
CIFASD Administrative Core
Late Fall 2021 Update
CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders
Ed Riley, CIFASD Coordinator and Admin Core 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


CIFASD4 – Late Fall 2021
Ed Riley, Coordinator
PI, Admin. Core U24
San Diego State Univ.
Michael Charness
Scientific Director
Harvard Medical School
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.
Tom Donaldson & Kathy Mitchell
Education and Outreach
National Organization on FAS (NOFAS)
Ganz Chockalingam
Apps and eHealth
Blue Resonance, LLC
Christie Petrenko & CristianoTapparello
PIs, Mobile Intervention U01
Univ. of Rochester
Claire Coles
PI, Adults U01
Emory Univ.
Scott Parnell
Johann Eberhart
PIs, Mouse and Fish Genetics U01
UNC - Chapel Hill
Univ. of TX - Austin
Ken Jones & Miguel del Campo
PI and Co-I, Dysmorphology Core U24
Univ. of CA - San Diego
Tina Chambers
PI, Ukraine U01
UC - San Diego
Rajesh Miranda
Co-I, miRNA
Texas A&M Univ.
Sarah Mattson
PI, Neurobehavior
San Diego State Univ.
Welcome
Jeff Wozniak
PI, Neuroimaging
Univ. of Minnesota
Tatiana Foroud
Leah Wetherill
PI and Co-I, Genetics (Informatics) U01
Indiana Univ. School of Medicine
Alison Noble & Mike Suttie
PIs, 3D Imaging U01
Univ. of Oxford
Joanne Weinberg
PI, Immune U01
U. of British Columbia
Annika Montag
Christine Austin
PIs, Biomarkers in Teeth UH2
UCSD and Mount Sinai
Susan Smith
PI, Choline UH2
UNC-Chapel Hill
Joe Wang
Program Official
NIAAA
Elizabeth Powell
Project Scientist
NIAAA

CIFASD ADMINISTRATIVE CORE

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

SCIENCE ADVISORY BOARD

John Hannigan
Sara Jo Nixon
James Reynolds
Daniel Savage

NIAAA ADVISORS

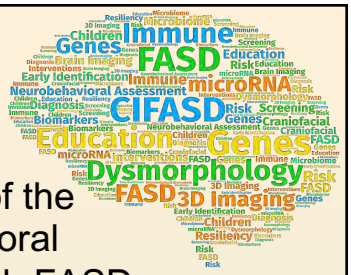
Elizabeth Powell, Project Scientist
Joe Wang, Program Officer
Previous: D. Hereld, B. Dunty

STEERING COMMITTEE
Chaired by Charness and Riley

C. Chambers	S. Parnell*/
C. Coles	J. Eberhart*
T. Foroud	C. Petrenko*/
A. Noble*/	C. Tapparello*
M. Suttie*	S. Smith
K.L. Jones	J. Weinberg
S. Mattson	J. Wozniak
A. Montag*/	
C. Austin*	* Multiple PI project

Recent UH2 PIs: K. Hashimoto-Torii, M. Torii, T. Blanchard, S. Mooney
Affiliated Scientists: K. Donald, R. Miranda, D. Sarkar, E. Sowell

CIFASD4 RFA Goals

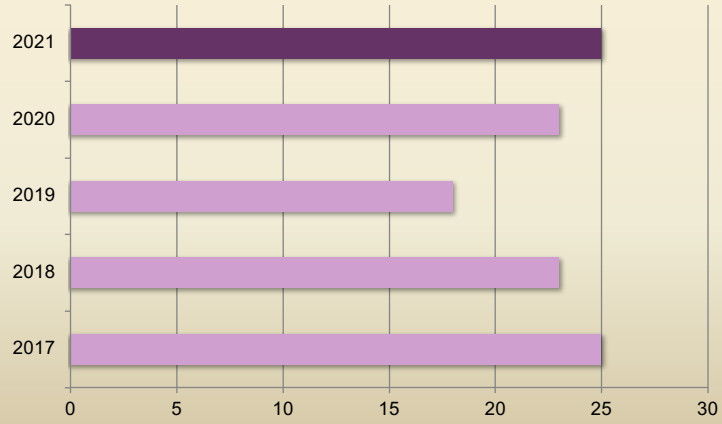


To enhance diagnoses of FASD at different stages of the lifespan based on biological, physical, and/or behavioral assessment and improve outcomes in individuals with FASD.

- Improve screening, case recognition and diagnosis of FASD (Face, Brain, Behavior, Biomarker)
- Assess impact of having an FASD across the lifespan
- Identify factors that impart risk/resiliency to FASD
- Develop intervention for FASD
- Employ eHealth technologies so that our research and its applications can be more broadly disseminated

Publication Productivity of CIFASD

Publications citing **CIFASD** funding in PubMed
2017 to present = 114
2021 = 25



Total PubMed
CIFASD Publications = **324**

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

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

June 2021 - Present CIFASD Publications n= 10

- Petrenko CLM, Kautz-Turnbull CC, Roth AR, Parr JE, Tapparello C, Demir U, Olson HC. Initial feasibility of the "Families Moving Forward Connect" mobile health intervention for caregivers of children with fetal alcohol spectrum disorders: Mixed method evaluation within a systematic user-centered design approach. *JMIR Form Res*. 2021, Dec 2;5(12):e29687.
- Bernes GA, Courchesne-Krak NS, Hyland MT, Villodas MT, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Wozniak JR, Jones KL, Riley EP, Mattson SN; CIFASD. Development and validation of a postnatal risk score that identifies children with prenatal alcohol exposure. *Alcohol Clin Exp Res*. 2021, Nov 21.
- Lussier AA, Bodnar TS, Moksa M, Hirst M, Kobor MS, Weinberg J. Prenatal adversity alters the epigenetic profile of the prefrontal cortex: Sexually dimorphic effects of prenatal alcohol exposure and food-related stress. *Genes (Basel)*. 2021, Nov 9;12(11):1773. PMCID:PMC8622940
- Fish EW, Tucker SK, Peterson RL, Eberhart JK, Parnell SE. Loss of tumor protein 53 protects against alcohol-induced facial malformations in mice and zebrafish. *Alcohol Clin Exp Res*. 2021, Oct;45(10):1965-1979. PMCID:PMC8602736
- Boschen KE, Fish EW, Parnell SE. Prenatal alcohol exposure disrupts Sonic hedgehog pathway and primary cilia genes in the mouse neural tube. *Reprod Toxicol*. 2021, Oct;105:136-147. PMCID:PMC8529623
- Rodriguez CI, Vergara VM, Calhoun VD, Savage DD, Hamilton DA, Tesche CD, Stephen JM. Disruptions in global network segregation and integration in adolescents and young adults with fetal alcohol spectrum disorder. *Alcohol Clin Exp Res*. 2021, Sep;45(9):1775-1789.
- Roos A, Wedderburn CJ, Fouche JP, Subramoney S, Joshi SH, Woods RP, Zar HJ, Narr KL, Stein DJ, Donald KA. Central white matter integrity alterations in 2-3-year-old children following prenatal alcohol exposure. *Drug Alcohol Depend*. 2021, Aug 1;225:108826. PMCID:PMC8299546
- Sidik A, Dixon G, Buckley DM, Kirby HG, Sun S, Eberhart JK. Exposure to ethanol leads to midfacial hypoplasia in a zebrafish model of FASD via indirect interactions with the Shh pathway. *BMC Biol*. 2021, Jul 1;19(1):134. PMCID:PMC8247090
- Chang RC, Thomas KN, Mehta NA, Veazey KJ, Parnell SE, Golding MC. Programmed suppression of oxidative phosphorylation and mitochondrial function by gestational alcohol exposure correlate with widespread increases in H3K9me2 that do not suppress transcription. *Epigenetics Chromatin*. 2021, Jun 15;14(1):27. PMCID:PMC8207718
- Boschen KE, Ptacek TS, Berginski ME, Simon JM, Parnell SE. Transcriptomic analyses of gastrulation-stage mouse embryos with differential susceptibility to alcohol. *Dis Model Mech*. 2021, Jun 1;14(6):dmm049012. PMCID:PMC8246266

CIFASD Visibility
Virtual ISBRA/RSA June 2021

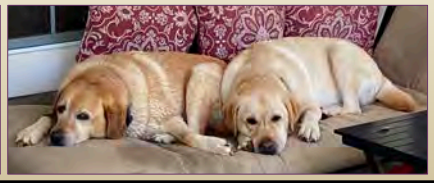
CIFASD Studies on the Role of Genetics in FASD

Pre-recorded talks and live virtual Q&A

Michael Charness - Introduction
Amanda Mahnke
Johann Eberhart
Scott Parnell
Olivia Weeks

Michael Charness - Moderator & Discussant

Cameos by Cheval and Renard



CIFASD Visibility
ESBRA October 2021
Romania - Virtual

CIFASD Symposium Session:

Diagnosis and Interventions in FASD: From Genes to eHealth

Edward Riley
Johann Eberhart
Scott Parnell
Mike Suttie
Christie Petrenko

CIFASD Visibility – Coming in 2022 or 2023
Symposia / Talks

EUROPEAN FASD ALLIANCE

EUFASD

September 11 - 14, 2022
Arendal, Norway

Using technology to move forward on the recognition and treatment of FASD

- Edward Riley
- Mike Suttie
- Sarah Mattson
- Christie Petrenko

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 and Fetal Alcohol Syndrome

- Edward Riley

CIFASD Outreach and Education

ASK Edward Riley about fetal alcohol syndrome

Exposure to alcohol during gestation can have far reaching impacts. ASK leading FASD expert Edward Riley your questions.

Expert answers & opinions: Edward Riley

7 QUESTIONS ANSWERED

ADDICTION | PARENTING | FETAL ALCOHOL SYNDROME

ASK Christie Petrenko about evidence-based treatments for fetal alcohol spectrum disorder

Why is it paramount that people with FASD get access to treatment as quickly as possible and what works best? ASK leading authority in FASD, Dr Christie Petrenko.

Expert answers & opinions: Christie Petrenko

ASK YOUR QUESTION NOW

FOR MENTAL HEALTH PROFESSIONALS | FASD | MENTAL HEALTH

Psychwire

CIFASD Outreach and Education

Jeff Wozniak participated in the FASD Hope podcast.

74 - Development is Lifelong - A Conversation with Dr. Jeffrey Wozniak

August 10, 2021

FASD Hope is a podcast about Fetal Alcohol Spectrum Disorder (FASD), through the lens of parent advocates with over nineteen years of lived experience.

The Foroud U01 team at **IU** is being interviewed for FASD Hope this month.

Christie Petrenko was on Jeff Noble's podcast in July 2021.

The FASD Success Show

Petrenko: Changing the Story About FASD

28,678	102
Downloads	Episodes

CIFASD Outreach and Education

- **Christie Petrenko** and her team launched a new ECHO FASD project in **Chile** in partnership with PAHO. There is interest to implement in the Dominican Republic as well.
- They also released a new documentary on FASD - #FASDStrong.

Project ECHO **ECHO FASD**

#FASDStrong

Tuesday, October 26, 2021 - 1:00 to 5:00 p.m. via Zoom

Fetal Alcohol Syndrome and the Courts

Introduction by **Tom Donaldson** and talk by **Christie Petrenko** attended by >330 attendees.

CIFASD Outreach and Education

UNIVERSITY of ROCHESTER MEDICAL CENTER Newscenter

Thriving while living with fetal alcohol spectrum disorders (FASD)

November 5, 2021

Rochester psychologists make the case for an approach to FASD based on patients' strengths rather than deficits.

Christie Petrenko will also be doing an intensive FASD workshop training to Pediatric Residents at UR every 6 weeks.

CIFASD Outreach and Education

Several CIFASD investigators promoted and participated in the FASD fun run in September.

CIFASD Outreach and Education

CIFASD Outreach and Education

FASD NEWS

Enroll in Study to Help Understand and Treat FASD and Earn $60 Incentive

DiG FASD (Dissecting the Genetic Contribution to FASDs), an ongoing clinical and genetic research study at the Indiana University School of Medicine, is seeking participants to help understand what makes each person with FASD unique and how genetics play a role in the effects of prenatal alcohol exposure.

Anyone with an FASD or prenatal alcohol exposure is eligible, including children and adults of any age.

Participates can earn up to $60 for helping researchers learn more about FASD.

The study can be completed entirely from home. Participants will be asked to fill out some online forms, take pictures of their face, and provide a saliva sample for DNA. All information shared with the researchers is kept secure and confidential.

Recent CIFASD Investigator Awards & Honors

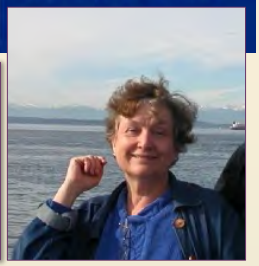
Emory receives $5.7 million NIH award to join national study on early brain development

Woodruff Health Sciences Center | Oct. 28, 2021

Emory School of Medicine researchers have been awarded a five-year, $5.7 million grant to lead Emory's role as one of 25 sites in NIH's HEALthy Brain and Child Development (HBCD) study.

EMORY UNIVERSITY SCHOOL OF MEDICINE | Department of Psychiatry and Behavioral Sciences

Claire Coles honored as a Distinguished Mentor, Science, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 2021.



Congratulations!

Recent CIFASD Investigator Awards & Honors

PRIZE-WINNING

RESEARCHER Around THE Green

BETHEL COLLEGE

JOHANN EBERHART '93

BIOLOGY, PSYCHOLOGY

BETHEL COLLEGE ALUMNI MAGAZINE

Growing up in Topeka, Johann dreamed about leaving Kansas after high school to pursue his love of science.

But a teacher in his high school gifted program, Lila (Waltner) Bartel '68, pushed him to check out Bethel. He clicked with biology professor, the late Wayne Wiens '58, and psychology professor Dwight Krehbiel '69. "I loved them – they had a passion for science and for what they were doing," Johann says.

In particular, he says, his developmental biology class with Wayne "blew my mind – it was amazing." He particularly remembers doing an independent research project in retinal development using chicken embryos.

Johann completed a master's degree at Wichita State University and a Ph.D. at the University of Missouri-Columbia, both in biology, and found his own passion in the research lab. It led him to a position as associate professor of molecular biosciences at the University of Texas at Austin in 2014 and, in 2019, to a multi-year multi-million-dollar research grant.

Johann received the Sustaining Outstanding Achievement in Research (SOAR) award from the National Institute of Dental and Craniofacial Research, in part for his work on Fetal Alcohol Spectrum Disorder, specifically how genes interact with the chemical. The award goes to only two individuals a year.

"My interest [in FASD] got started through an interest in phenotypic variations," he says. "FASD is remarkable in that way. Some children have exposure [to alcohol in the womb] and seem completely normal and some have very distinct physical manifestations.

"Over the long term, we have a goal of being able to identify and predict how chemicals are going to interact in humans. We've had some luck with that, working with alcohol. We will be looking at mutations in gene pathways and similar defects."

Johann hasn't forgotten where it all started.

"An added benefit, in the times we find ourselves in now, with racial and social injustice – at a small liberal arts college, you can't be insular [in choosing] your friends.

"You have to have a diverse group – only hanging out with biology majors would be a pretty small group of people. At Bethel, I got exposed to a lot of personalities and ideas."

A big [reason for attending a school like Bethel] is you get to know your professors better," he says. "I really cherish the relationships with Wayne and Dwight. That's the most important.

Congratulations!

Johann Eberhart featured in his alumni magazine and put together a career development and research talk available on YouTube.

Recent CIFASD Investigator Awards & Honors

Congratulations!

NIAAA-funded spin-off R21 (Riley, PI)
Smartphone-based application to assist in the screening/diagnosis of FASD

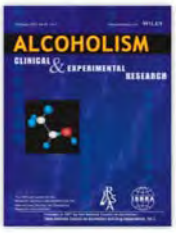
Recruited into the FASD Field - New

- Alex Tseng
- Alexandra Perez
- Alison Noble
- Alysson Muotri
- Annika Montag
- Carl Keen
- Carson Kautz-Turnbull
- Catherine Lebel
- Catheryn Wilson
- Charles Ben Lovely
- Charlis Raineki*
- Chris Nellaker
- Christine Austin
- Christopher Garcia
- Cleber Trujillo
- Desirè Buckley
- Diego Mesa
- Dorothy Strickland
- Eileen Moore
- Elizabeth Godin
- Erik de Water
- Florence Roussotte
- Gaby Ritfeld
- Ganz Chockalingam
- Gissela Borrego
- Gretchen Bandoli
- John Colby
- Katherine Narr
- Kelly Frazer
- Kristina Uban
- Laura Parfrey
- Li Shen
- Miguel del Campo*
- Mike Suttie
- Mingze Yuan
- Natasia Courchesne
- Nirelia Idrus
- Olivia Weeks
- Peter Hammond
- Puja K. Mehta
- Ralf Haesuler
- Ritika Ghosal
- Rob Lipinski
- Shameena Bake
- Shantanu Joshi
- Smita Paranjape
- Stefanie Bodison
- Tamara Bodnar
- Tom Rackham
- Utku Demir
- Yaling Yang
- Yun Liang
- Zeyu Fu
- Zvi Shapiro

* Working in alcohol field previously, but recruited to FASD and/or CIFASD research

Invited Guests – Monthly Meetings

- Sandra and Joe Jacobson, CIFASD Phase I PIs, presented on their recent findings in *ACER.*



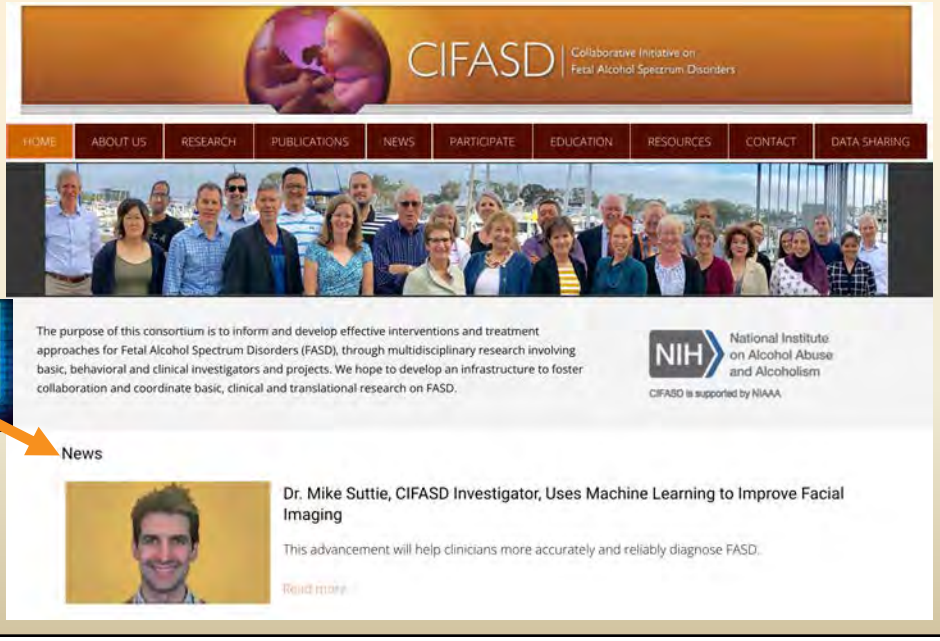
ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Original article

Evolution of the Physical Phenotype of Fetal Alcohol Spectrum Disorders from Childhood through Adolescence

Sandra W. Jacobson, H. Eugene Hoyme, R. Colin Carter, Neil C. Dodge, Christopher D. Molteno, Ernesta M. Meintjes, Joseph L. Jacobson

www.CIFASD.org



CIFASD.org Data Sharing

ACCESSING CIFASD RESEARCH DATA

The CIFASD makes archived data available for discovery and validation research, with the ultimate goal of improving diagnoses, interventions, and treatment of FASD. Archived data from the previous three Phases of CIFASD vary in terms of population studied and outcome variables.

For more information on each Phase and the type of data that are available, please click on the appropriate cell within the Table below.

PHASE	DEMOGRAPHICS	DYSMORPHOLOGY	3D FACIAL IMAGING	NEUROBEHAVIOR	GENETIC DATA	BRAIN VOLUME	INFANT DATA	CYTOKINE DATA
Phase 1 (2003-2007)	✔	✔	✔	✔				
Phase 2 (2007-2012)	✔	✔	✔	✔	✔	✔	✔	
Phase 3 (2012-2017)	✔	✔	✔	✔	✔	✔	✔	✔

To request data, an application for data use must be submitted online via the CIFASD Data Access Request Form.

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

CIFASD4 Progress Tracking

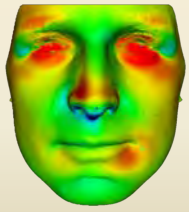
Wozniak U01 Neuroimaging	Current Month	Cumulative Total	May 2022 Goal	% to Goal	Overall Goal	Completion Goal Date	May 2018 Goal	May 2019 Goal	May 2020 Goal	May 2021 Goal	May 2022 Goal
MRI Scan #1	*Total =*	*101*									
MRI Scan #1 - PAE	0	49	45	109%	45	5/31/2020	15	30	45	45	45
MRI Scan #1 - CON	0	52	45	116%	45	5/31/2020	15	30	45	45	45
Cognitive Evaluation (Mattson NB Battery)	*Total =*	*101*									
Cognitive evaluation - PAE	0	49	45	109%	45	5/31/2020	15	30	45	45	45
Cognitive evaluation - CON	0	52	45	116%	45	5/31/2020	15	30	45	45	45
MRI Scan #2	*Total =*	*77*									
MRI Scan #2 - PAE	0	40	30	133%	30	1/1/2022	0	0	10	20	30
MRI Scan #2 - CON	0	37	30	123%	30	1/1/2022	0	0	10	20	30
	Start	**End**					Cumulative - at the end of each year.				
Current month (defined by project) =	10/29/2021	11/29/2021									
Date of project numbers update entry =	11/29/2021										

Resource Sharing

UC San Diego

UNIVERSITY of ROCHESTER

UNIVERSITY OF OXFORD

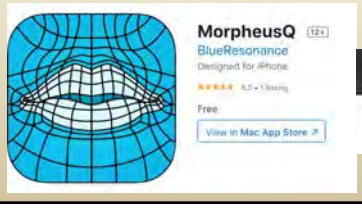


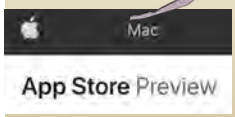
eHealth and App Development Subaward



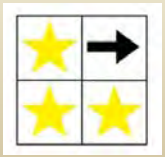




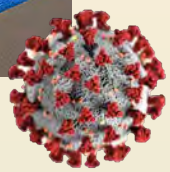








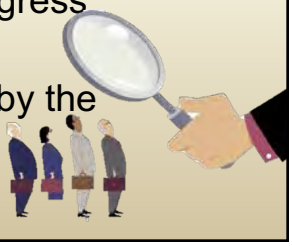

Recent Activities





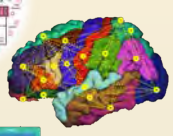
Science Advisory Board Members


- Science Advisory Board assisted greatly with reviews and rankings of the 1-page and 5-page potential CIFASD5 project proposals
- CIFASD4 Annual Reviews will be completed following the this meeting utilizing the progress reports and presentations
- Reviews will be distributed to Project PIs by the Consortium Coordinator early 2022

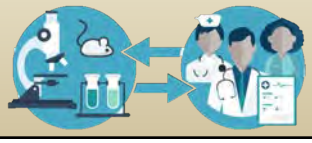
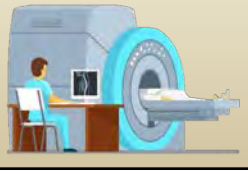
CIFASD5





- **1** Administrative Resource
- **1** Diagnostic-Telemedicine Resource
- **1** Data Coordination Resource
- **8** U01 Research Projects
- **2** UH2 Developmental Projects
- Submitted to NIH **August 2021**
- Earliest start date **June 2022**




CIFASD5

Proposed Composition
U24: Administrative Resource of the CIFASD - Edward Riley (SDSU)
U24: Diagnostic-Telemedicine Resource - Miguel del Campo (UCSD)
U24: Data Coordination Resource - Leah Wetherill (IUSM)
U01: Cardiovascular Disease in FASD - Caroline Burns and Geoff Burns (BCH)
U01: Whole Body Effects of PAE Across the Life Span: Early Markers of and Clinical Interventions for Children and Adolescents in Ukraine - Christina Chambers (UCSD)
U01: A Multisite Study of PAE: Effects of Inflammation and Endocrine Dysfunction in Adulthood - Claire Coles and Joanne Weinberg (Emory and UBC)
U01: Designing a Hybrid Intervention Strategy to Reduce Alcohol Exposed Pregnancies - Ralph J. DiClemente (NYU)
U01: Assessment of FASD Using Novel Web-Based Tools - Sarah Mattson (SDSU)
U01: Leveraging Technology to Increase Quality of Life for FASD Across the Lifespan - Christie Petrenko and Cristiano Tapparello (UR)
U01: Defining Translational Approaches for the Image-based Detection of PAE - Michael Suttie (Oxford)
U01: tDCS and Cognitive Training in FASD - Jeffrey Wozniak (UMN)
UH2: Lifelong Impact of PAE on Stem Cell Dynamics and Cellular Aging - Amanda Mahnke (TAMU)
UH2: Heightened Lifelong Inflammatory Burden as a Driver of Early Functional Decline Following PAE - Tamara Bodnar and Charlis Raineki (UBC)

Special Thanks to:

Joe Wang

Elizabeth Powell

Bill Dunty

Michael Charness

Jennifer Thomas

Jill Vander Velde

Science Advisory Board

Publications and Data Sharing Committees

Thank You

Thank You

NIH National Institute on Alcohol Abuse and Alcoholism

Dysmorphology Research Resource

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DYSMORPHOLOGY RESEARCH RESOURCE
New Findings June 2021 and December 2021

- Aim #1:

Assure consistency and accuracy in recognition of FASD at all CIFASD project sites. Additionally, we will use the established CIFASD training protocol to provide ongoing training

- Between June 2021 and December 2021, using the CIFASD physical examination protocol and classification system, neither Dr Jones nor Dr. del Campo performed any face-to-face physical examinations in any of the CIFASD clinical sites.

- However, to validate the use of telemedicine as a way to diagnose FASD, Dr. Jones and Dr. del Campo performed physical examinations by telemedicine at the UCSD/RADY Children's Hospital FASD Clinic on an average of 4 children per week who had been prenatally exposed to alcohol.

- In addition, Dr. Jones trained via telemedicine Dr. Zvii. -, a postdoctoral fellow in psychiatry at Emory working with Dr. Coles and Kable to perform physical examinations to diagnose FAS and Dr. Jones and Dr del Campo trained face-to-face 12 Pediatric residents and fellows who previously had no knowledge regarding the diagnosis of FASD

DYSMORPHOLOGY RESEARCH RESOURCE
New Findings June 2021 to December 2021

Significant Results from the Last 6 months

Aim #2: Further develop and refine the telemedicine approach.

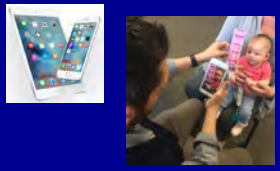
- Completed a paper entitled "The Use of Telemedicine for the Physical Examination of Fetal Alcohol Spectrum Disorder" and submitted it on September 16, 2020 to Alcoholism: Clinical and Experimental research. It was published December 14, 2020. The study documented that Telemedicine is a valid and reliable method for examination of the physical features of FASD.

- Held multiple meetings in Alaska and trained on physical examination and Morpheus Q two groups or providers including
  - the FASD diagnostic groups part of the comprehensive FASD diagnostic program of the Department of health and Social Services led by Hope Finkelstein
  - the Behavioral health providers consortium

Using Telemedicine (TM) for physical examination in FASD

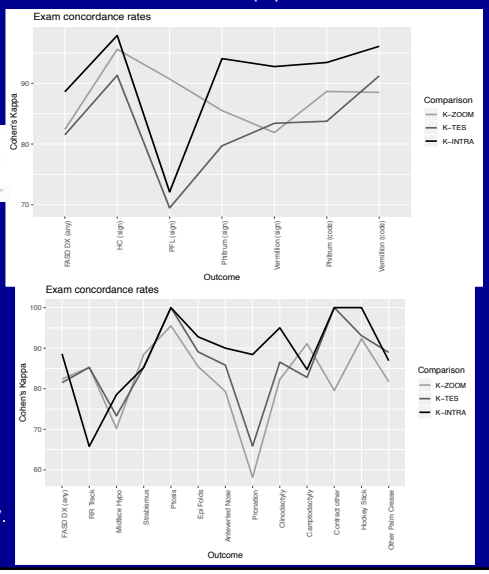
Transportable exam system for TM (TES)

Handheld smart device system for TM (ZOOM)



Alcohol Clin Exp Res. 2021 Feb;45(2):409-417. doi: 10.1111/acer.14533. Epub 2021 Feb 8. PMID: 33316074.

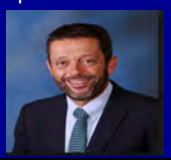
Agreement between face to face (F2F) and Telemedicine (TM) exams for the evaluation of the physical features of FASD

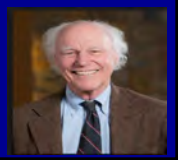


Results and conclusion

Telemedicine using TES or hand held devices is reliable and valid for the exam of the physical features of FASD. **We believe more precise measurements and more objective assessment of the features is necessary even face to face. We are trying new tools to improve precision and objectivity.**

The use of TM will increase the ability to make a diagnosis for all affected patients at an earlier age, in order to provide prompt services and improve outcomes





Alaska collaborations for CIFASD 4/5

- Hope Filkenstein

The State of Alaska Department of Health & Social Services funds a network of regionally based multidisciplinary/interdisciplinary FASD diagnostic teams. There is a limited number of FASD informed medical providers in the State.

- Marilyn Pierce Bolger

State of AK sponsored Neurodevelopmental Partners meeting

Ptarmigan Connections

Providence Hospital

Regional Native health clinics

Ryan Ray Set Free Alaska

Table 1. Alaska Behavioral Health Regions

Behavioral Health Region	Borough/Census Area
Anchorage Municipality	Anchorage Municipality
Fairbanks North Star Borough	Fairbanks North Star Borough
City and Borough of Juneau	City and Borough of Juneau
Kenai Peninsula Borough	Kenai Peninsula Borough
Matanuska-Susitna Borough	Matanuska-Susitna Borough
Northwest Region	Nome Census Area
	North Slope Borough
	Northwest Arctic Borough
Other Interior Region	Denali Borough
	Southeast Fairbanks Census Area
	Valdez-Cordova Census Area
	Yukon-Koyukuk Census Area
Other Southeast Region – Northern	Haines Borough
	Hoonah-Angoon Census Area
	Petersburg Borough
	Sitka City and Borough
	Skagway Municipality
	Wrangell City and Borough
	Yakutat City and Borough
Other Southeast Region – Southern	Ketchikan Gateway Borough
	Prince of Wales-Hyder Census Area
Y-K Delta Region	Bethel Census Area
	Kusilvak Census Area
Southwest Region	Aleutians East Borough
	Aleutians West Census Area
	Bristol Bay Borough
	Dillingham Census Area
	Kodiak Island Borough
	Lake and Peninsula Borough

Figure 3. Number of Assessments by Client Community

Morpheus Q Alaska

- trained **providers** from 9 diagnostic teams, last in June and July 2021
- Sent out 6 iPhones
- Ganz trained one on one multiple providers.
- Sarah Evans. NP with scholarship Duke to coordinate the project and most likely an Alaska subaward CIFASD 5

Examination techniques

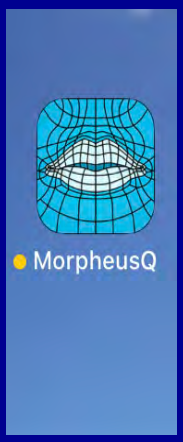
- Precise measurements
- Subjective evaluation of features

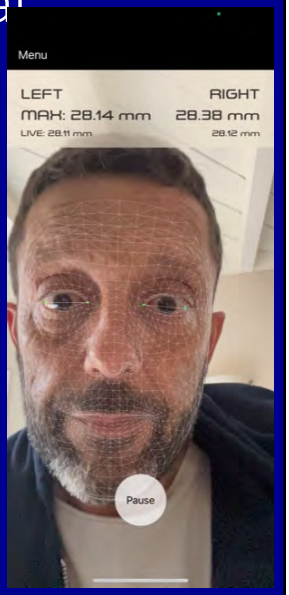
- 3 key features
  - Short palpebral fissure length
  - Smooth philtrum
  - Narrow vermillion of upper lip with loss of Cupid's bow shape

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

How to improve assessment of physical features

Precise measurement in 3-D photo





Continuous Morph scales for shapes of philtrum and upper lip

Watch 3 D image taken by Morpheus Q real time.

CIFASD5: Telemedicine diagnostic core U24

- Submitted proposal for CIFASD 5.
- Collecting preliminary data
- Talking to providers
- Helping set up collaborations in the Rady system

Preliminary data on comparison of standard methods and Morpheus Q in the clinic in 30 cases.

In 10 cases PFL measurements were also compared with a briefly trained resident.

Method (i)	Method (j)	Mean Difference (i-j)	Standard Deviation
PFL Ruler	PFL Mesh	0.06	0.12
	PFL Rotational	0.05	0.14
	PFL Ruler Trainee	0.17	0.08
PFL Mesh	PFL Rotational	-0.02	0.09

	Mean (SD) or n(%)
Age	15.70 (17.84)
Gender	
Male	17 (56.67%)
Female	13(43.33%)
Ethnicity	
African American	1 (3.33%)
Arab	3 (10.0%)
Caucasian	13 (43.33%)
Hispanic	13 (43.33%)

The difference between ruler measurement of PFL by the expert, considered standard, is less than 1mm with both Morpheus Q techniques but greater than 1 mm with a trainee

Morpheus Q will improve accuracy

Method (i)	Method (j)	% of agreement n (%)	Cohen's κ Coefficient
Philtrum Likert Score	Philtrum Morpheus Frontal	29 (96.7%)	0.89
	Philtrum Morpheus angle	30 (100%)	1.00
Philtrum Morpheus Frontal	Philtrum Morpheus angle	29 (96.7%)	0.89
Upper Lip Likert Score	Upper lip Morpheus	27 (90.0%)	0.73

The evaluation of the philtrum and upper with lip with lip-philtrum guide 5 point Likert score by an expert, considered standard, is in almost perfect agreement (K>0.8) with the evaluation using continuous scales in Morpheus Q for the philtrum and substantial agreement (K>0.6) for the upper lip. For the upper lip in Morpheus, the cut-off may have to be revised. The cut-offs were set by experts.

DYSMORPHOLOGY RESEARCH RESOURCE
New Findings June 2021 to December 2021

Significant Results from the Last 6 months

- Aim #3: Expand on the the San Diego FASD research subject pool that we have established at UCSD Rady Children's Hospital
  - We have recruited 7 new subjects prenatally exposed to alcohol seen in our UCSD/Rady Children's Hospital FASD Clinic for a total of 278 subjects recruited overall.
  - We have recruited and referred 8 subjects to Dr. Sarah Mattson's U01 Decision Tree at SDSU in the last 6 months for a total of 141 subjects referred overall
  - We collected and banked a total of 33 plasma samples to date from FASD Registry participants who enrolled in the FASD Research Biorepository. However, biorepository collections have been halted since March 2020 due to the COVID-19 pandemic; thus, no new samples were collected since that date.

Plans for Final 6 Months

- Schedule in real time telemedicine training with physicians and other healthcare providers in Alaska to ensure expertise in both standard assessments of the facial features with a ruler and lip-philtrum guide, as well as with the different features of the Morpheus Q App. We will then be able to develop a cadre of physicians and other healthcare providers in Alaska that will allow us to test the Morpheus Q App in hopes of establishing an FASD Prevention Program in Alaska in the future
- See patients by Telemedicine and Face-to-Face at our UCSD/Rady Children's Hospital FASD Clinic, continue to add subjects to our Research Registry, continue to recruit and refer subjects to Dr, Sarah Mattson's U01 Decision Tree at SDSU and to other clinical studies when they are requested as well as blood and urine samples from our biorepository
- Train by telemedicine more physicians and other health care providers on how to diagnose FAS

U01: Human Genetics

Tatiana Foroud
Leah Wetherill

SCHOOL OF MEDICINE

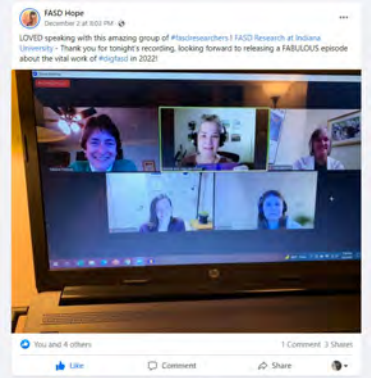
Aim 1: Online Recruitment and Participation

- Focus has been to try a range of resources to identify most effective approaches to engage potential research participants

- Began social media blitz on June 25, 2021

SCHOOL OF MEDICINE

Aim 1: Online Recruitment and Participation



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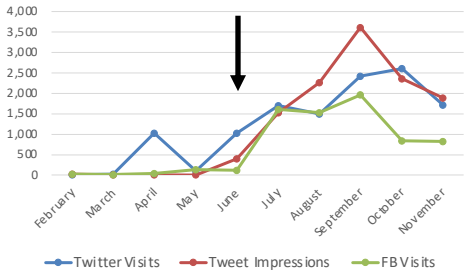
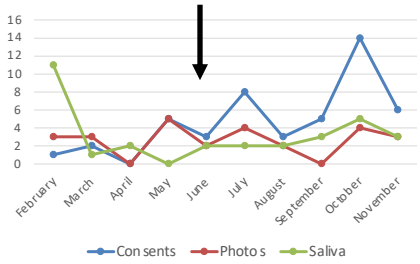
Online Recruitment: Lessons Learned





- Increased engagement in DigFASD based on social media outreach
- Did not result in substantial increase in enrollment

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Current Progress

- Target enrollment = 2,000
  - Current # consented = 609
  - Current # with some demographic or PAE information = 526
  - Current # with 2D photos = 346
  - Current # with saliva = 290
- Collaborate with other CIFASD4 projects
  - Implemented Brief Assessment of Individual Neurobehavior (BRAIN online (Mattson)
    - N=4 completed to date
  - Implemented Adult Health Questionnaire (Coles, Weinberg)
    - N=8 completed to date

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Aim 2: Genetics of FASD

- Original Aim: Obtain whole exome sequencing (WES)
  - Functional variants
  - Analyze using 2D and 3D phenotypes
  - Sample sizes from DigFASD + CIFASD4 too small to use as discovery, use sample to inform other projects for specific hypotheses
- Refocused efforts to support CIFASD4 projects using data from CIFASD 2 + CIFASD 3
  - WES (gene-based analyses)
    - Data for N=235 individuals with PAE
  - Genome-Wide SNPs (variant-based analyses)
    - Data for N=545 individuals with and without PAE
    - Re-cleaned and re-imputed using up-to-date methods and databases

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Aim 2: Genetics of FASD

- WES and GWAS can complement each other
- Analyses in GWAS allows test of association for alcohol*genotype interaction: does an individual with PAE and a particular genotype have a different outcome than an individual without PAE and the same genotype?
- Phenotypes from different CIFASD projects
  - Neurobehavioral measures (Mattson)
  - Brain volumes (Sowell)
  - 3D signature phenotypes (Suttie)
- Initial analyses focused on neurobehavioral measures to examine role of APOE

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Collaboration with K. Hashimoto-Torii (UH2)

Looked for biomarkers in immune cells, plasma and brain
- PAE decreased *APOE* levels in all 3

Administration of COG-133 (functions like *APOE*)
- Rescued motor learning
- Decreased anxiety (increased time in open arm of elevated plus maze)

Is there any role for *APOE* in human studies of PAE?
- SNP rs584007 in *APOE* is an eQTL
- Affects expression of *APOE* in brain

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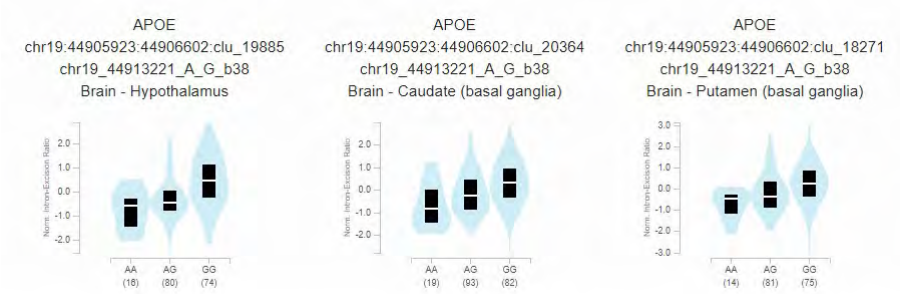
Collaboration with Dr. Hashimoto-Torii (UH2) And Sarah Mattson

- eQTL data (GTEx Portal): A allele decreases expression of APOE in different brain regions



GTEx Portal

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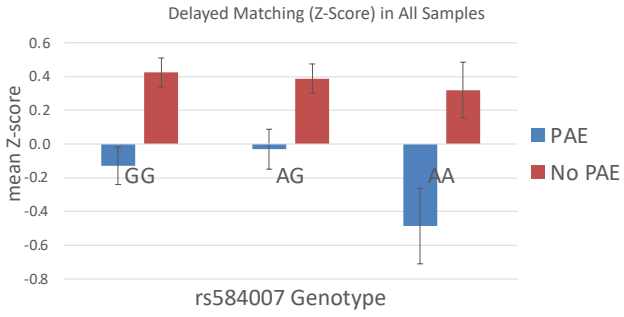
Collaboration with Dr. Hashimoto-Torii (UH2) And Sarah Mattson

GWAS in CIFASD 2 + 3 samples: delayed matching z-score

- Significant effect for allele: A allele associated with lower z-scores, p=0.014
- Individuals with AA genotype and PAE have lower scores vs those with AA genotype without PAE (Bonferroni corrected p=0.045)

Exposure	Genotype	N
PAE	GG	78
PAE	AG	68
PAE	AA	19
No PAE	GG	129
No PAE	AG	128
No PAE	AA	35



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Prepare for Close of CIFASD4 Data

- Will obtain WES and GWAS for all individuals with PAE in CIFASD4
  - DiGFASD (online) + CIFASD4 projects
- Complement with data from CIFASD 2 + 3 participants with PAE

- Combined GWAS projected # = 1,196
- Combined WES projected # = 713

- Continue to collaborate with CIFASD4 investigators with potential hypotheses
- All genetic data files will be uploaded and available

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NEUROIMAGING PROJECT UPDATE

Jeff Wozniak, Ph.D.
University of Minnesota
December 2021

THE UNIVERSITY OF MINNESOTA'S MASONIC INSTITUTE FOR THE DEVELOPING BRAIN



THE UNIVERSITY OF MINNESOTA'S MASONIC INSTITUTE FOR THE DEVELOPING BRAIN

THE UNIVERSITY OF MINNESOTA'S MASONIC INSTITUTE FOR THE DEVELOPING BRAIN

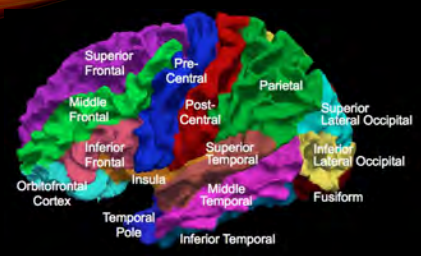
- Child & adolescent brain research
  - Academic Psychology research
  - Medical School research (incl. all FASD projects)
- Child & adolescent clinics
  - Psychiatry
  - Pediatric Psychology (incl. FASD Clinic)
  - Pediatric Neurology / neuropsychology
  - Developmental Pediatrics
- Institute on Community Integration
- Going forward:
  - Clinics, dedicated research space, faculty offices, 3 Tesla Siemens MRI machine, neuromodulation suites and resources, EEG/ERP, labs, etc. all under one roof.

PHASE 1: BASELINE MRI AND NEUROCOGNITIVE ASSESSMENT

- Target: recruit groups of 45 (PAE) and 45 (controls)
- Age range: 8 – 16 years old at enrollment
- Dysmorphology; MRI scan; neurocognitive testing
- Second scan after 15 month interval

PHASE 2: 15-MONTH FOLLOW-UP MRI

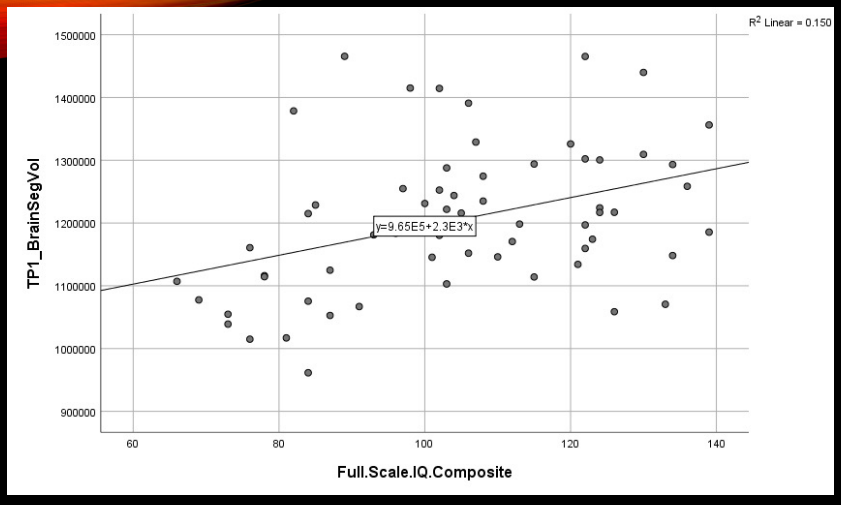
Wozniak U01 Neuroimaging	Current Month	Cumulative Total	Final Goal	% to Goal
MRI Scan #1	Total =	101		
MRI Scan #1 - PAE	0	49	45	109%
MRI Scan #1 - CON	0	52	45	116%
Cognitive Evaluation (Mattson NB Battery)	Total =	101		
Cognitive evaluation - PAE	0	49	45	109%
Cognitive evaluation - CON	0	52	45	116%
MRI Scan #2	Total =	77		
MRI Scan #2 - PAE	0	40	30	133%
MRI Scan #2 - CON	6	37	30	123%



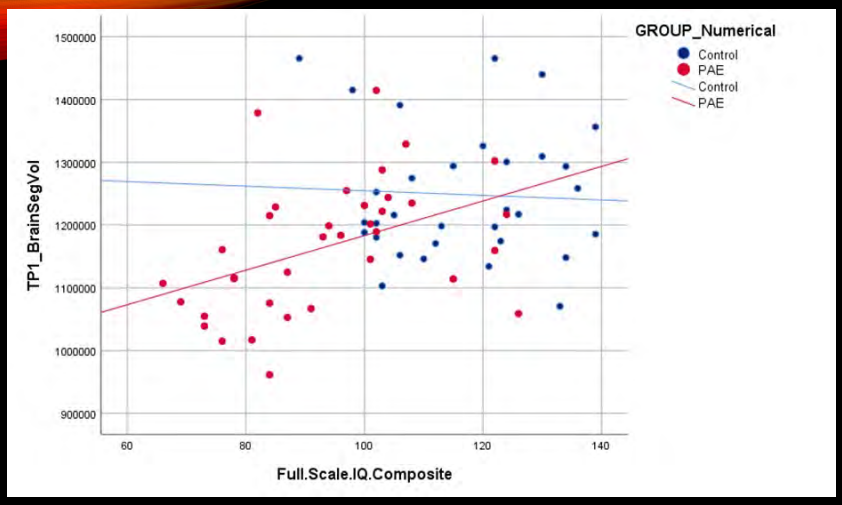
As expected, MRI #1 shows:

- Smaller overall brain volume in PAE
- Smaller cortical volume in PAE
- Smaller white matter volume in PAE
- Smaller subcortical gray matter volumes in PAE

- Evidence that we are studying an affected group



- Clear relationships between MRI#1 and cognition

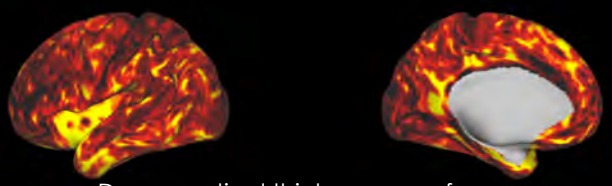


- Differential relationships between MRI#1 and cognition for PAE vs. Control

Analyses in Progress

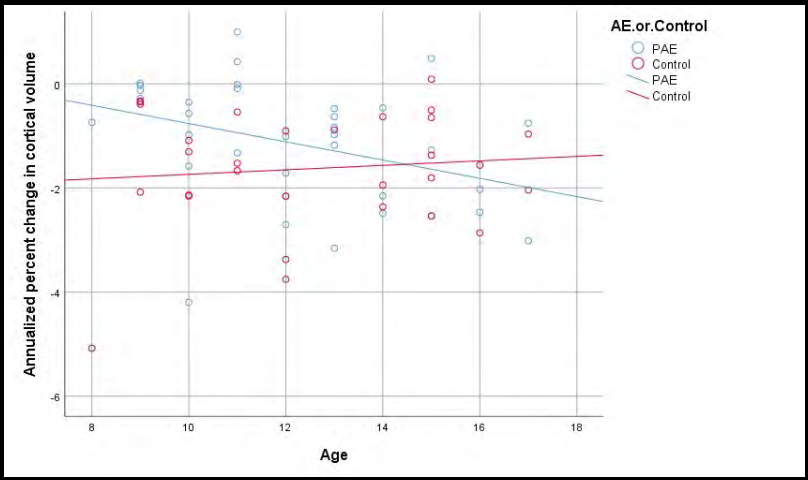
Longitudinal Analysis of Cortical Thickness

- Comparing the *rate* of cortical maturation (thinning) in AE vs control participants.
- Method is robust to larger than expected variations in follow-up time due to COVID-19.
- Other cortical features (regional surface areas, volume, gyrification) can be examined, as well as subcortical anatomy.

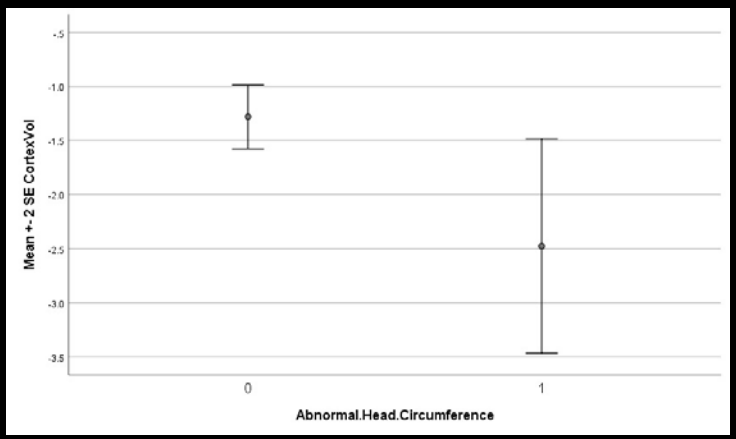


Dense cortical thickness map from CIFASD participant

Symmetrized percent change (annual) in cortical volume by age



Exploring relationships between severity (OFC, here) and a dynamic measure like rate of change in cortical volume



Analyses in Progress

TRACULA

- Individualized tractography of callosal and other major white matter tracts.
- Robust longitudinal pipeline allows for comparison of developmental trajectories in white matter microstructure.
- Can be combined with state-of-the-art diffusion signal modelling methods (e.g. Neurite Orientation and Dispersion Diffusion Imaging and Diffusion Kurtosis Imaging).

Callosal tractography of CIFASD participant

OVERALL PROGRESS:

PUBLICATIONS SINCE DEC, 2020

Roediger, D.J., Krueger, A.M., de Water, E., Mueller, B.A., Boys, C.A., Hendrickson, T.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & Wozniak, J.R. (2021). Hippocampal subfield abnormalities and memory functioning in children with fetal alcohol spectrum disorders. *Neurotoxicology & Teratology; dio:10.1016/j.ntt.2020.106944*.


Neurotoxicology and Teratology

Available online 21 November 2020, 106944

Hippocampal subfield abnormalities and memory functioning in children with fetal alcohol spectrum disorders

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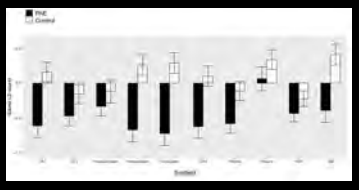


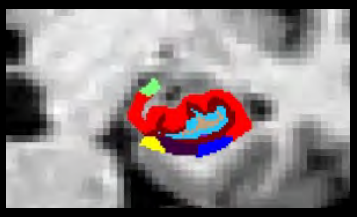
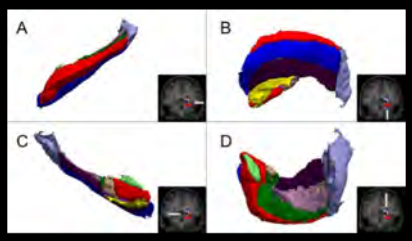


Table 3. Comparison of hippocampal subfield volumes between participants with prenatal alcohol exposure (PAE; n = 40) and control participants (n = 39)

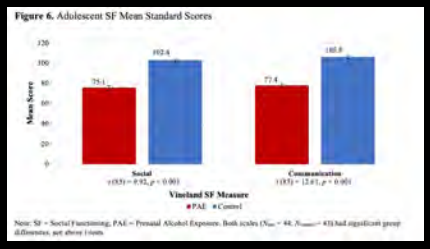
Subfield	Mean		SD		*t*	*p*
	PAE	*Control*	*PAE*	*Control*		
Parasubiculum	132	138	26	29	0.14	0.890
Presubiculum	693	782	101	94	-3.09	0.003
Subiculum	968	1089	136	114	-3.62	0.001
CA1	1599	1760	226	184	-2.48	0.015
CA3	498	523	65	65	-0.72	0.471
CA4	1201	1301	156	135	-2.16	0.034
HATA	96	101	17	14	-0.64	0.523
Fimbria	172	194	37	39	-1.35	0.182
Fissure	197	212	50	41	-0.56	0.579
Tail	1071	1189	163	146	-2.56	0.012

- Compared hippocampal subfield volumes in participants with PAE (*n*=40) vs controls (*n*=39), using a large, age-matched dataset (HCP-Development, *n*=514) for normative standards.
- Five of ten subfields were significantly smaller in PAE group *after* controlling for intracranial volume.
- No correlation between subfield volumes and memory performance.



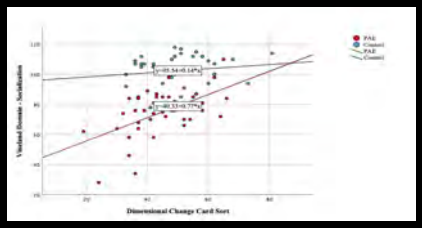
EXECUTIVE AND SOCIAL FUNCTIONING ACROSS DEVELOPMENT

Rockhold, Madeline; Krueger, Alyssa; de Water, Erik; Lindgren, Chris; Sandness, Kristin; Eckerle, Judith; Schumacher, Mariah; Fink, Birgit; Boys, Christopher; Carlson, Stephanie; Fuglestad, Anita; Mattson, Sarah; Jones, K.; Riley, Edward; Wozniak, Jeffrey **(2021: ACER. doi: 10.1111/acer.14538)**



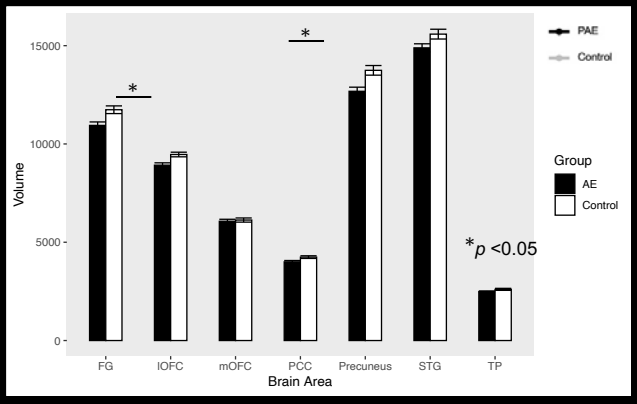
- Examined deficits in SF and EF in young children and adolescents w/ PAE
- Examined the relationship between these deficits in comparison to a control population

- Sig. correlations between SF & EF within the adolescent PAE group; not present in the control group or the early childhood PAE group
  - PAE moderated the EF/SF relationship
- At four-year follow-up (M_{age}= 8.5), those originally in the early childhood PAE group also demonstrated this EF/SF relationship



May highlight sensitive periods for SF and EF training in children with PAE and may suggest that FASD programs consider targeting EF training as a component in social skill interventions

de Water, E., Rockhold, M.N., Roediger, D.J., Krueger, A.M., Mueller, B.A., Boys, C.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & Wozniak, J.R. (under review). Social Behaviors and Gray Matter Volumes of Brain Areas Supporting Social Cognition in Children and Adolescents with Prenatal Alcohol Exposure. (2021: *Brain Research, DOI: 10.1016/j.brainres.2021.147388)*.

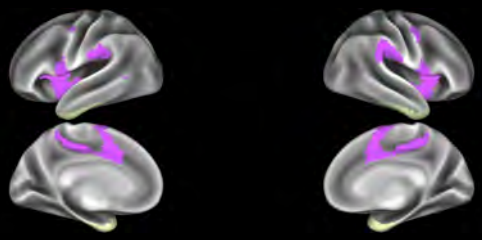


Smaller volumes in "social brain regions" for those with PAE;

Also, PAE group showed lower pro-social behaviors and more bullying / aggression

RESTING-STATE FUNCTIONAL DATA

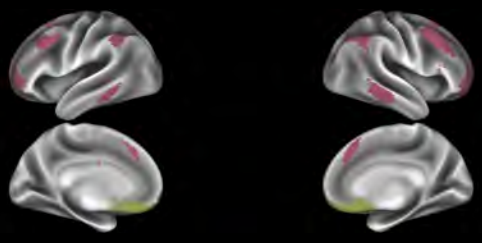
- Methodology development (longitudinal analyses)
- Data from cognitive training & tDCS study (n=35 completers)
- Human Connectome Project pipeline
- Schaefer 400 cortical parcellation
- 17 Yeo functional networks
- 1000 bootstrap iterations



Inflated cortical surface maps showing clusters representing the Salience A (magenta) and Limbic A (cream) networks, respectively (enrichment, p=.002).

RESTING-STATE FUNCTIONAL DATA

- Coupling between networks is altered by co-treatment
- Changes in networks over 1.5 years will be examined in CIFASD-4
- CIFASD-5: further use of these methods to measure treatment impact



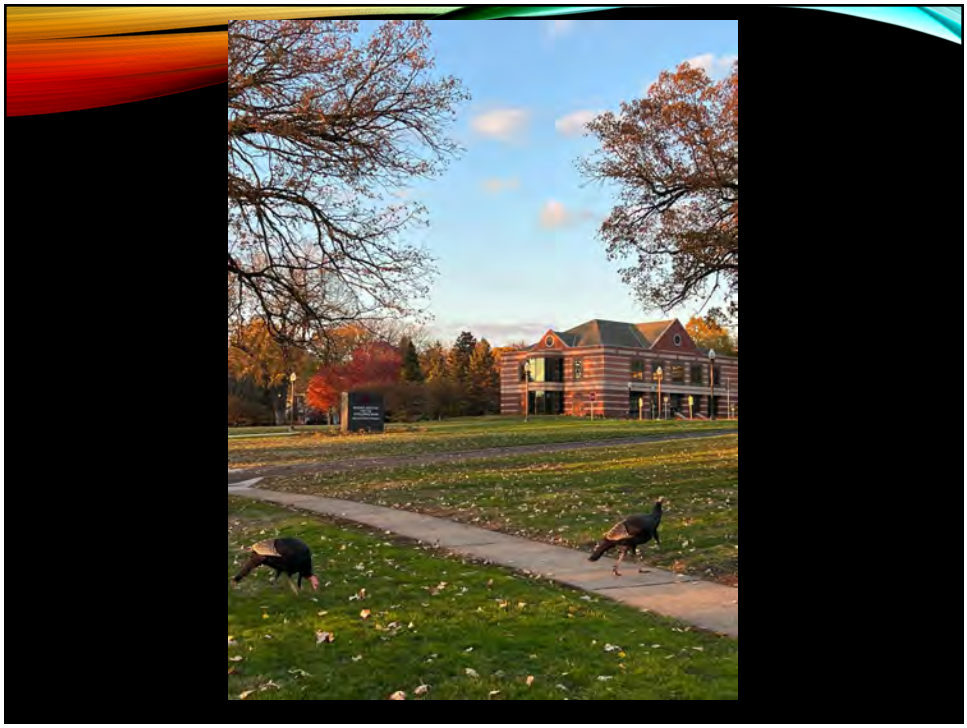
Inflated cortical surface maps showing clusters representing the Control B (maroon) and Limbic B (green) networks, respectively (enrichment, p < .001).

COLLABORATIONS

- **Mattson collaboration:** Neurocognitive data / Decision-tree data: 90 complete
- **Suttie collaboration:** 3D and 2D photos: 90 participants (PAE and controls)
- **Foroud/Wetherill collaboration:** Saliva sent (n=47ish), demographic data uploaded to Central Repository (Box)
- Jones / del Campo: providing dysmorphology data and trainees for remote training (upcoming)
- **Weinberg collaboration:** Blood samples for immune function study: 59 samples from 31 individuals sent, along with demographic, treatment, behavioral, and health-related data shared.
- Assisting **Montag group** in obtaining teeth
- Assisted **Petrenko group** with referrals

ABSTRACTS

- De Water et al. (2021, Feb.) Social Behaviors and Gray Matter Volumes of Brain Areas Supporting Social Cognition in Children and Adolescents with Prenatal Alcohol Exposure; International Neuropsychological Society
- Rockhold, M.N., Krueger, A.M., Schumacher, M.J., Mattson, S.N., Jones, K.L., Riley, E.P., & **Wozniak, J.R.** (2021, Feb.). *The Association of ADHD Symptoms and Learning Ability in Children with Prenatal Alcohol Exposure*. Poster to be presented at the International Neuropsychological Society Conference, San Diego, CA.
- Hendrickson, et al (2021, July). Cognitive training and tDCS as an intervention for prenatal alcohol exposure effects: a fMRI study. Poster presented at the annual meeting of the Organization of Human Brain Mapping



Multisite Neurobehavioral Assessment of FASD

Sarah Mattson, Ph.D.
Center for Behavioral Teratology
San Diego State University

Accomplishments since June 2021

Data Analysis and Paper Preparation

- ★ 1 paper in “early view”
- ★ 1 papers under review at journal
- ★ 2 papers with co-authors

Data Collection

Table 2. Number of Subjects Tested During CIFASD-4

CIFASD Site	FASD-Tree	NP Testing	BRAIN-online
San Diego	234	114	103
Minneapolis	92	101	13
Total	332	215	116
5y Goal	350	210	100
% of 5y Goal	95%	102%	116%

ALCOHOLISM
CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE | Full Access

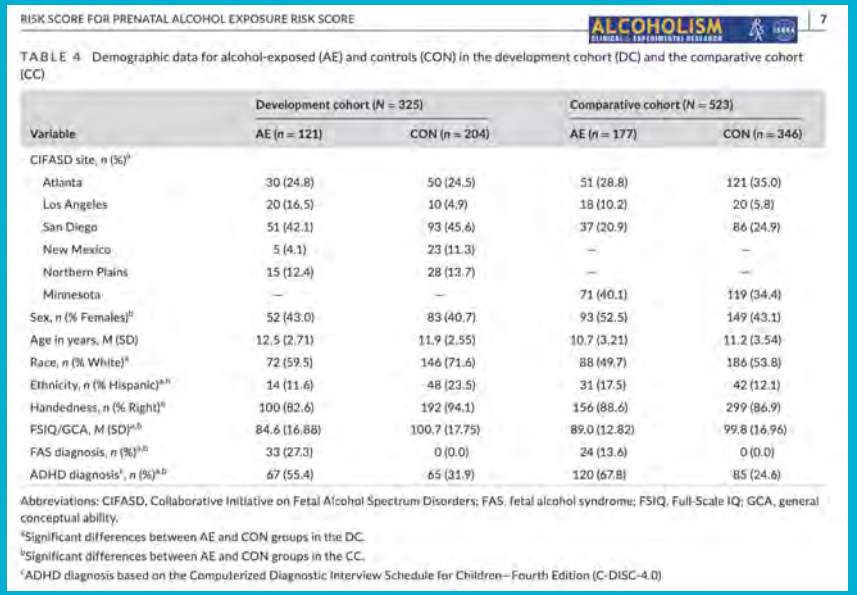
Development and validation of a postnatal risk score that identifies children with prenatal alcohol exposure

Gemma A. Bernes, Natasia S. Courchesne-Krak, Matthew T. Hyland, Miguel T. Villodas, Claire D. Coles, Julie A. Kable, Philip A. May, Wendy O. Kalberg, Elizabeth R. Sowell, Jeffrey R. Wozniak, Kenneth L. Jones, Edward P. Riley, Sarah N. Mattson, the CIFASD ... See fewer authors

First published: 21 November 2021 | https://doi.org/10.1111/acer.14749

General Methods

- Data from CIFASD-2 and CIFASD-3 were analyzed
- Participants were ages 5-17y
- Standard physical exam and neuropsychological assessment
- A risk score was calculated using regression techniques and C2 data and tested in C3
- Subjects were divided into two subgroups: (1) low risk and (2) high risk
- Chi-square (χ^2) determined classification accuracy and ROC curves were produced to assess the predictive accuracy
- Correlations between risk scores and intelligence quotient and executive function scores were calculated



RISK SCORE FOR PRENATAL ALCOHOL EXPOSURE RISK SCORE

ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

7

TABLE 4 Demographic data for alcohol-exposed (AE) and controls (CON) in the development cohort (DC) and the comparative cohort (CC)

	Development cohort ($N = 325$)		Comparative cohort ($N = 523$)	
Variable	AE ($n = 121$)	CON ($n = 204$)	AE ($n = 177$)	CON ($n = 346$)
CIFASD site, n (%)[b]				
Atlanta	30 (24.8)	50 (24.5)	51 (28.8)	121 (35.0)
Los Angeles	20 (16.5)	10 (4.9)	18 (10.2)	20 (5.8)
San Diego	51 (42.1)	93 (45.6)	37 (20.9)	86 (24.9)
New Mexico	5 (4.1)	23 (11.3)	—	—
Northern Plains	15 (12.4)	28 (13.7)	—	—
Minnesota	—	—	71 (40.1)	119 (34.4)
Sex, n (% Females)[b]	52 (43.0)	83 (40.7)	93 (52.5)	149 (43.1)
Age in years, M (SD)	12.5 (2.71)	11.9 (2.55)	10.7 (3.21)	11.2 (3.54)
Race, n (% White)[a]	72 (59.5)	146 (71.6)	88 (49.7)	186 (53.8)
Ethnicity, n (% Hispanic)[a,b]	14 (11.6)	48 (23.5)	31 (17.5)	42 (12.1)
Handedness, n (% Right)[a]	100 (82.6)	192 (94.1)	156 (88.6)	299 (86.9)
FSIQ/GCA, M (SD)[a,b]	84.6 (16.88)	100.7 (17.75)	89.0 (12.82)	99.8 (16.96)
FAS diagnosis, n (%)[a,b]	33 (27.3)	0 (0.0)	24 (13.6)	0 (0.0)
ADHD diagnosis[c], n (%)[a,b]	67 (55.4)	65 (31.9)	120 (67.8)	85 (24.6)

Abbreviations: CIFASD, Collaborative Initiative on Fetal Alcohol Spectrum Disorders; FAS, fetal alcohol syndrome; FSIQ, Full-Scale IQ; GCA, general conceptual ability.

[a]Significant differences between AE and CON groups in the DC.

[b]Significant differences between AE and CON groups in the CC.

[c]ADHD diagnosis based on the Computerized Diagnostic Interview Schedule for Children—Fourth Edition (C-DISC-4.0)

Distribution of Risk Scores

TABLE 6 Distribution of alcohol-exposed (AE) and control (CON) subjects on the risk score

Risk score, *n* (%)	Development cohort		Comparative cohort	
	AE	CON	AE	CON
0 points	7 (5.8)	81 (39.7)	6 (3.4)	98 (28.3)
1 point	21 (17.4)	75 (36.8)	24 (13.6)	106 (30.6)
2 points	16 (13.2)	23 (11.3)	30 (16.9)	64 (18.5)
3 points	19 (15.7)	14 (6.9)	34 (19.2)	42 (12.1)
4 points	33 (27.3)	10 (4.9)	61 (34.5)	28 (8.1)
5 points	25 (20.7)	1 (0.5)	22 (12.4)	8 (2.3)

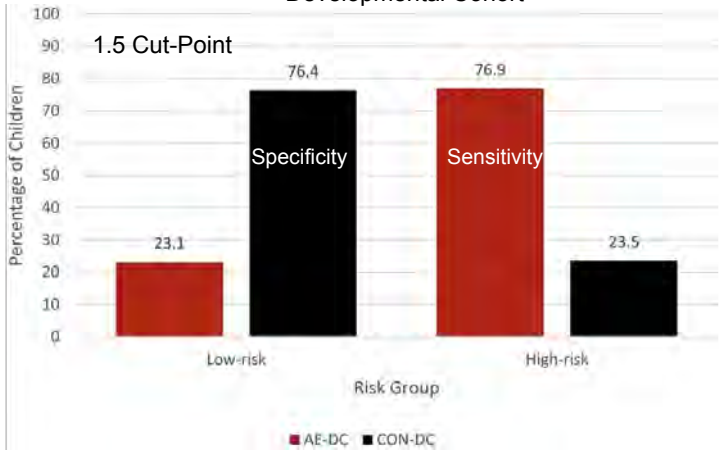
Overall accuracy was 78.8% in DC and 73.6% in the CC

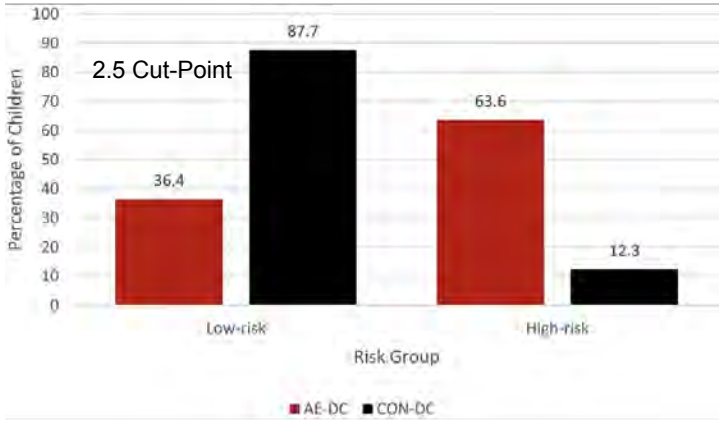
- Risk scores were categorized as low risk and high risk and two different cut-points were tested (based on ROC analysis)
  - Low (0-1) vs. High (2-5)
  - Low (0-2) vs. High (3-5)

Measure	High: 2-5	High: 3-5
Overall Accuracy	76.6%	78.8%
Sensitivity	76.9%	63.6%
Specificity	76.4%	87.7%
PPV	66.0%	75.5%
NPV	84.8%	80.3%

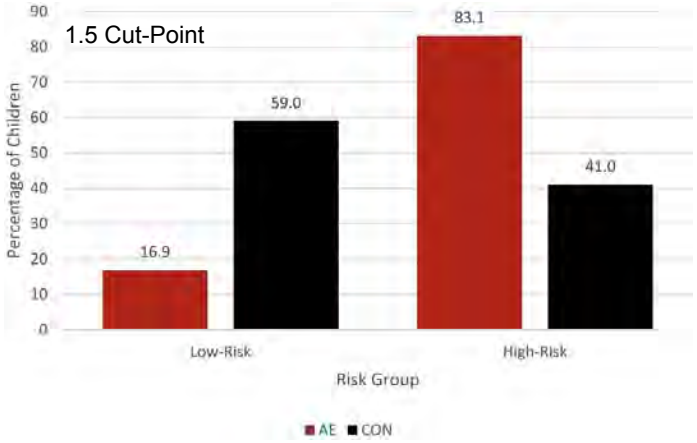
Percentage of alcohol-exposed (AE) and control (CON) subjects in each risk subgroup

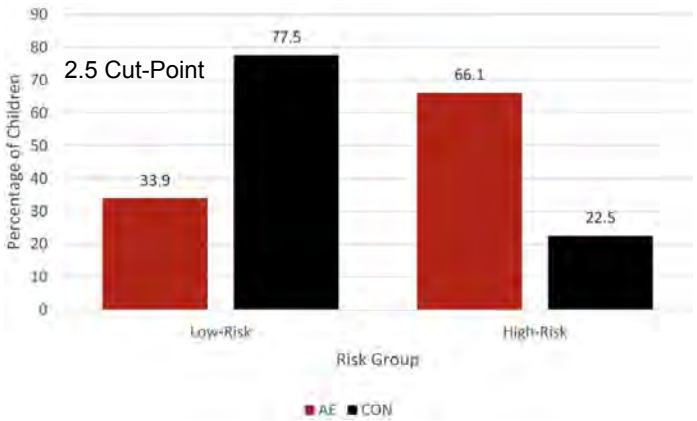
Developmental Cohort





Comparative Cohort



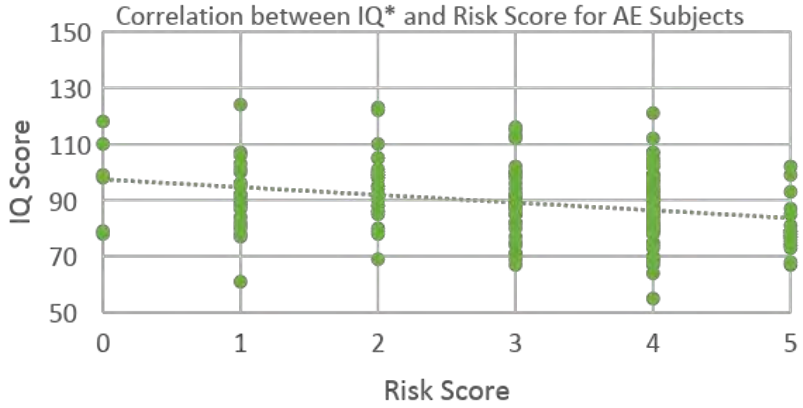


Development and validation of a postnatal risk score that identifies children with prenatal alcohol exposure

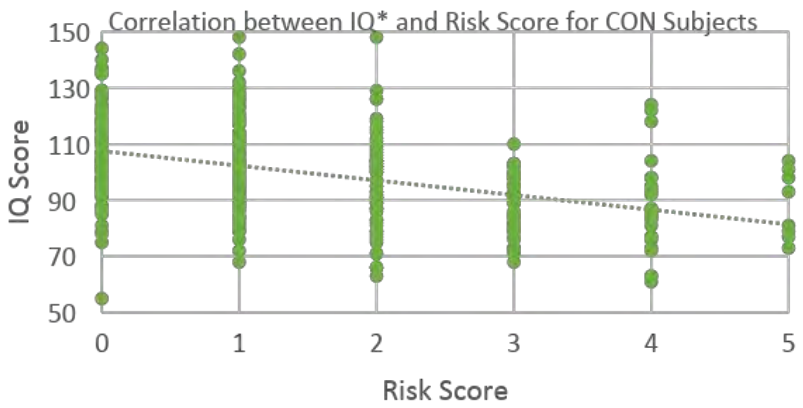
Alcohol Clin & Exp Res, First published: 21 November 2021, DOI: (10.1111/acer.14749)

Correlation between Risk and IQ Scores

AE Group



CON Group



Conclusion

The risk score significantly distinguished alcohol-exposed from control subjects and correlated with important cognitive outcomes. It has significant clinical potential and could be easily deployed in clinical settings.

Validation of the FASD-Tree as a Screening Tool for Fetal Alcohol Spectrum Disorders

Mattson, S.N., Jones, K.L., Chockalingam, G., Wozniak, J.R., Hyland, M.T., Courchesne, N.S., Del Campo, M., Riley, E.P., & the CIFASD

Status: Submitted 11/18/21

General Methods

- Data from CIFASD-4
- Participants (N=312) were ages 5-16y
- Standard physical exam and parent questionnaires
- Data were submitted to the FASD-Tree (aka the eTree)
- The FASD-Tree provides 2 outcomes
  - A dichotomous indicator (yes/no)
  - A risk score (0-5), as in Bernes et al., 2021
- Overall accuracy (ACC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the decision tree, risk score, and their combination
- Misclassified cases were examined for systematic bias

Table 2. Sample characteristics

	Alcohol-Exposed Group (n=226)	Non-Exposed Control Group (n=86)
Age in years [Mn (SD)]	10.0 (3.52)	11.7 (3.29)
Sex (at birth) [n (%)]		
Female	95 (42.0)	39 (45.3)
Race		
Black or African American	39 (17.3)	1 (1.2)
White	138 (61.1)	66 (76.7)
More than One Race	37 (16.4)	16 (18.6)
Ethnicity		
Hispanic or Latino	70 (31.0)	20 (23.3)
Not Hispanic or Latino	146 (64.4)	64 (74.4)
Unknown/Not Reported	10 (4.4)	2 (2.3)
IQ [Mn(SD)][b]	89.2 (15.79)	107.2 (17.41)
IQ Score <78	46	5
Diagnosis of FAS	22	0
History of prenatal alcohol exposure		
Confirmed	165	0
Suspected	61	0

[a] Gender identity was not collected for 25 participants in the control group.
[b] IQ score data were missing for 1 control and 36 alcohol-exposed participants.

Overall Classification = 84.2%

Overall Classification = 76.5%

Overall Classification = 81.4%

Table 3. Results

	Group		Statistic		
	Alcohol-Exposed [n (%)]	Control [n (%)]	Odds Ratio (95% CI)	X^2	p
FASD-Tree Outcome					
AE	177 (78.3)	23 (26.7)	9.89 (5.58-17.55)	72.01	<.001
Non-AE	49 (21.7)	63 (73.3)			
Risk Score Distribution [a,b]					
0	6 (2.7)	28 (32.6)	--	--	--
1	23 (10.2)	38 (44.2)			
2	31 (13.8)	7 (8.1)			
3	64 (28.4)	8 (9.3)			
4	65 (2892)	5 (5.8)			
5	36 (16.0)	0 (0)			
Risk Score Category 1 [a,c]					
Low (0-1)	29 (12.9)	66 (76.7)	22.30 (11.83-42.06)	119.58	<.001
High (2-5)	**196 (87.1)**	20 (23.3)			
Risk Score Category 2 [a,d]					
Low (0-2)	60 (26.7)	73 (84.9)	15.44 (7.98-29.87)	86.15	<.001
High (3-5)	165 (73.3)	13 (15.1)			
Combination of FASD-Tree Outcome and Risk Score					
Low Risk (0 indicators)	28 (12.4)	56 (65.1)	13.13 (7.25-23.80)	87.56	<.001
High Risk (1-2 indicators)	197 (87.6)	30 (34.9)			

[a] Risk score data were missing for one participant in the alcohol-exposed group
[b] Odds Ratio not reported for risk score due to cell sizes < 5
[c] Risk Score category 1 used the $\geq$ 2 cut-point for determining high risk
[d] Risk Score category 2 used the $\geq$ 3 cut-point for determining high risk

Conclusion

The FASD-Tree is an accurate and valid screening tool for FASD and should be used by clinicians who suspect that a patient has a history of prenatal alcohol exposure, even if that exposure is unknown.

Results of an FASD Screening Tool are Associated with Neuropsychological and Behavioral Measures

Hyland, M.T., Courchesne-Krak, N.S., Bernes, G.A., Wozniak, J.R., Jones, K.L., Del Campo, M., Riley, E.P., Mattson, S.N., & the CIFASD

Status: Under review by co-authors 12/17/21

General Methods

- Data from CIFASD-4
- Participants (N=175) were ages 5-16y
- Standard physical exam and neuropsychological assessment
- The relationship between the FASD-Tree dichotomous outcome and general cognitive ability, executive function, academic achievement, and behavior was tested with logistic regression
- Associations were tested in 3 samples
  - Whole sample (n=175)
  - Correctly classified sample (n=144)
  - Alcohol-exposed sample (n=133)

Table 1. Sample Demographics (N= 175).	
Variable	n (%)
Age ([M (SD)] range 5-16)	11.3 (3.1)
Male [n (%)]	92 (52.6)
White Race [n (%)]	96 (54.9)
Hispanic/Latino [n (%)]	45 (25.7)
Previous ADHD Diagnosis [n (%)]	95 (54.3)
Prenatal Alcohol Exposure [n (%)]	133 (76.0)
IQ	
WISC-V Full Scale IQ [M (SD)]	92.8 (19.6)
IQ < 85 [n (%)]	65 (37.1)
IQ < 70 [n (%)]	19 (10.9)
Executive Function	
D-KEFS EF Composite [M (SD)]	0.0 (1.0)
D-REF Total [M (SD)]	67.2 (13.7)
Academic Ability	
WIAT-III Math Problem Solving [M (SD)]	91.3 (20.1)
WIAT-III Word Reading [M (SD)]	98.5 (17.1)
WIAT-III Numerical Operations [M (SD)]	91.2 (19.1)
Behavior	
BASC-3 Externalizing Problems [M (SD)]	69.1 (17.4)
BASC-3 Internalizing Problems [M (SD)]	57.9 (11.4)
BASC-3 Behavior Symptoms Index [M (SD)]	67.1 (14.3)
BASC-3 Adaptive Skills [M (SD)]	38.5 (10.9)

Table 3: Analysis of Whole Sample by FASD-Tree Outcome (N= 175).					
Variable	FASD+ 124 (70.9%)	FASD- 51 (29.1%)	Odds Ratio [95% (CI)]	X^2	p value
Age ([M (SD)] range 5-16)	11.2 (3.1)	11.4 (2.9)	0.98 (0.88-1.09)	0.11	0.737
Male ([n (%)] ref = Female)	69 (55.6)	23 (45.1)	1.53 (0.79-2.94)	1.6	0.205
White Race ([n (%)] ref = no)	62 (50.0)	34 (66.7)	0.50 (0.25-0.99)	3.99	**0.046**
Hispanic/Latino ([n (%)] ref = no)	32 (25.8)	13 (25.5)	1.02 (0.48-2.15)	0	0.965
Previous ADHD Diagnosis [n (%)]	75 (60.5)	20 (39.2)	2.37 (1.22-4.63)	6.43	**0.011**
Prenatal Alcohol Exposure ([n (%)] ref = no)	113 (91.1)	20 (39.2)	15.92 (6.90-36.74)	42.09	**< 0.001**
IQ					
WISC-V Full Scale IQ [M (SD)]	86.5 (17.2)	108.1 (16.5)	0.93 (0.91-0.95)	32.97	**< 0.001**
IQ < 85 ([n (%)] ref = ≥ 85)	61 (50.0)	4 (8.0)	11.50 (3.90-33.92)	19.59	**< 0.001**
IQ < 70 ([n (%)] ref = ≥ 70)	18 (14.8)	1 (2.0)	8.48 (1.10-65.36)	4.21	**0.04**
Executive Function					
D-KEFS EF Composite [M (SD)]	-0.3 (0.9)	0.7 (0.7)	0.22 (0.12-0.40)	24.56	**< 0.001**
D-REF Total [M (SD)]	72.5 (11.3)	54.8 (10.6)	1.16 (1.11-1.21)	39.12	**< 0.001**
Academic Ability					
WIAT-III Math Problem Solving [M (SD)]	85.0 (17.7)	106.7 (17.0)	0.93 (0.91-0.96)	32.98	**< 0.001**
WIAT-III Word Reading [M (SD)]	95.0 (18.0)	106.5 (11.7)	0.95 (0.93-0.98)	13.7	**< 0.001**
WIAT-III Numerical Operations [M (SD)]	85.8 (17.0)	104.1 (17.9)	0.94 (0.92-0.96)	26.1	**< 0.001**
Behavior					
BASC-3 Externalizing Problems [M (SD)]	75.1 (15.5)	54.9 (12.9)	1.10 (1.07-1.13)	37.81	**< 0.001**
BASC-3 Internalizing Problems [M (SD)]	60.0 (11.3)	53.1 (10.3)	1.06 (1.03-1.10)	12.24	**< 0.001**
BASC-3 Behavior Symptoms Index [M (SD)]	72.1 (12.2)	55.3 (12.0)	1.12 (1.08-1.16)	37.29	**< 0.001**
BASC-3 Adaptive Skills [M (SD)]	34.1 (8.5)	48.6 (9.1)	0.85 (0.80-0.89)	39.65	**< 0.001**

Table 4: Analysis of Correctly Classified Participants by FASD-Tree Outcome (N= 144).

Variable	Correctly Classified: FASD+/AE [n (%)/Mean (SD)]	Correctly Classified: FASD-/CON [n (%)/Mean (SD)]	Odds Ratio [95% (CI)]	X^2	p value
All	113 (78.5)	31 (21.5)			
Age ([M (SD)] range 5-16)	11.0 (3.1)	12.0 (2.6)	0.89 (0.78-1.02)	2.95	0.086
Male ([n (%)] ref = Female)	63 (55.8)	13 (41.9)	1.75 (0.78-3.90)	1.84	0.175
White Race ([n (%)] ref = no)	53 (46.9)	27 (87.1)	0.13 (0.04-0.40)	12.82	**< 0.001**
Hispanic/Latino ([n (%)] ref = no)*	31 (27.4)	4 (12.9)	2.55 (0.83-7.89)	2.65	0.104
Previous ADHD Diagnosis [n (%)]*	73 (64.6)	4 (12.9)	12.32 (4.03-37.70)	19.36	**< 0.001**
Prenatal Alcohol Exposure ([n (%)] ref = no) *	113 (100)	0 (0.0)	-	-	-
IQ					
WISC-V Full Scale IQ [M (SD)]	85.0 (15.6)	116.3 (12.4)	0.86 (0.81-0.91)	28.08	**< 0.001**
IQ < 85 ([n (%)] ref = ≥ 85)*	58 (51.8)	0 (0.0)	-	-	-
IQ < 70 ([n (%)] ref = ≥ 70)*	17 (15.2)	0 (0.0)	-	-	-
Executive Function					
D-KEFS EF Composite [M (SD)]	-0.3 (0.9)	0.9 (0.6)	0.10 (0.04-0.27)	20.95	**< 0.001**
D-REF Total [M (SD)]	73.9 (9.9)	48.8 (7.8)	1.56 (1.27-1.90)	18.6	**< 0.001**
Academic Ability					
WIAT-III Math Problem Solving [M (SD)]	83.2 (15.8)	114.9 (13.7)	0.88 (0.84-0.92)	33.2	**< 0.001**
WIAT-III Word Reading [M (SD)]	94.1 (17.6)	109.7 (10.8)	0.93 (0.90-0.97)	15.49	**< 0.001**
WIAT-III Numerical Operations [M (SD)]	84.2 (15.0)	112.1 (16.3)	0.88 (0.84-0.92)	28.23	**< 0.001**
Behavior					
BASC-3 Externalizing Problems [M (SD)]	77.0 (14.1)	48.7 (8.2)	1.23 (1.14-1.33)	28.3	**< 0.001**
BASC-3 Internalizing Problems [M (SD)]	60.6 (11.0)	50.5 (9.8)	1.10 (1.05-1.15)	16.72	**< 0.001**
BASC-3 Behavior Symptoms Index [M (SD)]	73.6 (10.8)	48.8 (8.1)	1.32 (1.18-1.46)	26.07	**< 0.001**
BASC-3 Adaptive Skills [M (SD)]	33.1 (7.0)	53.1 (7.7)	0.67 (0.56-0.80)	20.85	**< 0.001**

Table 5: Analysis of Alcohol Exposed Participants by FASD-Tree Outcome (N= 133).

Variable	Correctly Classified: FASD+/AE [n (%)/Mean (SD)]	Incorrectly Classified: FASD-/AE [n (%)/Mean (SD)]	Odds Ratio [95% (CI)]	X^2	p value
All	113 (85.0)	20 (15.0)			
Age ([M (SD)] range 5-16)	11.0 (3.1)	10.4 (3.1)	1.06 (0.91-1.24)	0.55	0.46
Male ([n (%)] ref = Female)	63 (55.8)	10 (50.0)	1.26 (0.49-3.26)	0.23	0.634
White Race ([n (%)] ref = no)	53 (46.9)	7 (35.0)	1.64 (0.61-4.42)	0.96	0.327
Hispanic/Latino ([n (%)] ref = no)	31 (27.4)	9 (45.0)	0.46 (0.18-1.22)	2.42	0.12
Previous ADHD Diagnosis [n (%)]	73 (64.6)	16 (80.0)	0.46 (0.14-1.46)	1.75	0.185
Prenatal Alcohol Exposure ([n (%)] ref = no)	113 (85.0)	20 (15.0)	-	-	-
IQ					
WISC-V Full Scale IQ [M (SD)]	85.0 (15.6)	95.7 (14.1)	0.96 (0.92-0.99)	7.26	**0.007**
IQ < 85 ([n (%)] ref = ≥ 85)*	58 (51.8)	4 (20.0)	4.30 (1.35-13.66)	6.1	**0.014**
IQ < 70 ([n (%)] ref = ≥ 70)*	17 (15.2)	1 (5.0)	3.40 (0.43-27.11)	1.34	0.248
Executive Function					
D-KEFS EF Composite [M (SD)]	-0.2 (0.9)	0.8 (1.0)	0.28 (0.13-0.61)	10.33	**0.001**
D-REF Total [M (SD)]	73.9 (9.9)	64.1 (7.2)	1.15 (1.07-1.24)	13.4	**< 0.001**
Academic Ability					
WIAT-III Math Problem Solving [M (SD)]	83.2 (15.8)	93.9 (13.6)	0.96 (0.93-0.99)	7.04	**0.008**
WIAT-III Word Reading [M (SD)]	94.1 (17.6)	101.2 (11.5)	0.97 (0.94-1.01)	2.63	0.105
WIAT-III Numerical Operations [M (SD)]	84.2 (15.0)	92.2 (13.0)	0.96 (0.93-0.99)	4.64	**0.031**
Behavior					
BASC-3 Externalizing Problems [M (SD)]	77.0 (14.1)	64.7 (12.9)	1.07 (1.03-1.12)	11.14	**< 0.001**
BASC-3 Internalizing Problems [M (SD)]	60.6 (11.0)	57.1 (10.1)	1.03 (0.99-1.08)	1.74	0.187
BASC-3 Behavior Symptoms Index [M (SD)]	73.6 (10.8)	65.2 (10.1)	1.08 (1.03-1.14)	9.05	**0.003**
BASC-3 Adaptive Skills [M (SD)]	33.1 (7.0)	41.7 (6.5)	0.84 (0.77-0.91)	16.93	**< 0.001**

Conclusion

Results from the FASD-Tree screening tool were associated with neuropsychological and behavioral outcomes. Participants classified as FASD+ were more likely to have impairment in all domains tested. Results were unchanged when only correctly classified participants were included. These results lend evidence in support of the FASD-Tree as an effective screening tool in clinical settings, providing an efficient and accurate way to identify patients in need of additional evaluation.

Adaptive, Externalizing, and Internalizing Behavior of Children with Prenatal Alcohol Exposure: A Comparison of Three Parent-Report Questionnaires

Sobolewski, C.M, Courchesne-Krak, N.S., Hyland, M.T., Bernes, G.A., Wozniak, J.R., Mattson, S.N., & the CIFASD

Status: Under review by co-authors 12/10/21

General Methods

- Data from CIFASD-4
- Participants (N=156) were ages 5-16y
- Parent ratings of behavior
  - BASC-3
  - CBCL
  - VABS-3
- BASC-3 Adaptive Skills, Externalizing Problems, and Internalizing Problems scores were correlated (Pearson's r) with comparable scores from the CBCL (Externalizing and Internalizing Problems) and VABS-3 (Adaptive Skills)
- Sensitivity, specificity, and positive and negative predictive values were calculated for the BASC-3.

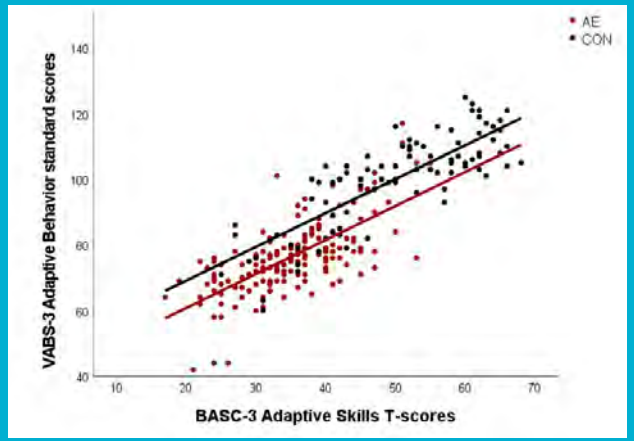
Table 1. Demographic Information by Group

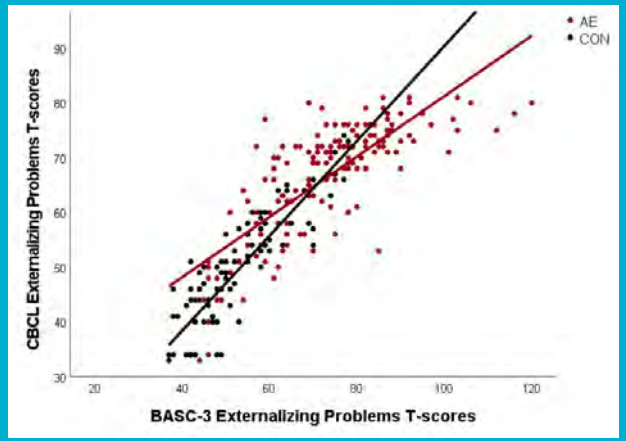
Demographic Variable	Group	
	AE	CON
Total [n (%]	164 (64.0)	92 (36.0)
Sex [n (%) Female]	73 (44.5)	46 (50.0)
Age [Mean (SD)]	11.2 (3.14)	12.3 (2.68)
Race [n (%)]		
White	102 (62.2)	82 (89.1)
Black/African American	41 (25.0)	8 (8.7)
American Indian/Alaska Native	15 (9.1)	0 (0.0)
Asian	4 (2.4)	4 (4.3)
Native Hawaiian/Pacific Islander	4 (2.4)	0 (0.0)
Other	29 (17.7)	4 (4.3)
Ethnicity [n (%) Hispanic]	43 (27.4)	23 (25.6)
Full Scale IQ [Mean (SD)]	87.9 (16.02)	108.8 (15.69)
Family Income [n (%) <$20,000/year]	15 (9.4)	9 (9.8)
CIFASD Site [n (%)]		
San Diego	119 (72.6)	48 (52.2)
Minneapolis	45 (27.4)	44 (47.8)

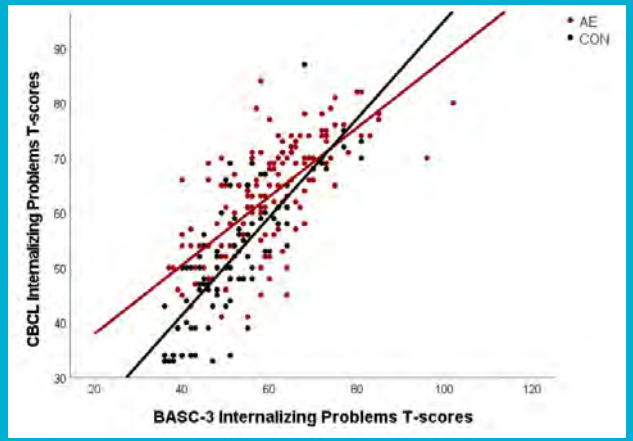
Table 2. Descriptive Data for the BASC-3, CBCL, and VABS-3 by Group		
Behavior Scales	**Group**	
	AE	CON
BASC-3 Adaptive Skills [Mean (SD)]	35.0 (7.50)	50.1 (10.94)
VABS-3 Adaptive Behavior [Mean (SD)]	76.4 (11.18)	100.0 (13.98)
BASC-3 Externalizing Problems [Mean (SD)]	72.9 (14.88)	52.0 (10.37)
CBCL Externalizing Problems [Mean (SD)]	66.3 (10.54)	48.8 (10.44)
BASC-3 Internalizing Problems [Mean (SD)]	59.4 (11.40)	51.6 (10.51)
CBCL Internalizing Problems [Mean (SD)]	62.6 (10.31)	51.8 (11.76)
AE, alcohol-exposed; BASC-3, Behavioral Assessment System for Children - Third Edition Parent Rating Scale; CBCL, Child Behavior Checklist Parent Report Form; CON, control; VABS-3, Vineland Adaptive Behavior Scales - Third Edition Parent/Caregiver Rating Form		

Table 3. Pearson's Correlations Among Corresponding Behavior Scales						
	AE		CON		Total	
Behavior Scale	*r*	*p*	*r*	*p*	*r*	*p*
BASC-3 Adaptive Skills						
VABS-3 Adaptive Behavior	0.69	**<.001**	0.81	**<.001**	0.86	**<.001**
BASC-3 Externalizing Problems						
CBCL Externalizing Problems	0.78	**<.001**	0.87	**<.001**	0.87	**<.001**
BASC-3 Internalizing Problems						
CBCL Internalizing Problems	0.70	**<.001**	0.80	**<.001**	0.76	**<.001**

Significant correlative differences were indicated between AE and CON groups for Adaptive Skills (z = 2.09, p = 0.04) and Externalizing Problems (z = 1.99, p = 0.05) scores, but not Internalizing Problems (z = 1.81, p = 0.07) scores.







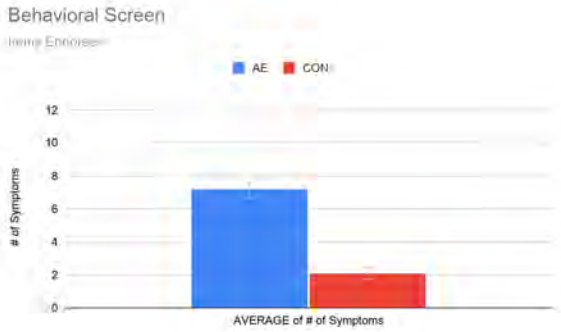
Measure	Sensitivity	Specificity	PPV	NPV
BASC-3 Adaptive	78.1%	79.4%	87.1%	67.0%
BASC-3 Externalizing	80.5%	80.4%	88.0%	69.8%
BASC-3 Internalizing	47.0%	81.5%	81.9%	46.3%

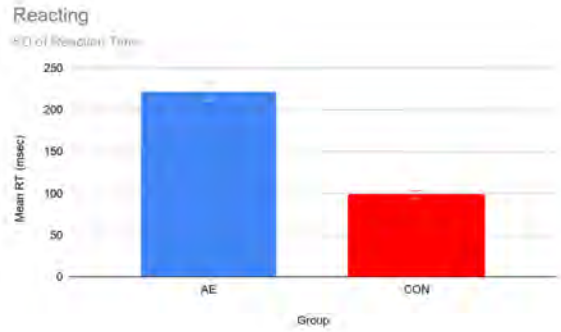
Conclusion

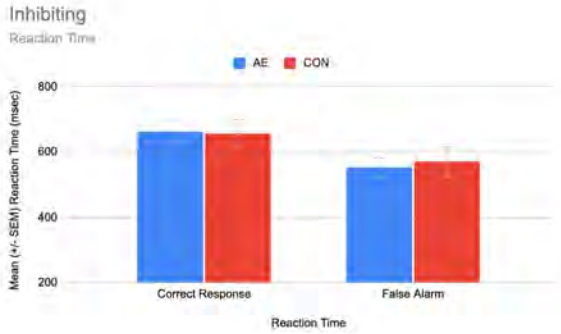
BASC-3 scores correlated with comparable CBCL and VABS-3 scores across groups and results replicated previous reports of behavioral and adaptive difficulties in youth with prenatal alcohol exposure. These findings provide support for using the BASC-3 in this population. Future studies should address whether the BASC-3 can be used in place of CBCL and VABS in clinical screening settings.

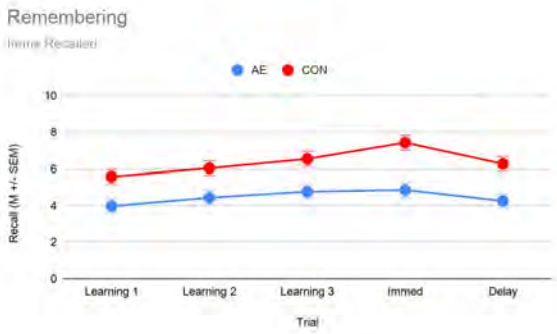
Other Accomplishments

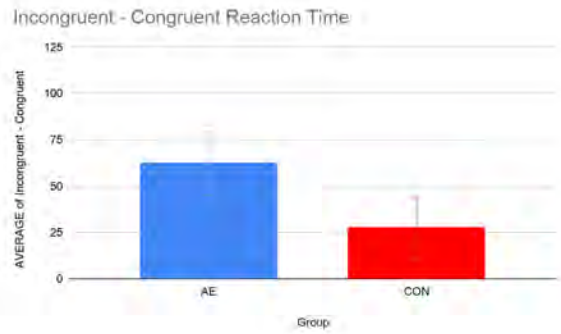
- ★ BRAIN-online in Youth Ages 6-16
  - 116 subjects tested
  - We hope to be able to present data at the 2022 RSA conference and the reverse site visit in early 2022.
- ★ BRAIN-online in young adults Ages 18-25
  - Our aim was to examine normative performance on this novel tool so that it can be used in adult populations by other investigators.
  - We have tested 750 SDSU students
- ★ Other preliminary studies
  - Testing the FASD-Tree as a screen for ARND specifically
  - Testing the role of IQ in behavior
  - Examining co-occurring maternal exposure and neuropsychological performance
  - Testing the BASC as a substitute for the CBCL and VABS in the FASD-Tree (a follow up to paper #4)
  - Examining parent reports of executive functioning (D-REF) vs. laboratory measures (D-KEFS)

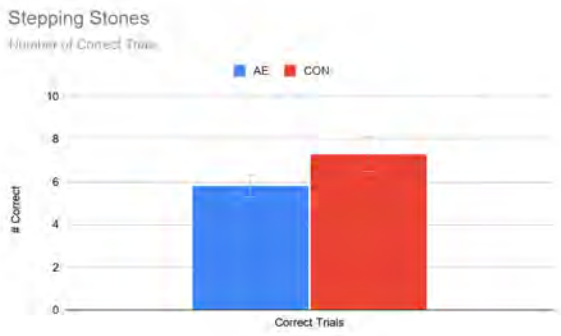


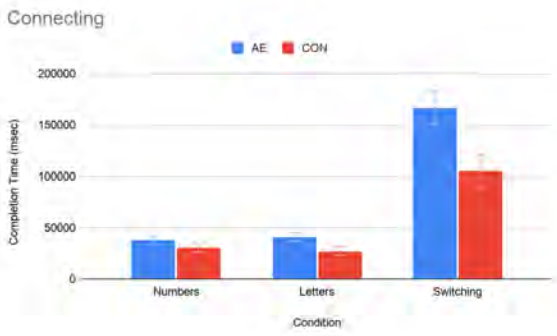






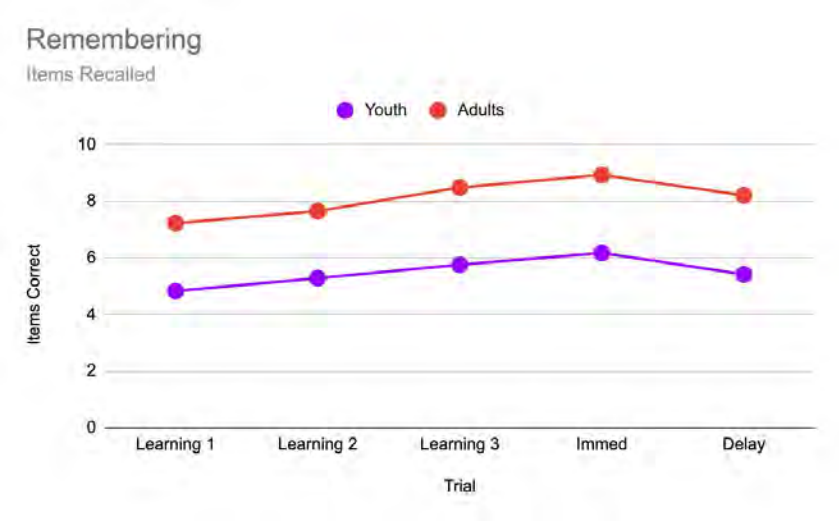


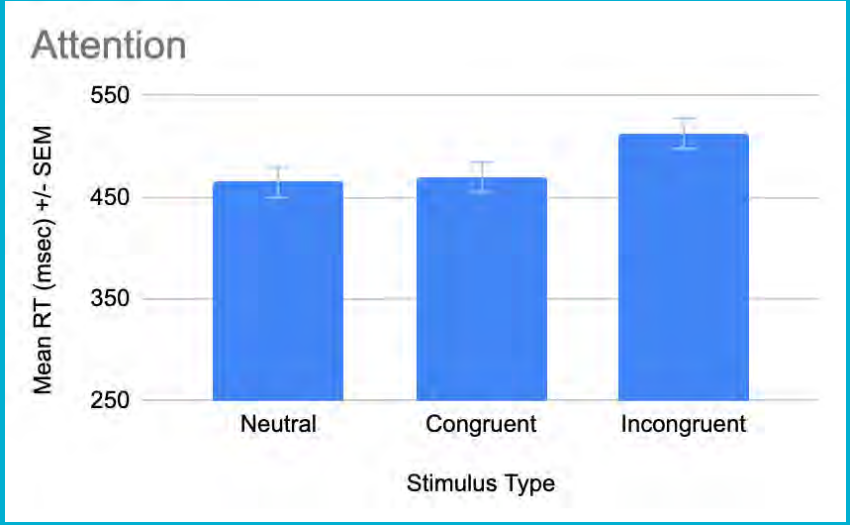




BRAIN-online results indicate that in comparison to controls, children with histories of prenatal alcohol exposure have: (1) higher scores on the behavioral screen (7.3 vs. 2.1 items endorsed), (2) lower scores (fewer taps) per 10 sec on Tapping, (3) longer and more variable reacting times on Reacting, (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.

BRAIN-online in Young Adults





Thank You!

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Image Analysis of Neurofacial Effects of Prenatal Alcohol Exposure

CIFASD 2021

Alison Noble
Michael Suttie
Ralf Haeusler
Zeyu Fu
Mingze Yuan

CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

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Clinical Software Validation Study

- Collaboration with Raja Mukherjee
  - Using UK data (n=112 exposed) and CIFASD background data (n=200 controls)
- Identification of cardinal features
- Comparison between automated 3D vs The FAS Facial Photographic Analysis Software

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Accurate Automated PFL Measurement

DOI: 10.1109/JBHI.2021.3110680 • Corpus ID: 237453802

Facial Anatomical Landmark Detection using Regularized Transfer Learning with Application to Fetal Alcohol Syndrome Recognition

Zeyu Fu, Jianbo Jiao, +1 author J. Noble • Published 8 September 2021 • Computer Science, Engineering, Medicine • IEEE journal of biomedical and health informatics

Landmark	L_{MAN} vs L_{AUTO}
Left Endocanthion	0.63
Left Exocanthion	0.73
Right Endocanthion	0.69
Right Exocanthion	0.69

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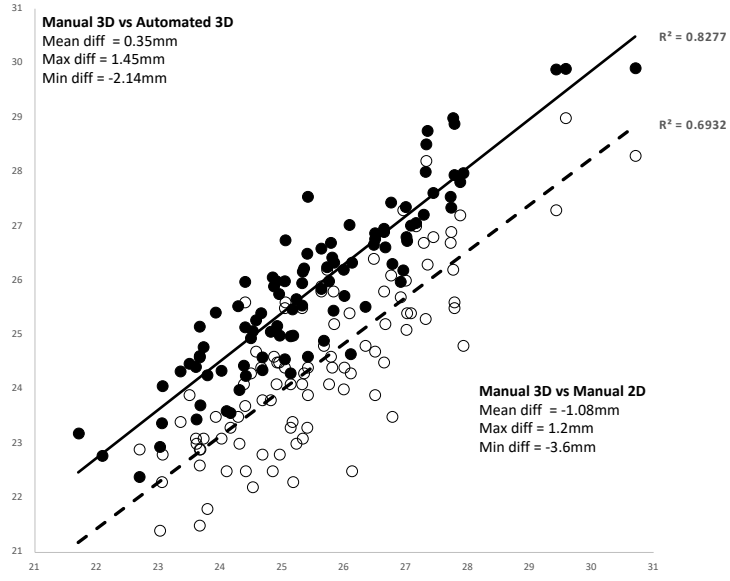

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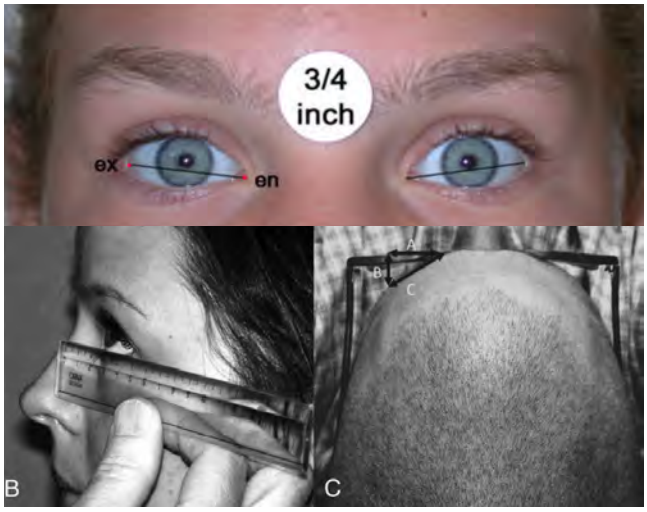
A reasonable non-offensive explanation?



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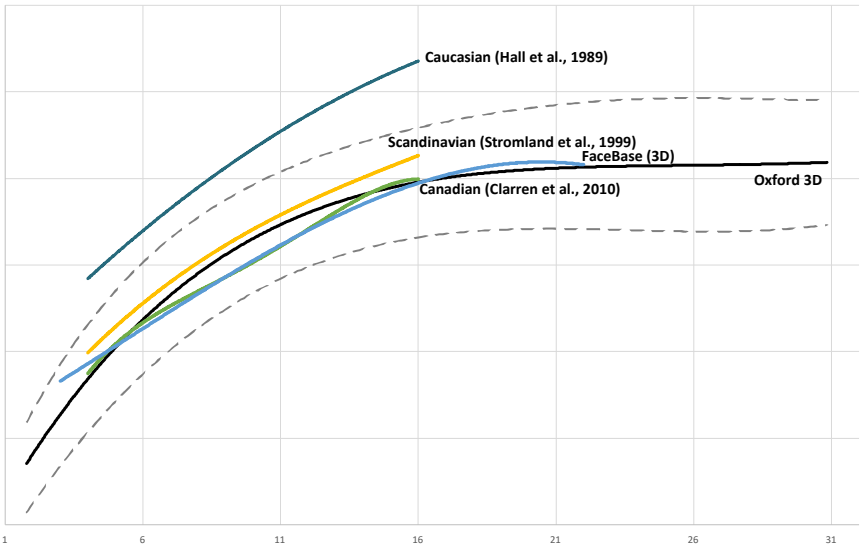

Results

- PFL measurements derived automated pipeline correlate with; manual, ruler, and 2D measurements.
- Automated classification of FAS individuals was not in agreement with the clinical diagnosis using the 4-digit code.
- Subtle FASD facial dysmorphism
  - midfacial hypoplasia identified in a significantly larger number of alcohol-exposed individuals compared to controls
- Automated philtrial smoothness in agreement with face-to-face dysmorphology examinations and 2D.

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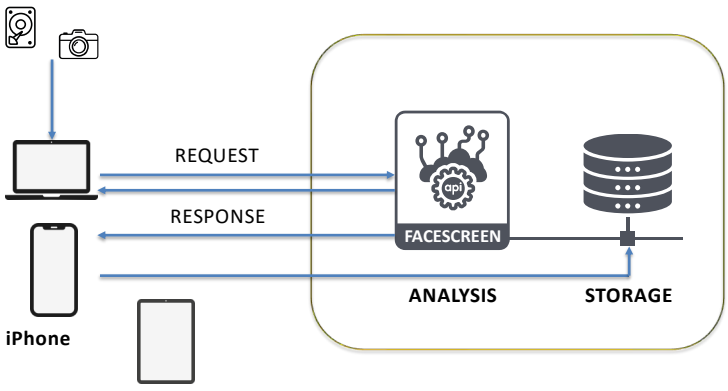
FaceScreen Development – Ongoing

Currently addressing :

- Security
- Storage
- Validation



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PASS Infant Analysis – Replication Study Collaboration with Peter Claes' Group

JAMA Pediatrics | Original Investigation

Association Between Prenatal Alcohol Exposure and Craniofacial Shape of Children at 12 Months of Age

Evelyne Muggli, MPH; Harold Matthews, BPsych(Hons); Anthony Penington, MDBS; Peter Claes, PhD; Colleen O'Leary, PhD; Della Forster, PhD; Susan Donath, MA; Peter J. Anderson, PhD; Sharon Lewis, PhD; Cate Nagle, PhD; Jeffrey M. Craig, PhD; Susan M. White, MBBS; Elizabeth J. Elliott, MD; Jane Halliday, PhD

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Ultrasound Analysis of GA Motivation

- **Small GA is a robust early indicator for FASD[1]**

  Fetuses or newborns are those smaller in size than normal for their gestational age, most commonly defined as a **weight below the 10th percentile for the gestational age**.

- **GA estimation:**

  Hypothesis: Our previous model trained with Intergrowth data may predict younger GA on the individuals with alcohol exposure compared with those of normal controls.

ORIGINAL ARTICLE

ALCOHOLISM

Gestational age and birth growth parameters as early predictors of fetal alcohol spectrum disorders

Julie M. Hasken[1] | Anna-Susan Marais[2] | Marlene de Vries[2] | Belinda Joubert[2] | Marise Cloete[2] | Isobel Botha[2] | Sumien Roux Symington[2] | Wendy O. Kalberg[3] | David Buckley[3] | Luther K. Robinson[4] | Melanie A. Manning[5,6] | Charles D. H. Parry[2,7] | Soraya Seedat[8] | H. Eugene Hoyme[6,9] | Philip A. May[1,2,3]

Abstract

1. JM. Hasken, et al. Gestational age and birth growth parameters as early predictors of fetal alcohol spectrum disorders. *Alcohol Clin Exp Res*. 2021
2. Lok Hin Lee et al. Calibrated bayesian neural networks to estimate gestational age and its uncertainty on fetal brain ultrasound images. In *MICCAI Workshops*, 2020..

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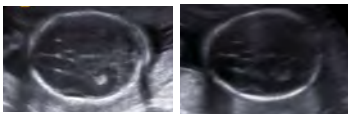
A Pilot Study

GA Estimation

- Obtained the TT planes from 29 US videos.



Unexposed Exposed

GA	Unexposed	Exposed
Ground truth	20w6d	20w5d
Estimation	20w	**18w**

Preliminary Results

- The model predicted similar GA on the data without alcohol exposure compared to the ground truth GA.
- The model predicted younger GA on the data with alcohol exposure compared to the ground truth GA.

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Unexposed

Exposed

12

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Quantitative Results

- Mean GA (days)

	HC (n=15)	PAE (n=14)
Ground truth	175.0±46.2	221.4±32.5
Estimation	173.6±44.7	209.5± 34.3

- The model predicted younger GA on the data with alcohol exposure compared to the ground truth GA.

	HC (n=15)	PAE (n=14)	P-value
MAE (days)	5.3±4.6	12.4±5.2	0.0007

- The GA prediction errors are significantly different between two clinical groups.

Ongoing work:

- Analysis of Uncertainty: find out whether the predicted uncertainty is a more robust indicator to characterize PAE.
- Visualization of saliency maps.
- Employ the markers for classifying the two clinical groups.
- More data (PASS)

1
3

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Publications Since June

Fu, Z., Jiao, J., Suttie, M., & Noble, J. A. (2021). Facial Anatomical Landmark Detection using Regularized Transfer Learning with Application to Fetal Alcohol Syndrome Recognition. 2194(c), 1–11.

Schölin, L., Mukherjee, R. A. S., Aiton, N., Blackburn, C., Brown, S., Flemming, K. M., Gard, P. R., Howlett, H., Plant, M., Price, A. D., Shields, J., Smith, L. A., Suttie, M., Zammitt, D. C., & Cook, P. A. (2021). Fetal alcohol spectrum disorders: An overview of current evidence and activities in the UK. Archives of Disease in Childhood, 106(7), 636–640.

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Collaboration:

Tina Chambers (San Diego) - Ukraine 3D facial images revisited with a preliminary analysis complete

Sarah Mattson (San Diego) – Planned synergy between decision tree and 3D facial analysis tool, testing tablet based image capture and transfer to produce automated measurements

Tatiana Foroud, Leah Wetherill (Indiana) – We have recently been working to investigate if any facial differences are apparent from the different gene carrier groups identified from whole-exome sequencing (*KIF2A, HTT and CRIPAK).*

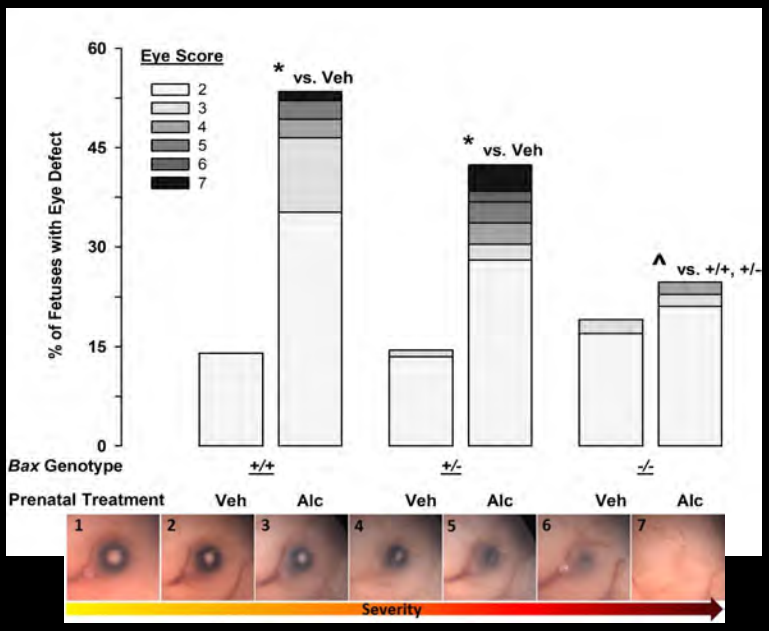
Tatiana Foroud, **Clare Coles** and **Joanne Weinberg** – working with these members to collect 2D and 3D image data.

Jeff Wozniak, worked closely in the analysis of face-neurocognitive-alcohol interactions publication

Scott Parnell, currently collaborating for infant/neonatal study where we are seeing smoke/drug-alcohol interactions.

Mouse Genetics

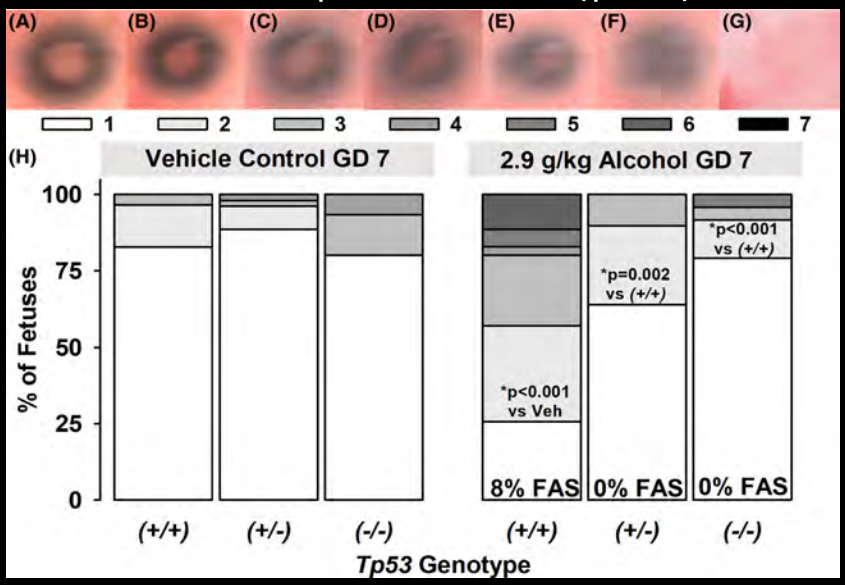
Apoptosis regulator Bax



C57Bl/6J Background

Fish, et al., in prep

Tumor protein 53 (p53)

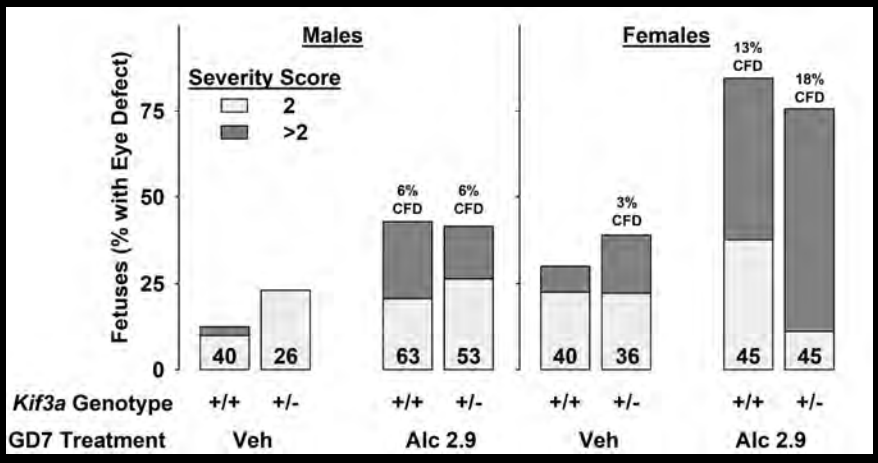


C57Bl/6J x 129S2 Background

Fish, Tucker et al., 2021

Kinesin Family Member 3a (*Kif3a*)

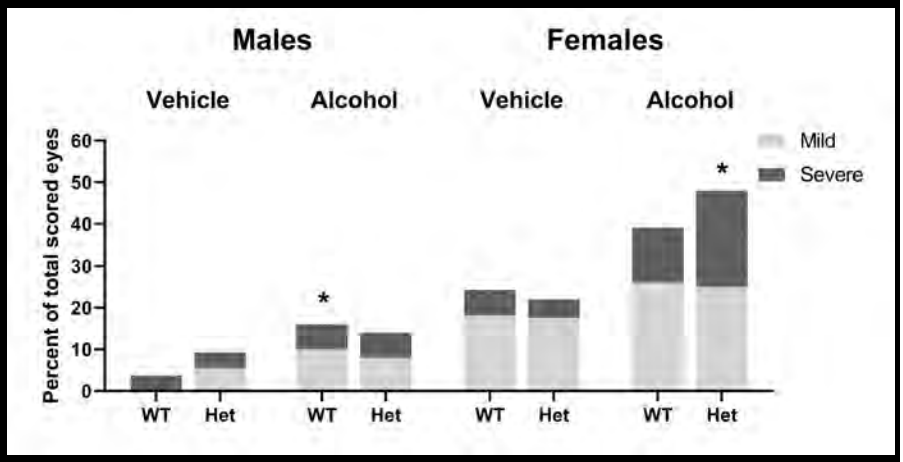
- Subunit of kinesin 2
- Major role in primary cilia formation and functioning.
- Anterograde transport.



C57Bl/6J x 129X1 x 129S1 Background

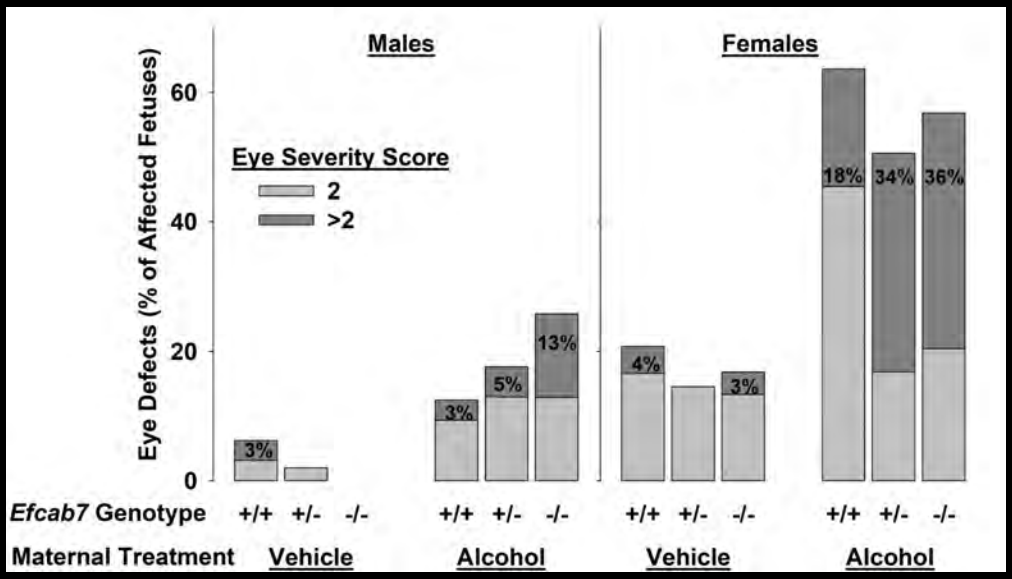
Huntingtin (*Htt*)

- Chemical signaling
- Role in repairing DNA
- Apoptosis
- Essential for normal brain development



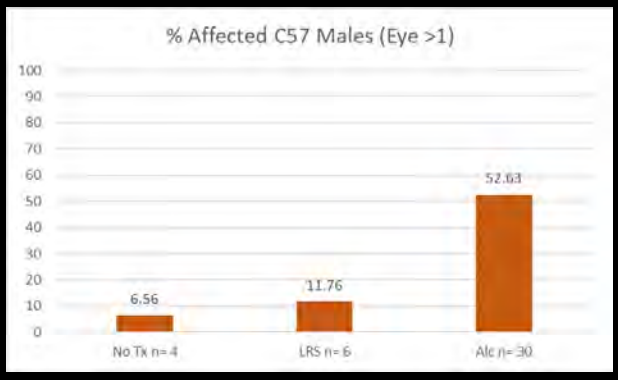
C57Bl/6J x 129S4 Background

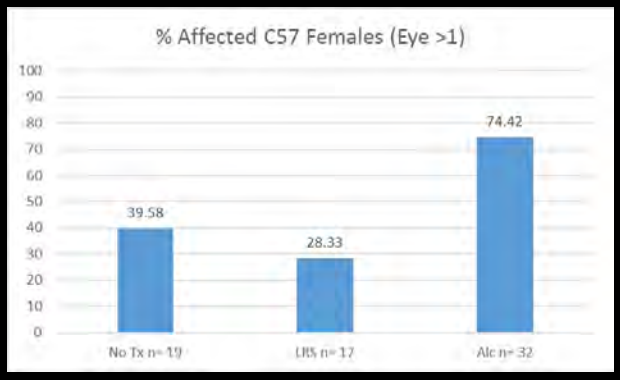
EF-Hand Calcium Binding Domain 7 (Efcab7)



C57BL/6NJ

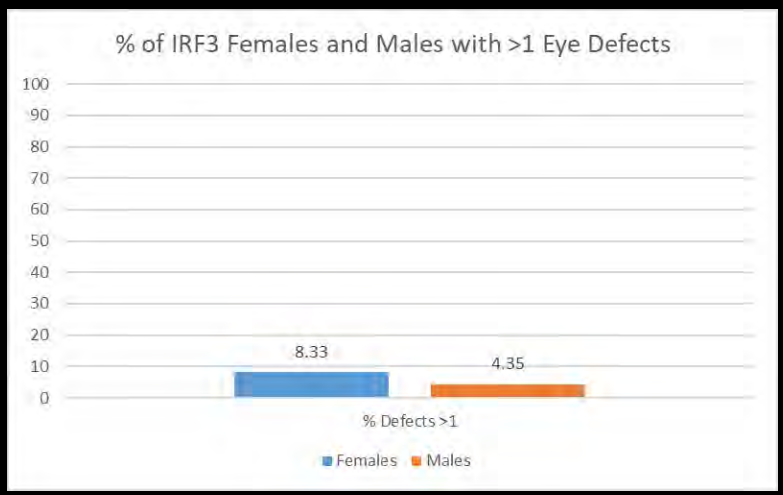
C57BL/6J (Jackson Laboratory)





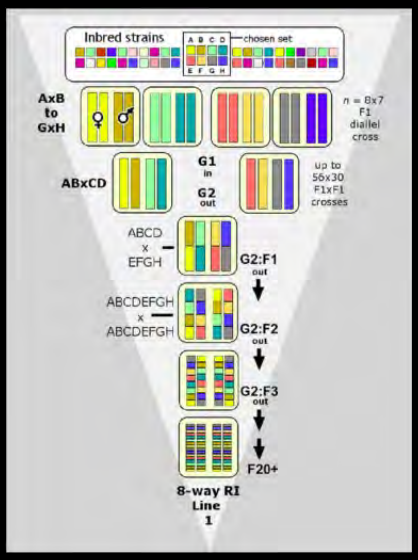
IFN regulatory factor 3 (*Irf3*)

- Transcriptional regulator of type 1 IFNs
- Essential for innate immunity



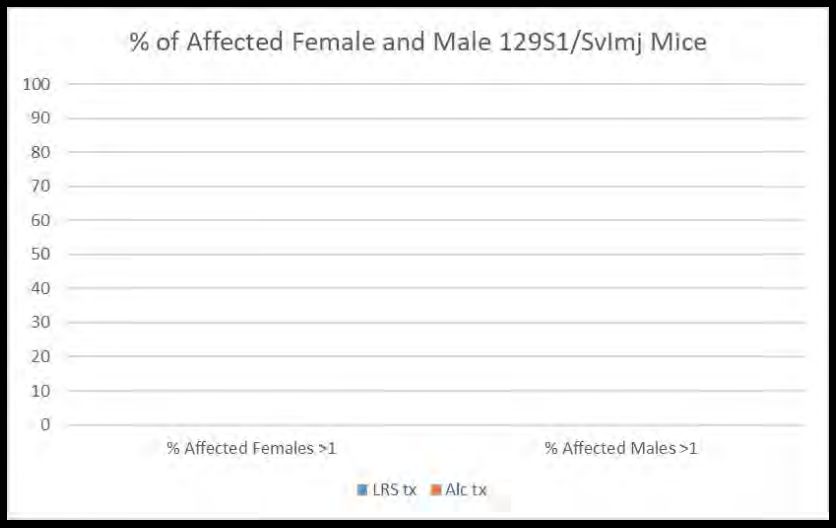
C57Bl/6J x 129 Background

Collaborative Cross



A/J, C57BL/6J, 129S1/SvImJ, NOD/LtJ, NZO/HlLtJ, CAST/EiJ, PWK/PhJ, and WSB/EiJ

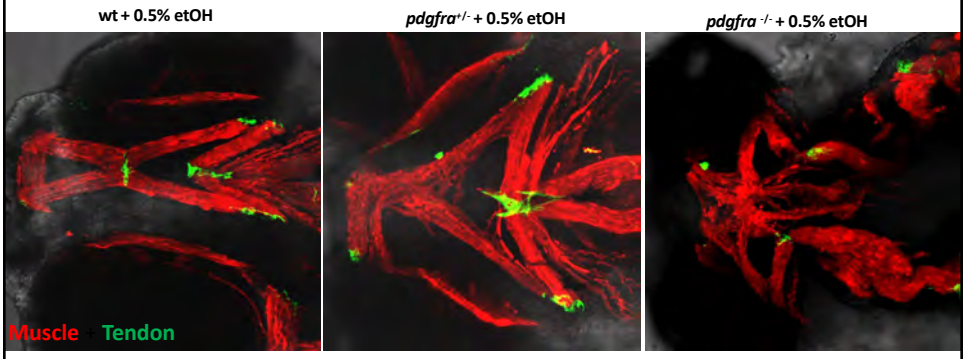
Collaborative Cross



129S1/SvImj

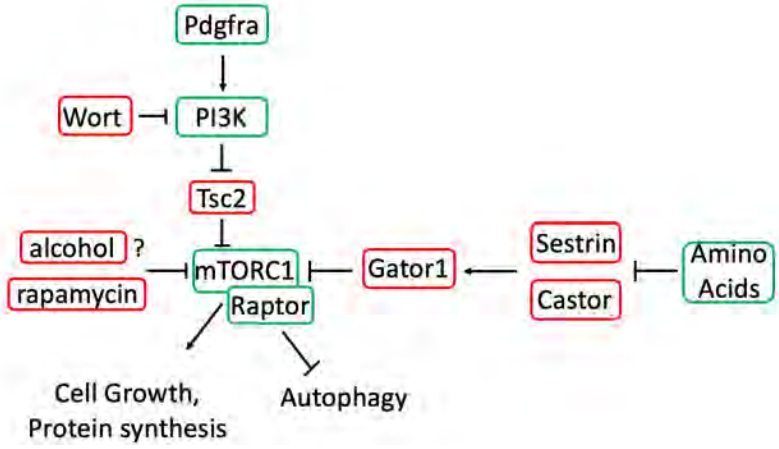
N = 16 Alcohol, 13 Control

Ethanol and pdgfra interact in cranial muscle patterning



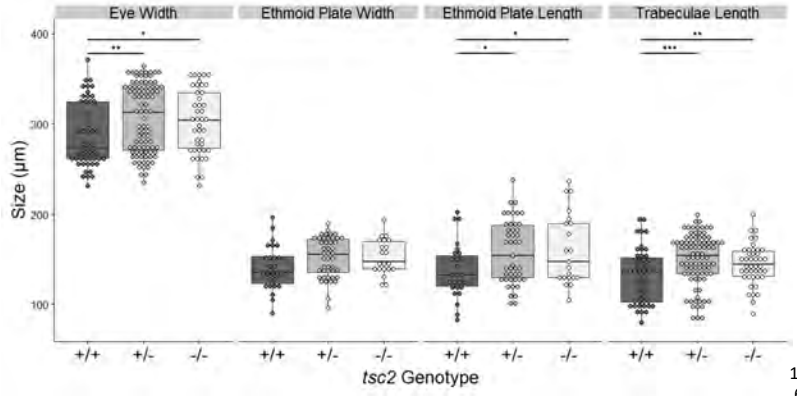
Ritika Ghosal

Pdgfra and the mTOR pathway



Activators
Inhibitors

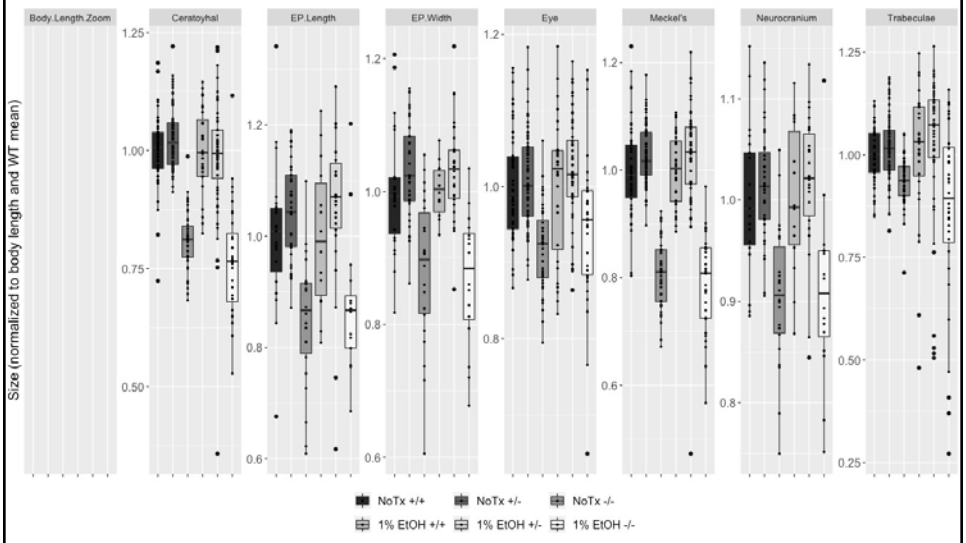
Activating mTORC1 ameliorates ethanol-induced craniofacial defects



1% Ethanol
6hpf-4dpf

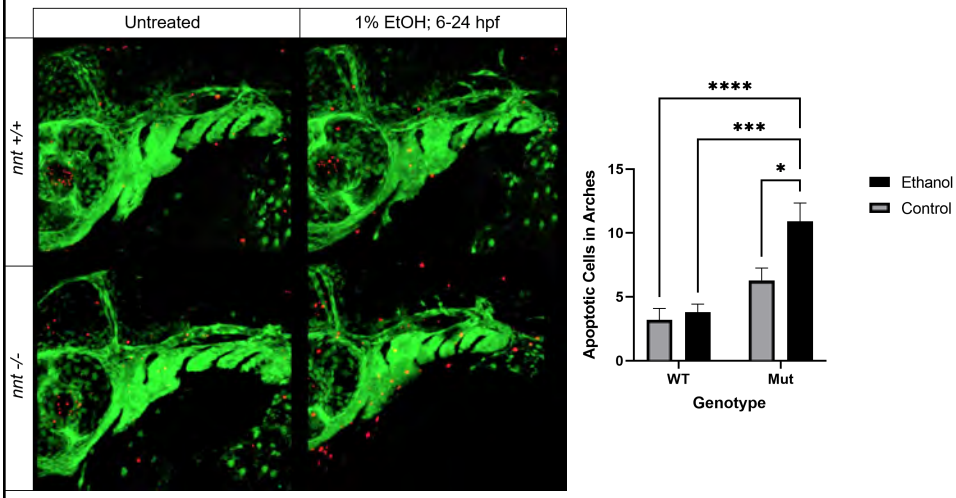
Scott Tucker

Ethanol does not interact with *raptor*



Scott Tucker

Candidate genes from mouse identify sensitizing and protective mutations

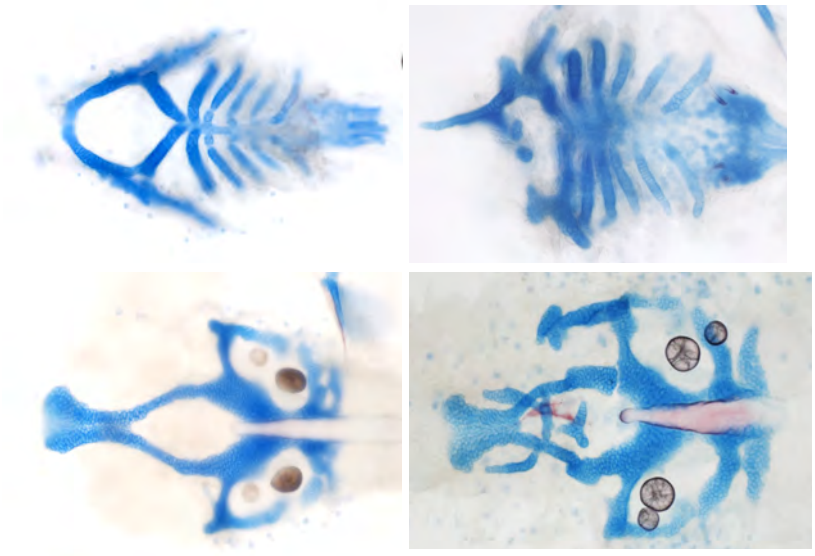


Rayna Mazumdar

Loss of histone acetylation causes crazy defects

moz$^{-/-}$ unexposed

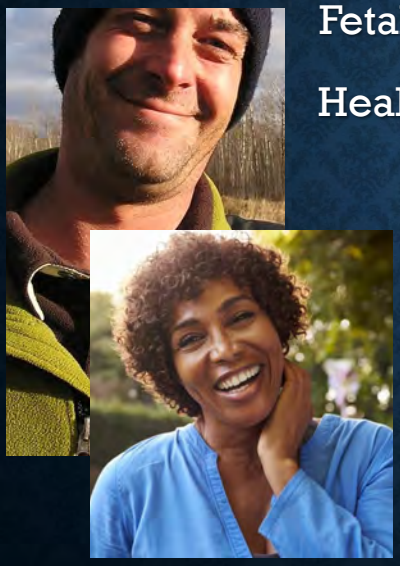
moz$^{-/-}$ + 1% EtOH



Ritika Ghosal

Other noteworthy items

- Yohaan Fernandes: Assistant Professor USD
- Desirè Buckley: Interviewing WSU, MSU, UMKC, and Wash. U
- Ritika Ghosal & Gissela Borrego: New to the ethanol field
- COVID problems: UT Austin accounting office



Fetal Alcohol Spectrum Disorders in Adults: Health and Neurobehavior: December 2021

NIH/NIAAA #: U01AA026108

CLAIRE D. COLES, PHD
EMORY UNIVERSITY SCHOOL OF MEDICINE

THERESE GRANT, PHD
UNIVERSITY OF WASHINGTON

And Edward P. Riley, PhD,
in collaboration with Joanne Weinberg, PhD

PROGRESS OF DATA COLLECTION: 12/21

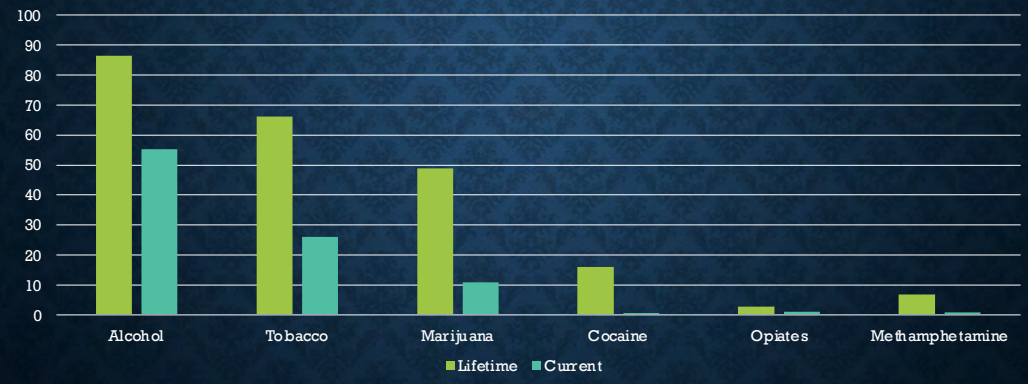
Project Activity	Number Completed: 11/2021
Registry	296
Tier 1 (Health Survey)	336
Tier 2 Tier 2 (Complete)	219
COVID-19 Supplement Activities	169

We are delayed in completion due to COVID-19 restrictions and funding.

QUESTION? IS PRENATAL EXPOSURE TO ALCOHOL ASSOCIATED WITH MORE ALCOHOL AND DRUG USE IN OFFSPRING?

- It is an accepted "fact" that children of drug/alcohol users are more likely to use themselves and there are a limited number of studies supporting this suggestion.(*e.g., Alati, et al., 2006; Baer, et al, 2003; Cornelius, et al, 2016;Goldschmidt, et al., 2019*) However, it appears to be non-specific and violence (childhood adversity) are often collateral factors and some studies do not find this relationship.
- There is animal work supporting for this hypothesis (see Choto, Arias & Lavola, 2007, for review).
- Thus, we are examining in this cohort the relationship between prenatal exposure/FASD diagnosis and later alcohol and drug use.

NATIONAL: SELF-REPORT OF USE BY MIDLIFE ADULTS, 2019-2020



National Survey on Drug Use and Health (NSDUH), 2021; http://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health

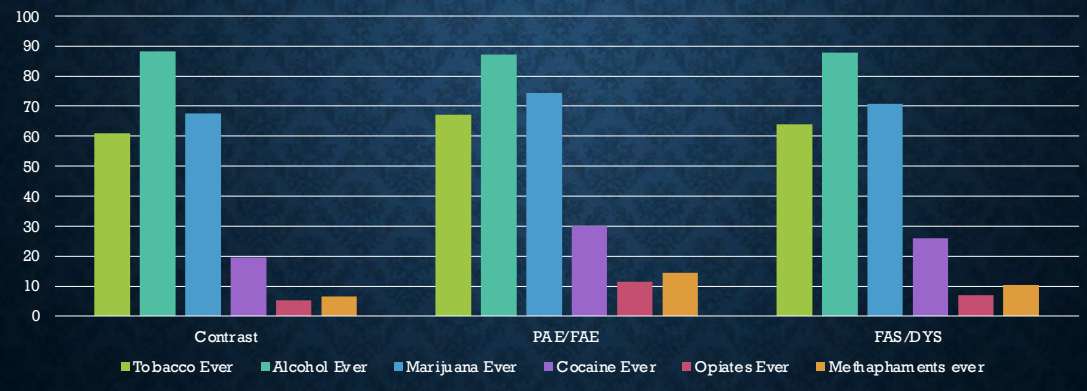
METHOD

- Individuals in Tier 2 of the Cross-Site Longitudinal Cohort study provided:
  - Self-Report: Responses to questionnaire about Alcohol and drug use that included information about Lifetime and current use of a range of substances.
  - Lab: The same individuals provided blood and urine for drug testing.

DEMOGRAPHICS OF SAMPLE (N=204)

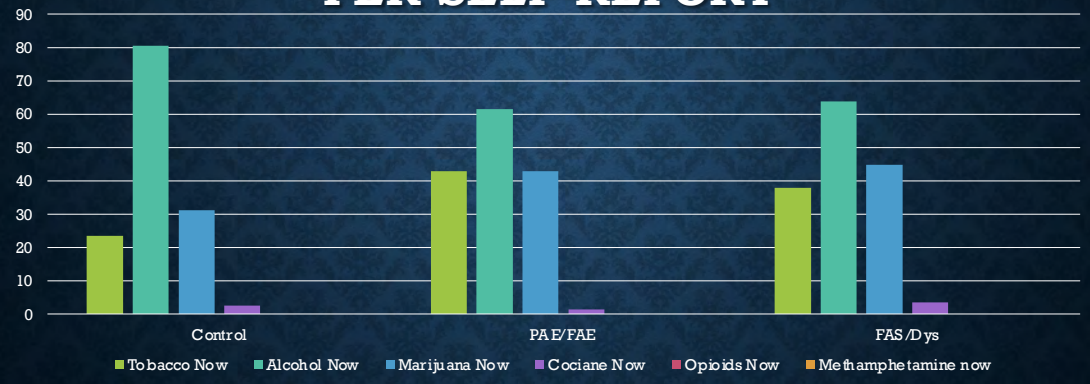
	Contrast (n=77)	PAE/FAE(n=69)	FAS/DYS (n=58)	
Age M (SD)	38.1 (5.2)	38.3 (7.0)	38.2 (5.3)	$F_{(2,201)} < 1$, NS
Gender (% male)	39.5%	33.3%	48.3%	$X^2_{(4)} = 3.8$, NS
Race % Native Amer	3.9%	4.3%	6.9%	$X^2_{(10)} = 8.2$, NS
Black	50. 6%	45.7%	46.6%	
White	40.3%	35.7%	34.5%	
More than one	3.9	12.9	10.3	
Marital Status (%)				
Married/Partnered	47.4%	42%	27.6%	$X^2_{(4)} = 9.3$, p=.05
Separated/Divorced	13.2%	11.6%	6.9%	
Never Married	39.5%	46.4%	65.5%	

USED DRUG/ALCOHOL EVER BY GROUP (%) PER SELF-REPORT



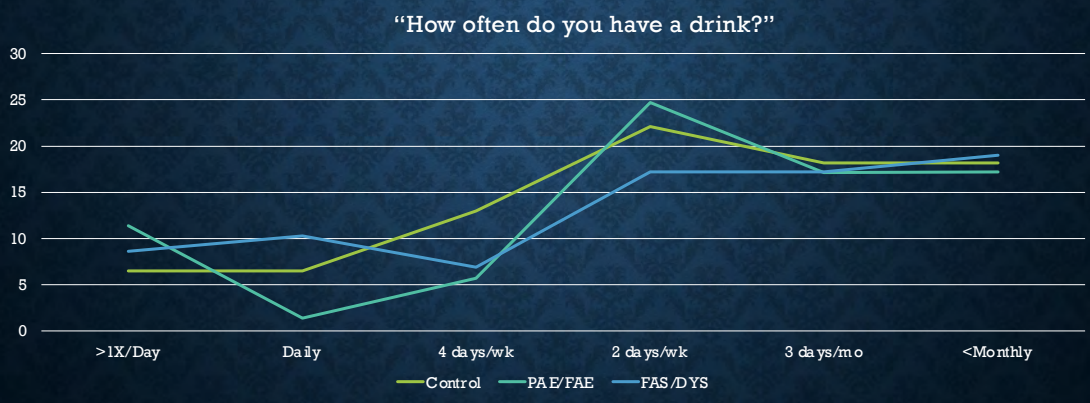
There are no significant differences in self report for any substance queried. (N=205)

USING DRUG/ALCOHOL NOW BY GROUP (%) PER SELF-REPORT



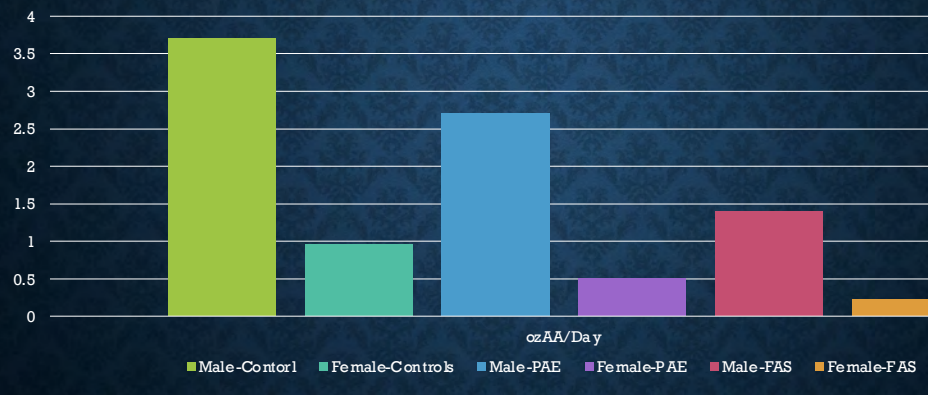
There are no significant differences in self report for any substance queried. (N=205).
There are trends for Tobacco, C<Alcohol (p=.08) and Alcohol (p=.06), C>Alcohol.
No participants reported opioid or methamphetamine use currently.

FREQUENCY OF ALCOHOL USE BY GROUP (%)



There are no significant group differences in frequency of alcohol use.

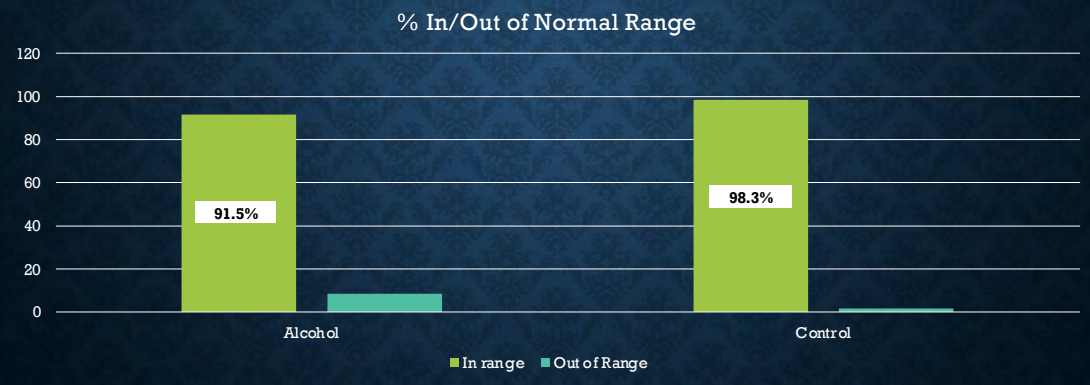
OUNCES OF ABSOLUTE ALCOHOL PER DAY BY GROUP AND GENDER PER SELF-REPORT



No significant Diagnostic group differences, $F_{(2,194)} < 1$, NS
No significant Gender group differences, $F_{(2,194)} = 2.54$, p=.08, but trend for M>F

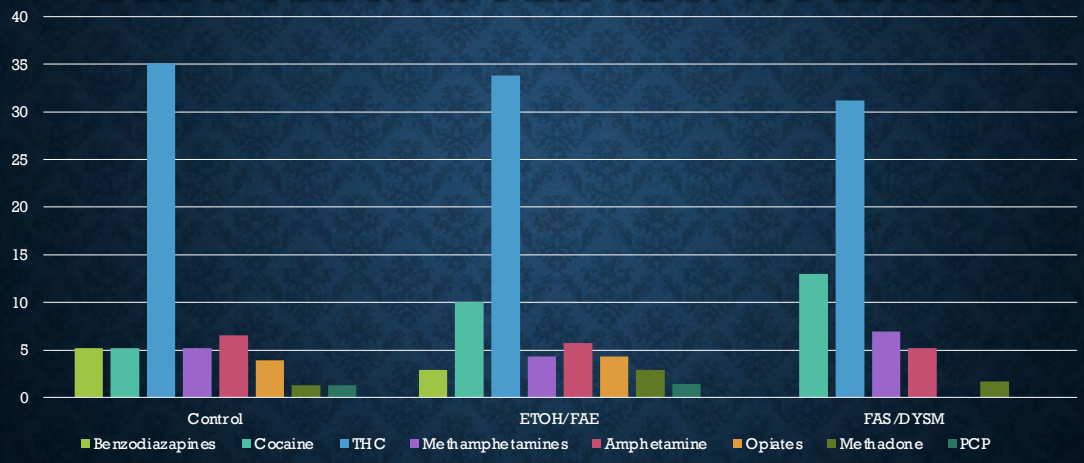
No correlations found between OzAA and Age, Race, SES, or Marital Status.

GGTP RESULTS BY ALCOHOL GROUP



$X^2_{(1)} = 3.79$, p=.051, Alcohol>Control
No Correlation between GGTP numbers and ozAA/day, R=.05, NS

DRUG USE NOW PER UDS: % POSITIVE



No Significant Group Differences in Drug Use based on UDS.

Other notes: Cocaine use A>S; Amphetamine use S>A

OZ/AA/DAY: GLR OUTCOMES

Parameter	β	Wald X^2	DF	Significance
Group (Control)*	2.06	2.73	1	p=.10
Site	0.206	<1	1	NS
Gender **	-1.79	3.56	1	p=.059
Childhood Aversity	.04	<1	1	NS
Age of Participant	-.058	<1	1	NS
SES	.002	<1	1	NS

* Controls>Alcohol Groups; ** Males>Females

Overall Model not significant

FACTORS AFFECTING FREQUENCY OF USE OF TOBACCO, MARIJUANA AND COCAINE: GLR OUTCOMES

Parameter	Tobacco		Marijuana		Cocaine	
	Wald $X^2_{(1)}$	p-value	Wald $X^2_{(1)}$	p-value	Wald $X^2_{(1)}$	p-value
ETOH Group	<1	NS	<1	NS	<1	NS
Site	2.29	p=.13[1]	3.35	NS	<1	NS
Gender	3.01	p=.08[2]	10.83	p<.001[2]	1.44	NS
Age	<1	NS	1.84	p=.18[3]	<1	NS
Childhood Adversity	8.85	p<.004[4]	1.95	p=.16[4]	4.15[4]	p<.05
SES	2.62	p=.11[5]	<1	NS	1.18	NS

[1] Atlanta>Seattle; [2] Males>Females; [3] Younger>Older; [4] More Adversity=More Drug use: [5] Higher SES= more Tobacco use.

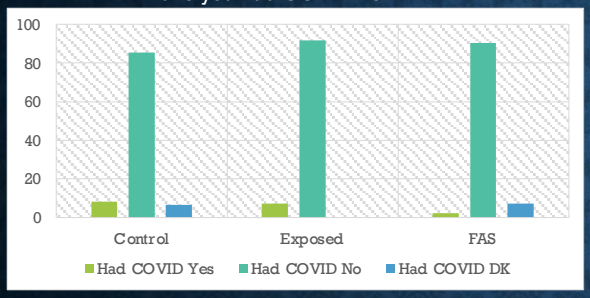
CONCLUSIONS FROM PRELIMINARY ANALYSES

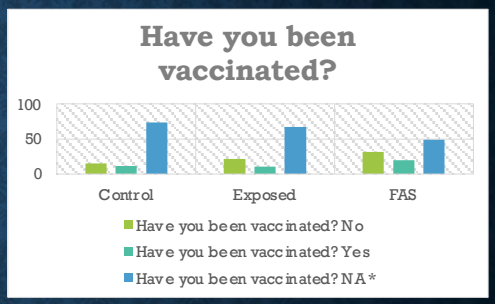
- Prenatal exposure does not appear to be related to current alcohol and drug use in this sample; indeed, males in control group appear to use more alcohol than other groups.
- Although **rates** of use are higher, individuals in these samples report very similar patterns of use to NIDA national samples for 2019 and 2020.
- Previous PAE studies have often sampled from clinically referred populations and this may have increased observed rates. However, the rates, overall seem quite high.
- Other, unmeasured, factors maybe accounting for use.

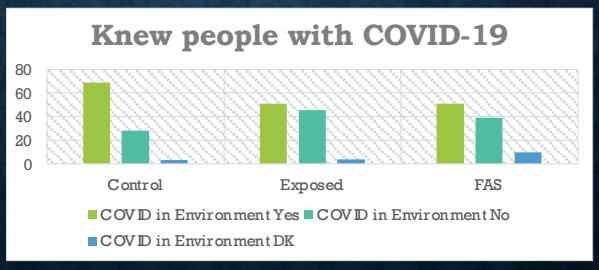
RESPONSES TO COVID-19 QUESTIONNAIRE BY GROUP

COVID-19 and the Adult Sample

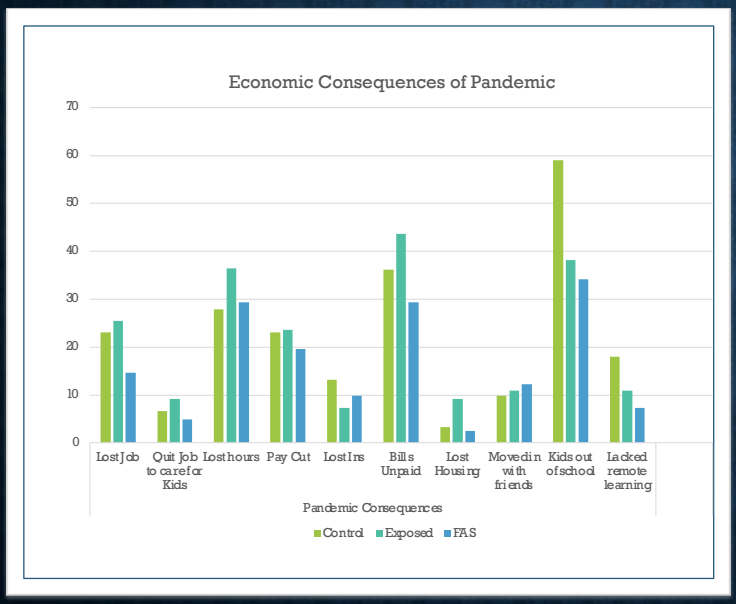
"Have you had COVID-19?"



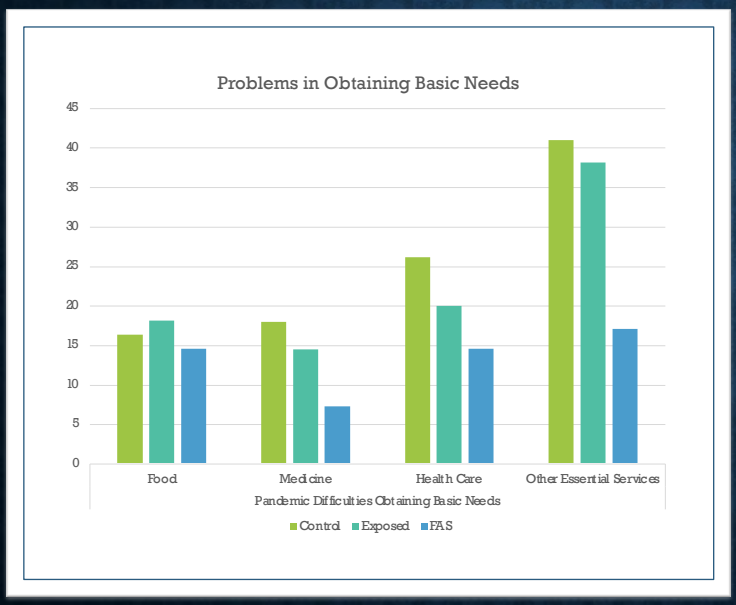




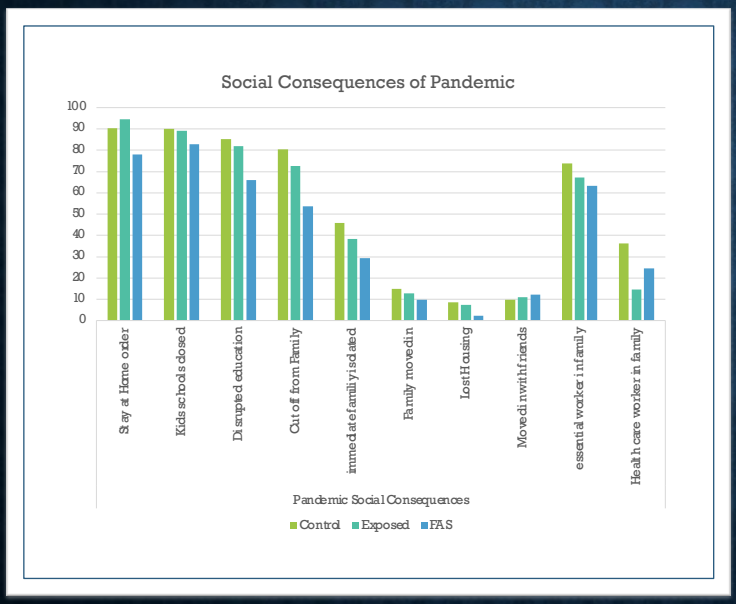
No significant Group differences



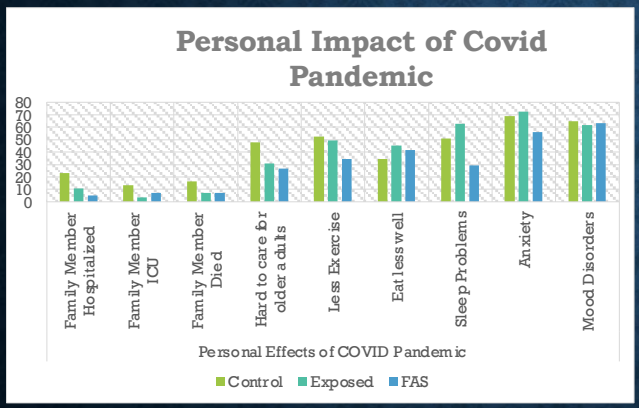
- Percentage responding "yes" to various consequences of the pandemic for work, housing and school. Many respondents have experienced negative consequences of the pandemic.
- "My children have not been able to go to school", $X^2=14.2$, $p<.03$ is more commonly endorsed by Controls who are more likely to have children than are the Alcohol Exposed groups. Groups do not differ on other consequences.



- % endorsing problems in these areas. There is a significant difference in the "Other" category with those with FAS reporting fewer problems ($X^2=11.23$, $p<.02$). Other areas do not differ.
- Items in the "other" category included: Toilet paper, personal care items (deodorant, feminine hygiene products), cleaning supplies, food, school supplies, dental care, medical supplies to assisted living, alcohol.



- Percentage responding that they have experienced these consequences, by group. The FAS group, overall, reports the fewest negative social consequences. This may be related to the degree to which they are isolated from typical social activities, pre-pandemic.
- There is a trend (X^2=8.29, p=.08) for those in the FAS group to report less "stay at home" orders. Similarly both alcohol groups reported being cut off from family less often (X^2=7.67, p=.11).
- There is a significant difference in reporting of children's education being disrupted (X^2=10.78, p<.03) with those in the FASD group reporting fewer disruptions. Similarly, they were less likely to endorse "We were unable to visit or care for a family member" (X^2=11.8, p<.01).
- There is also a different in the number reporting having a health care worker in the family who was affected by the COVID pandemic with those in the alcohol groups having fewer such family members (X^2=12.8, p<.01). Other social consequences did not differ among groups.



Percentage endorsing negative personal impact of Covid-19 pandemic in each of the diagnostic groups. Those in the control group reported more serious illness (X^2=12.33 p<.01) and death (X^2=8.5, p-.075) in their immediate families. This group also reported more problems in caring for older family members and those with disabilities than did those in the alcohol group (X^2=37.69 p<.001) perhaps because they are more likely to have such responsibilities.

Those in the FAS group were less likely to report a negative impact on their ability to exercise than the other groups (X^2=18.67, p<.04) and there was a similar trend for sleep problems (X^2=16.22, p=.09). All groups reported high levels of anxiety and depressed mood.

E-Health Applications

Ganz Chockalingam, Ed Riley, Sarah Mattson

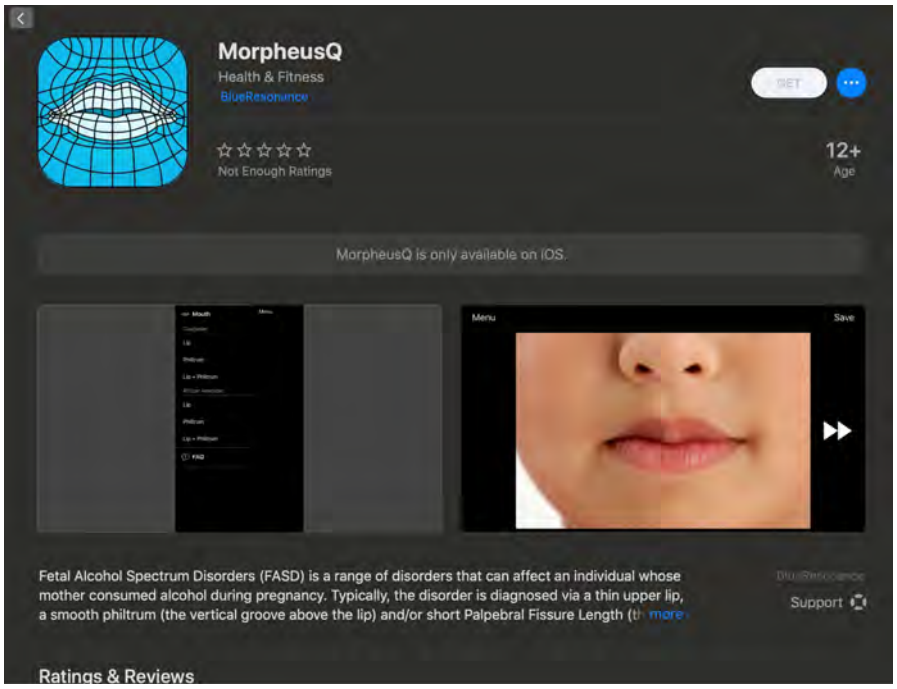
E-Tree
(Sarah Mattson)

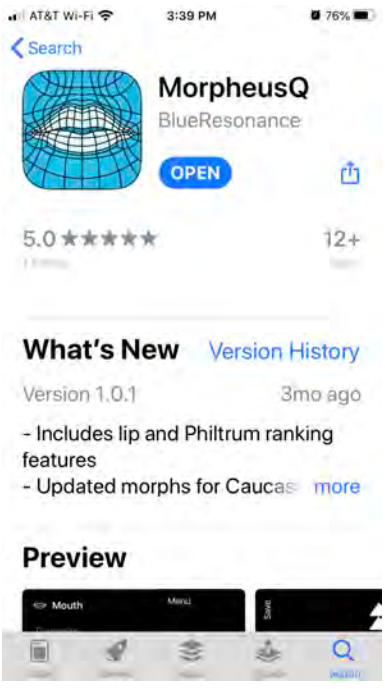
BRAIN
(Sarah Mattson)

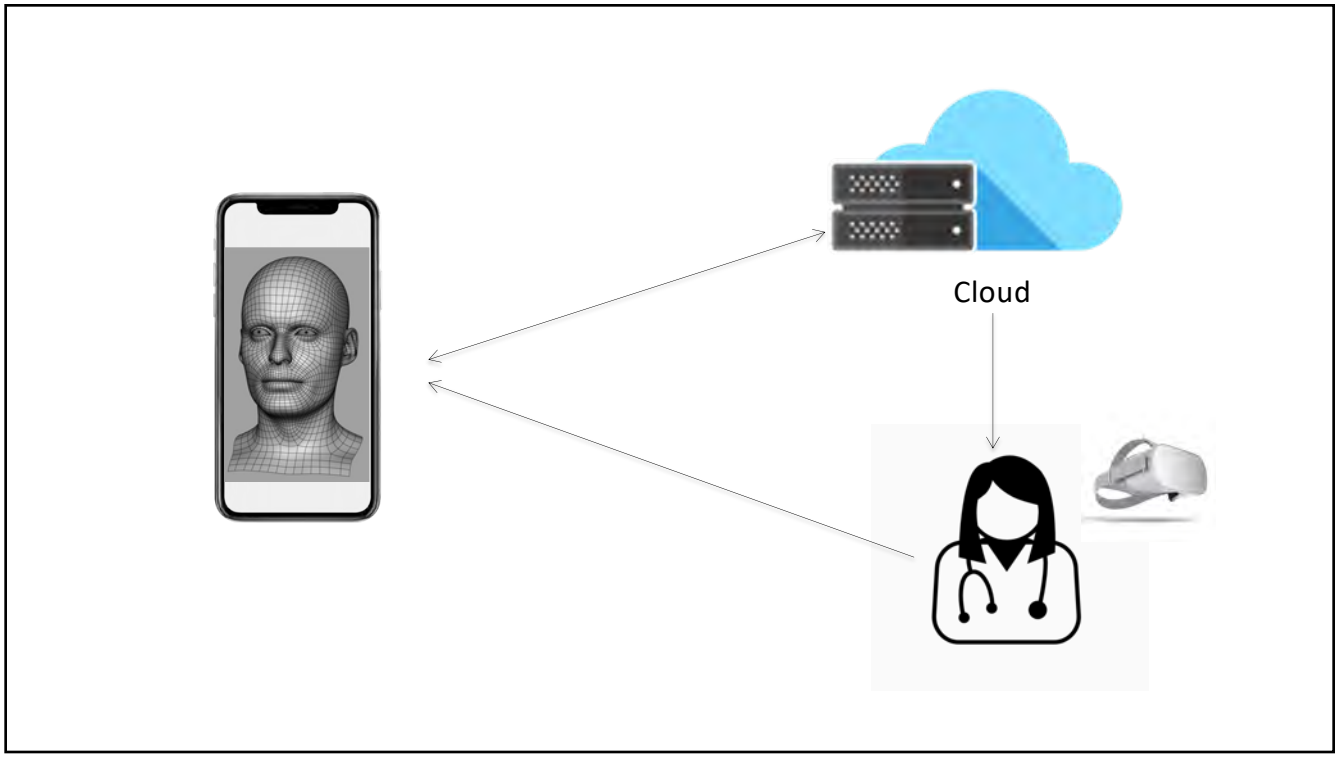
MORPHEUSQ

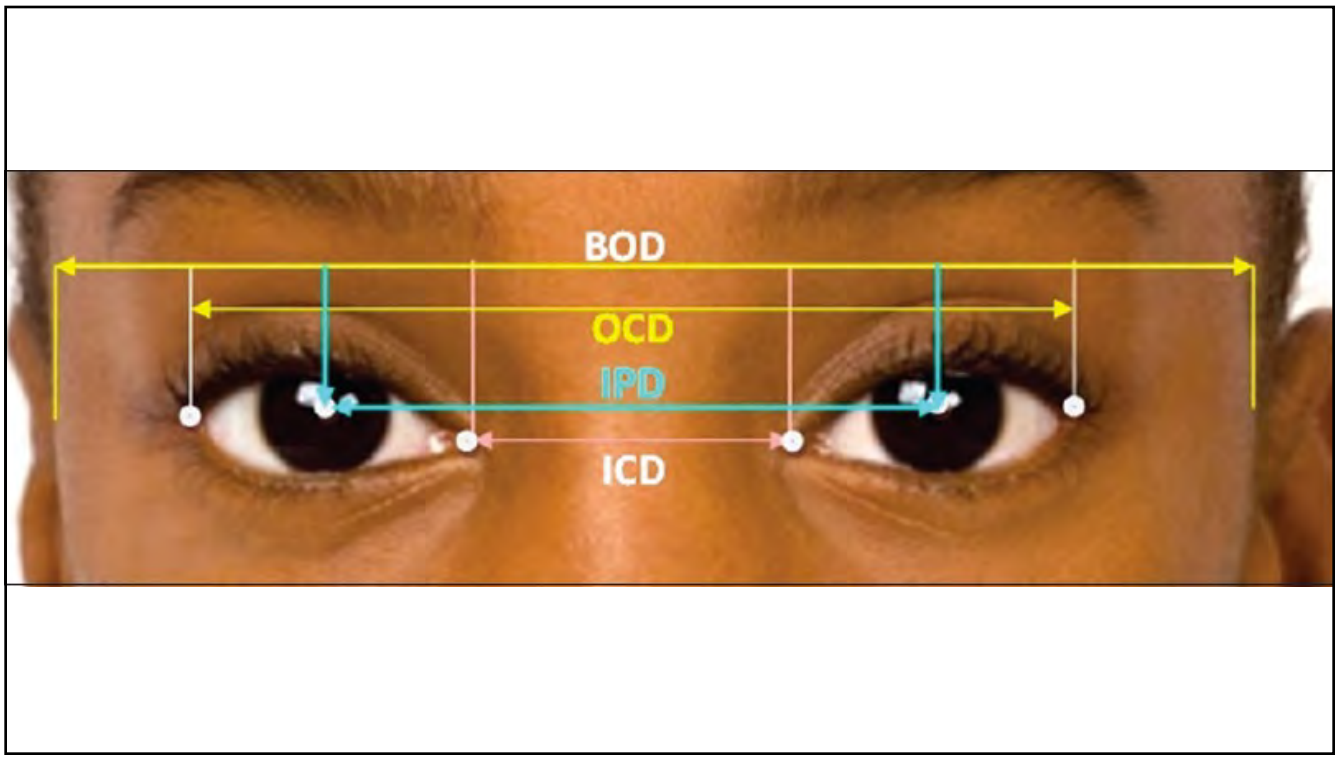
E-Tree
(Sarah Mattson)

BRAIN
(Sarah Mattson)



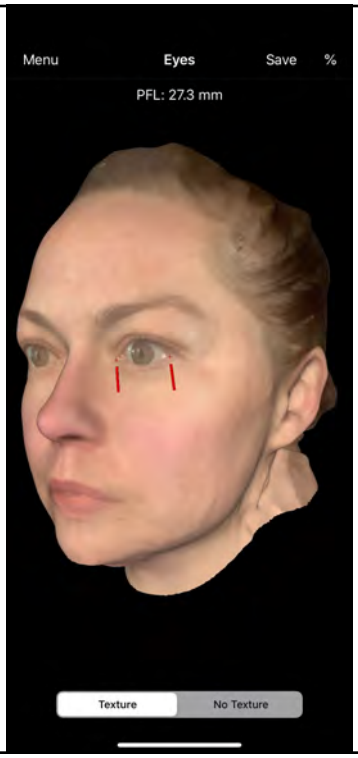



Cloud


BOD
OCD
IPD
ICD

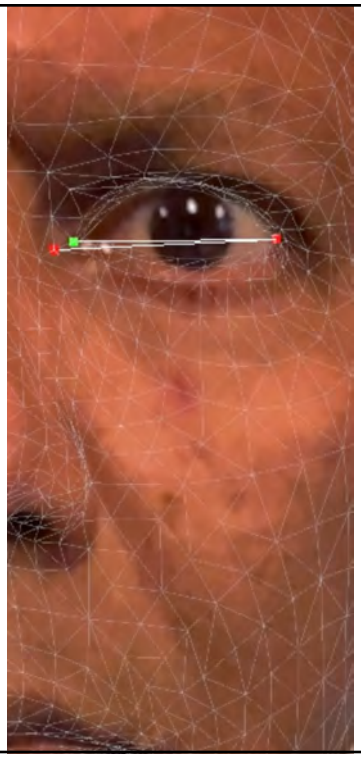
New Features

1. New way to measure PFL (and IPD, OCD, ICD)
2. Percentile Calculator for Age, Weight & Head Circ.
1. Android Version (without PFL feature)



* With Permission


LEFT
27.68 mm
LIVE: 27.67 mm
RIGHT
28.29 mm
28.25 mm
IPD
63.22 mm
ICD
32.77 mm
OCD
87.74 mm
Reset
Red Dot - Left: 31.57 mm / Right: 31.26 mm
Green Dot - Left: 27.68 mm / Right: 28.29 mm



Early Predictors of FASD in Ukraine

Christina Chambers

Rajesh Miranda

Claire Coles

Julie Kable

Fall Meeting CIFASD December 14-15, 2021

Aims

- ***Aim 1. Develop a panel of biomarkers that can predict FASD***
- Predictive value of **maternal and infant miRNAs** for FASD
- Predictive value of the **cardiac orienting response** for FASD
- Predictive value of **maternal and infant cytokines** for FASD
- ***Aim 2. Develop risk/resilience profiles that will predict preschool and school age performance***
- Develop a prediction model for FASD using social, environmental, economic, health, and other available data
- Incorporate biomarkers identified in Aim 1 in the model
- Test the prediction model using data from the CIFASD Phase II and III retrospective sample
- ***Aim 3. Collaborate with others in the CIFASD consortium***

Progress Enrollment

Visit	Enrolled/Data Capture	Goal
Pregnant women/blood samples	167	200
Ultrasounds in pregnancy	157	200
Testing 6 mo old infants	35	100
Testing 12 mo old infants	11	100
Blood samples infants	10	140
Testing school-age children	101	150
Blood samples children	58	70
3D images one site	41	65

Progress in Last 4 Months

- We have recruited 11 additional pregnant women for a total of 167 out of the goal of 200 in CIFASD 4
- In October, 2021, we shipped 21 plasma samples from Ukrainian children with matched maternal samples to Dr. Miranda's and Dr. Weinberg's labs for analysis of miRNAs and cytokines. Also sent samples from FASD Research Biorepository at UCSD.
- In November, 2021, we received a final shipment from Ukraine of 25 new maternal plasma samples and 7 new child plasma samples; these are being distributed to Dr. Miranda and Dr. Weinberg.
- In November, 2021, the two sites in Ukraine completed data entry for the school age sample for 89 participants, and these data were analyzed by Dr. Coles.
- In October, 2021, whole genome sequencing under the XO funding opportunity was completed by the contractor, Hudson Alpha. In November, 2021, the associated clinical data for those samples was uploaded to the data tracker. Release of the sequence data to UCSD awaits approval by the contractor of the clinical data files; expected in January, 2022.

School Age Testing

The analysis for the School Age testing battery administered for children in the cohort originally recruited prenatally and now 7-10 years of age was completed. Significant findings were still measurable in these children consistent with prenatal alcohol dose, after adjustment for SES, age, sex, and site. No significant Group differences were noted on WISC Spatial Span Forward or Backward, Tema Math Score, Recall of Objects, Digit Span Forward or Backward, Speed of Information Processing, or Rapid Naming.

School Age Testing Results

School Age Testing Battery Included:

Differential Ability Scales, 2nd Edition (DAS-II) –Nonverbal Cognitive Ability
BRIEF –Parent report of Child Behavior/Executive Function
Child Behavior Checklist (CBCL)-Parent report of Child Behavior
WISC-Spatial Span

Measure	N	ABO at Conception p-value	ABO Mid-Pregnancy p-value
DAS-II Recall of Designs	89	0.027	0.010
DAS-II Nonverbal Reasoning Standard Score	89	0.576	0.715
DAS-II Spatial Standard Score	89	0.086	0.012
DAS-II Nonverbal Cluster Composite Cluster	89	0.151	0.522

School Age Testing Results

Measure	N	ABO at Conception p-value	ABO Mid-Pregnancy p-value
CBCL Total Problem Score	56	0.008	0.003
CBCL Externalizing	56	0.009	0.046
CBCL Internalizing	56	0.060	0.004
CBCL Anxiety/Depression	56	0.033	0.008
CBCL Withdrawn/Depressed	56	0.314	0.049
CBCL Thought Problems T-score	56	0.002	0.011
CBCL Somatic Complaints T-score	56	0.014	0.001
CBCL Attention Problems T-score	56	0.034	0.053
CBCL Rule Breaking Behavior	56	<0.001	0.076
CBCL Aggressive Behavior	56	0.062	0.060

School Age Testing Results

Measure	N	ABO at Conception p-value	ABO Mid-Pregnancy p-value
BRIEF Global Exec Functioning Score	74	0.021	0.084
BRIEF Inhibit	74	0.012	0.009
BRIEF Working Memory	74	0.051	
BRIEF Behavioral Regulation	74	0.008	0.134
BRIEF Metacognitive Index	74	0.042	0.170
Beery VMI	74	0.019	0.076

Cardiac Orienting Response in Infancy Predicts School Age Working Memory

- 44 infants with and without PAE evaluated with Cardiac Orienting Response (COR) at 6 or 12 months of age
- The same 44 infants who completed the COR were evaluated at 7-10 years of age using the school age battery
- Focus in this analysis is on two indices of working memory
  - Spatial Span Backward subtest from the Wechsler Intelligence Scales for Children IV
  - Recall of Digits Backwards from the Differential Ability Scales, 2nd edition.

Cardiac Orienting Response in Infancy Predicts School Age Working Memory

- Heart rate (HR) responses were aggregated across the first 3 habituation and dishabituation trials and converted to deviation values relative to each participant's baseline HR.
- Z-scores were computed at each second relative to the mean of the participants (n= 931 Ukrainian infants who completed the COR previously were used as reference samples).
- Z-scores of ≥ 1 were then summed to compute a risk index for assessing deviancy from normal CORs to form a total cardiac orienting deviation index (CoDI).
- Participants were then categorized as having a delay if the total CoDI was greater than one standard deviation above the sample mean (>=10).

Cardiac Orienting Response in Infancy Predicts School Age Working Memory

- Greater deviance in the COR response in infancy was associated with poorer working memory skills at school age
  - Auditory Cardiac Orienting Deviation Index (CoDI): r= -.383, p < .010
  - Visual CoDI: r= -.363, p < .021
  - Combined CoDI: r= -.372, p < .013)
- Individuals identified as having a delay in any of the CORs performed in infancy had significantly lower scores on the working memory factor score than did those who had no evidence of an impaired COR in the infancy ($F(1,42) = 7.092$, $p < .011$)

Conclusions re Cardiac Orienting Response

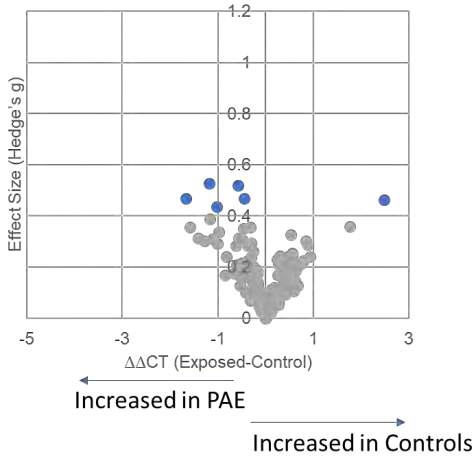
- We previously demonstrated in CIFASD4 that COR in infancy is predicts FASD at preschool age
- Preliminary data suggest COR findings in infancy may also be useful in predicting specific deficits at school age

miRNA Biomarker studies (TAMU)

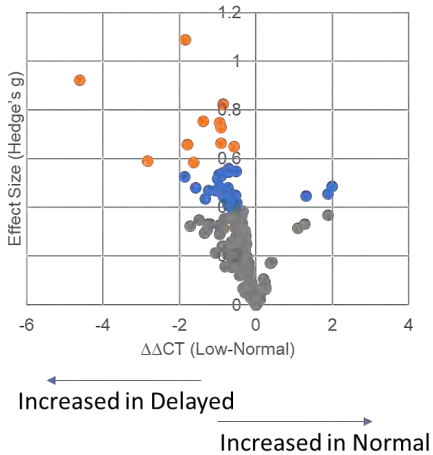
- Maternal samples
  - 93 completed
  - 30 shipped to us in June 2020 (Held pending completion of Child Samples)
- Infant Samples
  - 57 completed
  - 1 sample shipped to us in June 2020
  - 19 samples shipped to us in November 2021
  - In processing (~60% complete)
- Projected Outcomes
  - Maternal/child dyads = 56
  - Cytokine + miRNA combined analysis
    - Common Maternal Samples = 97
    - Common Child Samples = 20
- Resource Prioritization: Completion of Child Samples

Preliminary Analysis: Child Samples

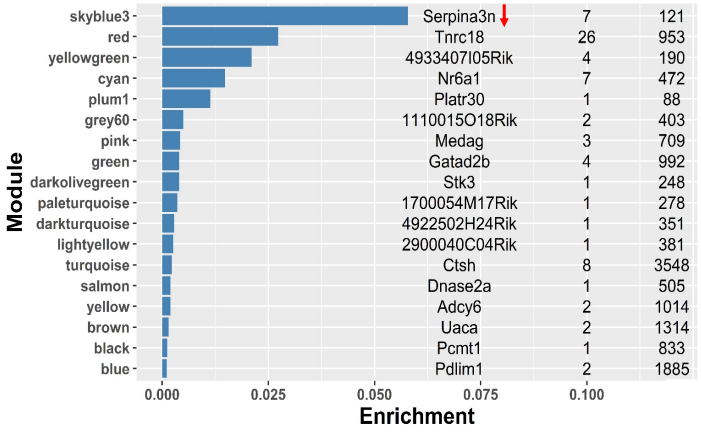
Prenatal Alcohol Exposure Status

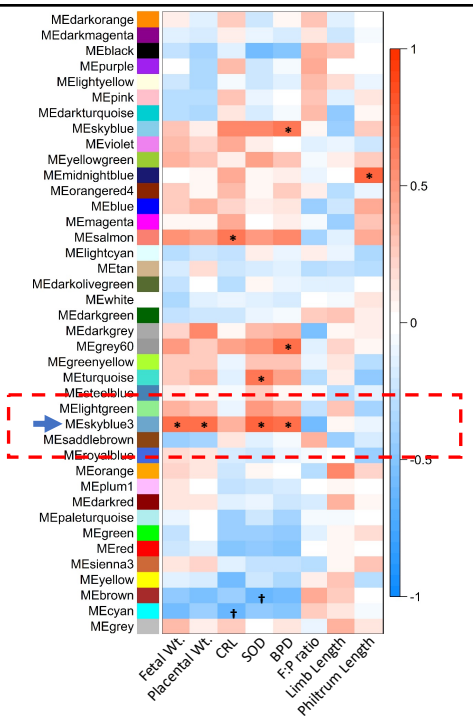


Neurodevelopmental Status



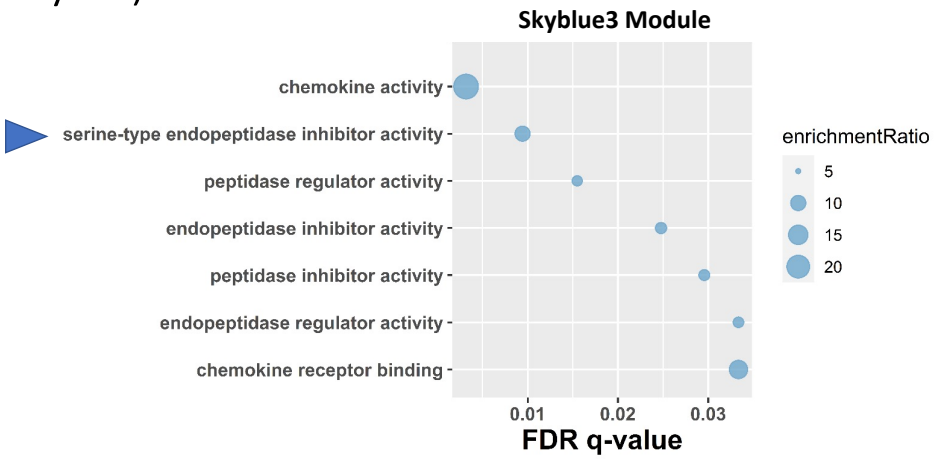
Maternal miRNA functional studies (WGCNA analysis)





Marisa R. Pinson, et al. *Maternal Circulating miRNAs Contribute to Negative Pregnancy Outcomes by Altering Placental Transcriptome and Fetal Vascular Dynamics.* (Submitted/In review).

Maternal miRNA functional studies (WGCNA analysis) continued.



Implicated in placental pathology and preeclampsia

Plans Coming Year

- We have completed Aim 1b: COR predicts preschool performance
- In the next 6 months, we will perform the analyses described in Aim 1a, 1c, 2a: predictive value of child miRNA, cytokines, COR for FASD outcome for the cohort retained at each age grouping (birth, infancy, preschool, and school age)
- We will perform the analysis of genome sequence data for the mother/child pairs with and without FASD and provide data to Susan Smith
- We plan a four session Ukrainian national webinar on FASD in February, 2022, co-sponsored by CIFASD
  - CIFASD presenters paired with Ukraine presenters, and panelists
  - Including Jeff Wozniak and Christie Petrenko in panels
  - The audience will be health care providers, and a large exsiting FAS parent support/advocacy group who will participate in the webinar as well

Publications

- Accepted or submitted: December, 2021
  - Kable J et al The Impact of Micronutrient Supplementation in Alcohol-Exposed Pregnancies on Reaction Time Responses of Preschoolers in Ukraine. Alcohol. (In press)
  - Pinson MR, et al Maternal Circulating miRNAs Contribute to Negative Pregnancy Outcomes by Altering Placental Transcriptome and Fetal Vascular Dynamics. (Submitted/In review)

Publications CIFASD4

- Coles CD, Kable JA, Granovska IV, Pashtepa AO, Wertelecki W, Chambers CD. Measurement of neurodevelopmental effects of prenatal alcohol exposure in Ukrainian preschool children. Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence. 2021 November;27(8):1088-1103. PubMed PMID: 33982636; DOI: 10.1080/09297049.2021.1919298.
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- Kautz-Turnbull C, Petrenko CLM, Handley ED, Coles CD, Kable JA, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Chambers CD. Partner influence as a factor in maternal alcohol consumption and depressive symptoms, and maternal effects on infant neurodevelopmental outcomes. Alcoholism, clinical and experimental research. 2021 June;45(6):1265-1275. PubMed PMID: 33999430; PubMed Central PMCID: PMC8254755; DOI: 10.1111/acer.14612.
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Publications

- Bodnar TS, Raineki C, 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. Immune network dysregulation associated with child neurodevelopmental delay: modulatory role of prenatal alcohol exposure. Journal of neuroinflammation. 2020 January 28;17(1):39. PubMed PMID: 31992316; PubMed Central PMCID: PMC6988366; DOI: 10.1186/s12974-020-1717-8.
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Publications

- Bandoli G, Coles CD, Kable JA, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Wells A, Granovska IV, Pashtepa AO, Chambers CD. Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development. Pediatrics. 2019 February;143(2). PubMed PMID: 30610099; PubMed Central PMCID: PMC6361345; DOI: 10.1542/peds.2018-2399.
- Bodnar TS, Raineki C, Wertelecki W, Yevtushok L, Plotka L, Zymak-Zakutnya N, Honerkamp-Smith G, Wells A, Rolland M, Woodward TS, Coles CD, Kable JA, Chambers CD, Weinberg J. Altered maternal immune networks are associated with adverse child neurodevelopment: Impact of alcohol consumption during pregnancy. Brain, behavior, and immunity. 2018 October;73:205-215. PubMed PMID: 29738852; PubMed Central PMCID: PMC6344127; DOI: 10.1016/j.bbi.2018.05.004.
- Coles CD, Kable JA, Taddeo E, Strickland D. GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Developmental neurorehabilitation. 2018 July;21(5):345-349. PubMed PMID: 29313400; PubMed Central PMCID: PMC6314185; DOI: 10.1080/17518423.2018.1424263.
- Sowell KD, Uriu-Adams JY, Van de Water J, Chambers CD, Coles CD, Kable JA, Yevtushok L, Zymak-Zakutnya N, Wertelecki W, Keen CL. Implications of altered maternal cytokine concentrations on infant outcomes in children with prenatal alcohol exposure. Alcohol (Fayetteville, N.Y.). 2018 May;68:49-58. PubMed PMID: 29453023; PubMed Central PMCID: PMC5820219; DOI: 10.1016/j.alcohol.2017.08.006.

Families Moving Forward Connect: Development of a Mobile Health Intervention for Caregivers Raising Children with FASD

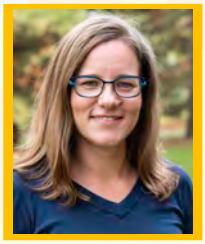
Christie L. M. Petrenko, Ph.D. & Cristiano Tapparello, Ph.D.

Mt. HOPE family center

UNIVERSITY of ROCHESTER

Families Moving Forward CONNECT

Heather Carmichael Olson, Ph.D.
SCRI / U. of Washington



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Programmer
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Families Moving Forward CONNECT

Aims

- **Aim 1**: Development of FMF Connect mHealth app for caregivers
  - Derived from Families Moving Forward (FMF) Program
  - Stakeholder feedback in focus groups on initial design
  - 2 rounds of beta-testing on iOS and Android prototypes
- **Aim 2**: Feasibility Study
  - Assessing feasibility of intervention, trial procedures, and caregiver implementation
- **Aim 3**: Hybrid Implementation-Effectiveness RCT
  - Testing efficacy of FMF Connect app and how caregiver usage relates to outcomes
  - Added coaching arm to test if coaching increases engagement and outcome improvement

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Aim 1- Completed

Publication #1 (June 2020)
Initial Design Focus Groups
***JMIR mHealth uHealth* IF=4.77**

Publication #2 (December 2021)
Two Rounds of Beta-Testing
JMIR Formative Research

Families Moving Forward CONNECT

Aim 2 – Analysis in Process

- Data collection completed
  - iOS: 1/31 – 10/21/2020
  - Android: 1/26 – 7/30/2021
- Analysis and manuscript preparation underway

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Feasibility Trial: Recruitment

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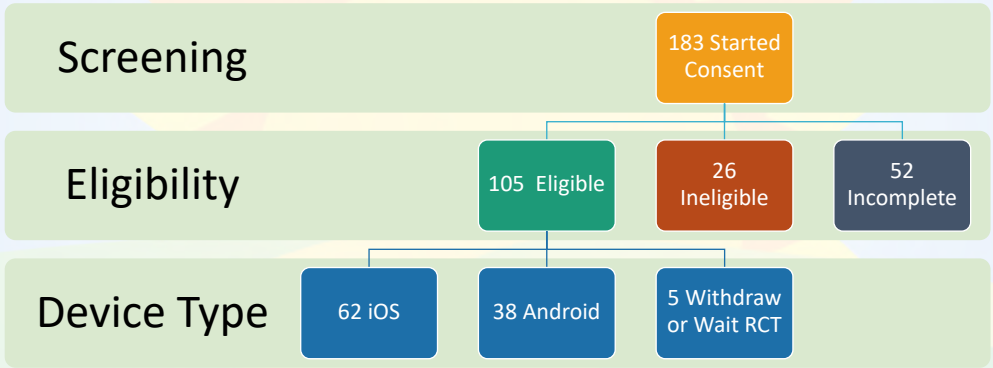
Families Moving Forward CONNECT

Trial Feasibility: Recruitment



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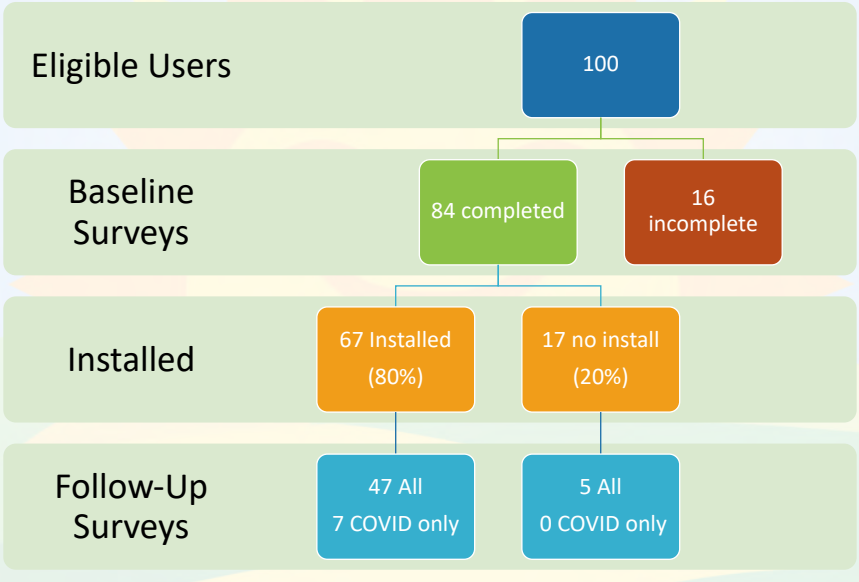
Feasibility Trial: iOS & Android Combined



84% completed baseline surveys

Comparable to the 25% non-starters see in F2F parenting interventions

68% completed any follow-up 56% installed and did all surveys

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Families Moving Forward CONNECT

Aim 2 Feasibility Pilot Trial Objectives

- Intervention Feasibility
  - 1a. Does FMF Connect work from a technological perspective?
  - 1b. Is FMF Connect acceptable to caregivers?
- Trial Feasibility
  - 2a. Do proposed recruitment and enrollment procedures produce sufficient rates to support a large-scale RCT?
  - 2b. Is the assessment battery acceptable and sensitive to change?
  - 2c. What is the optimal length between baseline and follow-up measurement?
  - 2d. What is the study attrition rate? What predicts attrition?
- Implementation
  - 3. What does caregiver implementation look like?

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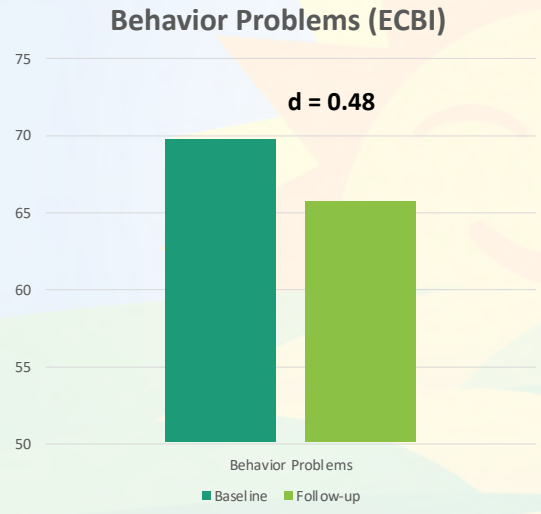
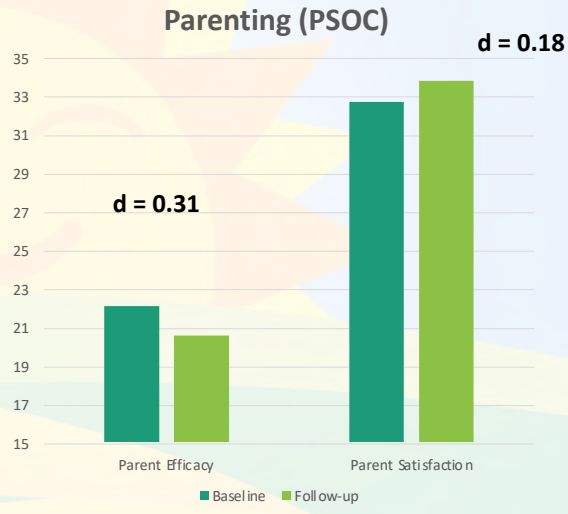
NEW: Quantitative Data





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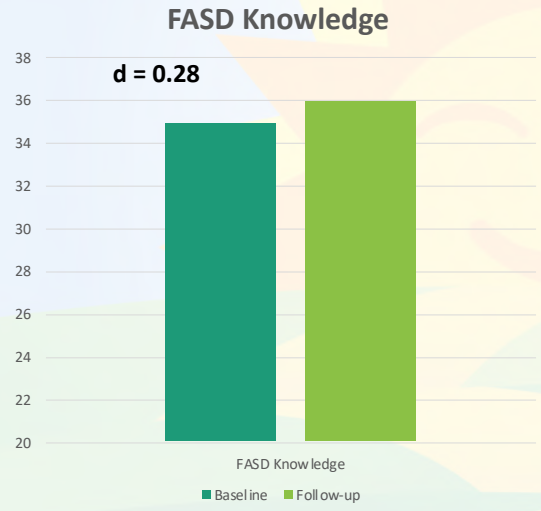
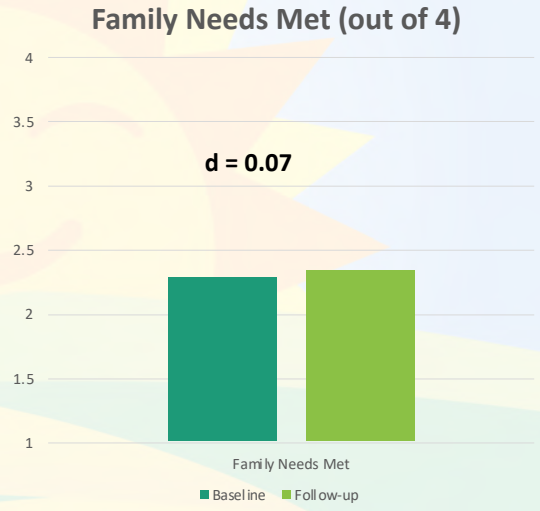
NEW: Quantitative Data





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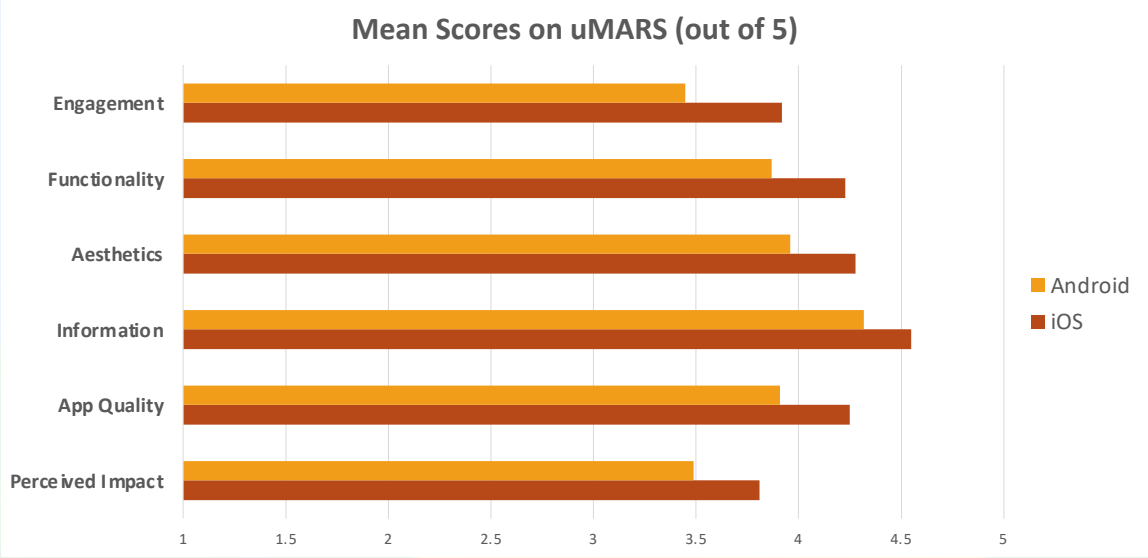
Mobile Application Rating Scale: User Version (uMARS)



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Aim 3: RCT

- Some delays… IRB, REDCap, AWS, Apple
  - Just need to do final testing of REDCap
- Given holidays, aim to launch Jan 3rd

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Families Moving Forward CONNECT

Coaching & Other Programming Updates

- Implemented functionalities to support the RCT coaching arm
  - Direct messaging + notifications
  - Tracking system and companion website
- Under the hood updates
  - Support for iOS 15
  - Fully revised and improved integration with AWS
  - Transitioned video library to a new AWS adaptive video streaming service
  - Added push notifications to Family Forum

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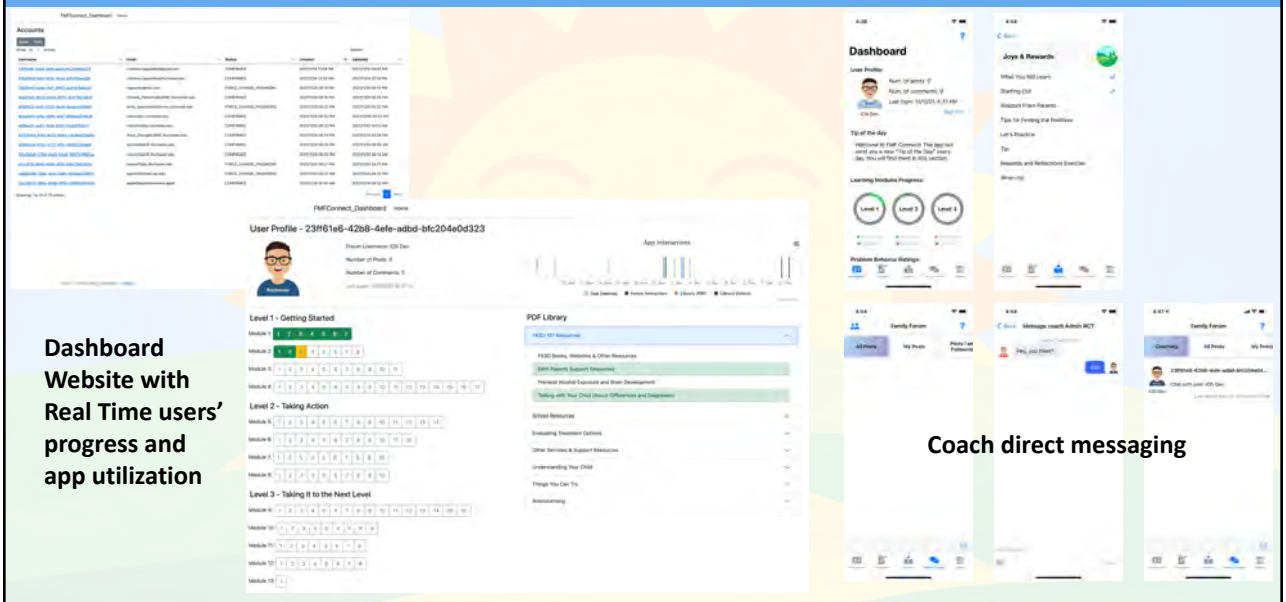
Families Moving Forward CONNECT

Coaching & Other Programming Updates (2)



Dashboard Website with Real Time users' progress and app utilization

Coach direct messaging

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Families Moving Forward CONNECT

Publication Update (Since June 2021)

Published

- Petrenko, C. L. M., Kautz-Turnbull, C., Roth, A., Parr, J, Tapparello, C., Demir, U., Olson, H. C. (2021). Initial feasibility of the "Families Moving Forward Connect" mobile health intervention for caregivers of children with fetal alcohol spectrum disorders: Mixed method evaluation within a systematic user-centered design approach. *JMIR Formative Research, 5,* e29687.
- Kautz-Turnbull, C., Petrenko, C.L.M., Handley, E.D., Coles, C.D., Kable, J.A., Wertelecki, W., Yevtushok, L., Zymak-Zakutnya, N., Chambers, C.D., & CIFASD. (2021). Partner influence as a factor in maternal alcohol consumption and depressive symptoms, with subsequent effects on infant neurodevelopmental outcomes. *Alcoholism: Clinical & Experimental Research, 45,* 1265-1275. PMCID: PMC8254755

In Preparation

- Kautz-Turnbull, C., Petrenko, C.L.M., & Rogge, R. (In preparation). Reasons for Children's Behavior: Development and Validation of a New Measure of Parental Attributions.
- Kautz-Turnbull, C., Rockhold, M., Olson, H.C., & Petrenko, C.L.M. (in preparation). Adverse childhood experiences (ACEs) in young children with fetal alcohol spectrum disorder (FASD) and effect on behavior problems.
- Petrenko, C.L.M., Kautz-Turnbull, C., Roth, A., Zhang, S., Rockhold, M., Tapparello, C., Olson, H.C. (in preparation). Large-scale feasibility trial of the Families Moving Forward Connect mHealth intervention for caregivers of children with fetal alcohol spectrum disorders.

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Families Moving Forward CONNECT

Other Highlights Since June 2021

- FASD Success Podcast

Thrive Lifelong
Health • Research • FASD Supports

- Thrive Lifelong lab newsletter: www.fmfconnect.com/news
- FASD and the Courts webinar - October 2021
- Conferences
  - ESBRA in October 2021
  - APSAD Special Interest Group Meeting 2021

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Immune dysregulation in FASD: Programming of health and neurobehavioral outcomes

Joanne Weinberg Update
Co-Is: Tamara Bodnar, Charlis Raineki, Tim Oberlander
With: Parker Holman, Linda Ellis, Wayne Yu, Christine Loock, Jan Lutke

CIFASD Late Fall 2021 Progress Meeting
December 16-17, 2021

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine
Department of Cellular & Physiological Sciences

CIFASD Collaborative Initiative on Fetal Alcohol Spectrum Disorders

NIH National Institute on Alcohol Abuse and Alcoholism

Aim 1. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes

- In collaboration with Tina - longitudinal study in Western Ukraine:
  - *Concept Proposal 90*: Raineki, C., Bodnar, T., Wertelecki, W., Yevtushok, L., Plotka, L., Granovska, I., Zymak-Zakutnya, N., Pashtepa, A., Wells, A., Honerkamp-Smith, G., Coles, C.D., Kable, J.A., Chambers, C.D., Weinberg, J., and the CIFASD. *Differential associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay.*
  - Data analysis almost complete and writing underway

Aim 1 (cont'd)

- In parallel with Dr. Rajesh Miranda, we have just received an additional shipment of samples from children and mother/child pairs from Ukraine; further samples to come
  - This significantly increases the number of overlapping maternal and child samples between the Miranda lab and our lab
  - Assays to be completed in January
  - Will work with Rajesh, Tina, and teams on a joint paper to assess whether 2 molecular markers (cytokines, miRNAs) in *maternal samples* can serve as stronger/more accurate *predictors* of child developmental trajectories, and in *child samples* can serve as stronger/more accurate *biomarkers* of PAE/FASD compared to either cytokines or miRNAs alone.

Aim 1 (cont'd)

- **Child study in San Diego with Tina and Ken**
  - Children recruited from San Diego FASD Research Subject Pool (Rady Children's Hospital)
  - Samples from 33 children in the FASD registry (n=11 ARND, 5 FAS, 10 PAE, 7 PFAS) received by us and by Miranda's group in November
  - Once assays are complete we will work together with Rajesh, Tina and teams to understand the power of the combined analysis of two molecular markers as biomarkers of PAE/FASD
  - For children born in San Diego County, possibility for Rajesh and our group to obtain:
    - Blood spots from children at birth and maternal mid-gestation blood samples to add to our analysis
    - This additional information would not only allow for a unique exploration of the *immune trajectory* of these children over time, but also provide *validation cohorts for our previous maternal and child studies* and for the *investigation of how the maternal immune environment influences child outcomes.*
- **Analysis of cytokines in plasma samples from children in Jeff's choline clinical trial**
  - 67 samples from 34 unique subjects received in October 2020; cytokine assays and pre-processing of the data completed last spring
  - In consultation with Jeff, analyses put on hold (several incomplete sample sets, difficult to assess pre/post choline outcomes) to wait for re-initiation of clinical trial and possibility of getting additional blood samples
    - However, while the clinical trial has resumed, no further blood samples will be collected
  - We will work with Jeff to analyze the cytokine data we currently have in relation to choline, eating behavior, changes in body weight, and health outcomes and to prepare a manuscript

Outreach to new collaborators

- Two new collaborative studies will expand our assessment of the association between plasma cytokine levels and health and functional outcomes.
- Complement the studies in Aim 1, and serve as validation cohorts to gain further insight into relationships among immune/inflammatory alterations, health and functional outcomes in children.
- **Dr. Natasha Reid, University of Queensland (UQ), Australia**
  - In her ongoing clinical study, Natasha is collecting blood samples from children 7-10 yr, with FASD and matched controls, to explore the development of biomarkers that reflect alcohol exposure *in utero*.
  - We will obtain blood samples (blood spots), as well as demographic and health information, and cognitive, language, and behavioral assessments on these children
  - Ethics approval is now complete and work is ongoing
- **Dr. Catherine Lebel, University of Calgary**
  - In one ongoing study, Catherine is investigating how brain abnormalities (MRI) are related to diagnosis, facial dysmorphology, mental health symptoms, and other exposures in children 2-18 years of age
  - We will obtain blood samples (blood spots) from these children for measurement of cytokines, and will have access to all of the other measures in her study.
  - Ethics approval is now complete and work is ongoing.

Aim 2. Extend our assessment of the immune system in individuals with FASD into adulthood

Adult Health Study (collaboration with Claire Coles and Therese Grant)

- To date, 72 adults recruited in Vancouver:
  - FAS/FASD/ARND = 46; Unexposed = 26
  - Mean age: Exposed, 37.5 yr; Unexposed, 32 yr
  - Restrictions in Canada/UBC have not allowed us to resume in-person testing; we hope to resume in person testing in the new year
- Recruitment and testing of adults has resumed in both Atlanta and Seattle
  - We have just received shipments of blood samples from both sites
    - Assays to be run in January
  - This will significantly enhance our database and allow for additional analysis and manuscript development over the next 6 months.

Aim 2 (cont'd)

- New collaboration - Dr. Kaitlyn McLachlan, University of Guelph, Guelph, ON
  - Kaitlyn's studies focus on FASD and neurodevelopmental disability across the lifespan
  - With Kaitlyn, we will reach out to adults with FASD and appropriate unexposed adults who are part of her research studies to recruit them to our Adult Health Study
  - Ethics application in progress
  - Testing and blood sample collection will be done through her laboratory at Guelph
  - This collaboration will help us reach our Aim 2 target numbers and will provide a comparison group to gain further insight into environmental/demographic factors influencing adult health and functional outcomes

Pre/Post COVID-19 Study on adult cohort

- Re-contacted participants already tested (total n=72) in our Adult Health Study to examine impact of COVID-19 on mental health status, stress levels, and other related domains.
  - Questionnaires selected from the NIH COVID-19-related resources
  - Beck Depression, Beck Anxiety, Perceived Stress Scale, Penn State Worry Questionnaires administered, as previously
  - Open-ended questions from the "telling our stories in the age of COVID-19" questionnaire.
- Preliminary results indicate that
  - Depression scores increased for both adults with FASD and unexposed adults, and pandemic stress levels were not different between groups
  - However, anxiety scores increased to a greater extent in those with FASD vs unexposed adults
- Presented at the 2021 FASDSG meeting and *Concept Proposal* submitted: *Impact of the COVID-19 pandemic on mental health and stress levels in adults with Fetal Alcohol Spectrum Disorders (FASD)*

Deliverables

- 2 new publications with bearing on the work of CIFASD
  - Lussier et al., *Genes*, 2021, 12, 1773. https://doi.org/10.3390/genes12111773
    - Overlapping phenotypic characteristics and DNA methylation patterns in FASD and ASD
  - Lussier, Bodnar, Weinberg, *Front. Neurosci. 15:788630. doi: 10.3389/fnins.2021.788630*
    - Epigenetic reprogramming of immune function could be the missing link between prenatal alcohol exposure and mental health disorders.
- In preparation:
  - Raineki et al, Differential associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay (in preparation). Concept Proposal 90.
  - Bodnar et al, Impact of the COVID-19 pandemic on mental health and stress levels in adults with Fetal Alcohol Spectrum Disorders (FASD) (in preparation). Concept Proposal submitted.
- Oral and Poster Presentations
  - 6 since June 2021
  - 31 total since 2017
- Broad collaboration across CIFASD:
  - Collaborations with Tina, Rajesh, Claire, Ken/Miguel, Jeff, Tatiana/Leah, Mike Suttie
  - 3 new collaborations to extend recruitment of children and adults

Activities for Year 5

- Move forward towards completion of our Specific aims:
  - Complete and submit our papers on
    - Associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay
    - The impact of COVID-19 on adults with FASD.
  - Focus on running assays, completing data analysis, and development of manuscripts
    - With Rajesh, Tina and teams on combined analysis of two molecular markers (cytokines and miRNAs) in mother and child samples from the Ukraine cohort and child samples from the San Diego FASD Research Subject Pool
    - Complete cytokine assays on plasma samples recently received from the Adult Health Study in Atlanta and Seattle; work with Claire and Therese on data analysis, relating cytokine levels to cognitive and functional outcome measures, and on mansuscript development
    - Work with our new collaborators to extend our recruiting efforts to additional cohorts of children that will complement the studies in Aim 1, and to adults for participation in our Adult Health Study to meet our target n=120. Data analysis and manuscript development will be ongoing.

UH2 AA029056-01 Choline Polymorphisms in FASD

Susan Smith
UNC Nutrition Research Institute
University of North Carolina at Chapel Hill

Background

- Collaboration with JRW identified 14-16 SNPs in the choline transporter SLC44A1 (CTL1) associated with greater cognitive benefit from 9-mo choline intervention.
- All are minor variants in SLC44A1
- All associated with improved cognition/memory performance in response to choline.

Hypothesis & Aims

Polymorphisms in SLC44A1 significantly influence cognitive outcomes in FASD, in presence and absence of choline intervention.

1) OMNI-Net choline intervention trial: Effect alleles in SLC44A1 are associated w/greater cognitive benefit in ALC pregnancies receiving choline.
2) CIFASD Phase 2/3: Effect alleles in SLC44A1 are associated w/worsened cognitive performance in absence of choline intervention.
3) Functional analysis of effect alleles to SLC44A1 activity.

Where are we at?

Aim 1. OMNI-Net choline intervention trial:

Sequencing data just completed. Now being reviewed & awaiting release. Projected Jan 2022.

Aim 3. Functional analysis of SLC44A1.

Designing CRISPR for mutational analysis. Pending confirmation from CIFASD2/3 analysis.

CIFASD2/3 - Process

- April – received access to phenotypic data
- June – received access to genetic dataset
- Extracted relevant genotypes
- Place data in format suitable for analysis.
- Reviewed all phenotypes & prioritized for first-pass analysis
- Identified covariates/confounders for the Association model

Complications – Data Cleansing

- Impute relevant SLC44A1 variants
- Merge CIFASD2/3 data dictionaries (3 – complete; 2 – partial)
- Merge CIFASD2/3 datasets (address inconsistencies in dictionaries)
- Provision of individual race/ethnicity to calculate eigen values from PCA
- Provision of rigorous diagnostic category for individuals (recruitedchildgroup, demgroupclass)
- Scrub inconsistent notation for missing variables (blank, NA, 9999)
- Remove raw values from calculations, check cells for accuracy & validation
- Identify and remove/consolidate overlapping individuals & their data (duplications, multiple visits/entries)
- Remove irrelevant data, impute missing information, remove comments, identify and isolate categorical vs. numerical information
- Much back and forth with the data repository (thank you, Leah!)

SNPs in SLC44A1

- 14-16 SNPs from JRW study
  - Associated with cognitive improvement in choline-treated children
- Two of these overlapped with CIFASD2/3 data base:
  - rs2771040 – present in CIFASD2/3; structural variant S344A
  - rs3199966 – imputed; 3' UTR of cell membrane isoform
- Three more SNPs were present in CIFASD2/3 dataset:
  - rs10991609 – SNV in intron 2; C>G
  - rs10991630 – SNV in intron 3; G>A
  - rs12379026 – SNV in intron 3; T>A

Population Frequency

% Frequency of Minor Alleles					
	Overall	European	**African**	Asian	Hispanic
rs3199966	19.6%	9.2%	**39.9%**	0.7%	11.5%
rs2771040	21.5%	12.3%	**42.0%**	1.0%	12.4%
rs10991609	**2.0%**	1.8%	-	-	-
rs10991630	**2.2%**	3.5%	-	0.03%	-
rs12379026	**2.2%**	3.5%	-	0.03%	-

Test Drive: Palpebral fissure length

- Very clean data (required little cleansing)
- Co-variates: age of examination, sex, and identity-by-descent
- 205 samples from Phase 3 that passed IbD

rs3199966	**Q = 0.0253**	**Increased w/Minor allele**	**R = -6.237**	**76/205 carriers**
rs2771040	**Q = 0.0468**	**Increased w/Minor allele**	**R = -5.686**	**84/205 carriers**

- Relevant effect alleles have sufficient representation
- Q-values in range of their association with cognition (JRW)

Hitting the Road

- Alcohol-Diagnosis + Normotypic Controls + Other Neurodevelopmental
- 5 SNPs in SLC44A1 x Phenotypes in working memory (+ briefs)
- Additive model

Select Associations:

Population	SNP	Q adj	Phenotype	Allelic Effect	Regr. Coeff.	% Minor
All participants	rs3199966 rs2771040	Q = 0.0070 Q = 0.0359	cvltperseverrz Free & cued recall	Incr. w/Minor allele (T) Incr. w/Minor allele (A)	R = -0.454 R = -0.374	75/288 84/288
All participants	rs3199966 rs2771040	Q = 0.0016 Q = 0.0080	dasiipattconstperc DASII pattern constr. %ile	Incr. w/Major allele (G) Incr. w/Major allele (G)	R = 10.15 R = 8.74	76/299 85/229
All ALC Dx	rs3199966	Q = 0.0164	conners_adhd_prob ADHD probability SEM	Incr. w/Major allele (G)	R = 14.11	28/80
All AfrAm	rs3199966 rs2771040	Q = 0.0367 Q = 0.0314	conners_odd_met_sc Conners symptom count	Incr. w/Minor allele (T) Incr. w/Minor allele (A)	R = -0.402 R = -0.401	47/69 47/69
AfrAm ALC Dx	rs2771040	Q = 0.0384	cvltpercrecprz CVLT % cued recall, Z-score	Incr. w/Major allele (G)	R = 0.891	15/28

Next Steps

- CIFASD2/3 are equivalent to placebo-controls in JRW study
- Repeat, adjusting for covariates (i.e., age, sex, site, ethnicity)
- Extend analysis to dysmorphology phenotypes showing association in JRW (i.e., height, weight)
- Repeat with Ukrainian / OMNI-Net choline intervention
- Request analysis of non-SLC44A1 choline SNPs showing associations w/cognition & dysmorphology in JRW (i.e., BHMT, FADS2, FMO3, CHDH, MTHFR, MTHFD)

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

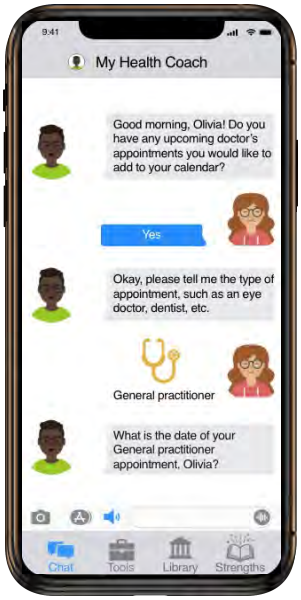
UH2 AA029050
December 2021

PARTNERSHIP WITH THE ADULT LEADERSHIP COMMITTEE OF FASD CHANGEMAKERS

AIMS

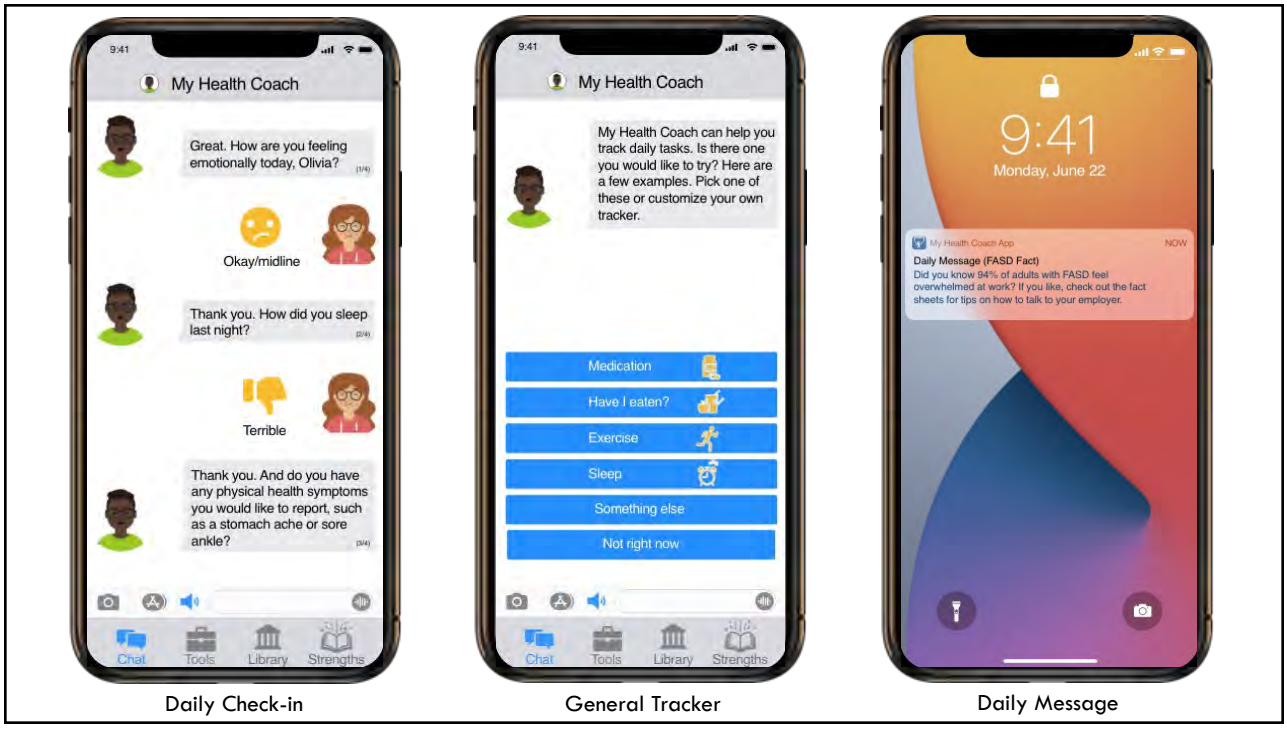
1) Development of "My Health Coach" app
- Identify & refine functionalities through focus groups and survey methods.
- Develop an iOS prototype for testing

2) Feasibility Study



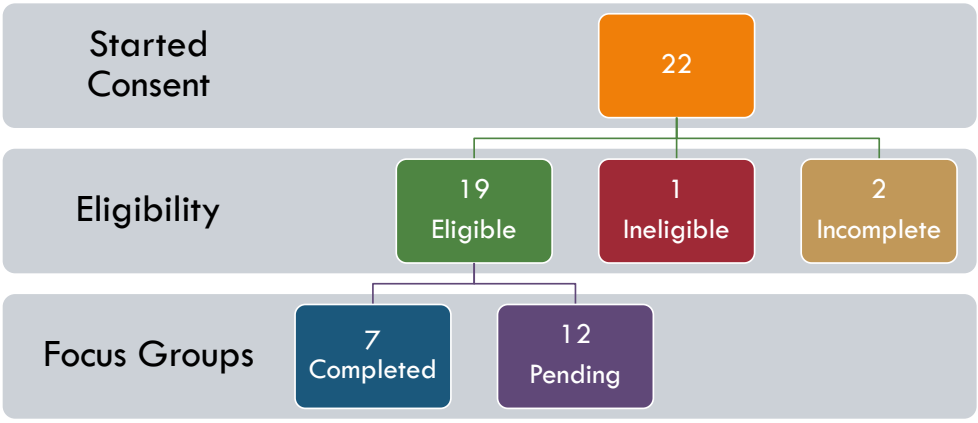
PROGRESS TO DATE

- 8 Advisory board meetings since June
- Continued development of interactive prototype design
- Started focus group data collection (Aim 1)



Daily Check-in | General Tracker | Daily Message

RECRUITMENT PROGRESS



EARLY FEEDBACK FROM FIRST FOCUS GROUPS

Global positive impressions

"I really think that this app would be very helpful for me."

"…the fact that it actually engages the individual…that's far off better than just having some generic response to everything you do."

"I really like the fact that you get to have choices, it helps feel more personal."

EARLY FEEDBACK FROM FIRST FOCUS GROUPS

Positive Features

Ability to customize

Strengths assessment

Daily check-in

Suggesting tools based on responses

Breathing tool

Visuals, video

Trackers

Library resources, factsheets

Daily message

Negatives / Things to Consider

Amount of time to enter medications or doctors appoints at start

Level of customization vs. simple choices – some users may find customization overwhelming (e.g., Avatar)

Length of videos should be short

Need more reminders for appointments

IDEAS AND SUGGESTIONS

Additional calming tools / breathing techniques

Being able to add appointments directly in calendar (vs. via chatbot)

Visual timer

Ability to share with partner, caregiver, or other support person

Ideas for more trackers

Overlays instead (or in addition to videos)

Wearables / sensors – can detect anxiety or arousal and offer help

PRESENTATIONS SINCE JUNE 2021

Petrenko, C.L.M., Cole, L., & Kautz-Turnbull, C. (2021). Leveraging technology to increase access to diagnosis and fetal alcohol spectrum disorder (FASD)-informed care across the lifespan. Australasian Professional Society on Alcohol and Other Drugs FASD Special Interest Group meeting. November 7, 2021.

Petrenko, C.L.M., Tapparello, C., Speybroeck, E., Griffin, K., Hargrove, E., Himmelreich, M., Lutke, C.J., Lutke, A., May, M., & Harth, M. (2021). "Nothing about us without us": Partnering with adults with FASD to develop mobile health tools for condition management. 2021 Proof Alliance Conference: ProofCon 2021: Empowered by the Proof., October 2021.

Petrenko, C. L. M. (2021). Development and evaluation of digital and mobile health interventions (eHealth) for FASD. Virtual Presentation in symposia "Diagnosis and Interventions in FASD: From Genes to eHealth." European Society for Biomedical Research on Alcohol, Timisoara, Romania, October 2021.

IDEAS TO FACILITATE RECRUITMENT?

Current and pending efforts:

1. Advisory board members social media networks – regular posts
2. Team members Twitter, Facebook groups, Thrive Lifelong newsletter
3. FASD United included in a couple of Weekly Round-ups
4. CIFASD members, AUCD SiG network
5. Presentations, podcasts
6. Jeff Noble creating promo video to share with his networks


Questions
Comments
Feedback

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

1 UH2 AA029062-01

PIs: Annika Montag & Christine Austin

CIFASD4 Late Fall 2021 Progress Meeting

UC San Diego School of Medicine

Rady Children's Hospital San Diego

Icahn School of Medicine at Mount Sinai

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.

Progress

- Agreements among participating institutions: Material Transfer Agreement, Reliance Agreement, Data Transfer Agreement, and Data Sharing Plan
- UCSD IRB approval: IRB research plan, Parent Consent/Permission, Child Assent, Adolescent Assent, Study flyer, Tooth Questionnaire, Permission to approach blurb, Recruitment phone script, Recruitment email script, and the Cover letter to parent/guardians
- Other materials designed and supplies obtained: Data spreadsheets, tracking tables, and collection forms. Internal flowcharts for workflow, storage, and shipment of samples. Envelopes and stamps for sending materials to participants and stamped return envelopes for participants to use in returning samples, consents, assents, and the tooth questionnaire. Stamps to Dr. Wozniak's group for dissemination of our flyer. Incentives for participating children.
- Drs. Mattson & Wozniak identified eligible participants and obtained permission to approach
- Mt Sinai lab: Finalized QA/QC procedures for tooth-metals analysis, including development of R shiny apps to monitor QA/QC parameters and matrix-matched hydroxyapatite calibration standards to improve accuracy
- Presented poster and video poster of POC pilot data at 2021 RSA; preparing manuscript for January 2022 submission
- Initiated recruitment
  - *6 families contacted*
  - *2 families fully consented, 1 additional family verbally consented*

Plans for Year 2

- Continue recruitment
  - Contact and verbally consent eligible cohort participants
  - Send materials to consented participants
    - Consent/assent, return envelope, tooth container, brief form, incentive
  - Process consent documents and enter data
  - Log and de-identify tooth samples
- Send samples to Austin lab for biomarker assessment
  - Direct & indirect biomarkers of alcohol, metals, co-exposures
- Obtain neurodevelopmental outcome data for participating children
- Analyze associations among measured exposures and outcomes
- Submit Proof-of-Concept manuscript in January 2022
- Submit methods manuscript in early 2022

Can Naturally Shed Baby Teeth From Young Children Be Used To Map Their History of Prenatal Alcohol Exposure?

Annika Montag[1] and Christine Austin[2]

[1] Division of Dysmorphology-Teratology, Department of Pediatrics, University of California, San Diego, CA
[2]Department of Environmental Medicine and Public Health at the Icahn School of Medicine at Mount Sinai, New York, NY

RSA 2021
Poster & Video
Abstract 377 Poster 656

Project Purpose

To obtain proof-of-concept that prenatal alcohol exposure can be identified using biomarkers in naturally shed deciduous teeth

Background

- Alcohol-exposed pregnancies result in a range of persistent cognitive and motor function deficits termed Fetal Alcohol Spectrum Disorders (FASD)
- Accurate diagnosis is crucial to obtaining effective, timely treatment and support, and avoiding negative secondary outcomes
- When facial and growth components are not present, documentation of prenatal alcohol exposure is often required for diagnosis. However, when children are adopted or in foster care, maternal self-report may be unavailable
- We need non-invasive, sensitive, readily accessible biomarkers that accurately reflect prenatal exposure that occurred many years ago
- Tooth development begins in the fetus in late first trimester to early second trimester. Circulating chemicals are deposited in tree-like growth rings
  - See Figure 1 for key aspects of tooth development

Biomarkers

Direct biomarkers of alcohol exposure
- Ethyl glucuronide (EtG)
- Ethyl sulfate (EtS)
- Select fatty acid ethyl esters (FAEEs)
- Phosphatidyl ethanol (PEth)

Indirect biomarkers of alcohol exposure
- Organic compounds such as amino acids and cholesterol sulfate

Methods

- Eligibility criteria
  - Parent/guardian of a 6-12 year old child with a diagnosis of FASD or known absence of prenatal alcohol exposure, and the child
- Recruitment
  - Participants were recruited through the National Organization on Fetal Alcohol Syndrome (NOFAS), through clinical and research colleagues, and the UC San Diego/ Rady Children's Hospital FASD Registry.
  - Consent and assents obtained
- Data & sample collection
  - Preliminary consent by phone
  - Materials were mailed to participants including cover letter, consent and assent forms, brief survey, envelope for tooth, stamped addressed return envelope, and small gift for the child
  - Samples: naturally shed deciduous (baby) teeth
- Pieter Dorrestein's Lab at UCSD: pulverized samples using liquid chromatography/tandem mass spectrometry (LC-MS)
- Christine Austin, Mount Sinai: targeted and untargeted approaches
  - Robot samples 2-mg dentin along growth zones (Figure 2)
  - For targeted analysis, extract aliquots were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS)
  - For untargeted analysis, the same aliquots were analyzed on a time-of-flight mass spectrometer with liquid chromatography (QTOF-LC-MS) in reverse phase and HILIC conditions

Figure 1. Key aspects of tooth development

Results

- IRB approval and recruitment in 2017
- 31 families recruited, 16 sample sets collected
  - Source of sample sets
    - NOFAS: 11
    - FASD Registry at UCSD: 3
    - Colleagues: 2 (controls)
- Dorrestein lab analysis: EtS and EtG below limit of detection (LOD)
- Austin lab analyses:
  - Targeted approach detected EtG and EtS in the prenatal dentine collected from a tooth from a child diagnosed with FASD. Neither biomarker was detected in prenatal dentine from control tooth (Figure 3 and Table 1)
  - Untargeted approach results indicated a dysregulation of amino acids in the FASD tooth compared to the control, as well as an increase in cholesterol sulfate (Table 2).
- For the first time, biomarkers of fetal prenatal alcohol exposure were documented in naturally shed teeth from children 6-12 years old.

Figure 2. Robot for high-throughput organics tooth analysis. Proprietary technology to microsample tooth growth rings

Compound	Mass (amu)	Prenatal	Postnatal
Inosine	268.0818	0.315	0.560
L-Isoleucine	131.0944	2.64	3.65
Tryptophan	204.09	8.57	5.94
D-Alanine	89.0477	1.93	2.02
L-Serine	105.0426	4.36	3.81
L-Histidine	155.0694	5.96	8.02
Cholesterol sulfate	466.3105	26.6	8.88

Table 2. Indirect Biomarkers. Feature intensity ratio in case vs control dentine fractions

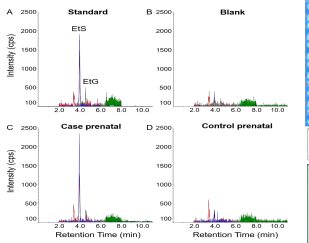


Figure 3. Direct Biomarkers
Extracted ion chromatograms showing measurement of direct alcohol exposure biomarkers (EtS and EtG) in prenatal dentine from an individual diagnosed with FASD.

Extraction method	Weight (mg)	EtG (ng/mL)			EtS (ng/mL)		
		Ex 1	Ex 2	Ex 3	Ex 1	Ex 2	Ex 3
FASD prenatal	2.29	<LOD	0.407	<LOD	<LOD	0.170	<LOD
FASD postnatal	6.63	<LOD	3.470	<LOD	<LOD	2.233	<LOD
Control prenatal	1.69	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Control postnatal	2.55	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Spiked tooth powder	15.03	7.609	2.947	<LOD	7.842	3.424	<LOD
Spiked water	NA	8.393	3.916	<LOD	6.829	2.843	<LOD

Table 1. Direct Biomarkers. Limit of detection (LOD) 0.1 ng/mL Spike 10 ng/mL Ex 1: acetonitrile:water (1:1, v/v), Ex 2: dichloromethane:diethyl ether (1:1 v/v), Ex 3: acetonitrile

Future Plans

- Demonstrate that PAE can be detected and quantified in gestational timing in teeth
- CIBASDM funding will be used to:
  - Determine sensitivity and specificity of direct and indirect biomarkers
  - Assess interactions among maternal and gestational timing of PAE with comorbidity and dyads
  - Explore interactions between PAE and exposure to economic and transitive stress during prenatal and early life
  - Explore potential biomarkers of co-exposure to illicit cannabis, tobacco, and opioids
- Increase understanding of mechanisms of damage caused by alcohol
- Identify potential modifiers of prenatal alcohol risk and effects

Conclusions

- Biomarkers in naturally shed deciduous teeth document prenatal alcohol exposure
- Indirect biomarker analysis supports dysregulation of amino acids and an increase in cholesterol sulfate with FASD compared to control
- Novel biomarkers may be helpful in obtaining a diagnosis of FASD where it may not otherwise be possible

Acknowledgements

We would like to express our appreciation to the NOFAS and UCSD / Rady Children's Hospital registry members who participated. We are grateful for support from Dr. Ken Jones, Dr. Pieter Dorrestein, Alexey Melnik, Dr. Syam Andra, Dr. Lauren Petrick, Dr. Manish Arora, and our coworker volunteers.