Cutting Edge or Crazy:

Is surgery the most effective treatment for NAFLD?

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Disclosures

- **No financial disclosures relevant to this presentation**
- **I will be discussing some non-FDA approved investigational treatments**

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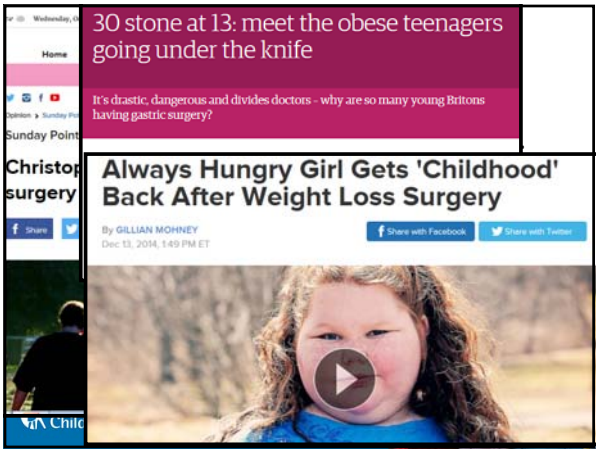


Learning objectives

- Review evidence and gaps in knowledge re: bariatric surgery as a specific treatment for NASH (compared to other available Rx)
- Understand current guidelines for when to consider bariatric surgery in youth
- Describe types of bariatric surgeries available to adolescents, risks and benefits

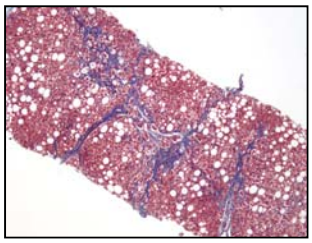
Why are we worried about NASH?

- NASH-related cirrhosis most rapidly rising indication for liver transplantation in the US
  - increased 6 fold over the last decade.
  - 14th to 3rd leading indication in only 10 years
- Predicted to outpace all other etiologies for liver transplant in adults by 2030.
- Lack of easily implemented treatments

Afzali, A. Liver Transpl 2012;18:29-37

Case Presentation

- 16 year old male with type 2 diabetes presents to your clinic with elevated liver enzymes
  - ALT 108 U/L, AST 89 U/L, GGT 96 U/L
  - BMI 38 kg/m^2
  - HgbA_1C 6.8 %
  - BP 139/85
  - ANA positive 1:640
  - Biopsy done →



What are his treatment options?

1. **Counsel him on lifestyle changes** (± RD referral)?
2. Counsel him on lifestyle interventions but **add high dose vitamin E?**
3. Discuss an **intensive lifestyle intervention program** and refer if interested (assuming one is available)?
4. Discuss **bariatric surgery** and refer if interested (assuming a program is available)?

Audience poll: your choice? (assume all options available)

1. **Office-based standard lifestyle counseling**
2. **Lifestyle counseling + high dose vitamin E**
3. **Refer to intensive lifestyle intervention**
4. **Discuss bariatric surgery**

Let's review the best available evidence behind each of these available treatments…

- **Gold standard: randomized controlled trial**
  - **2nd choice: well-designed prospective cohort study ± control group**
- **Histology-based NASH outcomes**
  - **NAS improvement ≥ 2 points (*common*)**
  - **Resolution of NASH (*preferred?)***

Option 1: "Standard" lifestyle counseling (SLC)

- **"Heart Healthy" Diet:**
  - Increase fruits and vegetables to 5/day
  - Avoid high sugar, high fat foods & drinks
  - Reduce take out/fast food meals
  - Eat healthy portion controlled breakfast
- **Increase Activity:**
  - Reduce screen time < 2 hrs/day
  - Moderate to vigorous activity 1 hr/day
- **Follow up every 3-6 months**

How well does this work?

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 B. 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.

N=58 in placebo + SLC (x 2 years):

17% sustained reduction in ALT (primary)
28% remission of NASH (n=11/39)
No significant change in BMI (z score -0.01)

Lavine JE. JAMA 2011;305:1659

Gastroenterology 2015;149:367–378

CLINICAL—LIVER

Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis

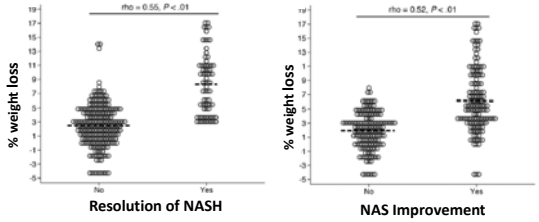
Eduardo Vilar-Gomez,[1,2] Yadina Martinez-Perez,[1] Luis Calzadilla-Bertot,[1]

- **N=293 (Prospective cohort)**
  - Every 8 week visits with behavioral focus on diet and exercise (30 min/day) x 12 months

25% achieved remission of NASH
47% achieved improvement in NAS ≥ 2 points
Mean weight loss 3.8%

Vilar-Gomez E. Gastro 2015;149:367.

Amount of weight loss matters!



If ≥ 10% weight loss, 90% resolution of NASH

Gastro 2015;149:367-78

Option 2 : Vitamin E (+ SLC)

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
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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.

Same TONIC study, over 2 years:
400 IU Vitamin E (RRR-α- tocopherol) BID (N=58)
Vs.
Placebo (N=58)

How well did this work?

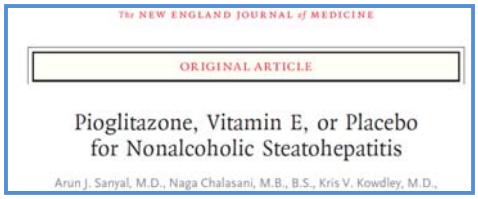
- **Adding Vitamin E was no better than standard lifestyle counseling for most primary and secondary outcomes.**
- **No significant differences** between
  - **ALT (primary)**
  - **BMI z score**
  - **HOMA-IR**
  - **Most histology outcomes except…**

Resolution of NASH

Same TONIC study, over 2 years:

- **58% resolution of NASH vitamin E (n=25/43)***
- **28% resolution placebo (n=11/39)** *P=0.006

- **Caveats of this secondary analysis:**
  - **Predominantly due to reduced ballooning**
  - **No effect on steatosis, inflammation or fibrosis**
  - **CVD risks and prostate cancer reported in adults taking high dose vitamin E…**



800 IU Vitamin E (n=84) vs. placebo (n=83) x 96 weeks

- **43% NAS ≥ 2 (vs. 19%, p=0.001)**
- **36% resolution of NASH (vs. 21%, p=0.05)**

Option 3 : Intensive Lifestyle Interventions (ILI)

- **Frequent visits (every 2 -4 weeks)**
  - **Moderate to high intensity programs work best for kids**
  - **26 to >72 contact hours per year**
- **Multidisciplinary support**
  - **MD with weight management expertise**
  - **RD with weight management expertise**
  - **Exercise options and targets**
  - **Behavioral support (goal setting, tracking, incentives)**

Lifestyle Intervention and Antioxidant Therapy in Children with Nonalcoholic Fatty Liver Disease: A Randomized, Controlled Trial

Valerio Nobili,[1] Melania Manco,[1] Rita Devito,[2] Vincenzo Di Giommo,[3] Donatella Comparcola,[1] Maria Rita Sartorelli,[1]

- N=53 randomized to intensive lifestyle intervention with antioxidant vs. placebo
- No benefit of antioxidant therapy over placebo (n=28 in placebo)

- 68% improved NAS score
- Resolution of NASH not reported
- Mean BMI down -2.88 units

Hepatology 2008;48:119

Randomized Controlled Trial Testing the Effects of Weight Loss on Nonalcoholic Steatohepatitis

Kittichai Promrat,[1,4] David E. Kleiner,[3] Heather M. Niemeier,[2,5] Elizabeth Jackvony,[2] Marie Kearns,[2] Jack R. Wands,[1]

- N=31 in RCT
  - ILI (n=21) vs. co
- 61% improved
- 67% resolve
- ILI lost mean 9.3

Gastro 2015;149:367-78

Limitations of many intervention studies:

- Minimal advanced fibrotic liver disease
  - Outcomes of more advanced fibrotic liver disease unclear
- Varying prevalence of severe obesity

Sobering facts about pediatric NASH and severe obesity

- **Many children with NASH are severely obese**
  - Mean BMI of 33-34kg/m^2 often seen in US literature
  - TONIC RCT: **mean BMI 34 ± 7** in mean age 13
- **Treatment of severe obesity is more difficult**
  - 2-4% of severely obese kids reduced BMI in intensive treatment trials
  - Not maintained for vast majority
- **No weight loss typical with SLC**

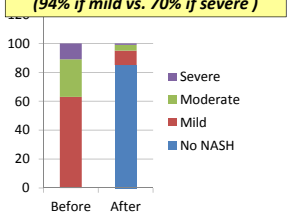
Option 4 : should this young man be counseled about bariatric surgery?

Bariatric Surgery Reduces Features of Nonalcoholic Steatohepatitis in Morbidly Obese Patients

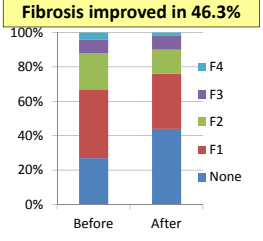
Guillaume Lassailly,[1,2,*] Robert Caiazzo,[3,4,*] David Buob,[5] Marie Pigeyre,[6] Hélène Verkindt,[4] Julien Labreuche,[7] Violeta Raverdy,[4] Emmanuelle Leteurtre,[5] Sébastien Dharancy,[1,2] Alexandre Louvet,[1,2] Monique Romon,[6] Alain Duhamel,[7] François Pattou,[3,4] and Philippe Mathurin[1,2]

N=109 adults (mean BMI 48.9) with NASH

85% Remission of NASH
(94% if mild vs. 70% if severe)



Fibrosis improved in 46.3%



Gastroenterology 2015; 149:379

Almost all data from adult studies

- **Improves steatosis > steatohepatitis > fibrosis**
- **69.5% resolution of NASH in meta-analysis**
- But **no studies randomized or controlled**
- Some patients showed a deterioration of fibrosis in larger studies with longer follow-up

> ***"lack of scientifically sound evidence precludes any recommendation to support or reject bariatric surgery in patients with NAFLD"***
>
> ***Cochrane Review 2010***

Mummadi RR. Clin Gastro Hepatol 2008;6:1396

ASMBS guidelines

ASMBS pediatric committee best practice guidelines

Marc Michalsky, M.D., F.A.C.S., F.A.A.P.[a,*], Kirk Reichard, M.D., F.A.C.S., F.A.A.P.[b], Thomas Inge, M.D., F.A.C.S., F.A.A.P.[c], Janey Pratt, M.D., F.A.C.S.[d], Carine Lenders, M.D., F.A.A.P.[e]

Selection criteria for adolescent weight loss surgery

BMI	Comorbidities
≥ 35	• Type 2 DM • moderate-severe OSA (AHI ≥ 15 events/hr) • pseudotumor cerebri • severe NASH
≥ 40	• Mild OSA (AHI>5 events/hr) • HTN • Insulin resistance/IGT • Dyslipidemia • impaired QOL or ADL

SOARD 2012;8:1-7

What do we know about bariatric surgery in adolescents with NAFLD?

CLINICAL—LIVER

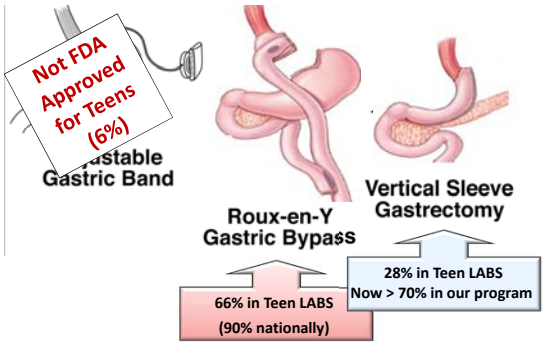
High Prevalence of Nonalcoholic Fatty Liver Disease in Adolescents Undergoing Bariatric Surgery

Stavra A. Xanthakos,[1] Todd M. Jenkins,[2] David E. Kleiner,[3] Tawny W. Boyce,[4] Reena Mourya,[1] Rebekah Karns,[5] Mary L. Brandt,[6] Carroll M. Harmon,[7] Michael A. Helmrath,[2] Marc P. Michalsky,[8] Anita P. Courcoulas,[9] Meg H. Zeller,[10] and Thomas H. Inge,[2] for the Teen-LABS Consortium

- N= 242 teens (13-19 yrs) undergoing bariatric surgery at 5 centers
- Baseline data collected ≤ 30 days of operation.
- Standard co-morbidity assessment

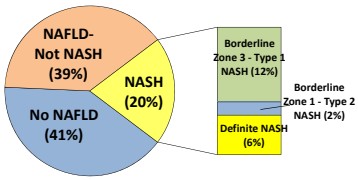
Gastro 2015;149:623

Bariatric procedures available to Teens



Prevalence of NAFLD and NASH among adolescent WLS

157 teens with intraoperative liver biopsies (BMI 52 kg/m²)
16 excluded due to medications (13) or insufficient tissue (3)



Mean BMI 52

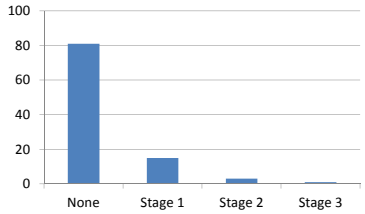
Xanthakos et al.. Gastroenterology 2015

Predictors of increasingly severe NAFLD/NASH

- ALT elevation
  - Mild (22-39 females, 26-39 males) OR 3.41
  - High (>40 U/L) OR 6.66
- Fasting glucose elevation
  - 100-125 mg/dL OR 1.48
  - ≥126 mg/dL OR 8.10
- WBC OR 1.17
- Hypertension OR 2.28

Xanthakos et al.. Gastroenterology 2015

Fibrosis was surprisingly mild



- Diabetes and ALT only significant predictor of fibrosis
  - Diabetes OR 2.56 (1.10, 5.96) p=0.03
  - ALT>40 U/L OR 2.41 (0.84, 6.98) p=0.08
- No patients with cirrhosis

Xanthakos et al.. Gastroenterology 2015

Why do only a minority of severely obese adolescents have fibrotic NASH?

- Referral bias? – *guidelines divergent on whether to use bariatric surgery to treat NASH*
- Selection bias? *NASH cohorts referred for elevated ALT*
- Biological differences in severe obesity? *No data yet to support this*

Characteristics of adolescents with NASH in WLS vs. NASH programs at CCHMC

Table 1: Historical Cohort of Severely Obese Adolescents (BMI >35) and NAS ≥ 4

Program	N seen 2010-2012	Median BMI* (IQR)	Median ALT* (IQR)	Gender*	Mean Age ± SD	Race/ Ethnicity
CCHMC NASH Center	23	**39** (37,44)	**86** (58, 96)	**78% M** 22% F	16.3 ± 1.9	87%White 10% Black **10% Hispanic**
Bariatric Surgery Program	31	**50** (45, 56)	**34** (25, 58)	**29% M** 71% F	17.5 ± 1.6	91% White 9% Black **0% Hispanic**

NIDDK K23 (PI: Xanthakos, SA) – unpublished data

What about outcomes of NASH in adolescents after WLS?

Of 9 adolescent bariatric surgery studies, only 4 include NAFLD and 1 with outcomes

Author, year	Study Type	Surgery (N)	Results
Boza C SOARD 2012	Retrospective case series	VSG (N=59)	Fatty liver in 10% *(not clear how measured)*
Holterman A J Ped Surg 2010	Prospective cohort	AGB (N=26)	65% US → "fatty liver" 88% "NASH" on biopsy 0 with cirrhosis
Holterman A J Ped Surg 2012	Prospective cohort	AGB (N=20)	Similar NAFLD among morbidly obese (BMI <50) & super obese (BMI ≥ 50)
Olbers T IJO 2012	Prospective cohort with control group	RYGB (N=81)	**Mean ALT and AST down 50%** at 1 and 3 years **No reported ALT/AST change in controls**

Same cohort

Preliminary Data: Efficacy of WLS in resolving NASH in adolescents

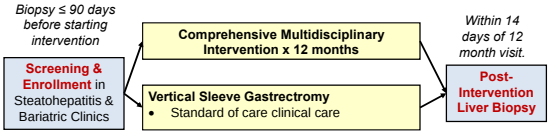
Liver histology changes after bariatric surgery in 18 adolescents with baseline NAFLD/NASH	
Median months between biopsies (IQR)	13 (12,19)
Mean change in overall NAS score	2.7 ± 1.4
Complete resolution of NAFLD	**15/18 (83%)**
Resolution of Definite/Borderline NASH to Not NASH	**10/11 (91%)**
Mean change in fibrosis score (95%CI)	-0.7 ± 0.9
Resolution of fibrosis to stage 0	**5/9 (56%)**

Xanthakos SA et al. Obesity 2007:15(Suppl1):A209

Limitations

- **Small observational cohort**
  - **No lifestyle intervention control group**
  - **Not all patients with NASH followed up or had 2nd biopsy**
  - **Timeline for FU biopsy variable (12-18 months)**
  - **Not representative of severely obese teens with NASH seen in Liver Clinics**
    - **Most patients did not have elevated liver enzymes**
    - **Histologically less advanced disease**
    - **More obese (higher mean BMI)**

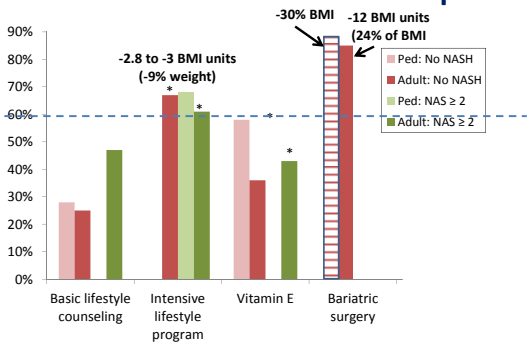
Outcome of NASH in Adolescents after Bariatric Surgery vs. Comprehensive Lifestyle Intervention (NASH ABC)



Inclusion Criteria

- **Biopsy-confirmed NASH**
- **BMI 35-60 kg/m2**
- **Ages 13-19 years**

Putting it all together – how do current treatments stack up?



Adolescent Postoperative Complications (≤ 30 days of WLS)

- 19 subjects **(7.9%)** → 20 Major Complications
- 36 subjects **(14.9%)** → 47 Minor Complications

- **Major:** Life threatening/permanent harm, organ loss, reoperation, blood transfusion, major deviation in anesthetic/operative management
- **Minor:** Unplanned perioperative events (liver/spleen lac), mesenteric hematoma, injury to adjacent organs, deviation from routine care (initiate non-oral enteric feeding, TPN administration, etc.)

	Major	Minor
RYGB	9.3%	16.8%
VSG	4.5%	11.9%
LAGB	7.1%	7.1%

No deaths

Inge et.al. JAMA Pediatrics, 2013

FABS-5: Nutrient status at 8 years

	RYGB (n= 58)	Non-Op (n=30)	p
Low albumin	2%	10%	0.13
Low ferritin	60%	7%	<0.01
Anemia	46%	4%	<0.001
Low B12	16%	11%	0.74
Elevated parathyroid	45%	21%	0.04
High Alk Phos	4%	4%	1.0
Low vitamin D	78%	82%	0.72
Low folate	0	0	

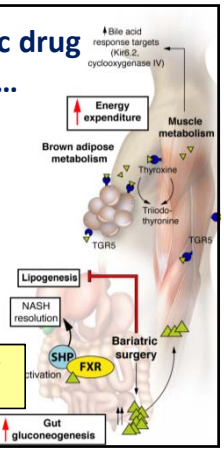
Inge et al. Unpublished data

Quest for a bariomimetic drug we're not there yet…

- FXR agonists promising
  - but raised LDL and decreased HDL cholesterol in recent RCT
- Challenge: identify which molecular agent(s) achieve the same effect as surgery without undesirable effects

22% resolved NASH in FLINT study
45% improved NAS ≥2 points

Kohli R and Setchell K. Hepatology 2015



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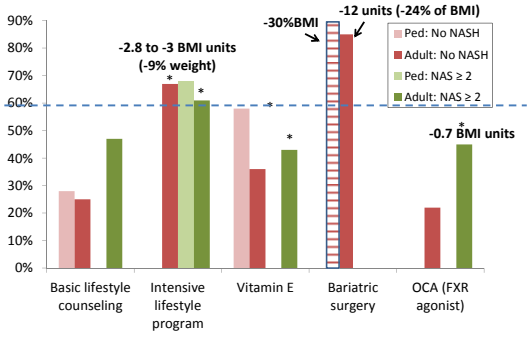
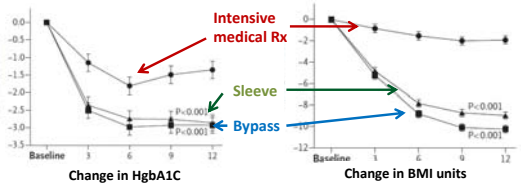


Effects of surgery likely multifactorial

It is not just "stomach stapling!"

Mediator	Bariatric Surgery
GLP-1	↑
Oxyntomodulin	↑
PYY	↑
CCK	↑
Bile Acids	↑
Ghrelin	↓

Bariatric surgery particularly beneficial for severely obese patients with ≥2 significant comorbidities:
Type 2 DM
Sleep Apnea
NASH
Hypertension



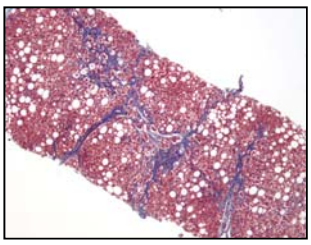
Schauer PR. NEJM 2012; Mingrone G. NEJM 2012: Zimmet P. NEJM 2012

Is Surgery a Panacea for NASH? Not yet….

- **No controlled or randomized studies, small Ns**
- **Long term outcomes and risks unknown** (most 1-2 yrs)
  - Remission vs. Cure?
- **Not accessible. Cost? (need cost-effectiveness studies)**
- **Not right for everyone**
  - Not severely obese (but ~ ½ of kids with NASH are severely obese)
  - Too young
  - Not psychosocially ready
  - Not interested (surgical risk)

Back to our patient…

- **16 year old male**
  - **Severe NASH, stage 3 fibrosis**
  - **Type 2 Diabetes**
  - **BMI 38**



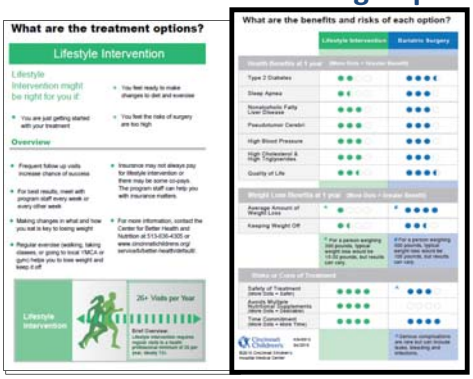
AASLD PRACTICE GUIDELINE

The Diagnosis and Management of Non-Alcoholic Fatty Liver Disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

- **Intensive lifestyle modification is first step**
- **No medications recommended**
  - Vitamin E: confirmatory studies needed.
- **Bariatric surgery not contraindicated**
  - but premature to recommend as specific Rx

Chalasani N. Hepatology 2012;55:2007

Shared Decision Making Important



Take-Home Messages

- **Highest rates of resolution of NASH are linked to ≥10% weight loss**

  *"…in the real world, **intensive lifestyle counseling** must be offered to **all NASH patients**, even though the applicability of these interventions depends largely on their **availability** and **real-world adherence** to these programs…"*

  Vilar-Gomez et al.Gastro 2015;149:367-78

- **Important to include bariatric surgery as a tool to achieve significant sustained weight loss (-30%)**
  - Data suggest significant benefit for NASH (& DM2, OSA, CVD)
- **Further study needed to determine long-term (10+):**
  - Maintenance of weight loss
  - Resolution of NASH and related diseases

Acknowledgements

- **Clinical Teams**
  - **NASH Program:** Kristin Bramlage, Rohit Kohli, Nikki Baer, Susan Wagner, Leah Barron and Emily Vale
  - **Bariatric Program**: Linda Kollar, Cassandra McDaniel , Penni Taylor, Michael Helmrath, and Tom Inge
- **Research Team**
  - Tom Inge, Kim Bernstein, April Carr, Rohit Kohli, Eileen King, Shelley Kirk, Megan Ratcliff, Kim Cecil, Alex Towbin, Suraj Serai, Deb Elder, and the Teen LABS Consortium
- **NIH/NIDDK**

Questions?

Appendix slides

	Weight change	Reduced NAS ≥2 points	NASH Resolved	Improved Fibrosis
Standard Counseling Pediatric (TONIC n=58) Adults (Villar Gomezn=293) (PIVENS n=83) (FLINT n=131)	P: -0.01 BMI z score A: -3.8 ± 2.7 kg (BMI +0.4 PIVENS) (BMI +0.1)	P n/a A: 47% (19% PIVENS) (21% FLINT)	P: 28% (n=11/39) A: 25% (21% Pivens) (13% FLINT)	P:40% A: 19% (31% PIVENS) (19% FLINT)
Vitamin E Pediatric (TONIC n=58) Adult (PIVENS n=84)	-0.03 BMI z score A: BMI up 0.1	P=n/a A;43%	P: 58% (n=25/43)* A: 36%	P=37% A: 41%
Intensive lifestyle intervention Nobili (n=28) Promrat (n=21)	P: -2.88 BMI units A:-9.3% of wt (-3 BMI units)*	P: 68% A: 61%*	P: n/a A: 67%*	P: n/a A:n/a
FXR agonist (OCA) (FLINT n =126)	A:-0.7 units (-2.3kg)*	A: 45%*	A: 22%	A: 35%*
Bariatric surgery Lassailly (n=109)	P:-30% BMI A: -24% (-12 units)	P:? A: n/a	P: ? A;85.4%	P:? A: 46.3%