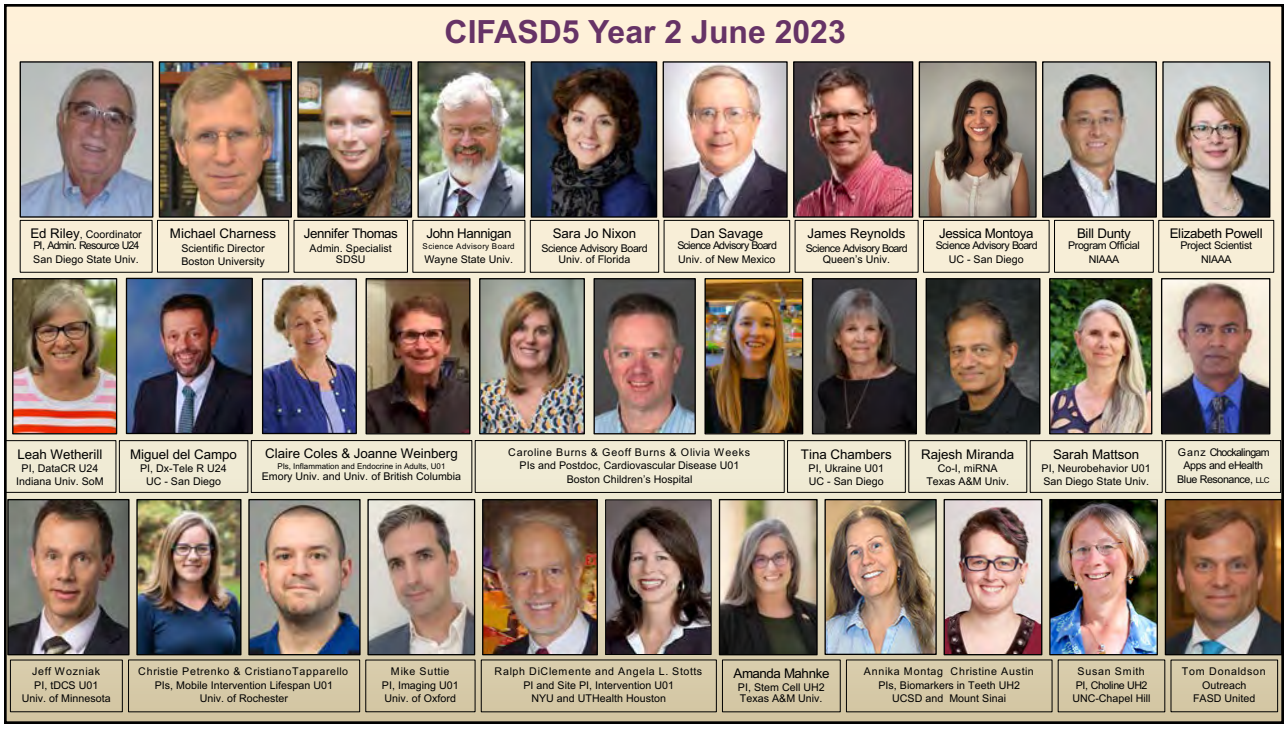
CIFASD5 YR1/YR2 Project Progress Meeting
June 2023
PPT Presentations

June 21, 2023 (Zoom)
June 23, 2023 (In Person pre-RSA Bellevue, WA)

Most of this data is pre-publication, so please keep confidential.
Please contact the project PI
if you wish to use a slide or information in another presentation.


CIFASD5 Progress June 2023
CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders
Ed Riley, CIFASD Coordinator and AdminR PI
PREGNANT?
DON'T DRINK.
ALCOHOL
CAN CAUSE
LIFELONG
BRAIN DAMAGE
TO YOUR CHILD.
"We agree with the CDC: There is no known amount of alcohol that is safe to drink while pregnant." - Dr. Mehmet Oz, M.D.
Join us at NOFAS.org

1


CIFASD5 Year 2 June 2023
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 PIs, Inflammation and Endocrine in Adults, U01 Emory Univ. and Univ. of British Columbia
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 Christine Austin PIs, Biomarkers in Teeth UH2 UCSD and Mount Sinai
Susan Smith PI, Choline UH2 UNC-Chapel Hill
Tom Donaldson Outreach FASD United

2

CIFASD5 Consortium Structure

ADMINISTRATIVE RESOURCE (AdminR)

PI, Coordinator:	Edward Riley, SDSU
Scientific Director:	Michael Charness, Harvard
Admin. Specialist:	Jennifer Thomas, SDSU
Admin. Coordinator:	Jill Vander Velde, SDSU

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 Charness and 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*^/ C. Austin*^
M. Suttie	S. Smith^
J. Wozniak	^ CIFASD4 UH2 PIs
* Multiple PI project	

3

Overall CIFASD Goals

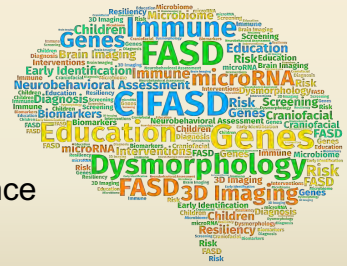
The **overall goals of CIFASD** aim to further refine definitive characteristics of fetal alcohol spectrum disorders (FASD) across the lifespan based on biological, physical, neurological, and/or behavioral assessment by:

- 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

4

Specific Aims of the AdminR

- Provide scientific and administrative direction, leadership, and oversight to the consortium
- Facilitate communication among the various projects and the 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 Altman Clinical and Translational Research Institute



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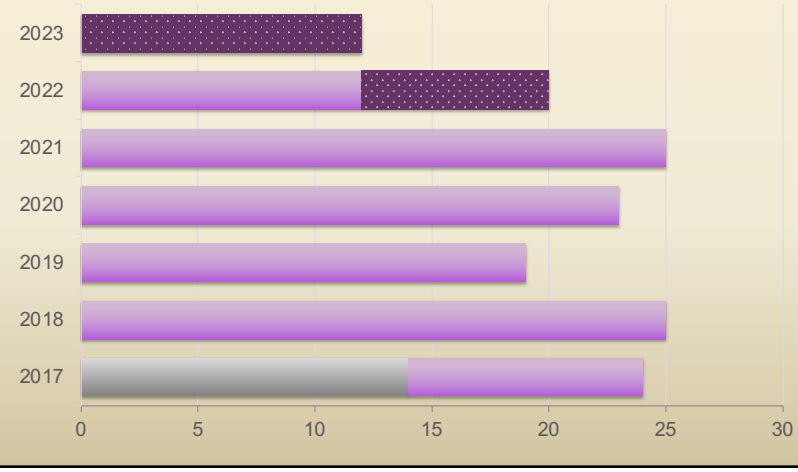
Publication Productivity of CIFASD

Publications citing **CIFASD** funding per PubMed
CIFASD4 (July 2017 - July 2022) = 114
CIFASD5 (August 2022 - present) = 20



Total PubMed
CIFASD Publications = **357**

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***

6

Publications Citing CIFASD Grants

Published in 2023 n= 12

- Boschen KE, Steensen MC, Simon JM, Parnell SE. Short-term transcriptomic changes in the mouse neural tube induced by an acute alcohol exposure. *Alcohol*. 2023 Feb;106:1-9. PMID: 36202274.
- Everson JL, Tseng YC, Eberhart JK. High-throughput detection of craniofacial defects in fluorescent zebrafish. *Birth Defects Res*. 2023 Feb 1;115(3):371-389. PMCID: PMC9898129.
- Everson JL, Eberhart JK. Gene-alcohol interactions in birth defects. *Curr Top Dev Biol*. 2023;152:77-113. PMCID: PMC9897481.
- Gimbel BA, Roediger DJ, Ernst AM, Anthony ME, de Water E, Mueller BA, Rockhold MN, Schumacher MJ, Mattson SN, Jones KL, Lim KO, Wozniak JR. Delayed cortical thinning in children and adolescents with prenatal alcohol exposure. *Alcohol Clin Exp Res*. In press. PMID: 37132064.
- Gimbel BA, Roediger DJ, Ernst AM, Anthony ME, de Water E, Rockhold MN, Mueller BA, Mattson SN, Jones KL, Riley EP, Lim KO; **CIFASD**; Wozniak JR. Atypical developmental trajectories of white matter microstructure in prenatal alcohol exposure: Preliminary evidence from neurite orientation dispersion and density imaging. *Front Neurosci*. 2023 Apr 24;17:1172010. PMCID: PMC10165006.
- Glass L, Moore EM, Mattson SN. Current considerations for fetal alcohol spectrum disorders: identification to intervention. *Curr Opin Psychiatry*. 2023 May 1;36(3):249-256. PMCID: PMC10079626.
- Kautz-Turnbull C, Rockhold M, Handley ED, Olson HC, Petrenko C. Adverse childhood experiences in children with fetal alcohol spectrum disorders and their effects on behavior. *Alcohol Clin Exp Res*. 2023 Mar;47(3):577-588. PMCID: PMC10050124.
- Mattson SN, Jones KL, Chockalingam G, Wozniak JR, Hyland MT, Courchesne-Krak NS, Del Campo M, Riley EP; **CIFASD**. Validation of the FASD-Tree as a screening tool for fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2023 Feb;47(2):263-272. PMCID: PMC9992228
- Pellowski JA, Wedderburn CJ, Groenewold NA, Roos A, Subramoney S, Hoffman N, Fouche JP, Joshi SH, Woods RP, Narr KL, Zar HJ, Donald KA, Stein DJ. Maternal perinatal depression and child brain structure at 2-3 years in a South African birth cohort study. *Transl Psychiatry*. 2023 Mar 20;13(1):96. PMCID: PMC10027817.
- Popova S, Charness ME, Burd L, Crawford A, Hoyme HE, Mukherjee RAS, Riley EP, Elliott EJ. Fetal alcohol spectrum disorders. *Nat Rev Dis Primers*. 2023 Feb 23;9(1):11. PMID: 36823161.
- McDonnell P, Fornell P, Ponce S, Dyer L. Baseline heart rate in infants with prenatal alcohol exposure: A systematic review and independent analysis. *Birth Defects Res*. 2023 Mar 1;115(4):474-487. PMID: 36515170.
- Oh SS, Kang B, Park J, Kim S, Park EC, Lee SH, Kawachi I. Racial/Ethnic Disparity in Association Between Fetal Alcohol Syndrome and Alcohol Intake During Pregnancy: Multisite Retrospective Cohort Study. *JMIR Public Health Surveill*. 2023 Apr 21;9:e45358. PMCID: PMC10147559.

7

Nature Reviews Disease Primers

nature reviews disease primers

nature › nature reviews disease primers › primers › article

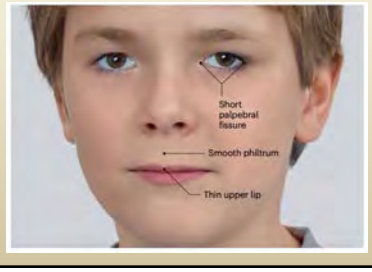
Primer | Published: 23 February 2023

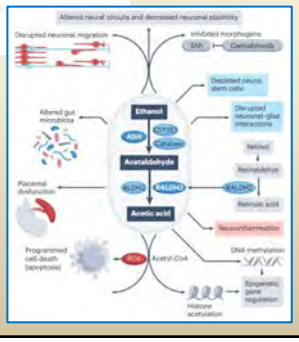
Fetal alcohol spectrum disorders

Svetlana Popova, Michael E. Charness, Larry Burd, Andi Crawford, H. Eugene Hoyme, Raja A. S. Mukherjee, Edward P. Riley & Elizabeth J. Elliott

Nature Reviews Disease Primers **9**, Article number: 11 (2023) | Cite this article

7932 Accesses | **2** Citations | **85** Altmetric | Metrics





Challenges for adolescents and adults with fetal alcohol spectrum disorders

- Involvement in child welfare services (75%)
- Disrupted school experiences due to learning and/or behavioural problems (61%)
- Interaction with the justice system (30% to 60%)
- Confinement (detention, prison, or psychiatric or alcohol/drug inpatient setting; 50%)
- Substance use disorder: alcohol and other drugs (50%)
- Inappropriate sexual behaviour (49%)
- Increased risk of metabolic abnormalities (includes type 2 diabetes, low high-density lipoprotein, high triglycerides, and female-specific overweight and obesity)
- Difficulties with independent living and trouble gaining and retaining employment (80%)
- Mean life expectancy (34 years; 95% CI 31–37 years) is considerably lower than in the general population; leading causes of death are 'external causes' (44%), including suicide (15%), accidents (14%), poisoning by illegal drugs or alcohol (7%) and other external causes (7%)

8

Publication Press

9

Monthly Meeting Invited Guests
International Adult Leadership Collaborative (ALC) of the FASD Changemakers

10

Monthly Meeting Invited Guests
FDNA

11

Potential Collaborations

Prof. Mauro Ceccanti

SAPIENZA
UNIVERSITÀ DI ROMA

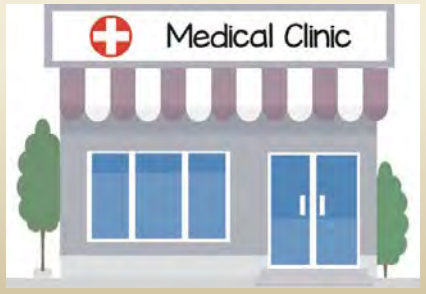
12

Collaboration Liaison

MorpheusQ

BRAIN-online

FASD-Tree



13

CIFASD AdminR Outreach and Education

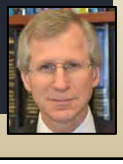
Examining FASD Diagnosis ECHO

UAA Center for Human Development
University of Alaska Anchorage

ECHO

Diagnostic Systems for FASD

Michael E. Charness, M.D.
VA Boston Healthcare System
Brigham and Women's Hospital
Harvard Medical School
Boston University

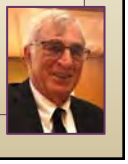


E-Health Endeavors in the Collaborative Initiative on FASD (CIFASD)

Edward Riley

Collaborative Initiative on FASD
Center for Behavioral Teratology
San Diego State University

CIFASD



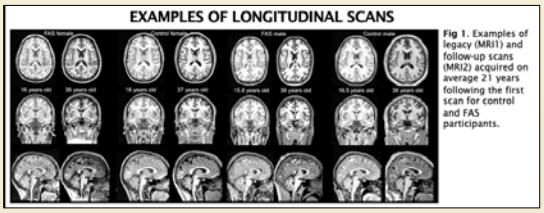
14

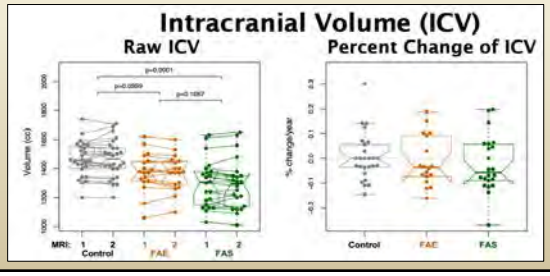
Consortium Coordinator Visibility & Networking

Alcoholism and Stress: A Framework for Future Treatment Strategies
Volterra, Italy - May 2023

Graded regional cerebellar volume deficits in adolescents and adults with Fetal Alcohol Effect (FAE) and Fetal Alcohol Syndrome (FAS)

E.P. Riley, K.M Pohl, A. Grethe, E.V. Sullivan, A. Pfefferbaum
San Diego State University, Stanford University School of Medicine, SRI International





15

CIFASD Research Visibility

46th Annual RSA Scientific Meeting

June 24-28, 2023
Bellevue, Washington

CIFASD Translational Research on FASD

- 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 lab), 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

Research Society on Alcohol

16

CIFASD AdminR Investigator Awards

Dr. Edward Riley Receives Lifetime Achievement Award

RSoA @RSAposts · Mar 20

Congratulations to our 2023 RSA Annual Award recipients!

2023 RSA ANNUAL AWARDS RECIPIENTS

It is a pleasure to announce this year's RSA Annual Awards' recipients. Award presentations will take place during the RSA Closing Ceremony, Wednesday, June 28 at RSA-2023.

RSA Lifetime Achievement Award - **DR. EDWARD RILEY**. This award is given to an individual who has had a long, balanced career including outstanding research, training, service and advocacy.

SDSURF @SDSU_RF

Congratulations to @SDSUsciences professor emeritus Dr. Edward Riley for receiving the Research Society of Alcohol's 2023 Lifetime Achievement Award for his long, balanced career of outstanding research, training, service, and advocacy!
#SDSU #research

17

CIFASD AdminR Investigator Awards

San Diego State University @SDSU · Mar 28

The inaugural Outstanding Scholar Awards recognized 10 faculty members for their scholarship, creative activities, innovation and public impact.

Read more about this year's recipients: bit.ly/3loQOJs

Postdoctoral Scholar Award:
Jessica Baker (Postdoctoral Scholar) and Jennifer Thomas (Mentor)

18

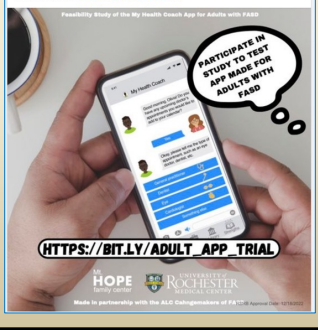
FASD United

facebook

FASD United
March 23 ·

My Health Coach is an app developed for adults with FASDs or Prenatal Alcohol Exposure (PAE). The app aims to provide adults with #FASD or #PAE evidence-based info about their condition along with tools to promote their self-management and health advocacy goals.
18 years or older?✅
Speak English from anywhere in the world?✅
Have an FASD/PAE history?✅

Participate: https://bit.ly/adult_app_trial



FASD United
Weekly Roundup

RESEARCH UPDATE

Featured: *Nature Reviews Disease Primers*: Fetal Alcohol Spectrum Disorders
"The social and economic effects of FASD are profound, but the diagnosis is often missed or delayed and receives little public recognition… Imperatives include reducing stigma, equitable access to services, improved quality of life for people with FASD and FASD prevention in future generations."

Huge Research Release! Article Share from *Nature Reviews* Focuses on FASD

We are excited to share the findings of significant research from *Nature Reviews* recently released on FASDs, their impacts, and the urgent importance for better diagnosis. We encourage you to read through and utilize this insightful research which speaks powerfully to how we can best support those affected by FASD.

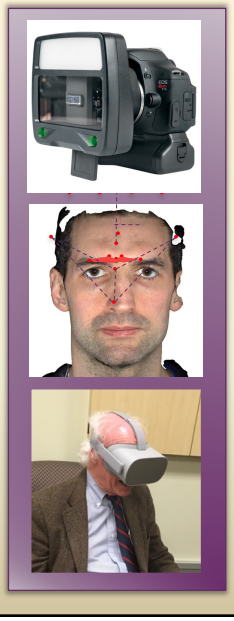
twitter

FASD United (formerly NOFAS) @FASDUnited · Apr 29
FASD United was honored to present at The #2023 Annual Public Meeting of the Interagency Coordinating Committee on #FASD, where the Family Navigation program was discussed
With @NIH

Blog Post: fasdunited.org/iccfasd-2023-v...

19

Blue Resonance, LLC



FASD-Tree

BRAIN-online

20

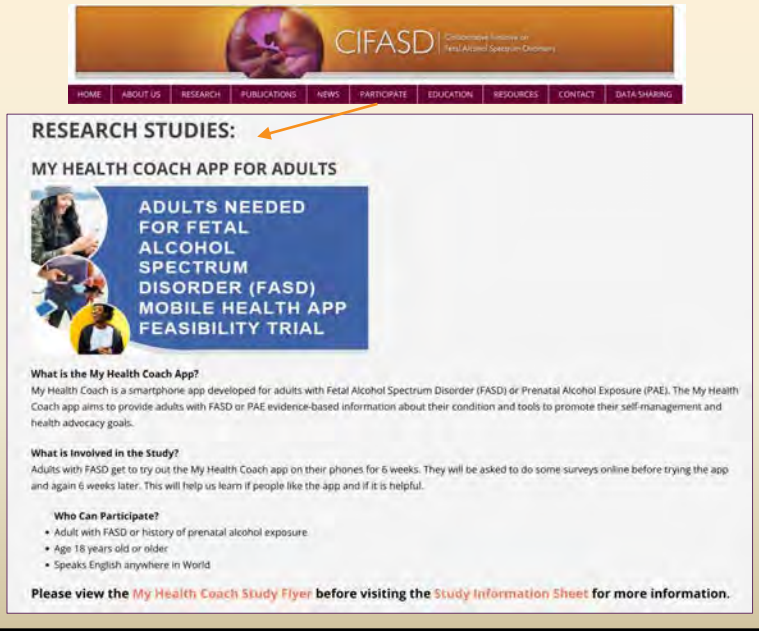
Dissemination and Implementation

- 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 Boot Camp
  - Online resources
  - Seminars
  - Special topic events

21

CIFASD.org Recruitment Assistance



22

CIFASD Publications Policy

CIFASD Publication Process

Policies and forms are housed within the secure section of the CIFASD website.

Concept Proposal
Complete the online
Concept Proposal Form

CIFASD Investigators
Review Concept Proposal:
Provide comments, indicate interest, define proposed contribution

Review Comments/ Respond to CIFASD Investigators

Analyses Proceed/ Manuscript Prepared
Provide updates to CIFASD ~ every 6 months to ensure progress

Prior to Submission
Complete the online
Manuscript Submission Template Form

Post-Acceptance
Complete the online
Post-Acceptance Form

Ensure Compliance
NIH Public Access Policy

23

Science Advisory Board (SAB) Members

- Members John Hannigan (Chair), Sara Jo Nixon, Dan Savage, and James Reynolds; New member Jessica Montoya
- SAB Evaluations will be completed following the this meeting utilizing the March progress reports and June presentations
- Evaluations will be distributed to AdvisoryC members and Project PIs by the Consortium Coordinator

24

Special Thanks to:

Bill Dunty

Elizabeth Powell

Science Advisory Board

Michael Charness

Jennifer Thomas

Jill Vander Velde

Publications Policy and Data Sharing Committees

25

U24 Diagnostic Telemedicine resource (DTR)

Miguel del Campo, MD, PHD

Kenneth L. Jones, MD

CIFASD5

Diagnostic Telemedicine Resource (DTR)

Aims

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

Accomplishments

1.Two groups had initial trainings completed: Mattson and Wozniak
2. IRB for physical exams/photos at UCSD/Rady Completed
Recruitment for Aim 2 running
3. Alaska aim in progress
Collaborations: Mattson and Suttie

Milestones

Collaborations protocols Mattson and Suttie
SOP trainings
SOP screening in Alaska
Two courses on Cultural sensitivity, research in AI/AN peoples
Cultural sensitivity courses completed

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 first session

U01 Sarah Mattson 3 trainees two sessions,

one in person

SOP: Two initial training sessions without subjects

Telemedicine exam of at least 2 subjects

Proctoring 2 exams and re-training after 10 subjects

Discuss in person proctoring

2

Specific Aim 2

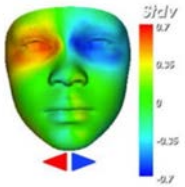
The DTR will test three novel eHealth tools that would provide accessible, scalable, low-cost solutions to screening and diagnosis for FASD, and compare each of these to the standard in-person **dysmorphology examination by experts** used in all previous iterations of CIFASD1-4. In Aim 2, we will: 1) **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.

49 cases (50/year)
30 cases preliminary data

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

PFL 3D scan 27 cases (50/year)
30 cases rot scan preliminary data

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



Working with IRB on storage and transmission of images. Ganz?

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:
Ethics course on research in AI/AN
Working on agreements with 2 diagnostic centers (Wasilla and Fairbanks)
Collaboration of anthropologist Travis Hedwig
Discussing IRB/regional tribal org.
SOP manual for the comprehensive screening process

2nd year. Obtain IRB approval
Initiate/complete recruitment

4

To do…

- Schedule initial trainings with other U01s
- U01 please include in IRB remote or in person supervision of physical examinations
- Feedback to revise training SOP as we go
- Start capturing Canfield photos
- Establish system to capture iPhone photos (more than 30 have consented)
- Establish system for secure transmission of images to Suttie
- Thanks for support Administrative Core Ed Riley Alaska

In San Diego

Systematic screening of the child welfare population

Systematic screening of the juvenile justice population

Making it research projects IRB

- Questions?

5

Data Coordination Resource (DCR)

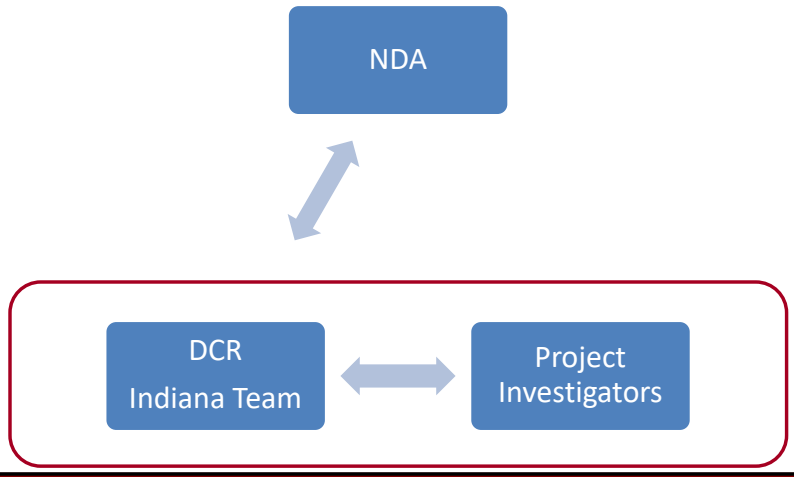
Leah Wetherill, Ph.D.

Abigail Erickson, BS, CCRP

SCHOOL OF MEDICINE

1

Project-Specific Progress

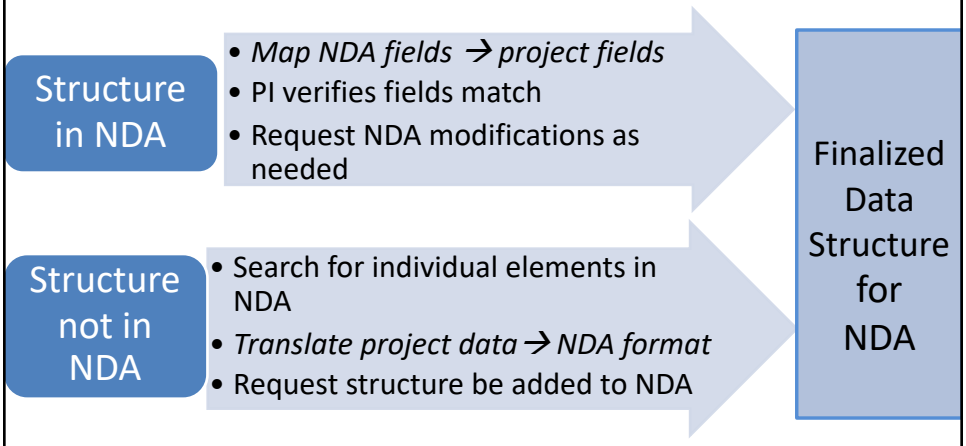


SCHOOL OF MEDICINE

2

Data Structures (e.g., questionnaires)

- 9 of 11 projects provided list of data structures



SCHOOL OF MEDICINE

3

Adapt Data Dictionary to DCR Format

- Iterative process: IU Team ⟷ Project PI
  - Ensure all required fields are included
  - Decide which variables to upload to NDA
  - Decide which participant data to upload to NDA
  - Data Dictionary is template for each project to upload data to DCR
  - *4 of 11 projects have data dictionaries ready for NDA approval*

SCHOOL OF MEDICINE

4

All Projects

- Should provide sample data
  - Crucial for IT team to set up automation
  - *3 of 4 projects have provided sample data*
- Should have access to NIH GUID tool
  - Required for data upload to NDA
  - *3 of 9 (consenting) projects have GUID access*

SCHOOL OF **MEDICINE**

5

Overview: Project-Specific Progress

PI	ICF DCR Approval	ICF IRB Approval	Data Collection Profile	DDs Started	Data Dictionaries & Upload Template(s) Finalized	Sample Data Received?	GUID	Target N	Enrolled
Suttie	N/A	N/A	✓	✓	✓	✓	N/A	?	
Mahnke	N/A	N/A	✓	✓	✓		N/A	36	
Wozniak	✓	✓	✓	✓	✓	✓	✓	70	
Burns Weeks	N/A	N/A	✓	✓	Dr. Weeks is implementating date masking	✓	✓	416	416
Mattson	✓	not implemented	✓	✓	working through templates and format		✓	1050	
Coles	✓	✓	✓	✓	Working with IU team			120	
Weinberg	✓	In Progress	✓	✓	waiting on final DD	only for NIH toolbox		120	
del Campo	✓	✓		✓				?	
Chambers	✓	✓	✓	✓				20	
DiClemente								?	

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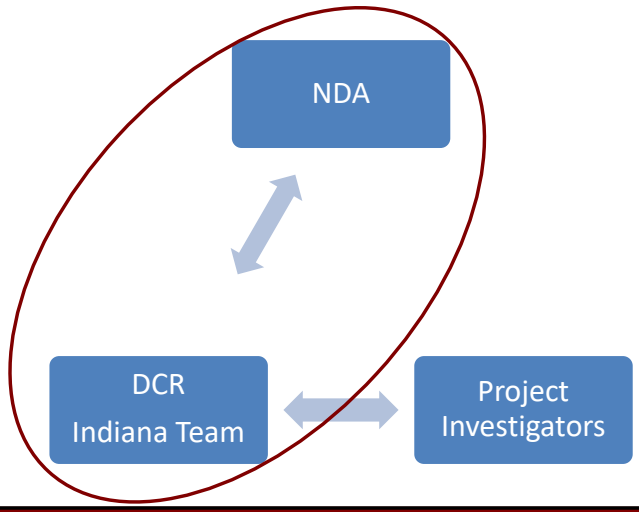
DCR-Specific Progress



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DCR Team: Automated Data Processing

- Data validation
  - –Compare sample/uploaded data to Data Dictionary
- Reformat data for NDA upload
  - –Merge data from non-consenting projects with "parent" project assigning GUID
    - 3d data (Suttie) for subjects from Wozniak, Coles, etc.
  - –Merge data from projects collecting data for same structure
  - –Assign consortium-wide "phenotype" of PAE (yes/no)
  - –*Final for: Wozniak and Suttie*

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Overview: DCR-Specific Progress

PI	Validation Completed?	Auto NDA Reformat Completed?	Any Data Transferred to NDA?
Suttie	Yes	No - waiting on NDA approval of structure	No
Burns & Weeks	Partial - waiting on implementation of masking	No - waiting on NDA approval of structure	No
Mahnke	No	No	No
Wozniak	Yes	Yes	Yes
Mattson	No	No	No
Coles	No	No	No
Stoner	No	No	No
Weinberg	No	No	No
del Campo	No	No	No
Chambers	No	No	No
DiClemente	No	No	No

Waiting on NDA approval

Waiting on Project data dictionaries

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9

Upload data to NIAAA Data Archive (NDA)

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10

11

Upload data to NIAAA Data Archive (NDA)

Data Expected	Targeted Enrollment	Initial Submission	Subjects Submitted	Initial Share	Subjects Shared	Status	Actions
Delis-Kaplan Executive Function System (D-KEFS)	470	04/01/2023	1	04/30/2029	0	Approved	
Behavior Assessment System for Children (BASC)	70	04/01/2023	1	04/30/2029	0	Approved	
Wechsler Intelligence Scale for Children	70	04/01/2023	1	04/30/2029	0	Approved	
Flanker Task	70	04/01/2023	1	04/30/2029	0	Approved	
Spence Childrens Anxiety Scale	20	10/01/2023	0	04/30/2029	0	Approved	
Substance Use Survey	360	10/01/2023	0	04/30/2029	0	Approved	
Symptom Checklist-90-Revised	360	10/01/2023	0	04/30/2029	0	Approved	
Beck Depression Inventory	120	10/01/2023	0	04/30/2029	0	Approved	
Beck Anxiety Inventory	120	10/01/2023	0	04/30/2029	0	Approved	
The Penn State Worry Questionnaire	120	10/01/2023	0	04/30/2029	0	Approved	
Brief_COPE	360	10/01/2023	0	04/30/2029	0	Approved	
Autism Spectrum Disorder (ASD) related basic information	360	10/01/2023	0	04/30/2029	0	Approved	
Maastricht Assessment of Coping Strategies	360	10/01/2023	0	04/30/2029	0	Approved	

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12

CIFASD Data Portal

- Ready to receive data
  - –Live demo

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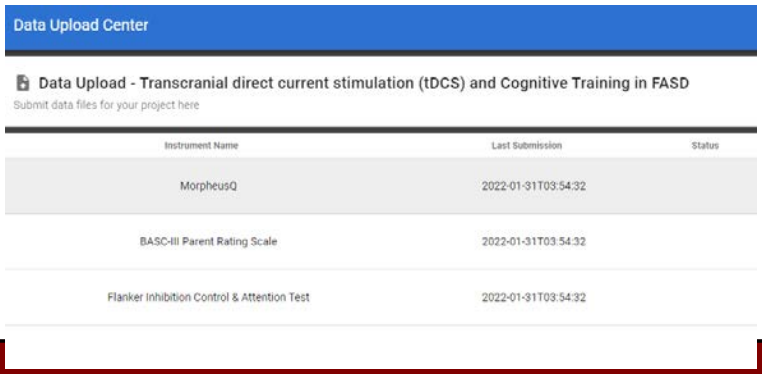
12

13

CIFASD Data Portal – Project View

- Overview for each project
  - Date of last successful upload
  - Status of uploaded instruments



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13

14

CIFASD Data Portal – Admin View

CIFASD Data Upload Center

Project Name	Current Status	
A Multisite Study of PAE: Effects of Inflammation and Endocrine Dysfunction in Adulthood_Coles	0/0 Successful Uploads	VIEW DETAILS
A Multisite Study of PAE: Effects of Inflammation and Endocrine Dysfunction in Adulthood_Weinberg	0/0 Successful Uploads	VIEW DETAILS
Assessment of FASD Using Novel Web-Based Tools	0/0 Successful Uploads	VIEW DETAILS
Cardiovascular Disease in FASD	0/1 Successful Uploads	VIEW DETAILS
Defining Translational Approaches for the Image-based Detection of PAE	0/1 Successful Uploads	VIEW DETAILS
Designing a Hybrid Intervention Strategy to Reduce Alcohol Exposed Pregnancies	0/0 Successful Uploads	VIEW DETAILS
Development of Biomarkers in Deciduous Teeth of Children with FASD that Predict Neurobehavioral Perforn	0/0 Successful Uploads	VIEW DETAILS
Diagnostic-Telemedicine Resource	0/0 Successful Uploads	VIEW DETAILS
Leveraging Technology to Increase Quality of Life for FASD Across the Lifespan	0/0 Successful Uploads	VIEW DETAILS
Lifelong Impact of PAE on Stem Cell Dynamics and Cellular Aging	0/0 Successful Uploads	VIEW DETAILS
Mobile Health Tools to Promote Health in Adults With FASD	0/0 Successful Uploads	VIEW DETAILS
Transcranial direct current stimulation (tDCS) and Cognitive Training in FASD	0/1 Successful Uploads	VIEW DETAILS
Whole Body Effects of PAE Across the Life Span: Early Markers of and Clinical Interventions for Children anc	0/0 Successful Uploads	VIEW DETAILS

14

U01 – CARDIOVASCULAR DISEASE IN FETAL ALCOHOL SPECTRUM DISORDERS

CAROLINE E. BURNS, PhD
C. GEOFF BURNS, PhD
OLIVIA WEEKS, PhD

BOSTON CHILDREN'S HOSPITAL
HARVARD MEDICAL SCHOOL

Boston Children's Hospital
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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

1

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Project Overview

Aim 1.		Aims 2 and 3.
HUMANS		ZEBRAFISH
Determine Incidence of Cardiovascular Diseases in Patients with FASDs.	Identify Mechanisms of Congenital Heart Defects in Zebrafish with Embryonic Alcohol Exposure (EAE).	Assess Lifelong Cardiomyopathy and Heart Failure Risk in Zebrafish with Embryonic Alcohol Exposure (EAE).
In progress	In progress	✅

- Congenital heart defect
- Myocardial infarction
- Cardiomyopathy
- Hypertension
- Cerebrovascular accident

2

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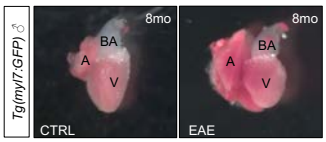
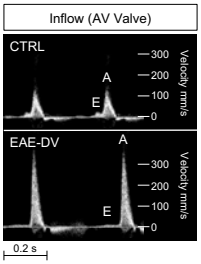
Major Research Accomplishments

We nearly completed data collection for Aim 3 of our project, which was to:
Evaluate cardiac function and cardiomyopathy incidence in an adult zebrafish FASD model

- Comprehensively described congenital heart abnormalities arising from embryonic alcohol exposure in zebrafish
- Documented **cardiomyopathy-like phenotypes** in male and female adults with embryonic alcohol exposure and quantitatively demonstrated **changes in atrial and ventricular chamber size** in a large population across the lifespan
- Utilized echocardiography to detect evidence of **diastolic dysfunction** and **heart failure with preserved ejection fraction (HFpEF)** in adults following EAE
- Performed **RNA sequencing** on male and female control and embryonic alcohol exposed ventricles to detect overlapping transcriptional alterations in the EAE group
- **Validated identified "biomarker" candidates** in a parallel animal cohort and identified at least 7 highly reproducible DEGs that distinguish CTRL from EAE hearts





3

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Major Research Accomplishments: Manuscript in Preparation

- Preparing a manuscript to submit this summer on Aim 3's embryonic and adult cardiac findings

Embryonic Alcohol Exposure is a Risk Factor for Cardiomyopathy and Diastolic Dysfunction in Adult Zebrafish¶

¶

Olivia Weeks[1,2], Xinlei Gao[1,2], Sandeep Basu[1,2], Fred Roberts[3], Dieter Fuchs[3], Kaifu Chen[1,2], C. Geoffrey Burns[1,2,4], Caroline E. Burns[1,2], CIFASD¶

¶

[1]Division of Basic and Translational Cardiovascular Research, Department of Cardiology, Boston Children's Hospital, MA, 02115, USA¶
[2]Harvard Medical School, Boston, MA, 02115, USA¶
[3] FUJIFILM VisualSonics Inc., USA.¶
[4]Harvard Stem Cell Institute, Cambridge, MA, 02138, USA¶

¶

Keywords: prenatal alcohol exposure, cardiomyopathy, congenital heart defect, diastolic dysfunction¶

4

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Major Goals for Aim 1 – Retrospective Human Cohort Study

AIM 1

HUMANS

Determine the Incidence of Cardiovascular Diseases in a Retrospective Clinic Cohort Study of Patients with FASDs

Subject Recruitment: Completed ✓
206 males (50% CTRL, 50% FASDs)
209 females (50% CTRL, 50% FASDs)

Data Dictionary (DD): Completed
- Returned initial data on all 417 patients through the DD platform

- Finalize retrospective medical chart review / data collection for at least half of all control and FASD patients
- Begin formal data analysis in collaboration with Wolfram Goessling's group

Area of input needed:

- Our male control cohort is less healthy than normal healthy males. What additional "normal/healthy" cohorts (NHANES) could we examine for broad data on USA cardiovascular or cardiometabolic health statistics?

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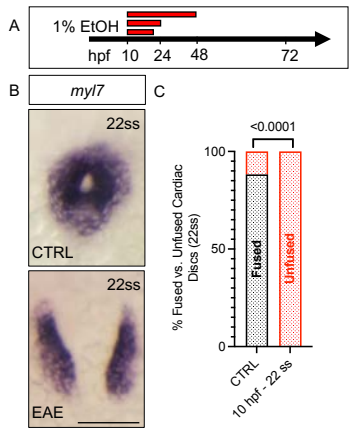
Major Goals for Aim 2 – Mechanisms Underlying EtOH's Impact on Zebrafish Cardiac Development

AIM 2

ZEBRAFISH

Identify Mechanisms of Congenital Heart Defects in Zebrafish with Embryonic Alcohol Exposure



Cardiac cone

- Isolate and perform RNA sequencing on migrating myl7+ cardiomyocytes from control and EAE embryos using FACS sorting on the transgenic *myl7:GFP+* line
- Perform gene set enrichment analysis (GSEA) on RNA-seq data to determine enriched pathways and processes
- Focus on *pdgfra* gene and PDGF pathway modulation as a mechanism of impaired cardiac cone formation downstream of EtOH exposure, with an eye toward perturbed PI3K signaling

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Ongoing Interactions

- Provided RNA sequencing data and suspected biomarker hits to multiple CIFASD groups, including Tina Chambers, to evaluate overlaps
- Chambers group investigated whether any of the genes identified as differentially expressed in our data set were enriched in her GWAS
- Her team returned potential areas of overlap between our transcriptomics data and her GWAS sequencing data, and we are awaiting additional analysis by her group before further collaborative plans are drawn

We are enthusiastic to share data and investigate areas of overlap between our project and others. Please contact us if you have ideas, gene or biomarker hits, or transcriptomics data to compare.

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Status of IRB and IACUC Approval, Year 2

IRB Approval

- Our IRB protocol will be up for renewal through continuing review at Mass General Brigham (PI: Wolfram Goessling) in November 2024
- Necessary documents will be submitted in late October/early November and likely approved within 1 week of submission

IACUC Approval

- Our IACUC protocol is approved until 04/2025; renewal will be requested at that time

Wolfram Goessling, MD, PhD
Chief, Division of Gastroenterology
Mass General Hospital

cayuse Animal Oversight

Boston Children's Hospital

PI :	Burns, Caroline
Protocol #	00001636
Status :	Approved
Approved :	04/22/2022
Expires :	04/22/2025
Title :	Zebrafish cardiovascular development, function, and regeneration

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine

Christina Chambers, Rajesh Miranda, Claire Coles, Julie Kable, Amanda Mahnke, Gretchen Bandoli, Wladimir Wertelecki, Lyuba Yevtushok, Natalya Zymak-Zakutnya

Collaborative Initiative on Fetal Alcohol Spectrum Disorders June June 21, 2023

UC San Diego School of Medicine

1

Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Selection criteria cases: **exposed/affected mother/child pairs**
  - Met criteria for moderate to heavy alcohol exposure around the time of conception with or without continued use at time of enrollment
  - Met criteria for having at least one dysmorphology exam with 2 or more facial features, and growth deficiency on at least one measure
  - Met criteria for at least one neurobehavioral evaluation with score 1 or more standard deviations below mean

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2

Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Selection criteria controls: **exposed/"unaffected"** mother/child pairs
  - Met criteria for moderate to heavy alcohol exposure around the time of conception with or without continued use at time of enrollment
  - Met criteria for having no facial features or growth deficiencies
  - Met criteria for at least on neurobehavioral evaluation but no scores 1 SD below the mean or greater

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- 268 samples associated with the selected cases and controls were sequenced
- 133 mothers and 135 children (two sets of twins)
- Sequencing data in dbGaP and associated clinical data uploaded April, 2023
- Preliminary analyses of a priori targets conducted by Katie Fisch Center for Computational Biology at UCSD

CCBB | CENTER FOR COMPUTATIONAL BIOLOGY & BIOINFORMATICS

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4

Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Targeted regions 10KB up and downstream
  - SLC44A1 (choline transporter) (Smith)
  - ANKRD9, DUSP2, DUSP4, SLC25A33, SPRY4, EDN1 (Weeks/Burns)
  - MTHFR
- Comparison of FASD vs Unaffected in total cohort
- FASD vs Unaffected in 1)vitamin-supplemented with choline or 2) with vitamin supplemented with or without choline

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Originally ~12,000 sites in SLC44A1 region (with no filtering).
- Following application of filters for minor allele frequency (exclude variants with MAF <0.05 in study population) and genotyping rate (exclude variants with genotyping rate rate <25% in study population), 56 variants remain. Note that most of the original sites are not common variants, and thus would not be expected to remain following these filters
- Note also that the total genotyping rate was quite low (~40%), adding to power issues

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- For SLC44A1
- Mothers: N = 132
- Affected child: N = 60
- Unaffected child: N = 70
- Vitamin supplementation:
  - None: N = 78
  - Vitamin/Mineral only: N =24
  - Vitamin/Mineral plus choline: N = 30
- Comparing affected vs. unaffected: 5 significant variants in mothers; 8 in children; numbers too small for strata by vitamin
- Susan to explore other avenues

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Mother of affected child: N = 59
- Mother of unaffected child: N = 70
- Significant SNPs at nominal p-value:
  - SLC25A33: 10
  - DUSP1: 1
  - DUSP4: 6
  - SPRY4: 3
  - EDN1: 11
  - ANKRD9: 2
  - MTHFR: 31

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- Affected child: N = 60
- Unaffected child: N = 74
- Significant SNPs at nominal p value:
  - SLC25A33: 10
  - EDN1: 5
  - DUSP2: 1
  - DUSP4: 2
  - SPRY4: 9
  - ANKRD9: 1
  - MTHFR: 2

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Whole Body Effects of PAE Across the Life Span: Early Markers of & Clinical Interventions for Children and Adolescents in Ukraine: WGS Gabriella Miller XO

- SLC25A33: main role to transport pyrimidine nucleotides to/from mitochondria
- May be induced by insulin-like growth factor I/mTOR signaling pathway to promote cell growth
- Knockouts cause mtDNA depletion, reduced oxidative phosphorylation, cell size and mitochondrial UTP levels, overall increased RPS levels
- PAE may impact mTOR signaling, and exacerbate effects of downstream variant

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2023 CIFASD pre-RSA updates – Chambers U01

Rajesh Miranda/Amanda Mahnke

Ukraine child miRNA analysis

20230621

6/24/23

1

Child samples – ran all samples and beginning analysis

- Plasma samples, 2-5yo

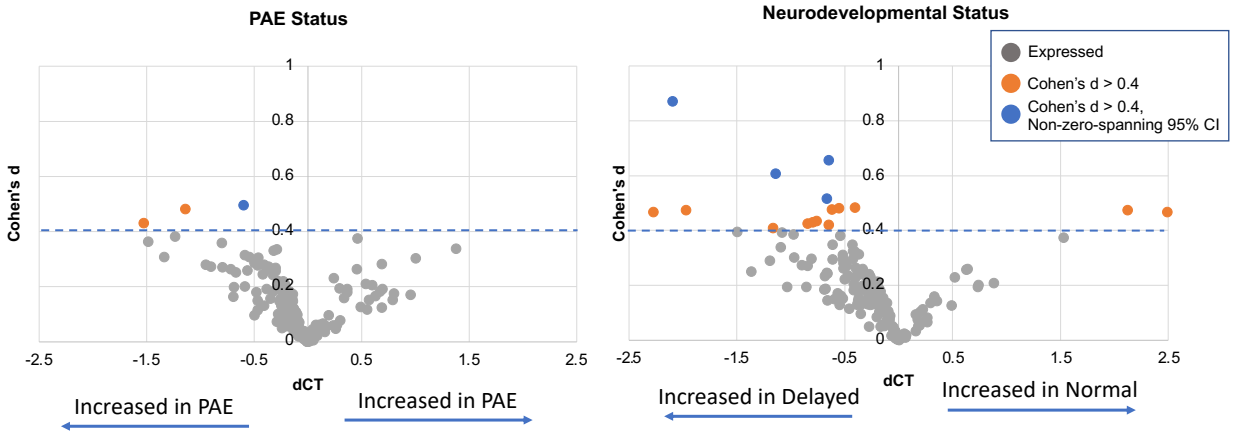
N=68	Neurodevelopment		
	Normal	Delayed	Unknown
no/low PAE	15	15	1
PAE	11	26	

162 miRNAs
Detected in >80% of samples

6/24/23

2

Childhood plasma miRNAs more reflective of neurodevelopmental status than PAE



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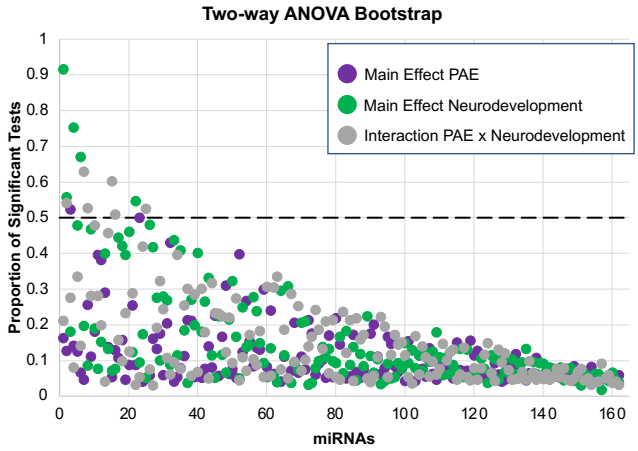
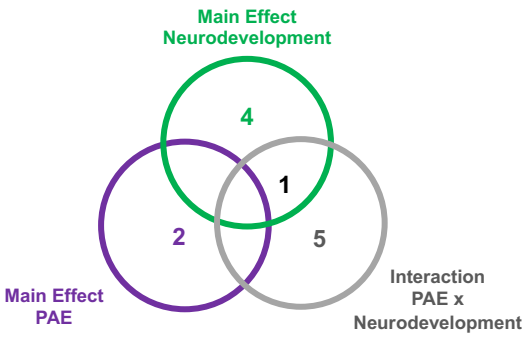
3

Two-way ANOVA bootstrap analysis identifies miRNAs that may differentiate PAE-neurodevelopmental delay





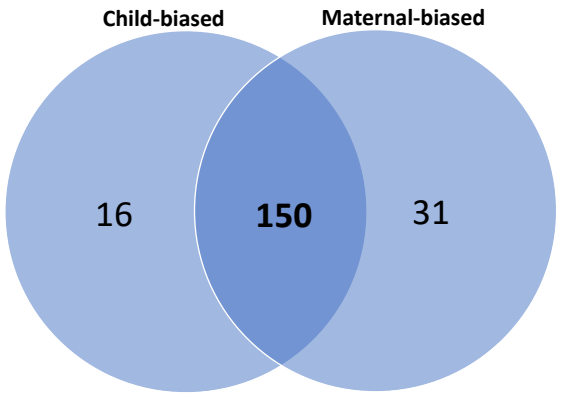
6/24/23

More in Gretchen Bandoli's Sunday Morning Seminar -
MACHINE LEARNING APPROACHES IN THE IDENTIFICATION OF INDIVIDUALS WITH FETAL ALCOHOL SPECTRUM DISORDERS

4

Beginning analysis of maternal/child dyads

N=31	Neurodevelopment		
	Normal	Delayed	Unknown
no/low PAE	6	8	1
PAE	5	11	



6/24/23

5

A Multisite Study of Prenatal Alcohol Exposure: Effects of Inflammation and Endocrine Dysfunction in Adulthood
NIH/NIAAA #: U01AA026108

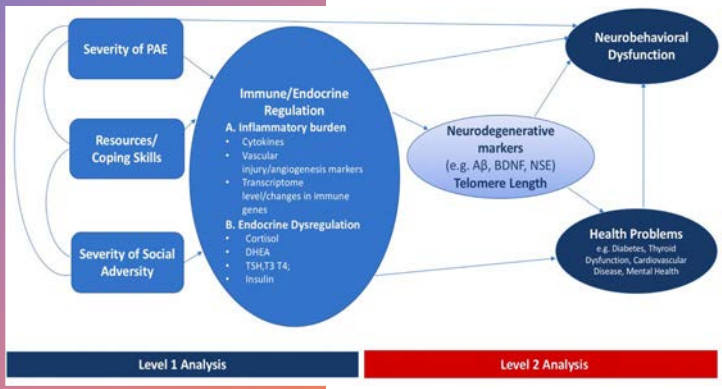
Claire D. Coles, PhD
Joanne Weinberg, PhD
and
Susan Stoner, PhD
Tamara Bodnar, PhD
University of Calgary, Alberta
Charlis Raineki, PhD
Brock University, Ontario

Sites

- ❑ Emory University School of Medicine
Atlanta, GA
- University of British Columbia
Vancouver, BC
- University of Washington
Seattle, Washington

1

Specific Aims:



- In Middle-Aged Adults with PAE, in comparison to SES and age-matched Controls and older healthy control contrast groups, evaluate the following:
  - *The role of immune and endocrine dysregulation in physical and mental health within the individual's social context (examining both negative and positive influences).*
  - *The impact of PAE as well as immune and endocrine status on neurocognitive performance and markers of early on-set functional deficits within the social context.*

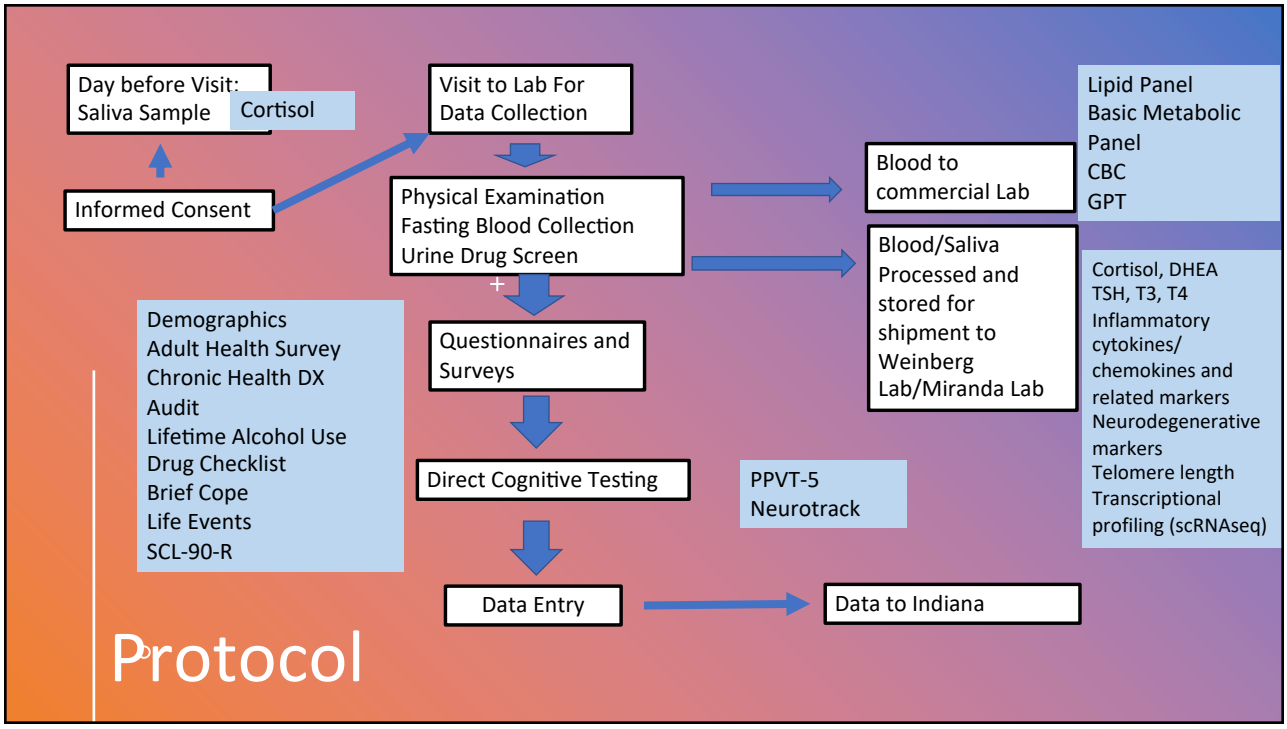
2

Progress Year I:

- IRB
  - *sIRB obtained for US site. Renewal will be is September 2023.*
  - *Approval from Canadian Clinical Ethics Review Board (CREB) approved March 2023.*
- Developed Multisite Team Organization and Activities
  - *Allowing smooth coordination of activities among sites and investigators.*
  - Semi-monthly Multisite meetings are on-going.
  - *Coordinating with Dr. Miranda at Texas A & M re data processing and sharing samples*
- Began Subject Recruitment and Data Collection

3

Protocol



4

- Identified Participant pools to facilitate recruitment. *Recruitment & Data Collection began June 2023*.
  - Atlanta. 121 Younger individuals identified from Longitudinal Cohort from which 90 will be recruited. 30 Older adults to be recruited from EUSM Department of Neurology's Health Aging Cohort and Emory Community.
  - To date, 7 individuals have been tested.

5

- The Seattle site will recruit 90 individuals (30 with FAS, 30 with FASD not meeting criteria for FAS, and 30 age- and sex-matched controls) from a pool of 123 individuals who participated in our CIFASD4 study. Additionally, 30 healthy older adults will be recruited from the community to serve as a second control group.
- To date, 3 individuals with FASD have been recruited, of whom 2 are in the process of completing the protocol.

6

- The Canadian site will recruit 60 adults with a confirmed FASD diagnosis (FAS, pFAS, ARND, ARBD etc.,) and 30 age- and sex-matched controls. Individuals will be recruited from the community in Vancouver, Calgary and Ontario. In addition, 30 older healthy adults (65+) will also be recruited through collaborators across Canada.
- To date 34 individuals with FASD and 21 unexposed controls have been approached and expressed interest in the study, with testing to begin over the summer.

7

- Data collection, storage, and sharing.
  - *Collaborating with Indiana Data Repository to create instruments consistent with their requirements and those of NIMH Data Archives.*
  - *Developed and refined multiple data collection and storage instruments in REDCap and Qualtrics.*
  - *Data dictionaries completed and shared with Indiana*

8

Publications, Presentations, and Abstracts:

Publications:

1. Bodnar, T.S., Chao, A, Holman, P.H., Ellis, L., Raineki, C. and Weinberg, J. Impact of the COVID-19 pandemic on adults with Fetal Alcohol Spectrum Disorder (FASD): Linking immune function to mental health status (*accepted*).
2. Coles, CD, Grant, TM, Kable, JA, Stoner, SA, Perez, A, and the CIFASD (2022) Prenatal Alcohol Exposure and Mental Health at Midlife: A Preliminary Report on Two Longitudinal Cohorts. Alcoholism: Clinical and Experimental Research. 46 (2) 232-242 PMID: 35157325
3. Kable, JA, Mehta, PK, Rashid, F, & **Coles, CD** (2022) Path analysis of the impact of prenatal alcohol on adult vascular function. Alcoholism: Clinical and Experimental Research, Online, November, 2022.
4. Lussier AA, Weinberg J (*in press*). Ethical considerations for biomarkers of fetal alcohol spectrum disorder and other neurodevelopmental disorders. In: Illes J & Gibbard B. (Eds). Neuroethics and Neurodevelopment, Vol 6 in Book Series: Developments in Neuroethics and Bioethics.
5. Raineki C, Bodnar T, Wertelecki W, Yevtushok L, Plotka L, Granovska I, Zymak-Zakutnya N, Pashtepa A, Wells A, Honerkamp-Smith G, Coles CD, Kable JA, Chambers CD, Weinberg J, and the CIFASD (*in preparation*). Differential associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay.
6. Shapiro, ZR, Kable, JA, Grant, T, Stoner, S, Perez, A, **Coles, CD**, and the CIFASD. (2023) Prenatal alcohol exposure and cognition at midlife: Evidence of Fluid Cognitive deficits in two cohorts. Alcohol: Clinical and Experimental Research, In revision.

Presentations:

1. Bodnar, T. Exploring the impact of prenatal alcohol exposure on health outcomes: Insights from a translational approach. University of Victoria Neuroscience Seminar, Victoria, BC, Canada, June 20, 2023.
2. Bodnar, T. A translational approach to exploring the impact of prenatal alcohol exposure on health: From pre-clinical models to Indigenous community partnerships. University of British Columbia Psychology Colloquium, Vancouver, BC, Canada, March 9, 2023.
3. Coles, C.D., Grant, T., Stoner, S., Perez, A . Adults with prenatal alcohol exposure underestimate COVID-19 risk, NIH/NIAAA Virtual Forum on COVID-19 Research, January 26, 2023 (Virtual)
4. Raineki, C. Unraveling the effects of prenatal alcohol exposure through translational approaches: Connecting immune system dysregulation and neurodevelopmental health. Department of Physiology, Federal University of Rio Grande do Sul, Brazil, June 2, 2023.
5. Raineki, C. Translational approach for understanding the developmental origins of health and disease: Effects of prenatal alcohol exposure. Lifespan Development Research Institute, Brock University, St. Catharines, ON, Canada, May 9, 2023.
6. Weinberg, J. Prenatal alcohol exposure, fetal programming and inflammation: Unmasking developmental origins of adult disease. In: Alcohol and neuro-inflammation. Gordon Research Conference, Alcohol-Induced End Organ Diseases: Multisystemic Pathophysiological Mechanism. Ventura, USA, March 26-31, 2023.
7. Raineki C. Using a translational approach to evaluate the links between immune system dysregulation and health problems in FASD: A possible role of the gut microbiota. 6th Annual FASD Eastern Ontario Symposium - ABLE2, January 24, 2023 (virtual).
8. Raineki C. Links between immune system dysregulation and health problems following prenatal alcohol exposure: A translational approach. 3rd Annual London and Region FASD Conference, October 26, 2022 (virtual).
9. Weinberg J. Fetal alcohol spectrum disorder: Can we develop biomarkers of risk based on altered neuroimmune function. 36th Annual Winter Conference in Developmental Psychobiology, Punta Cana, Dominican Republic, January 4-7, 2023.
10. Raineki, C., Bodnar, T.S., Loock, C., Oberlander, T., Coles, C., Grant, T., & Weinberg, J. Long-lasting changes in immune function following prenatal alcohol exposure: A multi-site study. European FASD Alliance (EUFASD) 2022, Arendal, Norway, Spetember 12 – 14, 2022.
11. Weinberg J. Immune dysregulation in FASD: From animal models to the clinic. In: Alcohol and Immunology Research Interest Group (AIRIG) (pre-meeting Special Interest Group - SIG) Satellite at the 55th annual Society for Leukocyte Biology. Big Island, USA, October 26-29, 2022.

Abstracts:

1. Bodnar, T.S., Raineki, C., Bandoli, G., Chambers, C.D., & Weinberg, J. Associations between prenatal depression and the maternal cytokine profile: Possible link to child development. Organization for the Study of Sex Differences (OSSD) 2023, Calgary, AB, May 7 – 11, 2023.
2. Raineki, C., Bodnar, T.S., Loock, C., Oberlander, T., Coles, C., Grant, T., & Weinberg, J. Immune dysregulation in adults exposed to alcohol during gestation: A multi-site study. Developmental Origins of Health and Disease (DOHaD) World Congress 2022, Vancouver, BC, August 27 – 31, 2022.

9

Major Goals for Year 2

- Data collection (increased to compensate for delays in Year 1)
- Analysis of CIFASD4 Data
- Presentations and Publications

10

Interaction with other CIFASD5 Investigators

Interaction with other CIFASD5 Investigators

- Rajesh Miranda, PhD, Texas A & M ,is a collaborator and will be analyzing scRNAseq from Canadian samples.
- Michael Suttie, PhD, University of Oxford, will be receiving 3-D images of Adults for data analysis.
- Leah Wetherill, PhD, Indiana University, is collaborating for data sharing.
- Miguel Del Campo, MD, UCSD, will provide oversight of dysmorphology exams.
- Amanda Mahnke, PhD, will receive peripheral blood cells for generation into human induced pluripotent stem cells (UH2 project).

11

DiClemente June 2023

BRIEF STATUS REPORT

DESIGNING A HYBRID INTERVENTION STRATEGY TO REDUCE ALCOHOL EXPOSED PREGNANCIES

SITES ARE RECRUITED (AWAITING NOA FOR UT SUPPLEMENT), IDENTIFYING KEY STAFF TO FACILITATE HIRING AS SOON AS FUNDS BECOME AVAILABLE


UTHealth

NO RECRUITMENT PENDING FUNDING OF THE UT SUPPLEMENT

ACCOMPLISHMENTS

- IRB HAS BEEN CEDED BY NYU TO UT AND APPROVED
- THE TEAM CONTINUES TO MEET VIA ZOOM TO DISCUSS PROTOCOLS AND MEASURES
- WE HAVE INTERACTED WITH COLLEAGUES TO STANDARDIZE THE COLLECTION, STORAGE, AND SHIPPING OF SPECIMENS
- WE HAVE HAD MEETINGS WITH OUR FORENSICS LABORATORY TO REVIEW PETH COLLECTION, STORAGE, SHIPPING, AND ANALYSIS PLANS
- (PLANNED) WE WILL PROPOSE PUBLISHING A MANUSCRIPT IN *J CLIN TRIALS THAT* PROVIDES THE CONTEXT AND OVERVIEW OF THE STUDY RCT
- *(PLANNED)* WE WILL PROPOSE A TEAM MEETING IN HOUSTON AS SOON AS FEASIBLE TO PROVIDE STAFF WITH AN OVERVIEW OF THE STUDY AND DEFINE THEIR STUDY-RELATED RESEARCH ACTIVITIES AND RESPONSIBILITIES
- *(IN PROCESS)* CHANGING THE CONSENT FORM TO INCLUDE GUID LANGUAGE

MAJOR GOALS FOR THIS PROJECT PERIOD INITIATE PROPOSED PROJECT ACTIVITIES NOT STARTED IN YEAR 01

U01: Assessment of Fetal Alcohol Spectrum Disorders (FASD) Using Novel Web-Based Tools

Sarah Mattson, Ph.D.
San Diego State University

1

Overall Aim of Project

- ★ **To improve the detection of fetal alcohol spectrum disorders (FASD).**
  - To achieve this aim, we will deploy web-based tools which aid in the screening and evaluation of FASD.
    - FASD-Tree
    - Brief Assessment of Individual Neurobehavior – online version (BRAIN-online).

2

Progress Toward Goals: C5 Data Collection

Year	Referrals	Enrolled	FASD-Tree	BRAIN-online	Morpheus Q	3D Photos	NP Testing
Pre Year 1 (6/1/22-8/11/22)	26	11	11	37	6	11	
Year 1 (8/12/22-4/30/23)	54	26	26	16	7	18	26
Year 2 (5/1/23-4/30/24)	5	15	13	12	6	7	9
Year 3 (5/1/24-4/30/25)							
Year 4 (5/1/25-4/30/26)							
Year 2 (5/1/26-4/30/27)							
Total	**85**	**52**	**50**	**65**	**19**	**36**	**35**

3

Accomplishments: BRAIN-online

- ★ Continuing to collect data with BRAIN-online in San Diego
  - 65 subjects tested locally during C5
- ★ Public study: Recruiting participants through targeted distribution
  - Indiana Alliance (Indiana Affiliate of FASD United)
  - Alaska Department of Public Health
  - Repost on FASD Collaborative Facebook Page
  - Public presentations (Riley/ECHO)
  - CIFASD investigators
- ★ Linked participation for CIFASD investigators
  - We are currently assisting Dr. Wozniak with collection of BRAIN-online for the participants in his U01 project
- ★ Developed a feedback report for use with BRAIN-online

4

BRAIN-online Participants by Source

BRAIN-online Source	N
CBT Participants (C4/C5)	138
Minnesota (C4)	13
DIG Study (C4)	43 (+71 with unk group)
iCAN Study (C4)	906
Public Study	25 (10 Adults/15 Children)

- ★ Age: 90% between 5-19 years
  - M = 12 years
  - Range 5-65 years
- ★ Sex: 49% Female
- ★ Race: 32% Non-White
- ★ Ethnicity: 29% Hispanic/Latino
- ★ Exposure: 68% with PAE

- ★ Age: 18-25 years; M = 20 years
- ★ Sex: 72% Female
- ★ Race: 48% Non-White
- ★ Ethnicity: 33% Hispanic/Latino

5

Accomplishments: BRAIN-online Data Pipeline

- ★ Data collected through 1 of 4 BRAIN-online portals
- ★ Data downloaded from Gorilla
- ★ Data are processed using **processing tool** (almost done) and imported to two places
  - FASD-Tree for storage and later download
  - Spreadsheet for manual calculation of z-scores for feedback reports and data analysis
- ★ Data downloaded from FASD-Tree (with FASD-Tree data) and uploaded to Central Repository (**download tool** under development)
- ★ Feedback report provided to participant if requested

With assistance from the Administrative Resource

6

Demographics (CIFASD)

N	197		
Age in Years (M)	10.86	**Race**	
Handedness		American Indian/Alaska Native	9
Right	165	Asian	8
Left	28	Black or African American	21
Mixed	4	More than One Race	29
Sex at Birth		Native Hawaiian or Other Pacific Islander	1
Male	105	Unknown/Not Reported	1
Female	92	White	127
Gender Identity		**Ethnicity**	
Male	104	Hispanic or Latino	56
Female	91	Not Hispanic or Latino	132
Does not identify with any of the options	1	Unknown/Not Reported	9
Prenatal Alcohol Exposure		**Device**	
Yes	99	Desktop	42
Suspected but Unknown	41	Laptop	146
No Information	6	Tablet with attached keyboard	9
No	39		

7

Behavior Screen

Below is a list of items that describe children and youth. For each item select the answer that best describes your child NOW OR WITHIN THE PAST 6 MONTHS. Answer all items as well as you can, even if some do not seem to apply to your child.

Acts too young
Yes
No

Clingy or dependent
Yes
No

Very talkative
Yes

Inhibiting

In this task, you will see a series of arrows that appear in a grid. When you see arrows that are facing the right (→), tap the spacebar. If you see an arrow facing the left (←), do not respond.

Stepping Stones

In this task you will see 10 blocks on the screen. These blocks will light up in a certain sequence. When you see "GO" click the blocks in the same order you saw them light up. You will only see them once, so pay attention.

Tapping

You will be asked to place your wrist on the surface and tap the spacebar as quickly as you can with your index finger for 10 seconds. Do not move your hand or arm, only your finger. Begin Tapping when you see "GO."

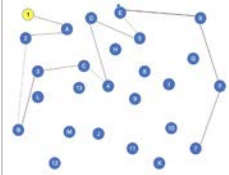
Let's try a practice trial for the right hand first!

Remembering

You are about to see some playing cards in a grid. Try to remember where each card is located.

Connecting

On the next screen, you will see numbers and letters in circles. Your job is to **click on the numbers as quickly as you can in order** (1,2,3, and so on) until you get to the end. Only connect the circles with numbers.



Reacting

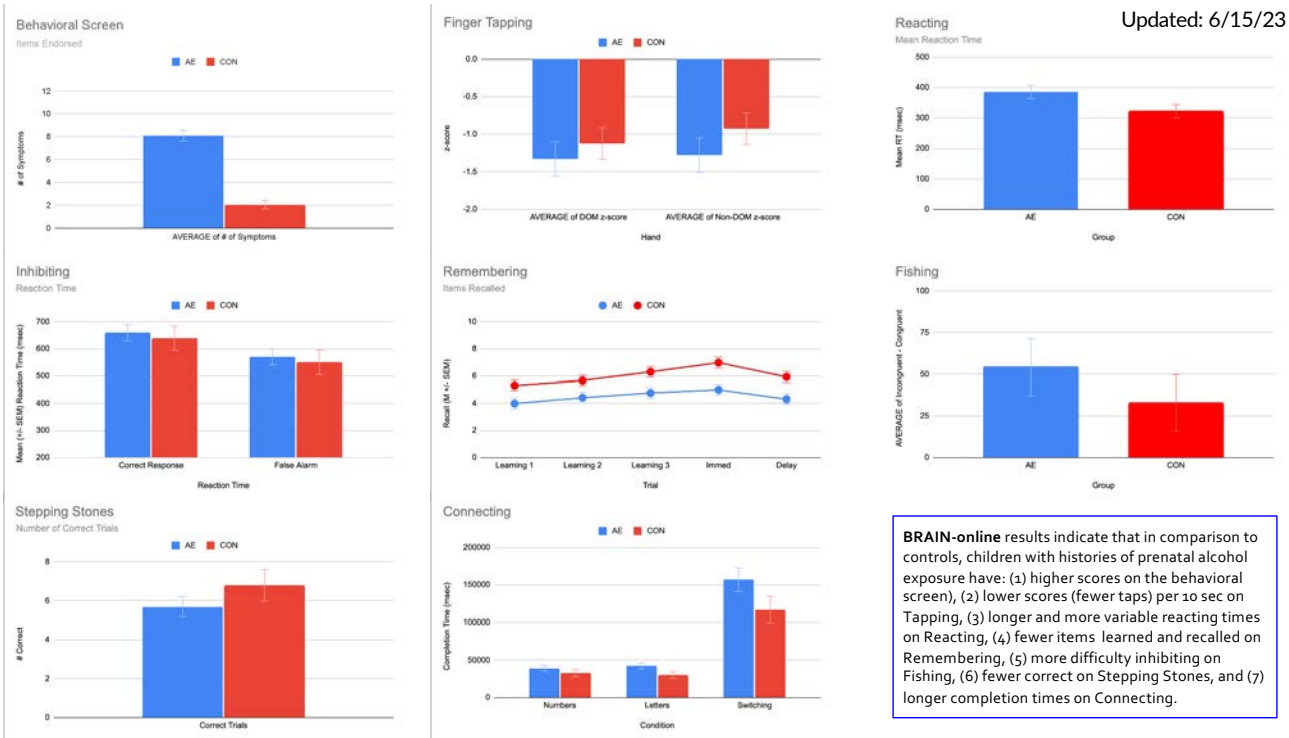
In this task, you will see a star (★) appear on the screen. Whenever you see the star (★), tap the spacebar as quickly as possible using your dominant hand.

Fishing

In this task you will see a line of fish swimming with each other. Only pay attention to the middle fish. If the fish is swimming to the left (🐠), tap the left shift key. If the Fish is swimming to the right (🐠), tap the right shift key.

BRAIN-online consists of a 14-item behavioral screen and 7 subtests that measure fine-motor speed, reaction time, response inhibition/impulsivity, attention, problem-solving, processing speed, memory, spatial working memory, and set-shifting and requires 30-45 minutes to complete. It is completed online independently by each subject and reaction time and accuracy measures are available.

8



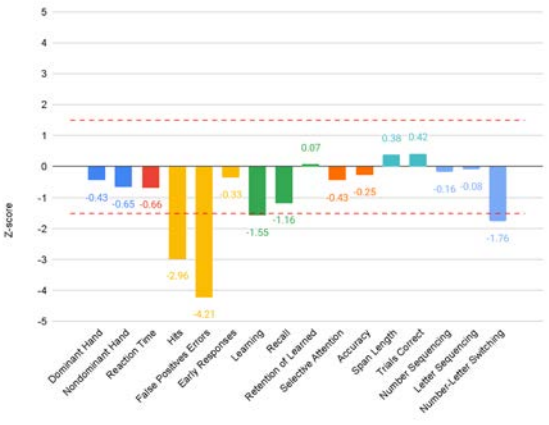
BRAIN-online results indicate that in comparison to controls, children with histories of prenatal alcohol exposure have: (1) higher scores on the behavioral screen), (2) lower scores (fewer taps) per 10 sec on Tapping, (3) longer and more variable reacting times on Reacting, (4) fewer items learned and recalled on Remembering, (5) more difficulty inhibiting on Fishing, (6) fewer correct on Stepping Stones, and (7) longer completion times on Connecting.

9

BRAIN-online Sample Feedback

Assessment Domain	Score	Range
Behavioral Survey Items Endorsed	7	
Reported Prenatal Alcohol Exposure	Unknown	
Tapping	**Assessment of motor skill**	
Dominant Hand	-1.04	Average
Nondominant Hand	-0.25	Average
Reacting	**Assessment of reaction time**	
Reaction Time	-1.68	Below Average
Inhibiting	**Assessment of behavioral inhibition**	
Hits	-1.24	Average
False Positive Errors	-0.56	Average
Early Responses	-0.33	Average
Remembering	**Assessment of learning and memory**	
Learning	-1.38	Average
Recall	-1.17	Average
Retention of Learned Information	0.08	Average
Fishing	**Assessment of attention**	
Selective Attention	-5.00	Below Average
Accuracy	-1.10	Average
Stepping Stones	**Assessment of working memory**	
Span Length	-1.33	Average
Trials Correct	-1.33	Average
Connecting	**Assessment of processing speed**	
Number Sequencing	-1.93	Below Average
Letter Sequencing	-3.33	Below Average
Number-Letter Switching	-2.86	Below Average

The scores in the graph and table are z-scores which tell you how your scores compare to the average score of people who have already taken the test. The dashed red line shows the average range, which is from -1.5 to +1.5.



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C5 Accomplishments: FASD-Tree

- ★ Working on adding improvements to FASD-Tree including:
  - Adding the full dysmorphology form (on hold)
  - Allowing storage and download of BRAIN-online and MQ data with FASD-Tree data (ongoing)
  - Adding/Fixing percentiles (ongoing)
  - Correcting field names (complete)
  - Adding checkbox for consent (complete)
  - Allowing repeat testing (ongoing)
  - Allowing for repeated participation (ongoing)
- ★ Completed the ARND algorithm and feedback mechanism. Hoping to incorporate this algorithm into FASD-Tree

11

C5 Accomplishments: Other Aims

- ★ Facial Imaging
  - MorpheusQ: 19 Subjects [Riley/del Campo]
  - 3D Images (Canfield): 36 Subjects [Suttie]
  - Monthly meetings
- ★ Dysmorphology: Two training meetings with Dr. del Campo to train for dysmorphology evaluations. A third meeting is planned
- ★ Alaska: traveled to Alaska with Miguel del Campo, attended research ethics meetings, made connections (May 2023)
- ★ Canada: Two planning meetings in 2022, presented to Canadian clinics (June 2023)

12

Publications

5 total since February

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE | Open Access

Validation of the FASD-Tree as a screening tool for fetal alcohol spectrum disorders

Sarah N. Mattson, Kenneth Lyons Jones, Ganz Chockalingam, Jeffrey R. Wozniak, Matthew T. Hyland, Natasia S. Courchesne-Krak, Miguel Del Campo, Edward P. Riley, the CIFASD

First published: 20 February 2023 | https://doi.org/10.1111/acer.14987 | Citations: 2

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

RESEARCH ARTICLE

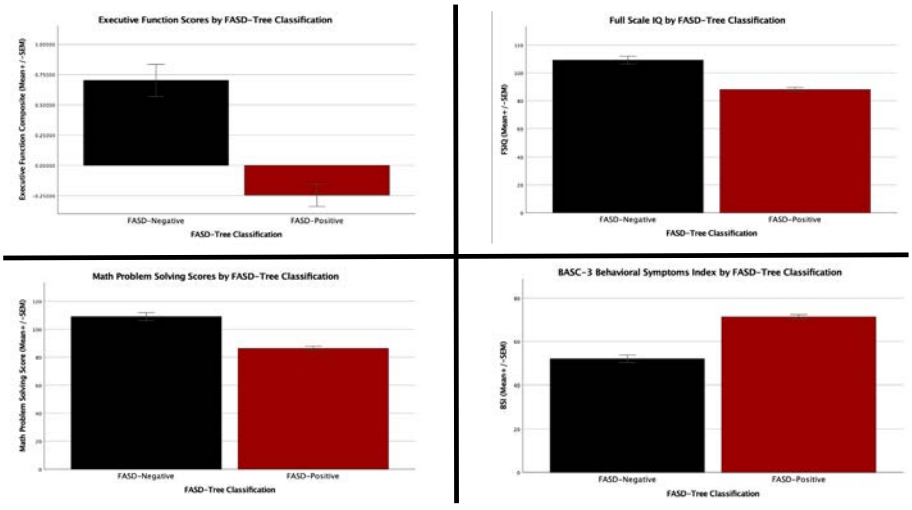
Results of an FASD screening tool are associated with neuropsychological and behavioral measures

Matthew T. Hyland, Natasia S. Courchesne-Krak, Gemma A. Bernes, Jeffrey R. Wozniak, Kenneth L. Jones, Miguel Campo, Edward P. Riley, Sarah N. Mattson, the CIFASD

First published: 16 June 2023 | https://doi.org/10.1111/acer.15133

13

FASD-Tree Outcome Relates to Neurobehavior



Hyland et al., 2023, ACER, in press.

14

Papers in Progress

- ★ BRAIN-online
  Mattson, S.N., Hyland, M.T., Chockalingam, G., et al., BRAIN-online: An online test of cognition in FASD
- ★ Other CIFASD
  Veziris, C. R., Hyland, M.T., Kable, J.A,. Wozniak, J.R., Coles, C.D.,May, P.A., Kalberg, W.O., Sowell, E.R., Riley, E.P., Mattson, S.N., & the CIFASD. Validation of the ND-PAE diagnosis in children with heavy prenatal alcohol exposure.
- ★ Other
  Felicicchia, R.J., Hyland, M.T.,Roesch, S.C. & Mattson, S.N. Differences in the family environment in children with and without prenatal alcohol exposure.

15

Other Accomplishments

- ★ Diversity supplement: Celeste Estrada (5/17/23-4/30/25)
- ★ Translation of BRAIN-online into Spanish
  - College students (primary Spanish vs. English speakers)
  - Children/clinic referrals

16

Distributed BRAIN-online Flyer to CIFASD Investigators

- ★ **OPTION 1:** Distribute flyer to your networks
  - ★ Anonymous participation through Public Study
  - ★ Feedback available if requested
- ★ **OPTION 2:** Link BRAIN-online to your study using study identification number
  - ★ Data collected without identifiers other than your study ID so you can link to your study data
  - ★ Normed data available to study

17

Plans for Y2 (Aspirational)

- ★ Continue data collection
- ★ Expand Public Project to include additional FASD United affiliates
- ★ Initiate data collection/feedback in Canada (in collaboration with Dr. Cook)
- ★ Continue to assist Dr. Del Campo in setting up the Alaska site
- ★ Support CIFASD Investigators who want to use BRAIN-online
- ★ Finalize updates on FASD-Tree
- ★ Increase recruitment of controls
- ★ Integration of FASD-Tree and BRAIN-online
- ★ Methods paper on BRAIN-online (with data)
  - BRAIN-online vs. In-Person Neuropsychological Assessment

18


Leveraging Technology to Increase Quality of Life for FASD Across the Lifespan
Christie L. M. Petrenko, Ph.D. & Cristiano Tapparello, Ph.D.
Mt. HOPE family center
1850 MELIORA
UNIVERSITY of ROCHESTER

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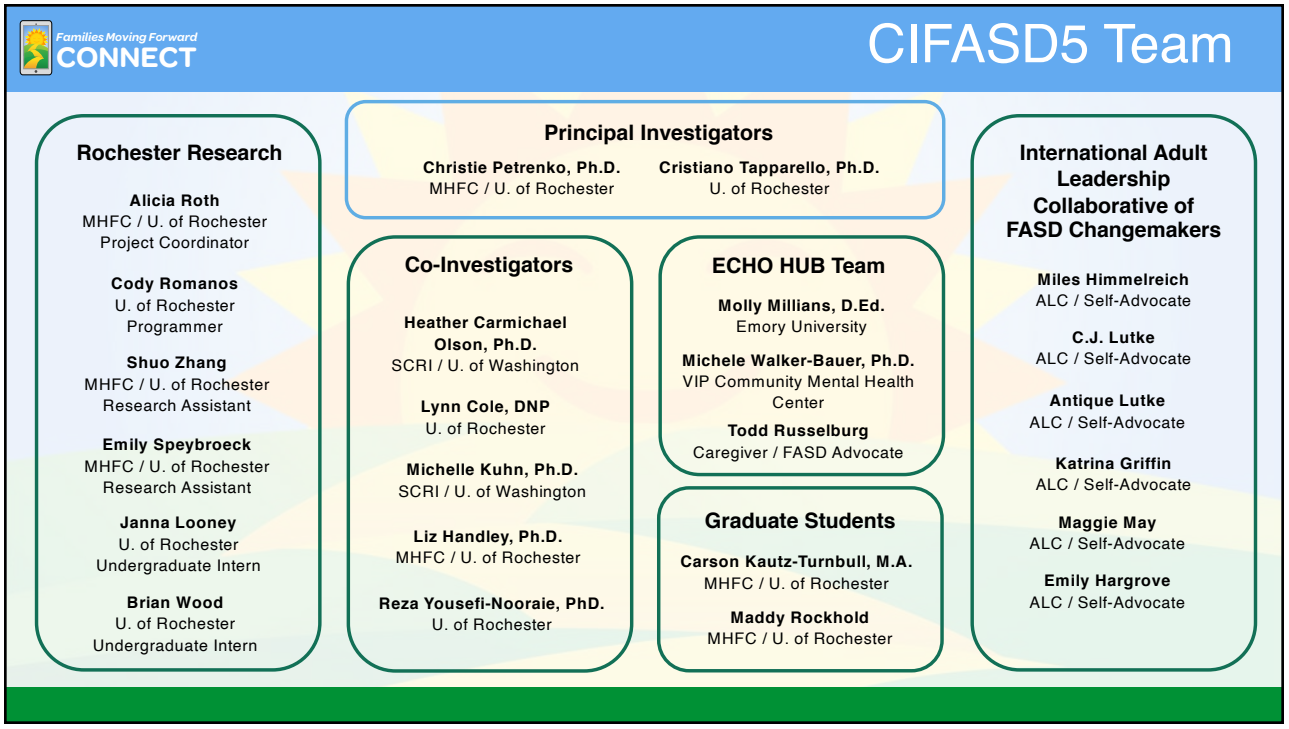
Families Moving Forward CONNECT
CIFASD5 Team
Rochester Research
Alicia Roth
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Programmer
Shuo Zhang
MHFC / U. of Rochester
Research Assistant
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Undergraduate Intern
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VIP Community Mental Health Center
Todd Russelburg
Caregiver / FASD Advocate
Graduate Students
Carson Kautz-Turnbull, M.A.
MHFC / U. of Rochester
Maddy Rockhold
MHFC / U. of Rochester
International Adult Leadership Collaborative of FASD Changemakers
Miles Himmelreich
ALC / Self-Advocate
C.J. Lutke
ALC / Self-Advocate
Antique Lutke
ALC / Self-Advocate
Katrina Griffin
ALC / Self-Advocate
Maggie May
ALC / Self-Advocate
Emily Hargrove
ALC / Self-Advocate

2

Families Moving Forward CONNECT

CIFASD5 Aims

- **Aim 1**: Provider-Assisted FMF Connect (Mental Health Providers - Child)
  - *Formative:* use focus groups and implementation mapping to design "FMF Connect Pro" and implementation packages (Year 1)
  - 3-parallel arm RCT with 250 mental health providers (Years 2-5)
- **Aim 2**: My Health Coach app (Adults with FASD) – from UH2
  - 2-parallel arm RCT with 120 adults with FASD (Years 2-3)
- **Aim 3**: Determined App system (Teens with FASD and Caregivers)
  - Use focus groups and advisory board input to design Determined app system (Years 3-4)
  - Usability testing with 10 teens and caregivers (Year 5)

3

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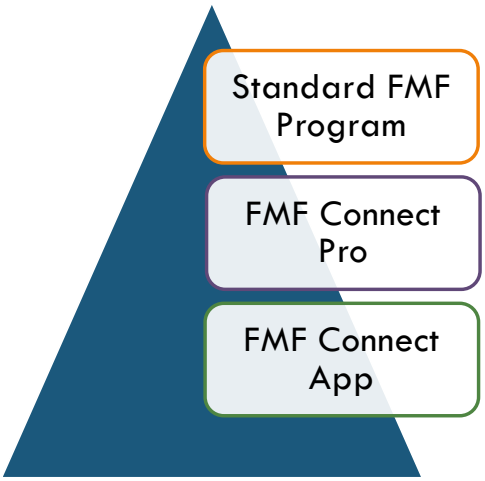
CHILDHOOD: BUILDING A CONTINUUM OF CARE



Families Moving Forward Program

1:1 Program with therapist
In home, clinic, or telehealth
7-9 months
Therapists – 40+ hrs training

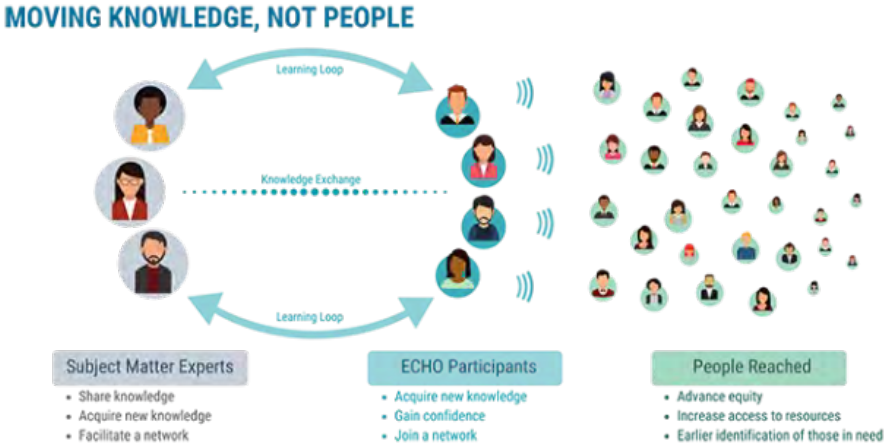
THIS PROJECT ☺

Families Moving Forward CONNECT

Self-directed app to be used by caregivers

4

PROJECT ECHO©
(EXTENSION OF COMMUNITY HEALTHCARE OUTCOMES)



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Families Moving Forward CONNECT

FMF Connect Pro Development

- Developed didactic training content and implemented in Canva for all sessions *(90% complete)*
  - Hub team provided feedback
- Provider Dashboard functionalities and design mocked up
- FMF Connect parent app transitioning to Flutter
- ECHO Hub Team members completed 2.5 day UNM training

13 Didactic Sessions
- Intro to Program and FASD
- Screening for FASD and stigma
- Applying DSM-5 ND-PAE
- Understanding strengths/differences
- Reframing
- Accommodations
- Self-regulation and adapting child interventions
- Caregiver needs and supports
- Trauma-responsive care
- Brainstorming – Parts 1 & 2
- Supporting success in school
- Looking Forward

6

6

Mental Health Provider Focus Groups

- 2 rounds of focus groups
  - 1st round (fall 2022) to determine acceptability, inform design
  - 2nd round (summer 2023) refine materials and implementation plan
- Four 1st round groups completed (n=28)
  - Recently discovered 18-19 were likely fraudulent ☹

7

7

Mental Health Provider Focus Groups

- 2 round of focus groups scheduled mid-July
  - Better protections in place to reduce impact of fraud (34 identified fraudulent)
  - Currently 54 eligible participants, actively recruiting

8

8

RCT Infrastructure Updates

- IRB materials in progress
  - Will review with CIFASD5 Coordinating Resource
- ClinicalTrials.gov registration in progress
- Initiated application for accreditation for CEU for social work and psychology
- REDCap database development

9

9

RCT Launch Timeline

- Aiming for October-ish (but prepared in case delays in one or more of infrastructure components)
  - Planning 7 cohorts over 3.5 years
  - Intervention for each cohort – 6 months
  - 3 evaluation timepoints: baseline, 6-months, 12-months
- My Health Coach (UH2) transitioning to U01 for refinement and RCT

10

10

Families Moving Forward CONNECT

Interactions

- CIFASD5 PIs sent out recruitment materials for our focus groups
- Used Morpheus Q in clinic prior to update/shared data, preparing to re-launch
- Sharing Sarah's BRAIN-online with clinic participants
- Collaborating with Annika/Tina to develop new grant application to evaluate potential for Native adaptation of FMF Connect

11

11

12

NIH National Institute on Alcohol Abuse and Alcoholism
NIH...Turning Discovery Into Health®

UNIVERSITY OF OXFORD

Defining Translational Approaches for the Image-Based Detection of Prenatal Alcohol Exposure

Michael Suttie

1

Nuffield Department of Women's and Reproductive Health, University of Oxford

UNIVERSITY OF OXFORD

Aim 1 **Identifying factors secondary to alcohol that may influence outcomes**.

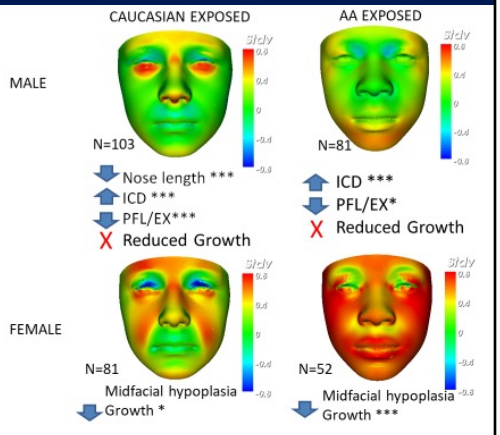
- Primary investigating sexual dimorphism and co-exposures on facial dysmorphism

Aim 2. **Investigating facial dysmorphism using 3D imaging**

- Age-specific FASD associated facial dysmorphism
  - **Neonates** to **adults**
- Assessing impact of intervention during pregnancy designed to reduced consumption

Aim 3 **Clinical Translation**

- Develop fully **automated** 3D facial analysis using machine learning suitable fc clinical deployment.
- Develop novel **multi-modal** deep learning architecture combining **face and neurocognitive assessment**
- eHealth App-Based Integration: Providing facial analysis access to apps to facilitate both clinical and research goals
- **Software distribution**. We will generate general-purpose face analysis software for facial analyses and clinical deployment



FaceScreen

2

Nuffield Department of Women's and Reproductive Health, University of Oxford

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Facial Dysmorphia Associated with Concurrent Prenatal Alcohol and Smoke Exposure

Exposures

None – no exposure

Continuous – any T1 + any thereafter

Low – T1 only **or** some exposure throughout the pregnancy (not meeting criteria for continuous)

Single exposures
Continuous Alcohol (n=42)
Continuous smoke (n=163)
Dual exposures
Continuous Smoke & Alc (n=183)
Continuous Smoke, Low Alcohol (n=170)
Controls (n=152)

3

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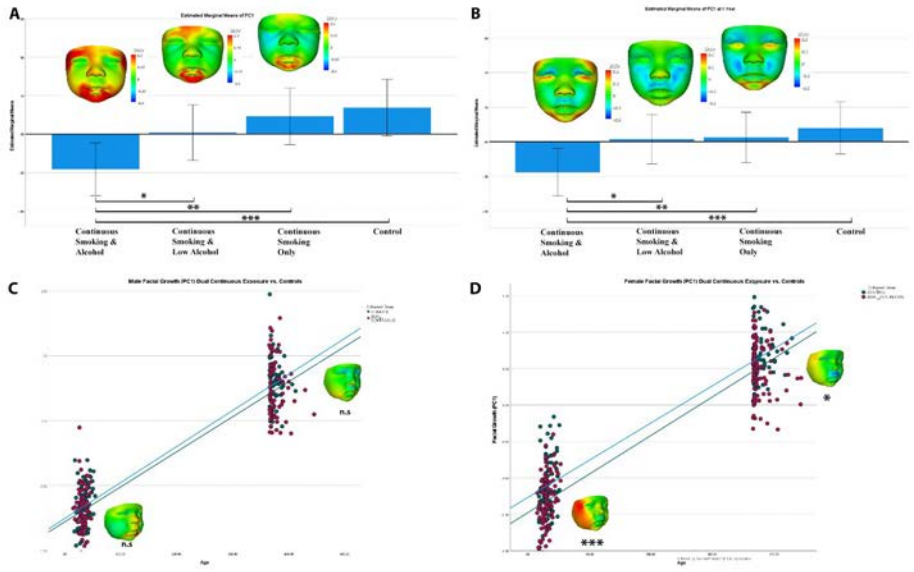

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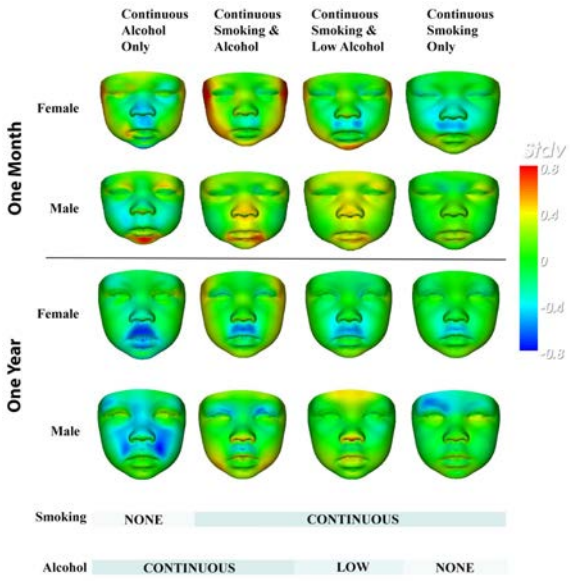

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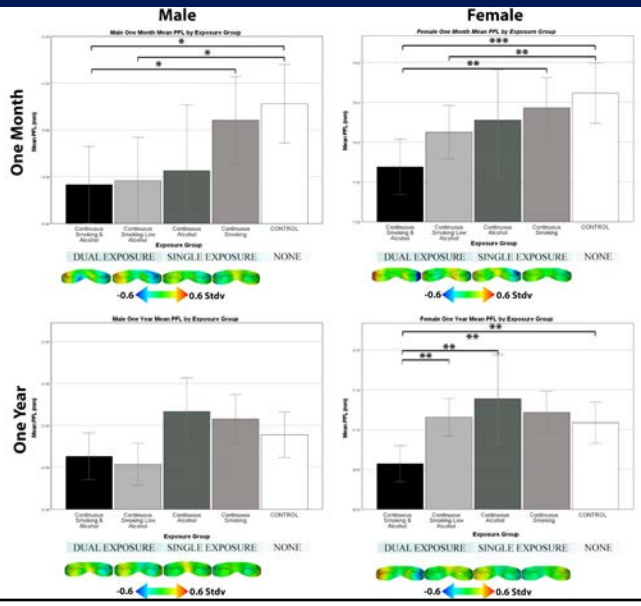

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Publication Progress

Imaging-Based Ocular Measurements for the Assessment of Fetal Alcohol Spectrum Disorder. Michael Suttie, Zeyu Fu, Raj Mukherjee, Alexandra Carlisle, Jeff Wozniak, Leah Wetherill, Tatiana Foroud, Ken Jones, Sarah Mattson, Alison Noble and the CIFASD. ***In draft***

Facial Dysmorphia Associated with Concurrent Prenatal Alcohol and Smoke Exposure. Michael Suttie, Leah Wetherill, Scott Parnell, Hein Oddendaal, Lut Geerts, Rosemary Meyer, Heidi Nolan, Lucy Brink, Tatiana Foroud, Peter Hammond and the CIFASD. ***Finalizing for submission.*** ~~Frontiers~~ in Neuroscience Research Topic on "Perspectives and Recent Advances in Fetal Alcohol Spectrum Disorders Research"

Resubmitting to **ACER** (or any better suggestions?)

Talks

University of Salford MANCHESTER

FASD IN THE UK

FASD in the UK: Building on 20 years of progress – Manchester, UK
March 2023
Plenary talk
3D imaging workshop

Research Society on Alcohol

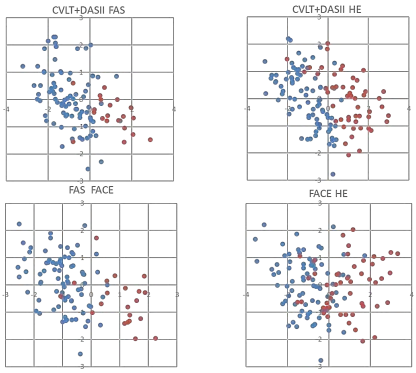
RSA June 2023
Multi-Modal 3D Face-Neurocognitive Analysis for the Identification of FASD

7

Nuffield Department of Women's and Reproductive Health, University of Oxford

UNIVERSITY OF OXFORD

Multi-Modal 3D Face-Neurocognitive Analysis for the Identification of FASD



FAS Neuro AUC 0.89
FAS Face. AUC 0.86

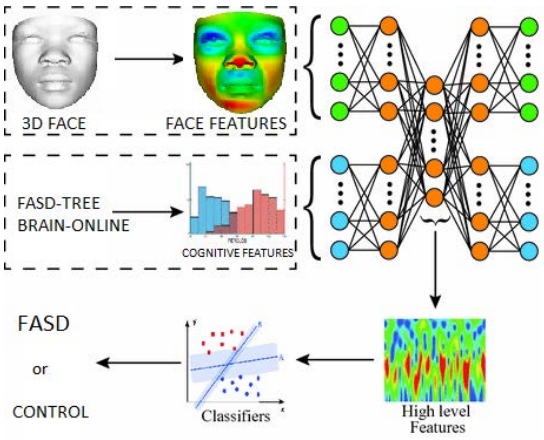
FAS Neuro+FACE = 0.94

HE Neuro AUC 0.86
HE Face. AUC 0.76

HE Neuro+FACE = 0.92

8

Ongoing Analysis – Year 2 Focus



- Optimizing ML models on early CIFASD data
- Combine all neurocognitive/behavioral data available with 3D facial models
- Improve recognition across the FASD spectrum.
- Investigate which diagnostic systems are best for accurate clinical categorization (face+cognition)
- Integrate FASD-Tree + Brain Online + Facial Analysis

9

Nuffield Department of Women's and Reproductive Health, University of Oxford

CIFASD Collaborations

- Dr Sarah Mattson – 3D Face <-> Neurocognitive assessment tools
- Dr Miguel del Campo – Clinical validation, image data/dysmorphology
- Dr Ralph DiClemente – Intervention assessment
- Dr Leah Wetherill – Data Coordination Resource

- Dr Jeff Wozniak, Dr Claire Coles, Dr Joanne Weinberg, Dr Christie Petrenko, Dr Tina Chambers

10

UNIVERSITY OF OXFORD

Member of the Order of the British Empire

Professor Raja Anindya Sekhar Mukherjee, Consultant Psychiatrist at Surrey and Borders Partnership NHS Foundation Trust, has been awarded an MBE for services to people with Fetal Alcohol Spectrum Disorders.

11

UNIVERSITY OF MINNESOTA
Driven to Discover℠

Wozniak, University of Minnesota: U01AA030164: *Cognitive Training +/- tDCS targeting executive functioning in 8-17 year olds with FASD*

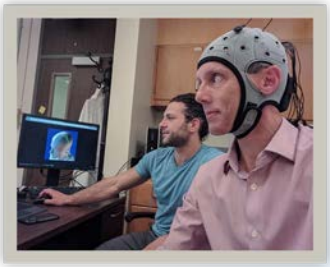
Aim 1. Evaluate the therapeutic benefits of 5 initial sessions of **active** tDCS (n=30) vs. **sham** tDCS (n=30) in conjunction with CT (n=60; all participants). Hyp1: With CT, **active** tDCS will yield improvement in sustained attention (CPT) and parent-reported ADHD symptoms compared to **sham** tDCS over the 5 initial sessions.

Aim 2. Incorporating additional sessions, quantify the dose-response relationship. Hyp2: In conjunction with CT (n=60; all participants), **10 active** tDCS sessions (n=30) will produce greater improvement in sustained attention (CPT) and parent-reported ADHD symptoms than **5 active** + 5 sham sessions (n=30).

Aim 3. Establish the durability of attention improvements and parent-reported ADHD symptoms from tDCS + CT. Hyp3: At two months post-intervention, sustained attention (CPT) improvements vs. baseline performance will remain. Hyp4: Dosage will be related to durability of the treatment effect (**10 active** sessions will provide a more durable response in sustained attention compared to **5 active** sessions).

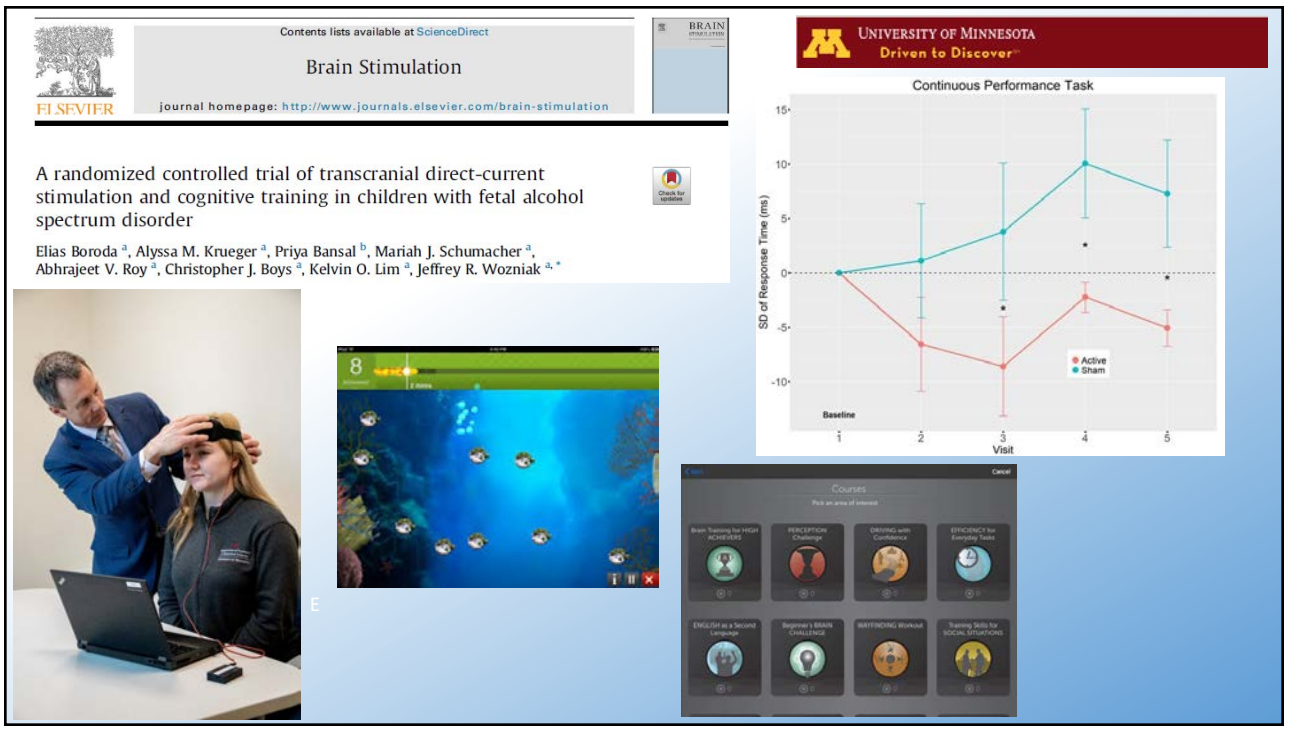
Aim 4 (exploratory): Employ fMRI to measure functional change in brain network activity between baseline and 5 sessions (active tDCS vs. sham tDCS). H4: Relative to baseline, those receiving 5 sessions of **active** tDCS (n=15) will show enriched connectivity and salience between limbic and control networks post-intervention compared to those receiving 5 sessions of **sham** tDCS (n=15).

1



- 70 participants with FASD, ages 8-17
- Compare 5 sessions CT+ Active tDCS to CT + Sham tCDS
- Compare 5 sessions to 10 sessions CT + Active tDCS
- Evaluate durability at 2 months post-intervention
- Evaluate changes in brain network connectivity

2



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Challenges / Successes

June, 2023 update

- Initial IRB / Regulatory challenges caused delays in starting
- Hesitancy from families on 11 in-person visits to UMN
- Technical challenges adding home-based sessions
- Behavioral challenges with participants

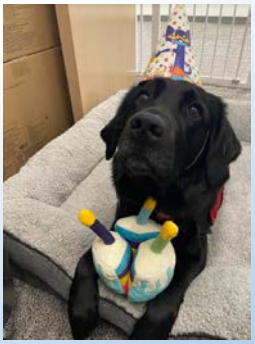
- Regulatory issues addressed for the time-being
- Home-based option (7) has significantly improved recruitment
- Technical challenges overcome for the most part
- Added resources to address behavioral challenges

4

Mock MRI scanner

- Now in our MR suite
- Saves time and money on the real MRI scanner
- Prepares participants
- Reduces anxiety
- May reduce movement / increase quality of scans

5



Child-Life Specialist Cala Hefferan, MA, CCLS and Jersey

6

Project Status

June, 2023

	#	Total goal	% of 2022/23 goal	% of total goal
Participants enrolled/scheduled	9	70	64%	13%
Participants terminated	1	-	-	-
Participants completed	4	60	33%	7%
Active participants	5	-	-	-
MRI Scans completed	10	100	100%	10%

7

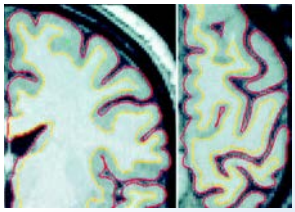
CIFASD 5 Collaborations

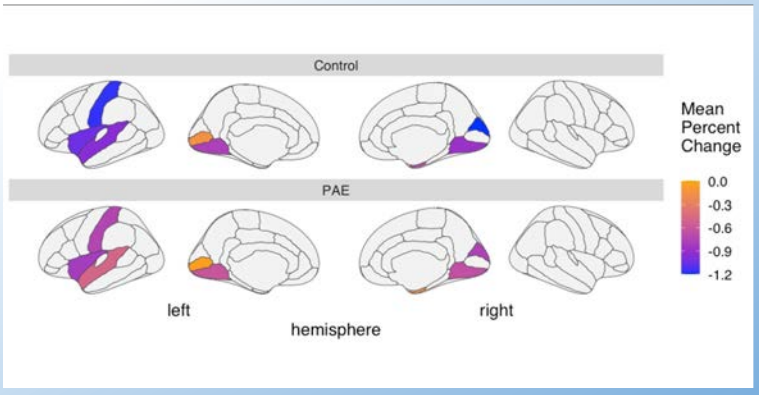
- Miguel del Campo:
  - Local personnel underwent dysmorphology training
  - Will share all dysmorphology data
- Mike Suttie:
  - Sharing 2D and 3D facial images from all participants
- Sarah Mattson:
  - Setting up to collect BRAIN-Online data
- Leah Wetherill:
  - Sharing data to the NDA (up to date)
- Christie Petrenko:
  - Sharing participants / assisting with recruitment

8

Ongoing CIFASD 4 Analyses

Gimbel, B. A., Roediger, D. J., Ernst, A. M., Anthony, M. E., de Water, E., Mueller, B. A., ... & Wozniak, J. R. (2023). Delayed cortical thinning in children and adolescents with prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research.



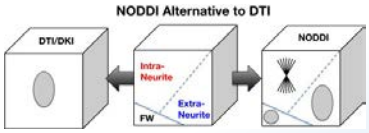


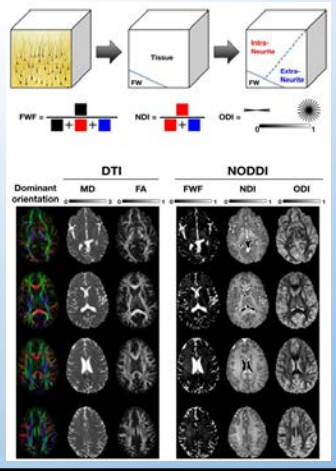
Blake Gimbel's CIFASD Symposium talk on Sunday

9

Ongoing CIFASD 4 Analyses

Gimbel, B. A., Roediger, D. J., Ernst, A. M., Anthony, M. E., De Water, E., Rockhold, M. N., ... & Wozniak, J. (2023). Atypical developmental trajectories of white matter microstructure in prenatal alcohol exposure: Preliminary evidence from neurite orientation dispersion and density imaging (NODDI). Frontiers in Neuroscience, 17, 623.





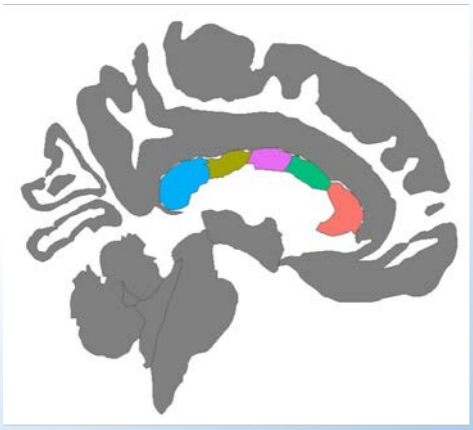
Neurite Orientation Dispersion and Density Imaging in Psychiatric Disorders: A Systematic Literature Review and a Technical Note

Nina Vanessa Kraguljac, Michele Guerreri, Molly Jordan Strickland, and Hui Zhang

10

Ongoing CIFASD 4 Analyses

Gimbel, B. A., Roediger, D. J., Ernst, A. M., Anthony, M. E., De Water, E., Rockhold, M. N., ... & Wozniak, J. (2023). Atypical developmental trajectories of white matter microstructure in prenatal alcohol exposure: Preliminary evidence from neurite orientation dispersion and density imaging (NODDI). Frontiers in Neuroscience, 17, 623.

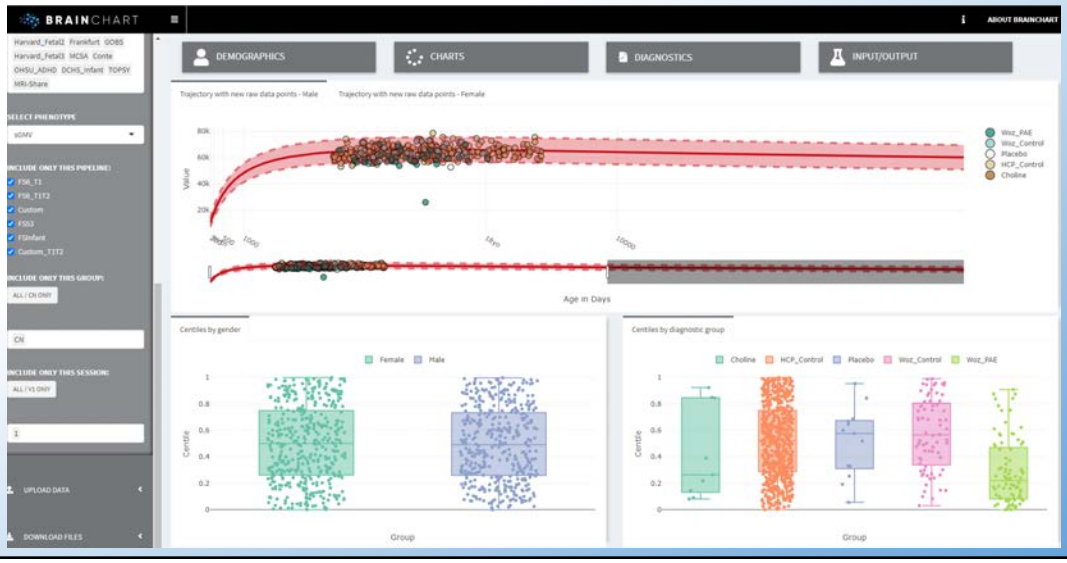


- Examined Corpus Callosum changes over 15 months
- Found altered trajectories in PAE compared to control
- Potential "catch-up" at older ages in PAE
- Found associations with cognitive functioning
- Blake Gimbel's CIFASD Symposium Talk on Sunday

11

Ongoing CIFASD 4 Analyses

Psychometric identification of abnormal brain growth in PAE



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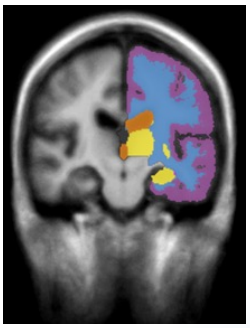
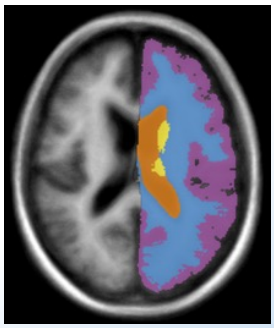
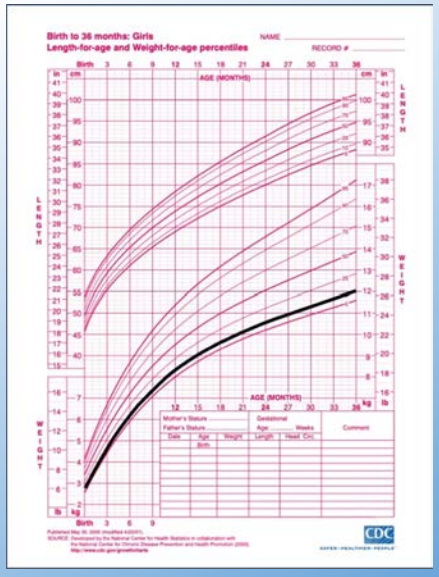






- Blake Gimbel's FASt Data talk tomorrow
- New method for characterizing brain anomalies in FASD at an individual level
- Improve sensitivity over traditional physical OFC measure
- Manuscript nearly complete

13

Ongoing CIFASD 4 Analyses

1. **Smith, S.M.**, Weathers, T.D., Virdee, M.S., Schwantes-An, T.H., Mattson, S.N., Coles, C., Kable, J., Sowell, E., Wozniak, J.R., Wetherill, L., and the **CIFASD**. (under review). Ploymorphisms in the choline transporter SLC44A1 are associated with reduced cognitive performance in both normotypic and prenatal alcohol-exposed children. American Journal of Clinical Nutrition.

2. **Hyland, M.,** Courchesne, N., Bernes, G., Wozniak, J.R., Jones, K.L., del Campo, M., Riley, E., & **Mattson, S.** (in press). Results of an FASD Screening Tool are Associated with Neuropsychological and Behavioral Measures. Alcoholism: Clinical and Experimental Research.

3. **Gimbel, B.A.,** Roediger, D.J., Ernst, A.M., Anthony, M.E., deWater, E., Rockhold, M.N., Mueller, B.A., Mattson, S.N., Jones, K.L., Riley, E.P., Lim, K.O., CIFASD, & **Wozniak, J.R.** (2023). Atypical developmental trajectories of white matter microstructure in prenatal alcohol exposure: Preliminary evidence from neurite orientation dispersion and density imaging (NODDI). Frontiers in Neuroscience.

4. **Gimbel, B.A.,** Roediger, D.J., Ernst, A.M., Anthony, M.E., deWater, E., Mueller, B.A., Rockhold, M.N., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & **Wozniak, J.R.** (2023). Delayed cortical thinning in children and adolescents with prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research.

5. **Mattson, S.N.,** Jones, K.L., Chockalingam, G., Wozniak, J.R., Hyland, M.T., Courchesne-Krak, N.S., Del Campo, M., Riley, E.P., and the **CIFASD.** (2023). Validation of the FASD-Tree as a screening tool for fetal alcohol spectrum disorders. Alcoholism: Clinical and Experimental Research, 47(2), 263-272; DOI: 10.1111/acer.14987.

7. **Bernes, G.A.,** Courschesne-Krak, N.S., Hyland, M.T., Villodas, M.T., Coles, C. D., Kable, J.A., May, P.A., Kalberg, W.O., Sowell, E. R., Wozniak, J.R., Jones, K.L., Riley, E.P., **Mattson, S.N., and the CIFASD.** (2022). Development and validation of a postnatal risk score that identifies children with prenatal alcohol exposure. Alcoholism: Clinical and Experimental Research, 46(1):52-65; DOI: 10.1111/acer.14987; PMID:34806190; PMCID: PMC8799504.

14

Lifelong impact of PAE on stem cell dynamics and cellular aging

UH2AA030186

AMANDA H. MAHNKE, PH.D.
ACES ASSISTANT PROFESSOR
TEXAS A&M UNIVERSITY SCHOOL OF MEDICINE
JUNE 23, 2023

1

Specific Aims

Aim 1 - Does PAE diminish stem cell function across the lifespan?

A) Create human-induced pluripotent stem cells (hiPSCs) from peripheral blood mononuclear cells obtained from diverse age CIFASD cohorts
- Neonate – DiClemente; Child/Adolescent – Chambers; Adult – Coles/Weinberg

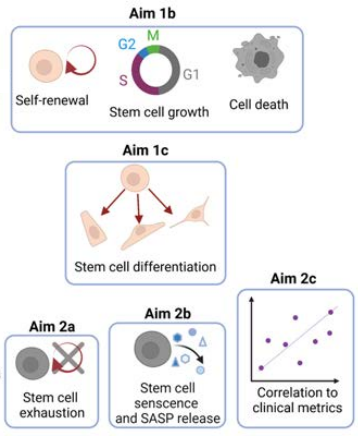
B) Assess hiPSCs for growth, renewal, differentiation

Aim 2 - Does PAE induce or exacerbate stem cell aging?

A) Assess metrics of stem cell exhaustion

B) Assess stem cell senescence and the production/release of senescence-associated secretory phenotype (SASP) molecules

C) Correlate changes in stem cell biology to clinical metrics



2

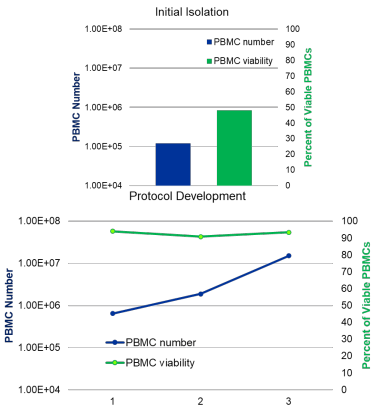
Progress Yr1/Early Yr2

- IRB and IBC approval (IRB as exempt)
- Personnel hiring
- Work with Data Coordination Resource (Wetherill U24) - data dictionary created and approved
- Worked with Canadian Adult Cohort (Coles/Weinberg) to include appropriate consent language for this project
- Working with Tina for the receipt of samples from the San Diego Pilot
- SOP development
- Assay development

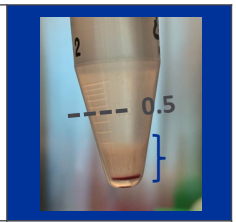
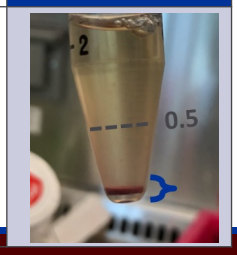
3

SOP development

- Yr 1 optimized protocol for viability and conditions appropriate for shipping



- Visual guide for pellet resuspension (for Ukraine) – Yr 2

Resuspend 1mL Take half, dilute to 10mL	
Resuspend 1mL Dilute up to 4mL	

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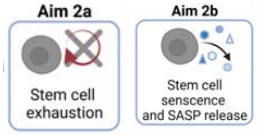
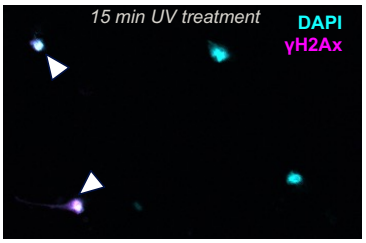
Assay Development

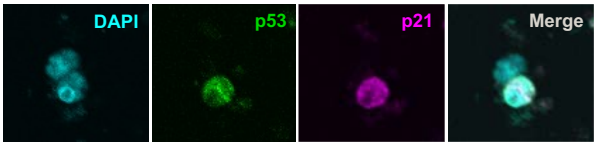


- qPCR panel for SASP and Senescence

Gene Target	Role	Sequenced	
IL-6	SASP	Yes	Validated
VEGFA	SASP	Yes	Validated
CXCL8	SASP	Yes	Validated
IL-1A	SASP	Yes	Validated
IL-7	SASP	Yes	Validated
CXCL8 (IL-8)	SASP	Yes	Validated
CSF2(GM-CSF)	SASP	Yes	Validated
GLB1	Senescence	Yes	Validated
p21/CDKN1A	Senescence	Yes	Validated
CDKN2B	Senescence	Yes	Validated
LMNB1	Senescence	Yes	Validated
TP53	Senescence	Yes	Validated
NOTCH1	Senescence	Yes	Validated
B2M	Housekeeping	Yes	Validated
HPRT1	Housekeeping	Yes	Validated
GAPDH	Housekeeping	Yes	Validated
ACTB	Housekeeping	Yes	Validated
ATP5B	Housekeeping	Yes	Validated
PGK1	Housekeeping	Yes	Validated
VEGFC	SASP	Awaiting Sequencing	
p16INK4A/CDKN2A	Senescence	Awaiting Sequencing	
p14ARF/CDKN2A	Senescence	Awaiting Sequencing	

- Immunomarkers for SASP and Senescence





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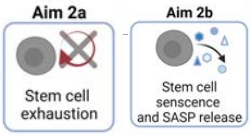
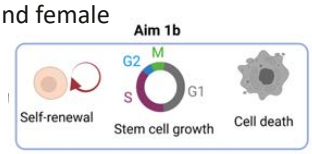
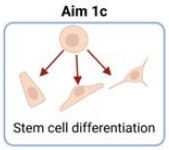
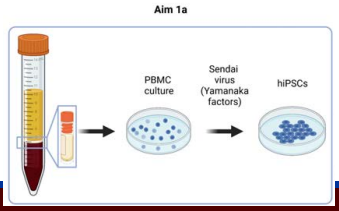
Summer/Early Fall Timeline



- Ongoing training for flow cytometry and validation of immunomarkers for flow
- hiPSC induction of Adult "contrast" PBMCs
  - From commercially available sources – 36-44yo male and female samples
  - Pilot assays
  - Beginning early July
- Obtain San Diego pilot cohort samples
- Obtain adult samples from Vancouver
- Continue coordinating with Houston site for neonatal samples
- hiPSC induction of patient samples early fall







6

Specific Aims

Summer/Early Fall YR2

Aim 1 - Does PAE diminish stem cell function across the lifespan?

A) Create human-induced pluripotent stem cells (hiPSCs) from peripheral blood mononuclear cells obtained from diverse age CIFASD cohorts

- Neonate – DiClemente; Child/Adolescent – Chambers; Adult – Coles/Weinberg

Fall YR2

B) Assess hiPSCs for growth, renewal, differentiation

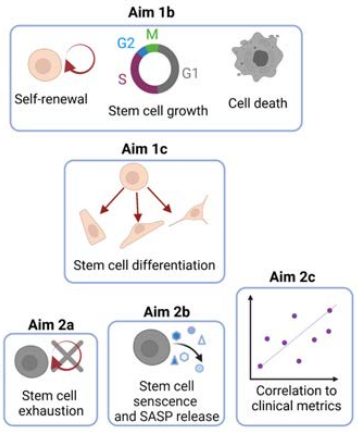
Creating Assays – YR1/Early YR2
Sample assessment Fall YR2

Aim 2 - Does PAE induce or exacerbate stem cell aging?

A) Assess metrics of stem cell exhaustion

B) Assess stem cell senescence and the production/release of senescence-associated secretory phenotype (SASP) molecules

C) Correlate changes in stem cell biology to clinical metrics



7

Development of biomarkers in deciduous teeth of children with FASD that predict neurobehavioral performance

1 UH2 AA029062-01

PIs: Annika Montag & Christine Austin

CIFASD at RSA 2023

UC San Diego School of Medicine

Rady Children's Hospital San Diego

Icahn School of Medicine at Mount Sinai

1

Specific Aims

Aim 1. Determine the sensitivity and specificity of direct and indirect biomarkers of PAE in deciduous teeth of 25 children with FASD and 25 children with known absence of PAE.

Aim 2. Assess associations among magnitude and gestational timing of PAE identified in the deciduous teeth of 25 children with FASD and 25 children with known absence of PAE and neurobehavioral deficits.

Aim 3. Explore the interaction between PAE and exposures to neurotoxic and nutritive metals during prenatal and early life.

Aim 4. (Added Aim from R21) Explore potential biomarkers of co-exposures including cannabis, tobacco, and opioids.

2

Main Accomplishments and Future Plans

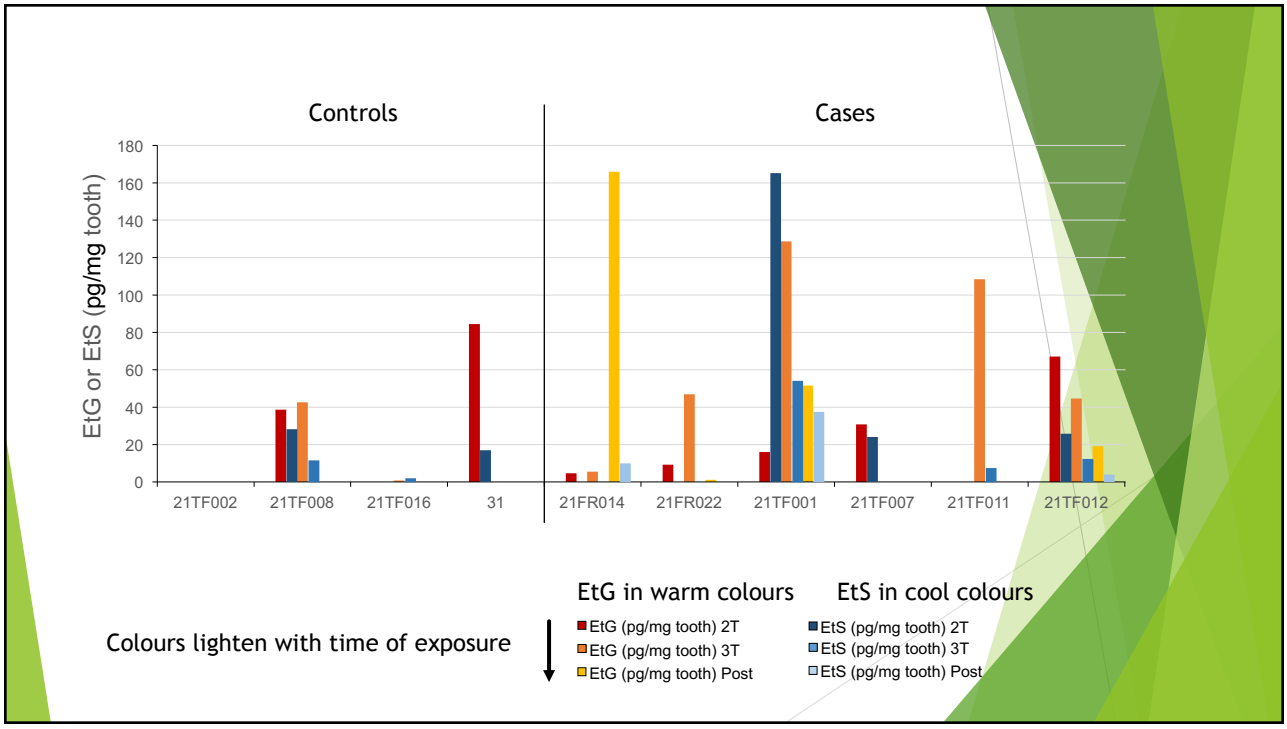
Main Accomplishments

- Recruitment from Mattson and Wozniak cohorts
  - 15 consented and samples received: 19 exposed, 12 unexposed
  - 49 samples, sent 8/1/22, include Jones/Del Campo registry participant and control samples, and Tooth Fairy pilot study participant samples for method development
- Two of four direct PAE biomarkers assessed: EtG and EtS
- Metals analysis

Future Plans

- Assess and analyze
  - additional samples for EtG and EtS
  - all samples for FAEEs and PEth
  - all samples for indirect biomarkers: amino acids and cholesterol sulfate
  - all samples for co-exposures: cannabis, tobacco, opioids
- Neurobehavioral data obtained from Mattson and Wozniak
- Analysis of associations of exposures and NB outcomes
- Methods manuscript submitted late summer; associations manuscript before end of year
- R01 submission

3



4

Aim 1: EtG and EtS Biomarkers

First run

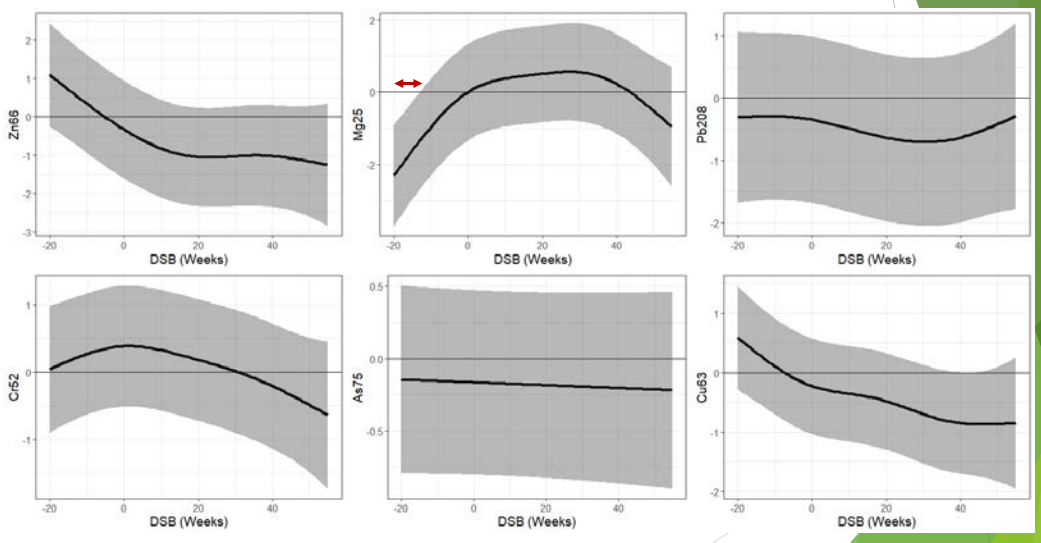
	2nd Trimester		3rd Trimester		Postnatal	
Donor	EtG (pg/mg tooth)	EtS (pg/mg tooth)	EtG (pg/mg tooth)	EtS (pg/mg tooth)	EtG (pg/mg tooth)	EtS (pg/mg tooth)
Cntrl 1	-	-	0.00	0.00	0.00	0.00
Cntrl 2	0.00	28.16	0.00	11.62	0.00	0.00
Cntrl 3	-	-	0.00	85.39	0.00	0.00
Cntrl 4	164.29	0.00	0.00	0.00	0.00	0.00
Case 1	66.89	0.00	84.52	0.00	159.63	12.18
Case 2	73.20	0.00	31.12	0.00	8.45	0.00
Case 3	0.00	230.49	0.00	55.88	0.00	43.73
Case 4	0.00	21.09	0.00	0.00	0.00	0.00
Case 5	-	-	0.00	16.96	0.00	0.00
Case 6	0.00	87.01	0.00	12.35	0.00	3.91

Second run

	2nd Trimester		3rd Trimester		Postnatal	
Donor ID	EtG (pg/mg tooth)	EtS (pg/mg tooth)	EtG (pg/mg tooth)	EtS (pg/mg tooth)	EtG (pg/mg tooth)	EtS (pg/mg tooth)
Control 1			0.00	0.00	0.00	0.00
Control 2	38.73	28.16	42.67	11.62	0.00	0.00
Control 3			0.79	2.05	0.00	0.00
Control 4	84.51	16.87	0.00	0.00	0.00	0.00
Case 1	4.63	0.00	5.45	0.00	165.91	9.99
Case 2	9.23	0.00	46.91	0.00	1.09	0.00
Case 3	16.01	165.07	128.65	54.19	51.56	37.51
Case 4	30.81	24.04	0.00	0.00	0.00	0.00
Case 5			108.49	7.49	0.00	0.00
Case 6	67.09	25.72	44.59	12.35	19.11	4.02

5

Aim 3: Metals Analysis



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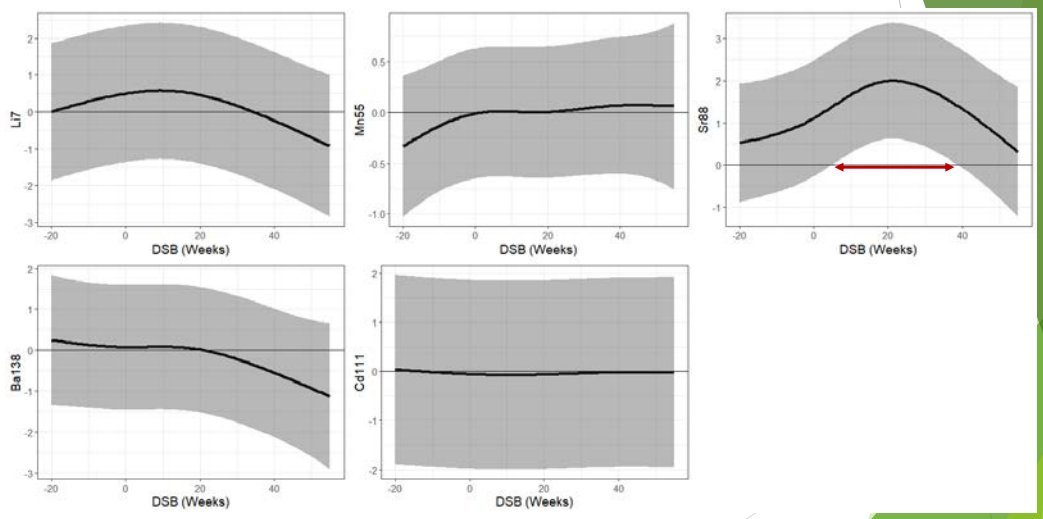
Aim 3: Metals Analysis



7

My Health Coach:

Mobile Health Tools to Promote Health in Adults with Fetal Alcohol Spectrum Disorder

CHRISTIE L. M. PETRENKO, PH.D.
CRISTIANO TAPPARELLO, PH.D

UH2 AA029050
June 2023

1

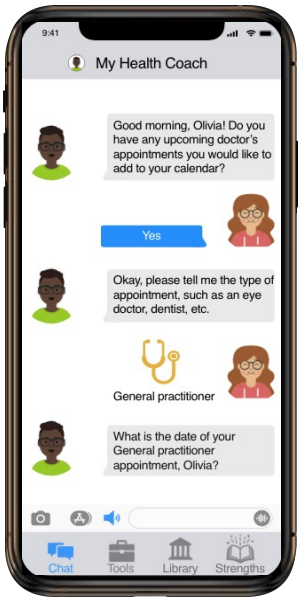
PARTNERSHIP WITH THE INTERNATIONAL ADULT LEADERSHIP COLLABORATIVE OF FASD CHANGEMAKERS

2

AIMS

1) Development of "My Health Coach" app
- Identify & refine functionalities through focus groups and survey methods.
- Develop an iOS prototype for testing

2) Feasibility Study



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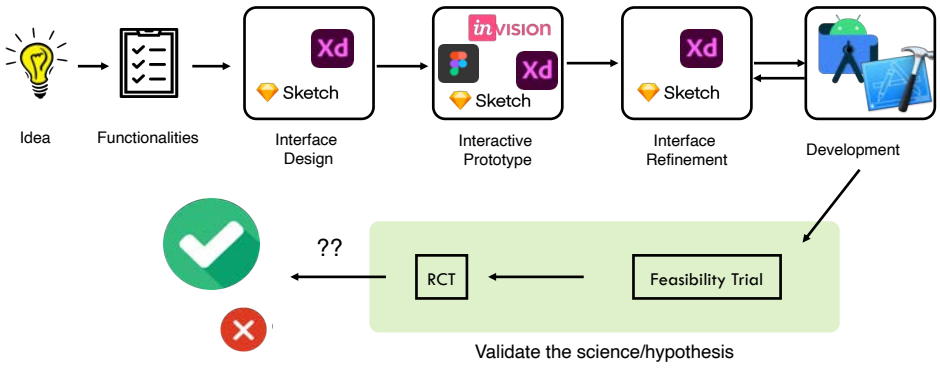
APP DEVELOPMENT



4

APP DEVELOPMENT

5

FEASIBILITY TRIAL OBJECTIVES

Trial Feasibility

- Is recruitment sufficient to support a larger trial? Who is reached?
- How much attrition occurs?
- Are measures acceptable and sensitive to change?

Intervention Feasibility

- Does the app work from technology perspective?
- Do users find it acceptable?

User Implementation

- What are usage patterns in the app?

6

TRIAL FEASIBILITY – RECRUITMENT/ENROLLMENT

Trial launched 3/20/2023
- Had 75% of eligible sample in 2 weeks

Target n = 40

As of 6/19/2023:
- **44 eligible**
- **6 ineligible**
- 7 incomplete
- 37 fraudulent

Who did we reach?
- 21% male, 67% female, 12% transgender, non-binary, other
- Mean age 31 years (19-60)
- 41% iOS, 59% Android
- Countries:
  - USA (25)
  - Canada (7)
  - UK (4)
  - Netherlands (4)
  - Ireland (1)
  - Italy (1)
  - South Africa (1)
  - New Zealand (1)

7

TRIAL FEASIBILITY - ATTRITION

As of 6/19/2023

	Eligible	T1 Complete	Received App	Installed App	T2 Complete	Interview Complete
My Health Coach	44	39	39	32	20	4
% Total		90.7%		82.1%	51%	

Higher rate of T1 completion than anticipated
App install rate similar to our other app studies
T2 and interviews started last week in May and still in progress
Working on increasing T2 and interview completion, assessing best methods

8

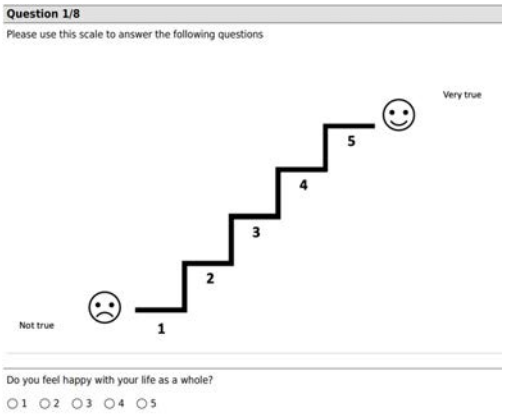
TRIAL FEASIBILITY - MEASUREMENT

Survey completion was better than expected

Participants able to complete surveys online with minimal reported issues or questions

Good variability

Spontaneous positive feedback

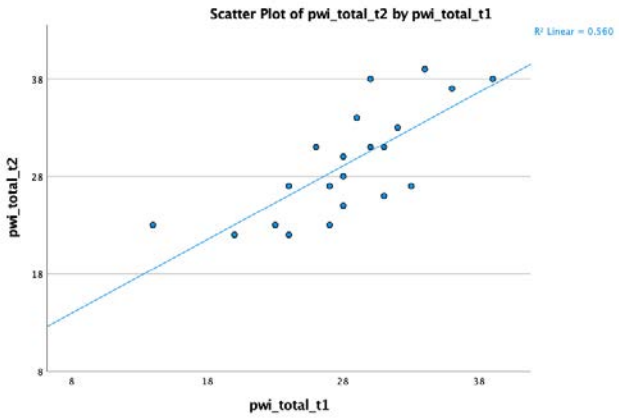


9

PRELIMINARY DATA: QUALITY OF LIFE

N=20

Cohen's d = 0.2



10

INTERVENTION FEASIBILITY

Most users able to install app without help or problems

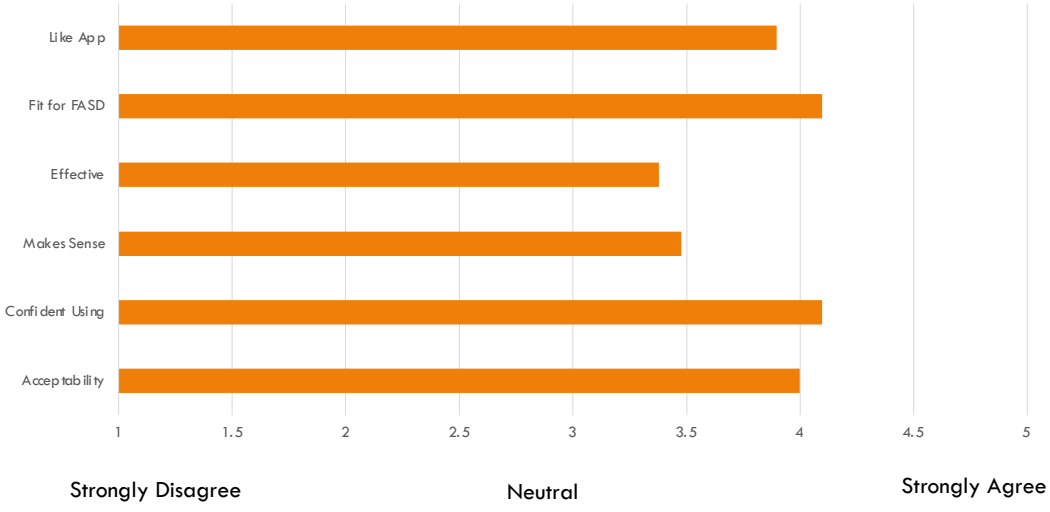
2 major updates released and 2 minor bug fixes

33 submissions in Feedback section of app, combination of:

- Problems
- Recommendations for future development
- Positive feedback

11

INTERVENTION ACCEPTABILITY



12

USER IMPLEMENTATION - PRELIMINARY

Over 6-week period (data for 21 users)**:**

App opened: Mean = 35 times (range: 0-129)

Chatbot interactions: Mean = 90 times (range: 0-353)

Daily Check-in: Mean = 9 times (range 0-31)

Strengths assessment: Mean = 31 items (of 37) (range: 0-37)

PDFs read in Library: Mean =2.5 (range 0-16)

Trackers set up: Mean = 4.9 (range 0-36)

Trackers completed: Mean = 69.5 (range 0-529)

13

PUBLICATION/PRESENTATION UPDATES

Manuscript on focus group and survey data from Aim 1 is complete and awaiting final feedback from ALC members prior to journal submission

Emily Speybroeck – trainee in lab – presenting at FASDSG

CAB best practices analyses progressing – aiming manuscript fall

14

UH2 AA029056
Susan Smith

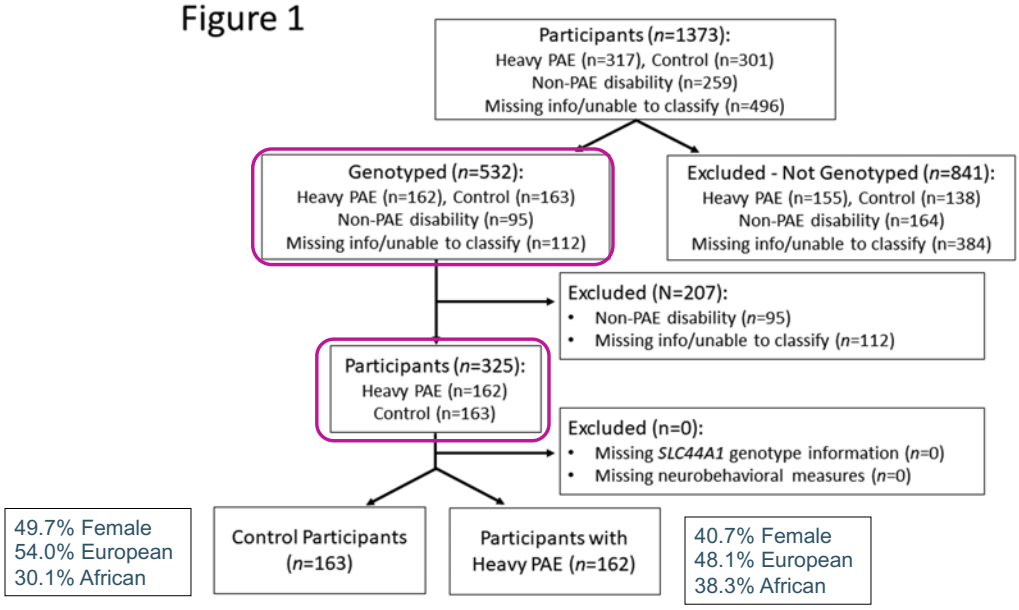
SNPs in choline transporter SLC44A1 that increase choline need will be associated with poorer cognitive outcomes in those with heavy PAE and conventional choline intake.

(that is, no choline supplement)

1

Participants: CIFASD 2 & 3

Figure 1



2

8 SNPs in *SLC44A1* are Associated with at Least 1 Behavioral Outcome

ID	Location	Type	Ref/Alt	MAF, this cohort	MAF, European	MAF, African Amer.	Function
rs75106836	Intron 1	SNV	T > C	2.9%	0.04%	5.5%	unknown
rs105185127	Intron 1	SNV	C > T	3.7%	0.8%	11.0%	unknown
rs143438338	Intron 1	SNV	A > G	3.0%	0.04%	5.5%	unknown
rs59370172	Intron 1	SNV	C > T	3.0%	0.04%	5.6%	unknown
rs12347364	Intron 1	SNV	T > A	5.6%	5.0%	0.7%	unknown
rs10991629	Intron 3	SNV	C > T	18.7%	11.8%	36.3%	unknown
rs3199966	Exon 15	SNV	T > G	19.1%	9.0%	41.5%	increases choline need
rs2771040	Exon 16 (3' UTR)	SNV	A > G	21.3%	12.0%	43.8%	increases choline need

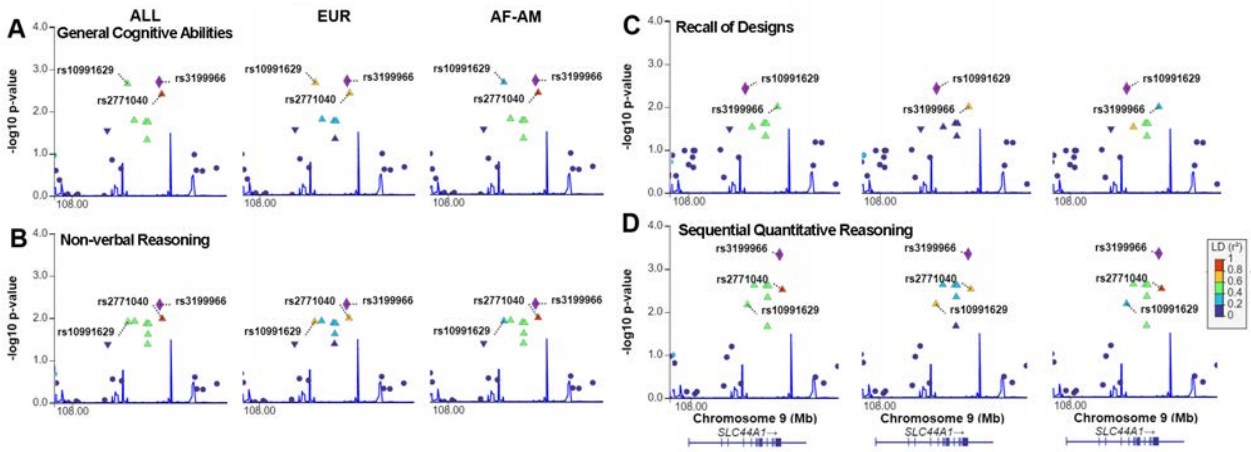
3

Associations w/Executive Function, Memory, Learning, & Reasoning

Cognitive Measure	SNP	ADD Q-Value	ADDxPAE Q-Value	Effect Allele
Perseverations (Free and Cued Recall Total), Z-score (CVLT)	rs150185127	0.0306	0.0200	T (C > T)
Serial Cluster Ratio, Z Score (CVLT)	rs12347364	0.0368	0.0116	A (T > A)
Conners Executive Functioning, T-Score	**rs2771040**	0.0306	0.0116	G (A > G)
General Cognitive Abilities, T-Score (DAS-II)	**rs3199966**	0.0306	0.0116	G (T > G)
	rs75106836	0.0475	0.0147	C (T > C)
Matrices, T-Score (DAS-II)	rs59370172	0.0481	0.0499	T (C > T)
Nonverbal Reasoning Cluster, T-Score (DAS-II)	**rs3199966**	0.0306	0.0114	G (T > G)
	rs2771040	0.0306	0.0117	G (A > G)
	rs10991629	0.0306	0.0118	T (C > T)
	rs12347364	0.0334	0.0146	A (T > A)
Recall of Designs, T-Score (DAS-II)	**rs3199966**	0.0306	0.0204	G (T > G)
	rs2771040	0.0334	0.0213	G (A > G)
	rs10991629	0.0306	0.0145	T (C > T)
Sequential and Quantitative Reasoning, T-Score (DAS-II)	**rs3199966**	0.0306	0.0113	G (T > G)
	rs2771040	0.0334	0.0113	G (A > G)
Internalizing behavior, V-score (VABS-2)	**rs3199966**	0.0306	0.0116	G (T > G)

4

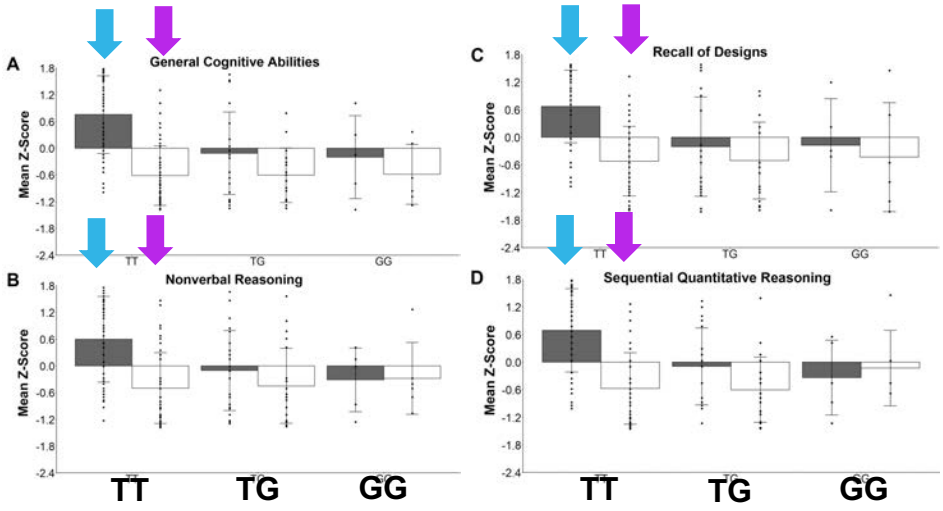
Multiple SNPs in LD w/rs3199966 are Associated with These Impairments



5

SNPs do NOT Protect against PAE when Extra Choline is Absent

Control
PAE

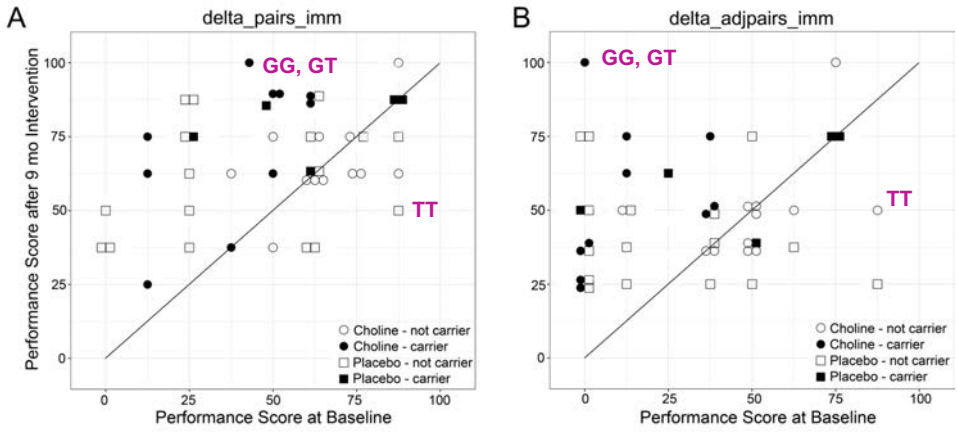


6

For those getting extra choline, SNPs are associated with greater pre/post cognitive improvement

EI memory task – pairs in order

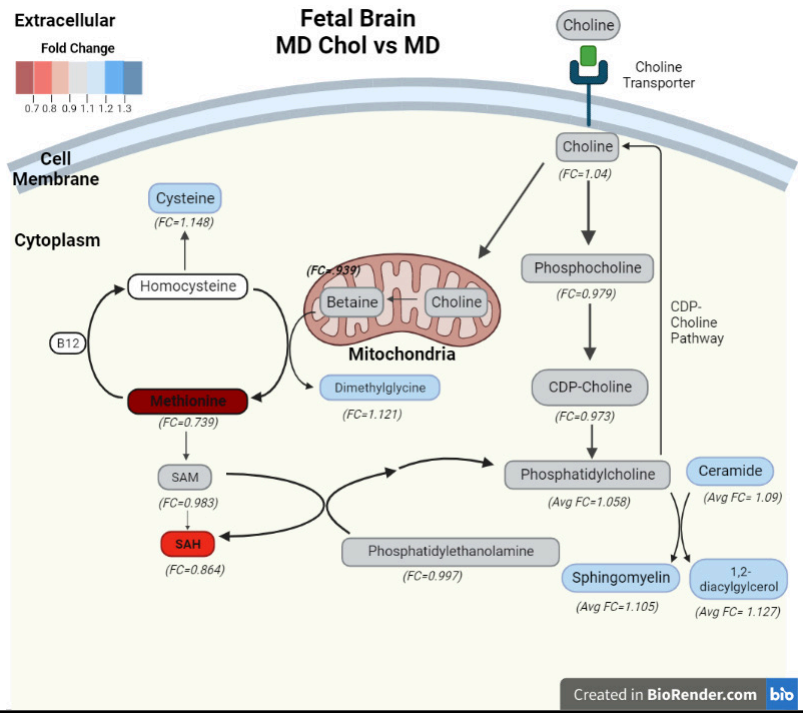
EI memory task – pairs any order

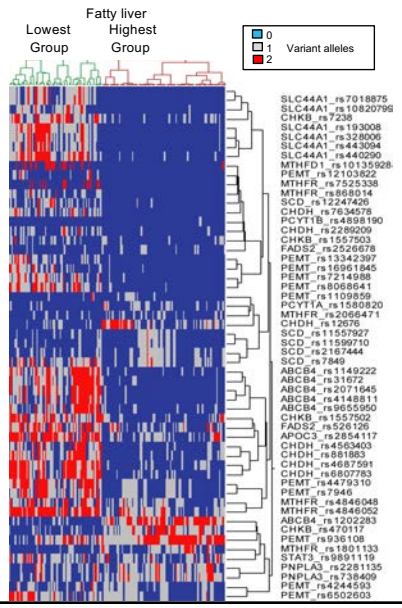


Smith Wozniak et al. 2021 *AJCN*

7

Many SNPs affect 1C & choline needs.





8

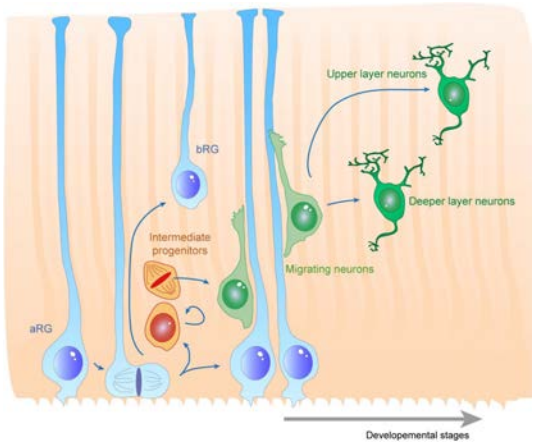
Ten 1-C Genes Associated w/Cognitive Function in Heavy PAE

Gene	# SNPs	Padj (range)	Alt Freq	Gene Name/Function
SLC44A1	7	1.46 – 3.24E-02	21.7%	Choline Transporter CTL1
ALDH1L1	**8**	**3.43 - 9.88E-04**	**5.38%**	**10-Formyl THF Dehydrogenase**
MTHFD1L1	5	3.25 – 7.34E-04	5.2%	Methylene THF Dehydrogenase, Mito
SLC25A26	5	2.57 – 7.57E-04	6.9%	SAM transporter, Mitochondrial
DMGDH	5	4.21 –7.58E-04	5.5%	Dimethylglycine Dehydrogenase
MMAB	6	4.53E-04	8.5%	Adenosyl-B12 Synthase
MAT1A	2	1.52 – 1.86E-04	7.1%	Methionine Adenosyltransferase 1A
BHMT	1	7.58E-04	5.5%	Betaine-Homocysteine Methyltransferase 2
GGH	1	6.0E-05	6.6%	Folate γ-Glutamyl Hydrolase
MSRA	1	1.01E-04	5.6%	Methionine Sulfoxide Reductase A
MARS	1	4.1E-05	4.7%	Methionyl-tRNA Synthetase 1
CYP2E1	19	2.20 – 6.76E-04	5.4 %	EtOH-Inducible Cytochrome P450 2E1

9

What does ALDL1L1 do in brain?

- Early brain – in radial glia
  - Influence neuronal migration?
- Later fetus/adult – astrocytes
  - Restricted to astrocytes
  - Key metabolic regulators in brain
- We have the KOs
  - Evaluating KO brain morphology
  - KOs have behavioral deficits

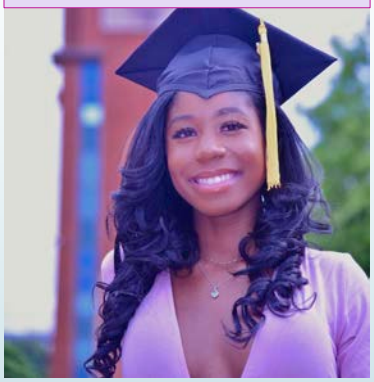


https://doi.org/10.3389/fcell.2020.578341

10

Acknowledgements

Torri Weathers
UNC-NRI



Leah Wetherill
IU School of Medicine

11

Summary

- In those with typical choline intakes, *SLC44A1* effect alleles are associated with reduced cognitive measures.
  - Their choline need was unmet by typical intake.
  - This transcends FASD; TT protects Controls but not PAE.
- These carriers have greater cognitive improvement when they receive supplemental choline.
  - Supplement meets their greater need.
- Endorses benefit of extra choline in FASD.
- Suggests current Choline requirement may be too low.

12