International Think Tank

# Paris NASH Meeting

## July 5 & 6, 2018
Institut Pasteur

### Organized by


**Veronica Miller**
UC Berkeley School of Public Health, Washington DC, USA

**Arun Sanyal**
Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

**Lawrence Serfaty**
Hôpital Hautepierre Hôpitaux Universitaires de Strasbourg, France


### Scientific committee

Quentin Anstee
Pierre Bedossa
Jean-François Dufour
Scott Friedman
Fabio Marra
Manuel Romero-Gómez
Frank Tacke
Michael Trauner

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AFEF
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THE FORUM
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Paris NASH Meeting

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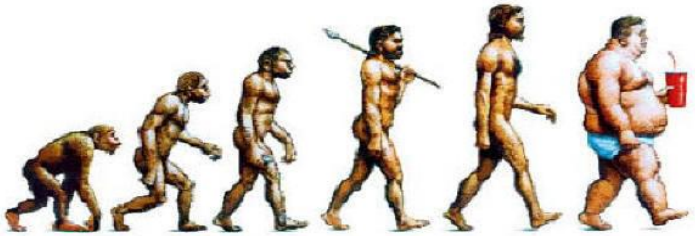
# The Evolution of NASH: From Childhood to Adulthood




Joel E. Lavine, MDPhD

Professor and Vice-Chairman of Pediatrics

Chief, Gastroenterology, Hepatology and Nutrition

Columbia University and

Morgan-Stanley Children's Hospital of New York Presbyterian


NIH National Institute of Diabetes and Digestive and Kidney Diseases


<jl3553@columbia.edu>


NASH CRN

I have the following disclosures; unrelated to presentation:

Consultant:

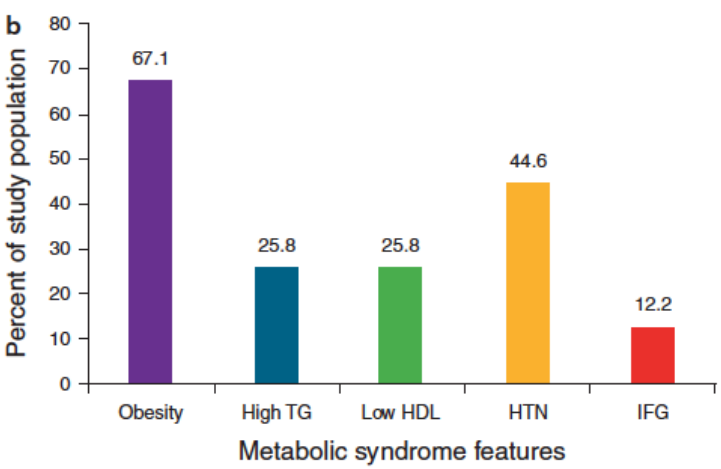
- Merck
- Janssen
- Gilead
- Allergan
- Pfizer
- Bristol Myers Squibb
- Viking
- Novartis

Grants/Research contracts: NIDDK/NICHD

# How Is NAFLD Suspected?



- Usually obese
- Hepatomegaly
- Elevated ALT (and ALT>AST)
- Liver imaging (MRI>U/S)
- Family history of NAFLD
- Other metabolic syndrome concomitants
- RUQ pain (+/-)
- Lack of abnormal tests indicating other cause




Patton et al AJG 2010

# Pediatric NAFLD Natural History

**No prior prospective studies in children**

NAFL NASH Cirrhosis

# Considerations Regarding Pediatric NAFLD



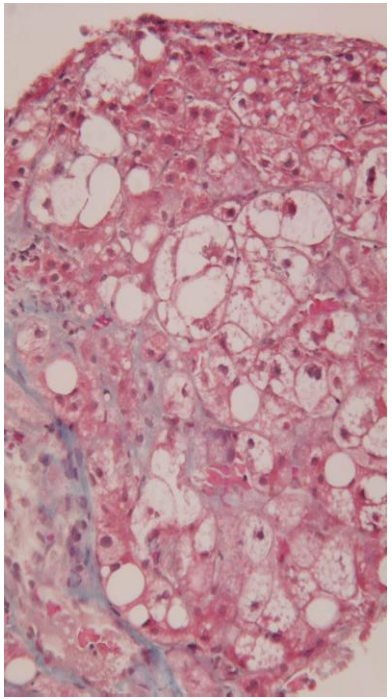
- **Enhanced genetic susceptibility and/or environmental susceptibility given early onset and severity**
- **Alcohol is minimally confounding**
- **Distinct and unique histologic subtypes with specific demographic differences**
- **Possible difference in etiopathogenesis and response to therapy(ies)**
- **Peripubertal hormonal fluctuations affecting histology and severity**
- **Longer duration of disease predisposes to worse adult outcomes**

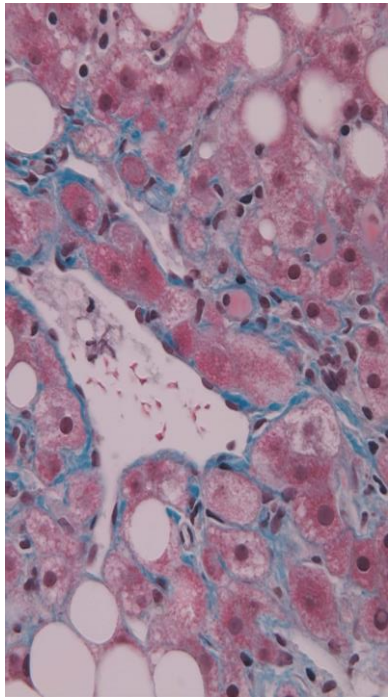
# Distinct Subtypes of Pediatric NAFLD



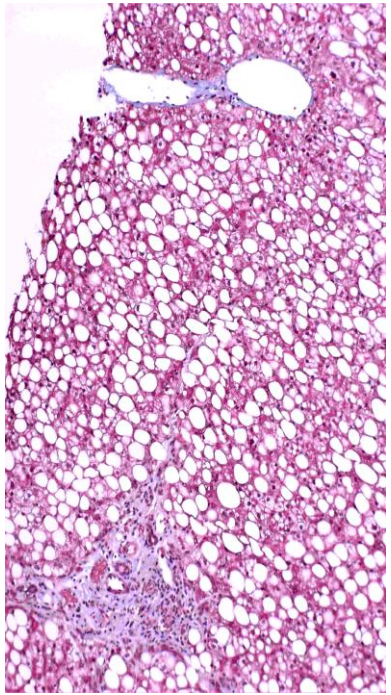
- 

**Type 1**





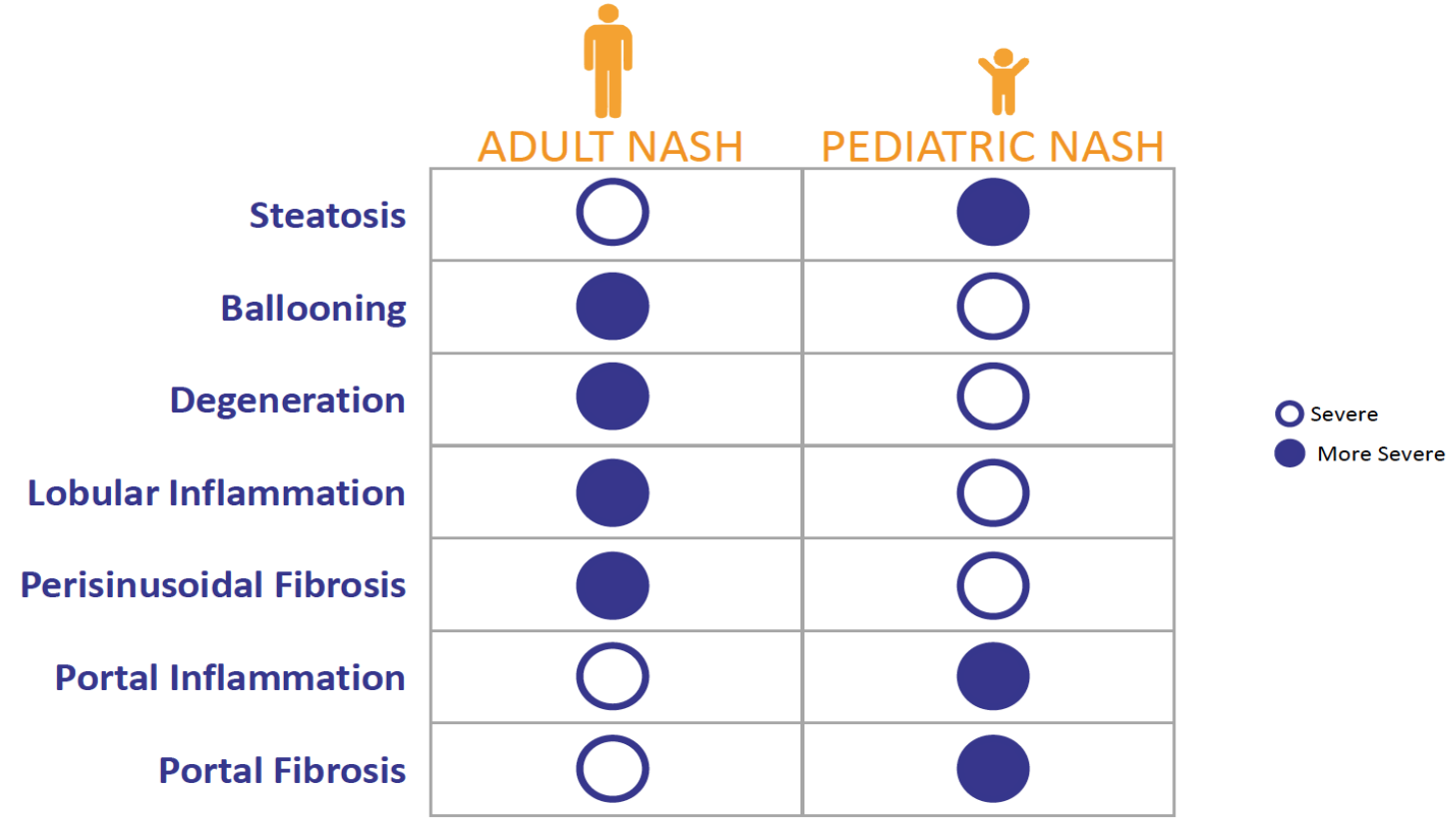
**Type 2/BZ1**



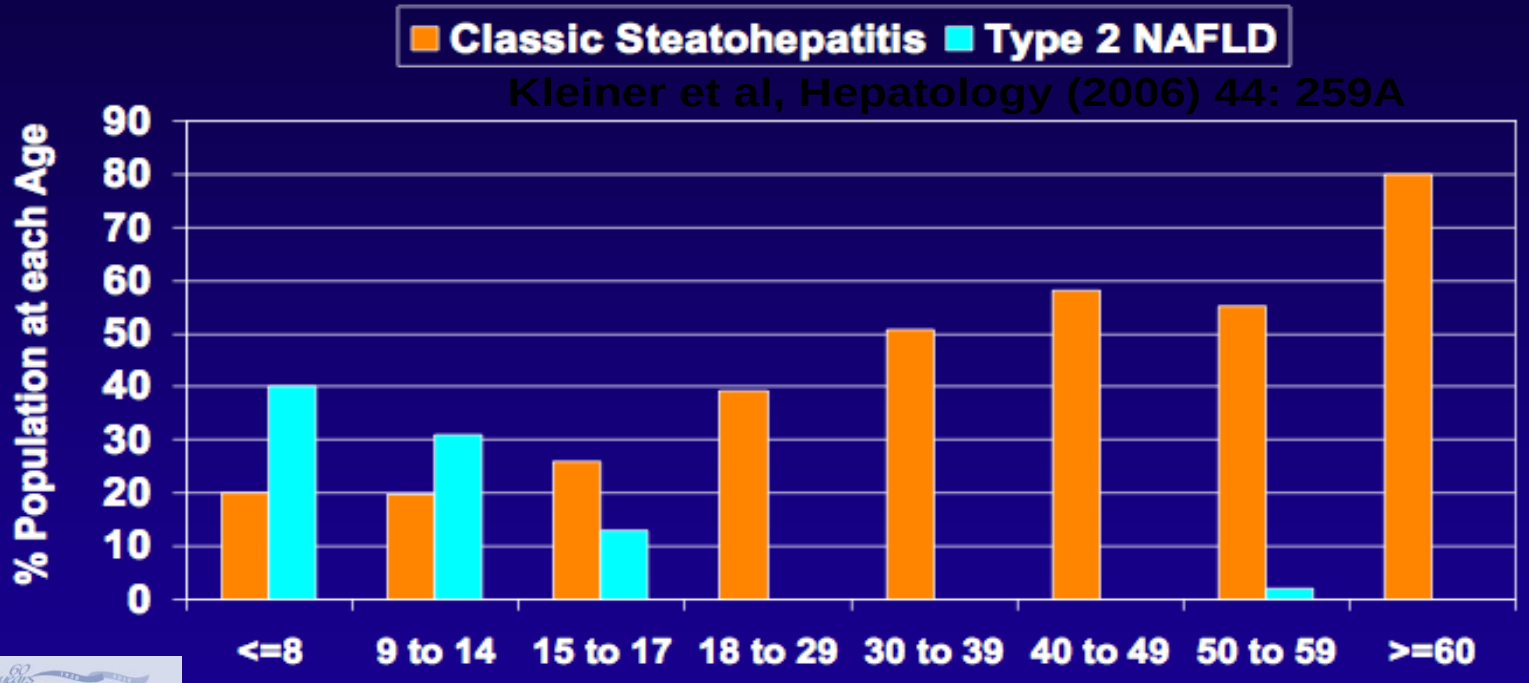
Schwimmer et al, Hepatology 2005

# Adults and Children Manifest NASH Differently

## Steatosis and Portal Inflammation are More Severe in Pediatric NAFLD



# Inverse Relation of Classic NASH and Type 2 NAFLD with Age



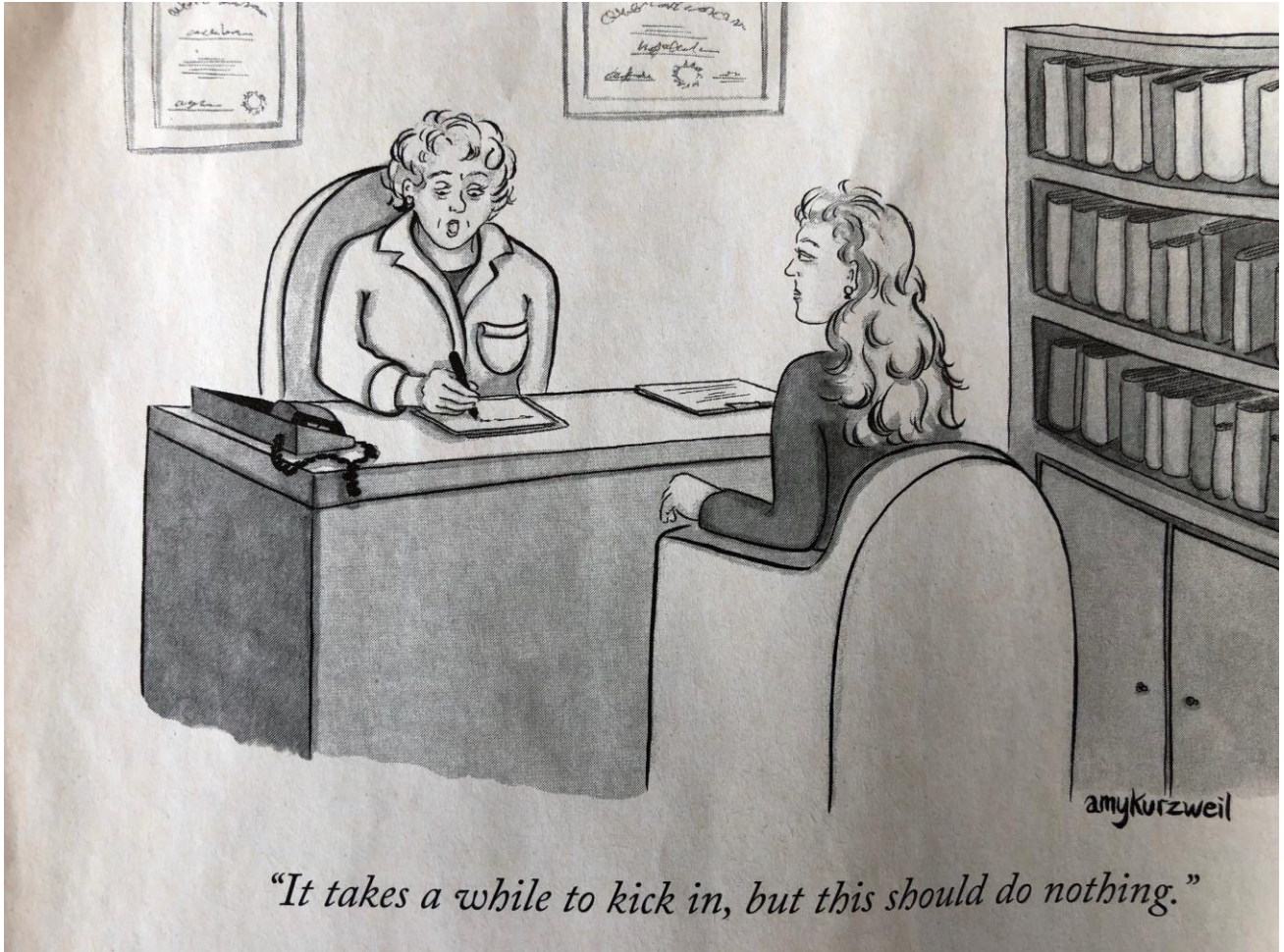

Research supported by NIDDK

NASH CRN

# How Can Prevalence or Natural Hx Be Studied?

- Autopsy series of unnatural deaths
- Use of surrogate markers in general pediatric populations
  - Serum ALT
  - Fat imaging on U/S, MRI
  - Other yet discovered ”omic” test
- Placebo arms of RCT trials with research-related liver biopsy

# Placebo in Pediatric NAFLD

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# Standard lifestyle counseling



- **Lifestyle advice provided by trained study staff using standardized written materials:**
  - TONIC: 9 visits over 96 weeks treatment, ~12 week intervals
  - CyNCh: 5 visits over 52 weeks treatment, ~12 week intervals
- **Consistent with American Academy of Pediatrics recommendations[1], including:**
  - 5 servings fruits/vegetables per day
  - Screen time ≤ 2 hours per day
  - Physical activity ≥ 1 hour per day
  - No sweetened foods/drinks per day
  - Limit fast food intake

[1]Barlow et al. Pediatrics 2007;120 Suppl 4:S164-192.

# Clinical Characteristics N=122



| | Baseline* | Changes after 1-2 years | P† |
|---|---|---|---|
| Male sex | 74% | -- | |
| White | 64% | -- | |
| Hispanic ethnicity | 71% | -- | |
| Age, years | 13.3 ± 2.6 | 0.9 ± 0.5 | P<0.001 |
| BMI, kg/m$^2$ | 32 ± 3 | 1.3 ± 5.5 | P<0.001 |
| BMI z-score | 2.2 ± 0.4 | -0.01 ± 0.21 | P=0.42 |
| ALT, U/L | 112 ± 71 | -19.9 ± 77.5 | P=0.006 |
| AST, U/L | 65 ± 38 | -10.9 ± 39.6 | P=0.003 |
| GGT, U/L | 47 ± 30 | -2.7 ± 20.5 | P=0.16 |
| HOMA-IR | 9.6 ± 13.1 | 1.8 ± 17.6 | P=0.28 |
| Diabetes type 2 (%) | 6% | 13% at FUP‡ | |

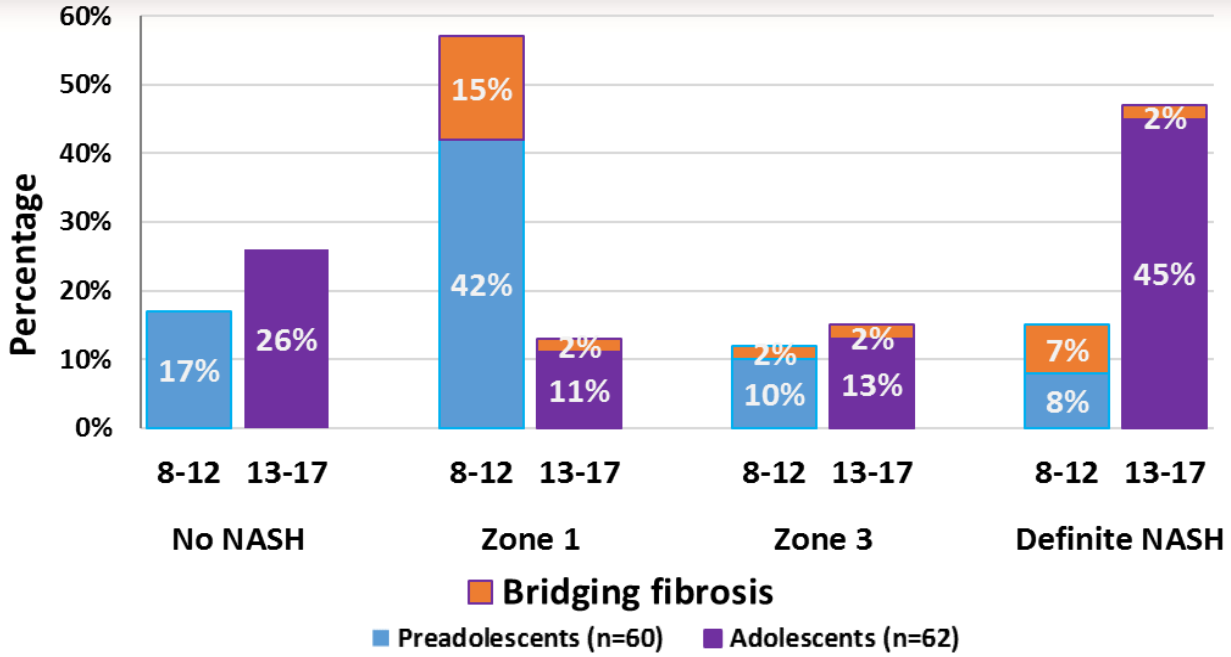
# Histological features



| | Baseline | Follow-up | P† |
|---|---|---|---|
| NASH Diagnosis, % | | | <0.0001 |
| None | 21% | 38% | |
| Borderline Zone 1 | 34% | 15% | |
| Borderline Zone 3 | 13% | 22% | |
| Definite NASH | 31% | 25% | |
| Fibrosis stage, % | | | 0.30 |
| None (0) | 28% | 39% | |
| Mild (1a, 1b, 1c) | 43% | 31% | |
| Moderate (2) | 15% | 15% | |
| Bridging (3)* | 14% | 15% | |
| NAFLD Activity Score | 4.6 ± 1.4 | 3.9 ± 1.7 | 0.0001 |

# Bridging fibrosis more prevalent in preadolescents






**Definite NASH is more prevalent in adolescents (13-17 yrs), P<0.001**
**Bridging fibrosis is more prevalent in preadolescents (8-12 yrs), P=0.008**

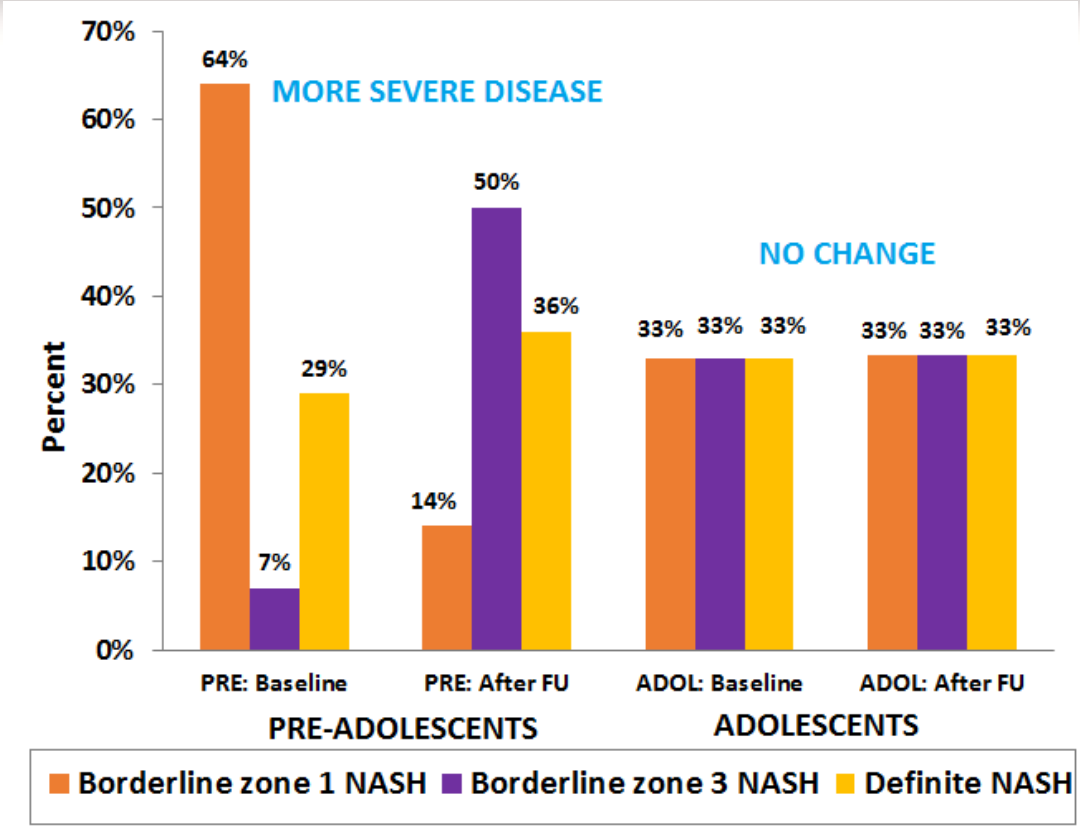
# Histological outcomes



| | % N=122 | RO* | P Adol Vs Pre |
|---|---|---|---|
| NASH Diagnosis | | | |
| Resolution of any NASH | 29% | 0.32 | **0.02** |
| Progression to definite NASH | 18% | 1.45 | 0.52 |
| Fibrosis | | | |
| Improvement ≥ 1 stage | 34% | 0.61 | 0.20 |
| Progression ≥ 1 stage | 23% | 2.05 | 0.11 |
| Progression in | | | |
| Fibrosis **or** to definite NASH | 36% | 2.86 | **0.02** |
| Fibrosis **and** to definite NASH | 11% | 1.27 | 0.74 |
| Improvement in | | | |
| Fibrosis **or** NASH resolution | 52% | 0.46 | 0.06 |
| Fibrosis **and** NASH resolution | 20% | 0.43 | 0.12 |

# NASH diagnosis pattern after 1-2 y of children with baseline bridging fibrosis (n=17)





# Characteristics associated with progression to definite NASH



| Characteristic | RO* | 95% CI | P† |
|---|---|---|---|
| ***At Baseline*** | | | |
| ALT (U/dL) | 3.2 | 1.3, 7.9 | **0.01** |
| AST (U/dL) | 6.6 | 1.3, 33.0 | **0.02** |
| GGT (U/dL) | 6.0 | 1.2, 30.6 | **0.03** |
| Total cholesterol (mg/mL) | 5.2 | 1.1, 25.0 | **0.04** |
| LDL cholesterol (mg/mL) | 7.8 | 1.2, 50.9 | **0.03** |
| ***After 1 to 2 years follow-up*** | | | |
| Increasing BMI z-score | 3.9 | 1.0, 15.0 | **0.049** |
| Increasing Hg A1C (%) | 3.4 | 1.0, 11.4 | 0.05 |

* # children with progression to NASH: 15/84 (18%)
† P determined from logistic regression models of progression to NASH on each characteristic. 17 baseline + 9 change over FUP characteristics were modeled.

# Characteristics associated with progression in fibrosis

| Characteristic | RO* | 95% CI | P† |
|---|---|---|---|
| ***Demographic*** | | | |
| White race (vs. other) | 3.3 | 1.1, 9.3 | **0.03** |
| ***After 1 to 2 years of follow-up*** | | | |
| ALT (U/dL) | 2.4 | 1.2, 4.8 | **0.01** |
| AST (U/dL) | 3.6 | 1.0. 13.1 | 0.06 |
| GGT (U/L) | 8.3 | 0.5, 129 | **0.002** |
| Hemoglobin A1C (%) | 2.3 | 1.1, 4.7 | **0.03** |

* No. children with progression to fibrosis: 28/122 (23%)
† P determined from logistic regression models of progression to NASH on each characteristic. 17 baseline + 9 change over FUP characteristics were modeled.

# Incidence rate of type 2 diabetes mellitus in cohort



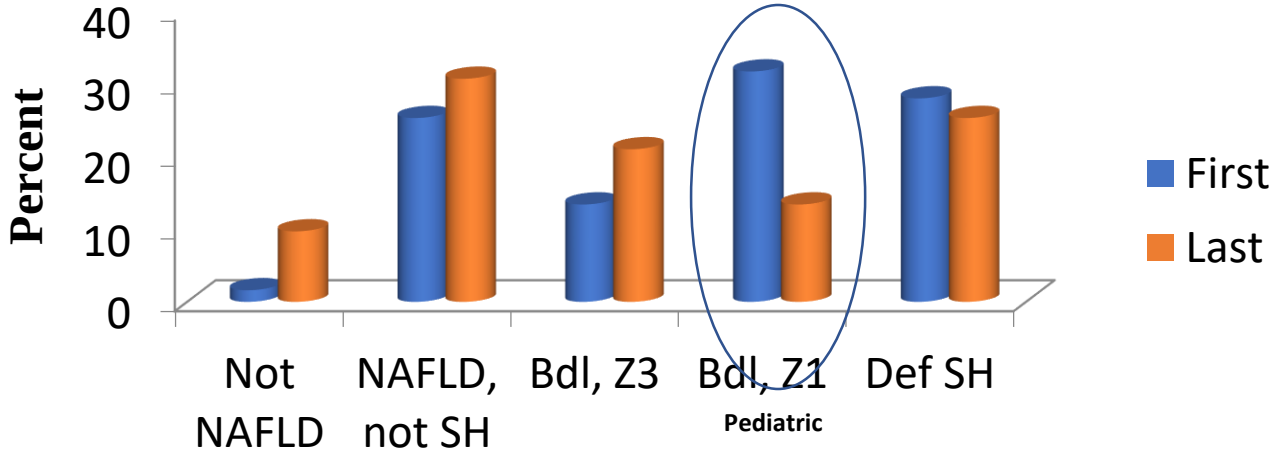
- Type 2 diabetes mellitus developed in 8% over period of observation
- Incidence rate of 44.3/1000 person years
- >300 fold the estimated incidence rate of 0.12/1000 person years in general population of adolescents[1]

[1]JAMA. 2007;297:2716-2724

# What Happens to **Pediatric Pattern** Biopsies? N=59



| 1st biopsy: Bdl 1b, Z1 | Def SH | Bdl 1a, Z3 | Bdl 1b, Z1 | NAFL, Not NASH | Not NAFL, Not NASH |
|---|---|---|---|---|---|
| Last Biopsy: | 12 | 4 | 18 (no change) | 18 | 7 (<5% steatosis) |



# Trial Considerations in Pediatric Studies



- First-in-class drug types not tested in children unless disease confined to pediatric ages
- Restricted procedures if more than minimal risk
- Societal benefit cannot offset risk
- Large differences in size/weight; dosing challenge
- Developmental inability or refusal to swallow pills
- Ability to understand/assent
- Fear of procedures
- Compliance monitoring
- Parent accompaniment/school and work considerations
- Limits on blood draw volume related to size

# Further Considerations in Pediatric Studies



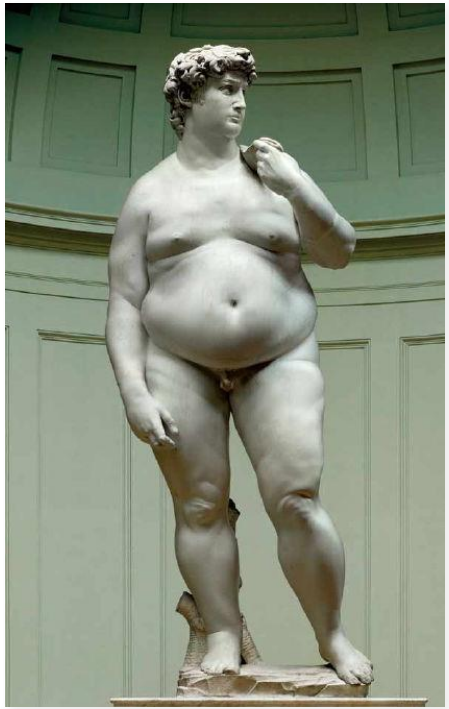
- **Pubertal changes affect hormone levels that influence histology (eg estrogen diminishes inflammation)**
- **Dosing during school hours**
- **Move away from home after high school**
- **Considerations over rapid growth phase/peripubertal**

# Likelihoods in Pediatric Studies



- The majority of subjects will be
  - boys (2:1 ratio)
  - Non-black Hispanics v. other (in US)
  - Obese based on BMI z-score (2.0+)
  - Have elevated ALT
- Only a minority will have:
  - F3 or F4 fibrosis (<15%)
  - Hypertension with age-based norms
  - Overt diabetes

# How Can We Treat It: Therapeutic Targets for NASH



## Decrease insulin resistance

- Lifestyle
- Metformin
- Thiazolidinediones

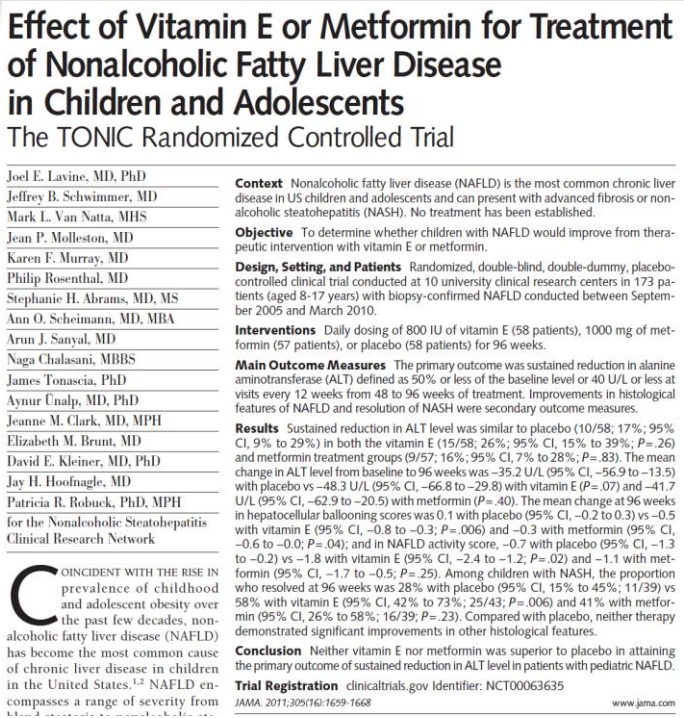
## Diminish oxidative stress

- Lifestyle
  - Weight loss
  - Diet
  - Exercise
- Increase antioxidants
- Diminish inflammation
- Decrease sleep apnea
- Antifibrotics

# Clinical Trial Design:TONIC



- Double-blind placebo-controlled randomized trial of vitamin E or metformin for treatment of children with nonalcoholic fatty liver (1:1:1)
- N=173 subjects @ 8 clinical centers
- Liver biopsy at beginning and end after 96 weeks of treatment
- Outcomes based on changes in blood and liver



## 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
Jean P. Molleston, MD
Karen F. Murray, MD
Philip Rosenthal, MD
Stephanie H. Abrams, MD, MS
Ann O. Scheimann, MD, MBA
Arun J. Sanyal, MD
Naga Chalasani, MBBS
James Tonascia, PhD
Aynur Ünalp, MD, PhD
Jeanne M. Clark, MD, MPH
Elizabeth M. Brunt, MD
David E. Kleiner, MD, PhD
Jay H. Hoofnagle, MD
Patricia R. Robuck, PhD, MPH
for the Nonalcoholic Steatohepatitis Clinical Research Network

**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 nonalcoholic steatohepatitis (NASH). No treatment has been established.

**Objective** To determine whether children with NAFLD would improve from therapeutic intervention with vitamin E or metformin.

**Design, Setting, and Patients** Randomized, double-blind, double-dummy, placebo-controlled clinical trial conducted at 10 university clinical research centers in 173 patients (aged 8-17 years) with biopsy-confirmed NAFLD conducted between September 2005 and March 2010.

**Interventions** Daily dosing of 800 IU of vitamin E (58 patients), 1000 mg of metformin (57 patients), or placebo (58 patients) for 96 weeks.

**Main Outcome Measures** The primary outcome was sustained reduction in alanine aminotransferase (ALT) defined as 50% or less of the baseline level or 40 U/L or less at visits every 12 weeks from 48 to 96 weeks of treatment. Improvements in histological features of NAFLD and resolution of NASH were secondary outcome measures.

**Results** Sustained reduction in ALT level was similar to placebo (10/58; 17%; 95% CI, 9% to 29%) in both the vitamin E (15/58; 26%; 95% CI, 15% to 39%; $P = .26$) and metformin treatment groups (9/57; 16%; 95% CI, 7% to 28%; $P = .83$). The mean change in ALT level from baseline to 96 weeks was −35.2 U/L (95% CI, −56.9 to −13.5) with placebo vs −48.3 U/L (95% CI, −66.8 to −29.8) with vitamin E ($P = .07$) and −41.7 U/L (95% CI, −62.9 to −20.5) with metformin ($P = .40$). The mean change at 96 weeks in hepatocellular ballooning scores was 0.1 with placebo (95% CI, −0.2 to 0.3) vs −0.5 with vitamin E (95% CI, −0.8 to −0.3; $P = .006$) and −0.3 with metformin (95% CI, −0.6 to −0.0; $P = .04$); and in NAFLD activity score, −0.7 with placebo (95% CI, −1.3 to −0.2) vs −1.8 with vitamin E (95% CI, −2.4 to −1.2; $P = .02$) and −1.1 with metformin (95% CI, −1.7 to −0.5; $P = .25$). Among children with NASH, the proportion who resolved at 96 weeks was 28% with placebo (95% CI, 15% to 45%; 11/39) vs 58% with vitamin E (95% CI, 42% to 73%; 25/43; $P = .006$) and 41% with metformin (95% CI, 26% to 58%; 16/39; $P = .23$). Compared with placebo, neither therapy demonstrated significant improvements in other histological features.

**Conclusion** Neither vitamin E nor metformin was superior to placebo in attaining the primary outcome of sustained reduction in ALT level in patients with pediatric NAFLD.

**Trial Registration** clinicaltrials.gov Identifier: NCT00063635

*JAMA. 2011;305(16):1659-1668* www.jama.com

COINCIDENT WITH THE RISE IN prevalence of childhood and adolescent obesity over the past few decades, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in children in the United States.[1,2] NAFLD encompasses a range of severity from

**JAMA 2011**

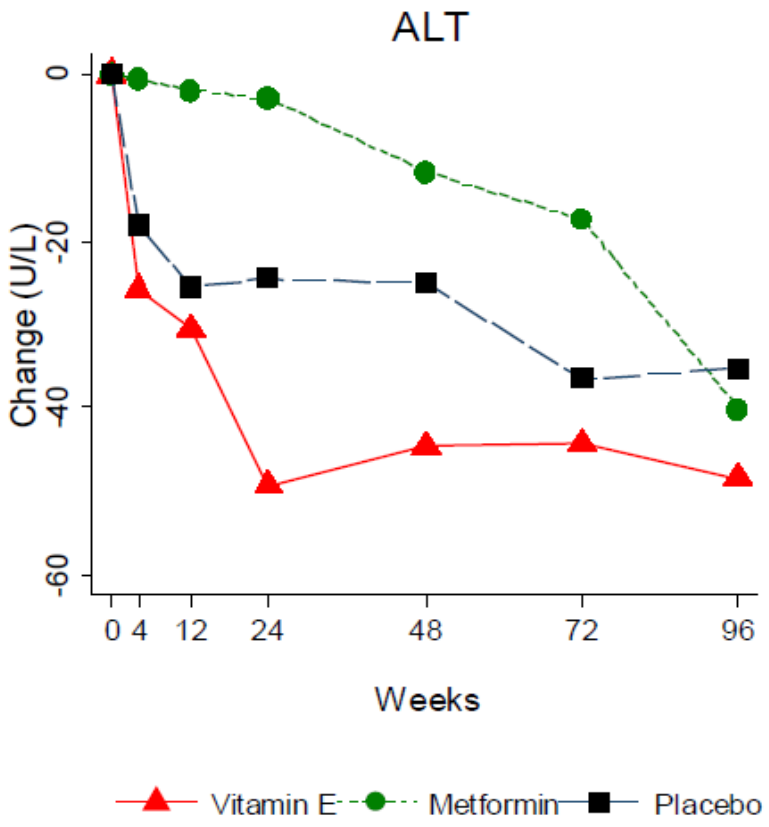
# Baseline Characteristics (N=173)

| Character (units) | Vitamin E N= 58 | Placebo N= 58 | Metformin N= 57 |
|---|---|---|---|
| Age (y) | 13.4 | 12.9 | 13.1 |
| Female (%) | 19 | 21 | 18 |
| Hispanic (%) | 62 | 67 | 54 |
| BMI (kg/m$^2$) | 34 | 33 | 34 |
| Waist circumference (cm) | 109 | 106 | 108 |
| Trunk fat (%) | 45 | 44 | 45 |
| ALT (U/L) | 121 | 126 | 121 |
| AST (U/L) | 70 | 74 | 69 |
| AlkPhos (U/L) | 220 | 229 | 237 |
| Triglycerides (mg/dL) | 154 | 153 | 151 |
| IR (HOMA-IR) | 8.6 | 11.0 | 7.9 |

**Lavine et al, JAMA 2011**

NASH CRN

# ALT Decreased in All Groups



# Vitamin E significantly improves NAFLD activity score



| | Vitamin E (n=50) | Placebo (n=47) | Metformin (n=50) |
|---|---|---|---|
| Mean change | -1.8 | -1.1 | -0.7 |
| P-value | 0.02 | | 0.25 |

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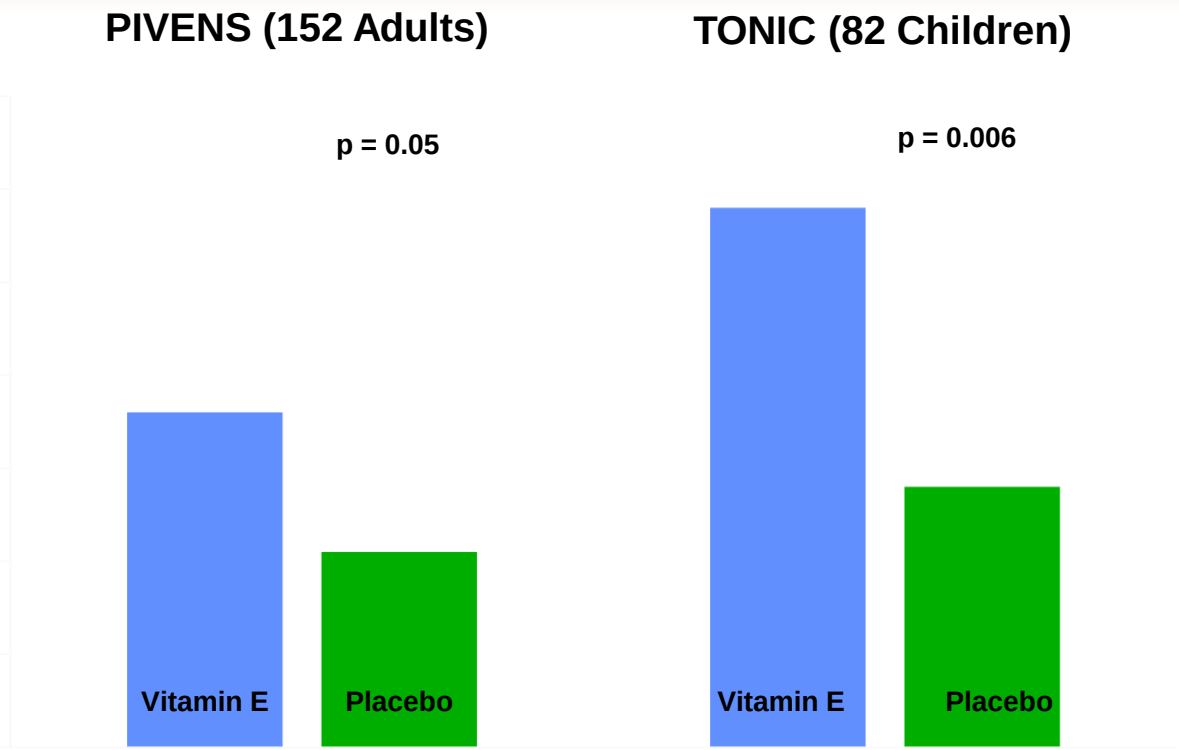
# Vitamin E increased resolution of NASH (from initial definite or borderline NASH)

| | Vitamin E (n=43) | Placebo (n=38) | Metformin (n=39) |
|---|---|---|---|
| Resolved (%) | **58%** | 28% | 41% |
| P-value | **0.006** | --- | 0.23 |

NASH CRN

# Resolution of NASH Histologically





# Practice Guidelines Recommend Vitamin E for Biopsy-proven NASH in Adults



GASTROENTEROLOGY 2012;142:1592–1609

AGA

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

NAGA CHALASANI, MD, FACG,* ZOBAIR YOUNOSSI, MD, FACG,† JOEL E. LAVINE, MD, PhD,‡ ANNA MAE DIEHL, MD,§ ELIZABETH M. BRUNT, MD,‖ KENNETH CUSI, MD,¶ MICHAEL CHARLTON, MD,** and ARUN J. SANYAL, MD††

***Recommendation***

21. *Vitamin E (α-tocopherol) administered at daily dose of 800 IU/day improves liver histology in non-diabetic adults with biopsy-proven NASH and therefore it should be considered as a first-line pharmacotherapy for this patient population.* ***(Strength – 1, Quality – B)***

*Gastroenterology*. 2016 December ; 151(6): 1141–1154.e9. doi:10.1053/j.gastro.2016.08.027.

Paris NASH Meeting

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# In Children with Nonalcoholic Fatty Liver Disease, Cysteamine Bitartrate Delayed Release Improves Liver Enzymes but does not Reduce Disease Activity Scores

**Jeffrey B. Schwimmer**[a,b], **Joel E. Lavine**[c], **Laura A. Wilson**[d], **Brent A. Neuschwander-Tetri**[e], **Stavra A. Xanthakos**[f], **Rohit Kohli**[f], **Sarah E. Barlow**[g], **Miriam B. Vos**[h], **Saul J. Karpen**[i], **Jean P. Molleston**[j], **Peter F. Whitington**[k], **Philip Rosenthal**[l], **Ajay K. Jain**[m], **Karen F. Murray**[n], **Elizabeth M. Brunt**[o], **David E. Kleiner**[p], **Mark L. Van Natta**[d], **Jeanne M. Clark**[d], **James Tonascia**[d], **Edward Doo**[q], and **for the NASH CRN**

- Double-blind, placebo-controlled trial evaluating DR-cysteamine over 52 w treatment
- SOC diet and exercise advice for all
- 10 clinical centers, NIDDK-sponsored 6/12 through 8/15
- 169 subjects (8-17 y) randomized; ITT design
- 52 week treatment with weight-based dosing, 9-12 mg/kg
- Primary outcome improvement in histology, with NAS improvement of 2 or more, no worsening in fibrosis

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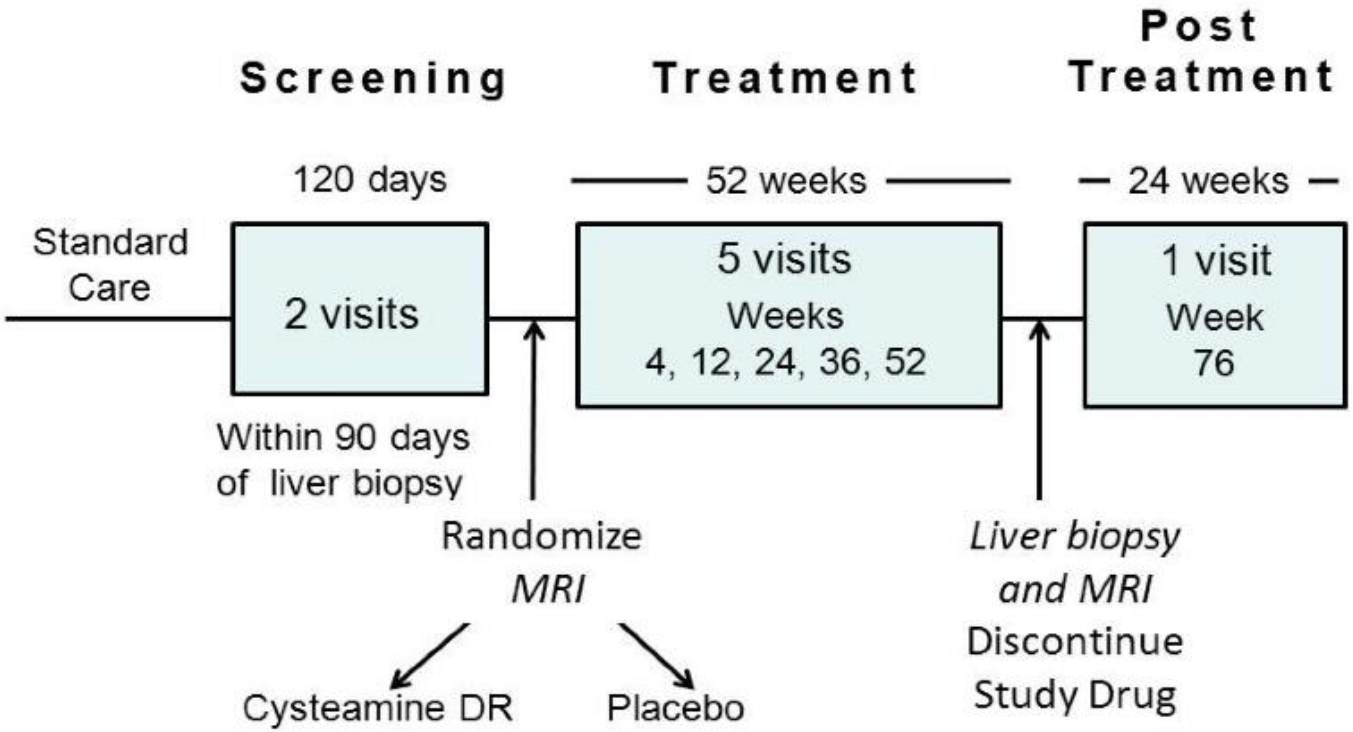
# CyNCh Trial



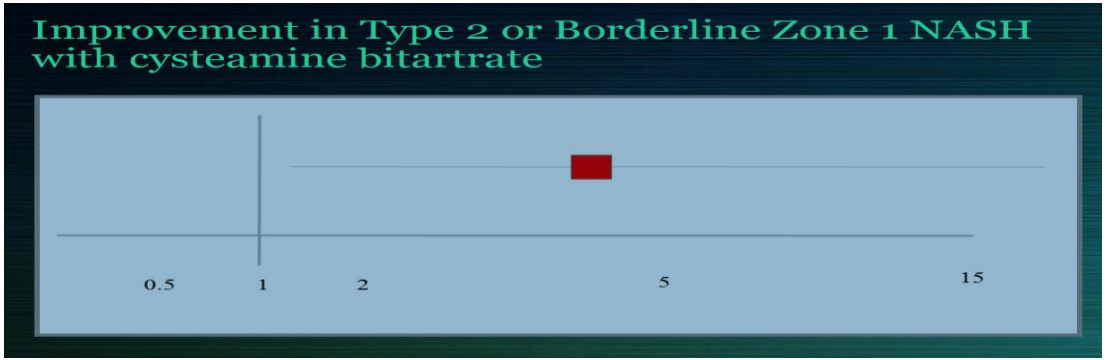

- Randomized, multi-center, double-masked, placebo-controlled trial
- Cysteamine bitartrate delayed-release, twice daily, compared to placebo

# Histology Outcomes

- 88 received DR-C, 81 placebo
- Mean age 13.7 y, 70% boys
- End of treatment biopsies in 81% on drug, 93% on placebo (p=0.03)
- No significant difference in response rates for primary outcome between drug and placebo groups with ITT (28% v 22%, p=0.34)
- ITT analyses of 4 histologic features including fibrosis, steatosis, ballooning and lobular inflammation not significant with statistical correction

# CyNCh Secondary Outcomes

- Those on drug had greater mean change in ALT and AST (p=0.02 and p=0.008, respectively) compared to placebo
- Reductions occurred within first 4 weeks and sustained through week 52 of treatment. Sustained after tx discontinued.
- No difference in adverse events or serious adverse events




Schwimmer, Lavine, et al, Gastroenterology, 2016

# Key Lessons from Pediatric Trials



- Enrollment targets exceeded
- Research-related percutaneous liver biopsies approved by IRB at all sites, accepted by parents and children
- No serious adverse events from biopsies
- NASH resolution and NAS improvement with vitamin E
- ALT improvement in CyNCh, but not NAS improvement
- NAS endpoint in Type 2, but not Type 1 NAFLD in CyNCh
- As in adults, current endpoints should include histology based criteria

# Evolution of NASH: Conclusions



- Genetic or environmental vulnerability makes pediatric onset NASH of concern, as children become young adults with possibly unrecognized disease
- A pediatric-specific subtype histologic pattern may have different etiopathogenesis/treatment response and natural history than “adult-type” NASH
- Standard of care lifestyle advice promotes changes that improve histology severity in placebo groups
- As in adults, vitamin E promotes resolution of NASH relative to placebo
- Effective and safe treatments in adults need to be tested in children to preclude more advanced disease later