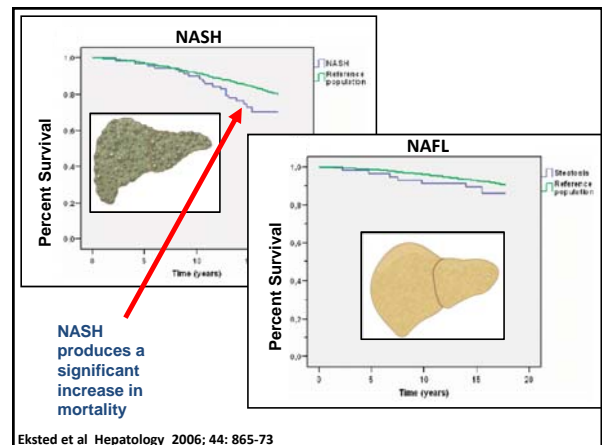
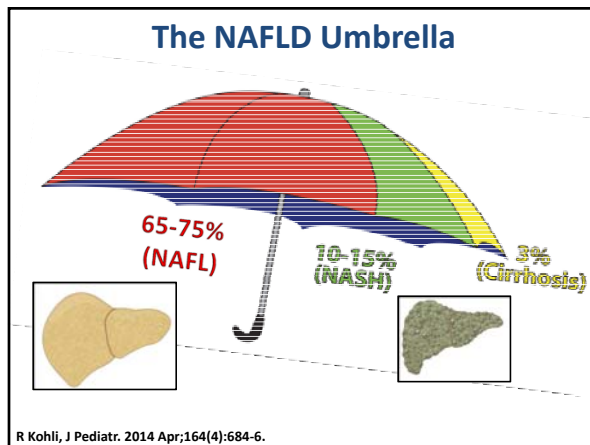


Disclosures

I have the following relationships to disclose:

- Ethicon Endo Surgery Inc.
- Galectin Therapeutics
- Synageva Biopharma
- Raptor Pharmaceuticals

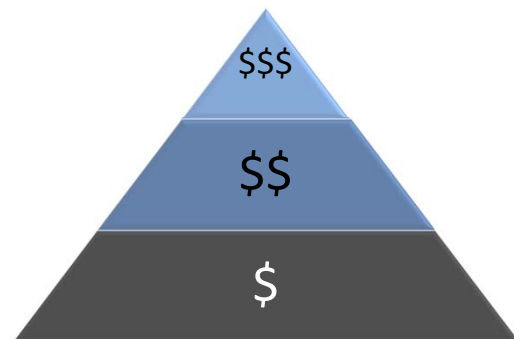
I will be discussing off-label use of medications in my presentation



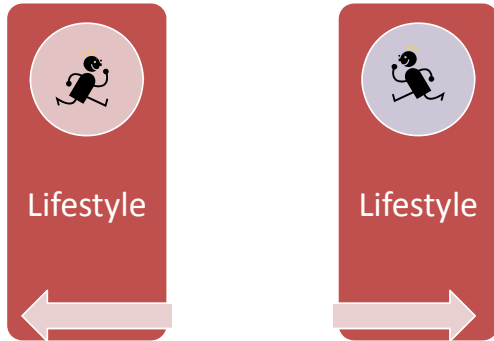
The Big Question:

What are the treatment options for NASH?

The Typical Therapeutic Pyramid



NASH Therapeutics



NASH Focused Clinic-Lifestyle advice

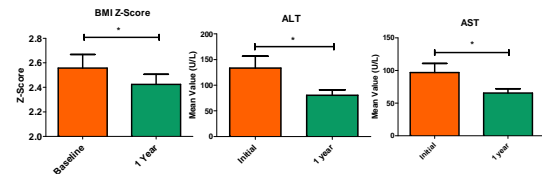
- **Diet:**
 - Increase fruits and vegetables
 - Eat healthy portion controlled breakfast
 - **Decrease/avoid sugar sweetened beverages**
 - Reduce take out/fast food meals
- **Activity:**
 - Increase physical activity
 - Reduce screen time
- **Hepatotoxins**
 - Alcohol in teens
 - **Hepatitis A** and B vaccination



*What have we learned?
Is such a **program effective**?*

Steatohepatitis Center: Outcomes

47% patients returned for 1 year follow-up



Significant reduction in BMI, ALT and AST (*p<0.05).

DeVore and Kohli et al. J Pediatr Gastroenterol Nutr. 2013 Mar 19.

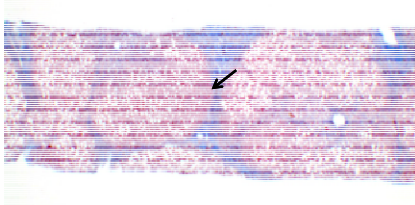
*What if all this does **not** work?*

How rapidly can fibrotic NASH worsen?

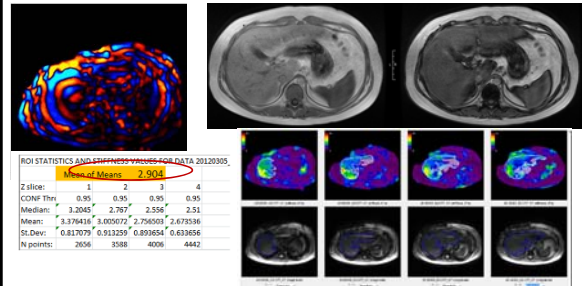
	Baseline labs JAN 2009	Follow up labs APRIL 2011
Age (years)	10	12
BMI	36.7	35.6
BMI %ile	99	99
Waist (cm)	110.2	118.7
HDL cholesterol	30	16
ALT	161	191
AST	59	114
GGT	43	63
Hgb A1C (on metformin)	4.7	5.1
Fasting glucose	100	107
Psychotropic Meds	Abilify, lithium	No change

Pediatric NASH with Stage 3 fibrosis

12 year old boy



Liver MR based Elastography

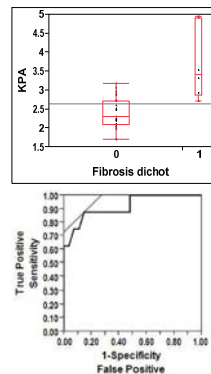


15 yo with NASH and mild/moderate diffuse fatty liver infiltration

Mean liver stiffness = 2.9 kPa (range 2.7-3.4)

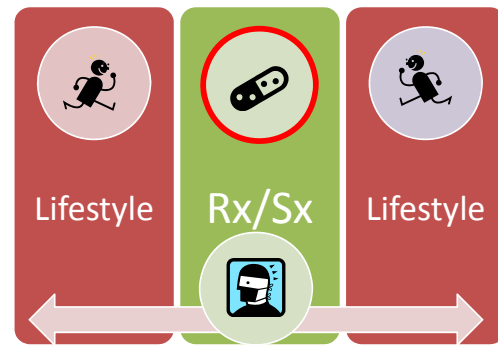
ROC Curve for MRE in Children

- NAFLD patients (n=35)
- AUROC = 0.92 (0.79, 1.00)
- MRE able to identify significant fibrosis vs. no fibrosis (p=0.03)
- 2.71 kPa
- 88% sens
- 85% spec



Xanthakos-Kohli et al J of Pediatr Feb 2014

NASH Therapeutics



Agents studied well for treating NASH

- Insulin sensitizers
 - Metformin
 - Thiazolidenediones
- Anti-oxidants
 - Vitamin E
 - Cysteamine*
- Omega-3 fatty acids – no RCTs with histology

ORIGINAL CONTRIBUTION JAMA 2011

Effect of Vitamin E or Metformin for Treatment of Nonalcoholic Fatty Liver Disease in Children and Adolescents

The TONIC Randomized Controlled Trial

Joel E. Lavine, MD, PhD
Jeffrey R. Schwimmer, MD
Mark L. Van Natta, MHS

Context: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in US children and adolescents and can present with advanced fibrosis or non-alcoholic steatohepatitis (NASH). No treatment has been established.

Landmark Randomized Placebo Controlled, Double Blinded Pediatric Trial for NAFLD with histologic outcomes

However, **histological outcomes more promising** for Vitamin E

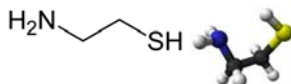
- Compared to placebo, the % with histological NASH resolution at 96 week follow up biopsy:
 - 28% with placebo
 - **58% with vitamin E** ($P = .006$)
 - 41% with metformin

Take Home Message: Vitamin E helps some, but not panacea for NASH

- Vitamin E reduces ballooning in NASH, and may lead to **resolution of NASH in over ½** of pediatric patients with **biopsy-proven NASH**
- Both vitamin E and metformin** no different from placebo in lowering ALT, AST levels after 2 years of therapy.

Cysteamine for the Treatment of NASH in Children (CyNCH)

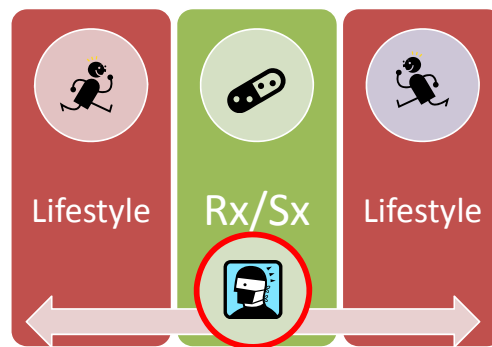
- Cysteamine bitartrate** – a cystine depleting agent



- Increases intracellular glutathione and increases adiponectin multimerization
- Pilot study of 11 children with NAFLD** – significant improvement in ALT and AST after 24 weeks of treatment

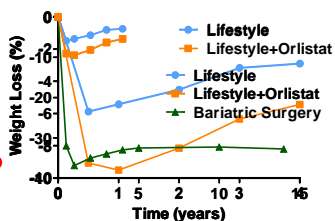
Dohil R et al. Alim Pharma & Therap. 2011;33(9):1036-1044
Dohil R et al. J of Pediatr. 2012; 161(4):639-645

NASH Therapeutics



Weight Loss Interventions

- Lifestyle
- Drug therapy
- Bariatric surgery**



Annals of Surgery 222(3):339-501995 (1995)
Diabetes Care 27(1):155-61 (2004)

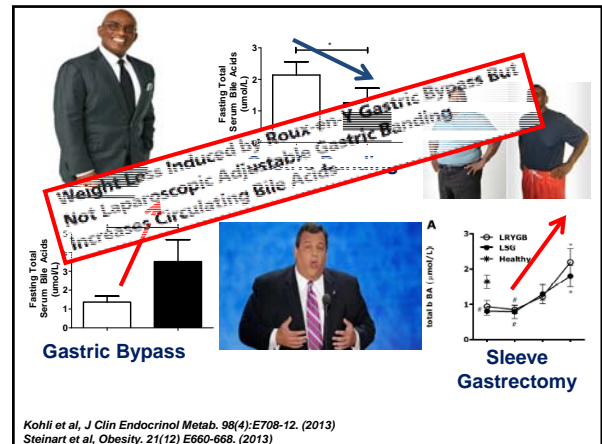
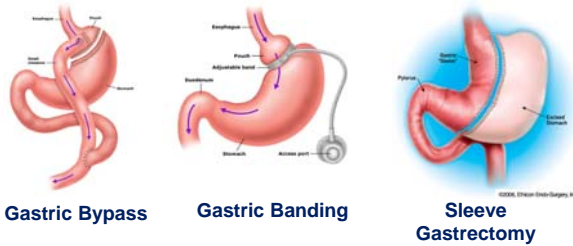
Severe NASH now considered indication for surgery in adolescents

Selection criteria for adolescent weight loss surgery

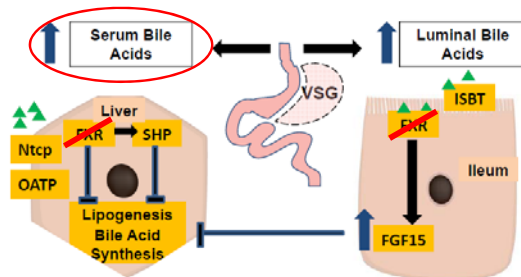
BMI	Comorbidities
> 35	<ul style="list-style-type: none"> Type 2 DM moderate-severe OSA (AHI ≥ 15 events/hr) pseudotumor cerebri severe NASH
> 40	<ul style="list-style-type: none"> Mild OSA (AHI>5 events/hr) HTN Insulin resistance/IGT Dyslipidemia impaired QOL or ADL

Pratt, JSA et al. Obesity 2009; 17:901

Common Bariatric Surgery Procedures



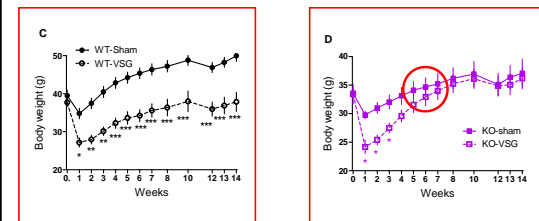
Bile Acid-FXR Pathway



Modified from Myronovych, Kohli et al Obesity 2014; 22 (2) 390-400.

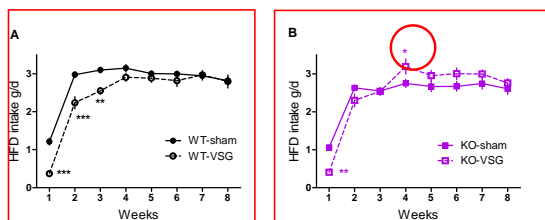
FXR is a molecular target for the effects of vertical sleeve gastrectomy

Karim K. Evans¹, Valentina Tremaroli^{2,3}, Christopher Clemmensen^{1,3}, Petia Kovatcheva-Datchary², Andriy Myronovych⁴, Matejka Kucera¹, Hilary E. Wilson-Perez², Darleen A. Sandwal¹, Robert Kohli⁴, Fredrik Backhed^{1,2,3} & Randy J. Seeley^{1,2,3}



Modified from Ryan, Kohli, Seeley et al Nature, May 8, 2014

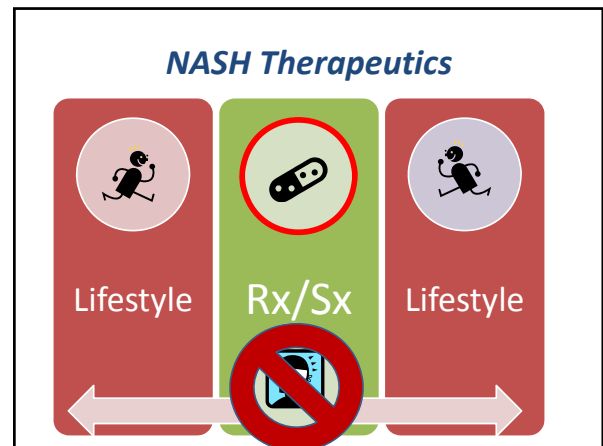
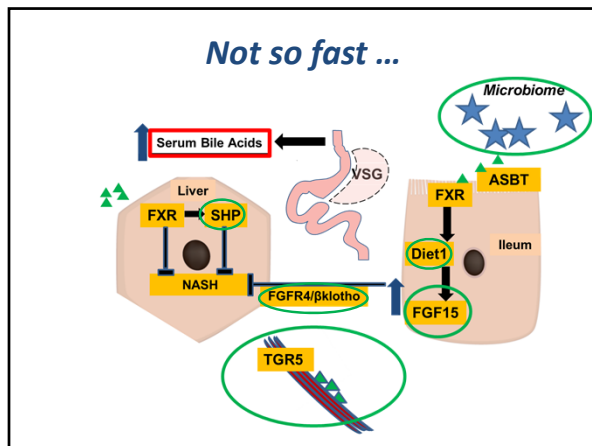
Fxr ko mice can eat through a smaller stomach!



Modified from Ryan, Kohli, Seeley et al Nature, May 8, 2014

So is that it?

Is **FXR** the answer?



What does the future hold?

