

FACTORS TO CONSIDER IN DEVELOPMENT OF DRUGS FOR PEDIATRIC NONALCOHOLIC FATTY LIVER DISEASE

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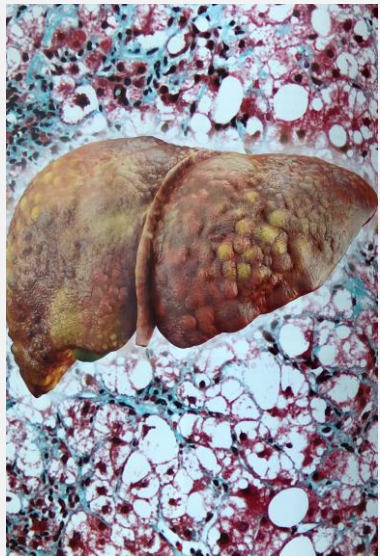
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KEY ISSUES TO CONSIDER IN PEDIATRIC NASH TRIALS: EPIDEMIOLOGY

- NAFLD in children is the most prevalent cause of chronic liver disease in the USA
- Majority do not know they have it and may subject themselves to deleterious hepatotoxic secondary insults
- The severity of histologic findings are only slightly reduced from that found in adults
- There is a unique substantial subset of children with NAFLD with particular histologic features that relate to age, gender, ethnicity and race
- The etiopathogenesis of the unique subset may be variant, have a different course, and variable response to treatment
- Hepatic, cardiovascular, endocrine adverse outcomes of NAFLD in children remain indeterminate

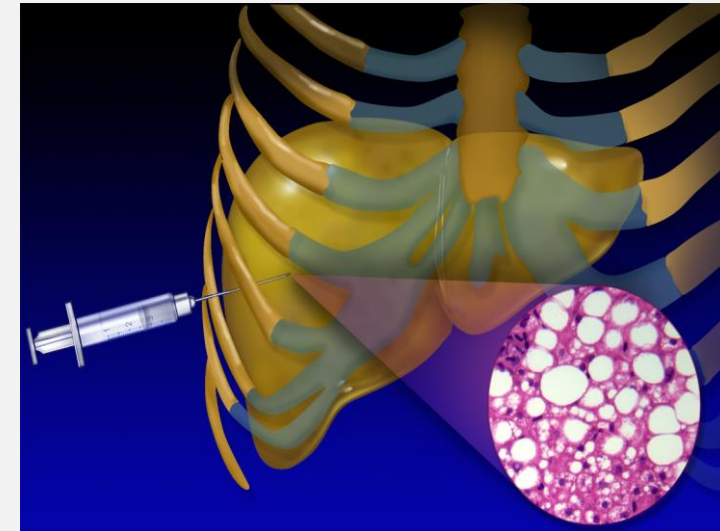
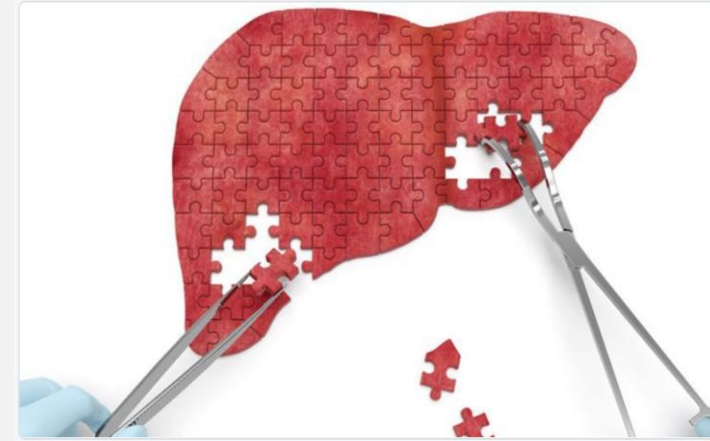
RECOGNIZING AT RISK POPULATIONS FOR NAFLD/NASH IN CHILDREN

- Presence of metabolic syndrome (age-adjusted) metabolic syndrome co-morbidities
- Family history of fatty liver disease
- Particular races and ethnicities
- Older children/adolescents
- Elevated serum aminotranferases, GGT
- Hepatomegaly or acanthosis on physical exam
- Evolving non-invasive imaging or serum biomarkers, less validated in pediatrics

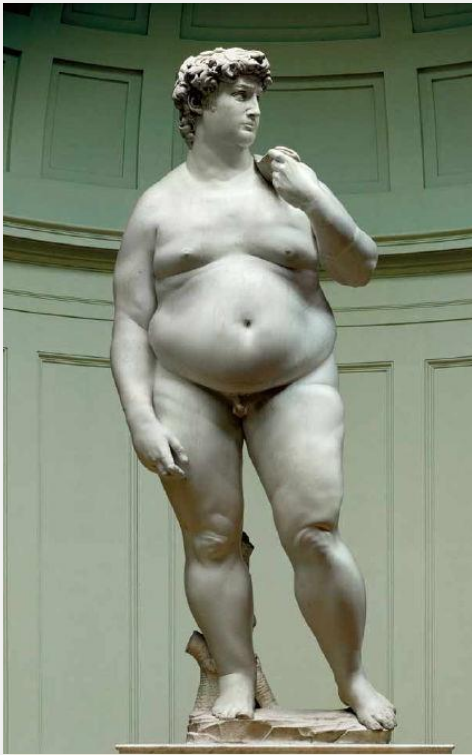


REGULATORY CONSIDERATIONS FOR PEDIATRIC TRIALS IN NASH

- There are no currently labelled pharmacologics for children with fatty liver disease and no phase 3 trials at present
- FDA requires initial pediatric study plan and the European Medicines Agency (EMA) pediatric investigation plan is that inclusion of children in research promotes their safety and well-being
- U.S. Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) mandates assessment of safe and efficacious drugs in children
- Protections for children dictates that more than minimal risk trials must have potential for specific benefits for the research subject, who must also assent (with adult consent). This has been allowed for past research liver biopsies
- Forum for Collaborative Research, a multi-stakeholder collaboration of academic, industry, patient, and regulatory experts is due to release recommendations for pediatric NAFLD trials this year.



TREATMENT CONSIDERATIONS FOR PEDIATRIC NAFLD/NASH



- Pediatric double-blind randomized controlled trials with histology endpoints have successfully enrolled intended sample sizes who complete histology after 1-2 years of treatment with over 86% subject completion
- Placebo and treatment groups all receive SOC lifestyle advice, which remains the mainstay of adult and pediatric NAFLD (diet composition and exercise)
- Vitamin E at 800 IU po qd for 96 weeks significantly improves resolution of NASH in children (TONIC trial, JAMA) and adults (PIVENS trial, NEJM)
- Consideration of the unique pediatric-type subset histology in a significant proportion of subjects should be included in a priori stratification, as treatment response and clinical outcomes may differ (CyNCh trial)
- Race/ethnicity, pubertal development, gender, age all important in design and analyses
- Drug dosing, formulation, route pose hurdles to be addressed
- Mechanism of action ideally addresses other co-morbidities

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- Submitted to Gastroenterology April 2019
- “Reject with Hope” decision received late May
- Title changed by Editor to above, from “considerations for clinical drug development in pediatric nonalcoholic fatty liver disease”
- A “Need to Know” section advised was excluded by the Editor
- A Lay Summary was added
- A graphic abstract was requested by Editor in Chief, but ???
- Manuscript addressed many of the items in the past 4 slides on epidemiology, recognition of at risk children, regulatory mandates and concerns in conducting trials in children, and current state of therapeutic development.