



**Goals of the NASH CRN and Opportunities for Collaboration**

Moving Forward: Research Priorities

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**Professor & Vice-Chairman  
Chief, Pediatric GI and Hepatology  
Columbia University**

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**Disclosures**

None relevant to this presentation  
Funding from NIDDK

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Science, July 3, 2013



**THE LIVER'S WEIGHTY PROBLEM**

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

Downloaded from www.sciencemag.org on July 3, 2013

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## Goals of the NIDDK NASH CRN

- Focuses on:
  - Natural history
  - Contributing factors
  - Etiopathogenesis
    - Genetics/epigenetics
    - Environmental contributors/toxins
  - Noninvasive imaging and biomarkers
  - Complications
  - Therapy




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## NASH CRN Centers



<b>Clinical Centers</b> # Cleveland, OH Case Western Reserve University # Cleveland, OH Cleveland Clinic Foundation # Cincinnati, OH Cincinnati Children's Hospital # New York, NY Columbia University Medical Center # Durham, NC Duke University Medical Center # Atlanta, GA Emory University # Indianapolis, IN Indiana University	# Baltimore, MD Johns Hopkins Children's Center # Chicago, IL Lurie Children's Hospital of Chicago # St Louis, MO Saint Louis University # Houston, TX Texas Children's Hospital # San Diego, CA University of California, San Diego # San Francisco, CA University of California, San Francisco # Seattle, WA Seattle Children's Hospital	# Seattle, WA Virginia Mason Medical Center # Richmond, VA Virginia Commonwealth University <b>Resource Centers</b> # Bethesda, MD National Institute of Diabetes and Digestive and Kidney Diseases # Baltimore, MD Johns Hopkins Bloomberg School of Public Health, Data Coordinating Center # San Diego, CA UCSD Live Imaging Group, Radiology Reading Center
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## Steering Committee with Pediatric Members Shown

- Steering Committee:**
- Joel Lavine (co-chair), CU ([j3553@columbia.edu](mailto:j3553@columbia.edu))
  - Arun Sanyal (co-chair), VCU ([asanyal@mcvh-vcu.edu](mailto:asanyal@mcvh-vcu.edu))
  - Sarah Barlow, BCM ([sbarlow@bcm.edu](mailto:sbarlow@bcm.edu))
  - Naga Chalasani, IU ([nchalasa@iupui.edu](mailto:nchalasa@iupui.edu))
  - Ed Doo, NIDDK ([edoo@nidDK.nih.gov](mailto:edoo@nidDK.nih.gov))
  - Anna Mae Diehl, DUKE ([annamae.diehl@duke.edu](mailto:annamae.diehl@duke.edu))
  - Saul Karpen, EU ([skarpen@emory.edu](mailto:skarpen@emory.edu))
  - Kris Kowdley, SMC ([kris.kowdley@swedish.org](mailto:kris.kowdley@swedish.org))
  - Rohit Loomba, UCSD ([roloomba@ucsd.edu](mailto:roloomba@ucsd.edu))
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  - Karen Murray, UW ([karen.murray@seattlechildrens.org](mailto:karen.murray@seattlechildrens.org))
  - Philip Rosenthal, UCSF ([prosenrh@peds.ucsf.edu](mailto:prosenrh@peds.ucsf.edu))
  - Claude Sirin, UCSD ([csirin@ucsd.edu](mailto:csirin@ucsd.edu))
  - Jeffrey Schwimmer, UCSD ([jschwimmer@ucsd.edu](mailto:jschwimmer@ucsd.edu))
  - Norah Terrault, UCSF ([norah.terrault@ucsf.edu](mailto:norah.terrault@ucsf.edu))
  - Brent Tetri, SLU ([tetrib@slu.edu](mailto:tetrib@slu.edu))
  - James Tonascia, JHU-DCC ([jtonasc1@jhu.edu](mailto:jtonasc1@jhu.edu))
  - Peter Whittington, NWU ([p-whittington@northwestern.edu](mailto:p-whittington@northwestern.edu))
  - Stavra Xanthakos, CINC ([stavra.xanthakos@cchmc.org](mailto:stavra.xanthakos@cchmc.org))

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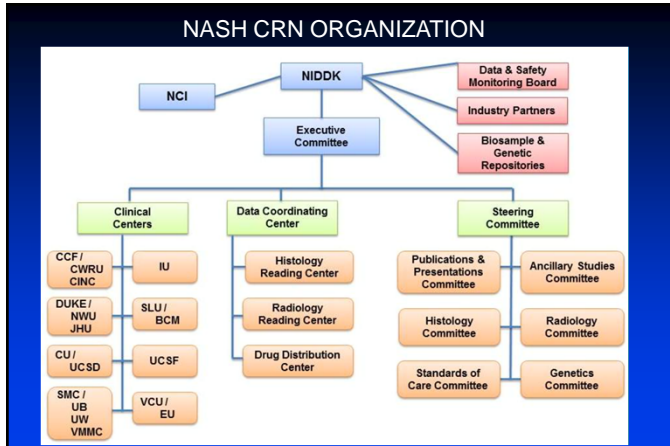
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## NASH CRN ORGANIZATION




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## NASH CRN Subject Enrollment

Study	Total patients
NAFLD DB	1,503
PIVENS	247
TONIC	173
DB2-Adult	1,754
DB2-Pediatric	675
FLINT	283
CyNCh	169
<b>All Studies</b>	<b>4,804</b>
As of 03Oct15	

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## Ancillary Studies: Summary

- Years of studies: 2004 to present and ongoing
- 106 Ancillary Studies:
  - 46 Active
  - 31 Completed
  - 19 Inactive or withdrawn
  - 10 Disapproved
- 12 Pilot and Feasibility Studies:
  - 8 Completed
  - 1 Resubmitted as Ancillary Study
  - 3 Inactive or withdrawn
- 38 Presentations and 35 Publications from Ancillaries
- 19,740 Biosamples and DNA on 1,474 patients analyzed (2013)

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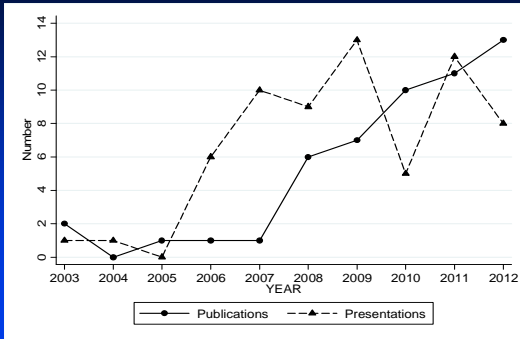
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## Publications (67) and Presentations (91)




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## Submitting a Proposal to the Network

**SF - Study Proposal**

**Prerequisites:** To describe the participants, design, methods, and resources of the proposed study.

**When:** Whenever an ancillary study is proposed that involves NASH/CRN patients, NASH/CRN staff, or other NASH/CRN resources.

**Completed by:** Investigator proposing an ancillary study.

**Responsible:** The form should be completed and signed electronically via iShare PDF by the proposing investigator for the ancillary study. The liaison who may be a NASH/CRN Steering Committee member must electronically sign the form. Once completed, forms go back via e-reporting, email, or fax to: [Sharon.Hess@jhuc.edu](mailto:Sharon.Hess@jhuc.edu) and the form [Sharon.Hess@jhuc.edu](mailto:Sharon.Hess@jhuc.edu) at the JHU.

**A. Administrative Information**

1. Name and contact information (telephone and email) for principal investigator for the proposed study:
2. List other collaborators (names, institutions):
3. NASH/CRN liaison contact by a NASH/CRN Steering Committee member:

**B. Study Design**

4. Study title:
4. Study objectives:
5. Estimated start and end dates of study:

- <https://jhuc1.us/nash/>
- Discuss proposal with liaison
- Obtain AS form from liaison
- Submit to liaison for submission to AS Committee
- Await comments or approval
- Receive data/samples

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## Ancillary Study Ground Rules

- Involves new data collection
- Funding comes from outside CRN
- Does not use central resources
- Requires Steering Committee liaison
- Ancillary and Steering Committees assess scientific/resource merit
- Publications/presentations from AS needs to be approved prior to submission

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## Publication Category

Type	No. Publications	Average Impact Factor
Clinical Trials	4	21.7
Epidemiologic	21	9.1
Genetics	4	13.2
Histology	7	11.9
Noninvasive Markers	10	6.5
Translational	7	10.6
<b>Total</b>	<b>53</b>	<b>9.3</b>

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STAGES OF TRANSLATIONAL SCIENCE	ACHIEVED and PROPOSED ACTIVITIES
T1: BASIC SCIENCE	<b>Genetics and Systems biology:</b> genetics, microbiome, lipidome, transcriptome, proteome <b>Biomarker discovery:</b> integration of "omics" approaches, <b>Identification of targets:</b> for diagnostics and therapeutics
T2: EARLY TRANSLATION	<b>Partnership with industry:</b> Pharmavite, Intercept, Raptor, Takeda, Echosens, GE, Somalogic <b>Partnerships with other NIH consortia:</b> NURSA, LIPIDMAPS, ChiLDREN, TEENLABS <b>Validation of diagnostic targets:</b> Fibroscan, MRI, biosamples <b>Phase 2 A trials:</b> ASBT inhibitor, NHR agonists/antagonists
T3: LATE TRANSLATION	<b>Phase 2b trials:</b> pentoxifylline, vitamin E, obeticholic acid
T4: DISSEMINATION	Inform practice guidelines and remove barriers to drug development by improved diagnostics
T5: ADOPTION	Outcomes and validation of quality of care in NAFLD- standard of care development

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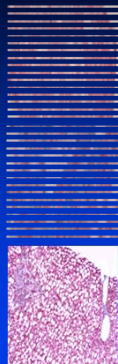
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### Sample of Pediatric Ancillary Studies (in progress)

- Hepatic nuclear hormone receptor expression related to NAFLD severity
- The microbiome in development and progression of NAFLD
- Sleep apnea relation to NAFLD histology
- Altered drug metabolism in pediatric NAFLD
- Proteomic biomarkers for NAFLD discrimination
- Hormonal influences on histology




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### Ancillary Study Ideas for Consideration

- Environmental endocrine disruptors
- Genetic variants explaining ethnic predisposition
- Maternal factors predisposing to NAFLD
- Epigenetic modifications affecting NAFLD
- Novel safe phase I therapeutics
- Sleep apnea interventions on NAFLD
- Lifestyle intervention effects on NAFLD

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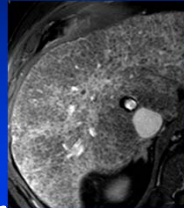
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### The NASH CRN is uniquely suited to perform such studies

- Diverse expertise in NASH
- Expertise in metabolism, development
- Pathology consensus and expertise
- Pioneers in liver imaging
- Expertise in gut endocrine function
- Subjects of varying ethnicity/races/geography/ages
- Strong record of collaborative research
- Superb biostatistical support via DCC




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### Severity of NAFLD in Biopsied Children in Comparison to Adult Enrollees

32. NAFLD Activity Score\*

NAS	Adult (n=3,005)		Pediatric (n=1,136)		Total (n=4,141)	
	No.	(%)	No.	(%)	No.	(%)
0	25	(1)	13	(1)	38	(1)
1	134	(4)	64	(6)	198	(5)
2	444	(15)	157	(14)	601	(15)
3	471	(16)	213	(19)	684	(17)
4	648	(22)	264	(23)	912	(22)
5	542	(18)	226	(20)	768	(19)
6	419	(14)	132	(12)	551	(13)
7	258	(9)	48	(4)	306	(7)
8	64	(2)	19	(2)	83	(2)

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## Pediatric NASH CRN Investigators

The NASH CRN is sponsored by the  
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

### Clinical Centers:

#### Principal Investigators

- BCM: Sarah Barlow
- Cincinnati: Stavra Xanthakos
- CU/UCSD: Joel Lavine/Jeff Schwimmer
- EU: Saul Karpén
- IU: Jean Mofreston
- JHU: Ann Scheimann
- NWU: Peter Whittington
- SLU: Ajay Jain
- UCSF: Philip Rosenthal
- UW: Karen Murray

#### Clinical Coordinators

- BCM: Leanel Fairly
- CWRU: Judy Whitwell
- IU: Ann Klipsch
- JHU: Kimberly Pfeifer
- SLU: Joan Stegner
- CU/UCSD: Elena Reynoso/Janis Durelle
- UCSF: Danuta Filipowski
- UW: Melissa Young
- VCU: Sherry Boyett

### Pathologists

- Elizabeth Brunt (WU)
- David Kleiner (NCI)
- Cynthia Behling (CU/UCSD)
- Melissa Contos (VCU)
- Oscar Cummings (IU)
- Linda Ferrell (UCSF)
- Cynthia Guy (DUKE)
- Matthew Yeh (UW)

#### Data Coordinating Center (JHU)

- Patricia Belt
- Jeanne Clark
- Milana Isaacson
- James Tonascia
- Aynur Unalp-Arida
- Mark Van Natta
- Ivana Vaughn
- Laura Wilson
- Katherine Yates



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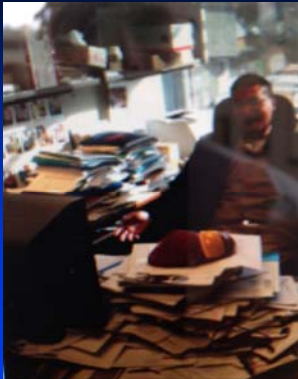
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**This man is overworked**



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YES  
YOU  
CAN

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