Fatty Liver Disease in Children

NASPGHAN
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

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Disclosures

Name	Role	Disclosure	Resolution
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Stephanie H. Abrams	Faculty	Nothing to disclose	N/A
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Pushpa Sathya	Faculty	Nothing to disclose	N/A
Jeffrey B. Schwimmer	Faculty	Nothing to disclose	N/A
Shikha S. Sundaram	Faculty	Nothing to disclose	N/A
Miriam Vos	Faculty	Nothing to disclose	N/A
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Elizabeth Yu	Faculty	Nothing to disclose	N/A
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Pediatric Nonalcoholic Fatty Liver Disease (NAFLD)

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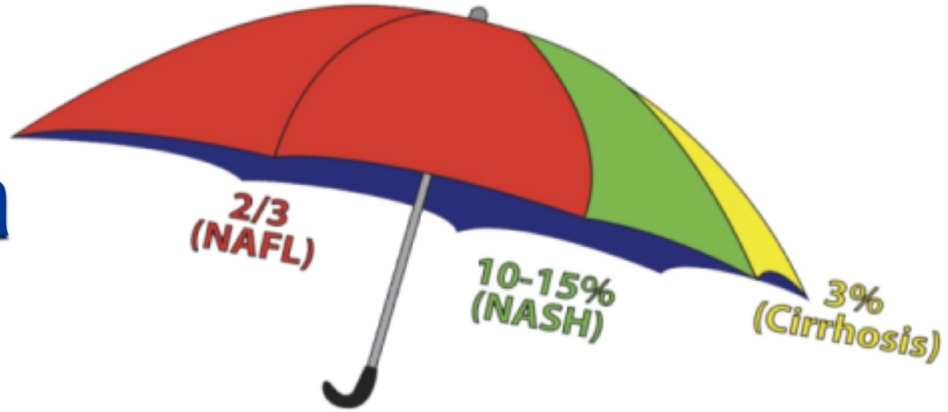
The NAFLD Umbrella

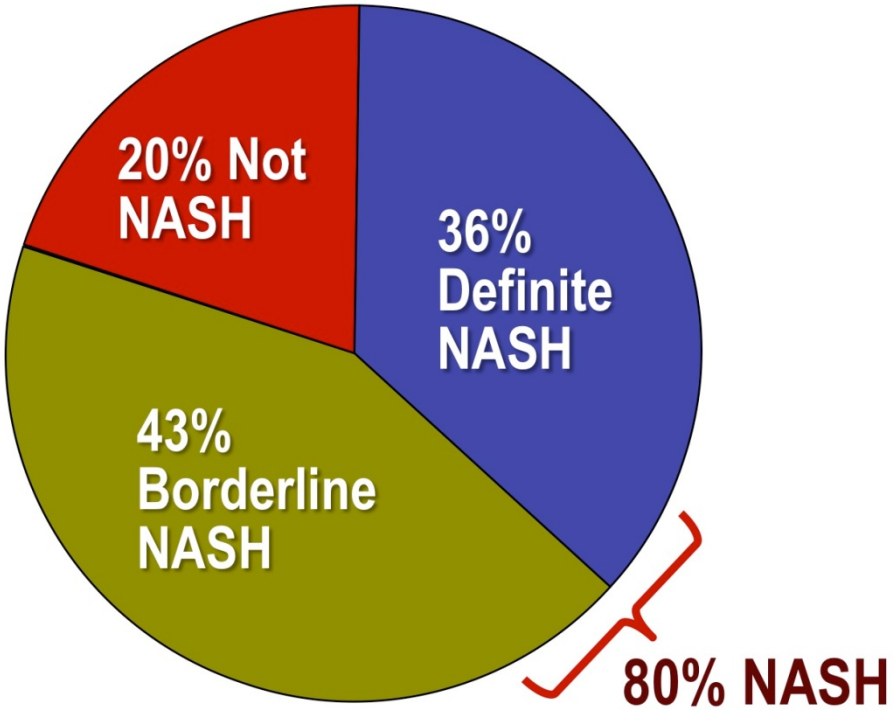


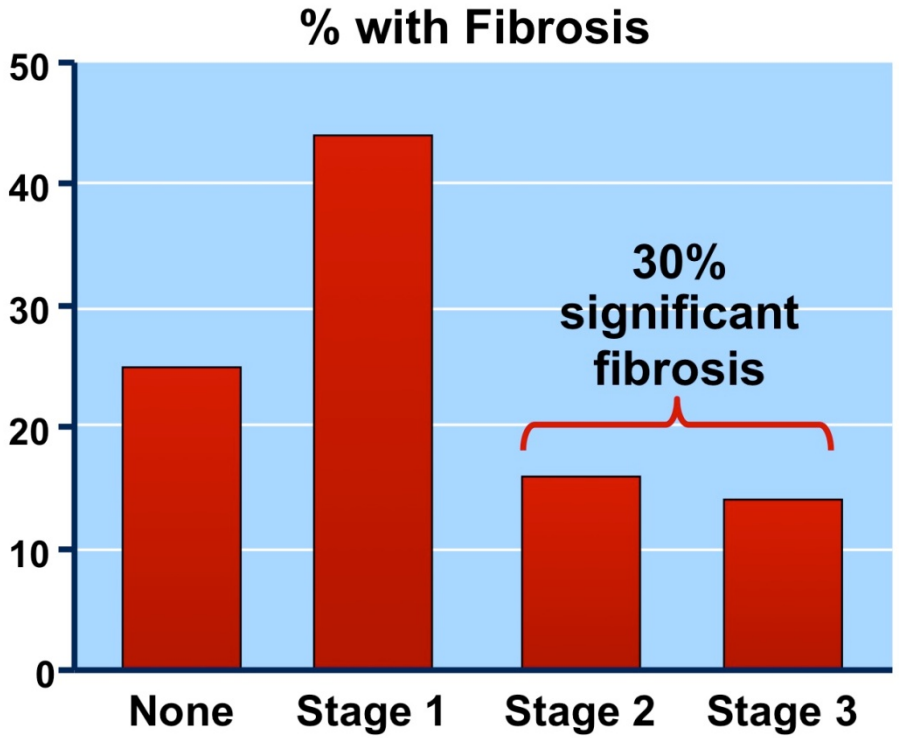
Phenotypes	
NAFLD	Fatty infiltration of the liver >5% by imaging or histology No significant alcohol intake No genetic disease No Medications that cause steatosis
(covers spectrum)	
NAFL	Bland steatosis
NASH	Steatosis with inflammation, ± hepatocellular injury (ballooning), ± fibrosis
NAFLD with fibrosis	NAFL or NASH with periportal, portal, sinusoidal or bridging fibrosis
NAFLD with cirrhosis	Cirrhosis in the setting of NAFLD

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017;64:319-334.

Spectrum of Pediatric NAFLD in NASH Clinical Research Network

176 children from 8 clinical sites in US, mean age 12 (6-17 years)





Notably, mean BMI 33 ± 5, (range 18-58)
BMI percentile 99.1 ± 0.8 %

Patton H et al. *Gastroenterology* 2008;135:1961-71.

Clinical Features Associated with More Severe Pediatric NASH

- Abdominal obesity - ↑ waist circumference
- Insulin resistance, prediabetes, diabetes mellitus T2
- Race/ethnicity: Hispanic > White > Black
  - Genetic polymorphisms (PNPLA3)
- ↑ Age (peri and post-pubertal)
- ↑ ALT (>80 U/L), plus ↑AST and GGT
- Dyslipidemia (↑ triglycerides)

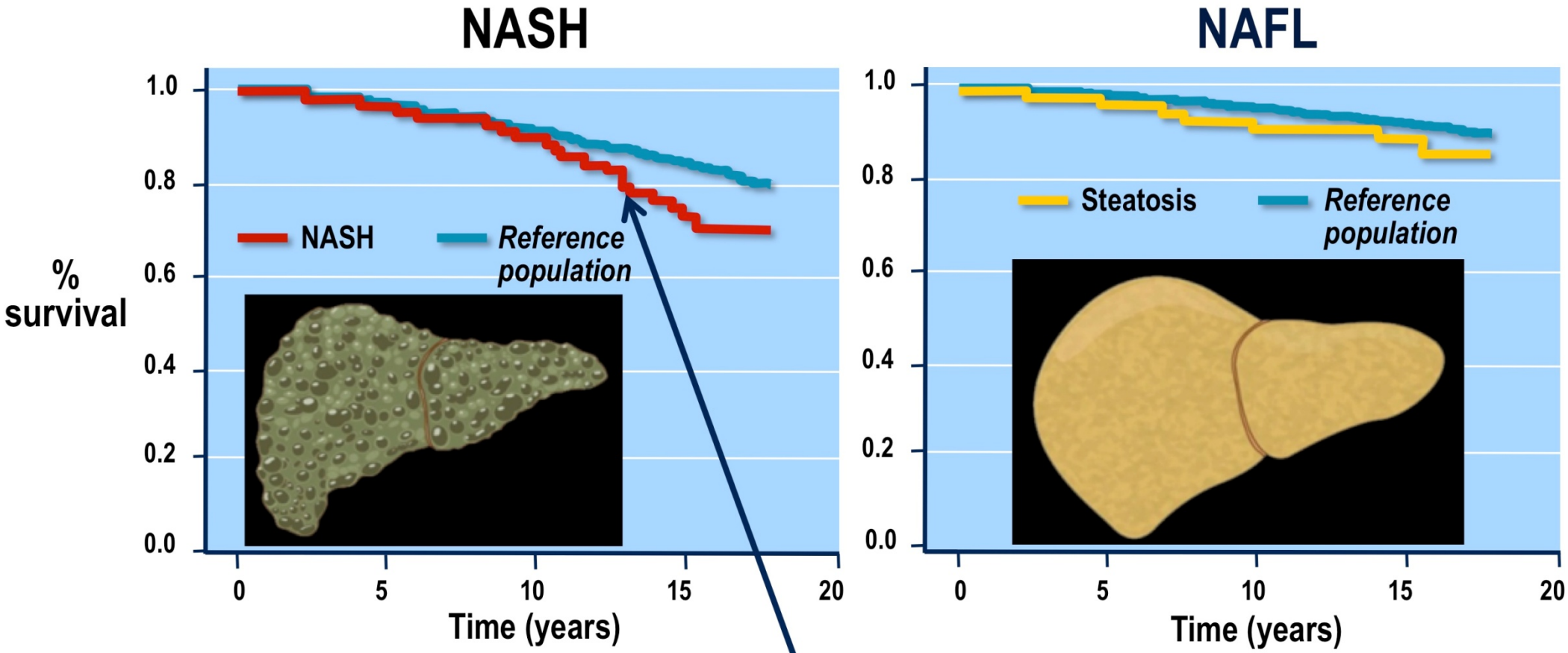
Alkhouri N et al. *Clin Gastro Hepatol* 2011;9:150-155.
Valenti L et al. *Hepatol* 2010;52:1274-1280.
Newton KP et al. *JAMA Pediatr* 2016;170:e161971.
Schwimmer JB et al. *Aliment Pharmacol Ther* 2013;38:1267-77.

What are Future Implications for Children with NASH?

- NASH-related cirrhosis in the United States alone has increased 6 fold over the last decade in adults
  - Now 2nd leading cause for liver transplantation (LT) in adults
  - Most rapidly growing indication for LT related to HCC
- Although long-term outcome of children with NASH remains unknown, these trends in adults are worrisome

Wong RJ et al. *Hepatol* 2014;59:2188.
Wong RJ et al. *Gastroenterology* 2015;148:547.

Natural History NASH vs. NAFL



NASH also associated with *significant increase in mortality in adults*

Eksted et al. *Hepatol* 2006;44:865-73.

Pediatric NAFLD

Prevalence

NAFLD – Prevalence in Children

- NAFLD is the most common cause of pediatric liver disease
- There are no studies describing the incidence of NAFLD in children

Welsh JA et al. *J Pediatr* 2013;162(3):496-500e1.

NAFLD – Prevalence in Children

Continued

- Prevalence of NAFLD parallels obesity
- 2.7 fold increase 1980's to current era

Welsh JA et al. *J Pediatr* 2013;162(3):496-500e1.

NAFLD – Prevalence in Children

Continued

- The prevalence of NAFLD varies with the age of the child, gender, race/ethnicity, and body mass index (BMI)
- There is an increased prevalence of NAFLD in children with certain risk factors such as pre-diabetes, type 2 diabetes, OSA and hypopituitarism

Welsh JA et al. *J Pediatr* 2013;162(3):496-500e1.

NAFLD – Prevalence in Children

Continued

- **Prevalence of NAFLD depends on:**
  - **the population being screened (general population vs. high risk population)**
  - **the screening method used (ALT, imaging, liver biopsy)**

Schwimmer JB et al. *Pediatrics* 2006; 118 (4):1388-93.
Wiegand S et al. *Int J Obes* 2010;34(10):1468-74.
Malespin M et al. *J Clin Gastroenterol* 2015;49 (4):345-9.

NAFLD – Prevalence in Children

Continued

- 2-4 years - 0.7%
- 15-19 - 17.3%
- Obese children by ALT elevation - 29-38%

Welsh JA et al. *J. Pediatr* 2013;162 (3):496-500e1. Schwimmer JB et al. *Pediatrics* 2006;118(4):1388-93.
Louthan MV et al. *J Pediatr Gastroenterol Nutr* 2005;41(4):426-9.
Strauss RS et al. *J Pediatr* 2000;136(6):727-33. Rehm JL et. *J Pediatr* 2014;165(2):e1.
Patton HM et al. *J Pediatr Gastroenterol Nutr* 2006;43:413-427.

NAFLD – Prevalence in Children

Continued

- 11-22 years - 4-fold increased risk for Hispanic children
- 10.2% in Asian children
- 8.6% in white children
- 1.5% in black children

Welsh JA et al. *J. Pediatr* 2013;162 (3):496-500e1. Schwimmer JB et al. *Pediatrics* 2006;118(4):1388-93.
Louthan MV et al. *J Pediatr Gastroenterol Nutr* 2005;41(4):4.
Strauss RS et al. *J Pediatr* 2000;136(6):727-33. Rehm JL et. *J Pediatr* 2014;165(2):e1.
Patton HM et al. *J Pediatr Gastroenterol Nutr* 2006;43:413-427.

NAFLD – Prevalence in Children

Comorbidities Associated with Higher Risk/ Severity of NAFLD

- Children with type 2 diabetes had a 48% prevalence of elevated ALT
- Obstructive sleep apnea (OSA) was associated with NASH in two pediatric studies, independently of BMI and standard metabolic risk factors
- Children with hypopituitarism have an increased risk of NAFLD/ NASH and even cirrhosis

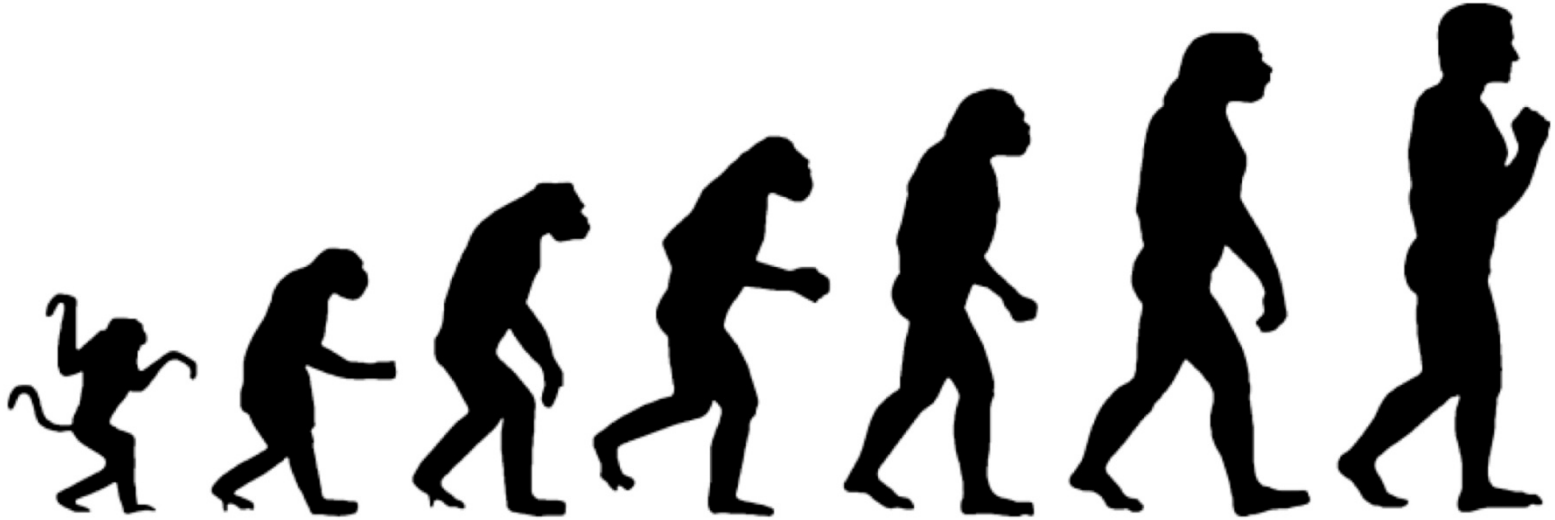
Nadeau KJ et al. *J Pediatr Gastroenterol Nutr* 2005;41:94Y8.
Nobili V et al.. *Am J Respir Crit Care Med* 2014;189(1):66-76.
Sundaram SS et al. *J Pediatrics* 2014;164(4):699-706.e1.
Adams LA et al. *Hepatol* 2004;39(4):909-14.
Nakajima K et al. *J Gastroenterol* 2005;40(3):312-5.

Summary- Prevalence

- The prevalence of pediatric NAFLD parallels the growing prevalence of obesity in children
- The prevalence of NAFLD varies with the population screened, level of risk, and modality used to detect NAFLD
- The prevalence of pediatric NAFLD is higher in certain sub-populations:
  - Overweight/ obese children
  - Males>Females
  - Ethnicity: Hispanics>Asian>Caucasian>Black
  - Pre-diabetes or type 2 diabetes
  - Obstructive sleep apnea (OSA)
  - Hypothalamic dysfunction/ hypopituitarism

Pediatric NAFLD

Natural History

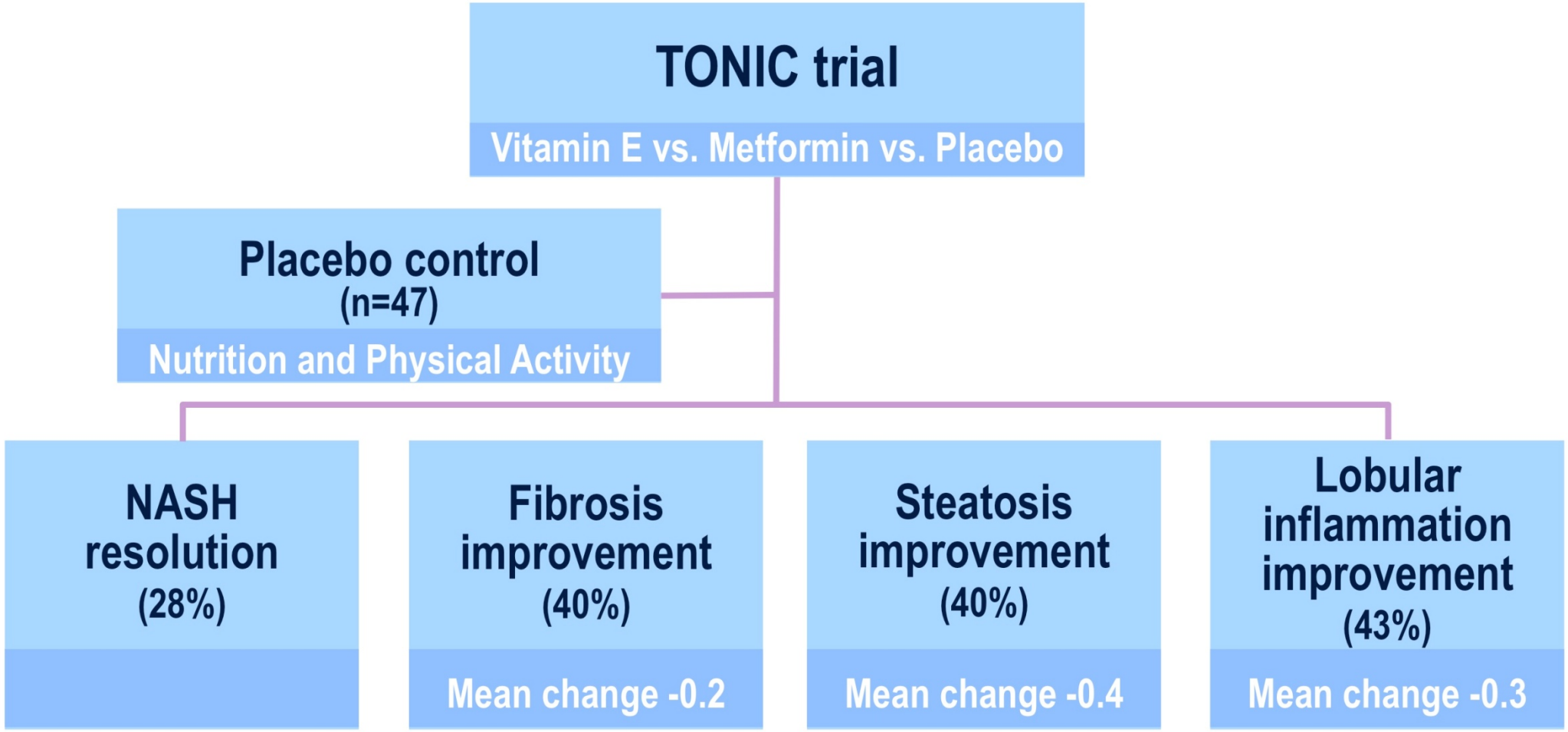


Natural History: A Retrospective Look

5 pediatric subjects Initial liver Biopsy Mean Fibrosis Stage: 0.2	41 +/- 28 months	5 subjects Increased fibrosis on repeat liver biopsy Mean fibrosis Stage: 2
18 pediatric subjects Biopsy proven NASH	28 months	No change in fibrosis: 8/18 (44%) Progression of fibrosis: 7/18 (39%) Regression of fibrosis: 3/18 (17%)

Feldstein AE et al. *Gut* 2009;58(11):1538-44.
A-Kader HH et al. *Clin Gastro Hep* 2008;6(7),799-802.

Natural History: A Prospective Look

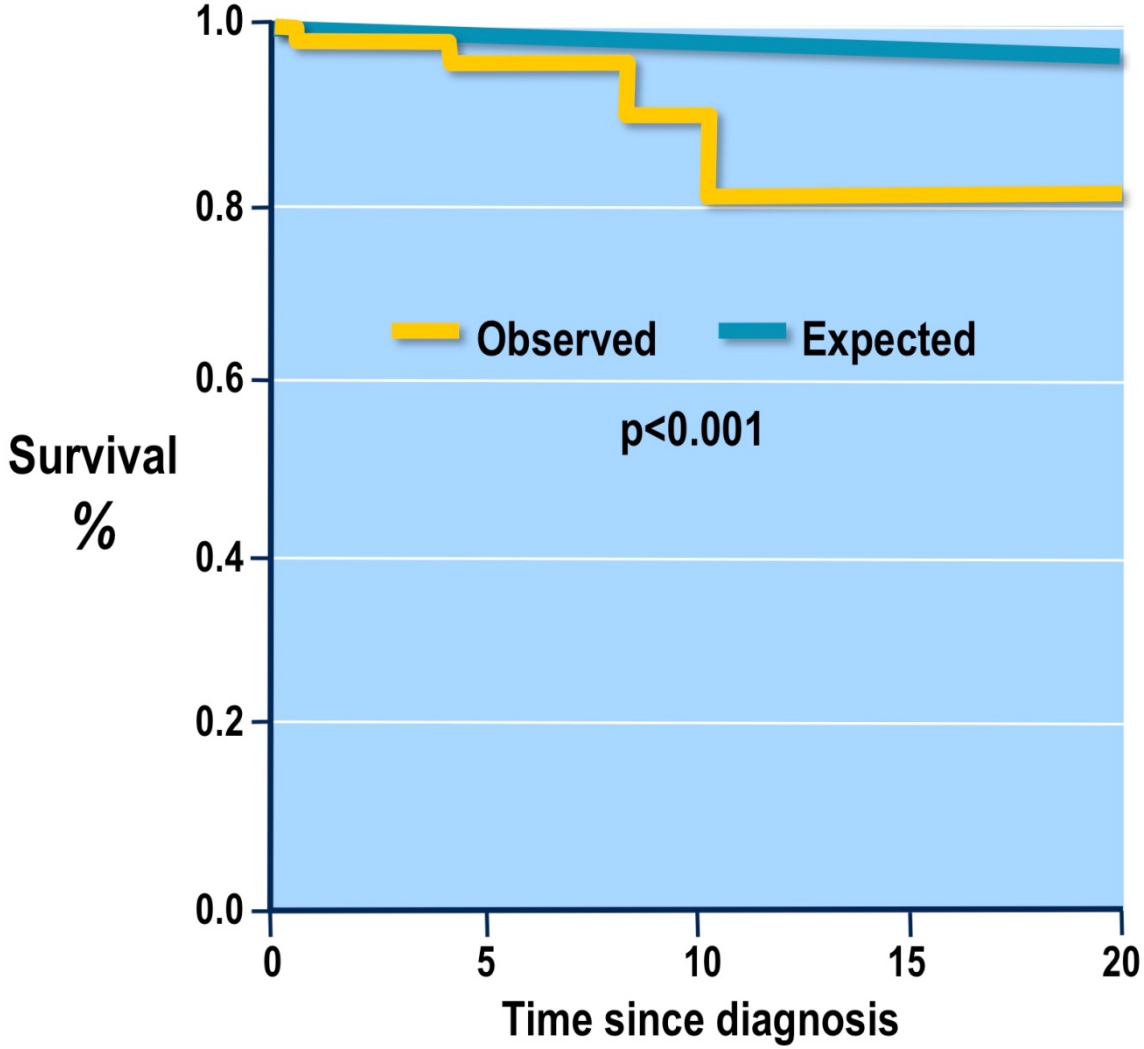


Histologic improvements based on change in NAS activity score
Mean change in ALT: -35

Lavine JE et al. *JAMA* 2011;305(16):1659-68.

Increased Mortality in Pediatric NAFLD

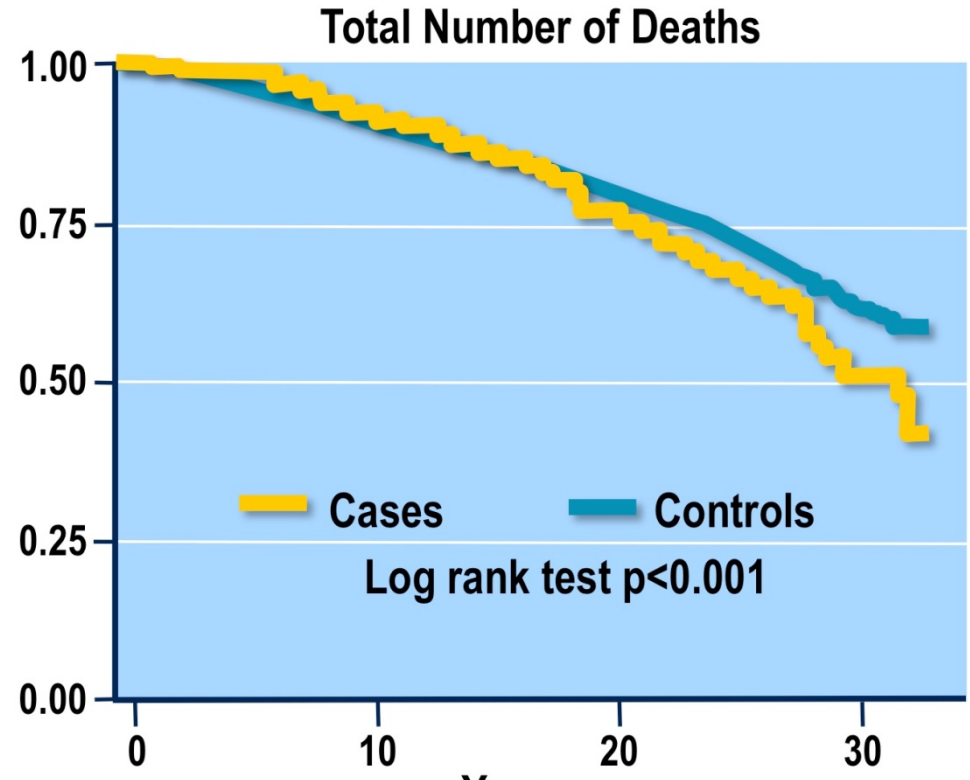
- 66 children
  (mean age 13.9 years)
  - Mean follow up: 6.4 years (Range 0.05-20 years)
  - Total of 409 person years follow up
  - 4 events
    - 2 patients died, 2 liver transplant
    - Observed vs. expected survival - p<0.001



Feldstein AE et al. *Gut* 2009;58(11):1538-44.

Increasing Mortality in Pediatric NAFLD

- 229 adults with biopsy proven NAFLD compared to National Registry of Population Data
- NAFLD mortality:
  - Increased overall (HR 1.29)
  - Cardiovascular (HR 1.55)
  - HCC (HR 6.55)
  - Infectious (HR 2.71)
  - Cirrhosis (HR 3.2)

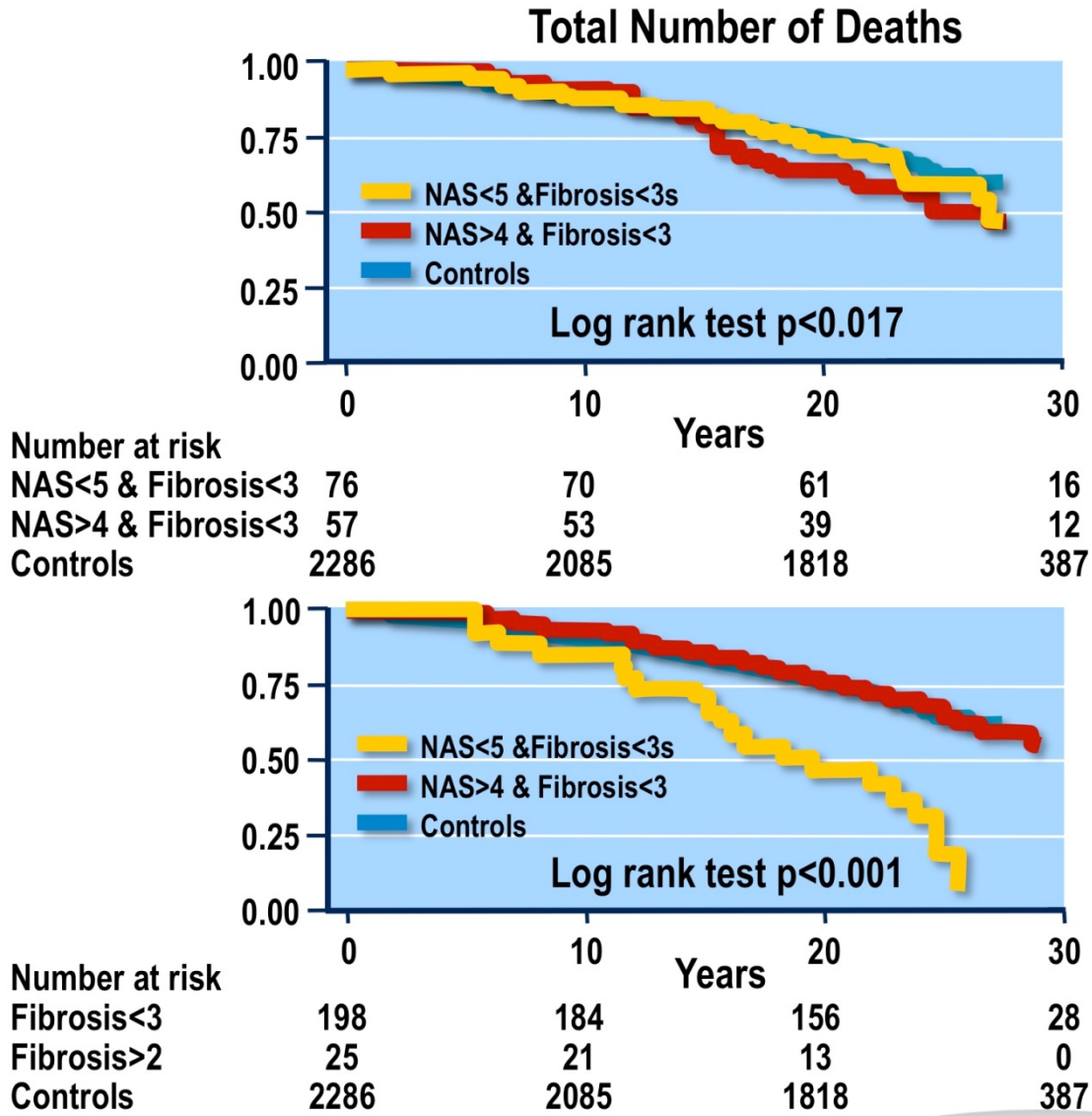


Number at risk				
Controls	2286	2085	1818	387
Case	229	210	174	31

Ekstedt M et al. *Hepatol* 2015;61(5):1547-54.

Fibrosis and Increased Mortality

- No increase in mortality with NAS 5-8
- No increase in mortality with fibrosis stage 0-2
- **Fibrosis stage 3-4**, irrespective of NAS with **increased mortality (HR 3.3)**



Ekstedt M et al. *Hepatol* 2015;61(5):1547-54.
Holterman AX et al. *Obesity* 2013;21(3):591-7.

Pediatric NAFLD: An Aggressive Phenotype?

Comparison of severely obese adults vs. adolescents at bariatric surgery (BMI ≥40)

Histologic Feature	Severely obese adults (n=24)	Severely obese adolescents (n=24)	p value
Definitive NASH	25%	63%	0.009
Mean NAS	2.5	3.3	NS
Presence of fibrosis	29%	83%	0.002
Mean fibrosis score	0.4	1.3	0.002

Select adolescents with NAFLD have more advanced disease than comparable adults

Holterman AX et al. *Obesity* 2013;21(3):591-7.

Summary-Natural History

- Limited data, from small series
- Extrapolation of adult natural history studies may be insufficient
  - Early onset of obesity
  - Increased severity of obesity
  - In utero exposure to maternal obesity and insulin resistance
- Delineation of clinical outcomes of pediatric NAFLD will require long term follow up of affected children into adulthood

Pediatric NAFLD

Screening

Upper Limit for ALT?

- Regional laboratories use local population for norms
  - Do not exclude overweight/obese or other causes of liver disease
  - Median ULN at children's hospitals 53 U/L (range 30-90)
- 95 percentile for ALT in healthy weight, metabolically normal, liver disease free, NHANES adolescent group (12-17 yrs)

ALT 25.8 U/L for BOYS

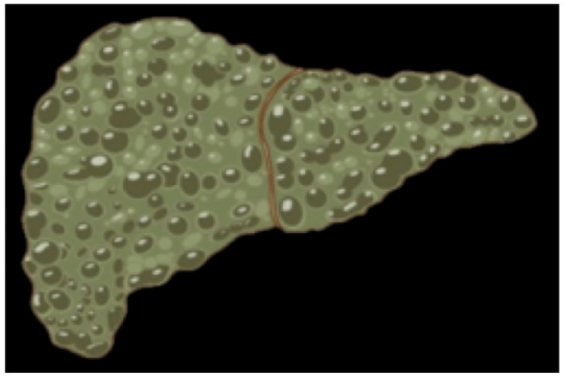
ALT 22.1 U/L for GIRLS

Schwimmer JB et al. *Gastroenterology* 2010;138:1357-64.
Colantonio DA et al. *Clin Chem* 2012;58:854-68.

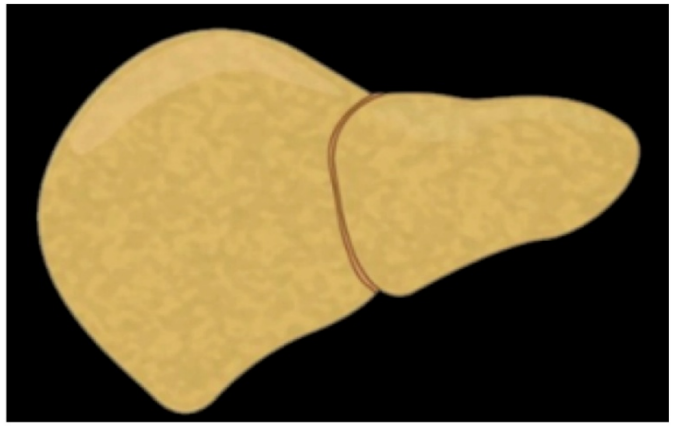
Limitations of ALT

- **Poor correlation** with histology
  - Some studies suggest AST, GGT better correlated with fibrosis
  - ALT changes even with **placebo!**
- Fluctuations over time
- **Cannot always differentiate** between

NASH



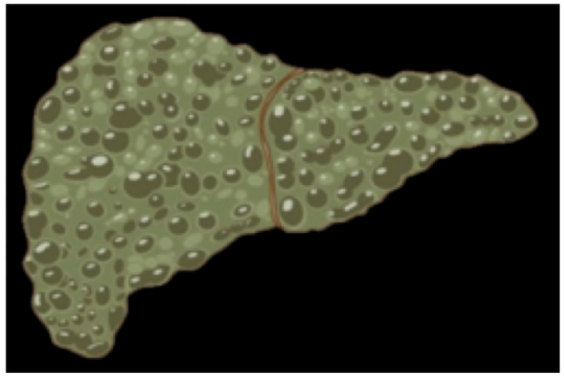
NAFL

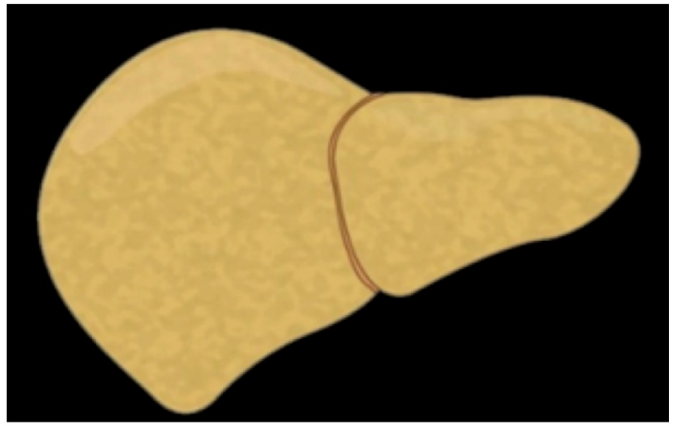


Loomba R et al. *Clin Gastro Hepatol* 2008;6(11):1243-8.

Ultrasound

- **Pros:**
  - Non-invasive
- **Cons**
  - Low sensitivity/specificity particularly lower degrees of steatosis (not recommended for screening in NASPGHAN Guidelines)
  - Cannot differentiate between

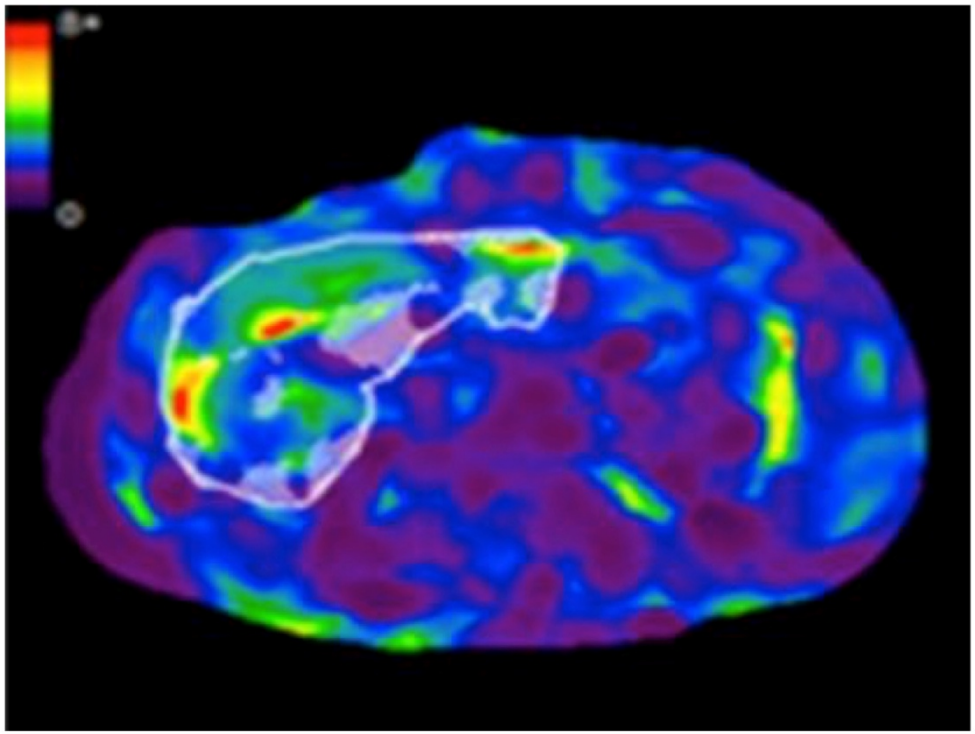
NASH 

NAFL 

Awai HI et al. *Clin Gastroenterol Hepatol* 2014;12:765–73.

Advanced Imaging

- Newer imaging techniques
  - Ultrasound based
    - Shear wave
    - Radiofrequency impulse
  - Magnetic Resonance based
    - Elastography
    - Spectroscopy
- Not widely available



Xanthakos SA et al. *J Pediatr* 2014;164:186–8.
Lin SC et al. *Clin Gastroenterol Hepatol* 2015;13:1337.e6–45.e6.
Schwimmer JB et al. *Hepatol* 2015;61:1887–95.

Recommendations-Screening

- Screening should be considered between 9 and 11 years for:
  - Children (BMI ≥95th percentile)
  - Children (BMI ≥ 85th and 94th percentile) with additional risk factors
    - Central adiposity, insulin resistance, prediabetes or diabetes, dyslipidemia, sleep apnea, or family history of NAFLD/NASH

Recommendations-Screening

Continued

- Earlier screening can be considered in younger patients with risk factors such as severe obesity, family history of NAFLD/NASH, or hypopituitarism

- Consider screening of siblings and parents of children with NAFLD if they have known risk factors for NAFLD

Recommendations-Screening

Continued

- **Best test currently- ALT**
  - Sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys)
  - Persistently (>3 months) elevated ALT more than twice the upper limit of normal should be evaluated for NAFLD
  - ALT of >80 U/L warrants increased clinical concern and timely evaluation

Recommendations-Screening

Continued

- Clinically available routine ultrasound is not recommended as a screening test for NAFLD
- Follow up screening recommended
  - Repeating ALT every 2 to 3 years if risk factors remain unchanged
  - Consider repeating screening sooner if clinical risk factors of NAFLD increase

Pediatric NAFLD

Diagnosis

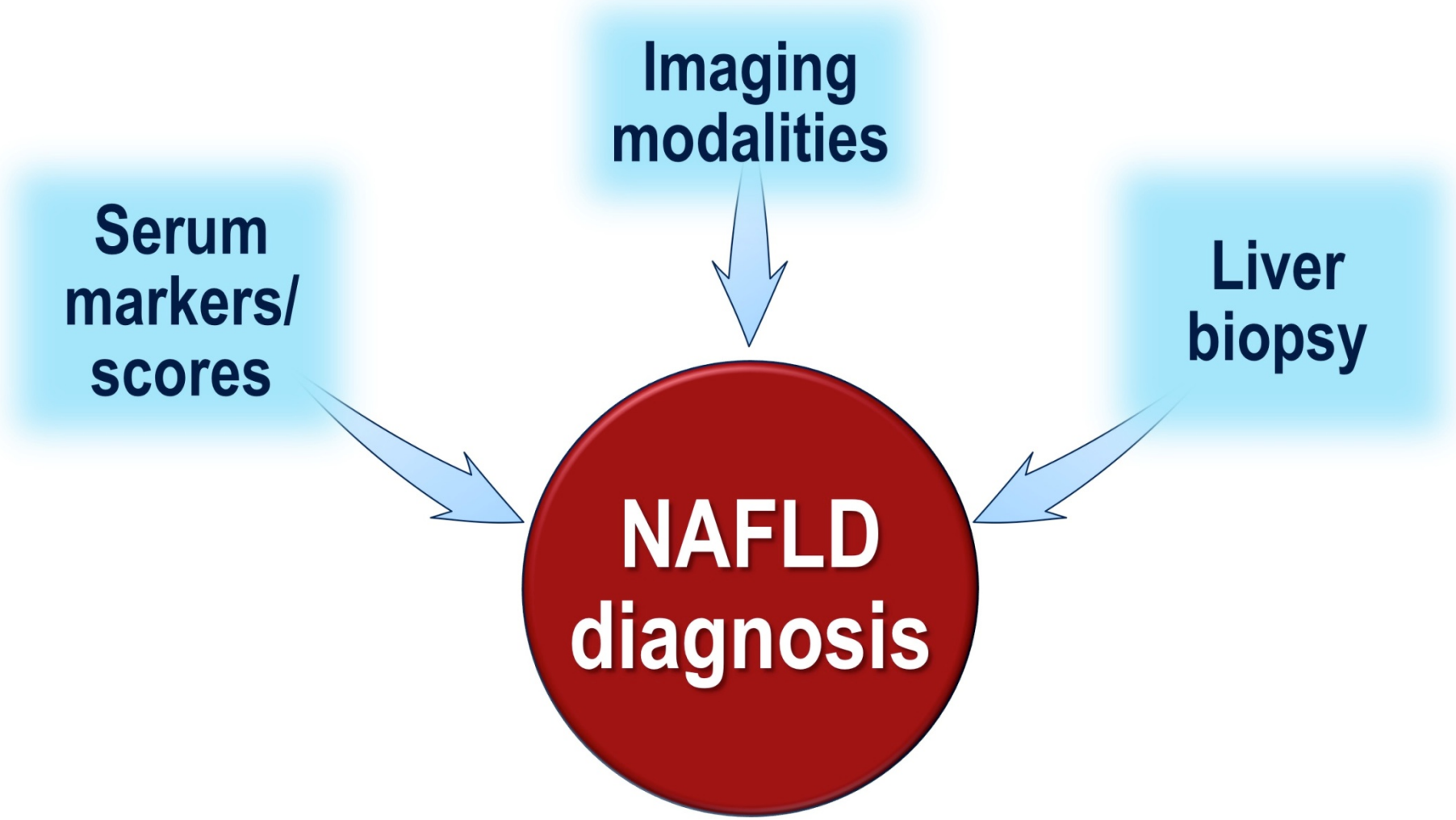
Diagnosis of Exclusion

Other causes of hepatic steatosis need to be excluded

Genetic/Metabolic disorders	Medications	Dietary causes	Infections
LAL-D	Corticosteroids	Alcohol	Hepatitis C (genotype 3)
FACD, citrin deficiency	Amiodarone	Rapid weight loss e.g., surgical	
Wilson's disease	Methotrexate	Parenteral nutrition	
Lipodystrophies	Antipsychotics	Protein-energy malnutrition	
Abeta-/hypobeta-liproproteinemia	Antidepressants		
Uncontrolled diabetes	HAART		

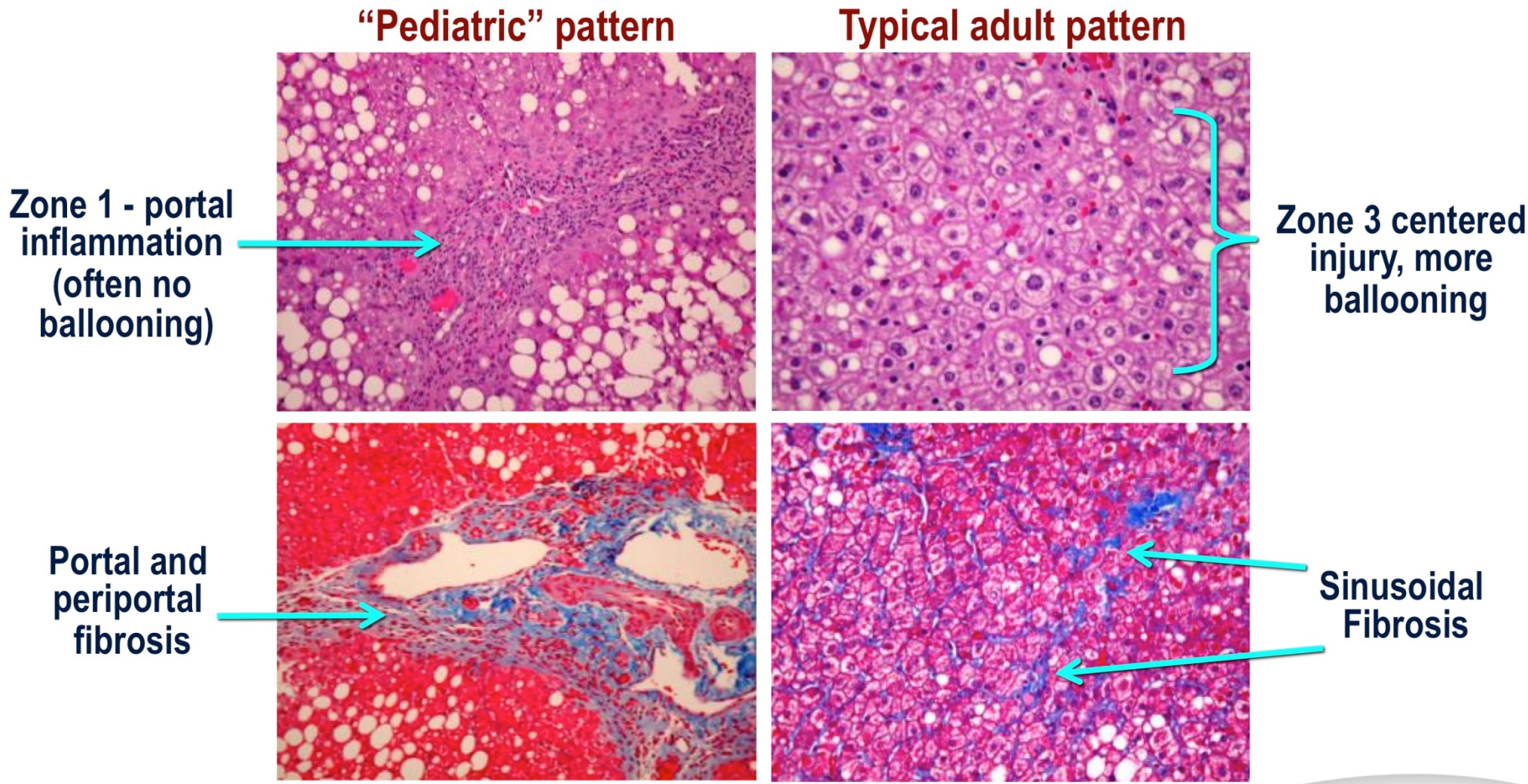
Vos et al. *J Pediatr Gastroenterol Nutr* 2017;64: 319–334.

How to Diagnose?



Vos et al. *J Pediatr Gastroenterol Nutr* 2017;64:319–334.

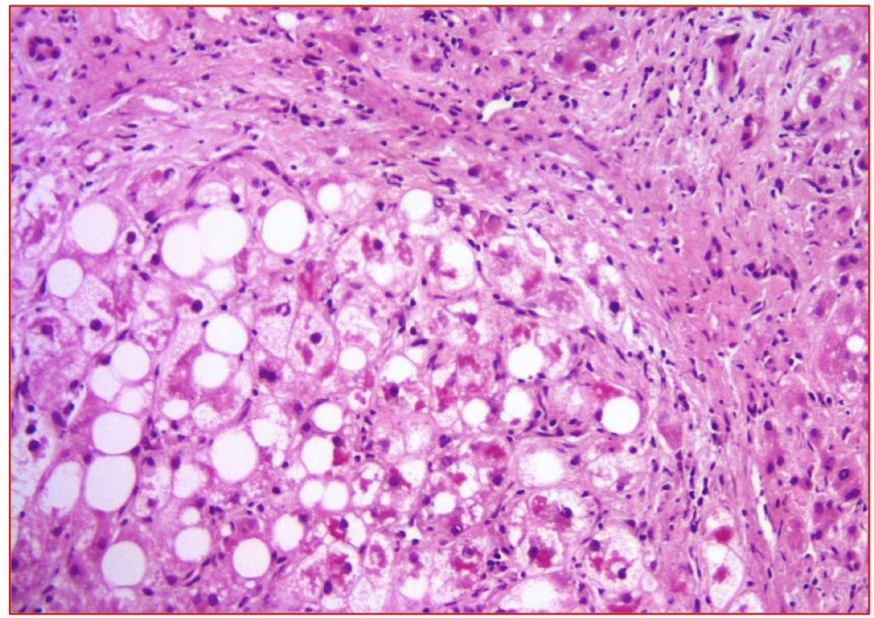
Portal Predominant NASH in Many Pediatric Patients, Rarely in Adults



Schwimmer JB et al. *Hepatol* 2005;42:641-49.
Carter-Kent C et al. *Hepatol* 2009;50:1113-20.

Assessment of Steatosis

- Liver biopsy
  - Traditionally used to quantify steatosis
  - Steatosis in >5% of hepatocytes is abnormal
  - NAFLD Activity Score (NAS)
    - Research: steatosis grading 0-3



- Imaging
  - Investigative ultrasonography
  - MR-based technologies

Cost and availability limit their use

Brunt EM et al. *Hum Pathol* 2004;35:1070-1082.
Kleiner DE et al. *Hepatol* 2005;41(6):1313-21.
Mencin AA et al. *Nat Rev Gastroenterol Hepatol* 2015;12:617-628.

Diagnosing NASH

Cannot distinguish NAFL from NASH

- Obesity severity
- Degree of metabolic dysregulatin
- Bloodwork (ALT, keratin 18, etc.)

- NASH more common in those with ALT>80 U/L
- Panhypopituitarism, T2DM associated with NASH

Can confirm NASH

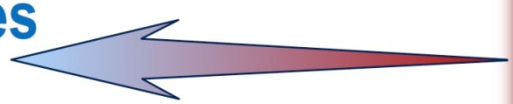
- Liver biopsy

- >2 cm length ⬆ likelihood of accurate classification
- NAS score (research) used to rate severity

Singh S et al. *Dig Dis Sci* 2008;53:279.
Fitzpatrick E et al. *J Pediatr Gastroenterol Nutr* 2010;(4):500-6.
Mandelia C et al. *J Pediatr Gastroenterol Nutr* 2016 Aug;63(2):181-7
Schwimmer JB et al. *Aliment Pharmacol Ther* 2013;38:1267–77.
Kleiner DE et al. *Hepatol* 2005;41(6):1313-21.

Liver Biopsy Considerations

- Safe in children, even if overweight
  - Extreme obesity: consider involving interventional radiology
- Optimal timing of biopsy
  - Not established
  - Shared decision with family
  - Biopsy can be helpful to identify:
    - Other liver diseases
    - Advanced NAFLD



May trigger pursuit of more intensive treatment strategies.

Matos H et al. *Pediatr Radiol* 2012;42:1322-5.
Scheimann AO et al. *J Pediatr Gastroenterol Nutr* 2000;31 (5):536-539.
Harwood J et al. *J Clin Gastroenterol* 2010;44:e253.

Determining the Presence of Fibrosis - Biomarkers

Parameter	ALT for >F2
Pediatric NAFLD fibrosis score	0.74
Pediatric NAFLD fibrosis score	0.62
Enhanced liver fibrosis	0.96
PNFI + ELF	0.94 any fibrosis

- ALT≥ 80 *predicts advanced fibrosis (F3/F4)*
  - *sensitivity 76%; specificity* 59%
- AST/PLT; hyaluronic acid; other biomarkers: remain to be validated in children

Alkhouri N et al. *PLoS One* 2014;9(8):e104558.
Alkhouri N et al. *Clin Gastroenterol Hepatol* 2011;9(2):150–5.
Nobili V et al. *BMC Med* 2009;7:21.
Kaneda H et al. *J Gastroenterol Hepatol* 2006;26:151–6.

Benefits and Limitations of Each Diagnostic Approach

Liver Biopsy

- ☑ Differentiates NAFL from NASH
- ☑ Excludes other liver diseases
- ☑ Clinical reference for diagnosis

Liver Biopsy

- ☑ Invasive
- ☑ Samples a small fraction of the liver

Serum Biomarkers

- ☑ Non-invasive
- ☑ Cheap

Serum Biomarkers

- ☑ Often have low sensitivity/specificity
- ☑ Some remain to be validated

Imaging Modalities

- ☑ Non-invasive
- ☑ Imaging of entire liver
- ☑ Can exclude certain conditions
- ☑ Cost varies

Imaging Modalities

- ☑ U/S has low sensitivity/specificity
- ☑ CT exposes to radiation
- ☑ MRI/MRS: diagnostic cutoffs unclear

Vos et al. *J Pediatr Gastroenterol Nutr* 2017;64:319–334.

Determining the Presence of Fibrosis - Imaging

- **Pediatric literature limited**
  - Small sample size
  - Few patients with advanced fibrosis
- **Transient Elastography**
  - ROC = 0.79-1.00 to predict ≥F2
- **Magnetic Resonance Elastography**
  - ROC = 0.92
    - Scanner and reader dependent

Further validation studies are required

Nobili V et al. *Hepatol* 2008; 48:442-448.
Fitzpatrick E et al. *J Pediatr Gastroenterol Nutr* 2013;6:145–150.
Xanthakos S et al. *J Pediatr* 2014;164:186–188.

Recommendations

- Exclude other liver diseases when evaluating a patient with suspected NAFLD
- Consider liver biopsy in children at risk of NASH and/or advanced fibrosis
- Ultrasound is not recommended to determine or quantify steatosis due to poor sensitivity/specificity
- CT not recommended for quantification of steatosis due to exposure to radiation

Pediatric NAFLD

Treatment

Goals of Treatment

1. Regression of NAFLD

- Defined as decrease in steatosis, inflammation, or fibrosis

2. Resolution of NASH

- These goals are defined and determined by liver histology

Liver Histology

- Assessment of change in fibrosis over time is reasonable as a treatment outcome in children over longer time periods (≥ 2 years) and currently requires a liver biopsy for staging

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Surrogate Markers of Treatment Response

- ALT
  - Decrease in ALT is associated with improvements in NAFLD, but how much of a change is meaningful for a given individual is still to be determined

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Surrogate Markers: Imaging

- **Ultrasound**
  - Not reliable
- **MRI**
  - Promising
  - Needs validation as a measure of change

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Other Treatment Goals

- Decrease in adiposity
- Improvement
  - Dyslipidemia
  - Insulin resistance
  - Blood pressure

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Potential Treatment Options

- Lifestyle
- Dietary supplements
- Medications
- Surgery

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Lifestyle Modifications

- **Lifestyle modifications to improve diet and increase physical activity are 1st-line treatments for all children with NAFLD**

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Lifestyle Targets

- Avoid sugar-sweetened beverages
- Healthy, well-balanced diet
- Moderate to vigorous exercise
- Limit screen time to < 2 hours per day

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Medications for NAFLD

- No currently available medications or supplements are recommended to treat NAFLD
- Bariatric surgery may be considered for selected adolescents with
  - BMI ≥ 35 kg/m^2, who have
  - non-cirrhotic NAFLD
  - Absence of other serious comorbidities

Vos MB et al. *J Pediatr Gastroenterol Nutr* 2017; 64(2):319-334.

Pediatric NAFLD

Extrahepatic Associations

Cardiovascular Disease (CVD)

- **Adult studies:**
  - **CVD is the leading cause of mortality in patients with NAFLD**
  - **NAFLD associated with CVD independent of BMI and other metabolic syndrome components**

Ekstedt M et al. *Hepatol* 2006;44(4):865-73.
Schindhelm RK et al. *Atherosclerosis* 2007;191(2):391-6.
Soderberg C et al. *Hepatol* 2010;51(2):373-5.

Pediatric Data

- **Dyslipidemia is common**
  - Suggestive of insulin resistance (↑TG, ↓HDL)

- **Early atherosclerosis seen in adolescents with NAFLD using surrogate markers and/or autopsies**

Nobili V et al. *Pediatr Res* 2010;7(6):665-70.
Schwimmer JB et al. *Circulation* 2008;118:277-283
Pacifico L et al. *Pediatr Res* 2010; 52:1643-1651.

Impact of Treatment

- **Treating dyslipidemia in the context of NAFLD:**
  - No data on hepatic impact of dyslipidemia treatment
- **Treating NAFLD – impact on dyslipidemia:**
  - TONIC: NASH resolution associated with improvement in cholesterol, not TG
  - DHA superior to placebo for TG improvement
  - Low fructose diet improved oxidized LDL

Lavine JE et al. *JAMA* 2011;305(16):1659-68.
Nobili V et al. *Nutr Metab Cardiovasc Dis* 2013;23:1066–1070.
Vos MB et al. *Arch Pediatr Adolesc Med* 2009;163(7):666-666.

Screening for Dyslipidemia

- As per published guidelines:

2-8 years old

- If risk factors exist
- If family history of dyslipidemia/CVD

9-11 years old

- Universal screening

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, *Pediatrics* 2011;128(5):S213-56.

Hypertension

- Increased risk of hypertension in children with NAFLD and obesity vs. obesity alone

- Treatment recommendations as per guidelines for overweight children

Schwimmer JB et al. *PLoS One;*2014;9(11):e112569.
Schwimmer JB et al. *Circulation* 2008;118:277-283.
Barlow SE et al. *Pediatrics* 2007;120 Suppl 4:S164-92.

CVD Recommendations

- **Children with NAFLD:**
  - Should be screened for dyslipidemia at diagnosis and periodically, as per published guidelines
  - Should have their blood pressure monitored

Insulin Resistance and Diabetes Mellitus

- **Increased risk of NASH if NAFLD with:**
  - Insulin resistance (OR: 1.8)
  - Diabetes mellitus (OR: 2.6)
- **Correlation between hepatic fat and prevalence of insulin resistance**
- **Baseline fat content predicts long-term (~2y) insulin sensitivity**

Newton KP et al. *JAMA Pediatr* 2016;170(10):e162199.
Cali AMG et al. *Hepatol* 2009;49(6):1896–1903.
Kim JY et al. *Diab Care* 2013;36:1547–1553.

Diabetes Recommendations

- Screen annually or sooner if clinical concern
- Screen using:
  - Fasting glucose
  - HgbA1c
  - OGTT if above suggest pre-diabetes

Obstructive Sleep Apnea (OSA)

- **OSA affects > 50% of children with NAFLD**
- **Independent of BMI and metabolic syndrome, OSA is associated with:**
  - NASH
  - Advanced fibrosis
- **Increased % of time with $SaO_2 \leq 90\%$ relates to:**
  - Hepatic necroinflammation and steatosis
  - Elevated transaminase levels

Sundaram SS et al. *J Pediatr* 2014;164 (4), 699-706.e1.
Nobili V et al. *Am J Respir Crit Care Med* 2014;189(1),66-76.

Pediatric NAFLD

Unanswered Questions and Research Priorities

Unanswered Questions and Research Priorities

- Natural history of NAFLD starting in childhood
- Risk factors in childhood NAFLD that predict progression to cirrhosis and HCC
- Non invasive diagnostics
- Longitudinal studies of biomarkers and imaging

Kohli R et *al J Pediatr* 2016;172:9-13.

Unanswered Questions and Research Priorities

- **Treatment questions:**
  - Role of dietary interventions
  - Type and duration of exercise
  - Validation of promising therapeutics
  - Role of weight loss surgery
- **Cost effectiveness and public health questions:**
  - Effective prevention strategies
  - Cost effectiveness of screening, diagnosis and follow up

Future Directions

- Improvement in understanding of the disease will lead to improved outcomes
- As pediatricians, prevention is a priority but not yet a focus for funding
- Collaborative efforts exist nationally and internationally
  - NASPGHAN NAFLD Scientific Advisory Board
  - The Liver Forum
  - NIH sponsored NASH Clinical Research Network
  - Industry supported Natural History studies
- These are all opportunities to get involved!