

# **Research in Alagille Syndrome**

## **Childhood Liver Disease Research and Education Network (ChiLDREN)**



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# **Disclosures**

- **Consulting with Roche, Ikaria and Yasoo Health**

# **The Challenge in 2000**

- **Most childhood liver diseases are rare**
- **Research at single centers could never move the science forward quickly enough**
- **Unprecedented ability to discover causes of diseases and develop novel treatments**
- **Although rare, cholestatic diseases like Alagille Syndrome take a huge toll on families, may lead to liver transplant in children, and therapies are not adequate**

# Birth of CHILDREN

- **Biliary Atresia Research Consortium (BARC)**
  - 2002-2009
  - 10 Hospitals and Data Coordinating Center
  - Funded by NIH
  - Biliary atresia, idiopathic neonatal hepatitis
- **Cholestatic Liver Disease Consortium (CLiC)**
  - 2004-2009, ORDR
  - 10 Hospitals (Same)
  - 5 liver diseases including ALGS





# History

- **BARC 2002-2009**

- **CLiC 2004-2009**



- **2009 BARC + CLiC = CHILDREN**

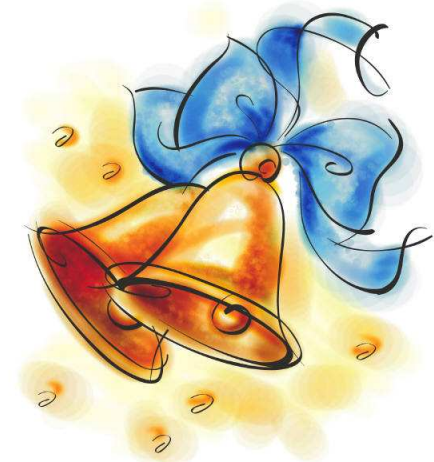
- **CHILDREN 2009-2014 16 Hospitals**

- **Funding**

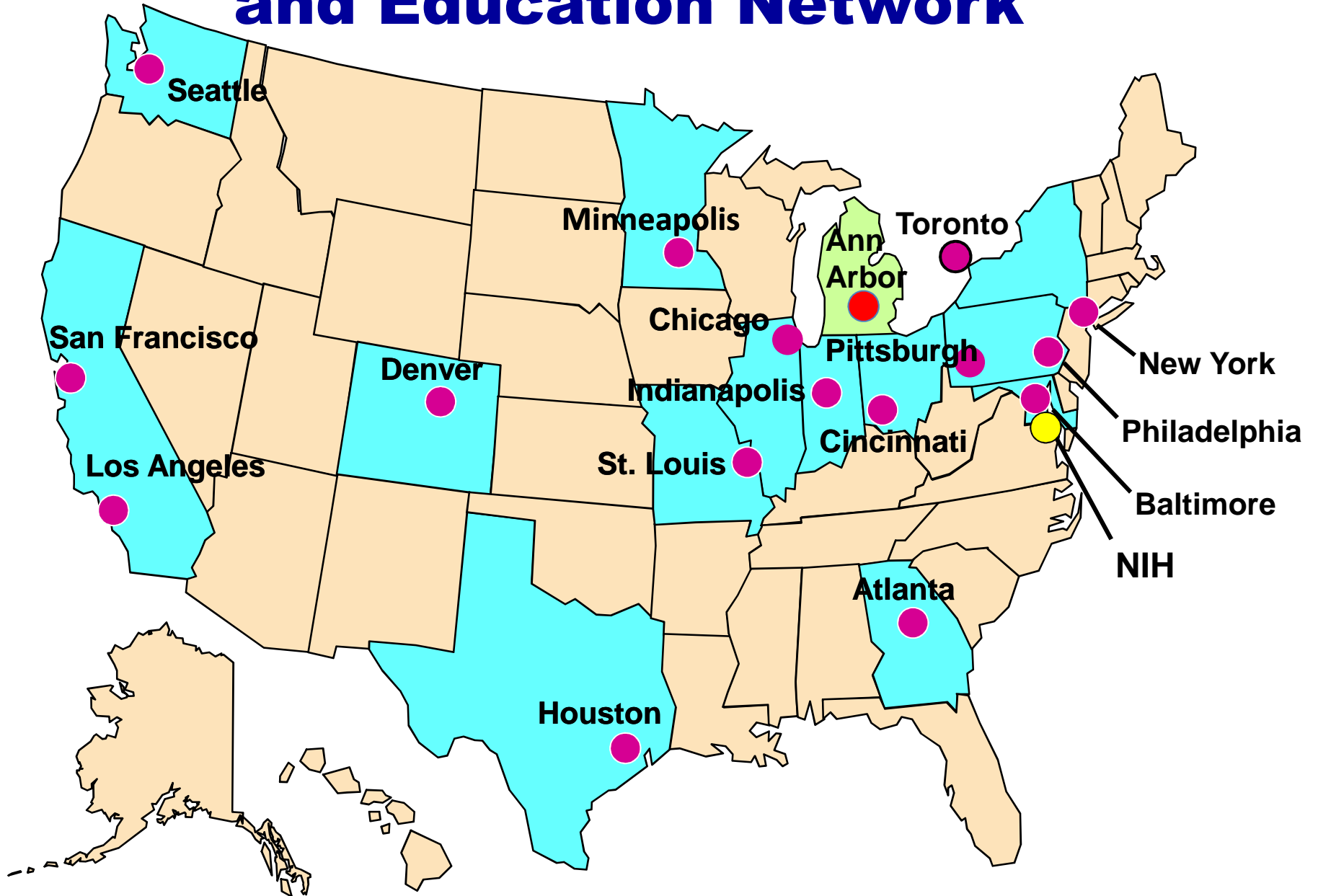
- NIH (NIDDK)

- Cystic Fibrosis Foundation

- Alpha One Foundation



# Childhood Liver Disease Research and Education Network



# CHILDREN Sites

## CLINICAL SITES

University of Colorado/Children's Hospital, Colorado  
Cincinnati Children's Hospital Medical Center, OH  
Mount Sinai School of Medicine, New York City, NY  
Johns Hopkins University Hospital, Baltimore, MD  
Children's Hospital of Philadelphia, PA  
Children's Hospital of Pittsburgh, PA  
Washington University, St. Louis, MO  
Children's Memorial Hospital, Chicago, IL  
Baylor College of Medicine, Houston, TX  
University of California at San Francisco, CA  
Indiana University, Indianapolis, IN  
St. Louis University, St. Louis, MO  
University of Washington, Seattle, WA  
Emory University, Atlanta, GA  
Children's Hospital Los Angeles, CA  
Hospital for Sick Children, Toronto, ON  
University of Minnesota, MN

## DATA COORDINATING CENTER

University of Michigan, Ann Arbor

## NIH PROJECT/SCIENTIFIC OFFICERS

## PRINCIPAL INVESTIGATORS

Ronald J. Sokol, MD  
Jorge Bezerra, MD  
Frederick Suchy, MD  
Kathleen Schwarz, MD  
Barbara Haber, MD  
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Rene Romero, MD  
Kasper Wang, MD  
Vicky Ng, MD  
Sarah Jane Schwarzenberg, MD  
  
John Magee, MD  
Patricia Robuck, PhD, Ed Doo, MD

# CHILDREN Diseases Studied

1. Biliary atresia
2. Idiopathic neonatal hepatitis
3. Alpha-one antitrypsin deficiency
- 4. Alagille syndrome**
5. Progressive familial intrahepatic cholestasis and BRIC types 1, 2, 3 and non-typeable
6. Bile acid synthesis defects
7. Mitochondrial hepatopathies – respiratory chain and fatty acid oxidation defects
8. Cystic fibrosis liver disease



# **Patient Advocacy Groups Involved in CHILDREN**

1. Alpha One Foundation

**2. Alagille Syndrome Alliance**

3. American Liver Foundation

4. Children's Liver Disease Foundation

5. Children's Liver Association for Support Services

6. Cystic Fibrosis Foundation

7. PFIC.org

8. United Mitochondrial Diseases Foundation

Recruiting, input into protocols/consents, communication,  
funding, providing data (CFF), etc.



# **ChiLDREN Website**

**<http://childrennetwork.org>**

- **10,000 visits per month**
- **Information about Alagille Syndrome, including helpful pictures**
  - **pages for doctors/scientists**
  - **pages for families and patients**
  - **Links to Alagille Syndrome Alliance**



# THE CHILDHOOD LIVER DISEASE RESEARCH AND EDUCATION NETWORK

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Password:

Login



**About the Network**



**Information for Families**



**Patient Support Groups**



**Information for Physicians**



**Our Research**



**Participating Centers**

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## INFORMATION FOR FAMILIES



The Childhood Liver Disease Research and Education Network strives to provide information and support to individuals and families affected by liver disease through its many research programs. Click here to print a [ChiLDREN Brochure](#).

The links below provide useful information for parents and patients about the diseases we study.

- [Alagille syndrome](#) (click to print an [English](#) or [Spanish](#) pdf version)
- [Alpha-1-antitrypsin deficiency](#) (click to print an [English](#) or [Spanish](#) pdf version)
- [Bile acid synthesis and metabolism defects](#) (click to print an [English](#) or [Spanish](#) pdf version)



**About the  
Network**

**Information  
for Families**

**Information  
for Physicians**

**Patient  
Support  
Groups**

**Our Research**

## ALAGILLE SYNDROME

### What is Alagille Syndrome?

Alagille syndrome (ALGS) is a condition affecting the liver, heart, spine, eye, face, kidneys and blood vessels that is caused by changes (mutations) in a gene called "Jagged1" in 94% of patients or "Notch2" in 1-2%. Most patients with ALGS have liver disease caused by "bile duct paucity," which means a decrease in the number of bile ducts in the liver. It is now recognized that ALGS is caused by abnormal development of many organs. In some patients, the heart problems caused by ALGS are much more important than the liver disease. Dr. Daniel Alagille, who recognized the organs affected in this disorder, described ALGS in 1969 and called it Syndromic Bile Duct Paucity. Since then, there have been great advances in the understanding and the therapy of ALGS, but there is much more to do.

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### What are the symptoms of the Liver Disease in Alagille Syndrome?

Infants with ALGS may show jaundice, pale stools, poor growth, or loose stools, and may have problems breathing or have pale or dusky skin color (if a heart problem is serious). Most patients with ALGS show signs and symptoms of liver problems at birth or soon after. They usually have a type of yellow eyes and skin called cholestatic jaundice (yellow color of the skin caused by decreased bile flow) in the first few months of life. Some infants are born small, and others have problems with gaining weight and growing. The lack of bile ducts causes a decrease in bile flow from the liver to the intestine. This lack of bile flow (cholestasis) causes a build-up in blood of substances that are normally eliminated from the body through the bile:

# **Aims of CHILDREN Studies**

- **Develop a better understanding of the cause, genetics, epidemiology, natural history and outcomes of these rare diseases**
- **Genotype-phenotype relationships**
- **Development and quality of life**
- **Develop and test new therapies**
- **Biobanking of blood, DNA, tissues**

# Ongoing CHILDREN Clinical Research Studies

## Six Studies – two involving ALGS

1. **PROBE** Prospective longitudinal study of infants and children with cholestasis
2. **LOGIC** Longitudinal study of genetic causes of intrahepatic cholestasis
  - Alpha One, **Alagille's**, PFIC/BRIC, Bile acid defects

# **PROBE Goals**

- 1. Enroll jaundiced infants (before 6 months old) at first time they are evaluated for liver disease**

**some of these infants will have ALGS**

- 2. Follow these children for at least 10 years to determine the course of their disease, outcomes, predictors**
- 3. Collect and store frozen blood, urine, DNA, pieces of liver biopsies for use in other studies = Biobank**

# **LOGIC Study Goals**

- 1. Determine course of ALGS and its natural history**
- 2. Determine frequency of poor growth and decreased bone mineral density**
- 3. Develop a bank of serum, plasma, urine, DNA, tissue and liver histology**
  - To be used in studies of Dr. Spinner, Piccoli, Kamath and others to identify new genes and modifiers of ALGS**

# **LOGIC Study Goals**

**4. Determine genotype-phenotype relationships in ALGS**

**requires hundreds if not thousands of patients**

**5. Determine if pancreatic problems and hearing problems are common in ALGS**

# **Inclusion Criteria**

- **Birth through age 25 years**
- **Diagnosis of one of the 4 liver diseases  
– ALGS**
- **Both genders, all races and ethnic groups**
- **Siblings of participants with AGS, who are affected but do not have evidence of liver disease**

# **Inclusion Criteria**

- **Children with ALGS**
  - **age up to 25 years**
  - **including those who have had a liver transplant**
  - **including siblings without liver disease**
  - **Must meet certain criteria for diagnosis of ALGS**

# **Study Visits**

**Must be seen at ChiLDREN Center**

- **At Enrollment, baseline visit**
- **Yearly visit x 5 yrs.**
- **History, examination and routine lab tests to be recorded**
- **Serum, plasma, urine, DNA/cell lines, tissue, parent's blood for DNA→ repositories**
- **Any liver biopsy slides**

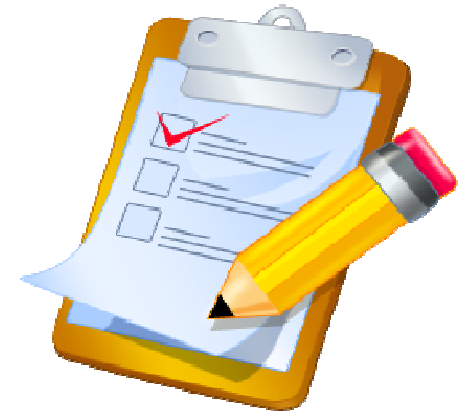
# Additional Testing

- DXA (age 5 or >) to test for bone density
- Neurodevelopment testing (age 2 or >)
- Questionnaire for quality of life – yearly
- Stool human elastase (age 1 or >) to test for pancreatic function – mail-in kit to be given to family
- Hearing test (age 3 or >) – paid by study
  
- Research Genetic Testing – JAGGED1 and NOTCH2. If done recently, not to be shared with families
  - Clinical gene testing may still be needed

# Current Enrollment

- **PROBE:**

- Alagille Syndrome **15**



- **LOGIC:**

- Alagille Syndrome **190** target of 250

- **Many ChiLDREN Centers have funds through this summer to assist with travel, housing, etc.**

# Results

- **Enrollment in LOGIC started in 2008**
- **Analyses of data now being done**
  - **Pancreatic disease**
  - **Bone problems**
  - **Growth**
  - **Complications and predictions**
  - **Neurodevelopment and QOL**
- **Opportunity for collaboration with Pharmaceutical Industry announced by NIH**
- **? Test new therapies (when available)**



# Thank You

- **Clinical Sites, Doctors, Study Coordinators, Surgeons, Pathologists**
- **DCC at U Michigan**
- **NIH – Pat Robuck, PhD, MPH**
- **Alagille Syndrome Alliance**
- **Families and children**