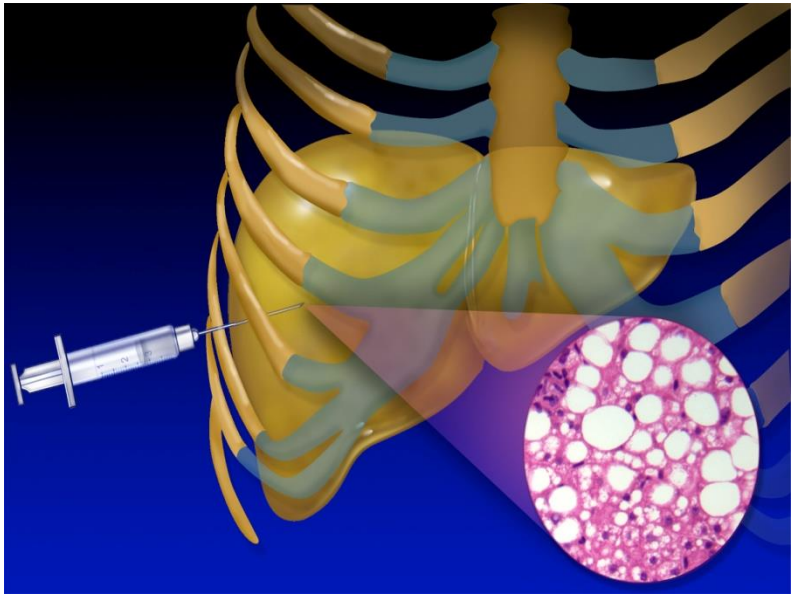
Pediatric Issues Working Group: Definitions and baseline parameters



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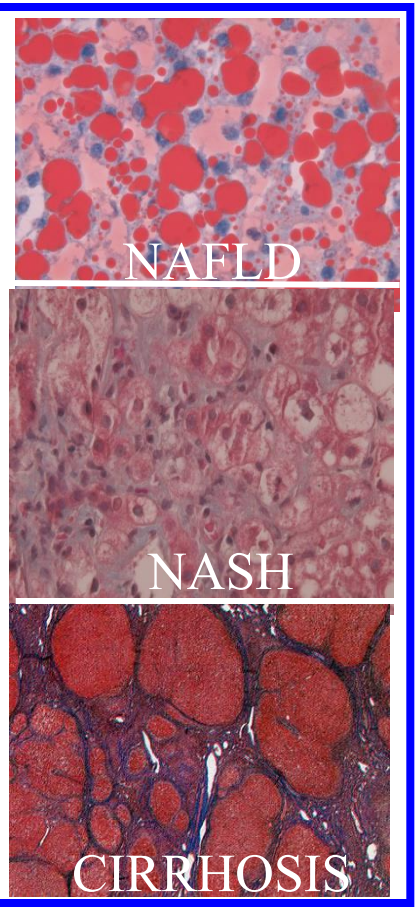
LF Pediatric Working Group

- Recruited new members
- Conference call
- Developed document summarizing current state
  - “Regulatory Considerations for Clinical Trials in Pediatric NAFLD”

Why is Pediatric NAFLD Important?

- Obesity prevalence increased rapidly
- Most common pediatric liver disease now
- Ethnic predisposition and severity
- Differs significantly from adult NASH
- Genetic penetrance
- Cirrhosis in childhood and beyond
- Liver disease co-morbidity
- Association with CV morbidity risk
- Limited treatment



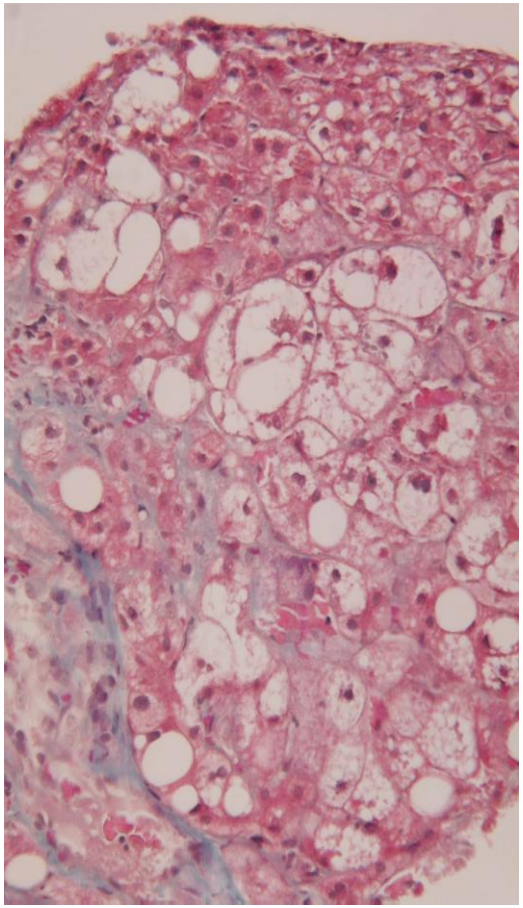
Clinical Definition of NAFLD

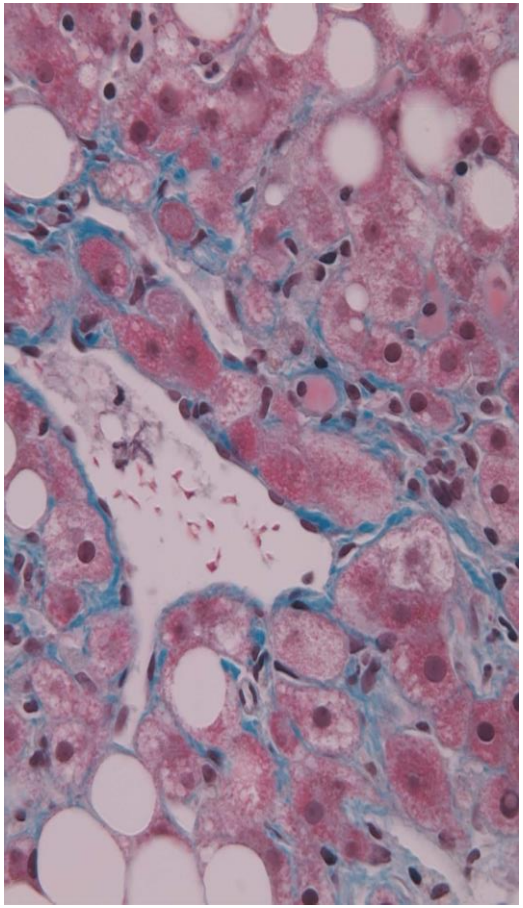
- Histological evidence of macrovesicular fat in >5% hepatocytes
- Lack of:
  - significant ethanol ingestion
  - other drugs or toxins
  - viral hepatitis, TPN,
  - inborn metabolic errors
  - autoimmune hepatitis
  - cystic fibrosis
  - Wilson's disease

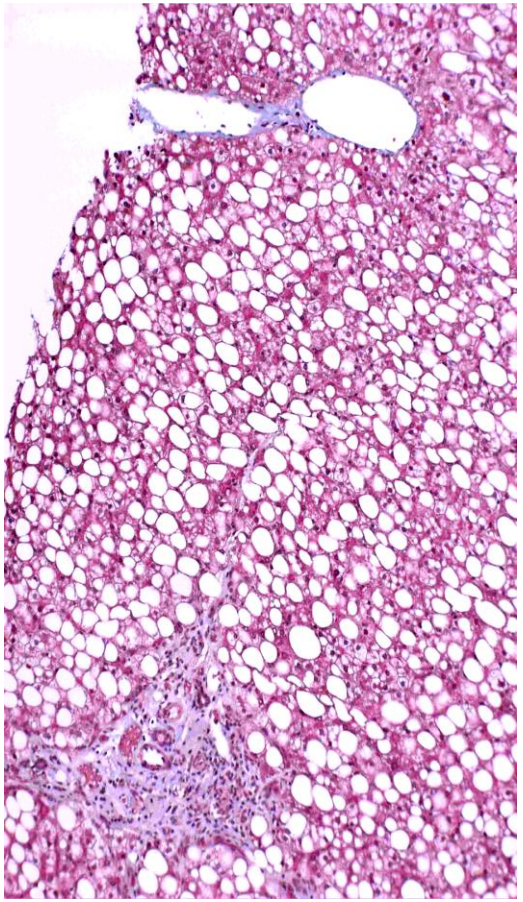
NASH-Histology in Children Can Be Different

Type 1

Type 2







Hepatology, 2005; 118: 641-49

Background

- In US, congressional mandates for pediatric study (PREA), same drug for same use in adults
- phase III in adult drug studies need pediatric study plan approved for registration

2 large Phase 2 RCT in children successfully completed

- TONIC – conducted by NIH NASH CRN
  - Primary endpoint sustained reduction in ALT (50% or less of baseline or <40 U/L
  - Also included biopsies
  - Both metformin and vitamin E were not superior for primary endpoint
  - Statistically significant improvements in histology using NAS reduction of 2 or more with no worsening of fibrosis with vitamin E

- CyNCH – conducted by NIH NASH CRN
  - Abstract presentation at AASLD
  - Primary histologic endpoint of change in NAS of 2 not reached.

Inclusion criteria considerations

- Age and size
- Means to ascertain diagnosis
- Severity of disease features
- Type of histology pattern
- Ability to swallow pills
- Alternative treatment tried, time of tx
  - Lifestyle
  - Vitamin E

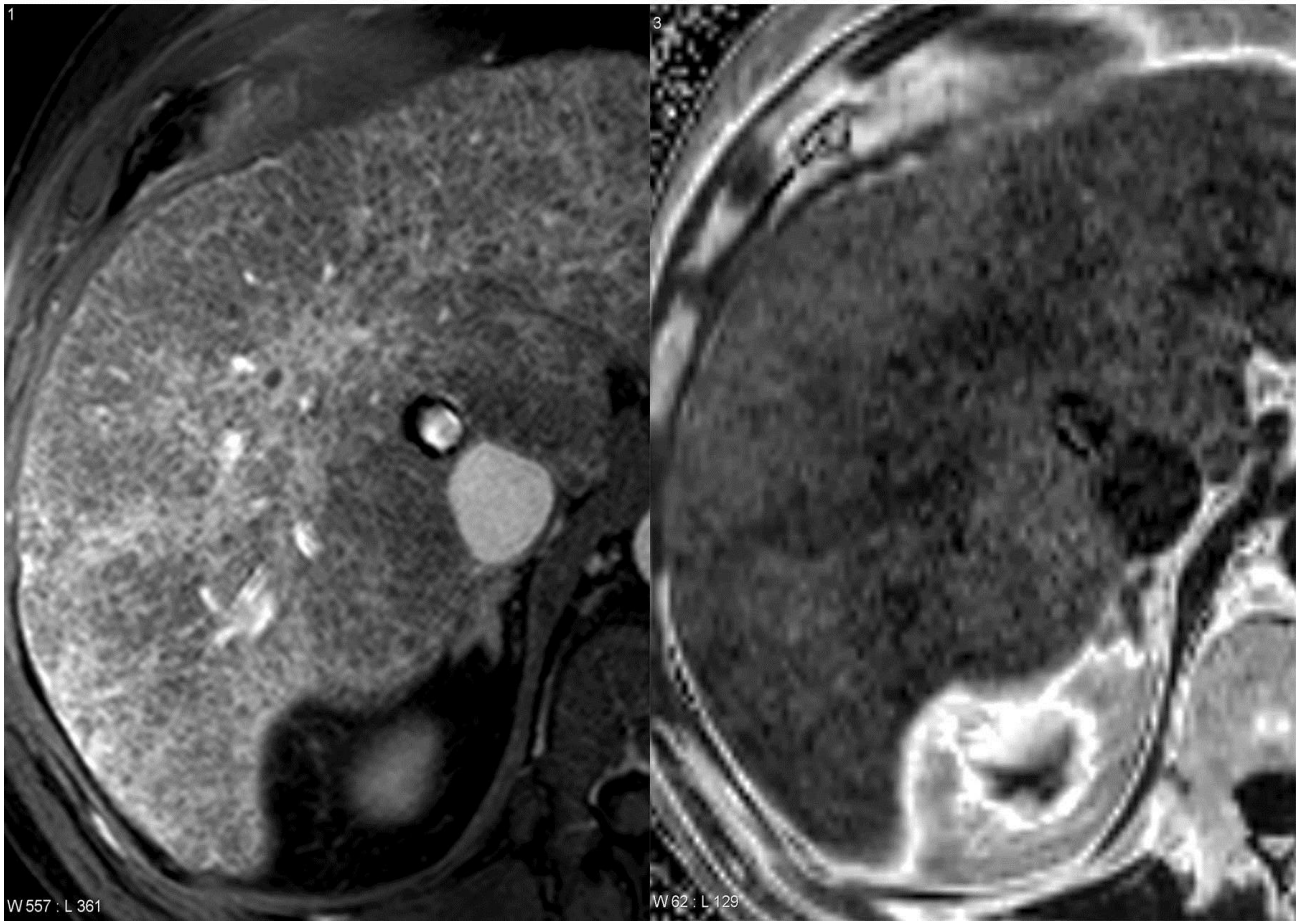
Trial Design Considerations

- Dose/pill v liquid/compliance issues
- Consent/assent considerations/aging out
- Fear of procedures
- Length of trial
- Benefit/risk re natural history (unknown) v side effects and complications
- Disease severity
- Possible recruitment difficulty
  - Note EOT liver biopsy usually 85% in two RCT in children

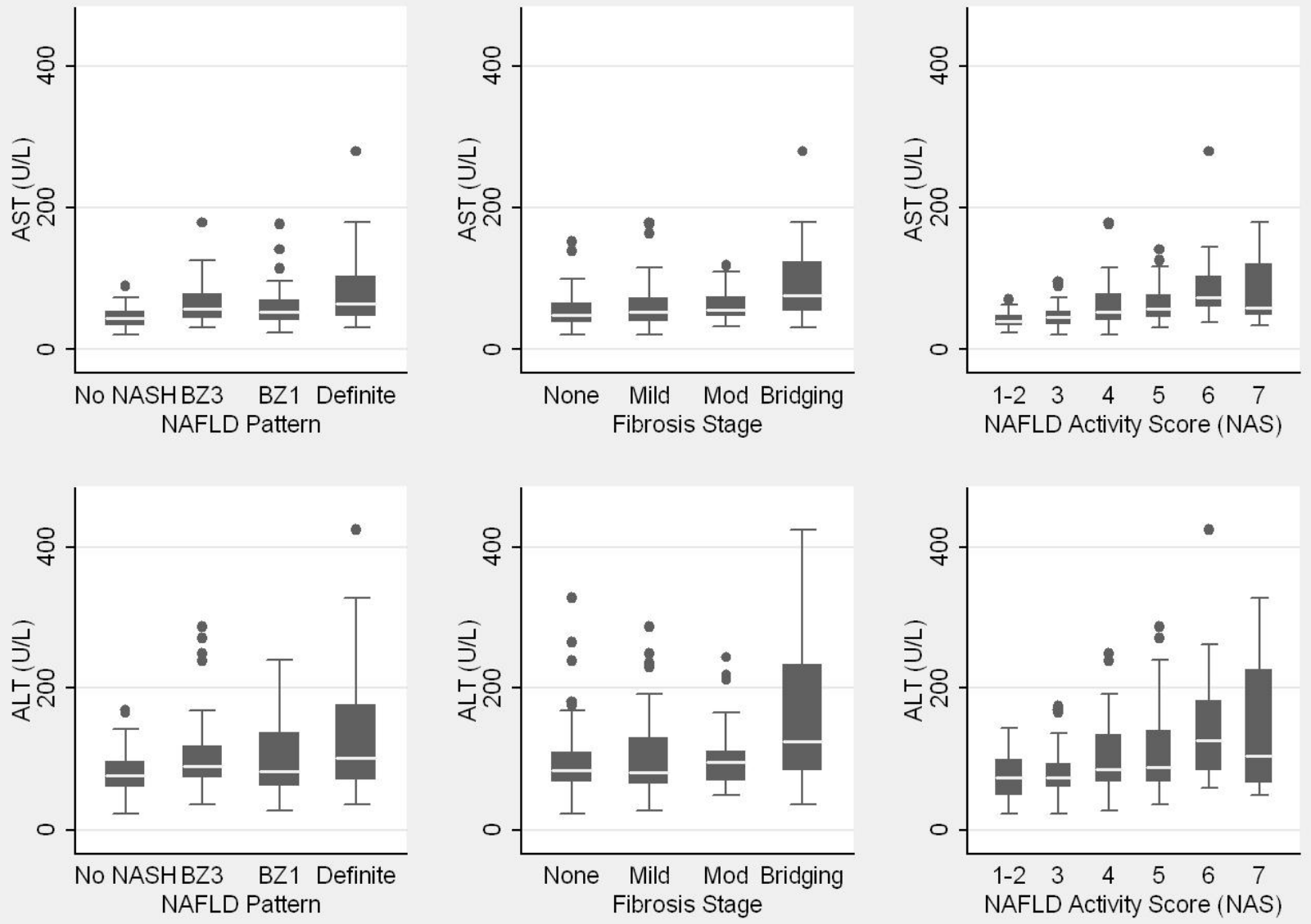
Noninvasive Bioimaging as Surrogate Endpoints for Fibrosis and Fat

Fibrosis

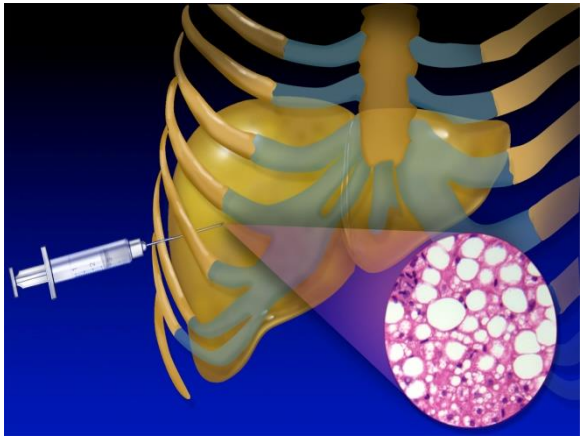
Fat



Relation of AST and ALT to Pediatric NAFLD Histopathology



Gastroenterology, 2008; 135(6):1961-1971



Unmet Needs for NASH

- Lack of noninvasive modality for NASH dx
- Lack of means of monitoring progression or likelihood of response to treatment
- Therapies used result in insufficient effect
  - 40-50% meet primary outcome endpoints
  - Generally histology based, not clinical outcomes
  - Vitamin E, pioglitazone, pentoxyfilline
- Direction from FDA on registration qualification

NASH Ideal Therapeutic

- Safe & well tolerated
- Efficacious for majority
- Oral, once a day or injectable, infrequent
- Affordable
- Addresses other metabolic syndrome co-morbidities (dyslipidemia, insulin resistance, obesity)
- Noninvasive means to follow response

Proper Registrational Endpoint Considerations

- Hx of NAFLD Activity Score reduction (2 or more points) with no progression of fibrosis
- Shift to endpoints for registration include:
  - Resolution in NASH with no worsening of fibrosis
  - Regression in fibrosis with no worsening of NASH
  - Diminution in hepatic venous pressure gradient
  - Co-primary endpoints
- Possible endpoints MR and US elastography for drugs intended to reduce fibrosis

Gaps in Knowledge

- Predictors of long term (>5 year) clinical outcomes
- Clinical outcomes of NAFLD that begins in childhood
- Effect of resolution of NAFLD on the increased risk of type II diabetes and CVD
- Validated surrogate endpoints

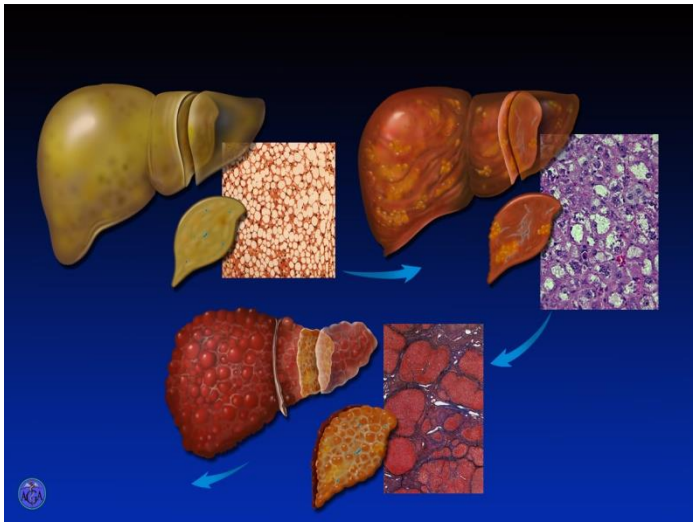
Future solutions

- Collaborative natural history studies
- Designing trials that roll into longitudinal cohorts to increase knowledge

Pediatric Natural History Framework

- TransAtlantic Initiative
- Needed to weigh benefit/risk of treatments
- Unknown how BZ1/T2NASH pattern evolves, ?different natural hx, ?different tx response
- Unknown how pediatric NAFLD impacts early onset adult disease
- Most genetically/environmentally susceptible cohort
- Loss of data moving from peds to medicine

Natural History:
What data should be uniform?

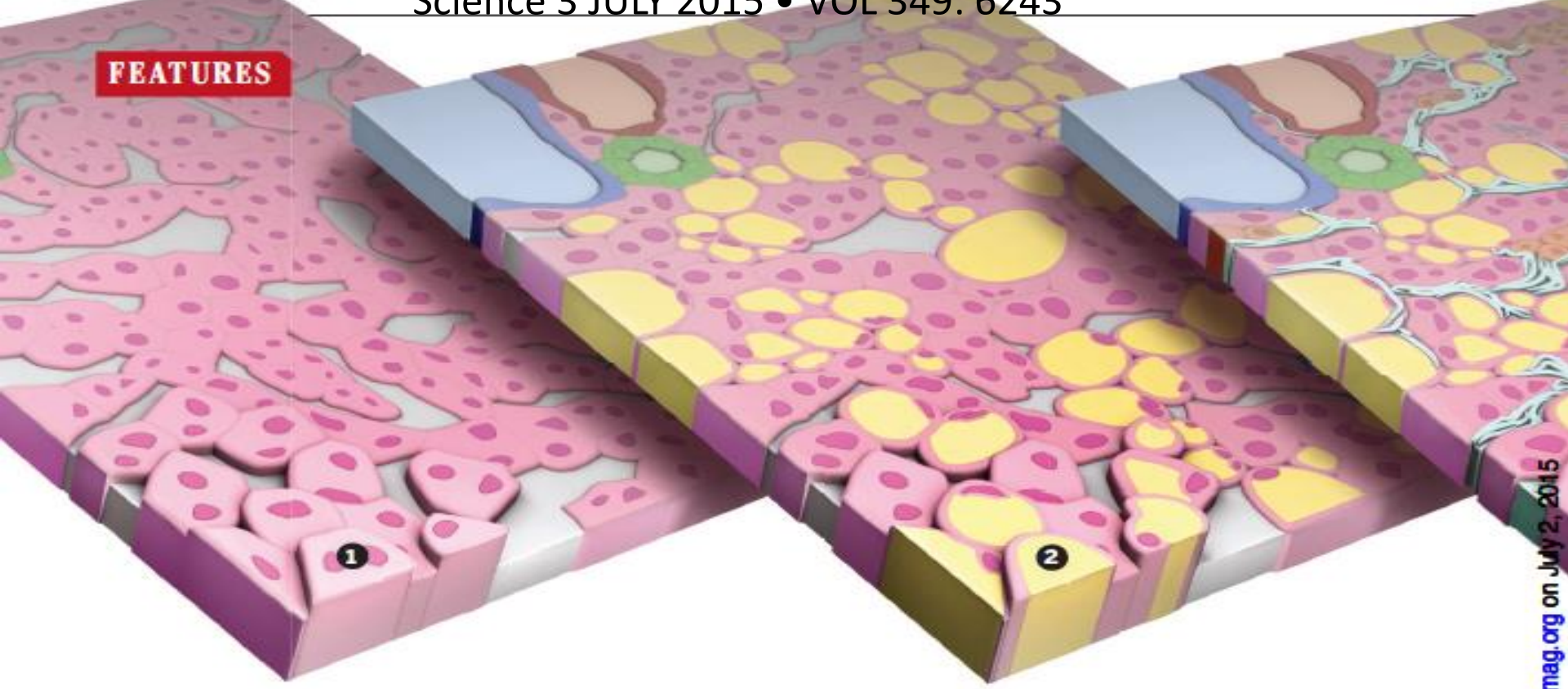


- Age
- Gender
- Race/ethnicity
- Pubertal status
- Weight, height, BMI z-score
- Metabolic syndrome co-morbidities
- Family history of liver disease
- Medications, other systemic disease
- NAS grades and fibrosis stage, NASH “type”

Next Steps

- Convene natural history working group
- Complete and release pediatric document
- Develop actionable plan for longitudinal follow up of pediatric subjects who participate in trials
- Develop actionable plan for natural history study

FEATURES



THE LIVER'S WEIGHTY PROBLEM

As obesity rates soar, a sometimes fatal liver disease is becoming epidemic *By* **Mitch Leslie**