Berkeley School of Public Health

FORUM for Collaborative RESEARCH

Session IV

Advantages and Disadvantages of Retrospective and Prospective Approaches in Developing a Natural History Cohort

Advantages and Disadvantages of Specific Designs in Developing a Natural History Cohort

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Outline

- Previous approaches in pediatric and adult NAFLD
- Requirements for high quality natural history studies
- Pros/cons of available approaches

Table 1
Longitudinal studies in pediatric nonalcoholic fatty liver disease

Study, y	Population	N	Age (y)	Follow-up (y)	Results
Peer-reviewed publications					
Molleston et al,[55] 2002	Single Site Pediatric Hepatology Clinic	2	10 and 14	N/A	• Patient 1: initial biopsy with cirrhosis • Patient 2: initial biopsy with NASH, within 2 y with portal hypertension, ascites, esophageal varices, and cirrhosis
A-Kader et al,[56] 2008		18	Range 7–19	2.3	• 8 patients: no change in fibrosis • 7 patients: progression of fibrosis • 3 patients: regression of fibrosis after losing weight • 2 patients with complete resolution of steatosis and fibrosis after decrease in BMI (23.9–19 kg/m^2 and 24.4–22.8 kg/m^2)
Feldstein et al,[54] 2009		5	Mean 13.9	6.4	• Grade of steatosis and lobular inflammation either worsened or remained the same in all follow-up biopsies • Progression of fibrosis in 4/5 patients • 2 underwent liver transplant at follow-up; they presented with cirrhosis, one of those 2 died after retransplantation
Preliminary reports					
Lavine et al,[59] 2012	NASH CRN	58	Range 8–17	1.8	• Histologic improvement associated with improvement in ALT, insulin resistance, alkaline phosphatase, and BMI • 26% with progression of fibrosis on follow-up
Brunt et al,[58] 2014	NASH CRN	102	Range 11–17	2.2	• 20% of patients with advanced fibrosis on follow-up biopsy
Alkhouri et al,[57] 2015	UNOS/OPTN database for 1987–2010	330	Range 4–40	N/A	Transplants for NASH: • 14 children • 20 patients between ages 18 and 25 • 13 patients required retransplantation for NASH recurrence

Goyal and Schwimmer, Clin Liv Dis 2016

“Form follows purpose”

- Design of natural history studies relies on the specific gaps in knowledge and the unique issues in a particular disease
- Important source of key knowledge points to drive therapy development
  - Choice of patients to treat (study)
  - Duration of studies
  - Clinical outcomes
  - Validate surrogate markers of clinical benefit

Adapted from Mark Walton, FDA, Natural History Studies Conference

Answers gained from Natural History

- Improve definition of disease (NASH?, important histologic features)
- Define distinct clinical phenotypes and stratify by future risk
- Identify time course of outcomes
- Variability in progression
- Validate histology and other surrogates by future outcomes

Key Components for NH Data Collection

- Data needs to be good quality
- Some data quality and monitoring should be included
- Prospective planning for data collection is essential
- Study design should result in broad knowledge acquisition to allow for wide range of future therapeutic possibilities
- Study design can change if early data inform later phases

Designs of NH Studies

	Pros	Cons
Medical literature review		
Retrospective chart review		
Prospective cross sectional		
Prospective longitudinal		
Combined approaches		

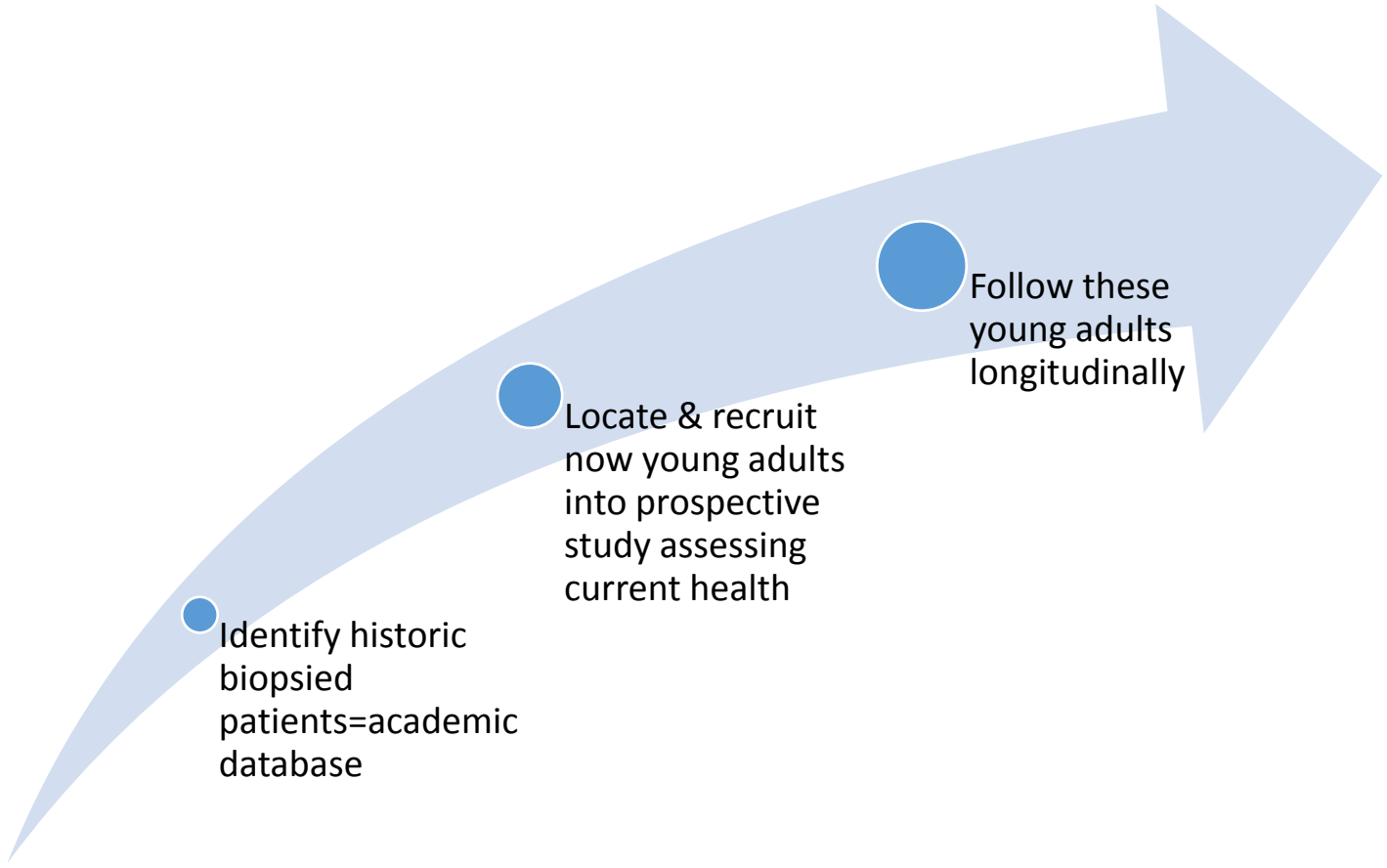
Designs of NH Studies

	PROS	CONS
Medical literature review	• Easiest starting point • Can guide longitudinal study	• Insufficient for many objectives • Biased by clinical care practices
Retrospective chart review	• Easy starting point • Can guide longitudinal study	• Insufficient for many objectives • Biased by clinical care practices • Variability of data available
Prospective cross sectional	• Provides high level of detail of variability of the disease	• Doesn't provide timeline of the disease • No long term outcomes unless wide range of disease length in the cohort • Relatively expensive for quality of data
Prospective longitudinal	• Most comprehensive • Longitudinal data • Sustained commitment from patients and investigators	• Expensive • Slow if disease is slowly progressive • Issues with drop out
Combined approaches	• Capitalize on methods best for questions suitable to specific disease • Interactive process • Shortened timeline	• Can accumulate cons from each design • Increased complexity

Design Considerations for Ped NAFLD NH

- Pediatric to adult gap in care – can't do a chart review
- Decreased frequency of health care in young adults
- Long time frame to NAFLD clinical outcomes
- Urgent need for data today, not in 20+ years
- Liver biopsy is a surrogate marker not a clinical outcome

Combination Retrospective-Prospective



Combination Retrospective-Prospective