CIFASD5 Progress November 2023

CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

Ed Riley, CIFASD Coordinator and AdminR PI

CIFASD5 YR2 as of November 2023

Name	Role	Institution
Ed Riley, Coordinator	PI, Admin. Resource U24	San Diego State Univ.
Michael Charness	Scientific Director	Boston University
Jennifer Thomas	Admin. Specialist	SDSU
John Hannigan	Science Advisory Board	Wayne State Univ.
Sara Jo Nixon	Science Advisory Board	Univ. of Florida
Dan Savage	Science Advisory Board	Univ. of New Mexico
James Reynolds	Science Advisory Board	Queen's Univ.
Jessica Montoya	Science Advisory Board	UC - San Diego
Bill Dunty	Program Official	NIAAA
Elizabeth Powell	Project Scientist	NIAAA

Leah Wetherill	PI, DataCR U24	Indiana Univ. SoM
Miguel del Campo	PI, Dx-Tele R U24	UC - San Diego
Claire Coles & Joanne Weinberg, MPIs; Tamara Bodnar & Charlis Raineki	Immune and Endocrine Function in Adults, U01	Emory Univ – UBC – Univ. of Calgary – Brock U.
Caroline Burns & Geoff Burns & Olivia Weeks	PIs and Postdoc, Cardiovascular Disease U01	Boston Children's Hospital
Tina Chambers	PI, Ukraine U01	UC - San Diego
Rajesh Miranda	Co-I, miRNA	Texas A&M Univ.
Sarah Mattson	PI, Neurobehavior U01	San Diego State Univ.
Ganz Chockalingam	Apps and eHealth	Blue Resonance, LLC

Jeff Wozniak	PI, tDCS U01	Univ. of Minnesota
Christie Petrenko & CristianoTapparello	PIs, Mobile Intervention Lifespan U01	Univ. of Rochester
Mike Suttie	PI, Imaging U01	Univ. of Oxford
Ralph DiClemente and Angela L. Stotts	PI and Site PI, Intervention U01	NYU and UTHealth Houston
Amanda Mahnke	PI, Stem Cell UH2	Texas A&M Univ.
Annika Montag & Manish Arora	PIs, Biomarkers in Teeth UH2	UCSD and Mount Sinai
Susan Smith	PI, Choline UH2	UNC-Chapel Hill
Tom Donaldson	Outreach	FASD United

Recruited into the FASD Field in CIFASD5

- Abigail Dorow
- Alexis Magre^
- Angela Stotts, PhD
- Ariadna Capasso, PhD
- Blake Gimbel, PhD
- Brittany Manuel
- Carolina Luft, PhD
- Catherine Wyss, PhD
- Chiara Scopice^
- Christina Veziris^
- Cody Romanos
- Deepa Upreti, PhD

- Hanie Moghaddasi, PhD
- Hector Mendez, MD
- Jen Galdieri
- Jennifer Brown, PhD
- Julianne Myers, PhD
- Kaifu Chen, PhD
- Kallio Hunnicutt-Ferguson, PhD
- Kennedy Howatt
- Manish Arora, PhD
- Marc Sherman, MD, PhD
- Marta Concheiro-Guisan, PhD
- Max Cheshire

- Mia Xu, MPH
- Mina Boyd
- Ralph DiClemente, PhD
- Shaan Khurshid, MD
- Shu Xu, PhD
- Sofia Rubi
- Stephen Olalde, DDS^
- Stephen A.-P. Beegle^
- Weiyi Li
- Xinlei Gao, PhD
- Yoly Villarreal, PhD

Purple = CIFASD5 PI/Site PI   ^ = Graduate Student

CIFASD5 Consortium Structure

ADMINISTRATIVE RESOURCE (AdminR)	
PI, Coordinator:	Edward Riley
Scientific Director:	Michael Charness
Admin. Specialist:	Jennifer Thomas
Admin. Coordinator:	Jill Vander Velde

SCIENCE ADVISORY BOARD

John Hannigan
Jessica Montoya
Sara Jo Nixon
James Reynolds
Daniel Savage

NIAAA ADVISORS

Elizabeth Powell, Project Scientist
Bill Dunty, Program Official

STEERING COMMITTEE
Chaired by M. Charness and E. Riley

U01 PIs	U24 PIs
C. Burns*/G. Burns*	M. del Campo
C. Chambers	L. Wetherill
C. Coles*/J. Weinberg*	**UH2 PIs**
R. DiClemente	A. Mahnke
S. Mattson	
C. Petrenko*^/C. Tapparello*^	A. Montag*^/ M. Arora*^
M. Suttie	S. Smith^
J. Wozniak	
	^ CIFASD4 UH2 PIs
* Multiple PI project	

CIFASD5

The **overall goals of CIFASD** aim to further refine definitive characteristics of fetal alcohol spectrum disorders (FASD) across the lifespan based on biological, physical, neurological, and/or behavioral assessment by:

- Improving screening, case recognition and diagnosis of FASD
- Assessing impact of having an FASD across the lifespan
- Identifying factors that impart greater risk/resiliency to FASD
- Developing intervention and prevention strategies for FASD
- Employing eHealth technologies so that our research and its applications can be more broadly disseminated

Specific Aims of the AdminR

- Provide scientific and administrative direction, leadership, and oversight to the consortium
- Facilitate communication among the various projects and dissemination of results
- Assist with data management strategies
- Provide annual evaluations of progress
- Provide outreach, eHealth, and implementation assistance
  - FASD United
  - Blue Resonance, LLC
  - UCSD ACTRI DISC

Facilitate Communication - Meeting Planning

- Monthly and Midyear Meetings
- Committee and Special Meetings (as needed)
- Face-to-Face Meetings

CIFASD5 YR1/YR2 In-Person Project Progress Meeting Agenda

Friday, June 23rd, 2023 • 2:00 PM - 6:00 PM Pacific
Hyatt Regency Bellevue (900 Bellevue Way NE, Bellevue, WA 98004)
LARCH room on the 3rd floor

Facilitate Communication - Meeting Planning

CIFASD in Seattle April 10th, 2024

Monthly Meeting

Potential Collaborators

CIFASD Affiliate Scientists

CIFASD Lab Junior Researchers

Adult Leadership Collaborative
of the FASD Change Makers

Sleep Time Variability Mediates Aspects of Neurobehavioral Functioning in Children with and without FASD

Coordinate Annual Evaluations

CIFASD-5 ANNUAL MEETING AND PROGRESS REPORTS: SCIENCE ADVISORY BOARD COMMENTS
June 23, 2023

OVERVIEW

It is Good to be Back Together.

The in-person annual meeting was much more effective than a Zoom meeting. Monthly calls are still valuable, but being together is good in its own right; it allows more time to get to know new members, examine each other's work closely, frankly discuss progress and concerns, and break out into smaller groups that can facilitate collaboration and cooperation. (For this review, the project reports from Drs. Chambers, Del Campo and DiClemente were made during the Zoom call the week before the in-person meeting.)

- **Science Advisory Board** (SAB) Members: John Hannigan (Chair), Sara Jo Nixon, Dan Savage, James Reynolds, and Jessica Montoya
- SAB **Annual Project Progress Evaluations** completed following the June meeting utilizing June presentations and YR1 RPPRs
- Complete evaluations were distributed to AdvisoryC members and individual evaluations to Project PIs by the Consortium Coordinator

Facilitate Interactions Regarding Problems and Progress

CIFASD DCR

Facilitate Dissemination of Results

46th Annual RSA Scientific Meeting

June 24-28, 2023

Bellevue, Washington

47th Annual RSA Scientific Meeting

June 22-26, 2024

Minneapolis, Minnesota

C. B. Lovely
Amanda H. Mahnke
Sarah Mattson
Tamara S. Bodnar
Michael E. Charness

CIFASD Translational Research on FASD

- Michael Charness, Introduction / Discussant / Moderator
- Olivia Weeks, Congenital heart defects and adult cardiovascular dysfunction in a zebrafish model of fetal alcohol spectrum disorders
- Susan Smith, Polymorphisms in choline transporter SLC44A1 are associated with reduced cognitive performance in those who experience heavy prenatal alcohol exposure
- Blake Gimbel (Wozniak U01), Atypical neurodevelopmental trajectories following prenatal alcohol exposure: Further evidence from cortical, subcortical, and white matter diffusion MRI paradigms
- Edward Riley, A smartphone app for the assessment of the sentinel facial features of FASD

- CIFASD Symposia at **RSA 2024** planning in progress
- Submission by December 1, 2023

CIFASD Research Visibility – RSA 2023

Machine Learning Approaches
in the Identification of Individuals with FASD

- Elizabeth Powell, Introduction / Discussant / Moderator

- Gretchen Bandoli (Chambers U01), Building an FASD classifier from maternal and infant features

- Julie Kable (Coles U01), Cardiac orienting responses as a biomarker of neurodevelopmental impairment in children with PEA

- Michael Suttie, Multi-modal 3D face-neurocognitive analysis for the identification of FASD

- Amanda Mahnke, Assessing miRNAs as predictive features in classifying PAE-associated neurodevelopmental delay

CIFASD Research Visibility-RSA 2023

Strategic Advances in Intervention for FASD: Basic Science to Community Based Treatment

- Christie Petrenko, Introduction / Findings from the pilot randomized controlled trial of the tuning in to kids parenting intervention for children with FASD

- Tamara Bodnar, Evaluating minocycline as a potential treatment following prenatal alcohol exposure: Targeting the neuroimmune system

- Blake Gimbel (Wozniak U01), Short and long-term outcomes following nutritional intervention in FASD

New Advances in Nutrient-Alcohol Interactions in FASD: From Preclinical Models to Clinical Translation

- Susan Smith, Introduction

- Sandra Mooney, Metabolic Deficits from PAE predict offspring cognitive performance and are mitigated by prenatal choline

- Bill Dunty, Discussant

Publication Productivity of CIFASD

Publications citing **CIFASD** funding per PubMed
CIFASD4 (July 2017 - July 2022) = 114
CIFASD5 (August 2022 - present) = 29
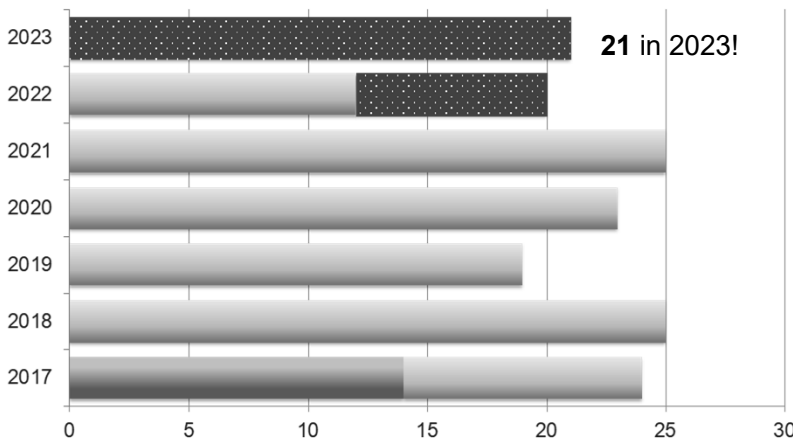
Total PubMed
CIFASD Publications = **366**

CIFASD investigators make significant contributions in high impact journals, such as:

- *Lancet – Neurology*
- *Nature – Reviews*
- *Nature*
- *Trends in Cognitive Sciences*
- *Journal of Neuroscience Development*
- *Journal of Pediatrics*
- *Proceedings of the National Academy of Sciences*

21 in 2023!

Publications Citing CIFASD Grants
Published June 2023 to Present n= 9

- Alex AM, Aguate F, Botteron K, Buss C, Chong YS, Dager SR, Donald KA, Entringer S, Fair DA, Fortier MV, Gaab N, Gilmore JH, Girault JB, Graham AM, Groenewold NA, Hazlett H, Lin W, Meaney MJ, Piven J, Qiu A, Rasmussen JM, Roos A, Schultz RT, Skeide MA, Stein DJ, Styner M, Thompson PM, Turesky TK, Wadhwa PD, Zar HJ, Zöllei L, de Los Campos G, Knickmeyer RC; ENIGMA ORIGINs group. A global multicohort study to map subcortical brain development and cognition in infancy and early childhood. *Nat Neurosci*. 2023 Nov 23, In Press.

- Pfefferbaum A, Sullivan EV, Pohl KM, Bischoff-Grethe A, Stoner SA, Moore EM, Riley EP. Brain volume in fetal alcohol spectrum disorders over a 20-year span. *JAMA Netw Open*. 2023 Nov 1;6(11):e2343618. PMCID: PMC10656646.

- Pinson MR, Tseng AM, Lehman TE, Chung K, Gutierrez J, Larin KV, Chambers CD, Miranda RC; **CIFASD**. Maternal circulating miRNAs contribute to negative pregnancy outcomes by altering placental transcriptome and fetal vascular dynamics. *PLoS One*. 2023 Nov 6;18(11):e0290720. PMCID: PMC10627460.

- Klem JR, Schwantes-An TH, Abreu M, Suttie M, Gray R, Vo H, Conley G, Foroud TM, Wetherill L; **CIFASD**; Lovely CB. Mutation in the Bone Morphogenetic Protein signaling pathway sensitize zebrafish and humans to ethanol-induced jaw malformations. *bioRxiv* [Preprint]. 2023 Oct 26:2023.06.28.546932. PMCID: PMC10327032.

- Shapiro ZR, Kable JA, Grant TM, Stoner SA, Coles CD; **CIFASD**. Prenatal alcohol exposure and cognition at midlife: Evidence of fluid cognition deficits in two cohorts. *Alcohol Clin Exp Res* (Hoboken). 2023 Oct;47(10):1978-1988. PMCID: PMC10605955.

- Poth LD, Love T, Mattson SN. Profiles of language and communication abilities in adolescents with fetal alcohol spectrum disorders. *J Int Neuropsychol Soc.* 2023 Oct;29(8):724-733. PMCID: PMC10154428.

- McMahan RH, Anton P, Coleman LG, Cresci GAM, Crews FT, Crotty KM, Luck ME, Molina PE, Vachharajani V, Weinberg J, Yeligar SM, Choudhry MA, McCullough RL, Kovacs EJ. Alcohol and Immunology: Mechanisms of multi-organ damage. Summary of the 2022 alcohol and Immunology research interest group (AIRIG) meeting. *Alcohol*. 2023 Aug;110:57-63. PMCID: PMC10330898.

- **Oh** SS, Kuang I, Jeong H, Song JY, Ren B, Moon JY, Park EC, Kawachi I. Predicting Fetal Alcohol Spectrum Disorders Using Machine Learning Techniques: Multisite Retrospective Cohort Study. *J Med Internet Res*. 2023 Jul 18;25:e45041. PMCID: PMC10394506.

- Hyland MT, Courchesne-Krak NS, Bernes GA, Wozniak JR, Jones KL, Del Campo M, Riley EP, Mattson SN; **CIFASD**. Results of a screening tool for fetal alcohol spectrum disorders are associated with neuropsychological and behavioral measures. *Alcohol Clin Exp Res* (Hoboken). 2023 Jun 16, In press.

CIFASD Visibility – Other Presentations
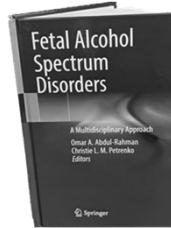
Visibility - Outreach and Education

LOOKING BACK, MOVING FORWARD
STATE-WIDE FETAL ALCOHOL SPECTRUM DISORDERS CONFERENCE

TREETOPS RESORT
3962 WILKINSON ROAD
GAYLORD, MI 49735

TUESDAY, SEPTEMBER 12TH

KEYNOTES FROM KATHY MITCHELL AND EDWARD RILEY PHD

COORDINATED BY PARTNERS IN PREVENTION

Fetal Alcohol Spectrum Disorders
A Multidisciplinary Approach
Omar A. Abdul-Rahman, Christie L. M. Petrenko Editors

Contributors
E.P. Riley
C.D. Chambers
R. Miranda
S. Parnell
J.K. Eberhart
K.A. Donald
S. Mattson

UF Center for Addiction Research & Education @UFCARE

@UFCARE Director, Dr. Sara Jo Nixon, has accepted the #redshoesrockchallenge from @BoginMunnsMunns and challenges @UFCARE and friends, @KatieWitkiewitz, @b_setlow, & Dr. Ed Riley #CIFASD boginmunns.com/wp-content/upl...

UF Center for Addiction Research & Education UNIVERSITY OF FLORIDA

August/September 2023 Newsletter

RED SHOES ROCK CHALLENGE 2023

One of the highlights from our Community Networking Event last April was the opportunity to meet Lindsey and Spencer Munns. Our Center benefited enormously from their willingness to share their lived experience. What a gift! Thus, when asked, we were delighted to be challenged by Spencer Munns in this year's RED SHOES ROCK Challenge. If you accept the challenge, you commit to wearing red shoes on "Challenge Day" and to challenging at least three others. When you wear red shoes, people notice… and ASK! A great opportunity to talk about the #1 Preventable Cause of Birth Defects—prenatal exposure to alcohol. Dr. Ed Riley, who leads the NIAAA funded Collaborative Initiative on Fetal Alcohol Spectrum Disorders, accepted our Challenge! (Cool Shoes; Weird Lacing).
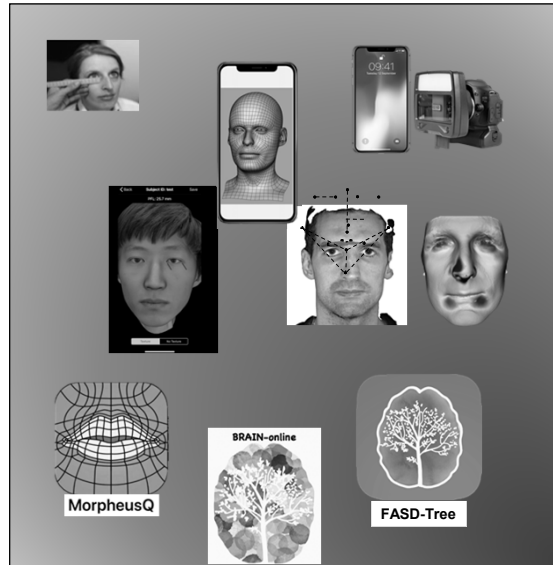

Outreach - FASD United

FASD United
THE NATIONAL VOICE ON FETAL ALCOHOL SPECTRUM DISORDERS
Formerly NOFAS
Weekly Roundup

facebook
X twitter

National FASD Impact Week
CELEBRATING 50 YEARS OF RESEARCH, POLICY AND PRACTICE
FASD @50
RESPECTING THE PAST, EMBRACING OUR FUTURE
SEPTEMBER 18-21, 2023
WASHINGTON, DC

Monday September 18th
Tuesday September 19th — Workshop: An Impactful Network: Widening the Circle (Full Day)
Wednesday September 20th — National Research Briefing (Full Day)
Thursday September 21st — Hill Day (Full Day)

FASD United Affiliate Network Starting at 1 pm

BRAIN-online recruitment also active through:

FASD United
THE NATIONAL VOICE ON FETAL ALCOHOL SPECTRUM DISORDERS

INDIANA ALLIANCE On Prenatal Substance Exposure

Alaska Department of Health **Division of Public Health**

BRAIN-online FASD Screening Tool
BRAIN-online is a new web-based screening tool that assesses cognitive and behavioral features known to be associated with fetal alcohol spectrum disorders (FASD). If you think that you or someone you care for may have FASD, BRAIN-online can act as the first step in connecting to a diagnosis.
TAKE THE TEST

CIFASD Collaborative Initiative on Fetal Alcohol Spectrum Disorders

HOME | ABOUT US | RESEARCH | PUBLICATIONS | NEWS | PARTICIPATE | EDUCATION | RESOURCES | CONTACT | DATA SHARING

Outreach eHealth / Apps Blue Resonance

# Dissemination and Implementation

- UCSD Altman Clinical and Translational Research Institute - Dissemination and Implementation Science Center (ACTRI DISC)

- Jessica Montoya, ACTRI DISC and SAB member

- The **ACTRI DISC** provides:
  - Consulting services
  - Training
  - Technical assistance
  - Mentoring
  - Proposal B*oot* C*a*mp
  - Online resources
  - Seminars
  - Special
    topic events
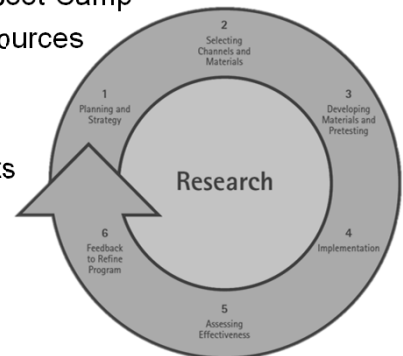
CIFASD Outreach - Education and Support
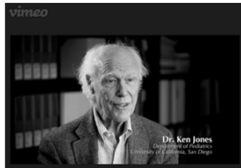
FASD United Red Shoes Gala – FASD & Stigma Documentary

RunFASD 5K

CIFASD Community Outreach and Support

CIFASD Outreach and Education

- Christie Petrenko joins host, Dr. Catherine Cerulli, in this podcast and has also given numerous community presentations
- Two **high school students** doing internships in the Burns lab completed short projects on the impacts of PAE on cardiac development in zebrafish and humans. Create "real world" opportunities in the STEM disciplines for motivated learners.
- CIFASD investigators participated in **trainings** & **grand rounds**

CIFASD Press

B1G Impact Research campaign featured Jeff Wozniak's Lab during nationally televised UMN football game
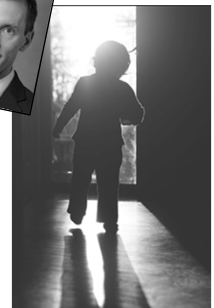

NEWS & FEATURES

UNDARK

For Children With Fetal Alcohol Exposure, A Gap in Support

Research-based interventions for children with fetal alcohol spectrum disorder exist, but few get access.

Visual: Jordan Parks Photography/Moment via Getty Images

I SCIENCE

NATIONAL GEOGRAPHIC

The overlooked toll of drinking alcohol while pregnant

Estimates suggest up to 5 percent of people in the U.S. have fetal alcohol spectrum disorders. Here's how scientists and activists are working toward better diagnoses and treatments.

CIFASD Press

Research aims to reduce alcohol-exposed pregnancies

By Roman Petrowski, Office of Communications
November 16, 2023

UTHealth Houston | McGovern Medical School

Angela Stotts, PhD, professor and vice chair for research in the Department of Family and Community Medicine, received a 5-year subaward from the National Institute of Alcohol Abuse and Alcoholism via New York University to lead a groundbreaking study on a novel intervention strategy aimed at reducing alcohol-exposed pregnancies.

Angela Stotts, PhD

UNIVERSITY OF CALGARY

Nov. 17, 2023

Azrieli Accelerator brings new strengths to neurodevelopment research across the lifespan

1st recruit of professorship program joins Faculty of Science

The **Azrieli Accelerator** professorship program at the University of Calgary breaks down barriers and makes it easier to forge important connections between departments and faculties, says the program's inaugural recruit.

Consortium Awards and Honors
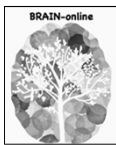
- $20,000 **seed grant** from the Masonic Institute on the Developing Brain, Wozniak postdoc Blake Gimbel, testing clinical utility of BRAIN-online neuropsychological battery

- **Circle of Stars Research Award** Christie Petrenko December 2022, FASD United
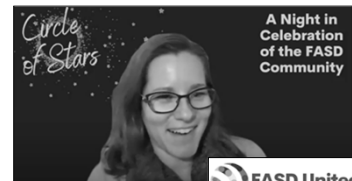
- **Timothy A. Cudd Award** Jackie Soja (Thomas lab), June 2023, FASD Study Group

- **Lifetime Achievement Award** Edward Riley June 2023, Research Society on Alcohol

Special Thanks to:

Jill Vander Velde

Bill Dunty

Elizabeth Powell

Science Advisory Board

Michael Charness

Jennifer Thomas

Publications Policy and Data Sharing Committees

FASD United (formerly National Organization on Fetal Alcohol Syndrome, NOFAS)

➢ National voice of FASD

➢ Educate professionals, policymakers, and the public

➢ Advocate for legislation and policy change

➢ Expand the FASD network

➢ Increase recognition, support, and services for the FASD community

1

CIFASD Education and Outreach, AdminR subaward

Project Aims

Aim 1: Disseminate published findings

Aim 2: Assist with study participant recruitment

Aim 3: Highlight scientists and their research

Aim 4: Serve as a liaison between scientists and the FASD community and FASD United partners

2

Major Accomplishments

Highlight CIFASD and disseminate findings:

- ➢ 34 pediatric and Ob/Gyn grand rounds in conjunction with AAP and ACOG FASD Champions
- ➢ 89 virtual and in-person briefings with policymakers; 22 featuring CIFASD investigators
- ➢ 40 organizations of the FASD United Affiliate Network
- ➢ 23 members of the FASD United external partners group (medical, behavioral health, disability, child welfare, legal aid, maternal and child health, addiction medicine, rural health associations, and Tribal organizations)
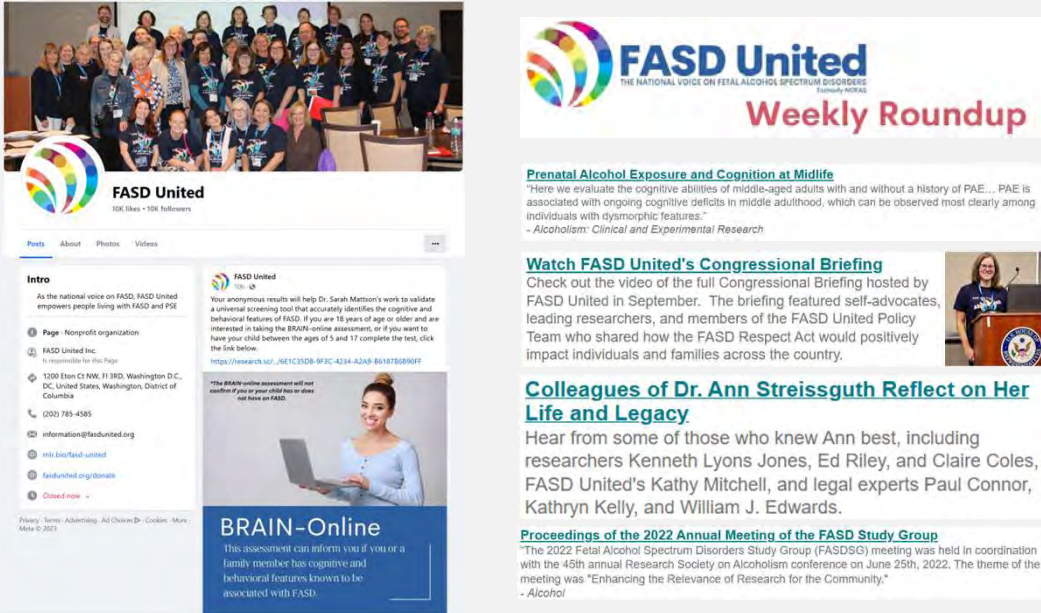- ➢ 20+ CIFASD-related *Weekly Roundup* and social media posts

3

Major Accomplishments

Highlight CIFASD and disseminate findings:

- ➢ Department of Defense
  Uniformed Services University of the Health Sciences, Fetal Alcohol Spectrum Disorders Prevention Research Project in the Military Health System

  2nd Annual Workshop on Fetal Alcohol Spectrum Disorders
  Strengthening FASD Clinical Management and Clinical Practice Guidelines
  Panelists:
  > Christie Petrenko, PhD, University of Rochester
  > Michael Charness, MD, VA Boston Health Care
  Federal Agency Updates
  Panelists:
  > Bill Dunty, PhD, NIAAA

- ➢ Centers for Disease Control and Prevention
  National Partnership to Address Prenatal Alcohol and Other Substance Use and Fetal Alcohol Spectrum Disorders
  > [American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists]
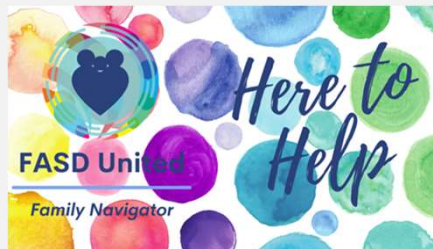
4

5

Major Goals through April 2024

- ➢ Amplify dissemination through presentations and media channels
- ➢ Showcase investigators, findings, and recruitment
- ➢ Expand BRAIN-online promotion and link throughout Affiliate Network organizations
- ➢ Provide support services to projects that research mobile or online tools.

6

Major Goals through April 2024

7

U24 Diagnostic Telemedicine resource (DTR)

Miguel del Campo, MD, PHD

Kenneth L. Jones, MD

CIFASD dysmorphology core

Institute for fetal alcohol spectrum

disorders discovery (IFASDD)

University of California San Diego

Aims
1. Training of examiners
2. Exam with standard techniques, Morpheus   Q and 3D photos
3. Screening In Alaska

Accomplishments

Data dictionaries, data collection forms, pilot data upload, and GUID training have all been fully completed. IRB protocols, IRB approval and consents are ready.

Multiple trainings initiated

IRB for physical exams/photos at UCSD/Rady Completed

Recruitment for Aim 2 running

1 site in AK has agreed to participate

IRB for Alaska in preparation

Cultural sensitivity courses completed

All milestones submitted.

SOP manuals

      Training and physical exams

      Screening in Alaska

1

Specific Aim 1

- The primary aim of the Diagnostic-Telemedicine Resource (DTR) is to ensure that participants recruited in CIFASD5 projects receive a standardized, comprehensive evaluation of the physical features diagnostic of FASD. To maximize CIFASD5-wide diagnostic efficiency and consistency, and to increase diagnostic capacity, **we will use telemedicine to complement in-person training of local health care providers** who will perform the majority of the evaluations at CIFASD sites. The DTR will ensure the fidelity of these exams using the telemedicine approaches previously developed and validated in CIFASD

Accomplishments:

U01 Jeff Wozniak Minnesota. 7 trainees 2 sessions

U01 Sarah Mattson 3 trainees first session, 3 trainees 2 sessions

U01 Coles Weinberg, Raineki, Bodnar

SOP: Two initial training sessions without subjects

Telemedicine exam of at least 2 subjects

Proctoring 2 exams and re-training after 10 subjects

Discussed telemedicine proctoring.

Training in Seattle with collaboration of adult FASD participants?

2

Specific Aim 2

The DTR will test three novel eHealth tools that would provide accessible, scalable, low-cost solutions to screening and diagnosis for FASD, and compare each of these to the standard in-person **dysmorphology examination by experts** used in all previous iterations of CIFASD1-4. In Aim 2, we will: 1) **determine the accuracy of MorpheusQ** in detection of the cardinal facial features of FASD compared to the gold standard in-person expert exam; 2) in collaboration with CIFASD5 Investigator Suttie's U01 project, determine **the accuracy of 3D facial signatures compared to the gold standard in-person expert exam.** Under Aim 2, we will also work with CIFASD5 Investigator Mattson's U01 project to evaluate the effectiveness of these and other eHealth tools (FASD-Tree and Brain-online) utilized in combination to support diagnosis of the full range of FASD classifications.

Figure 4. A and B. Correct measurement of the palpebral fissures with a hand ruler measuring between the two canthi, placing the ruler at the right angle of the face, parallel to the line that joins both canthi. C. Using the philtrum and lip guide and looking with a 45 degree angle.

47 cases (50/year) with full physical examination/Morpheus Q for Sarah Mattson U01 FASD tree

25 cases with full physical exams and Morpheus. Assign GUID

12 Canfield 3D photos. No 3 D photos uploaded but ready. Next clinic

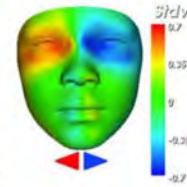**47 cases (50/year) 30 cases preliminary data**

Currently Del Campo + 2 other trained dysmorphologists. 50 cases. All types of participants.

PFL rotational scan 47 cases (50/year) 30 cases preliminary data

PFL frontal scan scan 47 cases (50/year) 30 cases preliminary data

Ready for storage and transmission of images

3

Specific Aim 3

- A major advantage of telemedicine is that it removes geographical barriers to screening and diagnosis. In Aim 3, we will demonstrate integration of the CIFASD5 DTR findings from Aims 1 and 2 into a real-world setting. In isolated communities in Alaska that are highly-impacted by prenatal alcohol, **we will train providers via telemedicine and test the application of our eHealth tools to improve access to accurate diagnosis.**

Years 1-2. 30 cases per year in FASD diagnostic centers. No recruitment yet

Accomplishments:
1 collaborating center Ptarmigan
Collaboration of anthropologist Travis Hedwig
Close to sending concept proposal to SCF
Working on IRB submission

2nd year. Obtain IRB approval Initiate/complete recruitment

4

Collaborations

Collaboration protocols Suttie/Mattson

Meeting with Mattson and Suttie

Del Campo Suttie Photos/subjective/measurements Midface hypoplasia and mandible volume

Del Campo/Mattson Facial measurements and Morpheus Q in same subjects (50+)

To catch up

- Continue to Schedule and complete trainings

- Recruit urgently more Morpheus Q before December. More trainees. 3D photos. 23 have already consented. 12 taken. Call participants for new photos

- Define Iphone 3D photo

- Study of standard measurements versus Morpheus Q

- Submit Alaska Area IRB

5

Outreach in San Diego:
- Actively developing screenings for FASD in both Juvenile Justice and Child and family welfare services departments.

- Education for nurses and probation department to perform screening for FASD.

- Training for resource parents in CFWS.

- Participating in FASD San Diego Workgroup. Develop and share all resources for FASD.

•Other research:

- Episignature of FASD.

- Other grant submissions. Vinpocetine clinical trial. Brain organoid model for FASD.

6

Seattle training for the recognition of physical features.

- 2 days 5-6 PM
- For CIFASD investigators
- For young investigators/trainees
- For clinicians
- In collaboration with Mattson/Suttie

7

CIFASD Ukraine U01 Update -

Nov 27, 2023

1

Recap

- Pilot project in San Diego substituted for initiating study in Ukraine
- Started evaluations in November, with 1-2 slots available every Tuesday in general pediatrics
  - 2 participants completed so far (6 and 12 year-olds, pFAS and confirmed PAE)
  - Completed questionnaires, nail fold capillary testing, blood draws and clinical labs completed; whole blood aliquot sent overnight to Mahnke lab; plasma aliquots banked for Miranda
  - Feedback to parent/guardian on lab results in consultation with general pediatrician; feedback on questionnaire results with applicable scoring cut-offs
- Data dictionary provided to Leah/Abby – some edits required

2

Recap

- Target sample size is 30
- Beginning with 3-12 year olds - pool of 37 eligible children 3-12 years being invited
- Anticipate 2 per week, and will complete the target pilot sample by end of March, 2024

3

Alternative plans for 2024 – Plan A

- No end in sight for Ukraine conflict
- Have discussed under current situation inviting children to return for assessments and many families have agreed
  - Collaborators are
    - confident nail fold camera can be shipped into Ukraine
    - Confident they can collect blood samples from children and can ship directly to U.S. but concerned about stable power source (prefer blood spots) – plan to ship more frequently
  - Collaborators concerned about 3D imaging refusal by participants
- Possible they think to achieve target sample size of 300 in 5th year

4

Alternative plans for 2024 – Plan B

- Extend pilot study to a full study
- Add Emory as a site
- Reduce sample size to 100 from each site (n=200 total)
- Budgetary implications
- All components of the study could be completed
- Power implications

5

Alternative plans for 2024– Plan B

Comorbidity	N-PAE Ukraine	N – No PAE Ukraine	RR Detectable	Power	N – PAE US	N – No PAE US	RR Detectable	Power
Hypertension	165	135	3.5	84%	130	70	4.5	80%
Borderline Cholesterol	155	125	1.7	85%	120	65	1.9	84%
Anxiety (6-19 Years)	120	100	1.7	83%	94	51	1.9	83%
Sleep Disturbance	155	125	1.5	82%	120	65	1.6	82%

6

3

Publications

• Bandoli et al, Predicting fetal alcohol spectrum disorders in preschool-aged children from early life factors; Alcohol: Clinical and Experimental Research Acceptance Date: 11/14/23

• Schaffer et al, Breastfeeding and neurodevelopment in infants with prenatal alcohol exposure; Pediatric Research Acceptance Date: 9/28/23

7

Biological samples

• Miranda lab prepared to receive samples from other consortium investigators

8

CIFASD Ukraine U01 Update - miRNAs

Nov 27, 2023

9

Pubs/presentations

- Suttie M, Kable J, **Mahnke AH**, Bandoli G. (2023) Machine learning approaches in the identification of children affected by prenatal alcohol exposure- a narrative review. Alcohol: Clinical and Experimental Research. *Submitted.*

- Hwang HM, Yamashita S, Matsumoto Y, Ito M, Edwards A, Sasaki J, Dutta D, Mohammad S, Wetherill L , Schwantes-An TL, Abreu M, **Mahnke AH**, Mattson SN, Foroud T, **Miranda RC**, **Chambers** C, Torii M, Hasimoto-Torii K. (2023) Reduction of APOE accounts for neurobehavioral deficits in fetal alcohol spectrum disorders. *Submitted.*
  - Utilized child plasma samples

- **Pinson MR**, Tseng AM, Lehman TE, Chung K, Gutierrez J, Larin KV, **Chambers CD**, **Miranda RC**; CIFASD. Maternal circulating miRNAs contribute to negative pregnancy outcomes by altering placental transcriptome and fetal vascular dynamics. PLoS One. 2023 Nov 6;18(11):e0290720. doi: 10.1371/journal.pone.0290720. PMID: 37930978; PMCID: PMC10627460.

- 2023 RSA: *Assessing miRNAs as Predictive Features in Classifying PAE-Associated Neurodevelopmental Delay.* In Symposium: *Machine learning approaches in the identification of individuals with Fetal Alcohol Spectrum Disorders.* 2023 Research Society on Alcohol Annual Meeting.
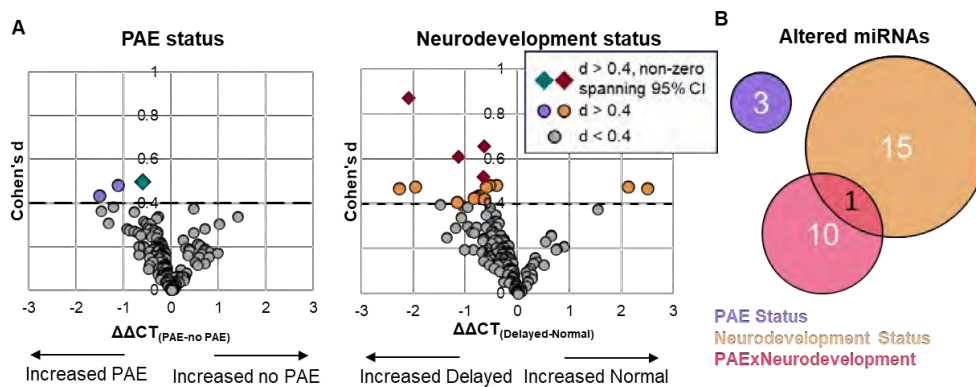
10

Child Samples

- Average age at blood draw: 3.1 ± 1.6 yo
- 68 samples

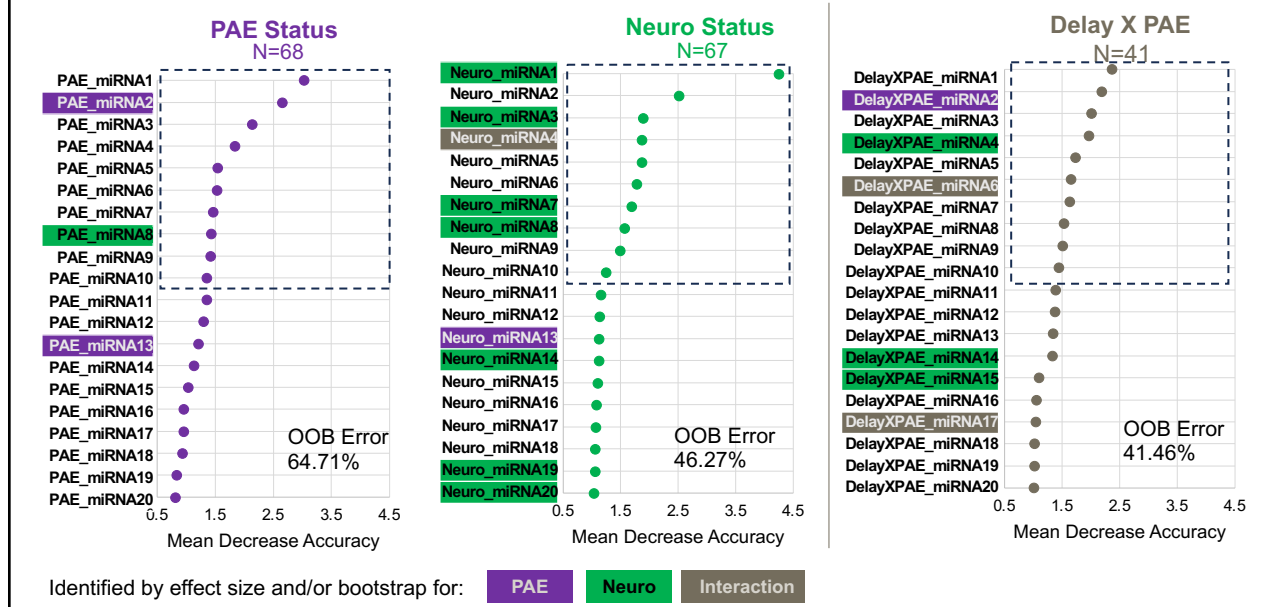|	Neurodevelopmentally Normal	Neurodevelopmentally Delayed	No Neurodevelopmental status
No PAE	15	15	1
PAE	11	26	

11

Unique groups of miRNAs indicate PAE and neurodevelopmental status in early childhood

12

Preliminary RFA supports miRNAs discriminate between PAE- and non-PAE-neurodevelopmental delay

Identified by effect size and/or bootstrap for: **PAE** **Neuro** **Interaction**

13

Preliminary models from forward stepwise logistic regression for PAE and neurodevelopmental status perform well

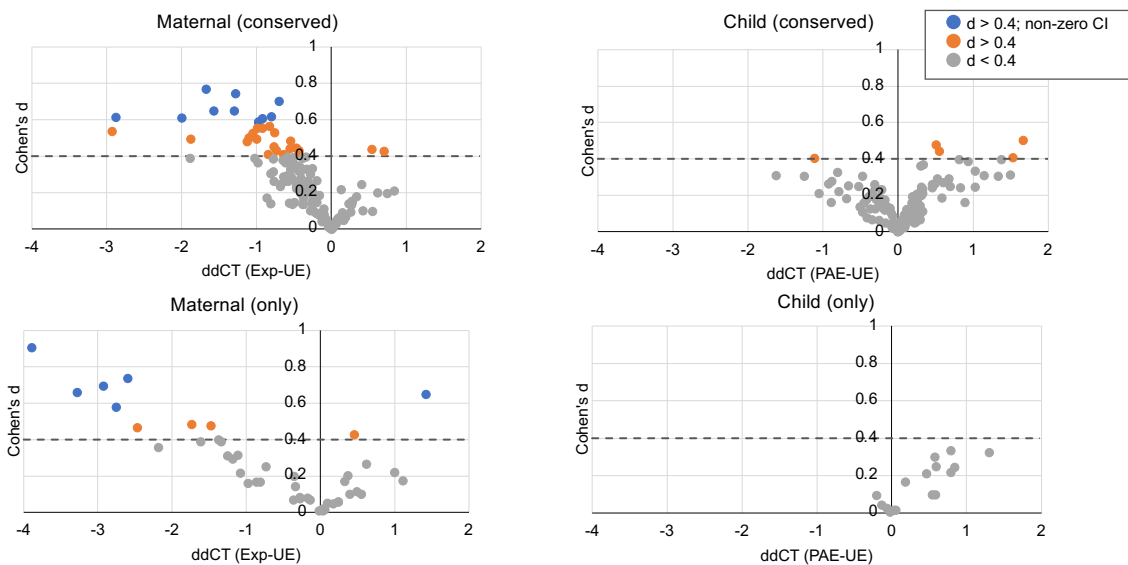| Model (# miRNAs)	AUC
PAE (3)	0.716
Neuro (2)	0.776
DelayXPAE (2)	0.605

14

7
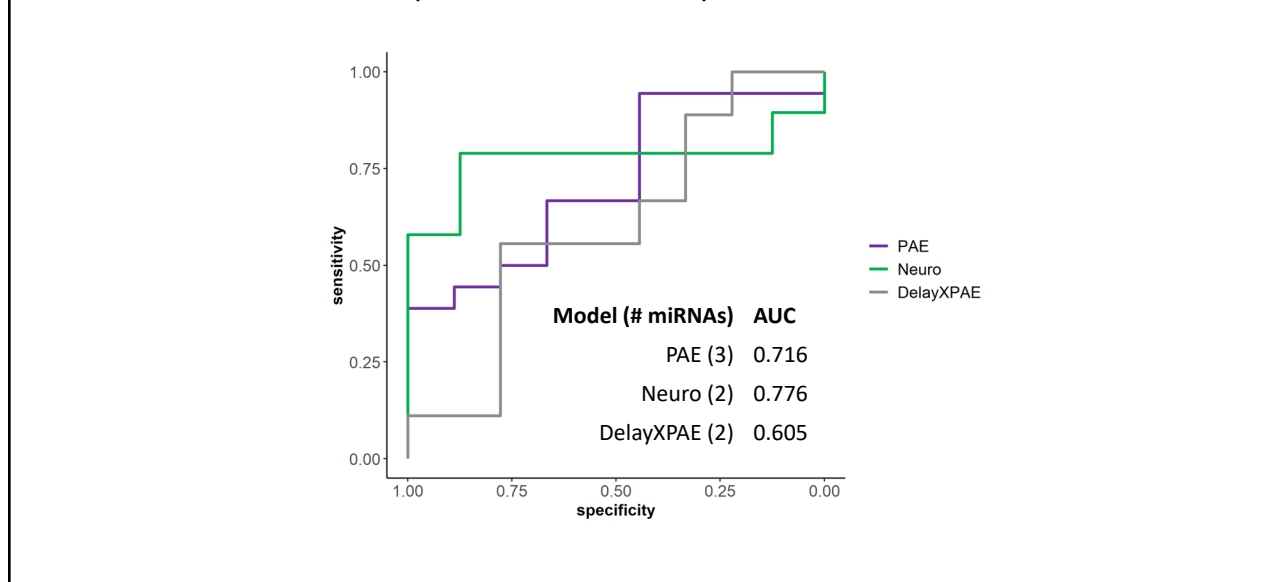
Maternal/Child dyads

- 52 dyads

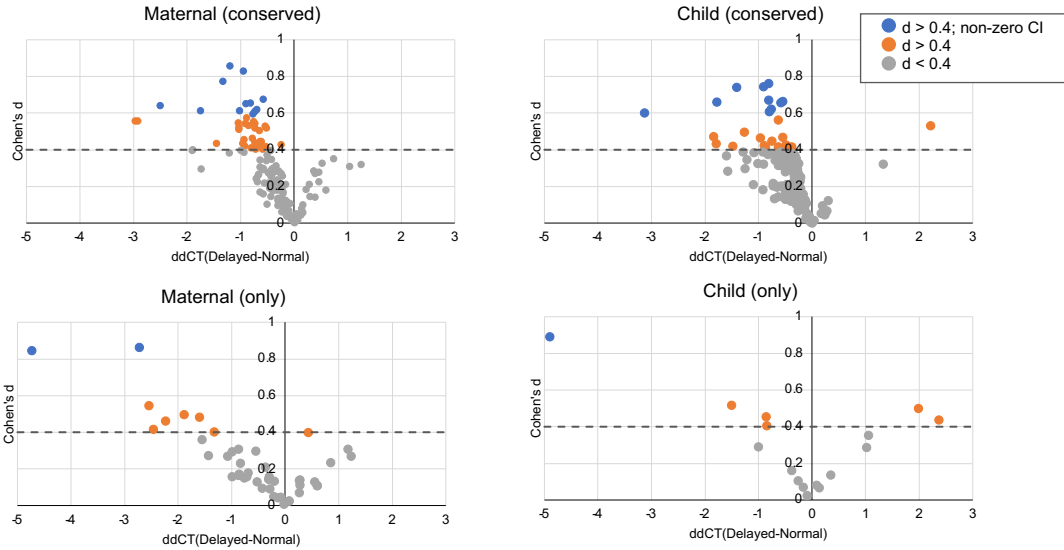|	Neurodevelopmentally Normal	Neurodevelopmentally Delayed	No Neurodevelopmental status
No PAE	11	11	1
PAE	9	20	

15

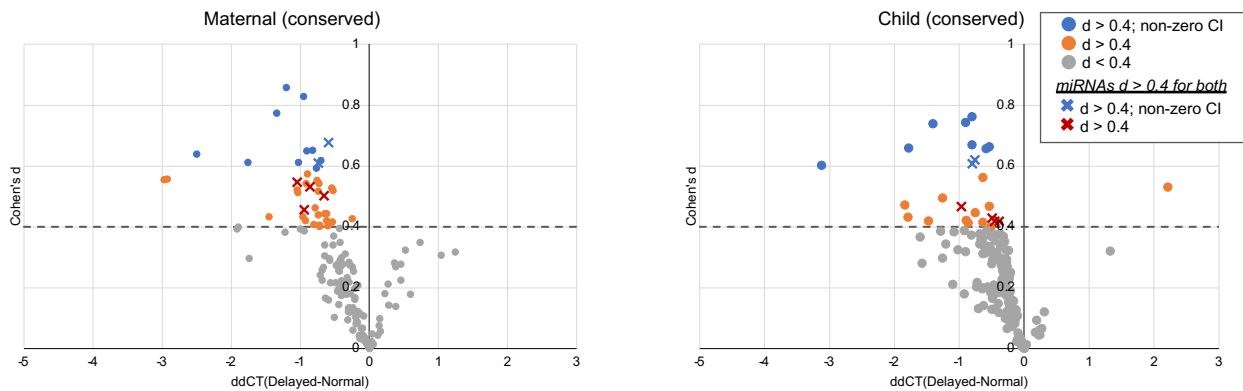# miRNAs by Ethanol Status

16

miRNAs by Neuro Status

17

Neuro Status miRNAs in mother and child

18

Designing a Hybrid Intervention Strategy to Reduce Alcohol-Exposed Pregnancies: Mid-year Report

November 27, 2023

1

Research Team

Main site (Coordination & Biostatistics) led by Dr. Ralph DiClemente, PI

Implementation team, led by Dr. Angela Stotts, PI

Intervention team, led by Dr. Jennifer Brown, PI

Dr. Ariadna Capasso, Assessment lead

Dr. Marta Concheiro-Guisan, Biospecimen analysis lead
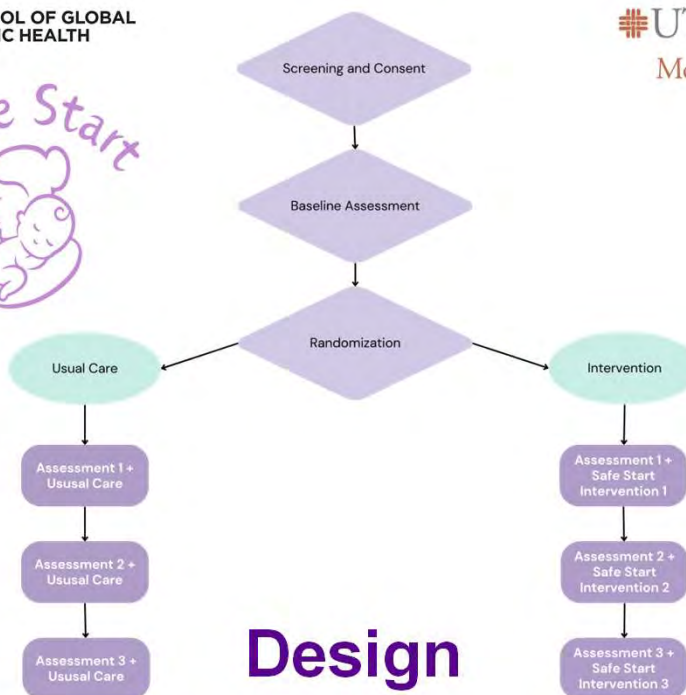
2

2

Specific Aims

Aim 1. To determine whether a greater proportion of women randomized to receive the intervention condition (usual prenatal care plus the alcohol intervention) have a negative PEth test in the second and third-trimesters relative to women receiving the comparison condition (usual prenatal care only).

Aim 2. To determine whether a smaller proportion of infants born to women randomized to receive the intervention condition (usual prenatal care plus the alcohol intervention) are identified with adverse birth outcomes relative to infants born to women receiving the comparison condition (usual prenatal care only).

3

3

4

4

Slide 5

NYU SCHOOL OF GLOBAL PUBLIC HEALTH · Safe Start · UTHealth Houston McGovern Medical School

Eligibility Criteria

- \> or = 18 years of age

- < 28 weeks pregnant

- ETG positive or self-reported drinking past 21 days
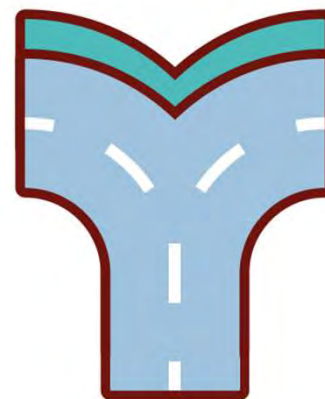
- Willing to provide informed consent

5

5

Slide 6

NYU SCHOOL OF GLOBAL PUBLIC HEALTH · Safe Start · UTHealth Houston McGovern Medical School

Intervention

Two-arm RCT to assess the efficacy of the intervention, relative to usual prenatal care, in reducing:

1) Alcohol use among women in prenatal care, and
2) Poor infant birth outcomes

6

6

Intervention

Two brief components:

1) Self-paced, tailored computer-delivered component designed to enhance knowledge, norms, and motivation for alcohol reduction, and

2) Project Research Nurse-delivered component

Based on Motivational Enhancement Theory (MET), and MET enhancement strategies

Where do you rate yourself on this scale?

0 1 2 3 4 5 6 7 8 9 10
Not at all concerned   Extremely concerned
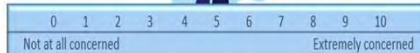
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7

Clinical Sites

- Onboarded
- Ongoing meetings with clinical directors to promote the project, coordinate patient flow and biospecimen handling, develop detailed protocols
- Agreement with Quest for biospecimen collection

BIG WIN: **Adoption of EtG testing as standard-of- care for all pregnant persons**

8

8

Key Milestones

- UT IRB: Approved (Jan 23)
- GUID Training: Completed (Oct 23)
- Randomization Protocol: Developed (Oct 23)
- Branding: Completed (Nov 23)
- Women's Advisory Group: Recruited (Oct 23)
- Data Safety and Monitoring Board: Confirmed (Oct 23)

9

Key Milestones: Protocols

- Recruitment and enrollment protocols: to be completed Q4 '23
- Participant management & tracking tools (Consent, Enrollment, Reminders): developed & programmed on REDCap
- Pilot testing: Q1 '24
- Participant enrollment: Q2 '24

10
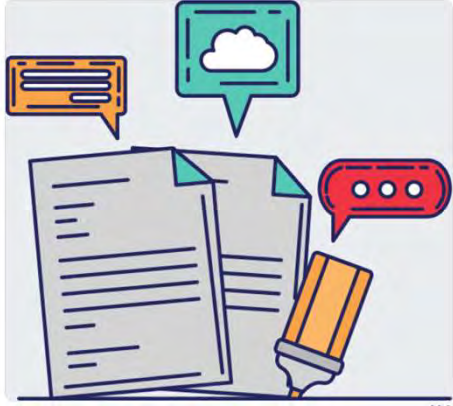
Key Milestones: Biospecimens

- POC EtG and DBS PEth
- Collection, storage and shipment protocols: consolidated and adapted (Fall '23)
- Materials: purchased (Fall '23)
- Quest contract: in progress

Key Milestones: Assessment

- Extensive interview developed & programmed on REDCap, with voice capability
- Pilot testing: ongoing

Slide 13

NYU SCHOOL OF GLOBAL PUBLIC HEALTH
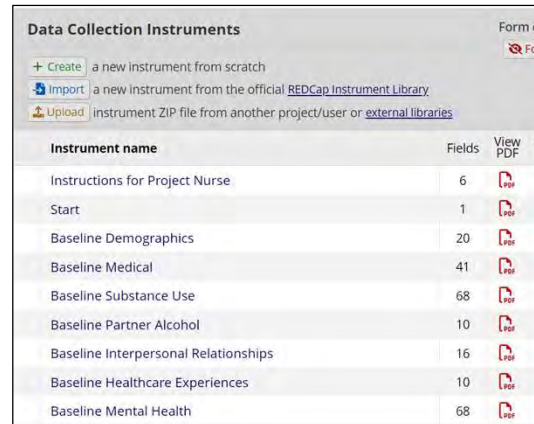
Safe Start

UTHealth Houston
McGovern Medical School

Key Milestones: Assessment

- Demographics
- Medical/Reproductive History
- Substance Use: Alcohol, Tobacco, Other
- Partner Alcohol Use
- Interpersonal Relationships: Quality & Interpersonal Violence
- Healthcare Experiences
- Mental Health: Depression, Anxiety, Pregnancy-related stress, Coping, Self-efficacy

Data Collection Instruments

Form o

+ Create a new instrument from scratch

Import a new instrument from the official REDCap Instrument Library

Upload instrument ZIP file from another project/user or external libraries

Instrument name	Fields	View PDF
Instructions for Project Nurse	6	PDF
Start	1	PDF
Baseline Demographics	20	PDF
Baseline Medical	41	PDF
Baseline Substance Use	68	PDF
Baseline Partner Alcohol	10	PDF
Baseline Interpersonal Relationships	16	PDF
Baseline Healthcare Experiences	10	PDF
Baseline Mental Health	68	PDF

13

13

Slide 14

NYU SCHOOL OF GLOBAL PUBLIC HEALTH
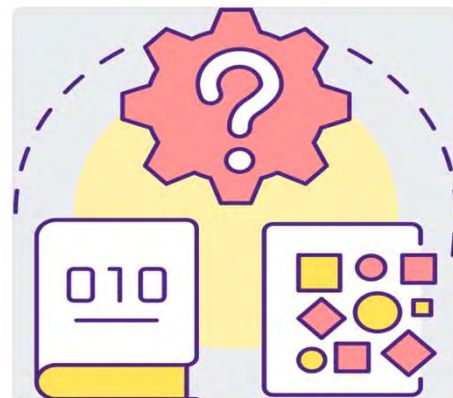
Safe Start

UTHealth Houston
McGovern Medical School

Key Milestones: Data

- Database development & testing ongoing

- Data dictionary completed

- Data set uploads: testing ongoing

- To be completed: Q4 '23

14

14

Key Milestones: Intervention

- Design in progress – first draft

- Devices & MediaLab software purchased & installed

- To be completed: Q1 '24 following WAB piloting & PN training
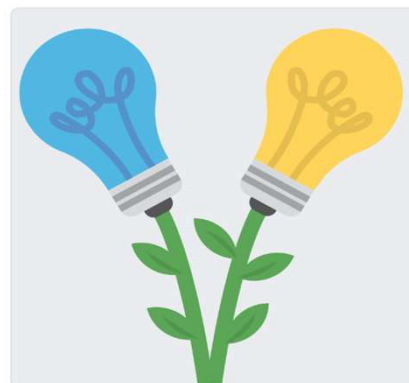
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15

Key Milestones: CIFASD 5

1) Chambers: Collection of self-reported measures for cross-cohort comparisons

2) Chambers & Miranda: Collection of maternal plasma for miRNA analysis (n=60 x 2)

3) Mahnke: Collection of cord blood for stem cell research (n=20)

16

16

Slide 17

Looking ahead

- Phase I-Preparation: To be completed Q1 '24
- Staffing & collaborations in place, processes & equipment for implementation, intervention, assessment, & data collection: progressing as planned & to be completed after pilot
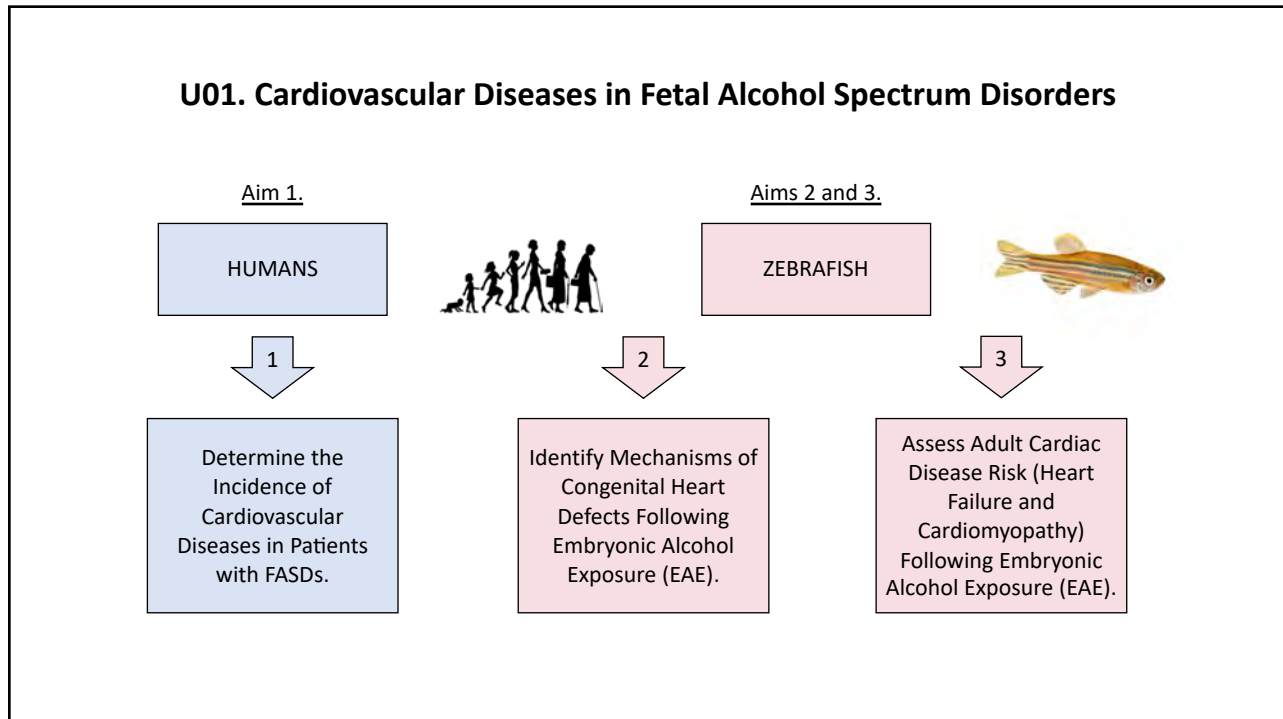- Participant enrollment: Begins April '24

17

Slide 18

18

18

U01. Cardiovascular Diseases in Fetal Alcohol Spectrum Disorders

Aim 1.

HUMANS

Aims 2 and 3.

ZEBRAFISH

1

2

3

Determine the Incidence of Cardiovascular Diseases in Patients with FASDs.

Identify Mechanisms of Congenital Heart Defects Following Embryonic Alcohol Exposure (EAE).

Assess Adult Cardiac Disease Risk (Heart Failure and Cardiomyopathy) Following Embryonic Alcohol Exposure (EAE).

1

Aim 1: Perform a retrospective cross-sectional analysis to determine cardiovascular disease (CVD) prevalence in an adult FASD patient cohort.

✅ **IRB:** Approval granted through Fall 2024, with an option for continued renewal after that date.
✅ **Data Dictionary:** Completed.
✅ **Data Upload with DCR:** Completed for first two rounds of data uploads; confirmation of "success" received.
✅ **pseudoGUIDs:** psudoGUIDs were provided by the NIH and assigned to each patient identified thus far in the study.
✅ **# Samples collected and analyzed:** ~ **408 adults**, 50% with FASDs and 50% without. Efforts to expand our control cohort up to at least 500 – 1,000 patients are underway.

Major Research Accomplishments:

- Discovered increased lifetimes rates of cardiovascular disease disease diagnosis (CHDs, MIs, etc.) in females with FASDs.
- Identified increased rates of screening for cardiovascular diseases by echocardiography in FASD patients.
- Found that >6% of males with FASDs also have a congenital heart defect (normally 1% in the general population); however, the matched male controls are unhealthy and have similar rates of CHDs.

Future Goals:

- Add up to >1,000 additional controls through our new collaboration with Shaan Khurshid, who will leverage machine learning and his "C3PO" platform to identify new matched patients
- Collect in-depth quantitative data from echocardiography, which was previously excluded from the initial data collection
- Incorporate a heart failure with preserved ejection fraction (HFpEF) scoring rubric for patients without a formal diagnosis

Results will be presented at the April 2024 International FASD Meeting in Seattle.

2

Aim 1: Perform a retrospective cross-sectional analysis to determine cardiovascular disease (CVD) risk in an adult FASD patient cohort.

Data Acquisition Plan

Personal	Control	FASD
Biological Age		
Study Age		
Race		
Ethnicity		
Metabolic Parameters		
Body Mass Index		
Overweight/Obesity (0 = underweight, 1 = normal, 2 = overweight, 3 = obese)		
LDL Cholesterol		
HDL Cholesterol		
HDL Cholesterol < 40 mg/dL (0 = no, 1 = yes)		
Triglycerides		
Hyperlipidemia (0 = no, 1 = yes)		
A1C Level		
T2DM (0 = no, 1 = yes)		
Multiple metabolic abnormalities (0 = no, 1 = yes)		
Cardiac Testing		
Electrocardiogram (0 = no, 1 = yes)		
Echocardiogram (0 = no, 1 = yes)		
Stress Testing (0 = no, 1 = yes)		
iCPET (0 = no, 1 = yes)		
Congenital Heart Defects		
Heart murmur (0 = no, 1 = yes)		
Congenital heart defect diagnosis (0 = no, 1 = yes)		
Septal defect (0 = no, 1 = yes)		
Conotruncal defect (0 = no, 1 = yes)		
Other defect (0 = no, 1 = yes)		

Adult Cardiovascular Diseases		
Hypertension (0 = no, 1 = yes)		
Pulmonary Hypertension (0 = no, 1 = yes)		
Cardiac Arrythmia (0 = no, 1 = yes)		
Subtype		
Atrial Fibrillation (0 = no, 1 = yes)		
Cardiomyopathy (0 = no, 1 = yes)		
Dilated Cardiomyopathy (0 = no, 1 = yes)		
Hypertrophic Cardiomyopathy (0 = no, 1 = yes)		
Arrhythmogenic cardiomyopathy (0 = no, 1 = yes)		
Restrictive Cardiomyopathy (0 = no, 1 = yes)		
Left Ventricular Noncompaction (0 = no, 1 = yes)		
Heart Failure (0 = no, 1 = yes)		
HFpEF (0 = no, 1 = yes)		
HFrEF (0 = no, 1 = yes)		
Congestive Heart Failure (0 = no, 1 = yes)		
Heart Valve Disease (0 = no, 1 = yes)		
Myocardial Infarction (0 = no, 1 = yes)		
Atherosclerosis (0 = no, 1 = yes)		
Coronary Artery Disease (0 = no, 1 = yes)		
Stroke/Cerebral Vascular Accident (0 = no, 1 = yes)		
Pulmonary Embolism (0 = no, 1 = yes)		
Echocardiography Parameters (if available)		
LVEF/ Ejection Fraction (%)		
LVIDed		
LVIDes		
Interventricular Septum/IVS		
Posterior Wall Thickness/PWT		
LA A-P		
LA Volume		
LA Volume Index/LAVI		
Ao sinus		
Asc Ao		
E/e'		
Septal or lateral e'		
E/A		
TR Velocity		

3

Aim 2: Identify molecular mechanisms underlying impaired cardiac precursor migration during cardiac cone formation.
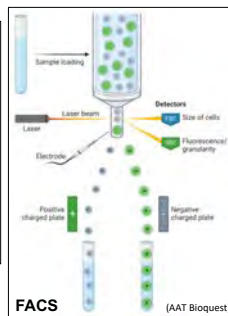
Major Research Accomplishments:

- Performed a developmental analysis of the impacts of embryonic alcohol exposure on migrating anterior lateral plate mesoderm, endoderm, and cardiac precursor cells.
- Characterized CHDs arising from embryonic alcohol exposure.
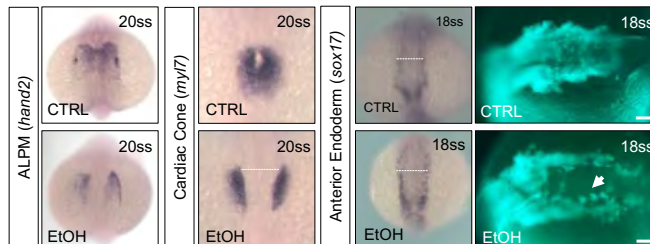
Future Goals:

- **Molecular analysis** of the impacts of embryonic alcohol exposure on gene expression, cell composition, and cell-cell interactions in migrating anterior lateral plate mesoderm, endoderm, and cardiac precursor cells.

ALPM (hand2) — 20ss CTRL, 20ss EtOH
Cardiac Cone (myl7) — 20ss CTRL, 20ss EtOH
Anterior Endoderm (sox17) — 18ss CTRL, 18ss EtOH, 18ss CTRL, 18ss EtOH

Fluorescence Activated Cell Sorting (FACS)
Tg(sox17:eGFP): endoderm
Tg(nkx2.5:ZsYellow): cardiac progenitors in the ALPM

Single Cell RNA Sequencing
(10x Genomics® Chromium™ and Illumina® NovaSeq™ 6000)

Computational Analysis
Cell clustering, differentially expressed genes (DEGs),
gene set enrichment analysis (GSEA),
cell-cell interaction analysis

FACS (AAT Bioquest)
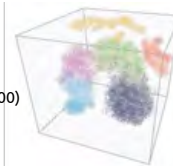
4

Aim 2: Identify molecular mechanisms underlying impaired cardiac precursor migration during cardiac cone formation (Pdgfra signaling pathway).

Major Research Accomplishments:

- Preformed a preliminary **developmental analysis** of the impacts of *pdgfra* mutation on cardiac development in the presence and absence of embryonic alcohol exposure.

Future Goals:

- Utilize **RNA scope** to evaluate the expression pattern of *pdgfra* during early cardiac development and the impact that embryonic alcohol exposure has on its distribution pattern.

- Characterize the impacts of *pdgfra* mutation and embryonic alcohol exposure on PI3K signaling.
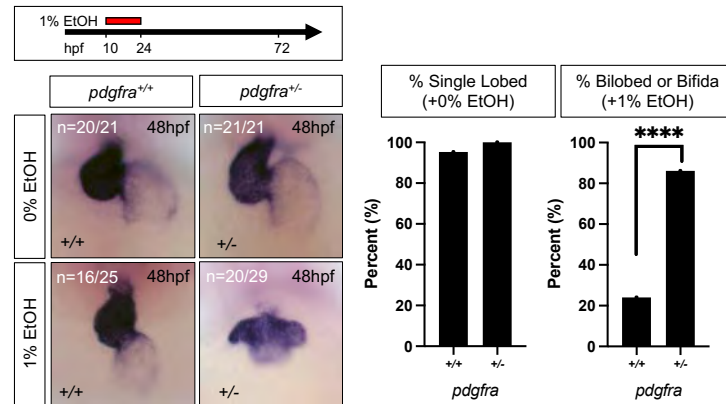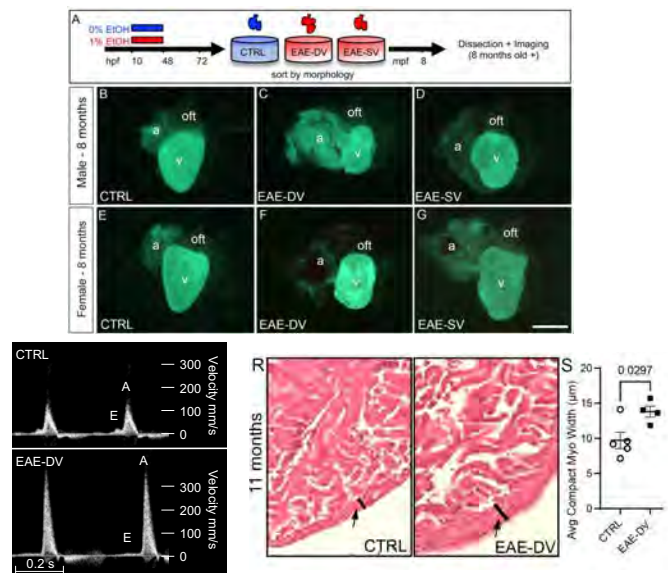

5

Aim 3: Evaluate cardiac function and cardiomyopathy incidence in an adult zebrafish FASD model.

Major Research Accomplishments:

- Characterized ventricular wall defects resulting from post-gastrulation embryonic alcohol exposure (EAE) in zebrafish

- Determined that **EAE causes acute recoverable systolic failure, but has no effect on atrial or ventricular chamber size during development** (only shape)

- Demonstrated that **EAE adults with and without a prior documented CHD develop cardiomyopathy**, characterized by increased atrial:ventricular size

- Demonstrated that **EAE adults have preserved systolic function and impaired diastolic function**, which worsens with age, and is accompanied by changes in ventricular wall thickness

- Utilized RNA sequencing to **identify 7 highly reproducible cardiac biomarkers of EAE** whose expression levels are associated with the degree of diastolic dysfunction identified by echocardiography


6

3

Aim 3: Evaluate cardiac function and cardiomyopathy incidence in an adult zebrafish FASD model.

Future Goals:

- **THIS WEEK:** Submit the manuscript covering Aim 3 to *Circulation Research.*
- **Characterize candidate biomarker** gene expression across the lifespan using in situ hybridization, qPCR, and immunohistochemistry.
- **Build CRISPR-Cas9 mutants** for candidate biomarker genes *eya4, ankrd9, slc25a33,* and *spry4.*

Larvae (♂, ♀; 20 dpf)

Adult (♂, ♀; 5 mpf)

CRISPR Mutants: *eya4*   *ankrd9*   *slc25a33*   *spry4*
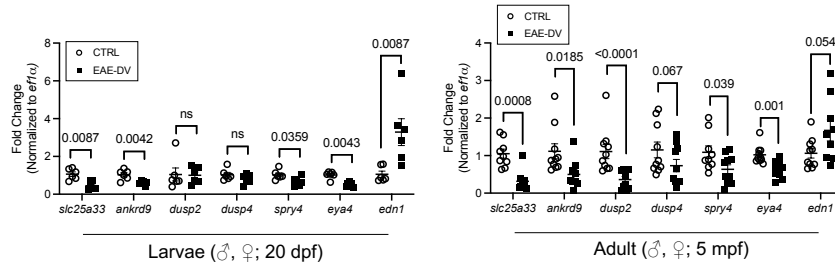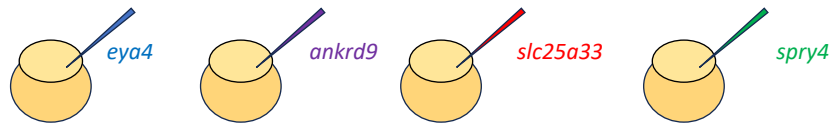
7

Ongoing Collaborations

UH2. Mahnke	U01. Chambers	U01. Petrenko	U01. Thomas and Wetherill

- **Sent protein and RNA** from the kidney marrow (the major site of hematopioesis) of 15-month-old CTRL and EAE zebrafish for examination of age-related expression changes.

- **Shared RNA sequencing data** from ventricular tissue; Amanda found a signature of increased aging.

- **Shared RNA sequencing data** from ventricular tissue. Tina found significant SNPs in *slc25a33, dusp2, spry4, edn1, ankrd9,* and *dusp4* using her GWAS of FASD vs unaffected offspring.

- Future: **Compare rates of heart murmur and CHDs** in her Ukraine cohort with our adult cohort.

- **Applying for IRB approval** to receive **child EKG data** from their in-person FASD behavioral studies. We will examine the incidence of rhythm abnormalities in their cohort.

- Consideration: **we have no CTRL population**, so we need to determine how we will compare rates of affected individuals with the general population

- **Shared data** related to per1a/per1b and circadian rhythm gene expression in isolated heart tissue.

- Leah plans **to look for genetic variants** in circadian rhythm genes and their regulators in GWAS data.

- **Group meeting** will occur after the holiday season.

8

Acknowledgements

For information on available archived CIFASD data, please visit https://cifasd.org/data-sharing/.

Boston Children's — Where the world comes for answers