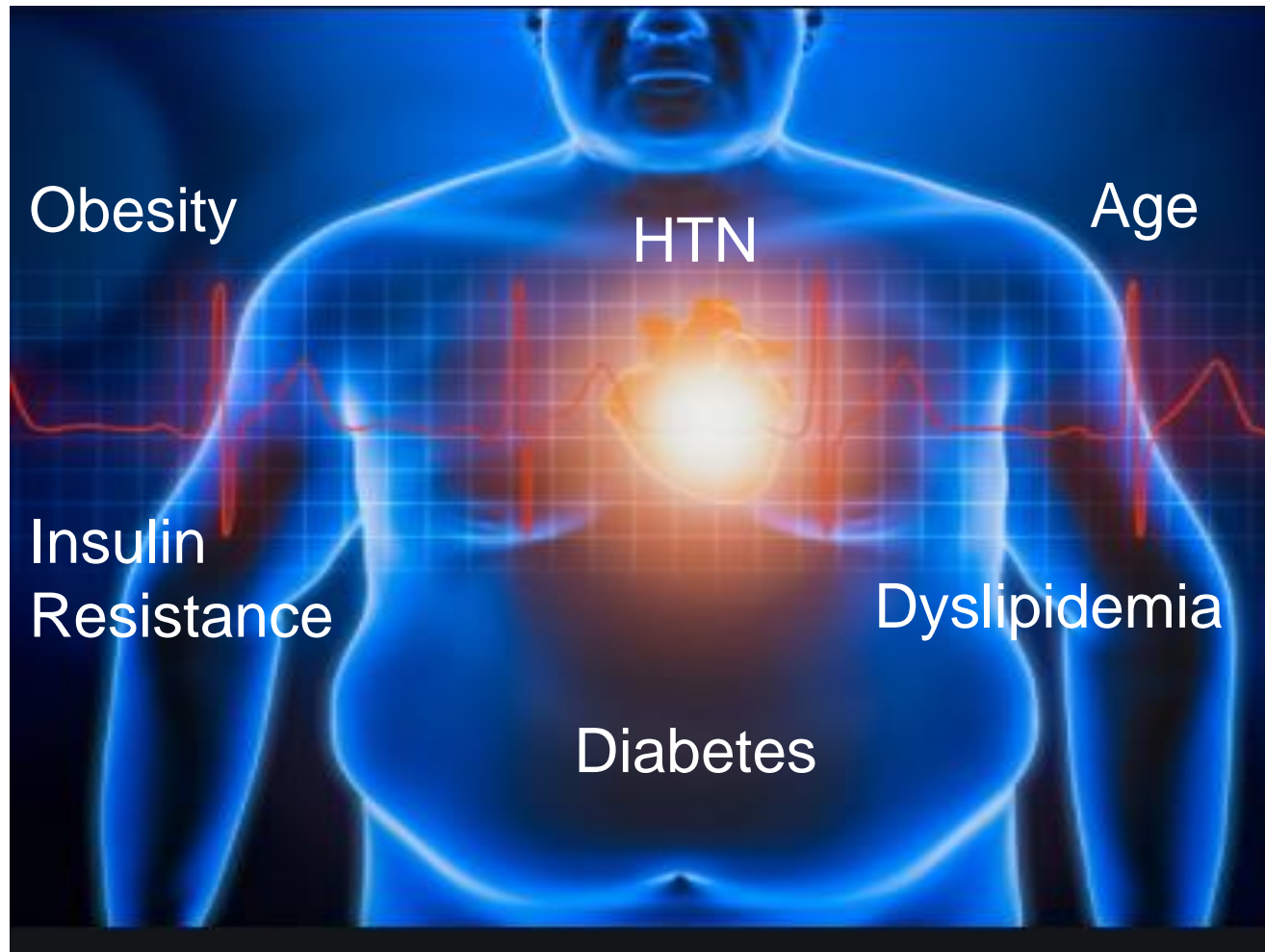
Objectives

1. Name the “Link” between NAFLD/NASH and IBD
2. Recognize the Roles of Secondary Bile Acid
3. Describe Unique Characteristic of the IBD - NAFLD/NASH Patient
4. Discuss Possible Predictors of NAFLD/ NASH in IBD Patients

NAFLD Prevalence



Typical Risk Factors of NAFLD: METABOLIC SYNDROME



Complex Pathogenesis

“MULTI-HIT” Phenomenon

Lipid Accumulation

- Poor Diet & Inactivity
- Increased De Novo Synthesis in Liver
- DOWN reg B-Oxidation and UP Reg Insulin Resistance

Oxidative Stress and Hepatocyte Death

- ER- Activates NF-KB Release and Remodeling

Cytokine Release

- Kupffer and Stellate Cells active IL-6, TNF α , IL-1B, TGF-B, along with TLR, NLR, JAK2, STAT3 signaling
- Infiltration of MAC, DC, Tcells PMN & INSULIN RESISTANCE

Organ X-talk

- Adipose tissue is active, suppress B-oxidation and increase Insulin Resistance
- Dysbiosis/ Translocation BA cant appropriately conjugate

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Prevalence of NAFLD by MS, Underweight and IBD

Metabolic Syndrome

- 19-34% by US
- 34-46% by BX

Underweight

- Underestimated
- Understudied
- Overlooked
- Prominent in Anorexia Nervous and AIDS population



IBD Patients

- 8-59%
 - 26-40% CD
 - 26-36% UC
- 6-10% Fibrosis
- 75% LEAN and UNDERWEIGHT

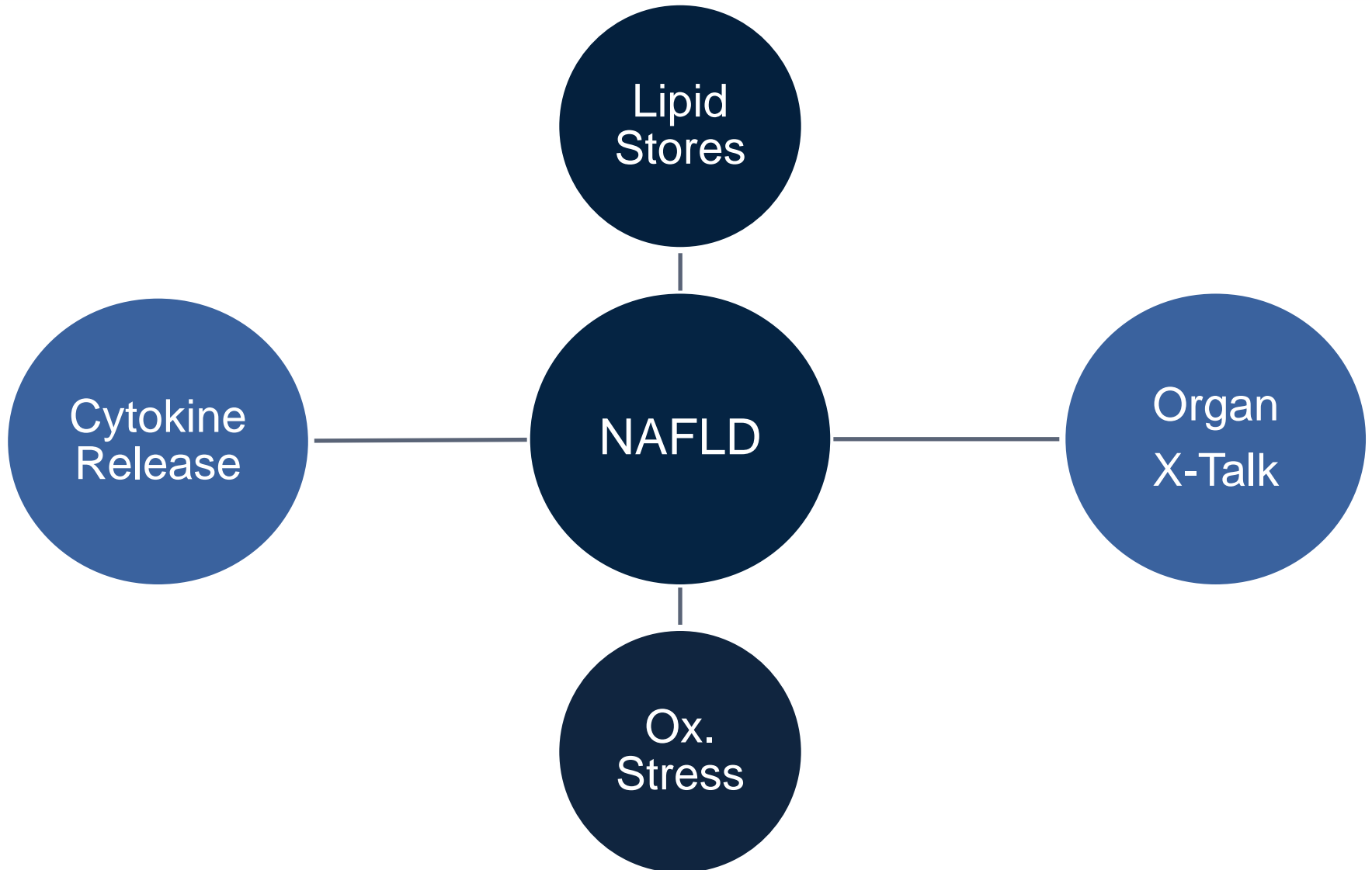
The Argument:

- *Is the LEAN IBD Overlooked for NASH Evaluation?*
- *Why would this be ?*
- *Should it become part of Health Maintenance in our GI assessment of IBD patient?*



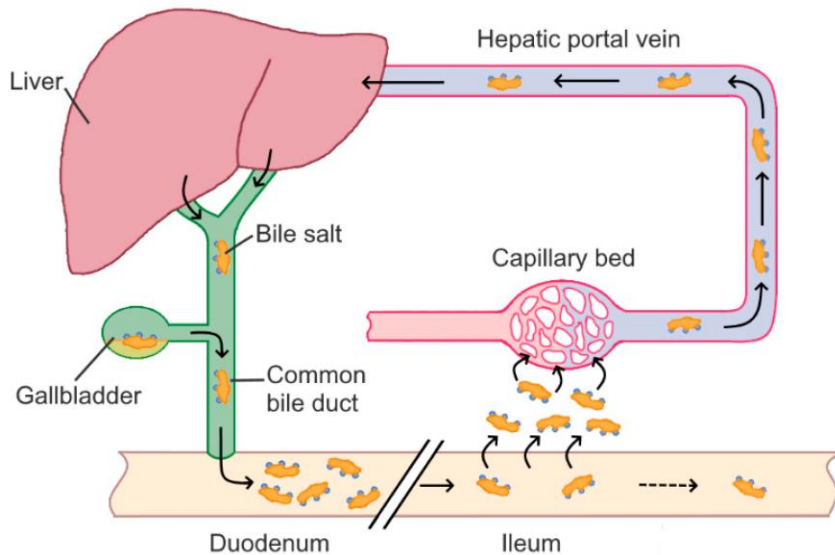
**Who has IBD?
Who has NAFLD?**

“Multi Hit” Pathogenesis of NAFLD



Organ Cross Talk

The Anatomy and Physiology



- *Primary Bile Acids made in Liver

- *Conjugate with Taurine and Glycine to Bile Salt drain through CBD to Small intestine

- *MICROBIOTA in Small intestine deconjugate to Secondary Bile Acids

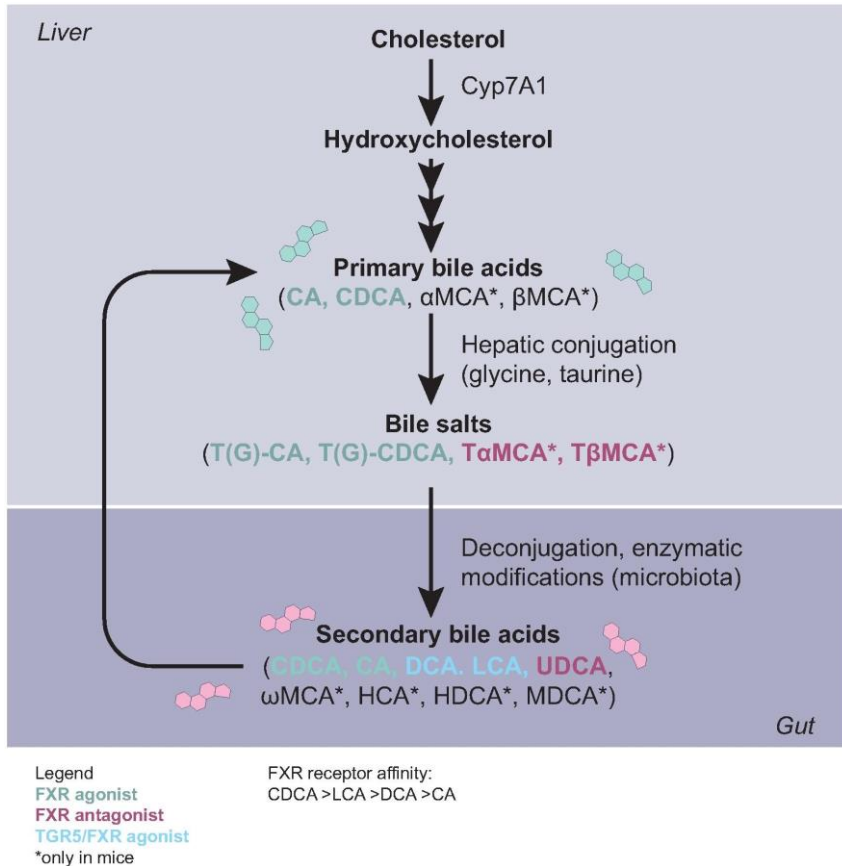
Ileal Re-uptake

~5% Bile Acid loss in Stool

Organ X-Talk

The Biochemistry

Creating Secondary Bile Acids

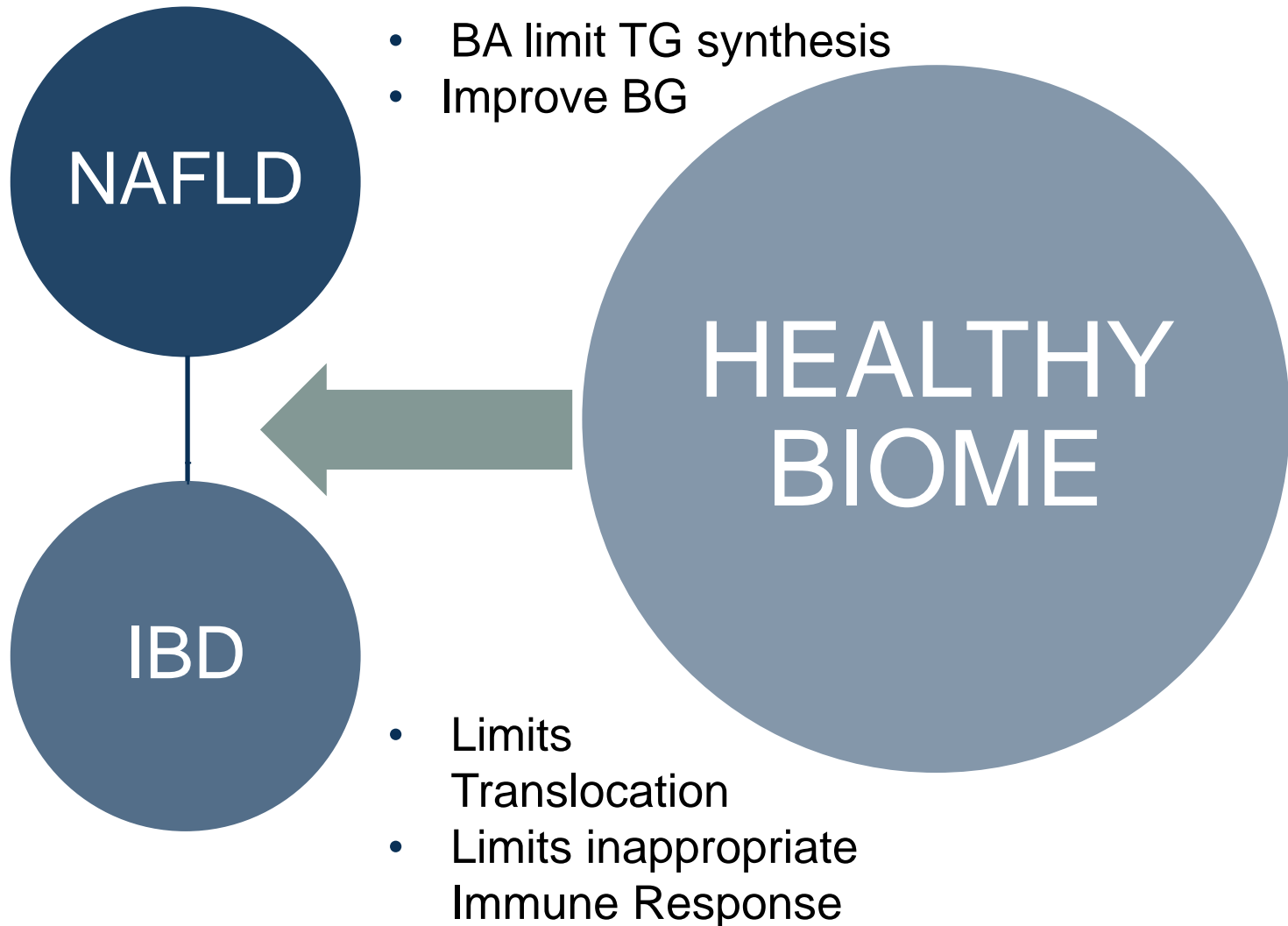


Healthy Biome Promotes Deconjugation

- Bacteroides
- Bifidobacteria
- Proteobacteria
- Strepocaccacea
- Enterobacteriaceae
- Ruminococcacea

“Good Bacteria”

Organ Cross Talk

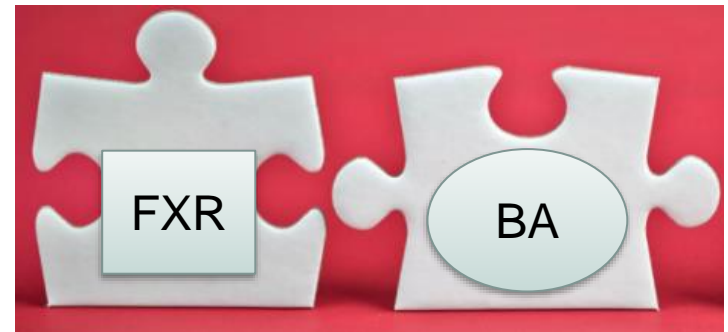


Cytokine Functions:

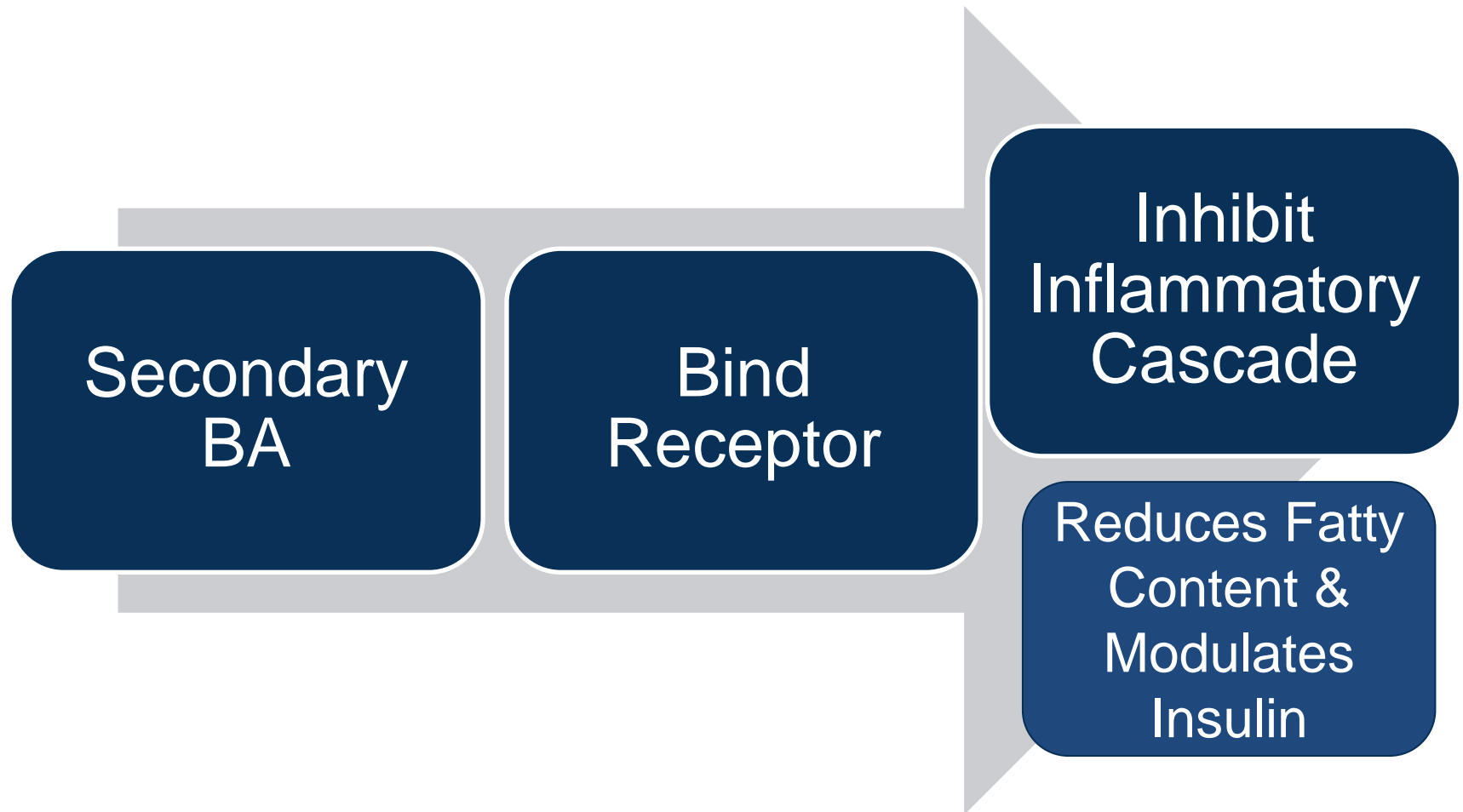
Secondary Bile Acid Functions – LIGANDS

Bile Acid Receptors are *Ligands* for Hormones and Cytokines

- Farsenoid X
 - Down regulates hepatic Lipid Production
 - Improves Insulin Signaling & B- Oxidation
 - Decrease expression of NF-KB, Inhibits TNF, IL1-B, Il-6, MAC and DC signaling
 - Promotes Treg Il-10
- RORyx & GPBAR1
 - Inhibits Transcription in TH17, TH1 pathway
 - Decrease IL-17A, Il-23A, INF-y
 - Increase Treg
 - Inhibits NLR



Secondary BA Prevent NAFLD Progression



Organ Cross Talk in the Pathogenesis of NAFLD

Metabolic Syndrome

Dysbiosis

No Conjugation
to Secondary
Bile Acid

No activation of
Receptors

Crohns / Colitis

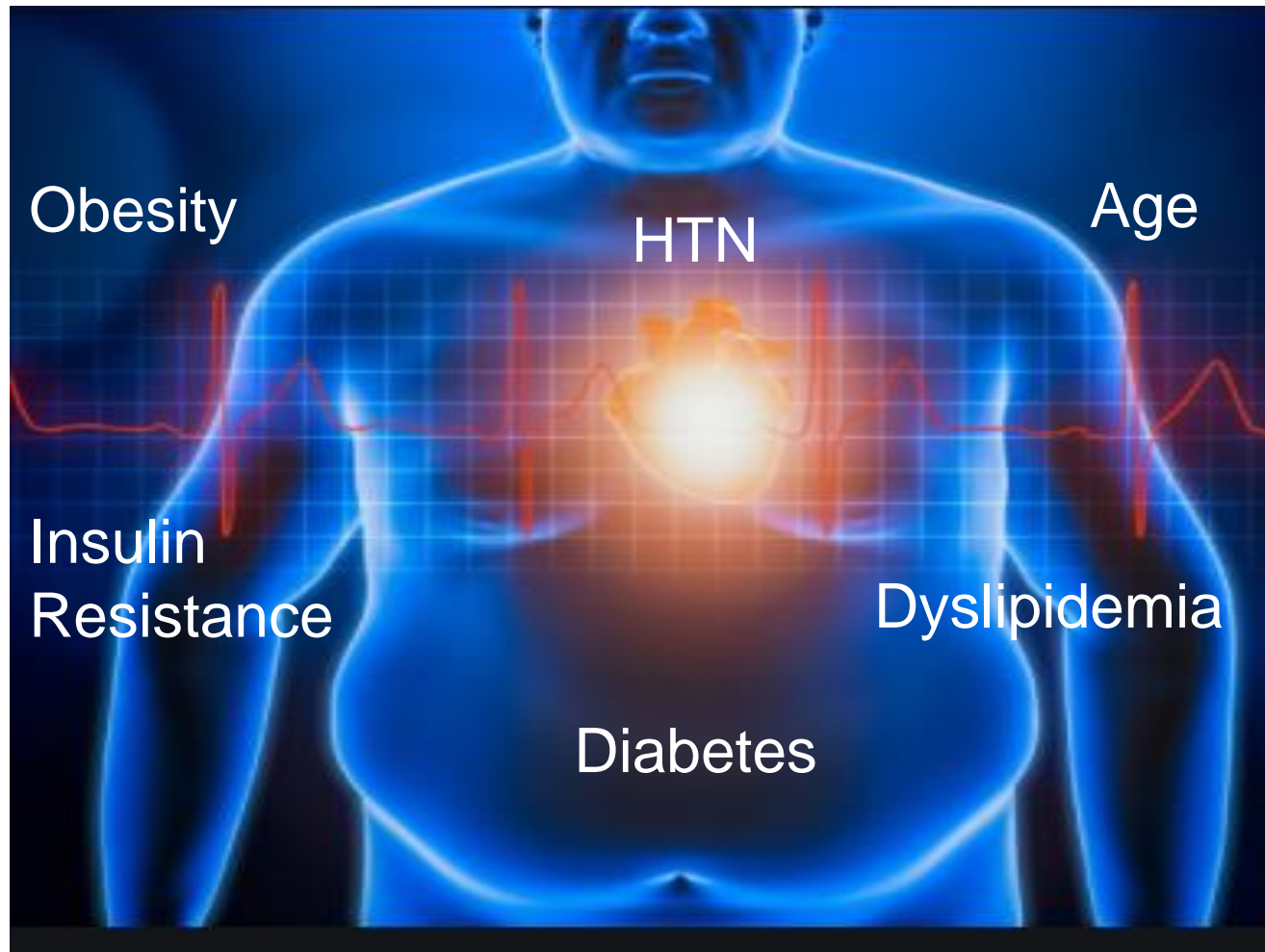
Ileal Surgical
Resection or
Inflammation

Diminished BA
Reuptake in
Ileum & Liver

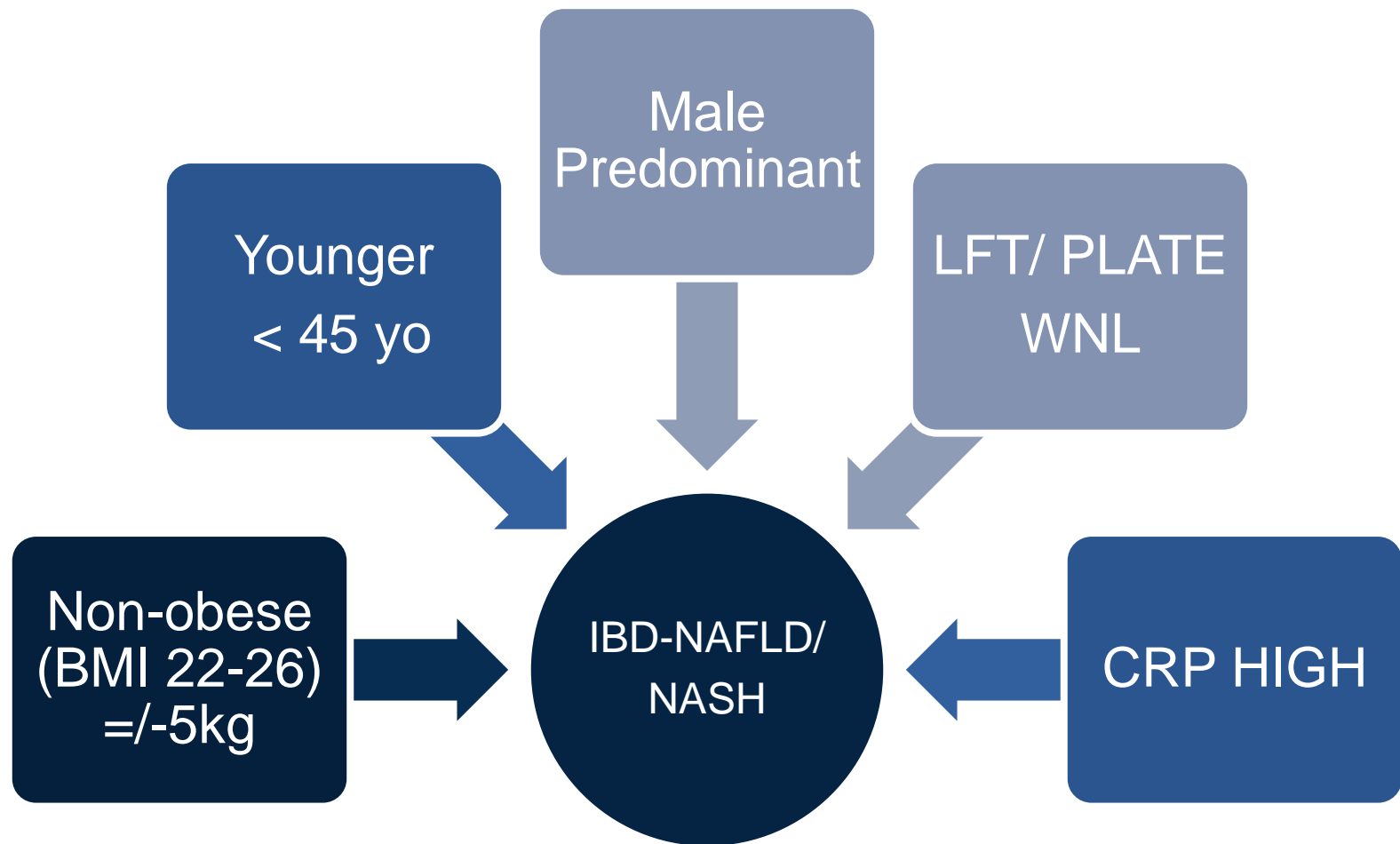
Limited
Receptor/Ligand
Activation

Organ X-talk is the Link !

Typical Risk Factors of NAFLD METABOLIC SYNDROME



Characteristic of IBD Patients With NAFLD



Proposed Predictors of NAFLD in IBD Patients

Disease Activity

Disease Duration

Dysbiosis/Permeability

Surgical Resection

+/- Medications

TPN

IBD-NAFLD

Observed Phenotypes

Milder IBD

1. < 1 Flare a year
2. Regardless of Metabolic Risk

S1, S2 Disease

Moderate IBD

1. > 1 Flare a year
2. Extensive geographic location
3. Severity
4. Surgical Intervention
5. Regardless of Metabolic Risk

S3 Disease

Proposed Additional Mechanisms to Pathogenesis of IBD-NASH Phenotype

Surgical Resection

- Interrupt **Entero-Hepatic Circulation**
- 1*BA to 2* BA
 - Deconjugation
- EFA & Carnitine Deficiency

Parenteral Nutrition

- Not Unique in IBD
- Observed NAFLD by day 5

Medication

- Corticosteroid
 - *Exacerbate* not cause
- MTX in RA *not IBD
- Anti-TNF protects+/-

IBD Medications

ANTI-TNF

- Shared Cytokine, Decreases proinflammatory signaling in the Stellate Cells and subsequent remodeling (NF-KB)
- Indirectly Increases Insulin Signaling, result is improved Gluconeogenesis and B-oxidation

IMM

- AZA may worsen
- MTX 13.1mg/wk = in RA, NOT IBD

Steroids

- Rodent Studies direct correlation, not Human
- Exacerbate in Human

Looking Ahead for the IBD Patient

EIM ?

?When
Fibroscan

Impact IBD
TX?

?MS
NAFLD
and TX

Summary

- NAFLD is not Limited to the Metabolic Syndrome Patient
- NAFLD has a Heterogenous Population and of Various Phenotypes
 - IBD = Non-obese < 45 yo , Male, LFT/ PLATE wnl
- Early Screening is May Indicated In IBD
 - CD > UC

**Will the Presences of NAFLD
Change your Prescribing Practice
in IBD?**