National Institute of Environmental Health Sciences

A Catalytic Workshop Series

Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome

July-August, 2022

Final Series Proceedings – v.7.0

This report contains all the notes from each of the five topical workshops and the final, prioritization workshop. This is an unreviewed draft of rough notes taken during breakout sessions.

*Let's keep connecting and collaborating. Contact any conveners or participants to learn more about these issues. Find them in the **Exposomics Action Group at LinkedIn**. Propose new exposomics research projects. Grow your exposome network. Keep looking for ways to "Do the Exposome," together, from wherever you do your work!*

TABLE OF CONTENTS

Series Invitation **6**

What Happened? **9**

What Participants Said Along the Way **11**

VIRTUAL WORKSHOP #1: Tools, Technologies, and Methodologies **15**

ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi-dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics 16

ISSUE #2: Diversity and the exposome 18

ISSUE #3: Using GIS/Geospatial methods to better define and quantify the Exposome, Indoor air pollution, and light at night 20

ISSUE #4: Integrating Causal Inference Approaches 21

ISSUE #5: Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues 23

ISSUE #6: All About Drinking Water 26

ISSUE #7: Time and critical windows for the exposome 27

ISSUE #8: Epigenetics and the Exposome / Exposome and Cellular ‘endpoints’ (adducts (e.g. DNA, protein), epigenetics, mutations – what, how, why / Epitranscriptomics 30

ISSUE #9: Integrating exposure over time, with long lived markers such as DNA and protein adducts 33

ISSUE #10: Dietary exposome 35

ISSUE #11: Underrepresented areas of the exposome: social (social determinants of health) environment, context, and behavior 38

ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility 40

ISSUE #13: Toxicant-induced Loss of Tolerance (TILT) and Mast Cell Sensitization 42

ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome 44

ISSUE #15: Strategies for scaling and diversifying the external exposome measurements (citizen initiatives?) 46

ISSUE #16: Personal interventions/report back and personalized risk models (multiple topics combined) 51

VIRTUAL WORKSHOP #2: Biological Responses and Impact on Health and Disease **57**

ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes 58

ISSUE #18: EXPOSOME as a FRAMEWORK that focuses on identifying OPTIMAL CONDITIONS for HEALTH and HEALING 61

ISSUE #19: Multiple Exposures....65

ISSUE #20: Extrapolating human exposures to internal doses/exposures and then to animal and in vitro models for mechanistic studies....66

ISSUE #21: Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments....68

ISSUE #22: Creative solutions for scaling exposomic research to the population scale....70

ISSUE #23: Maximizing value from biobanked samples....71

ISSUE #24: Modeling and Prediction in Gene x Environment....73

ISSUE #25: Exposure Epigenetics, multi-omics at GxE interface, inter-individual variations....74

ISSUE #26: Exposure co-variance matrix and Linkage Disequilibrium....76

ISSUE #27: The Disease Exposome: Effects on Treatment and Disease Progression....79

ISSUE #28: Functional exposomics....82

ISSUE #29: Exposome on a shoestring: Making the exposome accessible for community based research....84

ISSUE #30: Identifying - then protecting, the most vulnerable....86

ISSUE #31: Maternal Exposome & implications for health outcomes....88

ISSUE #32: Harmonizing exposome data across studies....90

VIRTUAL WORKSHOP #3: Future of Clinical & Prevention Trials, Cohorts and Epidemiology....92

ISSUE #33: Merging data from existing longitudinal studies....93

ISSUE #34: Indoor Air....95

ISSUE #35: Fast but not Furious: A Case for Accelerated Longitudinal Designs for Exposomics....97

ISSUE #36: EWAS and GWAS similarities, Exposome wide association studies, Epigenomic association studies, GWAS-traditional....100

ISSUE #37: Beneficial Exposome Conditions for Health Research and Healthcare Services -- First, Do No Harm!....102

ISSUE #38: Communicating aspects of exposome research/impacts of exposome with the general public....107

ISSUE #39: Issues in building inclusive and representative populations for exposome studies....109

ISSUE #40: Reporting Standards Replication....112

ISSUE #41: Mining the Electronic Health Record for Exposomics Research....114

ISSUE #42: Studying Effects of Exposures in Small Clinical Populations....116

ISSUE #43: Developing and implementing intervention studies in the context of the human exposome....118

ISSUE #44: Innovative clinical systems and models of care aligned with interdisciplinary exposomic interventions and advancing clinical epidemiology designs, particularly in environmental justice communities....120

ISSUE #45: Decision Support Tools to help physicians incorporate exposomics into patient care 123

ISSUE #46: Integrating adverse health outcomes (ex: respiratory pathologies, cancer, etc) with environmental pollution burdens, and newer sensor technologies.....126

VIRTUAL WORKSHOP #4: Social and Societal Impacts.....128

ISSUE #47: How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience.....129

ISSUE #48: Extrapolating/merging SDOH and exposures from alternative data sources (EHR, social media, purchasing histories).....132

ISSUE #49: Causal Pathways, teasing out the sequencing of policy, SDOH, and Chemical Exposures 136

ISSUE #50: Characterizing exposome and SDOH disparities within and between levels of analysis and causal pathways to health outcomes. 139

ISSUE #51: Defining the ecto-exposome across the life-course (built, natural, physical and social environment).....142

ISSUE #52: Fragrance Free Exposome - Allow Environmental Refugees to Access Healthcare and rejoin Society.....145

ISSUE #53: What social determinants of health should we consider in exposome research? 148

ISSUE #54: Unintentional consequences, making sure we do no harm, not mixing diversity with disparity… How to ensure diverse voices are incorporated? Both community and investigators 150

VIRTUAL WORKSHOP #5: Data Infrastructure, and Data Analytics 155

ISSUE #55: Managing the Spatial Exposome.....156

ISSUE #56: Methods to advance “exposome-wide association studies”.....158

ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data 160

ISSUE #58: Data about exposure to trauma as related to the exposome/epigenetics.....163

ISSUE #59: Exposure Ontologies and Definitions Sources | Pathways | Receptors.....165

ISSUE #60: Integrated High Dimensional Multiomic Analysis with Exposomics Data.....169

ISSUE #61: Towards consensus standards for exposome data and metadata: development, coordination, and adoption.....171

ISSUE #62: Validated Tools for Integrating Health Effects and Exposures.....176

ISSUE #63: How data analytics can facilitate mechanistic study of the impact of environmental compounds on human health?.....178

ISSUE #64: Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis 180

PRIORITIZATION WORKSHOP 185

Now What? Identifying Priorities, Connections and Immediate Next Steps.....186

Chart of Voting Results: Total Votes and Unique Voters for All Issues 187

Table of Raw Voting Data and Connections Between Issues..... 189

ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome..... 190

ISSUE #12: Data sharing in exposomics..... 191

ISSUE #32: Harmonizing exposome data across studies 192

ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data..... 194

ISSUE #8 Epigenetics and the Exposome 196

ISSUE #21: Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments. 197

ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes 199

ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi-dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics..... 202

ISSUE #5: Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues..... 202

ISSUE #33: Merging data from existing longitudinal studies 203

The Way Forward: Themes for Demonstrating the Value of the Exposome 204

Theme #1: What to measure (when, why)?..... 205

Theme #2: How to measure (methods)? 206

Theme #3: Share and harmonize (data standards, ontologies, …) 207

Theme #4: Integrate, analyze, and interpret..... 208

Theme #5: Translate and impact..... 209

Other Important Issues..... 210

Series Invitation

Accelerating Precision Environmental Health: Demonstrating the Value of the Exposome

A Virtual Workshop Series: July 22, August 5, 12, 19, 26

Overview

Please join us at this pivotal moment to catalyze the shift from defining the exposome to doing it. Together, we will shape the future of exposomics at the intersection of environment and health/disease research.

The comprehensive and systematic analysis of the environmental drivers of health and disease requires us to solve complex challenges collaboratively and chase exciting opportunities:

- Tools, Technologies, and Methodologies *(measuring the exposome)*
- Biological Responses and Impact on Health and Disease, *(integrating multi-omics with biomarkers of exposure, response, effect, susceptibility, vulnerability, and resilience)*
- Future of Clinical & Prevention Trials, Cohorts and Epidemiology *(designing studies, calculating power, approaching pooling)*
- Social and Societal Impacts *(integrating social determinants of health, diversity, health disparities, privacy, trust, etc...)*
- Data Infrastructure, and Data Analytics *(sharing data and harmonizing it; analyzing, interpreting, visualizing, and modeling data)*

Collaboration Will be Central to Our Success. Please join us in expanding and catalyzing the emerging exposomics community dialogue, to discover, determine and design the best ways to operationalize every aspect of exposomics, in an effort reminiscent the evolution of genomics, from replication to genome-wide-significance to functional genomics.

A Virtual Workshop Series and In-person Summit Event. We will hold six virtual workshops this summer, to address the challenges and opportunities in the areas described above. A subset of virtual attendees will be invited to attend an in-person summit in Research Triangle Park, North Carolina in mid-September [that went virtual due to COVID restrictions.]

An Ambitious Goal and Pivotal Moment. In these working sessions, we will explore what it means to conduct exposomics experiments, develop new tools, techniques, and technologies, share data for maximizing in silico experimentation, and cultivate the research continuum from fundamental to population health. All this work will contribute to developing a framework for demonstrating the value of the exposome in environmental health.

Your Participation Is Important to Our Success! This is also your opportunity to collaborate with a large, diverse group of scientific leaders representing a spectrum of disciplines, geographies, and perspectives. Together we will design a purposeful approach,

put exposomics into action, demonstrate its value, and lay a solid foundation for advancement and widespread application and adoption.

What Will the Sessions Be Like? Open and Active! You will help create our working agenda. Anything you care about can be considered and advanced. You will direct your own involvement and be able to maximize your own learning and contribution. You will be able to connect personally and practically with everyone else who joins and receive copies of all the notes from all our many working, breakout conversations. During the last virtual session, you'll help sort out priorities for moving forward with individual and collaborative efforts. Throughout these sessions, you'll have the flexibility to come and go as you need to, but please make this work your top priority on these days.

Join us now on LinkedIn

and

Register for the first workshop, July 22

Getting Started… And Keeping it Going. Registration for the virtual sessions will open one weekly workshop at a time. In the meantime, join our new LinkedIn group where we'll be posting registration announcements, notes from each working session, and any relevant items you care to share/raise there – before, during and after the series. This is also where you can see who else is coming.

Invite Your Colleagues and Networks! Once you've joined the LinkedIn group and registered for the first workshop, please invite friends and colleagues who might learn from this experience, will contribute valuable insights and perspectives, and work collaboratively toward realizing the vision of Precision Environmental Health.

Save These Dates!

The series will be hosted on Zoom, on the following dates:

- Working Sessions on Fridays: July 22, August 5, August 12, August 19, and August 26
- Prioritization Session on Wednesday, August 31, 2022 – by invitation only, for those who have participated in any of the first five workshops

Workshops will be held from 11:00 a.m. – 4:00 p.m. EDT, and will include an Opening, Agenda Creation, two rounds of small group working sessions, and a brief wrap-up.

Prioritization on August 31 will be held from 11:00 a.m. – 1:00 p.m. EDT

Registration

Registration for this workshop series will be on a rolling basis. Registration for each workshop will open at the conclusion of the previous workshop.

Register now for the July 22, 2022 workshop:

Register Now

NIEHS Contacts

David Balshaw, Ph.D.
Acting Director, Division of Extramural Research and Training

L Michelle Bennett, Ph.D.
Contractor - Senior Advisor for Strategic Initiatives

Yuxia Cui, Ph.D.
Health Scientist Administrator

Alexandra T. Law, Ph.D.
Contractor — Scientific Program Analyst

What Happened?

The Series Invitation (previous pages) was extended broadly, via NIEHS email listserve groups and through active collegial sharing. Pre-registration was required on a rolling basis. Over 400 colleagues participated in some or all of the workshops and hundreds more registered their interest.

By the time Rick Woychik, NIEHS Director, opened the first workshop almost 300 colleagues had joined the LinkedIn group and the initial registration cap of 250 participants had been slightly exceeded.

The workshops were conducted in an Open Space* format, each starting with a broad theme and no pre-determined agenda. In each session, all participants were invited to create their working agenda, based on their own personal passion and experience in the field.

WORKSHOP #1: More than 190 participants joined for some portion of the first workshop. In the Opening Session, they posted more than 40 issues for discussion, sorted and combined them into about 20 breakout sessions, in two 90-minute timeslots.

WORKSHOP #2: More than 170 participants joined for some portion of the second workshop. In the Opening Session, they posted about 20 issues for discussion, then made some combinations into 15 working sessions.

WORKSHOP #3: About 130 participants joined for some portion of the third workshop. In the opening session, they posted about 20 issues, some of which were combined or discarded, leaving 13 working sessions.

WORKSHOP #4: About 90 participants joined for some portion of the fourth workshop. They posted 13 issues, made a few combinations, resulting in eight working sessions.

WORKSHOP #5: More than 80 participants joined for some portion of the fifth workshop, posting 14 topics for working sessions, made a few combinations and deletions, leaving 10 sessions in our final agenda.

In each of the five workshops, participants self-facilitated all of the breakout sessions and captured the notes shared in this document. These notes are rough, mostly taken directly during the sessions, with little time to review and refine. The intention was to capture the most important points, for now, so that all these conversations can continue – and expand.

WORKSHOP #6: In a final, two-hour workshop, 85 colleagues worked to begin identifying priorities, connections and immediate next steps. After they “voted,” the top 10 issues were discussed in ten separate breakout rooms, where the work focused on identifying connections and immediate next steps. See the voting section for the ballot form, voting results, tabulation and notes from the short discussion sessions.

Rick Woychik closed the series like this:

Thank you all for the efforts you put into all five workshops leading up to today's meeting. Clearly, there are a lot of things we're grappling with, other issues that didn't come up today, and some key stakeholders not in the session today. We all have our day jobs.

*For more about Open Space Technology, visit michaelherman.com and openspaceworld.org.

This has been a mechanism to gather information. Now there will be some next steps. I suspect Beth and Alex and Michelle will be communicating with all of you, about next steps in September and ultimately it comes back to me and the senior leadership team at NIEHS to pull something together, a better definition of how do you further operationalize the exposome.

Thank you for your input. We'll be in touch, and in the relatively short term, I'll have a definition to take to the other IC directors at NIH, to understand how to do an exposomics experiment. I know they're anxious to hear the outcomes from these workshops.

In the meantime, everyone who cares about this work can continue the learning and contributing. Take the issues you have contributed to and the work this community has done and put it to use. Propose new exposomics research projects, continue conversations on these topics, recruit new scientists into your exposome network. New conversations and actions can be started at any time, by anyone. Notes, news and learnings can be shared by anyone via the LinkedIn group. Contact anyone in the group to learn more about what happened here and what's happening now. Keep looking for ways to "Do the Exposome," together, from wherever you do your work! If this document has found it's way to your screen, you almost certainly have something to add to this movement!

What Participants Said Along the Way

At the end of each workshop, we asked participants for closing comments, to capture something of the spirit of these conversations, beyond all the content notes. Here is what they posted in the Zoom chat.

Comments from Workshop #1

14:32:13 Kirsten Overdahl: Really exciting discussion. I loved the abundance of topics we were able to cover in our breakout sessions.

14:32:38 Neil Zhao: Seeing science evolve in real time brings about fascinating and engaging discussions.

14:32:44 Robyn Tanguay- Oregon State U.: Once we got our bearing straight, this was effective

14:32:58 Susan Sumner: Really excited about participating in the next workshop. This was awesome. Enjoyed meeting new people with similar interest!

14:33:17 Seung-Hyun Cho: enjoyed dynamic discussions and learning from each other.

14:33:25 Michael Snyder: I think the discussion was good. I think the most important items are the next steps going forward

14:33:33 Huichun Xu: We need more coordinated , centered efforts to build infrastructure such as annotated data, accessible analysis tool, cloud to facilitate the growing of this field.

14:33:34 Debbie Bennett: Once we settled into our rooms it was really great

14:33:37 Rima Habre, USC: I agree with Robyn, i think i also learned it's maybe better to not try to overly merge or join topics together when they emerge because it can become very big to tackle in one session.. but super interesting and learned a lot.

14:33:39 Alan Jarmusch: the breakout room discussions were great - covered a lot of ground

14:33:43 Ryland Giebelhaus: really effective, great to see so many passionate people. Inspired new research ideas

14:33:44 Ghada Soliman, CUNY-SPH: Very helpful and thoughtful discussions. I hope we can follow up on the action items, opportunities and next steps

14:33:44 Roel Vermeulen: Great sessions. Many very concrete ideas. Also was struck that there is a lot to learn from each others and from other global programs.

14:33:49 NIRMALA PRAJAPATI: It felt like brainstorming and collection of different ideas, the discussions were very rich and interesting, However I am also wondering what will be the outcome of this workshop series.

14:34:02 Chris States: Discussions can be far-ranging and can introduce ideas novel to others.

14:34:17 Pothur Srinivas_NIH: skeptical at first but pleasantly surprised

14:34:28 Emily Krueger (NIH/NCI Fellow): It was great to hear about everyone's foci in this field and loved connecting to others about their science.

14:34:32 Nigel Walker: great discussions and engagement by all in a very open and fluid virtual environment. At first i was a tad apprehensive over the format but it really worked IMO.

14:34:36 Arcot Rajasekar: great workshop. enjoyed. thanks.

14:34:50 Tim Fennell: A great workshop, with an opportunity to bring your burning questions for discussion. Enjoyed the opportunity.

Comments from Workshop #2

15:32:38 Graham Parker WSU CURES: Very enjoyable & useful, and very egalitarian!
15:32:44 Pothur Srinivas: a very constructive and inclusive discussion
15:33:08 Taka Williams: It was a great experience. All the breakout rooms that I attended were very knowledgeable.
15:33:36 Alex Merrick: Seems like we are getting used to using the term 'Exposome' although its meaning is still broadly interpreted
15:33:36 Rima Habre: feel the same, great time to think big ideas and future with brilliant people.. learned a ton, always opens horizons of how we think about important questions..
15:33:38 Maeve MacMurdo: Great discussions- it was wonderful to connect
15:33:42 Brian Berridge: Great exchange of ideas!
15:33:45 Ghada Soliman, CUNY-SPH: This was an amazing interdisciplinary workshop with different views that added depth to our individual fields
15:33:55 Guillermina Girardi: it was an amazing learning experience. A great opportunity to network and in my role working at NIH a good opportunity for identify gaps for research. Thank you
15:33:58 Ming-Kei (Jake) Chung -HMS: Enjoyable and informative discussion. It is great to know where the consensus in exposomics is and what are the interests of the community
15:34:07 Chris States: Good discussions, lots of gaps to fill!
15:34:08 Antonia Calafat: Great exchange of ideas and great facilitators as well. Thank you
15:34:10 Gary Miller: the range of ideas was inspiring.
15:34:11 Arcot Rajasekar: Great topics. great discussions
15:34:13 David Balshaw: Its amazing how deeply you can probe a topic in 90 minutes; we covered a whole lot of ground!
15:34:23 Robert Clark: Excellent discussions in all room I attended
15:34:29 Susan Pinney: The interdisciplinary discussion are what we need more of! Great workshop. I am coming away excited about new research questions.
15:34:33 Qiwen Cheng: Now I have three new research ideas!
15:34:38 Ariana Haidari: awesome to have so many great minds in one place - the Zoom format is very democratizing
15:34:39 SRIMATHI KANNAN: A very insightful, considerate, creative, and new knowledge-inspiring discussion. Thanks to the session facilitators and participants.
15:34:43 Gary Miller: I did feel that I was missing out on so many other interesting topics.
15:34:53 Erin Dierickx: Wonderful collaborations across diverse participants. Discussions sometimes veered off initial topics but addressed new concepts to consider and highlighted the complexities of defining and applying an exposome.
15:34:59 David Jett: Fantastic meeting for sure. Very interesting and fun!
15:35:09 David Balshaw: Same Gary, would have been fun to be in other conversations as well!
15:35:30 Robert O Wright: Incredible and insightlful discussion that led to many novel ideas!
15:35:31 Hina Narayan: @Gary Miller… same here
15:35:59 Carrie Breton: Truly enjoyable experience to connect and think about the future !
15:36:17 Yuxia Cui: Great to see many familiar names and faces the first workshop two weeks ago!!
15:36:49 Jessica Worley: I'm excited about the collaborative spirit showcased in today's discussions and 'big goals' of exposomics.
15:37:06 David Balshaw: Also want to say thanks to all of our international participants who either joined incredibly early intheir day or gave up a Friday evening to be with us!

15:37:13 Irva Hertz-Picciotto: Appreciated the breadth - discussions at the molecular to the clinical to the solution-oriented…and some very forward thinking and maybe even dreamy ideas…
15:37:25 Garret Bland: Very insightful discussion all around. Thanks everyone! There's a lot of potential in this space.
15:38:03 Jessica Castner: Thank you for convening this research community of practice. The brilliant contributions and interdisciplinary perspectives were inspiring and engaging. I especially appreciated the ability to attend virtually and join groups that included intramural and extramural scientists at various career stages.
15:38:21 Hina Narayan: Thanks everyone!
15:38:58 Nisha Vijayakumar: It was a great learning experience. Thank you for having this series.

Comments from Workshop #3

15:38:28 Robert O Wright: Great discussion-especially on importance of implementation science!
15:38:43 Graham Parker: Great positive energy creating actionable items
15:38:47 Hina Narayan: thanks for this great session!
15:38:50 Ariana Haidari: Appreciated a very rich and respectful multidisciplinary discussion on clinical translation
15:39:11 Shannon Bell: very useful discussions- looking forward to notes for the topics I could not attend
15:39:16 Chris States: Great discussion on EWAS. The time is ripe.
15:39:21 Michelle Bennett: I attended some amazing discussions today - thanks to everyone for bringing your passions, expertise, and energy!
15:39:39 Rima Habre: Thanks to the session conveners for such exciting discussions! We definitely brought up tough questions and hopefully identified priorities/ways to move the field foward
15:39:39 Antonia Calafat: Thank you for the thoughtful discussions
15:39:54 Jason Niu: Love the discussion. Really helpful to think forward of studying exposome.
15:40:07 Gary Miller: constant reminder of the incredible breadth and expertise in the field. Bridging disciplines will be an ongoing challenge.
15:40:17 SRIMATHI KANNAN: A valuable learning-Friday and unique and innovative ideas including multidisciplinary collaboration opportunities for the future. Thank you.
15:40:28 Jessica Castner: Really appreciated the brilliant synergy this engagement and community of research practice creates. Thank you.
15:40:36 Jeffrey Kopp: Ideas, energy, interactions…
15:40:40 Yuxia Cui: Thanks to everyone for your contribution to the discussion!
15:41:24 Allison Cook: Nice sessions (Accelerated Long Designs and Small Clinical Populations) and I'm looking forward to the two upcoming workshops. Also seems pertinent to new PACT legislation which is looking at exposures open burn pits in US veterans.
15:42:00 Rosalind Wright: Exciting to see us moving to incorporate exposomics into clinical translational science and precision medicine. Great to see so many innovators take this on!
15:43:30 Bren Ames: Salugenesis to ya'll!
15:43:57 Ghada Soliman: Thank you everyone. Have a wonderful weekend
15:45:15 Robert Clark: Thank you

Comments from Workshop #4

15:31:09 Michelle Bennett: I heard some really amazing and inspiring conversations today! I'm very excited for this space to grow and advance.
15:31:26 Rima Habre: I will say I thoroughly enjoyed this and really appreciated everyone's passion and enthusiasm.. we could have spent another hour talking!
15:32:01 Maeve MacMurdo: Great to hear about the amazing work that everyone is doing! We had some excellent conversations today!
15:33:06 Hina Narayan: thanks for the great discussion
15:34:14 SRIMATHI KANNAN: I really appreciate how everyone (facilitators and session(s) participants) generously shared their ideas, findings, tools, models, and thoughts--thanks!
15:34:30 Rhema Bjorkland: Thought-provoking. Enjoyable conversations. Thank you.
15:34:33 DARRYL HOOD: …the catalyst framework really is innovative, thank you Michelle and Michael!
15:35:09 KATERINA GRAFANAKI: Thank you for this exciting workshop series! I hope the outcome will be game-changing in the field!

Comments from Workshop #5

15:32:04 Robert Clark: Discussions were superinformative! Thanks for organizing these sessions!
15:32:33 Gary Miller: Today made it clear that we need to invest in infrastructure for the mass of data. Exposome data is special and needs investment.
15:32:52 Ghada Soliman: Great discussion and fresh insightsdifferent prospective, great thought-provocative sessions
15:32:59 David Conti: +1 for @Gary comment
15:33:11 Graham Parker: Thank you all for your wisdom and candour! perhaps it is the end of the beginning...
15:33:12 Hina Narayan: great conversations! thank you everyone
15:33:17 Bren Ames: +1 more for @Gary comment
15:34:09 Ghada Soliman: Thank you for the super informative workshops
15:34:24 Gary Miller: Raja Rajasekar would agree with me if he was here, but he is putting the finishing touches on an NSF grant proposal to build some of the data infrastructure.
15:34:30 Rima Habre: Agree with Gary too, and really enjoyed wonderful conversations today in both sessions, thanks to the conveners and everyone who participated for their energy and insights!
15:35:57 SRIMATHI KANNAN: Concur with Gary Miller's comments plus those noted by others! Thanks everyone.
15:37:03 Peter James: Another +1 for Gary's comment. Wonderful discussion today! Thanks for putting this together.
15:44:44 Rima Habre: That [summary] was so comprehensive and excellent thank you Charles!
15:45:36 Ghada Soliman: Thank you very much

VIRTUAL WORKSHOP #1: Tools, Technologies, and Methodologies

A high-level view of our first virtual workshop space: our theme, a view of what this would normally look like as a physical gathering, our agenda "wall," and supporting spaces for initial orientation, tech support, announcements, capturing and sharing session notes, and introducing participants to each other. It's a big space. Much of the detail won't scale to be easily readable, but it gives some sense of the messy, organic, creative nature of our working space.

ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi-dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics

CONVENER(S): Farida Akhtari

PARTICIPANTS: Farida Akhtari, Seung-Hyun Cho, Cheryl Walker, Kimberly Berger, Arcot Rajasekar, Jeannete Stingone, Ram Siwakoti, Jiwon Oh, Stephen Edwards, Blessing Akintunde, Nicolas Lopez, Susan Teitelbaum, Huichun Xu, Qiong(Joan) Zhang, Xiuxia Du, Brian Berridge, RickWoychik, Peng Gao, and others…..

SUMMARY OF DISCUSSION:

- Big data: Issues of data collection, storage and computing resources. Part of FAIR Data and Data management workshop sessions.
- Challenges of simultaneously modeling multiple disparate high-dimensional exposures to assess their effects on health outcomes

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Using AI to construct shared data tools
- Data standardization for exposomics data
- Use models from different fields for visualization, etc. like Genome Browser. Multi-dimensional axes – space, time, disparate data types, etc.
    - Build workbench for modeling, analyses, etc. to provide tools, resources for easier and reproducible analyses
- Cross-fertilization across different fields
    - Training next generation
- Common ontology
    - Semantics of exposures and how/when they were measured are important
    - Disparate datatypes – social determinants of health vs physiological measures vs survey responses. Accounting for uncertainty, recall bias, etc. Linkage of epidemiological measures to exposome measures – integrated intermediate linkages using surrogate biomarkers.
- Quality control of exposomics data –
    - Use of ML/AI for QC and preprocessing
    - Extraction of information from Mass spectrometry data
    - Standards for accurate measurements
    - Collect individualized exposure data to understand uncertainty and impute surrogate data
- What data do we need - if we had all the data we wanted, how would we do/use it
    - Use archived data as a preliminary database
- Visioning how to do it – borrowing from different fields like Genomics, where they split different chromosomes across different teams
- Environmental data spread across different databases and challenges of accessing them + Need for essential data repositories.
- Using AI to link Exposomics to health effects
    - Key question to be answered
    - Different perturbations of interest
    - Use of AI to assist with uncertainty measurements

    - Using AI to find surrogates of health effects – surrogates/biomarkers that occur earlier than health outcomes
    - Use of AI to build AOPs, networks.
- Use of archived data
    - Use of EPA resources – CompTOX chemicals dashboard
    - Previous epidemiological studies
    - Opportunity to build tools to integrate archived data
    - Use of AI to impute missing data, need validation datasets
- Entity resolution
    - use of AI to do this and remain HIPAA compliant
    - De-identification of participants

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Standardization for data collection and measurements
- Data standardization
- Harmonization and Quality control of exposomics data
- Computing resources for data collection, storage and analyses
- Disparate datatypes – social determinants of health vs physiological or lab measurements vs survey responses. Accounting for uncertainty, recall bias, etc.

ISSUE #2: Diversity and the exposome

CONVENER(S): Penelope (Jenny) Quintana

PARTICIPANTS: Penelope Quintana, Deepak Kumar, Claudia Alberico

SUMMARY OF DISCUSSION:

Diversity has many forms, we should develop a 'best practices' for exposomics.

What are uses and inappropriate uses of race / ethnicity?

How do you define exposome in terms of equity?

How do we map what is important? Social factors affect epigenome (as an example).

Should best practices for the exposome include measurement of nutritional and stress-related differences, as an example, when measuring biomarkers of effect?

Individual level measurement does not give a pass to community/ neighborhood level and occupational factors which must be considered.

Create a framework for the exposome similar to
https://www.nimhd.nih.gov/about/overview/research-framework/nimhd-framework.html

If you cannot measure all these factors, always acknowledge the limitations as a best practice.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Studying environmental exposure is important and even if the effects may be worsened or confounded by stressors and behaviors that result in susceptibility, it is still the environmental exposure causing it - focus on preventing exposures, for example with implementation science.

Be aware that dose-response relationships developed in affluent populations with adequate nutrition etc. may hugely underestimate the effects of exposure in disadvantaged populations, as the exposure-response relationship may differ.

Encourage and fund measurement of multiple factors at different levels in exposome studies. Apply principles to the exposome in the article by Yoshira Ornelas Van Horne
Van Horne YO, Alcala CS, Peltier RE, Quintana PJE, Seto E, Gonzales M, Johnston JE, Montoya LD, Quirós-Alcalá L, Beamer PI. An applied environmental justice framework for exposure science. J Expo Sci Environ Epidemiol. 2022 Mar 8:1–11. doi: 10.1038/s41370-022-00422-z. Epub ahead of print. PMID: 35260805; PMCID: PMC8902490.
https://pubmed.ncbi.nlm.nih.gov/35260805/

Be aware that discussions of race/ ethnicity should always consider income, and be careful to disentangle income from race/ethnicity.

Also be aware that other countries may have other approaches to disparities. For example, in Brazil, health disparities focus on income rather than race/ ethnicity for example. In US, it can be the opposite.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Need to integrate the community into exposome studies, but funding barriers for adequate compensation exist (for example, cannot use some funds for refreshment at meetings, IRBs think that incentive payments that adequately compensate participants for their time are 'coercive'). And, money should be available at each institution or funding agency to give feedback to the community after the award has ended, as findings are published.

Measuring biomarkers associated with nutritional, stress and other factors (such as cotinine) in biological samples can be seen as very expensive, yet can be very important in understanding vulnerability - increase funding for this or routinely perform these tests for free at NIEHS? (in a faster and easier way than through current processes (HHEAR). This may also mean providing more funding for archiving samples past the date of the award.
More funding for implementation science and translation!!

ISSUE #3: Using GIS/Geospatial methods to better define and quantify the Exposome, Indoor air pollution, and light at night

CONVENER(S): Kristin Eccles, Andrew Hoisington, Nirmala Prajapati

PARTICIPANTS: Yuxia Cui**,** Erica Fossee**,** Zenobia Moore**,** Carol Hamilton**,** Qiong (Joan) Zhang, Deborah Bennett, Fred Liao, Michelle Bennet

SUMMARY OF DISCUSSION:

- How do we integrate outdoor air and indoor air pollution
- GIS methods are not as useful for microenvironments
- Spatial and temporal exposure of GIS data
    - How much data is needed?
    - There is a big gap in indoor and outdoor air pollution –
    - Are contaminants in indoor data
- Dust and wearables can be a useful tool for quantifying indoor air exposures
- GIS can be used to track social behavior and help defines exposure patterns
    - EJ, redlining, social vulnerability
- How to retrospectively get exposure info from survey addresses using GIS
- How to translate environmental exposures to personal exposures?
- How to prioritize what chemicals have the greatest effect?

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- GIS methods/ data are available for specific use cases e.g., light at night, greenness, outdoor air pollutants

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Need computational approaches for spatial-temporal analyses and complex multidimensional contaminants data
- How to get the expertise needed in multidisciplinary projects from study design to data analysis stages
- Privacy and ethics related to collecting and using GIS data

ISSUE #4: Integrating Causal Inference Approaches

CONVENER(S): Marta Jankowska, Perry Hystad, Gwen Collman

PARTICIPANTS: Claudia Alberico, Janet Hall, Neil Zhao, Claudia Miller, Farida Akhtari

SUMMARY OF DISCUSSION:

Causal inference approaches and natural experiments and Dr. Jankowska "is that going to get us where we want to go?"

Our initial discussion: "how to do an exposomics study?"

Is there an exposomic study that is ok? Or adequate?

Using exposome approach to collect data, rather than calling a lifetime exposure a "longitudinal" study.

Is it even an experiment when we can't reproduce it? Do we need to look at causal relationships? We need more measures but how do we get causal associations if that is our goal?

Exposome – we want to understand the push and pull and see how they all are interacting together. How do we understand the mixture of exposures (social, environmental) from a PH perspective, are there thing we can do to improve the exposures?

Exposome is a discovery science. If you have a set of goals, how do you find someone's exposure along their life. We don't need to start from the causal associations, rather from an ecosystem aspect where "what puts out a higher risk?" and then find whether the health outcomes are different because of all those exposures. And from there, then specify a causal relationship to seek for an actual association.

Dr. Hystad doesn't think it's useful because you don't know if it is a true outcome or if it is confounded by other factors.

Effect strength and dilution

Janet Hall: A Multi-Science approach is necessary to understand the exposomics

Dr. Collman we need to determine the framework for exposome that will be able to be applied in any field, as if to guide the process and that can improve the way the information is gathered, analyzed, and disseminated.
How can we get to a metric that is a composite of many different exposures? Should we?

Dr. J: When we use exposomess, it is cumulative, it goes up and down, and it doesn't mean it won't change again later. Using a mean does not show anything.

Define subgroups what information did you use for susceptibility

How do you accommodate that people have other experiences and some are further along and a small quantity would be enough to reach the tipping point.

The question of DOSE is an important one that has been often overlooked. Even studies that can follow participants for a certain period of time lack the full picture when it comes to dose.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Clarification of dose/response relationships.
Pulling methodologies and structures from other fields, previous sciences.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

(none identified)

ISSUE #5: Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues

CONVENER(S): Sophia Miryam Schüssler-Fiorenza Rose, Kimberly Berger

PARTICIPANTS: Seung-Hyun Cho, Emily Lax, Jenna Hua, Alexandra White, Eleanor Simonsick, Jiwon Oh, Neil Zhao, Lenore Launer, Nicolas Lopez, Ram Siwakoti, Lisa Rider, Farida Akhtari, Susan Sumner

SUMMARY OF DISCUSSION:

- Integration exposomic measures in the blood which may include 1000s of chemicals with other measures
    - Note: that depends on question interested in:
- Potential Methods mentioned:
    - Models that use demographics as confounders (unsatisfying) vs. their own "chemical class", neighborhood as "factor" in model
    - Bayesian hierarchical modeling
    - Borrowing techniques from Complex Survey approaches to deal with clustering in neighborhoods and other clustering
    - Indexes (like Cal-Environmental Screen, Healthy places Index)
    - Scores (developed similarly to polygentic risk scores: aka polyenvironmental risk scores
    - BKMR
    - Is there a way to weight different components or subgroups of interest
    - Prediction models such as bayesian network models (MXM package/R)
    - Network analysis (can include hierarchical networks and interacting networks or single network with both psychosocial and environmental components)
- Note that similar methods may have different names in different fields so need to break down these silos and apply across fields
- Great need for methods
- Sharing knowledge about methods
- Different exposure categories very different – how to handle them differently when modeling (versus collapsing into same model)
- Data sources mentioned: Wearable data – exposome bands, monitors, Fitbits; GPS data from phones; neighborhood level pollution or census; indices like healthy places index or cal enviro screen; questionnaire data; specimens; commercial sources like Purple Air air monitors, administrative data (birth records, hospital discharge records)

Additional Notes:

- Question: many chemicals and socio-demographics, same modeling, Bayesian hierarchical models, regression, demographics as confounders – race and income and where you live huge factors in life – larger than any single chemical exposure
- Alexandra White: Methods designed for mixtures and outcomes – such as clustering methods, how we incorporate other factors such as neighborhood, clustering approach looked at together as co-exposures
- Emily Lax- Biomonitoring projects, NJ HANES, 130 chemicals NJ, questionnaires – household, lifestyle, ?other measures including diet… Reports: Lead, arsenic,

mercury and 1 other, - Question when get data on 130 chemicals how to summarize into report for participants

- Eleanor Simonsick - intramural NIA – geocoding project – historical current addresses Baltimore Longitudinal aging – trying to understand how we manage data via geocoding to understand how earlier life exposures may affect the aging process. Starting to play now. How define neighborhood level data
- Seung Hyun Cho - ? international – looking at chemical exposure factors and social factors education level social factors how exposure and health outcomes – handling social determinants of health data – how best to incorporate this into large study. Like to learn best approach and current trends to think about future study.
- Jenna Hua– Million Marker – DTC EDCs individual feedback – feedback and intervention. Collect product information as well as dietary information – combing information and feeding back information to people using products. Goal assess total exposome and green space – what additional things to help people on better trajectory
- Lenore Launer – Intramural research program at NIA – project use existing data – already collected cohort data – develop model predict expsosome exposure in older people – see risk for later disease and functional impairments – lot of data out there to put in an index on different geospatial levels relative to individual cohort data
- Jiwon Oh- Prenatal exposure- autism spectrum disorder and neurodevelopmental outcomes. How model different chemical using mixture models
- Savannah Sturla – 2nd year PHD student Univ Michigan – superfund birth cohort in Puerto rico (protect) – how to integrate different types – spatial data types and biomarkers how to integrate into models –
- Nicolas Lopez – assistant professor -?university – focus on collection of first hand measurements on different population exposed different contaminants – e.g. migrant farm workers, families and children – dust, urine, etc match different contaminants to each other and questionnaires – 150 farm workers and families in Arizona and San Diego study. Many people move constantly – at the beginning we try to collect secondary data – collect address data is that accurate any more given how often they move. Provide results to communities Non targeted analysis – looking into 1000 of chemicals and lots of plastifiers and pesticides and figuring out what to do with data
- Farida Akhtari teasing apart social exposores, from chemical exposures socioeconomic exposures and health outcomes
- Susan Sumner - advocate of data hub - precision nutrition, metabolomics and integrated omics

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Next Steps – Find more statisticians

- Literature review on modeling methods/methods in different fields that could be applied to other fields
- Robust tools that aggregate this social information – tools that have been validated to create indices of social vulnerability
- Convenient to be able summarize where someone might be on a continuum on psychosocial stress – challenges – when we homogenize the data for practical reasons we overlook how these different factors interact with one another. Study where there is a lot more diversity (ex. Baltimore most toxic environments/most toxic psychosocial – lack of comparison)
- Can we combine data across studies

- List of modeling techniques needed
- Identify sources of data and connect with analysis approaches
- **Data Hub:** Beyond list of data sources - ideally would create a data hub where people can deposit data including geographical local connected to list of tools
    - This would help in combining data across projects
        - Idea - something that looks like purple air - which would root this data into geographical location
        - Include both indoor and outdoor air quality
        - Move beyond PM2.5 data to other contaminations/pollution
        - Which would help in comparison group problem
        - Allow researchers to incorporate other types of data into their study which may not have the resources to collect
- Github space where people put their programs and allow people to look at program and see if they are doing more or less what doing – addressing some of these questions (a few of these exist - see links below)
    - https://github.com/isglobal-exposomeHub/ExposomeDataChallenge2021
    - https://github.com/niehs-prime
    - https://reporter.nih.gov/search/15EEC90E4B8DCFD17598B8961CAA4A01A2FFCEB861BF/publications?shared=true&legacy=1
    - https://arxiv.org/abs/2202.01680

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Methods we need might not exist or may be more theoretical than applicable right now
    - Translation gap between people who can develop new statistical methods – and applied researchers who want to apply them but may not have the mathematical/coding skills
    - Methods can be silo'd in fields with different terminology referring to same/similar methods
- What if you have a large cohort with a breadth of data (e.g. neighborhood level air pollution) and a small subset with an additional depth of data (e.g. fitbit data, qx).. Is it possible to impute the "depth" data for the rest of the cohort?
- How to combine various types of exposure sources when those sources may affect health outcomes at such different scales

ISSUE #6: All About Drinking Water

CONVENER(S): Eleanor M. Simonsick, PhD NIA IRP

PARTICIPANTS: In addition to me, Megan May, Tom Young and Katherine Manz.

SUMMARY OF DISCUSSION:

For water, the chemical landscape is always shifting and importantly local household exposures may differ from local community exposures as water source and water transport systems both contribute and/or modify toxic exposure and water quality.

Water quality is an emerging interest in aging-associated conditions including Parkinson's Disease.

Many challenges exist as over time the chemical landscape may shift with one toxin replacing another.

Timing of potential toxic exposure is an additional challenge.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Develop/Consider broad scoop screening combined with individual/local level assessment.

Possibly capitalize on serial human biological sample collection over several years and possibly decades.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

How do we identify the source of exposure if/when we identify a toxin exposure at the individual or community level?

Different toxic compounds may settle in different tissues or bodily systems.

ISSUE #7: Time and critical windows for the exposome

CONVENER(S): Penelope (Jenny) Quintana and Lily Wu

PARTICIPANTS: Penelope Quintana, Carol Hamilton, Constantinos Makris, Nigel Walker, Gail Prins, Lily Wu, Ben Berridge, Stephen Edwards, Katherine Manz, Konstantinos Makris

SUMMARY OF DISCUSSION:

How can modeling (rodent, in vitro models) inform exposomics in people? Machine learning, computation for making human models for how exposures and routes of exposure work over time, use to understand community exposure pathways and likely times?

Behavioral modeling also helpful

Gadgets that measure behavior can be incorporated

Chronotoxicity, early precursors to disease, must be considered

> Scientifically very interesting, at the same time regulatory scientists and implementors might not be able to apply it

How do we talk about time in the exposome?

How do we contextualize exposure in time?

How can we define and study critical windows (e.g. in utero, early life)

How can we apply reverse dosimetry, for example DDT

Host response (short and long-term markers) vs exposure in time separate concepts

Integrative exposure and response markers

Single time point may not reflect trends

Phys/Chem properties can help nowadays

Social vulnerabilities (non-chemical stressors) on top of exposures (e.g. Access to healthcare)

Chrono dimension, internal response to external exposures, diurnal issues with responses and exposures (for example, if people cannot be cool at night they have more stress and cannot sleep in heat waves).

> https://onlinelibrary.wiley.com/doi/full/10.1002/bies.202100159

Regulating 1 by 1 for chemicals (traditional risk assessment) cannot capture complexity, and is not the lived experience

Toxicity has a time dimension (dose rate and time of day)

Can AI help?

Behavior affecting exposures and exposure affecting behavior

Move to intervention research? What do we do with genotype and susceptibility from a community level ?

Combined exposures - how do we integrate these into a regulatory framework?

Integrate within a disease endpoint - efforts at NIEHS (adverse outcome pathways) need more data and to translate to epidemiology

> Possibly integrate other translational sciences (key characteristics, mode of action, etc) to build weight of evidence approach

If you can model using networks you might be able to capture sequential activities that can affect current pathways. Capture modulating factors?

Reducing exposures good but interventions should take place at the source, so more source research is important for understanding intervention

But it is hard to find the source in a complex mixture like water or air - fund research in this area?

Are there fundamental principles here? should we be measuring paired samples (paired exposure vs host, as well as temporally paired). Can be generated by modeling in toxicology to inform human studies.

Informed priors using Bayesian framework can help borrow prior information.Bring probability and uncertainty.

Key characteristics - exposures - group knowledge in different way?

> Ex: groups of chemicals (PFAS and what we know) intersected with translational sciences exposomics/key characteristics(KCs) / adverse outcome pathways (AOPs), mode of action (MOA)

There should be a renewed focus on sources as well as exposures - that is how we can reduce exposures. Can we use new technologies to find out where similar molecules in the body or in the air actually came from?

Regulation needs to catch up to community, for example if each of three sources are individually in compliance, they cannot be censured, but communities are exposed to all three.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

If time is a key factor for toxicity (critical window) then can we have **annotations by chemical** (like gene nodes).

Utilize repositories to go back in time.

Fund more sampling and storage of samples over time? (need to understand stability).

Modeling may help understand exposures over time and life stage.

Also sensitivity analysis of adverse outcome pathways or other complex models can inform most important approaches/ markers in human studies.

Cumulative impact studies are the future for communities and populations.

- Include assessments from multiple routes of exposures and in multiple media (air, water,soil)

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Hard to go back in time to understand early life exposures, especially for short half-life chemicals in body.

Hard to find markers and samples from past exposures (teeth, hair may help).

Current regulatory frameworks do not adequately incorporate.

- Integrating of “newer” sciences (ex: exposomics) into the risk assessment paradigm for implementation (regulatory entities)

Bridging different data sets such as GIS mapping of pollution sources, translational sciences, monitoring, modelling – and the need for a shared framework.

ISSUE #8: Epigenetics and the Exposome / Exposome and Cellular 'endpoints' (adducts (e.g. DNA, protein), epigenetics, mutations – what, how, why / Epitranscriptomics

CONVENER(S): Dana Dolinoy, Marcus Cooke, Chris States

PARTICIPANTS:

Chris States	Yuxia Cui	Burnley Truax
John House	Erica Fosse	Chiung-Wen Hu
Jen Fernandez	Sri Kannan	Marilyn Silva
Cheryl Walker	Emily Krueger	Kimmie Sala-Hamrick
Sarra Bridges	Shelia Newton	Edith Eaton
Margaret Quaid	Jaya Viswanathan	Ariana Haidari
Ron Johnson	Alex Merrick –	Yuan Li
Zenobia Moore	epigenomcs and tissue of	Michelle Bennett
Arun Pandiri	origin	Tim Fennel
Charles Schmidt	Blake Rushing	Huichun Xu

SUMMARY OF DISCUSSION:

1. Consider acute vs chronic exposure exposures and the role of adaptation. Time course J shape course. (CS) The exposome is constantly leaving fingerprints on the genome via adducts, epigenetic modifications and mutations, that may be short-lived, last a lifetime, or even inherited.

2. Distinguish between within lifespan versus transgenerational and how the differ from an exposome point of view (CS)
    a. Generational influences over time (stress, poor diet, age of reproduction). Env Justice eg multigenerational slavery exposures
    b. Pb exposure during trimester 3

3. Need exposomic (e.g. metabolomics) to help relate these biological responses (adducts etc.). internally generated changes vs external (MC). Include or exclude genetic variation/mutation here? Need more here on whether its exogenous or endogenous (AP)

4. How to get at prior exposure? WGS, define mutation spectra /reprogramming

5. Endogenous inflammatory milieu from diet/bmi/chronic health conditions -> different epigenome -
    * Enforcing loops
    * Differential response to exposure
    * Temporal nature between this changing epigenome and the emergence of disease (JH)

6. (AM) Liquid biopsies – looking for changes in amount but sequence variants to transcriptomic changes indicative of chemical exp or disease. DNAm promising for tissue or origin. Looking at cohorts. TaRGET II consortia.
    a. Desire for standards

7. ncRNAs linked to exposures? (AP); alternative splicing; posttranslation machiney
    a. CS As kero cells and splicing

b. Environmental deflection of age related change

8. (YC) To the point of adaptation - I would like to think, besides serving as a proxy for past exposures, can epigenetic changes/profiles provide insight regarding resilience and vulnerability? realize this is also of point of John's.

9. Long vs short biomarkers, adducts

10. Genomics of CVD – data with air pollution and epigenetic change, wish for a database of exposure to omic change. Could NIH coordinate collection/storage of date.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Need ways to generate and fund descriptive science and mapping omics databases (NIH RFAs?)

Can we take advantage of complex in vitro systems (tissue on a chip, organoids, body on chip). Steroids and IPSCs to cardo. Are we there yet? But step beyond 2D cell culture. Example – snake venom production, organoid cultures can produce whats in vivo!

Need baseline data on normal tissue? Systematic (GTEX equivalent)
Single env agents on adductome etc. (proxy measurements). Is ToxCast doing this? They are highly validated system but chemicals by chemicals. Elimination of animal testing. ICE Integrated Chem Env PPBK and IVIE models and PubChem – good resources / Limitation of metabolism (liver chemical does this okay, developing neuronal)

When does an epigenetic mark become an adduct? (MC)

(JH) Need to understand temporal stability of epigenetic signatures is still understudied
* Not well understood if intervention that changes signature -> more norms results in improved condition
* Light under the lamp issue - imperative need for high read depth WGBS (vs arrays). And methylome is only one piece of epigenetics. ChIP are still difficult, repeatable, enough tissue (a mouse liver lobe can only do a few ChIP)
Need to reduce the cost (compared to GWAS); Federal level support (CHEAR eliminated Biological Reponses when went to HHEAR)

How many time points do we need to see if the epigenetic is changing over time? How soon can we detect (does it persist); aging clocks in adults, but not kids
review about -omic aging clocks
https://www.nature.com/articles/s41576-022-00511-7

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Desire for standards of biological responses (ontologies, categories – need to use same terms across field)

Signature of exposure bc of internal vs external processes

Temporal change over time

State of adductomics – is it scalable; look at multiple at a time?

> DNA/nucleic acid = 100s relative high TP mass spec; data analy slower, but some databases coming online to help. Behind metabolomics. Only 300 identified DNA. 10K adducts detected in urine. **WANT to form consortium between A and M to advance;** was successful in Ox stress in past.
> Need genome wide map of all adducts across genome nuclear and mitochondria*
> Can this be done with antibody? Perhaps. Need Sequencing Mass Spec. Nanopore sequencing w/ MS
> But cell type and developmental state will affect adducts
> Hemoglobin as an adduct source (people don't keep, plea to store).

Difficulty of translating the MODEL to human dosage. What about diet and stress?

> Relate to internal human exposure
> Plethora of models is overwhelming, don't need to be expert in all.

Pharma and others have scalable systems, less so in academic and govt labs

Great need for multi-generational models to sort out generational exposure (chemical, social, diet). Models and reproducible. Biological endpoints here? Multiple exposures in Env (may not enter body), perhaps internal biological measures appropriate here.

Capture was the study of epigenetic marks as mediators of exposure —> disease. Comes into play though again with difficulty of temporality

ISSUE #9: Integrating exposure over time, with long lived markers such as DNA and protein adducts

CONVENER(S): Tim Fennell

PARTICIPANTS: Suramya Waidyanatha, Debra MacKenzie, Homero Harari, Elisabeth Cook, Lang Wu

SUMMARY OF DISCUSSION:

Markers with different lifespans

Hemoglobin adducts – long term biomarker, zero order removal, different adducts from different chemicals. Integrated over lifespan, 120 days. Adducts accumulate over the lifespan of the red cell, and can reach steady state with repeated exposure. Can be used to calculate internal dose (AUC) in blood.

Albumin adducts. First order removal, shorter half life 21 days.

DNA Adducts. Very long life span of DNA, adduct stability can be an issue e.g. with depurination.

Metals - reservoir in bone, tissues. Changing forms, organic, inorganic.
Chemicals with long half lives, e.g. PFAS chemicals, TCDD, PCBs. Reservoirs in fat, liver.
Chemicals and metabolites with short half lives. May be removed quickly after a short term exposure.

Matrices

Hair and nails
Teeth – deciduous teeth, permanent teeth? Materials deposited over years.
Urine. short term markers.
Blood, plasma, serum
Feces
Placenta
Cord blood
Amniotic fluid
Meconium
Saliva
Breath, breath condensate
Sweat

Exposure duration

Long-term repeat exposure
Intermittent exposures
Are the exposures captured in a spot sample?

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Need a resource that lists advantages and disadvantages of short and long term markers, windows of exposure.

Measures of what is seen and how to incorporate long and short term exposures.
Long lived exposure marker, vs. multiple serial samples. Can we learn more that way?
Reverse dosimetry methods for relating exposure to long-lived markers. PB-PK models blood and tissue levels, and incorporation of adducts.

Lead as a long term marker. Blood vs bone.

Expansion of methods for adducts. Adductome

Translation from animal exposures to humans.
Small human exposure studies

What can we learn from workplace exposures and industrial hygiene. ? ACGIH guide.
Occupational exposures opportunity to evaluate approach using long term biomarkers.

Sources of samples. Albumin from plasma is widely available. Hemoglobin widely available, but red cell pellets are not widely collected.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Adduct methods are much more limited in focus. Expansion of methods. Support for adduct investigations.

Sample availability – see above.

Intermittent exposures, exclusion/inclusion of analytes if not detected in participant.

How does biomarker relate to disease? Risk assessment.

ISSUE #10: Dietary exposome

CONVENER(S): Susan Sumner and Lissa Soares

PARTICIPANTS: Allison Cook, Daisy Fry Brumit, Ryland Giebelhaus, Yuan Li, Srimathi Kannan, Tim Fennell, Srimathi (Sri) Kannan, Dana Dolinoy, John House, Blake Rushing, Jeffrey Kopp, Collin Kay, Emily Krueger, Jason Stanko, Lisa Rider, Debbie Bennett, Deepak Kumar, Christopher Gaulke

SUMMARY OF DISCUSSION:

The dietary exposome can have some mitigating effect on the role of the environment on human health. They key issues we considered in our discussions are the following:

- Supplement intake. A source for mixture of exposures.
- Multiple sources comprise the diet (medication, substance use, supplements, botanicals, nutrients and environmental exposures)
- Interactions.
- Taking into account other exposures. Metabolome, exposome, microbiome; how to deal with polymorphic data to be interpretable.
- Intolerance
- Developmental exposures. Epigenetic mechanism
- Diet as its own endogenous exposure system (Lissa: how to characterize this?).
    - How co-exposures enter through the diet.
    - Its own class of exposures
    - Assessment?
        - What is available for consumption
        - What happens internally (factors in age)
- Characterization of the dietary exposome: chemicals that get into foods, contaminants, bioactive substances in foods
- Exposures through drinking water among persons on dialysis
- Characterizing the phytochemical diversity of the human food chain
- Environmental science meets nutrition sciences
- Myositis
- Internal exposome
- How does this dietary exposome relate to perturbations in host metabolism that correlate with disease phenotypes. What are those co-exposures and how do they differ across diverse populations?
    - Addressing health outcomes related to health disparities
        - Food security (nutrient density or food availability). How to talk about food security?
- Two components: environmental chemicals that get into food pre and post-processing.
- Could we classify diets by processing levels in a way that captures environmentally relevant exposures?
    - I like considering the exposures in the context of production timeline. at the crop growth, harvest, formulation and packaging, and microbiome metabolism.
- Other types of dietary exposures:

Recognized the importance of the dietary exposome. Comprised of elements that are beneficial or not to human health (good or bad components).

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Characterization of the dietary exposome.

- No existing mechanism (database). We don't know the extent of the variability of the composition of foods. Food composition library (USDA, food metabolome dictionary) that exist are somewhat limited.
- Untargeted analyses of the diet, the internal exposome/ composition of biological fluids.
    - What can we seen from untargeted platforms: metabolites, a multitude of environmental relevant compounds including some pesticides, PFAS, phthalates, tobacco compounds, VOCs (conjugates to molecules that are found in high temperature processing of things like tobacco or acrylamide from fries), PAHs, parabens (food packaging), food metabolome compounds, benzonic acids (phytochemicals breakdown products), cyclines, phenoamines, ketones, phytoestamines, drug and medication panels (includes supplement intake), OTC (ibuprophen), herbicides and inscecticides, micotoxins, microbiome related products.
    - Metabolites of host systems + these environmentally relevant compounds listed above can be seen simultaneously
    - Metals can be addressed, but not simultaneously
    - Opportunity to understand co-exposures
- Monday's presentation: https://hhearprogram.org/hhear-exposomics-webinar-series
- Nutritional epidemiology
    - Nutrition and air pollution: used databases available for food composition (food technology base and www.eurofir.org EuroFIR AISBL) for diverse diets. Phytonutrient and flavonoid analysis in foods (.).
        - "The EuroFIR eBASIS (Bioactive Substances in Food Information Systems) is a unique Internet deployed food composition and biological effects database for plant-based bioactive compounds with putative health benefits". for phytochemicals/phytonutrients, flavonoids etc... in the context of biological effects. https://www.eurofir.org/our-tools/ebasis/
    - Bringing in tools from agriculture.
    - Draw from biomedical databases that considers bioavailability factors
    - Are these data geographically bounded
- Understanding metabolic individuality as it relates to diverse populations and health outcomes
- Climate change
    - combine databases on nutrient in food and CO2 databases with a link through specific food items
    - Agricultural methods (e.g. crop protection) impact on the link between climate change and nutrition
    - Plant metabolism
    - Mycotoxins

- Back to the Metabolic Individuality. I think of conceptualizing this as given the same exposure, it is affected by the intersection of Metabolic Individuality
    - * Genetic
    - * Epigenetic
    - * Microbiome
- Study nutrient-drug interactions and biochemical-drug interaction, phytochemical-drug interactions

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Food composition. How do we better map changes over time in dietary exposome?
- Database construction. How could they be integrated for practical use to overcome some challenges of future methods. A data ecosystem? A database to link out to information about the metabolite, the parent compounds, and so on.
- Translation from animal models to human subjects.
- Needed database that integrates research on the external exposome and the link to what is measured in the internal exposome
- The foundation for dietary assessment instruments is weak (and the strong tools are very intensive to use). Needed development of novel tools and technology to assess the diet as an endogenous exposure at the individual level. Precise measurements.
- Development of wearables integrated into the assessment of the exposome. A mix of the dietary intake, exposures, and physiological measurements.
- Poorly understood geospatial variability of dietary exposome.
- Do we have or can we draft a working or standard definition of the dietary exposome?
    - It should at least include everything mentioned above.

ISSUE #11: Underrepresented areas of the exposome: social (social determinants of health) environment, context, and behavior

CONVENER(S): Roel Vermeulen, Andrew Geller, Chris States

PARTICIPANTS: Amy Kalkbrenner, Robert Wright, Batel Blechter, Jaime Hart, Enki Yoo, Nigel Walker, Perry Hystad, Kimpberly Thigpen Tart, Jennifer Woo, Savannah Sturla, Sophia Miryam Schussler-Fiorenz, Kavita Berger, Sarra Bridges, Emily Lax, Jason Wong, Wei Hu, Eric Bind, Lawrence Engel, Sheila Newton, Anne Dunlop, Shosha Capps, Lenore Launer,

SUMMARY OF DISCUSSION:

1. Available data include questionnaires, surveys, deprivation indices – What is needed to take these data further?
    a. Can we build better constructs based on administrative data? Mapping social networks, using social media?
    b. Note that these are conventional data sources; when considering environmental justice, need to consider methods of community engaged research, participatory research and, ultimately, data ownership issues and report back to participants
2. Surrogate measures do not necessarily help us understand the social domain; in practice it can be very difficult to separate environmental exposures from social condition data, e.g., air pollution and social deprivation especially when full activity patterns are taken into account
    a. Machine learning approaches may be helpful for defining the most important social exposures and pathways.
    b. Besides data-driven approaches it is also important to think about what exactly we want to quantify if we talk about the social domain. Current constructs and available data may not capture these constructs very well.
3. Recognition that exposome can become technology driven – there is a need to fully understand the constructs underlying social, environmental, and behavioral data collected through mobile apps
4. It is critical to ensure that social exposure data are used as fully intentional, well-operationalized constructs, not just included as an added social variable, especially when considering stressors such as early life trauma, neighborhood stress
    a. This points to importance of qualitative data to validate surrogate measures and the need for mixed methods to be able to use quantitative and qualitative data
    b. Need to incorporate perceptions of exposures through individual and cultural lenses and develop uniform methods to capture these factors in a standardized way
5. Need to be able to build databases through multiple cohorts; need to consider data sharing, data standards, FAIR data, data ontology to facilitate building large data bases that would facilitate doing stratified analyses.
6. Challenges and concerns about privacy with respect to social data, social determinants of health
    a. Legal limitations on use of cell phone data, and monitoring devices when data is stored at servers of commercial entities; need to develop specialized apps for collecting these data.
    b. Differences between American and European health data accessibility for merging data sets.
7. Concerns about data representativeness

   a. Participants Collecting daily activity data – with study cohorts of a few hundred or even 1000 – may not be representative of general population
   b. Participation in surveys of health and social data (e.g. state or National Health and Nutrition Examination Surveys (NHANES) are often biased; oversampling and other focused approaches are needed to collect data from underrepresented groups and communities
   c. Concern about representation of urban and rural behavioral and social data
      i. This may be exacerbated by differences in response rates and new data methods.
8. Need for behavioral data, potential present in behavioral modeling
   a. Behavioral data, eg health behavior, is critical;
   b. Need for educational attainment data at finer scale with respect to health literacy
   c. Great opportunities to build far more representative data sets for human activity data using mobile apps to collect intensive individual data
   d. Use these data in agent-based behavioral modeling to scale up to population sample sizes
9. How to incorporate integrated measures, surrogates for social stress in to experimental, including in vitro, studies. How to build an evidence base for use in larger epidemiological studies
   a. Possibility of using epigenetic markers associated with social stressors.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Setting standards for social and behavioral data collection, data interoperability, and data sharing to allow combining of cohort data sets.
  - Note that US Core Data for Interoperability v3 (July 2022) - standardized set of health data classes and constituent data elements for nationwide, interoperable health information exchange – now includes social determinants of health https://www.healthit.gov/isa/united-states-core-data-interoperability-uscdi#uscdi-v3

- Opportunities to build more representative data sets for human activity data using mobile apps to collect intensive individual social and environmental data
  - Use these data in population-based behavioral modeling to scale up to population sample sizes
- Research identifying biological markers of exposure to social stressors for use in experimental studies or in larger scale molecular epidemiological studies.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Data availability: Applicable data such as anonymized community mobility reports and trends data are available but very expensive; Support need: a national program to make these data available for exposomal research

- Availability of address-level social determinants of health and environmental data

- Challenges of merging available administrative data collected at individual level with environmental data such as air quality or green space accessibility collected at larger scale

ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility

CONVENER(S): Jarmusch, Kirsten Overdahl, Michael Snyder, Arcot (Raja) Rajasekar

PARTICIPANTS: Farida Akhtari, Douglas Walker, Jeanette Stingone, Pothur Srinivas, Stephen Edwards - RTI International,Ghada Soliman-CUNY-SPH,Brandon Pierce,Amy Leang,Colin Cay,Deepak Kumar,Richard Kwok,Lissa Soares,Ram Siwakoti ,Peng Gao,Xiuxia Du,Kristin Eccles,Chiung-Wen Hu Blake Rushing,Ryland Giebelhaus,Allison Cook,Arcot (Raja) Rajasekar - INC Chapel Hill,Tom Young-UC Davis,Yuan Li, Charles Schmitt, Susan Sumner, Nirmala Prajapati

SUMMARY OF DISCUSSION:

1. **What data to share?** There was general consensus that data should be shared, and that data should include raw data, metadata, and data relevant to the interpretation, processing, etc. The difficulty of sharing and reusing metadata was noted multiple times. Generation of metadata is time-intensive and therefore demanding on individual researchers. Specific funding for metadata and data sharing might be beneficial. Metadata generation would benefit from ontology specific to exposomics. It is particularly difficult to capture certain aspects of exposure currently such as food and medication. Conveying confidence and measures that go into metabolite measures is important, but not well captured currently.

2. **Location of data and data access.** A large part of discussion was about the various options for data location and access of data. It was discussed if there is a database for exposomics data for which specific databases were mentioned that serve as a place for data deposition (e.g. metabolomics workbench), but were not originally designed with exposomics in mind and therefore fail to capture some of the information relevant to exposomics. The strategy for database creation was discussed, such as a specific database for all data or specific databases for different purposes with linkages between them. Agreement that linkage between databases and information is vital. If data is prohibitively large or otherwise restricted in use, having user-facing tools to enable analysis is useful. Someone (likely at the level of NIH or similar institution) should define the necessary components, standards, and information in the database.

3. **How to encourage data sharing?** This question had a variety of different answers covering both reward (i.e. carrots) as well as putative (i.e. sticks) measures. There was the idea of linking data sharing with funding scores (with sharing being rewarded), the inclusion of journal and publications in formulating requirements, and that sharing should be included in metrics upon which people are evaluated (h-index, citation of digital object identifiers (DOI), tracking downloads). There was discussion about why people may or may not want to share data including the fear of being “scooped” and that current solutions (e.g. embargo periods) and new solutions would be of benefit. Use cases, vignettes, stories all would be useful in demonstrating how data can be reused and the purpose of data sharing.

4. **The role / responsibility of community report back.** There was a discussion about the role and responsibility of reporting back results to community participants and

stakeholders. This converged with a discussion about data ownership and data handling requirements (regulations such as NIH data and GDPR).

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Database development including interoperability (linkage) with existing databases
- Tools for data conversion into compatible formats and tools that make data submission easier on users and uniform.
- Ontologies and metadata support
- Working groups to promote sharing of data and help educate individuals, including database deposition, metadata collection, consider data sharing permissions during IRB process

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Reluctance of open data deposition / sharing
- Incomplete metadata reporting
- Challenges in conveying data confidence
- Consent for data sharing
- Regulations on data sharing e.g. GDPR
- Ontology: especially nutrition, mediciation

ISSUE #13: Toxicant-induced Loss of Tolerance (TILT) and Mast Cell Sensitization

CONVENER(S): Claudia S.Miller, MD, MS, Professor Emeritus, University of Texas

PARTICIPANTS: Initially myself and subsequently with participants in Issue #11

SUMMARY OF DISCUSSION:

Toxicant-induced Loss of Tolerance (TILT) is characterized by multisystem symptoms and intolerances for chemicals, foods and drugs which appear to result from the sensitization of mast cells by a single high level or repeated lower level exposures to *toxic particles and/or VOCs* arising from 1) fossil fuels—coal, oil, natural gas—their combustion products and/or synthetic derivatives, and 2) biological sources such as mold or blue-green algae.

Toxicant-induced Loss of Tolerance (TILT) is a new mechanism or theory of disease first proposed a quarter of a century ago (Toxicology 1996, EHP 1997, Chemical Exposures: Low Levels and High Stakes,Wiley 1998). To date, researchers in 17 countries have used the internationally validated Quick Environmental Exposure and Sensitivity Inventory (QEESI) to document chemical, food and drug intolerances in populations on five continents.

In the U.S., 20% of adults report *multisystem symptoms and intolerances for chemicals, foods and drugs.* Half of them attribute their illnesses to specific exposures, e.g., 9/11, breast or other implants, pesticides, the Gulf War, a “sick” house, school, or office building, burn pits, mold, or VOCs during remodeling or new construction. Once “TILTed” (as patients call themselves), extraordinarily low level exposures to these substances as well as structurally unrelated chemicals, foods and drugs, trigger symptoms such as fatigue, brain fog, headaches, musculoskeletal pain, and digestive difficulties.

TILT involves *both* classical dose/response toxicology and allergy/immunology: Genetic differences such as low PON1 detoxification capacity for organophosphate pesticides (Clem Furlong) predispose to TILT. A single acute exposure, e.g., to a pesticide) or repeated lower level exposures (e.g., indoor air VOCs) appear to *sensitize* our ancient, cell-mediated immune (CMI) system’s first responders—mast cells (Miller et al., 2021). CMI involves the other “arm” of the immune system and differs from humoral immunity mediated by immunoglobulins like IgE.

We discussed the internationally validated BREESI screening questionnaire and 50-item QEESI (Quick Environmental Exposure and Sensitivity Inventory). To date, the QEESI has been translated and used by researchers from 17 countries, resulting in ~150 peer-reviewed publications. It is a tool that NIH, EPA, CDC/ATSDR, FDA and other US agencies should be using.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

1) Help NIEHS, EPA, NIOSH, FDA and other research groups, epidemiologists, toxicologists, and physicians understand, administer, and document health changes resulting from large-scale exposures to oil spills, fracking, fires, burn pits, implanted devices

(FDA), taking advantage of the published and validated BREESi, QEESI, pre/post symptom severity scales, and exposure histories.

2) Host a virtual meeting focused on TILT, bringing together basic mast cell researchers, toxicologists, physicians, public health representatives and patients to discuss the two-step mechanism for Toxicant-induced Loss of Tolerance: a) *initiation* via sensitization of mast cells and b) subsequent *triggering* of cascades of mediators and inflammation by everyday chemicals, foods/additives, and drugs. The purpose of this gathering would be to review current data, propose approaches for research, and explore potential interventions, prevention, and treatment. The output would be a series of recommendations to address research, public health, and medical needs, as well as housing, interventions, possible treatments and needed accommodations.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

NIEHS could approach the Marilyn Brachman Hoffman Foundation, and other environmental agencies and private funders to help support an international meeting on TILT. Fogarty and NIEHS funded the first international meetings on TILT in Tokyo and Resesrch Triangle Park, NC. Now that a plausible and researchable two-stage biomechanism for TILT involving mast cell sensitization and triggering has been published, a path forward has emerged at last.

ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome

CONVENER(S): Doug Walker, Emory University

PARTICIPANTS: Ghada Soliman, Krem Jbebli, Alan Jarmusch, Alex Merrik, Alexandra White, Brandon Pierce, Elisabeth Cook, Heather Patisaul, Jayalakshmi Viswanathan, Jennifer Fernandez, Michael Snyder, Neil Zhao, Pothur Srinivas, Robyn Tanguay, Scott Sundseth, Doug Walker, Suramya Waidyanatha

SUMMARY OF DISCUSSION:

The goal of the session was to discuss approaches for exposome (omic-level) biomonitoring of the human exposome. Much of the discussion resolved around untargeted high-resolution mass spectrometry methods for measuring the internal exposome. To begin discussion, the first question posed to participants was to describe barriers to including untargeted exposome methods into human studies. Barriers included:

1. Complexity of data and understanding untargeted deliverables.
2. Understanding processing methods for extracting and analyzing complex untargeted data.
3. Standardization of data, for example, how to evaluate annotations from different laboratories.
4. Access to exposome analytical and research resources, especially when there is no clear operational definition of the exposome.
5. Annotations and unknown. Major concerns included important findings that may not be possible to assign metabolite IDs.
6. Uncertainty about the state of the field and best resources for exposome capabilities. For example, some assays are considered exposome focused, but may be based upon metabolomic measures.

Later discussions focused on standardization and requirements to create analytical workflows for large-scale exposome biomonitoring. It was well recognized by attendees that it will not be possible for a single assay or lab to provide these capabilities. The following needs were discussed:

1. Standardization is important for all aspects of the analytical process to develop harmonizable approaches for exposome biomonitoring.
2. There is a need to develop benchmarks for untargeted high-resolution mass spectrometry to evaluate suitability for harmonizing exposome data.
3. Suggestions included pairs of reference samples and standards that can be evaluated in each batch to test method suitability.
4. Ontology and naming conventions for chemical annotation results.
5. Strategies to ensure appropriate reporting of method details and parameters.

It was noted that while there were many opportunities for round robin testing in metabolomics, no similar opportunities have existed for the exposome. Additional discussions included data sharing, FAIR principles, and making results accessible, the ease of use of vendor software vs transparency of open-source software, and the wide range of

methodologies used for untargeted analysis, which is usually driven by the focus of the laboratory. Quantitative strategies for untargeted data were also discussed.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

1. Identify clear goals and deliverables for an operational measurement of the exposome using untargeted HRMS (i.e. what is an acceptable measurement).
2. Reference samples and standards for untargeted exposome studies (rather than metabolomic studies), possibly through NIST.
3. Development of universal chemical databases to support annotation of exposome data with common identifiers and ontology.
4. Deciding on a framework for exposome databases.
5. Round robin and proficiency testing for exposome assays.
6. Benchmarks for successful untargeted exposome data.
7. Additional opportunities for training in exposome research methods.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

1. There is currently no funding to support development of exposome infrastructure for untargeted HRMS method development. There is a need to establish key operational parameters and benchmarks that form a consensus across the research community.
2. Stakeholder engagement to hold researchers accountable to open and FAIR data requirements.
3. There is no clear definition of exposomics methods. Are untargeted HRMS methods optimized for the metabolome detecting many exposome signatures? Or is it limited to high-abundance exposures?
4. There is not a clear pathway to developing an unambiguous ontology for untargeted exposure data.
5. We need clear metrics of success for what it means to implement large-scale exposome biomonitoring.

ISSUE #15: Strategies for scaling and diversifying the external exposome measurements (citizen initiatives?)

CONVENER(S): Roel Vermeulen, Rima Habre

PARTICIPANTS: Robyn Tanguay, Debbie Bennett , Scott Sundseth , Savannah Sturla, Nirmala Prajapati , Lisa Rider, Yuxia Cui

SUMMARY OF DISCUSSION:

- Scalability of external exposome measurements is very important.
- Different actors can play a role in achieving this goal including citizen scientists (crowdsourcing sample or data collection – apps, smartphones, crowdsourced reporting/annotation) as well as the private sector (companies enabling large scale data collection of environmental measurements or biospecimens for environmental exposure profiling, eg, Google Street View mobile monitoring; environmental scans on take-home self-measurement kits or commercial chips/assays etc. already included in funding model for healthcare provision, exposome scans at every health checkup)
- Collecting external environment samples is generally cheap but analysis cost is very expensive and a barrier right now to scaling up. We need to achieve economies of scale where large number/volume of samples is being analyzed to drive costs down, could be a two-pronged model with one central lab equipped to run these analyses with standardized methods and protocols at scale and lower cost, and several other labs in the network working on smaller scale discovery, methods refinement, new protocols development, new chemical identification etc. (handling smaller number of samples but having the right expertise). Can follow genomics model.
- There is perhaps a misconception that internal exposure measurements in biospecimens are more informative or useful, when we have plenty of evidence to show how valuable (and less invasive) external exposure measurements can be. For example, cotinine has a short lifetime in blood and can be informative to gauge short term exposure, but questionnaire measures on smoking might do a better job at identifying or assessing longer term smoking exposure. This is also a communications/PR challenge where actors in this field perhaps have had a harder time or spent less time on articulating or communicating the incredible value of external environmental measurements.
- Need for envirobanks similar to biobanks, with diverse samples and representation across geographies, cultures/populations, global region, various contexts etc.. We seem to be at a point where technology is driving the field vs the other way around (similar to genomics), important to think about how to get low tech and low cost technologies and methods to LMICs to truly diversify representation in datasets in a global sense
- External exposure measurements (for the most part) have been well established, are easy to collect and relatively affordable, but analysis costs are still a bottleneck. For example, house dust chemical analysis (SVOCs, VOCs, allergens, etc.) captures exposures relevant to where people are and spend the majority of their time and what they are exposed to across multiple routes and pathways (not just dermal but also inhalation and ingestion).

- Scalability and diversification discussion is also about balancing precision vs bias. We need more data of all kinds – high quality research grade in perhaps more limited samples and lower cost/higher noise but greater sample sizes. Parallel discussion related to targeted and untargeted (discovery) methods, we need both.
- How to choose what to measure? We need to infuse risk screening concepts into prioritization schemes for choosing which set of chemicals for example we should always screen for in external samples, in which media (not just air, also water, dust, etc.), using which protocols and samplers (eg, wristbands, etc.) – combine emissions/production volumes with behavioral and intake data to rank chemicals.
- We should also consider totality of chemical, physical, biological, social, built env etc environmental exposures and not just chemical. We should define the exposome in the broadest way possible so all these components eventually are equally efficient or feasible to measure.
- Think about aggregate/cumulative risk and mixtures
- Effects directed analysis- Collecting complex mixtures and fractionating them based on a measured activity. Examples include the zebrafish. Cell based assays such as receptor based analyses of chemical mixtures effects in external environmental samples is also very powerful, eg, oxidative potential or other properties of particular chemical mixtures or environmental samples.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Partnerships with private sector
- Crowdsourcing and citizen science initiatives
- Leveraging existing infrastructures or population studies and cohorts to tag on environmental exposure scans (eg, blood drives, occupational health screens, etc.)
- Funding (or lowering cost) for large screens of existing banked environmental samples like house dust, air filters, wristbands etc..

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Prohibitive costs of chemical analysis at scale still (samples available but very costly to analyze)
- Harmonization of protocols and methods
- Balancing need for high quality data vs more data (precision vs bias)
- Balancing need for untargeted AND targeted methods – both play important roles
- Diversification on a global scale in terms of developing, applying and learning from these methods and datasets

ADDITIONAL NOTES (messy brain dump from session)

Risk concepts: aggregate and cumulative risk…

How to select what to measure with external exposures?
Do we need personal exposure measurements for everything? Or a combo of outdoor + questionnaire data? Or indoor + personal measurements? Not just PM2.5 mass, ultrafines, components…

External measurements, scalability and reaching larger populations – how ? citizen science, alternative approaches
Scalability on few exposures, diversify things we measure, and populations/time/scale/other factors that matter…opportunities for other exposures that are less done?

Passive sampling in various media, citizen scientists want to be engaged and know what they are exposed to, if not measuring from biological sample/human not always appreciated/valued (challenge), scalability beyond biosampling.. scalability of analytical effort with sample collection.. to be ablet o unravel interactions

Silicone wearables capture semivolatiles which have longer timeline in env, dust good matrix, capture so many compounds in the home, impo component in exp and with short half lives and very important. need to get analytical cost down for either of those to do it more broadly.. eg, EPA efforts for cheaper VOC measurements but we need to figure out a way to make these analyses cheaper

Self measurement kits for people to collect their own data – apps to collect information about your environment, harness citizens to collect env data not necessarily on person themselves (not necessarily personal). Eg, validation of food environment

Diversity of data? Representativeness? EJ communities + high SES/education communities, easiest or perhaps usually more motivated to collect the data..

Measuring what we know to measure or easier to measure for a while.. .risk prioritization? Other chemicals can be more difficult to measure but also more concerning.. are we measuring the things we care about when we care about them and where?

Street level light at night.. how to use citizen initiative to measure this?

Exposure measurement error – need to understand personal exposure but often outdoor more scalable/attainable – sensing devices, cell phones, low cost sensors, etc. with same data quality / privacy issues..

Bias/precision tradeoffs – eg, house dust, can/if people collect it challenges to analyze ($'s) – standardized methods available?

Facilitate studies that allow self-collection and citizen engagement.. to characterize variability

National core laboratory? Are we just going to look at fixed number and targeted? Or discovery/untargeted to understand what's there that we're not measuring? Analytical chemistry approach of targeted vs data driven untargeted methods.. need for standards

Investments similar to in genomics needed.. global implementation if only have few labs with best technology? Economies of scale.. volume of samples

Two-pronged approach? One centralized lab for affordable points, and smaller labs spending time on new questions/ what else to measure/ develop new standards and methods.. R&D.. keeping up with the research and new chemicals on market etc..

Global diversification? How to optimize/standardize learning for developing methods for the exposome? Where are the standards available, need ground-truthing with research quality data collection in more diverse contexts (profiles within subgroups that are more similar to each other)?
Not let go of power of measuring chemicals near people/continuously and where they are exposed, more valuable than spot samples sometimes.

External exposome, noninvasive, across chemical space – easier in a sense, no biomarkers of exposure always

Biological screens / biobanks , never scaled external exposome tools to same level, collecting more (10K) wristbands for example but bottleneck is funds to analyze them. how do we demonstrated that extensive external measurements can be more predictive if we cant do these analyses at scale?

In body vs external (chemicals, social, non-chemical, built, physical etc.) - Define exposome in broadest way so all these components eventually are equally efficient or feasible to measure.

Technology driving the field vs other way around (genomics example from Scott) - methods still challenging, international hundred K consortium, LMIC countries how to bring them technologies to measure env exposures that are low tech and low cost, ‘exposome bank’ – diversity question along exposures and ancestry region specific – global thinking, methods easily used in global north transferable?

Teach epidemiologists on how to do their studies to be able to measure environmental exposures or bank samples to incorporate later

Envirobank same as biobank.. how to do this? house dust, wristbands, stable? Integrated samples a bit easier/more stable but less time resolved – there are transferable methods and technologies, exporting biological samples very challenging across borders

Academic training / community partnerships / detailed protocols/ regionality approach to scaling up , needs less engagement than individual level, watch people doing a protocol to train with videos

Scalability by engaging/interacting with private sector? Mobile campaigns scaled with partnerships with Google for example – existing business model for companies to provide that data to local governments and research use, 23&Me example thinking about adding env exposures to their measurements.. how to think about this.. part of annual checkup (env screen)? Eg, lead in kids in northeast..

Balance between measure good enough at scale vs much greater accuracy? ‘fit for purpose’

Occupational health services eg in Netherlands (private entities) – exposome scans into health checkups – pay model very important and cost-effective.. blood banks with large populations that come back regularly.. biased population but helpful longitudinal data, and existing infrastructure..

Crowdsourcing environmental data collection and/or assessment of quality or perception of neighborhoods.. food access, neighborhood safety, etc..

Need more data – more data helps build better models/simulations.. bias vs precision, way more data but also way more noise? Balancing act? Need more data regardless.. as cost of analysis gets lower, relative cost of collection becomes more manageable

Biocrates?? Is there a parallel example for external env? Chip/kit/set to measure most important chemicals for cheap? How to determine which chemicals to measure? Analytical chem challenge.
Nontargeted analysis to samples we are already heavily exposed to, need both…

Who decides what to put on that panel? Risk prioritization concepts? Intake fractions? Based on what we know now but we have to regularly update our prioritization based on newer tox and exposure data we get? chemicals of emerging concern screen.. + occurrence/production volume data + risk/tox data to prioritize/rank , refine this over time…

Remote sensing – noise/data quality issues and availability of ground monitoring and validation data globally and quality/representativeness of that data

ISSUE #16: Personal interventions/report back and personalized risk models (multiple topics combined)

CONVENER(S): Konstantinos Makris, Janet Hall, Marta Jankowska, Rima Habre

PARTICIPANTS: Amy Leang , Jenna Hua, Homero Harari, Lenore Launer , Batel Blechter , Claudia Miller, Gwen Collman, Alexandra Torres , Jennifer Harker, Heather Patisaul , Marilyn Silva, Michelle Bennett, Fred Liao, Yuxia Cui , Emily Lax

SUMMARY OF DISCUSSION:

- This session combined the following four topics (posted by four different conveners):
  - Behavioral Change, interventions and the exposome (Konstantinos Makris)
  - Providing adjudicated information on an individual level (Janet Hall)
  - Moving into Citizen Science or just in time intervention approaches (measuring exposome in real time w/reporting feedback/intervention) (Marta Jankowska)
  - What do we need to build individualized exposure risk prediction models (methods, data, etc.)? How we actually interpret individual risk and how can we use this knowledge or why do we even need to (outline value proposition)? (Rima Habre)

- The group agreed that exposomics and exposomics tools are valuable for designing and evaluating interventions, for measuring markers of exposure, its metabolites or intermediates, measures of susceptibility or health endpoints and effects (doesn't have to just be focused on one of the above).
- How we materialize exposome into interventions? Focus on exposures, metabolites or intermediates, susceptibility measures and effects
- The outcome of the intervention itself can be to reduce 'exposome' type exposures or mixtures, or exposomics can be used to understand what to intervene on and understand personal risk
- In all cases we need responsible return of results, to provide actionable information based on environmental exposures (and their interactions with genes or mixtures or other long term, low dose exposures)
- How do we present data in a way that makes sense for a certain population, especially considering whether it is in their power to change or intervene upon this exposure? For example, issues related to occupational exposome might be different than for pediatric populations, and how you message or report results or intervene in those two settings can be very different. In general, we cannot just put the burden on individuals to change their exposures, we have to recognize upstream and institutional/societal factors and barriers etc.
- In citizen science realm, sharing data with the people who generated it themselves, can we get to a point where a person's own choices can be made on their own data? And how to think about time matching or integrating the information needed (how often to collect, when to collect, episodic/continuous/minute-level vs longer term or time integrated or snapshots – driven by the question)
- Population wide risks are often averaged out or washed out effects that could be way more pronounced in certain subgroups or individuals, how do we get to holistically looking at the exposome (multi-level, multi-lifestage, multi-scale etc.) and communicating about personal risk? Without causing harm. There are some "known bads" when it

comes to exposures but a lot of combinations of grey zones that are harder to make statements or design interventions around (or very context specific).

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

How do we return info to individuals? In a way that is helpful, educational campaigns? Emphasize certain elements that may be more important? Hair products, chemicals and association with cancer for example in African American communities. Specific **educational** opportunities, and trying to integrate information into medical records and health records that relates to the environment.. 1) get questions or formulate questions at intake, and 2) how to link to a resource / data/ information that tells the practitioner what the individual risk might be for the individual? (pricing, how will exposome framework help us frame better these questions and how to return results?)

Entry points for intervening: **broad education, doctor and patient relationship/time in office at visit (standard set of questions and analyses** that would be requested to inform this on every patient – what data/measurements are needed? Eg, PFOS for medical community to manage exposome landscape), just as we have diabetes educators same for environmental health.. training people to interpret results and how is it relevant for you and your exposures..

We can **learn a lot from existing successful clinical intervention programs that incorporate exposome/env exposures like in occupational medicine** (or even pediatric asthma for example where environmental exposure information is highly integrated into intervention design and deployment). Challenge is to scale up from one or two exposures (eg, asbestos or lead) to the exposome. Often one specific exposure fighting in occupational setting maybe – how we get to full exposome?

Comprehensive lifestyle audit last 24 hrs and provide actionable report based on assessment data (not enough), based on products used and consumption behavior – higher income, higher education have easy time (and maybe option to change) behavior. Lots of handholding needed for those with fewer resouerces, need a ‘councilor’ to guide people on what to do

We need multilevel models and multipronged intervention programs that can really incorporate the exposome (which acts across several levels of influence – integrates neighborhood with personal external and internal measurements) to design successful interventions that incorporate env exposures. **Can model on Diabetes prevention program for example or pediatric asthma interventions** – have assessment but can put people through intervention programs, individuals lack tools or models to make changes.. nice example to follow – multipronged approach probably why works, food pyramid and several pieces or levels multilevel intervention

Think of **upstream regulatory interventions**, for example, regulation of products (Amy) – Safer Products for Washington Act to look at high priority chemicals regulations, **driving demand for safer products** within the state (Washington) vs leaving it up to individuals to choose what they use or buy– upstream thinking and approach – how do we prioritize exposures and what sort of products should we look at for prevention?

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Jenna: problems we've been encountering, EDCs, personal care products, what are the challenges? **Physicians ask for causal data but we don't have it**, to demonstrate that these chemicals impact specific medical outcomes (for a specific person). Physicians want to be able to say if I detox a person it will improve their chances of IVF success for example… how much can we improve a clinical endpoint by intervening on this?

Also physicians don't have assessment tools to understand where people are getting exposed, how much, and what are they exposed to? Piloted in Nevada – people very interesting in understanding exp and how to reduce but don't know where to start. We don't have anything available comprehensively to see what people are exposed to where and when and how.

Prioritize exposome based on the question? **How much data is enough? How do we rank/prioritize?** Timely manner of generating key dataset for everyone to benefit from with enough temporal/spatial granularity with specific health outcome(s) in mind, can be effective. Eg, prediabetes population , still reversible, causal data/intervention data plus mechanistic data.. to inform future care..

ADDITIONAL NOTES (messy brain dump from our session)

- Responsible return of results, actionable information based on environmental exposures (gene environment interaction)
- Keywords from Konstantinos: Non-pharmacological interventions, dietary, climate change, neurotoxicity
- Health disparities
- Personalized interventions/ individual risk quantification/prediction/communication
- Citizen science, sharing data with people who generated it, can we get to a point where a person's own choices can be made based on their own data? Time to point matching of how often data is collected, and what data is collected, how to link counseling of one-time vs minute-level data-based feedback?
- How to present data in a way that makes sense for certain population, specially occupational exposome (eg out of work, people with no power to change their living conditions? Cannot just put burden on person)
- Methodologies of connecting individual level data with geographically or larger level data (climate, greenness, neighborhood level etc.) – ecologic bias from an epidemiology point of view.. data at level greater than individual

Tools for assessment and report back

Homero: occupational medicine clinic, precision EH used in occupational medicine clinic netwrks already, have been doing interventions last 30 years, occupational medicine has been providing this advice (asbestos, etc.) can acknowledge what already exists and use it, many models existing and used.. learn from those physicians and examples already doing env and occ medicine.

Scalability of this approach? How to do this looking at entire exposome/life?

What kind of markers are we looking at ? of exposure or effect? Or susceptibility? How will we advise our patients?
Are those educational tools or behavioral change tools Homero?

Can model on Diabetes prevention program – have assessment but can put people through intervention programs, individuals lack tools or models to make changes.. nice example to follow – multipronged approach probably why works, food pyramid and several pieces or levels multilevel intervention – often one specific exposure fighting in occupational setting maybe – how we get to full exposome?
Exposome can be used for prevention – public health!! Before needing treatment

Exome testing into routine clinical care, exposome testing, maybe not even primary care, obgyn preconception time, before in utero exposures happen – start education, put people in program, based on physician encounters need causal data and effective interventions (need to do these to understand what works and doesn't) to get wide adoption

We will learn a lot looking at pediatric prevention and intervention programs
With existing knowledge and applied knowledge for intervention, we are still missing how to think about and do prevention esp in high-risk populations, and public health messaging – invest more in exposome for public health prevention … engage other Ics not just NIEHS, pilot

Regulation of products (Amy) – safer products for Washington act to look at high priority chemicals regulations, driving demand for safer products within the state (Washington) – upstream thinking and approach – how do we prioritize exposures and what sort of products should we look at for prevention?

Reduction in exposomics measures based on interventions? Exposome based metrics as outcomes in interventions..?? how to do this (Gwen). Not documenting exposure but what to do with this information? Action, solutions, regulations, … how we use exposome methodologies in interventions and implementation
Exposomics can be tool for intervention/prevention – we want to understand where chemicals are coming from (home vs work, others)… draw interventions

Providing feedback to people is already an intervention – change behaviors? Top-down approach can be informative but reporting back persistent vs transient dose for example, have to think about what people can do with that information? Limitations here.. mixture impacts still concerning with persistent chemicals..

What wouldn’t we tell someone about persistent chemicals in body burden? How to enact change? Participate in citizen science.. vs purchase a testing service.. (commercial service setting) – what is actionable

How we materialize exposome into interventions? Focus on exposures, metabolites or intermediates, susceptibility measures and effects

What do we report and how do we report it? Determining what is there and tissue effects of exposure – don’t know enough – need better understanding, biological intermediates or markers of heart disease.. cancer etc.. early detection/risk

Lead and BLL in children marker of exposure in last 3 months (kids), vs in bones in workers in smelter company .. to reduce levels, exposome metrics will be different based on population and question – exposure, susceptibility, effect? Need to consider these when reporting back.. still need a lot to understand what these exposome measures mean?

Individual risk models: multilevel, multilife course everything.. all at once.. how do you package that into an intervention? Individual risk model… how do we get to a point where a child has several things / risk factors/ exposures customized to that person based on the individual differences and life course… shouldn't focus on just one thing, or intervene on one thing, holistically intervene on something with several
We know enough about some things, like lead in children, can make sweeping statements on, but so many areas where harder to know and so particular about context and susceptibility/conditions… "known bads" but more the middle ground where there's a lot uncertainty and variation in population… EH studies eg greenness on health, still a lot of conflicting evidence population wide, washed out or averaged out effects without nuance about subgroups or individuals..

Eg, patients who are at high risk of covid, health messages were focused on comorbidities, age etc.. but lifetime env/chemical exposures not in there.. what health care/protection/prevention needed? How do we build exposome into these risk models? Genetic risk models, disease specific, personalized medicine, all missing env… dpes measure of risk change when add exposure to mix? Clinical world starting to factor some of this in but still early (eg pediatric asthma further along with env angle) – risk scale developed for that disease and how is exposure incorporated? Multiple risks/env factors, how will help improve clinical manage

Multilevel modeling – how to integrate multiple data tupes into one model, not happening regularly at scale or very well yet… if we get there, becomes a tuning (eg one thing goes up and or decrease the next outcome changes that much..) equity questions, eg, move to a place with better air pollution vs 10 more steps of PA today? How do we get to a point where action is equitable? There's only so much individuals can do, has to go back to policy …

How do we get to knowledge generation..

Link social determinants to mechanism.. better understanding… need transcdisciplinary groups to put people together (epi, mechanistic, etc.)

How often do we collect this data to make risk model more meaningful? Longitudinal data key , we know temporal dimensions of disease process key esp for early phases.. exposome can help boost this knowledge.. sampling points.. track ecologic time interval for exposure and outcome.. resolution / recovery phase..

Naturopaths and functional medicine thinking more in this vein/realm but not traditional medicine.. All of Us data? We need to collect all this data?

The individual risk model could include current knowledge and willingness to act

Data input/output – groups or categories of information based on buckets of information or things we know about or will make a dent… 'communication buckets' informatics wise we have the capability to communicate this effectively now.. (Marta)

How do we report and organize this data? Aggregate exposure pathways framework (Amy Leang) – a way to prioritize or rank risks? Risk assessment concept..

Report back can also be a stepwise approach – still a big challenge , as tech becomes more mature can go back to the data and pool it/harmonize it to fully understand.. don't have harmonized methods yet to interpret and measure the data.. can we draw conclusions from various studies?

What do we mean by exposome? Everything? How to report environment? What are we reporting back? Volatile chemicals at home and at work, we know we cannot capture all of them…

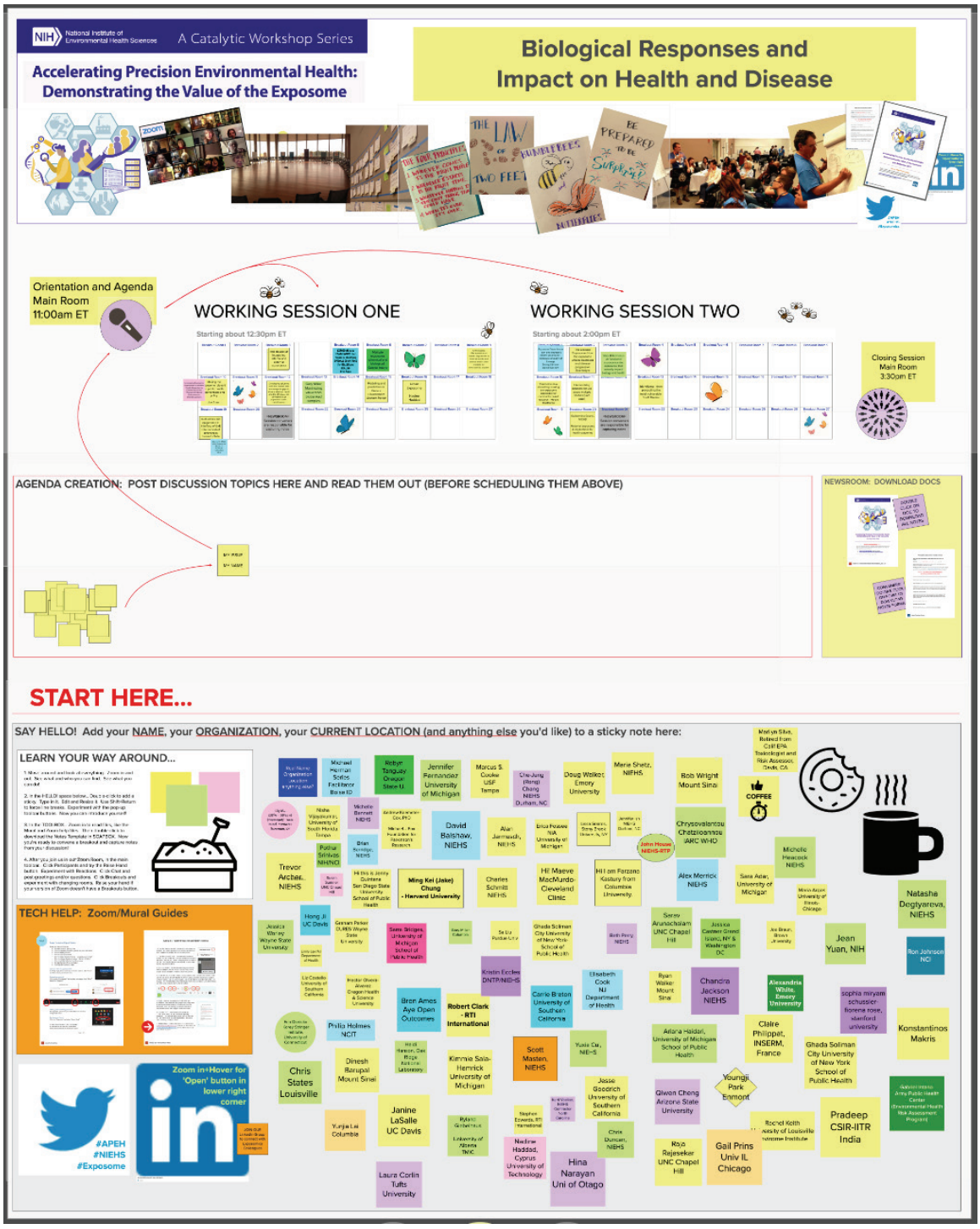
Harm question important…

Can we leverage novelty of exposome/tools to convince people to change behaviors to their benefit? Can we use exposome to improve evaluation of testing/effectiveness behavioral or other specific environmental interventions?

Prioritize exposome based on the question? How much data is enough? How do we rank/prioritize? Timely manner of generating key dataset for everyone to benefit from with enough temporal/spatial granularity with specific health outcome(s) in mind, can be effective. Eg, prediabetes population , still reversible, causal data/intervention data plus mechanistic data.. to inform future care..

We need to prioritize… lots of archived data (comptox, pubchem, integrated chemical env data) need to start with some prioritization – low doses and coexposure can change response , or NOT

VIRTUAL WORKSHOP #2: Biological Responses and Impact on Health and Disease



A high-level view of our second workshop space, including our agenda and the space we used to create it. Much of the detail won't scale to be easily readable, but it gives some sense of the messy, organic, creative nature of our working space and how it evolved after the first workshop.

ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes

CONVENER(S): Robert Wright

PARTICIPANTS: Doug Ruden, Brian Berridge, Hong Sheng Wang, Erin Dierckx, Chris States, Robert Clark, Kristin Eccles, Carrie Breton, Jennifer Ish, Ryan Walker, Hong Shen, Nadine Haddad, Dinesh Barupal, Konstantino Makris, Muhamed Rahman, Raja Rajasekar, Youngji Park, and five to ten others.

SUMMARY OF DISCUSSION:

Concept is creating a searchable index capable of multiple maps that can co-locate 1) Traditionallly mapped expsoures- Air pollution/Climate/Green space/build environment etc) 2) Exposure Biomarkers (blood lead, urine phthalates, etc) 3) Biological Markers of Effect (epigenetics/transcripton etc), and 4) phenotypes (myocardial infarction, Parkinson's Disease, Cancers, etc.

Maps allow us to better understand exposure sources and distribution and if co-located with molecular biomarkers and phenotypes may provide clues on disease caused by exposome exposures. Maps will uncover environmental justice issues- toxic exposures likely correlate with redlining for example. They will help us to understand what the covariance structure of all these measures is by location, and over time.

Data will include

- Person Age (to address life stage)
- Calendar year (to address change in environment over time)
- Housing data (e.g. HUD, Zillow mining)
- Social Exposome (income, education) from Census and other databases
- Redlining data

Sources of data

- EPA, USGS, USDA, NASA, NOAA, HUD, State health departments
- What is a minimal spatial density? 1 km^2 Will/can it be less or more for other variables?
- What is the temporal density (monthly? Annually?)
- How do we get past data on biomarkers? Can existing cohort plot biomarkers? NHANES (Can geospatial information be obtained?)
- Phenotypes?(EMR may help)

Co-Issues:

- What role can experimental toxicology play in exposomics?- need partnerships with epidemiology/experimental biology to guide experiments.
- How do we define questions that can be answered is a major goal- 1 step is "what is there" (Exposure science) 2nd step is what do they do? (epi/toxicology)
- **Input from Workshop Participants- quoted when possible.**

- Incorporate Census track/group block into geospatial maps of exposomics, internal exposome and biological effect(e.g epigenome or disease)
- Temporal dimension/dynamics of exposures needs to be addressed, maps need to be time varying- chronotoxicity/chronobiological effects- factor in life stage (critical windows)
- Additional maps- social determinants of health- NC health community data toolkit, medical records data, hyperlocal mapping of social stressors(income, education, among others
- Redlining- historical maps to overlay with pollution maps;
- Access to app data- Zillow- housing quality/cost (Housing as an important variable for health and exposome)- HUD map on deteriorating paint
- Biobanks as a means of mapping biomarker data
- Maps should be interactive similar to vulnerability risk score maps- filter to age, location, exposure,
    - How would a exposomic map visually express results of interest to a user
    - Rather than re-invent- Covid-19 map as example integrate different streams of information.
- Rural data on pesticide use (inspection? Farms get inspections- data are publicly available from the State databases
    - Animal data- wild animal evaluations (infections- encephalitis as an example)These data are geospatial in nature.
- Can we identify “lay of the land” air, water, soil (EPA, USGS, HUD, NOAA, USDA, (food), Forest service other?, state DEQ) need for common ontology/language
- Taste sensitivity- phenotype related to nutrition maps are being created- Flint is an example, helpful for CBPR
- Heat vulnerability indices, urban vs suburban vs rural, housing, exposure over time and **adaptation** – temporal some are dependent on each other.(Behavioral/social adaptations). Adaptation reflects feedback loops.
- 1000 foot view of putting all these data together. Systems dynamics analysis- demonstrate linkages across time/space; feedback loops are modeled. Inputs lead to change over time in oral/social adaptations
- EPA study with Duke (CathGen) looks at social determinants, genomics, air pollution, green space etc.
    - How do we bring together cohorts for a mapping project?
    - Addresss movement over time as well.
- How to build trust with research participants-
- What ELSI projects are needed to address ethical issues on exposomics?
- https://healthycommunitiesnc.org/community-data/ or https://www.hcinnovationgroup.com/population-health-management/social-determinants-of-health/news/21274497/healthy-communities-data-tool-provides-insights-on-sdoh-in-nc
- https://covid19pvi.niehs.nih.gov/
- Social Environment Core Data for interoperability, including SdoH: https://www.healthit.gov/isa/united-states-core-data-interoperability-uscdi#uscdi-v3
- Examples of heat vulnerability mapping and indices: https://www.heat.gov/pages/tools-information https://ehp.niehs.nih.gov/doi/full/10.1289/EHP4030
- mapping polygenic taste scores in diverse communities through assessing taste sensitivity – bitter, sweet, sour etc. https://www.medicalnewstoday.com/articles/your-

taste-genes-might-determine-what-you-like-to-eat-and-your-health#Taste-related-genes-and-cardiometabolic-health

- How does Life Stage play into maps?
- What maps are available now?
    - Air pollution, enviornemtnal data, disaster (flooding),
- What data are available but not mapped yet?
    - Biological markers (epigenome, transcriptome etc)
    - Indoor Air- how to create maps of indoor air for predictive and research purposes- relate symptoms to exposure
- How do we map “omic” data?
- Data visualization Challenges- new tools needed
- How do we factor in Time Varying maps?
- How do we start?
- What can map/atlas be used for?

OPPORTUNITIES FOR ACTION:

- RFAs on mapping of biomarkers
- Policies on collecting address and methods to map that toggle geocoordinates.
- ELSI grants on role of place and health and ethical issues related to mapping

IMMEDIATE NEXT STEPS:

- Investigative Groups dedicated to different types of mapping need to meet. Cohorts with biomarker data will need to link to address and provide data to mappers. Phenotype and biomarker data. Depositories (HHEAR, Metabolomics Workbench etc) need to be involved.

- New tools of data visualization beeded

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Very complicated idea but if successful will allow for estimating/imputing different aspects of the exposome when measures don’t exist. Will be a unique and key tool for understanding geospatial variability of both exposure and effect.

ISSUE #18: EXPOSOME as a FRAMEWORK that focuses on identifying OPTIMAL CONDITIONS for HEALTH and HEALING

CONVENER(S): Bren Ames

PARTICIPANTS: Sophia Miryam Schüssler-Fiorenza Rose, Claudia Miller, Yuxia Cui. Taka Williams & Phillip Holmes also stopped in.

SUMMARY OF DISCUSSION:

We have the opportunity to understand how low level exposures are resulting in chronic adverse outcomes for 20% of the population, and to harness that understanding to guide development of conditions conducive for health for all.

Our discussions are reflected in the sections below.

OPPORTUNITIES FOR ACTION:

1. To advance understanding of *multisystem symptoms and intolerances for chemicals, foods and drugs* -- and beneficial interventions -- **NIEHS could** share with researchers, practitioners and the general public the internationally validated three-question BREESI screening tool and the 50-item validated QEESI questionnaire:

QEESI -- Quick Environmental Exposure and Sensitivity Inventory
< http://qeesi.org/>

BREESI -- The Brief Environmental Exposure and Sensitivity Inventory
Three questions for identifying chemically intolerant individuals in clinical and epidemiological populations:
< https://pubmed.ncbi.nlm.nih.gov/32936802/>

Reiterating from the July 22, 2022 Workshop, ISSUE #13 Summary:

1) Help NIEHS, EPA, NIOSH, FDA and other research groups, epidemiologists, toxicologists, and physicians understand, administer, and document health changes resulting from large-scale exposures to oil spills, fracking, fires, burn pits, implanted devices (FDA), taking advantage of the published and validated BREESi, QEESI, pre/post symptom severity scales, and exposure histories.

2. Host a **virtual meeting** with Part 1/Day 1 focused on the intersection of the Cell Danger Response (CDR) and TILT theories, with a Part 2/Day 2 focused on the Healing Cycle and Environmental Medical Units:

Reiterating from the July 22, 2022 Workshop, ISSUE #13 Summary:

2) Host a **virtual meeting** focused on TILT, bringing together basic mast cell researchers, toxicologists, physicians, public health representatives and patients to discuss the two-step mechanism for Toxicant-induced Loss of Tolerance: a) *initiation* via sensitization of mast cells and b) subsequent *triggering* of

cascades of mediators and inflammation by everyday chemicals, foods/additives, and drugs. The purpose of this gathering would be to review current data, propose approaches for research, and explore potential interventions, prevention, and treatment. The output would be a series of recommendations to address research, public health, and medical needs, as well as housing, interventions, possible treatments and needed accommodations.

TRANSLATION TO PRACTICE: NIEHS could provide guidance and support towards offering indoor air, food and water quality conditions conducive for health and healing for:

- Healthcare Providers and Researchers
    - Environmental Medical Units for diagnosing and treating environmental injuries/illnesses
- Childcare and Eldercare facilities (so that these facilities do not contribute to the development/exacerbation of chronic conditions including, yet not limited to autism, ADHD, asthma, Alzheimers…)
- General public
- Recognize and address structural issues/barriers that make healthy air, food and water physically and economically inaccessible to individuals.
- Policy positions and practices that dismantle these barriers

MEASURE: Biological Responses (giving priority to filling gaps, and replacing inappropriate indicators with increasingly meaningful measurements).

- Inflammation
- Mast cell activation, sensitization
- Compartmentalization of CO / Oxygen availability
- Heme Oxygenase (HO-1)
- Cell Danger Response (mitochondria)

IMMEDIATE NEXT STEPS:

Identify, Contact, and Propose **SPEAKERS for the virtual meeting** (Action Opportunity #2)

GATHER (Available/Existing) TIMELINES:
Assemble and juxtapose evolution timelines for:

- mast cells, mast cell theory
- cell danger response theory
- toxicants
    - combustion products and practices
    - organophosphate (OP) compound development and use
    - agricultural
    - consumer
- biological toxins
    - Mycotoxins
    - Cyanotoxins
    - Bacterial origin…
- Impairment of membrane/compartment integrity
- built environment conditions
- chronic health conditions
- Status of ‘omics knowledge about conditions conducive to healthy biological function

USE CASES:

Explore how the following Use Cases could guide expansion of the AOP and Exposome frameworks to include conditions conducive for health and healing:

- **Broaden the Adverse Outcome Pathways (AOP) framework to 'Outcome Pathways'** -- to be more inclusive of the SPECTRUM of outcomes: from Adverse Outcomes to << no identified impact >> to Beneficial Outcomes.

- **Robert K. Naviaux's cell danger response (CDR) theory** (that he presented clearly as far back as 2013). Beginning with Naviaux's 2019 journal article "Metabolic features and regulation of **the healing cycle**—A new model for chronic disease pathogenesis and treatment". Open access: <https://www.researchgate.net/.../326946742_Metabolic..> <https://naviauxlab.ucsd.edu/publications/>

- "**The Healing-Centered Framework**" by Chicago Beyond <https://chicagobeyond.org/healing-centered-framework/>
  NOTE: This example intersects with the '**Urban Exposome**' topic posed by Nadine Haddad (Room 16)

Trauma-engaged
Not only understanding and being aware of trauma, but proactively promoting collective healing as a whole school system while responsively meeting the individual wellness needs of each student.

Culturally-responsive
Centering equity in healing by promoting a liberatory consciousness, recognizing a broad understanding of trauma (including historic and generational trauma), and affirming all cultures in the healing process.

The Healing-Centered Project is an opportunity to build on the work of OSEL to provide school communities with **restorative and trauma-sensitive supports.** It is an opportunity to bring together the many offices that work to ensure the whole school, whole community, and whole child are our focus.

Chicago Public Schools
OSEL: Office of Social and Emotional Learning
773-553-1830 | healingcentered@cps.edu

- Explore how the 'Level of Detail' concept might support broadening of the AOP and Exposome framework views, while not getting bogged down in detailed data (while seeking the big picture).

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Time
Attention
Funding

…Too obvious?

Need to build exposome framework that can integrate:

- Diverse voices (e.g., today!)
- Academic knowledge gained from various specialties (silos)
- Wisdom gained from experience
    - Individuals
    - Populations
    - Practitioners
- filling gaps between specialties
- overcoming (rather than perpetuating) biases and limited vision and vocabulary
- ongoing validation of the foundations of various assumptions and 'settled science'
- …and iterate toward a more complete vision of conditions conducive to physical health, general wellbeing, biodiverse life.

REFERENCES

Project TENDR makes a strong case for creating conditions conducive to health. Project TENDR is a unique collaboration of leading scientists, health professionals and children's and environmental advocates, issued a Policy Resolution in 2020, to provide clear, science-based proposals for reducing toxic chemical exposures, especially to women of child-bearing age and children, that can harm brain development and contribute to learning, developmental and behavioral disorders.

Project TENDR recommendations are based on substantial scientific evidence linking toxic environmental chemicals to neurodevelopmental disorders such as autism spectrum disorder, attention deficits, hyperactivity, intellectual disability and learning disorders.

2020 Project TENDR Policy Resolution
Appendix A: Published Project TENDR Policy Recommendations
2016 Project TENDR Consensus Statement

Examples of creating conditions conducive for health and healing:

Environmental Medical Units (Clinics, Hospitals) <https://annmccampbellmd.com/wp-content/uploads/2020/07/Chemical_Exposures_Low_Levels_and_High_Stakes_2nd_Ed-min.pdf>

Clean Air Oasis https://tiltresearch.org/2021/03/26/7-steps-to-creating-a-clean-air-oasis/

ISSUE #19: Multiple Exposures

CONVENER(S): Gabriel Intano

PARTICIPANTS: Ryland Giebelhaus, Hong-Sheng Wang, Irva Hertz-Picciotto, Rima Habre, Taka Williams, Pradeep Sharma, Elisabeth Cook

SUMMARY OF DISCUSSION:

General discussion focused on problem of multiple exposure dose-response. Impacts of social inputs must be considered to help identify exposure scenarios. There are lots of bits and pieces of information available, but picking out what is important is difficult unless you have a very specific question to answer.

OPPORTUNITIES FOR ACTION:

Collaborative and information-sharing opportunities are important.

IMMEDIATE NEXT STEPS:

Establish communication between Army Public Health Center environmental risk assessors and researchers with knowledge, information, and data to help establish collaborations.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Characterizing mixtures.
What chemicals are important? Many unknown biological/physiological activities.
What physiological activities overlap?

ISSUE #20: Extrapolating human exposures to internal doses/exposures and then to animal and in vitro models for mechanistic studies

CONVENER(S): Chris States

PARTICIPANTS:

- Susan Sumner UNC Chapel Hill, internal exposome, link to perturbations in host metabolism, PB/PK modeling to extrapolate back to human systems
- Hong Ji UC Davis, epigenetics, epigenomics, human transitioning to primate models.
- Robyn Tanguay OSHU, ze
- David Balshaw
- Jesse Goodrich pdf, USC, interest in human cohorts, translational to human or cell models
- Beverly Duncan – SRO,
- Marilyn Silva, retired from dept pesticide regulation CA EPA, computational toxicology
- Qiwan Cheng, postdoc Ariz State U, microbiome & environmental exposures impact of exposures
- Marcus S. Cooke, oxid stress USF metabolomics
- Guillermina Girardi, NIH NICHD program officer social environment determinants of health, mouse / in vitro models
- Michelle Heacock – NIEHS, superfund res. Program
- Jolyn Fernandes
- Pradeep Sharma, CSIR, mechanisms, risk assessment, endocrine disruptors
- Tim Fennel RTI, RTP, understanding animal models, using Hb adducts as tool for estimating internal dose, human exposures
- Gabriel Intano, microbiologist, risk assessment, Army env hlthctre, multiple exposures, burn pits
- Laura Corlin
- Ryland Giebelhaus PhD student UA Edmonton, exposomics, cannabis in pregancy

SUMMARY OF DISCUSSION:

- We will be identifying human exposures that we have not identified before with untargeted exposome analyses.
- Understanding impact of microbiome and impact on microbiome is important.
- Database improvement to better support predictive software – biomarker development to infer prior exposure is needed.
- Timing of exposures – acute vs chronic; continuous vs intermittent – also important
- Natural rhythms (e.g. diurnal variation) in endogenous levels of metabolites/hormones.

OPPORTUNITIES FOR ACTION:

- NECRI – non-targeted analyses of drinking water to identify new chemicals that we don’t have data on, to introduce to models, then back to human data, Exposome as

discovery. Surveillance assessments. Need to have dosimetry calculations. Impact of microbiome on ingested chemicals.

- Acute vs chronic exposures contributions to disease models.
- Risk assessment lacks mechanistic information on impact/ resistance. Toxcast info is useful
- Microbiome can detoxify some chemicals, can contribute to excretion by direct binding
- Model organisms for G x E n- characterizing limitations & best model
- Models for impact of psycho-social stress / impact of exposure on behavior
- Understanding influence of chemicals and interactions on microbiome balance
- Developmental stage influence,
- Biological toxins
- Useful tool: integrated chemical environment tool at NTP (https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-ice/ice.html#:~:text=The%20Integrated%20Chemical%20Environment%20(ICE,the%20safety%20assessment%20of%20chemicals)
- DOD blood bank repository is potential source of biological materials
- Translation of real world mixture exposures to model sytems

IMMEDIATE NEXT STEPS:

- Cataloguing of metabolites by various organisms – need to build out the data
- Better understanding of species specificity of PK/PD for key chemicals
- Communication in data sharing

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Reliability of prediction tools, challenges and vagueries of ADME
- Natural variation: Diurnal rhythms – incorporating/determining natural flux
- Identifying the timing of exposure that is important – total dose/time averaging vs frequency
- Availability of human samples to correlate with animal studies
- Integration of metabolomic profiling into PB/PK models
- Databases of endogenous metabolites that infer prior exposures (biomarkers)
- Access to high exposure groups
- Characterizing ever-changing real world mixtures
- Cost of defined diets for animal studies (contamination as well)

ISSUE #21: Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments

CONVENER(S): Joe Braun & Chandra Jackson

PARTICIPANTS: Jenny Quintaina, Lily Wu, Jessica Castner, Daisy Bruit, Sara Adar, Claire Philippat, Sarra Bridges, Chandra, Sarra Bridges, Nisha, Vijayakumar, Rachel Keith, Sharon Ross, Andrew Geller, Andrew Koemeter-Cox, Antonia Calafat, Joe Shearer, Liz Costello, Rob McConnell, Maeve MacMurdo, Nadine Haddad, Jennifer Ish

SUMMARY OF DISCUSSION:

- How do we make exposome relevant for changing policy?
- Can interventions have impact on multiple exposures (even simple interventions)
- Health equity as a cross-cutting theme
- Do investigators in the exposome field represent the demographics of our scientific field and populations we work with?
- Regulation of chemicals represent a snapshot in our exposure history and aggregate exposures.
    - Can we use chemical groups or other exposome characteristic to better inform policy and regulation?
- Documenting exposure can shine a light on disparities
    - Can we see changes on finer time scales?
    - Can we better quantify the totality of exposure disparities?
- Can you use exposome data to show that they are exposed historically?
    - Could be used for regulation and litigation.
- How do other 'layers' of exposome impact each other? (e.g., micronutrient and air mixtures)
- Are there sentinels for lifestyle, chemicals, etc. so that they can be regulated and monitored?
- How do we make sure that interventions don't enhance disparities where only rich/white/educated people can take advantage of them?
- Need for quantifying past exposures for diseases with long latency (e.g., Parkinson's disease).
- Can we have more local-level impacts to reduce exposure. E.g., air filters or local-level regulations.
- Can we put pressure on industries to reduce exposure through reductions in production or phase outs (e.g., BPA)?
- What are levels of risk we are willing to take when we phase out one chemical and replace it?
    - Are there some uses that "essential" and "non-essential"? Who decides this?
    - There is a need to document changes in exposome.
- Quantify economic costs of these changes.
- Interaction between chemical and biological exposures
    - E.g., air pollution and COVID
    - Air pollution and microbial
- There is a need to communicate findings

    - More sharing and open source
- See if changes in exposure are also impacting health
    - Need strong interventions, strong exposure-outcome effects, sensitive outcomes, large sample sizes, or combination of them
- There is a need to break down silos between groups

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Satellite data and Google Street View before and after interventions
- Biobanks?
- Develop exposure signatures (e.g., epigenetic signatures of smoking)
    - Highly exposed populations with before and after biospecimens
        - E.g., burn pit exposures
        - Wildfires
- Identify biobanks with interventional components
    - DoD
    - Cancer studies
- Use exposome to do real time monitoring of consumer products or food, diet, etc.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Getting larger sample volumes or easier access
- The need for large sample sizes to identify health effects of interventions.
- Silos between exposure disciplines (smoking vs. EDCs vs. social environment)

Links:

NCI-DoD-VA initiative part of Cancer Moonshot
https://proteomics.cancer.gov/programs/apollo-network

NCI biorepositories https://prevention.cancer.gov/resources/biorepositories

NIH biobanks compiled here: https://dpcpsi.nih.gov/onr/onr-nutrition-science-data-and-biospecimen-resources-portal#repositories

https://www.theguardian.com/us-news/2022/apr/12/harmful-chemicals-toys-discount-stores-us

ISSUE #22: Creative solutions for scaling exposomic research to the population scale

CONVENER(S): Heidi Hanson

PARTICIPANTS: Maria Shatz (NIEHS, Office of Data Science), Stephanie Holmgren (Office of Data Science, NIEHS)

SUMMARY OF DISCUSSION:

Current barriers that exist for studying the exposome at the population level:

- Harmonization and curation of data across medical institutions and individual researchers biobanks
  - EHR, omic, and biospecimens
  - How do we come up with approaches to standardize the data at scale?
  - Metadata
  - Storage size – if we start centralizing all of the data, will we run into data storage issues?
- Is it possible to take a distributed learning approach to the problem?
  - Benefits: We would be able to distribute storage and compute across centers, identifiable information would not need to be passed between researchers (only de-identified model parameters).
  - Road blocks:
    - Data use and other agreements between collaborating institutions. Assuring ethical use of data.
      - Example of road block: Linking PEGS biospecimens to Duke and UNC EHRs. Coordination data use agreements and consents took over 4 years and the process is still not complete. Ispy2B is a tool to aggregate metadata and to build virtual cohorts.
      - Potential solution: Creating a consortium for project specific approvals with common consents and data use agreements to enable data reuse across the consortium members and authorized investigators. The institutions buy into to the data share and have the ability to buy-in to or opt-out of a research run.
    - Patient consent: What type of patient consent is necessary for population level research?
      - Potential Solution: Is it possible to get waivers of consent when the risk is deemed low and it is a limited dataset?
      - Potential Solution: Is it possible to create masked linkages that allow the analytic dataset to be de-identified?
        - Problem: What would the man hours be for this type of arrangement

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:
Continue discussion in the Aug 26th meeting with more data oriented folks in the room.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:
See above – further discussion with more contributors.

ISSUE #23: Maximizing value from biobanked samples

CONVENER(S): Gary Miller-Columbia University

PARTICIPANTS: Susan Pinney, Jake Chung, Alison Motsinger-Reif, Gada Soliman, Chrysovalantou Chatziioannou, Alan Jarmusch, Brian Berridge, Porthur Srinavas, Rima Habre, Jean Yuan, Elisabeth Cook, Garret Bland, Laura Corlin, Antonia Calafat

SUMMARY OF DISCUSSION:

There was broad agreement that there is great value in the various biobanks in the world

Not all biobanks are equal. It is essential to ascertain the procedures for collection and storage and set standards for biobanks thought to be amenable to exposomics.

Most of the discussion was on mass spectrometry-based analysis. There is good evidence for stability of hundreds to thousands of molecules (data from 20-50 year old samples).

We discussed disease agnostic biobanks like All of Us and UK Biobank. These may be better for large-scale studies

We also discussed disease-based biobanks. These could be helpful in advancing exposome research, but with the disease focus the findings may not be as broadly applicable. There is room for both, but the disease agnostic biobanks may ultimately be more powerful (and will have incident cases of many disease in the not-too-distant future.

We must be realistic about our ability to scale and the needed capacity. We should look to other related efforts to gauge feasibility (whole genome sequencing, epigenetics, proteomics-in genetics they had to overcome many similar issues). Group did agree that scale was important. The statistical value of 100k participants is very attractive.

Harmonization among labs and platforms should be of high priority. Without it the field will lack credibility.

All agree that there would be value of repeated sampling in biobank populations as this helps address causal relationships and capture the changing environment

Enrollment criteria are critical.

We need to emphasize the need to develop actionable information. How can biobank findings influence care?

While we discussed untargeted and some semi-targeted (biocrates-like) approaches, they are mid-to-long term solutions.

In short term, chemical measurement in biobanks will still rely on targeted measurement. One thing I encountered with Chirag when working with biobanks is that it is often not possible to do comparison because biobanks do not coordinate to measure the same set of chemicals. If All of Us is going to do chemical measurement, it will be nice to take reference from NHANES to maximize the impacts of the investment.

Team liked the idea of semi-targeted measurement kit because it could make measurement easier and more standardized (just as gene chip), but technology development is needed to min. sample use. Current, many environmental chemicals require enrichment before LCMS measurement. If there is a single universal enrichment step for all the selected measurement in the kit, we are one step closer to make the exposome concept actionable.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Need to develop staging. We do not need to start with perfection. If current technologies can provide data on 1000 compounds it would be a good start even if the goal is a much larger collection of targeted compounds and untargeted features.

Conduct a landscape assessment of biobanks that may be suitable for exposomic analysis (agnostic and disease-specific biobanks)

Develop harmonization protocols so that merging of data across biobanks may be possible.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Working with biobanks that don’t have high QC standards could backfire. Must prioritize those that follow best practices.

Pilot studies that demonstrate reliable measures in biobank samples are needed.

ISSUE #24: Modeling and Prediction in Gene x Environment

CONVENER(S): Graham Parker

PARTICIPANTS: Daisy Fry Brumit

SUMMARY OF DISCUSSION:

Understanding the difference between biostatistics and bioinformatics

Making large data sets interpretable

Recognizing that even though large omic data sets might share features that appear tractable and analyzable may not yield an analysis that makes sense.

This is even more difficult when trying to analyze the interaction between an omic data set and, for example, a likert scale of a behavioural measure.

The importance of Bayesian Inference

Knowing that Neural Network approaches differ and the importance of using the most appropriate model

Retention time prediction increases the identification rate in liquid chromatography and subsequently leads to an improved biological interpretation of metabolomics data.

Building consensus models

Understanding the power of regression

OPPORTUNITIES FOR ACTION:

Shared educational opportunities to better understand the biostatistical underpinning of a design.

IMMEDIATE NEXT STEPS:

Symposia to advance understanding of modeling disparate outcome measures for analysis and prediction generation

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Limited opportunities to network with others with the skill sets necessary to advance resolution of these issues. Today was a happy start!

ISSUE #25: Exposure Epigenetics, multi-omics at GxE interface, inter-individual variations

CONVENER(S): Janine LaSalle and Hina Narayan

PARTICIPANTS: Gail Prins, Kimmie Sala-Hamrick, Qiwen Cheng, Alex Merrick, Stephen Edwards, Lissa Soares, Jeffery Kopp, Mersh, Yuxia Cui, Garret Bland, Ariana haidari, Robert Clark, Jolyn Fernandes, Dinesh Barupol, Michelle Bennett, Irva Hertz-Piccioto

SUMMARY OF DISCUSSION:

- Single CpG/ genes vs clusters/ DMRs vs genome-wide sequencing
- Challenge with array-many parts of genome missing
- Corroboration with multi-omics data, for instance comparison of a study where an exposure was directly studied for “signature” to a study where disease state was studied
- Mechanistic study: cause-effect, best done by comparison to animal models of exposure
- Exploring causality through epigenetically edited animal models
- Effect of mixtures over individual chemicals as models for human exposures
- Relevance of epigenetic signatures of exposure: identification and development
- Tissue specificity of changes, potential use of surrogate tissues (such as placenta and cord for in utero), saliva for larger studies
- Issues with little or none statistical power in epigenomic studies that only consider individual CpG sites, differentially methylated regions (DMR) have better power
- Modules of multiple genes using systems approaches such as WGCNA can improve multi-variable studies and power to detect effects
- Epigenetic biomarkers of exposure
- We discussed the respective benefits of one assay over a large number of samples versus smaller but deeper cohorts (better characterized across tissues, multi-omes, exposures)
- Use of animal models, including natural experiments for exposures such as wildfire smoke exposure in outdoor macaques, maybe domestic animals
- Inter-individual variations and how systems approaches can help understand why not everyone responds the same way to the same exposure

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Funding opportunities for epigenomics and multi-omics to get at inter-individual differences in exposures
- Engaging citizens in science for exposures important to them, remote collection of samples from humans and animals
- Data handling, improved visualization; recruiting data scientists, AI/Machine Learning, and data visualization specialists
- Employ natural exposures in domestic and wild animals

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Multi-discipline
- Training needs
- Funding for multi-omics studies in existing and new cohorts
- Translational and applicability of data
- Conducting research, dearth of samples in pandemic

ISSUE #26: Exposure co-variance matrix and Linkage Disequilibrium

CONVENER(S): David Balshaw, NIEHS

PARTICIPANTS:
Qiwen Cheng, Arizona State University, Michelle Heacock, NIEHS, Irva Hertz-Picciotto, UC Davis, Antonia Calafat, CDC/NCEH/DLS, Tim Fennel, RTI, Dinesh Barupal, ISMMS, Susan Pinney, UC, Konstantinos Markis, Cyprus, Rima Habre, USC, Nisha Vijayakumar, Savaranan Arunauchalam, Jennifer Ish, Jean Yuan, Doug Ruden, Mersh, Sophia Miryam Schussler-Fiorenza Rose

SUMMARY OF DISCUSSION:

- Don't have to measure everything: can measure a subset of the most informative analytes. We do well with acute exposures (short half life), less well on historical.
    - Measuring something is better than nothing
    - Whether that can inform on past exposure is doubtful
- Data from NHANES is available and can inform
    - But we know there are circumstances where that will work (IHP paper on dioxin-like PCBs; can't rely on just 153)
- Need to point to biological effects and opportunities to intervene
    - Regulatory framework will require the specificity of exactly what
- Emphasis here is cross-class correlations rather than within class.
- Directly leads to mixtures
    - Not only joint effects, but also correlation in time (measure today, predict potential for a future time)
    - Could also think about a geospatial analogy
- Tendency to fall back on the NAS biomarker continuum
    - Potential for biological markers as surrogates for the exposure covariates; complicating factor of differential metabolism and differential biomarkers
- Don't actually measure exposures, we measure concentrations, may have been a much higher concentration earlier
    - NHANES – designed to be representative, if you look at data individually (phenols), just going from one set of samples to another and can identify patterns of exposure that reflect product use behaviors/lifestyle
        - Profiles can identify something that is different between populations and individuals
    - Susan has seen the same thing in their data (clean living versus multi-product use)
- Rephrase Linkage Disequilibrium to Dynamic Equilibrium, intrinsic to the exposome, better characterized by spatio-temporal dimensions.
    - Need new study designes to better characterize markers of exposure and effect in a spatio-temporal framework
    - linkage disequilibrium is very similar to non-stationarity in space (in spatial covariance)
- We've fpcused on the toxicants, need to remember the positive exposures (nutrients) as well. Can identify easily and report back
    - Sometime toxicant exposures (pesticides and fruit juices, arsenic with rice) will track with those

    - in terms of the good things, does the concept of ratios also apply? example balance of potassium relative to magnesium etc..? meaning also looking in multivariate sense
        - people are already used to thinking in that we (cholesterol)
- Is the goal for early detection or finding the extremes or associations

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Perhaps rather than focusing on correlation of exposure focus on correlation of biological effect (Effects-based monitoring)
    - Depends on the nature of the study whether you want to correlate exposures or effects.
- For short half-life chemicals there is some intra-person correlation but not enough to support a correlation matrix. There is correlation by biological effect (body composition) for persistent chemicals not for non-persistent
- To develop a predictor set would need a very large repository, multiple exposures on every sample, longitudinal (DOD repository may be better.
- Opportunity to prospectively map product use (scan barcodes, feed through CPDat, and compare exposure profiles)
    - Could map to household, family, neighborhood, etc.
- Exposure database tied to multi-generational families
- Clustering analysis; identify the 'norm' then the ways that others vary away from that
    - NHANES is not a true normal but it is a good starting place, recognizing limitations in time and geography.
        - We need to remember that it is not 'normal' for anyone to have PFAS in serum, but the NHANES serum concentration are very good in representing background levels and changes over time.
        - Compare and contrast to the fact that there are background levels of some things (metals) that we all have. Reference (and reference ranges) would be preferable
- Could it get us to a dosimeter for body burden and cumulative exposure
- Could help in defining recommended ranges or warning signs (early detection) either in positive or negative risk. Multiple analytes inform the message and interpretation of hazard.
    - Analogy to a car code reader/sensor systems check
    - Statistical Process Control (indicator of a change in the system, could be good or bad)
    - For clinical laboratory data, they do look for changes I variance or shifts over time. Called the 30 day moving average..

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Differences in individual metabolism, renal/hepatic/microbiome function, and how that impacts excretion of metabolites.
- Single measure of short half life is better than nothing but insufficient
    - Animal models can help tease out the patterns that reflect the exposure, map the vectors of variation
- Finding the population that will give us the diversity of the training data. True diversification is a major challenge. It may be too ambitious of a goal and defeat the point

    - Exposome projects in EU, leverage existing studies and develop new to enhance the diversity
    - Prospectively create de novo
    - Working closely with vulnerable communities and giving them some control can help (https://nativebio.org/)
- Do we actually need representative data? Representative of what?
- Gonna need a whole lot of mass specs
    - But don't necessarily need to be on the scale of AoU; can learn a lot from smaller studies
        - Help inform standards for sample collection, storage, sharing, data analysis, harmonization
    - Fit for purpose, some times smaller studies can enable a deeper dive

ISSUE #27: The Disease Exposome: Effects on Treatment and Disease Progression

CONVENER(S): Robert Wright

PARTICIPANTS: Sophia Miryam Schussler, Chris States, Pradeep (CSIR), Robert Clark, Brian Berridge, Rachel Keith, Gail Prins, Irva Hertz-Piccioto, Hong Sheng Wang, Gabriel Intano, Andrew Koemeter-Cox, and a few others.

SUMMARY OF DISCUSSION:

Concept is that exposome does not just cause a disease, it will also impact existing disease. Exposome may affect 1) whether or not a treatment is effective; 2) how rapidly a disease progresses 3) highlight pharmaceuticals that either affect metabolism of toxincants, or toxicants that affect metabolism of drugs. Also involves the hospital exposome- i.e. exposures unique to hospital seting- phthalates in IV fluids as an example- they will bypass liver via IV.

Approaches and issues included basic science- organ on a chip, enrollment in randomized trials, cohorts of patients with a disease (Parkinsons, Prostate Cancer, Spinal Cord injury), engaging physicians to care about the environment in their patients (key is giving them actions to address exposures and mitigate exposure and exposure effects), equity of interventions, and policies needed (Rx for air conditioning in a heat wave, or indoor air monitor for someone with severe asthma etc).

Direct Input from Workshop Participants:

- Drug induced toxicity- disease is a susceptibility factor-concept long held in toxicology but little work done.
    - How do we identify agents that create co-morbidity (or just morbidity) in people with a disease
    - Use conditions tagged to disease (hypeglycemia) in in vitro models for experiments.- IPF/organoids as a tool for disease modeling- grow organoid from disease tissue
    - Organ on a chip- disease state.
        - Consider adding treatment to models (L-Dopa in Parkinson's) and vice verse (terfenidrine and antibiotics- affected parent drug metabolism and induced cardiac toxicity) a medical related mixture in other words.
    - What is the exposome of say Parkinson's (and other diseases)? To inform basic science studies.
        - Are there feedback loops in which disease causes exposures and then affects disease
        - How does social isolation get modeled in vitro or in animals, also life stages.
- What are design options? How does exposome affect clincal trials and enrollment
- Chronic Disease as a vulnerable population (similar to pregnancy, childhood)
    - Different than studying cause of a disease
- The hospital exposome (phthalates in IV fluid). – consider hospital food as a source.
- How to build partnerships with clinical researchers

- What educational/engagement activities are needed? Information has to be actionable. Databases need to include what can be done to reduce exposure. The intervention needs to be part of the research. Average visit is 15 minutes long.
- How to engage Clinical trial Networks?
- Cancer as a paradigm disease- mutations affecting drug/chemical metabolism. Can affect exposure and impact other organ systems. Or induce metastatic condition or progression.
- How does diet affect disease progression? Heart Disease is a paradigm- role of culture which impacts food choice,
- Wild fires- impacting people with disease (also induces stress)
- Intrevention needs to address health equities, policy issues to make sure intervention reach everyone. (filtation system, air conditioning, air monitors) Need to address policy- Physicians need to become advocates for patients on exposomic issues which do have interventions.
- How do we measuring the exposome- commercial labs, increase capacity. SBIR grants to promote commercial application of exposomic measures. Apps can simplify interventions- give information on exposure reduction.
- Will insurance companies be a advocate or adversary?
- Employers may be advocates (i.e. Total Worker Health approach)
- We need to address early childhood experiences as part of the exposome.
- And understand biological/chemical interactions on disease- COVID as an example. – increased disease severity not just risk of contracting infection. Chemicals impacting immune system and risk of infection.
- What about prior disease as part of the exposome (hypertensio-heartdiase) may be a modifier of cardiotoxic exposure.
- CTSAs?
- Role of EMR?
- Clinical training programs?
- Understandings factors that improve treatment as well as those that interfere.

OPPORTUNITIES FOR ACTION:

- RFAs on Understanding role of environment in medical treatment (Precision Medicine)
- Partnerships with Clinical Trial Networks
- Partnerships with CTSA program
- Partnerships with Disease oriented Institutes and Centers at NIH

IMMEDIATE NEXT STEPS:

- Encourage research on cohorts of patients and on measuring the hospital exposome.
- RFAs in partnership with other institutes
- Case control studies can follow cases to form longitudinal cohorts
- Work with biobanks to measure exposure
- Existing cohorts can collect address and address role of external environment.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Buy-in from Medical health care providers needed- researchers needed to include actions that can mitigate exposures and show that it benefits patients. Research can help build partnerships with clinicians who care for patients.
- Build partnerships with physician/nursing groups and patient advocacy groups
- Need to think outside the box on Climate and health- Air Conditioners covered by health insurance for example.
- Prevention research is very different than clinical research- there may be concerns that prevention will be left out (i.e. if funding is seen as replacing public health funding). Needs to be advertised as an expansion of exposomics, not as a replacement for public health research.

ISSUE #28: Functional exposomics

CONVENER(S): Gary Miller-Columbia University

PARTICIPANTS: Kristin Eccles, Alex Merrick, Youngi Park, Jacqui Marzec, Gabriel Intano, Kavita Berger, Jennifer Fernandez, Kai Zhang, Jessica Worley, Sharon Ross, Robyn Tanguay, Graham Parker, Nish Vijayakumar, Saravanan Arunachalam, Hong Ji, Lang Wu, David Jett, Jake Chung, Alison Motsinger-Reif, Gada Soliman, Che-Jung Chang, Garret Bland

SUMMARY OF DISCUSSION:

Started with discussion of functional exposomics. The idea is to focus on exposures that impact biology. By using biological outputs to identify exposures we let biology do the prioritization. Adductomics, epigenomics, functional assays (zebrafish, C. elegans), receptor binding. Measuring everything is daunting. Only measure those that change the biology. This will help prioritize what to measure. 1000s of compounds, starting with mixtures, is better than addressing the totality.

Tox21 has a wealth of data that can help guide these efforts. Take advantage of those datasets, QSAR models, etc. There is concordance among the platforms-don't ignore it.

Must consider dose, duration, timing, etc.

This is not merely a biological model issue. Geospatial data can demonstrate where there are adverse health effects at the population level, e.g. liver disease near PFAS factory. Could use these data to guide future experimentation. Can liver function be measured in such a population? Combined with biological data, such efforts could merge seemingly disparate data sets. Exposome maps could really help link exposures to disease via biology.

Where do chemicals co-locate and affect health, at what concentration, leveraging existing data (tox 21) to understand geographical distribution/difference.

Linking exposure and function as outlined in Jake Chung's recent paper in Environmental Health Perspectives.
https://ehp.niehs.nih.gov/doi/10.1289/EHP8327
This paper provides an excellent description of the concepts.

Effect-directed analysis provides a more holistic examination of biological effects.
Powerful example study from Tian et al.
https://www.science.org/doi/10.1126/science.abd6951

Can one take plasma samples and subject them to cellular systems to determine overall level of activation of a specific pathway? Are the systems sensitive enough?

Important to learn from clinicians/physicians about the patterns and signatures that lead to diseases. Stress is important in disease development. Also to integrate molecular biology and biological pathway sinto social and health disparity research to understand how the social constructs impact health and lead to different health outcomes. Vulnerable populations in different geographical areas. (Extreme exposures and rare diseases)

All Of Us: high-resolution analysis in a subset of population could help frame future studies

Current workflows to interpret the unknown compounds in untargeted measurement requires compound identification. When a compound is annotated, it is possible to search toxicity information in the literature and synthesize standard to comfirm identify and conduct wet-lab experiment. Compound identification is the bottleneck in EWAS to translate discovery to clinical/policy impacts

Using the functional exposome concept and conducting measurement with protein affinity-based methods, it is possible to interpret the biological effects of unknowns before compound identification (because the biological function of bait protein is known). Compound identification is still needed to leverage the rich literature information, but this step can be done in parallel instead of being the bottleneck.

However, these methods are not applied in epidemiological study and need development, optimization and validation.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Conduct analysis of Tox21, ToxCast, etc. to determine what tools and datasets are available for functional exposomics. Consider how to incorporate this approach in humans and animal models. Model organisms and in vitro systems will be very useful, but strategies must be developed.

Also consider whether or not functional exposomics is a thing or does it represent how all exposomic studies should be conducted?

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

This is a very interdisciplinary issues. Stats, modeling, pharmacology, toxicology, epidemiology, geospatial, biophysics, etc. Need to figure out how to build needed teams.

ISSUE #29: Exposome on a shoestring: Making the exposome accessible for community based research

CONVENER(S): Maeve MacMurdo

PARTICIPANTS: Erin Dierickx, Srimathi Kannan, Hina Narayan, Yuxia Cui, Sarra Bridges, Raja Rajasekar, Pothur Srinivas, Janet Hall , Taka Williams

SUMMARY OF DISCUSSION:

There are new technologies which may make measuring the exposome more affordable for community based research.

- Lost cost sensors can measure chemical exposure, temperature, light and humidity- these typically cost less than $200 and organizing and analyzing the data can be a great way to get school aged children engaged in citizen science.
- Also opportunities for measurement utilizing personalized monitors
- These monitors have limitations- need for internet access (though newer models can work with Bluetooth, and can be connected to wireless phone networks improving accessibility), difficulties with calibration and validity of measurements are all major concerns.
- Cross-calibrating low cost sensors, or deploying multiple low cost sensors may allow us to improve validity- but still potentially a major expense, particularly for studies with a small budget.
-

When thinking about the exposome, do we measure individuals or the community?

- Many exposures are mediated by internal factors (microbiome, genetics). Community level exposome may be more important however- also cheaper and easier to measure.
- Thinking about exposures in the community as “Eco-markers” which can be used to characterize an individual’s risk.
- Starting with community level exposome, then working back to the individual exposome may be the most cost-effective way to incorporate both

How do we include the community in exposome based research

- Including community members as key stakeholders in grants
- Including community from early in the research development- letting the identified needs of the community determine what and how is measured.
- What we think is the problem may not be the problem.
- It can be frustrating to measure without intervening- example from Dr. Kannan about her work with the Detroit group. They engaged community members from the beginning of the research, and partnered with local healthcare providers to return the data collected about individual exposures back to the patient’s and their care providers, to inform their care. Also connected participants with community resources, and partnered with the community to develop interventions. .
- Building on connections and resources that already exist within the community can make this more cost effective.

- Dr. Dierickx gave an example of the work her group is doing- partnering with key stakeholders in each state to assess what their policies are around heat exposure, and how this impacts risk and risk mitigation.
- When your health is impacted, you are very aware of exposure. Community partnerships can often insight at a very high level.
- Costs are upfront- once the technology/communication tools are developed, it's much more efficient.

How do we include the internal exposome?

- How do we define the internal exposome? This varies.
- Differential heterogeneity is important to consider and explore- individuals within the community have different outcomes despite the same exposure
- Measuring the internal exposome can be expensive. Need for validation, and for IRB approved storage of samples.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- Developing and validating low cost monitors for deployment in the community
- Identify specific communities and prioritize the exposures most meaningful to them, then thinking about measurement
- Showcasing examples of where this has been done well, and sharing success stories and templates for success.
- Involving local health departments in assessment of the community exposome

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Rigor of monitoring. This is still a major barrier, especially when communicating back risk.
- Cost of making sure that results are valid, and appropriately certified.
- How do we incorporate the internal exposome into community level exposome research? More work is needed here.

ISSUE #30: Identifying - then protecting, the most vulnerable

CONVENER(S): Scott Masten, NIEHS/DNTP

PARTICIPANTS:

- Daisy Fry-Bumit, UNC-Charlotte, bioinformatics graduate student in a precision nutrition lab building ML models to develop take-home biosensors for kidney disease risk
- Guillermina Girardi, NICHD, extramural program director
- Jessica Castner, emergency nursing researcher and clinician

SUMMARY OF DISCUSSION:

Defining vulnerable and vulnerability

- what have we been missing-ignoring-doing a poor job at
- beyond genetics, SES, demographics
- 'molecular' vulnerability

Precision

- personalized medicine for individual
- prevention measures that could be applied at population level (public health)

General vs specific use cases – within defined context of an exposed population at risk of adverse health outcome (PECO)

Barriers to identifying risk factors?

- limitations in scientific approaches
- hard to study situations and groups

Identifying factors that associate with 'health' – National Institutes of Health NOT Disease

- inverse of vulnerable is flourishing, resilient
- biological measures of resiliency offer targets for intervention

Sensors that achieve trifecta allowing high frequency use: reliability + low cost + convenience

Data that will be useful to characterize allostatic load, psychosocial stressors >> genomic + metabolomic profiles, biobanked samples

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Data mining for features that reflect stress and bereavement

- what are specific data needs, availability, methods?
- often discarded or treated as confounder when trying to link omics to health outcomes

Better clinical history tools, questionnaires, leverage technology we carry around in our pockets

- increase speed at which new approaches that work can be applied throughout research community

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Who owns your data, consenting to use by researchers vs handing it over to an app

- serious issues with improper disclosure, e.g. sociopolitical, employment, domestic violence

Technological requirements that allow access to secure anonymized data ‘warehouses’

- is possible and achievable yet a very heavy lift for research groups and institutions, even gov agencies
- need help from, partnerships with large commercial organizations
- scaling down and replicating *All of Us* type research models

ISSUE #31: Maternal Exposome & implications for health outcomes

CONVENER(S): Guillermina Girardi (NICHD)

PARTICIPANTS: Carrie Breton, Ryland Giebel, Janine LaSalle, Marylin Silva

SUMMARY OF DISCUSSION:

- Few studies have evaluated environmental exposures in women that may influence future health of their offspring
- Among the harmful environmental exposures, we discussed cannabis (THC) consumption during pregnancy, climate changes and pesticides. We also linked pesticide exposure to cannabis consumption.
- We talked about the almost 9% increase in preterm delivery associated with a 10^{o}F increase in temperature.
- We discussed the effects of chlorpyrifos, and how together with (THC) they affect the endocannabinoid system, affecting gut microbiota with a proinflammatory effect.
- We talked about how the potency of cannabis increased by almost 2-folds in the last decade and that most animal studies use the purified compound.
- WE highlighted that a big percentage of pregnant women use cannabis for morning sickness and they believe it is ok because it is a “natural” compound.
- We discussed urban vs rural exposure and acute vs chronic.
- We recognized that pregnancy in particular is a very complex scenario as it includes 3 converging exposomes (mother, fetus and father)
- Father’s cannabis use increases the risk of miscarriages and other pregnancy complications
- We discussed the effects of fires in CA and the lack of studies characterizing what is there in the smoke.
- Fear of punitive actions to mothers prevented the measurement of cannabis and nicotine in meconium samples
- We also discussed the use of opioids during pregnancy. Are there any pregnant women in the lawsuits against the Sackler laboratory?
- We discussed how animal studies to test toxicity will be banned by 2035 and the current physiomimetic strategies such as organoids, organ on a chip. While they are useful to test transport, they don’t resemble the clinical situation in regard to maternal changes (liver function, metabolism, expanded volemia) and they don’t include a fetal component, such as fetal metabolism.
- We discussed the exacerbated vulnerability of pregnant women in U3 populations (understudies, underrepresented and underreported) living in areas with increased chemical exposure and weather-related stressors (heatwaves, floods, fires, hurricanes, etc)

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

- There is need for biological markers
- Need to include in electronic health record social and environmental factors, not only tobacco and alcohol use in a protected manner to prevent punitive measures towards the mother in particular during the current political circumstances (fetal personhood)

- Because of budget restrictions, few samples are tested during pregnancy and we recognize that pregnancy is associated with cardiovascular, metabolic and immune changes though pregnancy with clear distinction between trimesters

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Pregnancy should be considered a crucial and vulnerable state. It is crucial that authorities implement measures to safeguard the health of the expectant mother and therefore, the health of the offspring.
- Research in pregnancy is currently in jeopardy due to the current anti-abortion laws in certain states.

ISSUE #32: Harmonizing exposome data across studies

CONVENER(S): Sara Adar

PARTICIPANTS: Maria Shatz, Chris Duncan, Stephanie Holmgren

SUMMARY OF DISCUSSION:

Core issue: Desire to encourage coordinated attempts to gather and curate exposome data that can be applied to multiple scientific studies to improve efficiency, quality, and comparability across cohorts.

It would be beneficial to have a catalogue of curated information where experts have identified and evaluated the best publicly available options for different types of data. Recommendations could be made with linkages to the data and guidance information.

There was a conversation about if NIH funding could require that data from one of these curated sources be used to ensure quality and harmonization across different studies but challenges were raised over this. It was thought that maybe study section members could be looking for this type of harmonization and evaluating if it is conducted when appropriate in their review of the science.

Data sources were also highlighted including the Environmental Health Language Collaborative, an NIH initiative for better data finding, sharing, harmonizing and standardizing language. This initiative includes use cases including a place-based exposure use case and data harmonization by integrating various studies. The Gateway to Global Aging was another example of harmonization of data streams and the Climate change and human health catalogue (DR2 portal) was discussed.

OPPORTUNITIES FOR ACTION:

NIH funding or staff could help to create a curated data repository of publicly available exposome information that could be used to encourage efficiency and harmonization across different research projects.

There were also suggestions to leverage information obtained through the current NIH data sharing policies. Guidance could also be made regarding where to store data and what standards to use. Study section members could also be encouraged to check that researchers were using the most recent and recommended data sources when available and appropriate.

IMMEDIATE NEXT STEPS:

NIH staff scientist working on data transparency might pursue opportunities to provide information.

Workshops at scientific conferences might be organized for these efforts.

Existing projects like the Gateway to Global Aging might be leveraged when possible.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Funding for data cataloging would be valuable either as an internal effort by the NIH or funded to scientists to help create a curated exposome data repository.

Periodic updates would be needed and experts identified. One mechanism for accomplishing this could be through workshops at annual conferences such as the International Society for Environmental Epidemiology and International Society for Exposure Science.

VIRTUAL WORKSHOP #3: Future of Clinical & Prevention Trials, Cohorts and Epidemiology

A high-level view of our third workshop space, including our agenda and the space we used to create it. Much of the detail won't scale to be easily readable, but it gives some sense of the messy, organic, emergent nature of our work.

ISSUE #33: Merging data from existing longitudinal studies

CONVENER(S): Lida Chatzi

PARTICIPANTS: Roel Vermeulen, Rima Habre, Joseph Braun, Michelle Bennett, Susan Teitelbaum, Ander Wilson, Antonia Calafat, Brittney Baumert, Chris Duncan, Colin Kay, Hong Zhao, Jesse Goodrich, Roel Vermeulen, Jessica Worley, Kai Zhang, Krystal Pollitt, Liz Costello, Michael Merchant, Philip Holmes, Rosalind Wright, Sarah Rock Saravanan Arunachalam, Scott Sundseth, Shawna Stegall, Susan Laessig, Xiuxia Du, Yau Adamu, Yi-Han Hu, Yuling Hong, Yuxia Cui, Gwen Collman, Jason Niu, David Balshaw, Jeffrey Kopp

SUMMARY OF DISCUSSION:

Study Design

- How can we collaborate to design future studies which allow for data harmonization?
    - Create guidelines for specimen collection, lab protocols, etc.
    - Establish set of questionnaires to pull from

Benefits of historical cohorts vs new cohorts to conduct exposome research

- Historical cohorts
    - Money has been allocated to develop cohorts – we can use these resources rather than starting up a cohort
    - They have valuable longitudinal data
- New cohorts
    - Our exposome has changed – need to continue to design new studies and capture current exposures
    - Historical studies have limitations that

Data Analysis and Harmonization

- There is a need for harmonization of tools, questionnaires, sample collection, protocols
- This is challenging due to
    - Limited time, funding, and resources to do this work
    - Heterogenous protocols, questionnaires, sample collection, sample types, storage
    - Loss of data when harmonizing
- Ex. HHEAR
    - Currently, there are a lot of independent projects ongoing, but in time, there will be enough data to analyze as a whole
    - Roadmap of all existing studies in HHEAR available online (46 studies as of August 12, 2022)
    - Two ways to access the data
        - Harmonized data
        - Study-specific files
- Ex. European Network- (HELIX and ATHLETE)
    - Meta data is available -done for all the consortia

    - They are currently building catalogs for cohorts to use to harmonize up front because we lose specificity harmonizing after data collection
- Ex. ECHO
    - In depth protocols for data harmonization have been developed. Still they are issues because cohorts are so geographically dispersed
- Ex. AllofUS
    - They are planning to explore environmental factors, include in the exposome
- Ex. NHANES-
    - Cross-sectional study
    - NHANES Longitudinal Study - Participant Page (cdc.gov)
      They are contacting people who were examined in the NHANES during 2007-2014. They have started with a smaller group of 800 who live in 8 of the dozens of locations we went to during those years. If successful in locating and talking to this group of 800, they intend to contact all other adults examined during those years as well.

Important Questions

- What are the best approaches to combining these datasets?
- What are the resources we need for harmonization? Time and money are the issues with harmonization. Can we share harmonization protocols?
    - This is difficult because we are looking at different questions
    - There can be a few harmonization protocols that are applicable
- How do we fund data harmonization?
    - European mechanism will fund large-scale cohorts
    - US seems to be lacking this
        - New data sharing policy – you can include funds in your budget for data sharing, this could be used in the future to make your data sharable. There is also cohort maintenance RFA
- How do we ensure that we do better exposome studies?
    - The exposome from 20 years ago is different to the exposome now – exposures have changed
    - We need new, large-scale studies

OPPORTUNITIES FOR ACTION:

- Harmonization protocols for existing US exposome studies
    - Idea: collaborate to write small papers on harmonization
    - Idea: write STROBE exposomics guidelines – Braun
    - Using existing protocoles
- NIEHS funding opportunities for data harmonization and data analysis in existing longitudinal cohort studies
- NHANES longitudinal study

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Lack of resources to perform data harmonization – need funding opportunities
- Lack of homogeneity in protocols, questionnaires, etc.

ISSUE #34: Indoor Air

CONVENER(S): Claudia Miller

PARTICIPANTS: Brianna Moore, Lance Wallace, Deborah Bennett, Rachel Keith

SUMMARY OF DISCUSSION:

Overall rationale:

- Indoor air quality is extremely important, as we spend ~90% of our time indoors.
- Additionally, the literature has historically focused on outdoor air.
- Certain exposures (such as semivolatile organic compounds [SVOCs]) may be more relevant indoors.
- Some exposures, we do not have metabolites in urine.

Some populations may be especially vulnerable.

- Certain individuals, such as children and aging adults, may spend more time indoors.
- Also be monitored through biomonitoring, however, half-life is so short, we may be missing some of the exposures.

Chemical intolerance is becoming more common.

- Based on data from the Quick Environmental Exposure and Sensitivity Inventory (QEESI), approximately 20% of the U.S. population has chemical intolerance.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

Improve exposure assessment:

- SVOCs:
- Consider measuring SVOC exposures in dust. Hundreds of chemicals can be measured in dust and the concentrations are fairly stable over time.
- VOCs:
- Fresh Air wristbands

Study vulnerable populations:

- There is a need to recruit cohorts with specific exposures (e.g. house cleaners, indoor house painters, nail technicians, chefs)

Characterize chemical intolerance.

- QEESI can be easily administered to understand the extent of chemical intolerance

Environmental health recommendations about how to improve indoor air quality is lacking.

- There is a need for clinicians and public health officials to educate the public about how to reduce their exposure (for example: https://tiltresearch.org/2021/03/26/7-steps-to-creating-a-clean-air-oasis/)

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Improve exposure assessment:

- VOCs: Watch the field for low-cost, portable monitors to get a better measure of VOCs. Of note, the EPA currently has a grant mechanism to develop less expensive monitors.
- There is a need for monitors that capture ultrafine particulates.

ISSUE #35: Fast but not Furious: A Case for Accelerated Longitudinal Designs for Exposomics

CONVENER(S): Robert Wright

PARTICIPANTS: Gwen Collman, Konstantinos Makris, David Balshaw, Allison Cook, Blessing Akintunde, Dana Dolinoy, Deborah Watkins, Edith Eaton, Muhammed Idris, Sharon Ross, Sophia Myriam Rose, Lynnea Wright

SUMMARY OF DISCUSSION:

Background: In addition to leveraging existing studies, there will very likely be a need for intentional new enrollment to fill gaps in knowledge of the reference exposome. Lifestage is a critical aspect that drives both risk of exposure and the dose response curve of the health effects that arise from exposure including latency effects. A traditional longitudinal design would take decades to complete. An alternative design- the Accelerated Longitudinal Cohort Design (ALD) may be able to address many of the barriers to understanding the time varying/life stage varying nature of the exposome (see attached papers on the methodology) An ALD differs from an traditional longitudinal cohort in that enrollees are selected to be at different ages at enrollment and followed longitudinally. Even just a subset can be followed longitudinally to reduce costs and there are methods to use longitudinal analysis (growth models, mixed models etc) as long as a subset cross into the different life stages and can represent the within person variance over time of the larger cohort. They can be a more efficient way to increase sample size for analysis and may save costs in an exposomic study.

An ALD will also provide the needed cross sectional data that will inform life stage specific exposome- similar to how pediatric growth charts were first created.

The discussants agreed that the ALD may be a useful method for intentional enrollment but that when possible there should also be leveraging of existing cohorts. *A pilot ALD study is recommended* to better understand the feasibility of leveraging extant cohorts to go with new enrollment.

Below are 3 relevant papers on ALDs:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5302089/pdf/10.1177_0962280214547150.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5967414/pdf/nihms962704.pdf
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8363832/pdf/main.pdf

Direct Input from Workshop Participants:

Should keep in mind “pragmatic” Exposome.- May need multiple ALD studies (extant and newly enrolled) with goal of merging/pooling them.

ALD won’t fix all problems but will provide more data in a shorter time frame. Analogy of growth charts used in pediatrics. Original Pediatric growth charts were made using an ALD design and followed by a true longitudinal design over 20 years. ALD design was very accurate and gave immediate data.

There is a need to develop a reference exposome which will need more repeated measures in shorter time intervals. Capture more temporal variability – This need has been noted in European studies. A subset of an ALD will need to have more intensive follow up and evaluation to address temporal variability which is largely unknown.

Existing Cohorts not designed for exposome and epigenomic Data collection that is representative of the U.S. population

Nonetheless, they should be evaluated for inclusion in an ALD and some cohorts may be ideal and have samples, addresses, work history etc.

Geography- need to address geographic variability simultaneously to life stages- same for Sex/Race/Ethnicity/SES

What is biobanked- Blood, urine, hair, Teeth
Brain/tissue banks post mortem

Can do in clinical populations- Cystic Fibrosis (study infants, children, adults in an ALD design)

How do we capture latency?- maps help that can reconstruct past exposure or impute it. As to blood spots, teeth – should be do able with ALD design as well.

Epigenomic biomarkers used as intermediate markers of latent health outcomes.

Need to integrate implementation science methods- health coaches, financial incentives that may vary by life stage.

Intramural program cohorts may be leveraged for an ALD

RFA's to add exposomics to exiting cohrots needed that can incentivize researchers to participate in ALD cohort.

Need for ELSI studies to add exposomics to existing cohort studies (home address is PHI for example)

Multi-site infrastructures will allow for geographic variability and for pooling. This would be novel.

Challenge is that medical centers are urban and recruitment is centered on medical centers- how to capture rural populations. How do we support field teams- needed to be an objective.

Blood spots, teeth also capture early life environment, as do maps

Exposomic markers may be used for extreme exposures

Leverage existing cohorts whenever possible.

Chronic conditions interact as well as may serve as intermediate steps.

Add link for ALD methodologies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5302089/

There is a need for intentional design to complement existing cohorts to ensure we fully capture exposomics.

What are the measures needed- Address and address history, wearables, biosamples, Work history,

Logistical challenges (elderly/infants)

EU Horizon Exposomic projects? Do they use ALD? (Konstantinos thinks “no”)

OPPORTUNITIES FOR ACTION:

- RFA for existing cohorts
- Persistence in adding to ideas for NIH common fund projects an ALD design.

IMMEDIATE NEXT STEPS:

- Pilot study using ALD is needed. Including how to leverage existing cohorts. First step pilot may be based on extant datasets.- HHEAR as an example.-
- Google health and NHANES are examples of studies that may piggy back on to an ALD- not just NIH funded studies.
- EU studies, ECHO and All of Us another resource to start an ALD
- Methodology for connecting/harmonizing and pooling data is needed especially for extant studies/data- further shows need for a pilot..

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- ALD will have Asynchronous age windows- infants enrolled in 6 month windows, children annually, >20 & <50 years in 10 year windows, >50 in 5 year windows as examples.
- Asynchronous follow-up windows-infants followed more often than middle age adults for example.
- Field teams may be evaluating children and elderly at the same site (unusual for a cohort) and will need broad expertise in evaluation.

ISSUE #36: EWAS and GWAS similarities, Exposome wide association studies, Epigenomic association studies, GWAS-traditional

CONVENER(S): Trevor Penning (UPenn)

PARTICIPANTS: Gary Miller, Cheryl Walker, Chris States, Dayne Okuh, Alina Peluso, Hina Narayan, Peng Gao, Blessing Akintrude, Lisa Rider, Irva Hertz, Arcot Rajasekar, Elizabeth Scholl, Yuxia Cui, Michelle Bennett

SUMMARY OF DISCUSSION:

- Exposure (>80,000 chemicals); physical exposures (UV light and radiation etc); GWAS (30,000 genes)
- Diseases of environmental etiology complex genetic traits/environmental complex traits
- Epigenome a good reporter of environmental exposures/ and imprinting (plastic/persistent/reversible/causal)-difference between consequential and non-consequential changes
- Microbiome wide association studies-capture in metbolomic studies
- **Multiomic /integration/**
- Multigenic/epigenic//exposures relationship with a disease trait/ e.g. ASD
- Network correlation of exposures/ patterns of exposure rather than individual chemicals/
- **Haplotype analysis (condense multimeasures of exposures)-experienced in group e.g. incinerator emissions**
- Geographic (GIS) Loci (clusters) analogous to families in genetics
- Demonstration project e.g. asthma endotypes (with equivalent of Manhattan plot for chemicals-grouped by haplotype) e. g. diabetes
- Should be shared with other NIH Institutes (disease specific)
- Equivalent of polygenic risk score/polyexposures risk score

https://pubmed.ncbi.nlm.nih.gov/35348899/
https://pubmed.ncbi.nlm.nih.gov/34950191/

Highly penetrant rare variants/low penetrant highly prevalent variants
[High exposures low incidence/low exposures high incidence]

OPPORTUNITIES FOR ACTION:

- Disease frequency and geolocation e.g. SEER data/ CDC
- New clusters acting quickly
- Geospatial analysts and informaticians
- Disease incidence in EJ communities and other marginalized pops
- Sensor technology e.g. wearables – link to cell phone GIS

IMMEDIATE NEXT STEPS:

Identify model high impact diseases e.g. neurodevelopment and neurodegeneration [ASD, ADHD, cognitive impairments, Alzheimers], metabolic disorders [diabetes & obesity,

NFALD;] cardiovascular [MI and stroke]; cancer, [lung, oral, prostate, breast, bladder, skin and thyroid cancer] to work from disease backwards towards an EWAS framework

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Need for geospatial analysts and informaticians; statistical models for dealing with mixtures
- Education-training programs in environmental statistics
- G x E
- Biobank samples UK-biobank/ All-of-us for population surveillance-generate exposure haplotypes? 5,000 features from 100,000 and group
- Application of Moore's Law will reduce expense
- Reduce complexity of analytical methods
- External exposures and relationship to internal exposures need both
- Longitudinal measurements are an issue? And dose?

ISSUE #37: Beneficial Exposome Conditions for Health Research and Healthcare Services -- First, Do No Harm!

CONVENER: Bren Ames

PARTICIPANTS: Jessica Castner, Hyun Chung, Ryland Giebelhaus, Charles Sneiderman,

SUMMARY OF DISCUSSION & OPPORTUNITIES FOR ACTION:

Issue Overview: **Standard baseline exposome quality for the full range of healthcare facilities and practices should align with our ideal of 'First, Do No Harm'**.

Offer healthcare services without inflicting further harm.

Clean Air Oases and Environmental Medical Units (EMUs) for research to minimize research confounders and for testing/treatment/recovery of susceptible individuals.

Also, Exposome Quality for the full range Of Healthcare services, including: Emergency (EMTs, Ambulance, ER), ICUs, Surgical, Medical and Dental Clinics, Long-Term Care Facilities.

- Facilities and services that can serve susceptible people without harm are ~unicorns.
- Susceptible people dealing with environmental injuries and chronic conditions:
    - triggered/exacerbated by harmful exposures now ubiquitous throughout society, including in healthcare and health research settings.
    - Need **Access, free of harmful emanations, & Reasonable Accommodations**
        - Designated Cleaner Air Rooms and Designated Access Paths need Environmental Medical Units (EMUs) – with exceptional exposome conditions and exposome quality testing capacity – for respite, clinical and research testing, treatment and recovery.
            - Unravel exposome influences on chronic complex conditions.
            - Minimize confounders by reducing, controlling and measuring exposures (IAQ, food & water quality, personal care products (PCPs), PPE, treatment and therapy devices); biological response attributes; and links.
            - EMUs for RCTs: call for strict subject inclusion and exclusion criteria to reduce the 'noise' of other variables in assessing treatment outcomes.
            - EMUs for n=1: Theron Randolph's first-gen EMUs for food intolerances. Premise: At home, patients experience overlapping symptoms due to everyday exposures (masking). In an EMU, patients breathe filtered air, drink pure spring water, and fast. Patient brought to a 'clean baseline', then tested with organic foods, one at a time. Then tested with 'everyday' exposures. Microbiome Presentation (Miller 2022).
- The most ubiquitous and unavoidable triggers are fragrances/flavorants/deodorizers produced from petrochemicals. Some delivered via nanoparticles that cross barriers more readily. Increasingly designed to be persistent.
- Also hard to avoid releases from combustion, synthetic substances and pesticides.

- **Healthy and accessible environments**, at the most elemental level, must be **smoke, pesticide, and fragrance-free with minimal electromagnetic pollution.**

Group discussed the **range of Healthcare facilities and services where such baseline exposome quality improvements would benefit everyone** -- research participants, healthcare patients and staff (incl. nursing, cleaning, maintenance, security and laboratory):

- Routine – Medical, Dental and Research Clinics. Home, Daycare and Long-Term healthcare. Chronic condition care.
- Acute Emergency -- EMTs, Ambulance, ER, Surgery, Shelters
- Chronic Climate Emergency -- Planned retreat options – needed, increasingly urgent.

Facilities requiring more stringent measures for people at exquisitely susceptible development/life stages, situations and conditions:

- NICUs, ICUs, Surgical units, EMUs and access paths to those.

Hyun Chung & Jessica Castner: REDUCING EXPOSURE RISKS FOR FRONT LINE STAFF-- including ER and Emergency Services, ambulance, cleaning, maintenance and security personnel

- Staff don't want to work ER – so much exposure to third hand smoke, tobacco and cannabis and e-cigs. Fire victims. Thirdhand Smoke Beliefs and Behaviors among Healthcare
- Uptick in exposures, 2nd hand & 3rd hand emanations from people and e-cigs, associated with cannabis legalization in US -- dramatic change inside public transit. Less noticeable in Canada. Flavorants in e-cigs. Surgical smokes.
- COVID (and other) transmission, mask/PPE availability, mask mandate removal
- Latex gloves & other triggers associated with equipment, supplies.
- Diesel school bus and ambulance **idling exposures**
    - Other opportunities for RISK REDUCTION AT HEALTHCARE FACILITIES
    - Bren: Low hanging fruit for reducing exposome triggers within in our healthcare facilities includes going Fragrance Free, like the CDC Fragrance Free policies - CDC and US Access Board. Fragrances are just one category of substances that .Could make a big difference for a lot of people. Propose that A few of the many guidelines/procedures for improving exposome quality
    - facilities within the Kaiser network, including incinerators.
    - Exposome-based public health interventions for infectious
    - How U.S. hospitals cleaned up their toxic trash | PBS NewsHour
    - Coordinate with
        - Insurance, Risk Reduction -- traditionally driven by research
        - Sustainability coordinators – tasked with enacting the concept, accustomed to looking at various environmental exposures
        - Purchasing departments
        - Policies tend to change if patients, parents demand it.
        - Chemotherapy patients have demanded such improvements.
        - Learn from secondhand tobacco research, policies, practices and education

Discussed EXPOSOME STUDIES NEEDED

- Anywhere healthcare is provided and research is conducted
- Replicate healthcare exposures in controlled chamber environment

- Surgical smokes
- Ubiquitous use of substances that trigger susceptible people are being discussed also in Claudia Miller's Session (concurrent) and the session about Dollar Store exposures. Bren: Neighborhood scale exposome – including indoor and outdoor air quality, laundry chemicals, fragrances, personal care products, pesticides. Laundry exhaust has become a major trigger.
    - My mother was a nurses aid whose fav thing to do was work with premies—even a LONG time ago, she was required to launder her uniform with fragrance free castile (Ivory) soap. Not sure it that remains a requirement __ nano – more persistent, barriers more
    - One category of things that having certain policies on product use within research and healthcare facilities could make a big difference for a lot of people. Even CDC has a fragrance free policy. This would be low hanging fruit.
    - What are the situations, equipment, opportunities that participants have access to that could also measure improvements to research and/or delivery of healthcare?
- Ryland Giebelhaus: Influence of contaminants, emanations from personal care products and infant care products. Researching **emissions from** both scented and 'scent-free' **diapers for neonates**.
    - Headspace measurements & Urine analyses
    - Found emanations even from those claiming to be 'scent free'. Some smelled harsh, like rubber, some like a pine tree
    - Need for long-term testing, after infants have gone home.
    - Need more studies on effect of cannabis use for pregnant patients, 2nd and 3rd hand exposures on fetuses and infants
    - Effects on tumor suppressors, other treatments
    - Prop 73 ER work
- Bren: FYI 'unscented' and 'scent-free' labeled products commonly contain deodorizing / masking chemicals to cover harsh chemical odors evident in the product.
- Consider the clinical and research work of Albert Donnay (discussed later) &
    - Dr. John Molot, (2014 book) 12,000 Canaries Can't Be Wrong: What's Making Us Sick and What We Can Do about It, Environmental Sensitivities (ES-MCS) Status Report & Service Gaps,2010, Academic and Clinical Perspectives, Ontario Centre Of Excellence In Chronic Complex Conditions, 2013, pg 22 - Linking Divergent Chronic Conditions and the Environment: cellular & liver detox, mitochondrial function and metabolism, redox, oxidative stress, changes in mito and cell function, pollution and systemic inflammation. Environmental control and reduction of exposures to known triggers are essential for both treatment of susceptible people and RCT research.

        - Charles Sneider: Seeking to develop a systematic way of working with people in residential environments to understand the potential connections between their exposome, their medical record and symptoms/manifestations.

COHORTS – group brainstorm

- Long-Term Care Facility residents, if provided exceptional and measured exposome conditions with fewer confounders could advance research across the full spectrum of chronic conditions including longitudinal studies of memory/cognitive function.
- Residents of military housing
- Veterans -- in need of services covered by the PACT Act. Burn pit and other toxic/toxicant substances associated with military actions – veterans and long-term residents in conflict zones. Veterans with Gulf War Syndrome &/or PTSD

IMPROVE MEASUREMENT DEVICES, MEASUREMENTS & INTERPRETATION

- **Develop toolkit –** prioritizing **low cost** Procedures, Supplies and Equipment that could be adopted and deployed broadly for measuring Exposome Quality:
    - Measure Patient/Resident/Participant responses to improved Exposome conditions – for research and to guide clinical recommendations, patient choices/lifestyles
    - **Social determinants, including racism**, racial weathering, inescapable stresses.
    - Bren: example of racism, Skin Tone Bias in Pulse-Ox Devices.
    - Advance the use of BREATHOMICS, exhaled breath studies
        - Need to use more accurate, more granular, less biased CO and Oxygenation information
    - Non-invasive screening
    - Look for indicators of food intolerances, metabolites in the breath.
    - Investigate how the digestive system responds to lactose, lactose intolerance, metabolism, and alterations in the microbiome terrain.
    - Big data challenge -- Recognizing what is important.
    - Bren: Other groups are looking at what could be the minimal amount of information to share so we don't get overwhelmed by information. Instead, I'd like to see a framework -- for exposome and outcome pathways – where we could put that information into context -- where is it in the universe of –omics? A way to keep the universe in view w/o getting overwhelmed with detail, gradually draw the links between things, as evidence is produced, and have the weight of evidence become more recognizable. Also important to prune away assumptions that are not reliable, faulty.
    - Group: Important to allow people to generate hypotheses. Experience having hypotheses get shot down before they can be considered and tested…Hopefully – hypothesis generating tools will allow more creativity. Challenge assumptions should be encouraged.
    - Bren: Limitations include requiring us to look only at pathogenesis. We need to regenerate beneficial exposomes from micro to macro-terrain. From beneficial microbiomes to a resilient planet that support healing and health. If we don't envision the beneficial side, we're never going to create conditions to support it.

Ryland: Noticing that metabolites may indicate beneficial processes as well as pathology.

Bren: e.g., **CO is protective in some circumstances.** Just one example of needing to put biomarkers context. If we don't consider that CO may be protective then we might ignore how important that may be in chronic CO and COVID. See related 8/26 notes. Also, the need

to clarify measurement limitations, like those of fingertip pulse-ox devices. This was brought to my attention by Albert Donnay: “most studies of endogenous CO interpret its close positive correlation with these acute conditions as protective, with some going so far as to recommend treating ARDS with inhaled CO.” This looks beyond pathology. Pays attention to biomarkers that may indicate healing, health.

    - Bren: I just saw a cool video clip of the plant Cell Danger Response. It parallels Dr. Robert K. Naviaux’s model that spans from the human cell danger response (CDR) to the Healing Cycle. NaviauxLab’s work, centered on mitochondrial functions, Offers that spectrum of vision, including obstacles and treatment to support the Healing Cycle. A framework for pulling together a lot of pieces, putting mounting evidence into context, with plausible mechanisms for healing pathways, salugenesis. Also, recognizes that we have to create a healthy exposome.

- Let’s broaden the Adverse Outcome Pathway (**AOP**) **framework to XOP** - the **full spectrum (xpectrum) of Outcome Pathways.** *There is **no need to wait** for a full understanding of the pathophysiology of chronic conditions before we should act to prevent them and find pathways to recovery and healing.*

IMPLEMENTATION, TOOLKIT HERE

- Gather current versions of policies and procedures, synthesize feasible guideline that could be implemented in a stepwise fashion for the various applications. Ratchet down adverse exposures, in situations we have control over. May be limited to Clean Air Oases for a while. Maybe those could spread. EMUs for people that are really susceptible and appropriate for research
- Implement in places where a broad cross-section of people will encounter the concepts and experience healthy exposome, i.e., Clean Air Oases.
- __Document and make such case studies/oases visible so people can see successful implementations,

IMMEDIATE NEXT STEPS:

First, Do No Harm

- **Adopt BASELINE policies and practices** for facility operation and employee conduct for healthcare environments that are **smoke, pesticide and fragrance-free with minimal electromagnetic pollution**.
- Adopt/adapt guidelines/procedures for iteratively improving exposome quality for various healthcare and research settings, from Clean Air Oases-type general practices to instrumented EMUs.
- Encourage Cleaner Air / Clean Air Oases-type practices at home for staff and patients.
- **Use devices already present** (i.e., for measuring air quality in surgical, ICU and NICU units**) for additional clinical and research environmental measurements**.
    - Baseline exposome and ‘omics snapshots.
    - Track and correlate exposome and chronic condition attributes as exposome is improved (moving beyond risky ‘challenge’ testing).
- Jessica Castner: **Decarbonize the healthcare sector. Planned retreat for healthcare services. Respond to climate crisis.**

ISSUE #38: Communicating aspects of exposome research/impacts of exposome with the general public

CONVENER(S): Shannon Bell (RTI),

PARTICIPANTS: Ariana Haidari (UMich), Sarra Bridges (UMich), Elizabeth Cook (NJ Dept of Health), Srimathi Kannan (UMich/UTexas), Dayne Okuhara(NCI-DCEG), Maria Fe Lanfranco Gallofre(NIA), Yuxia Cui(NIEHS)

SUMMARY OF DISCUSSION:

- Community input, community needs; academic research should be in support of the community needs.
- How do you take the information and distill it down so you can talk to a mom with gestational diabetes about what changes she can make in her life or how her choices impact her condition
- How do we communicate results in a way that is relatable and not scary
- Complex information that requires bringing things together; operationalizing definition and the parts:
    - Biomarkers/biomonitoring
    - Location, nutrition
- Is there a need for communication framework: risk factors, protectors?
- Are there established/best practices for communication that can be more broadly communicated
- Impacts response rate; using NHANES recruitment model (mailing)
- Folks don't always understand the impact of levels found
- There is a lot of simplification of data/results (one factor being attributed to outcome)
- How do we make something a public **concern** without making it a public **panic**?
    - Its important research and important context but boiling it down to avoid X and use Y it can become an equity/access issue
    - Avoid gimmicky language
- Fact sheets for public:
    - How can you reduce (recognizing limits of reality)
    - Accessible language
- Wholistic approach when doing research dissemination that is focused at community level
- Use of technology
    - Can be mixed experience for the individual
    - Can be very helpful in showing data to impact change
    - Lots of information is available online
    - Move the burden off of the individual
- At what point in hypothesis *generating* researching do start engaging the community? How much evidence is needed before we can have an established knowledge base
    - Making data available quickly/piecemeal or waiting for the comprehensive results to communicate
    - Relevance to individual and to the area/community
- Exposures not just "common" but also community specific (ex PTSD/agent orange for veterans)

OPPORTUNITIES FOR ACTION:

- Clarify the community
    - Community-specific impact and make the community/population considered very clear
    - Engagement of target communities/community partners in each step of the research
- Sharing of research
    - Critical review of research publications to enhance clarity on limitations, populations, and study intent
    - Community is involved in the data review, analysis, and feedback
    - Creating templates, subsets of data, code/data that can be shared
    - Training (academic, community/subpopulation partnerships)

IMMEDIATE NEXT STEPS:

- Establishment reference points for comparison
    - A way for individuals to compare what *they* are exposed to on a regular basis and put that into context (not to encourage panic but to calibrate and help make choices that are better for their personal situation)
    - Useful for researchers to put their data into context
    - Useful for communities to establish a “baseline” that could be used to drive public policy

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Funding to support data accessibility and sharing
- Increasing participation
- Data sharing requirements
    - A way to make data from different studies accessible and available to use
    - Increase availability of other data from communities (may not be exposure levels but environmental conditions, past community events that drive exposure)
    - Standardizing the data that is being collected and has been collected (not just methods for chemicals but also questions/surveys)
        - Deviations that are community specific or differentiating between small- and large-scale efforts
- Dashboard to make data available to general public
    - Data coming from different resources
    - Data from studies

ISSUE #39: Issues in building inclusive and representative populations for exposome studies

CONVENER(S): Grier Page, Katerina Grafanaki

PARTICIPANTS: Emily Beglarian, Eric Bind, Yuxia Cui, Lily Wu, Sohia Schussler-Fiorenza, Philip Holmes

SUMMARY OF DISCUSSION:

Many of the underrepresented groups can be overrepresented in negative exposures

Underrepresentation in studies is not limited to just race, but also:

- Race
- Ethnicity
- Poverty
- Education
- Sex/Gender
- Sexual orientation
- Immigration
- Rural/Unban
- Education
- Life stage
- Income.

It is important to understand representation of studies by tracking the data.
Important to compare observed populations to references
Many of the potential reference such as NHANES and Census have some biases and incompleteness.

Samples weights, while often helpful, are not perfect and especially an issue if there is bias in missingness.

Communities have a lack of awareness of exposure to risk and why exposures are a risk.

There aren’t enough hours in the day and desire to participate.

Basic scientists can have issues intersecting/communicating with policy and population health.

Need both work and home exposure.

Incentives (or lack of them) are a real barrier to participation.

Getting testing results back is a positive, but different groups can value different incentives.

Telling the truth – transparency is important.

Mistrust of governments.
More trust with academic institutions than government.

Offering language services. Diverse languages.
Language – translation of surveys is an issue. Is more acute in Hybrid and remote trials.
Many studies rely on internet access which is also a barrier.

Justice – underrepresented groups like that all groups are being studied and that their group are not being singled out.

Trusted groups – radio, barber shop, church partners – black males recruited through their wives/sisters. Are important for study success.

Approach people as fellow residents not as the government.

Community based participatory research.

Diverse populations don't like pre-fab study designs. They want a role.

Listen to the populations to understand what they care about and make sure the studies are addressing end points/questions that are important to them.

Get early community and participants in planning of studies.
Pay the community study planners.

Some groups being studied want control or strong influence on use of their data such as the Native American biobank. https://nativebio.org/

Mentoring is critical for increasing the diversity of researchers, especially across the entire research hierarchy.

There needs to be consideration in exposome research of race vs social determinants of health in the causes/etiology.

Many groups are thinking about these issues and have useful information. Cross fertilization of data and ideas could increase speed of adoption.
https://calepa.ca.gov/about/calepa-racial-equity-home/ "Data and Resources" tab

We/CA also have an interesting "Pollution and Prejudice" story map that shares some of the historical intersections "we" see that have contributed to our systemic/infrastructure issues.

Many scientists are uncomfortable having talk about diversity. Especially in balancing competing need and priorities..

OPPORTUNITIES FOR ACTION:

- Better understanding of barriers for participation through research and community engagement.
- Training to make uncomfortable conversations about diversity comfortable.
- Develop more diverse researchers through mentoring.

- Develop training (and research) in community based participatory research.
- Require studies to engage in community based participatory in study planning. This could be mandated through grant and contract requirements.
- Lack or nominal compensation for participating in study planning and study participants is a major barrier.

IMMEDIATE NEXT STEPS:

- Engage with All of Us Recruitment and retention project (and other similar projects) to better understand what they have discovered about strategies for increasing recruitment and retention. Understand how that information could be applied for exposome research.
- Require tracking/reporting of how well the study populations represents the actual populations of interest.
- Better connection and transparence of information (e.g. https://calepa.ca.gov/about/calepa-racial-equity-home/) among governmental groups (states to federal) and across governments care reduce the costs of understanding and increase the speed of knowledge dissemination.
- Develop educational materials about importance and goals of exposome and environmental research that communicate to diverse groups in language and messaging that is useful for them.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Funding barriers to participant in scientific meetings (high cost) that limit governmental and participant involvement in these meetings..
- This working group itself was not very diverse, more knowledge could be obtained from the input from more diverse peoples.
- Mistrust of government and scientists.
- Funding for the conduct of successful inclusive research is needed.

ISSUE #40: Reporting Standards Replication

CONVENER(S): Roel Vermeulen

PARTICIPANTS: Colin Kay, Liz Costello, Jason Niu, Ander Wilson, Lily Wu, Gary Miller, Grier Page, Hina Narayan, Robert Clark, Saravan Arunachalam, Shudi Pan, Yuling Hong, Jessica Castner, Tram Lam, Carmen Dickinson, Bren Ames, Carmen Chen, Lisa Rider, Peng Gao, Dakota Maguire

SUMMARY OF DISCUSSION:

The field of exposome research is developing and moving from its infancy to adulthood. This brings several responsibilities with it with regard to:

- Replication
- Reproducibility of findings
- Ontology and minimal reporting standards.

OPPORTUNITIES FOR ACTION:

1. Operational definition of an exposome study. What needs to be studies at what dimension to call it an exposome study. In analogy studying 4 SNPs would not be called a GWAS study.

2. Operational definition of what we expect from replication and what it means when we have a lack of replication.
    a. Replication can be achieved in different ways
        i. Internal replication / re-draws /
        ii. External replication with a like studies
        iii. External replication by using different study designs
        iv. External replication by using different experimental (orthogonal) designs (in-vitro, in-vivo, in-silico)
    b. Requirements for replication needs to be developed and facilitated.
        i. Ontologies, minimal reporting standards (Strobe-Exposomics)
        ii. Design standards
        iii. Common data standards

3. There is a risk of not putting in rigor in design, reporting and replication standards in Exposome research:
    a. Research would be non-reproducible, reducing acceptance of results in science and society.
    b. The overwhelming number of non-reproducible results could lead to reduced acceptance of exposomic results.
    c. Research efforts trying to replicate spurious findings would be a de-investment in science.

IMMEDIATE NEXT STEPS:

- Work on guidelines for:
    - Ontology of exposomics
    - Minimal reporting guidelines (Strobe-Exposomics)
    - Standard (view) on replication
- Replication requires access to data and results
    - Foster open science and data sharing
    - Setup funding schemes on:
        - Open science
        - Data sharing (including data cataloguing)
        - Data harmonisation efforts

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Obstacles are that many of the standards, ontologies have not been worked out to date. Doing so is hard and laborious work that often is difficult to fund under standard funding schemes. This may require different funding schemes.

ISSUE #41: Mining the Electronic Health Record for Exposomics Research

CONVENER(S): Trevor Penning (UPenn)

PARTICIPANTS: Yau Adamu/Elizabeth Scholl/Chris Duncan/Carol Hamilton/Tram Lam/Lisa Rider/Yuxia Cui

SUMMARY OF DISCUSSION:

- Different EHR by health system and institution
- Standardization of record
- Occupation captured
- Billing codes-IC-9 codes (streamlined)
- Residential address and publicly available exposure data
- NCATS data translator-UNC

- https://pubmed.ncbi.nlm.nih.gov/31077269/
- https://researchsoftwareinstitute.github.io/data-translator/apps/icees

- Biomarker/biometric data in the record
- Drug information – prescription drug usage
- Other data that is mineable-gender/age/pregnancy history etc
- Environmental Health Literacy of Physicians-can they take an exposure history?
- Information in written notes: natural query language (query list)
- Should there be nudges to gather exposure data outside the standard EHR
- Longitudinal data
- Identification of clusters/for epidemiology studies
- Environmental health forensics-work back from disease to locality

OPPORTUNITIES FOR ACTION:

- Cross linking of EHR for aggregate data capture across health system
- Other sources of data gathering-wearables etc.
- Geographic data (GIS)-spatial temporal exposure data

IMMEDIATE NEXT STEPS:

- Standardize EHR in federally supported programs e.g., Medicare/Medicaid/VA
- RFA's for improving EHR by NIH to track environmental exposures
- Tiered approach-Core questions first

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Consistent health records across health care provider
- Will make us fall behind our European counterparts e.g. UK biobank

- Privacy concerns in sharing data
- Universal consent
- Loss of deidentifiable data
- Geospatial data and health effects-misuse by insurance companies;
- Homeowner values

ISSUE #42: Studying Effects of Exposures in Small Clinical Populations

CONVENER(S): Sophia Miryam Schüssler-Fiorenza Rose

PARTICIPANTS: Allison Cook, Jeffrey Kopp, Rachel Keith, Lisa Rider, Carmen Chen, Yuxia Cui

SUMMARY OF DISCUSSION:

Questions:

1. Study a rare genetic condition, how to combine study of genetic risk factor and environmental risk factors, how to broaden studies to study other exposures, dietary factors and modulating those factors as well as behavioral and lifestyle factors.
2. How to study in smaller cohorts including growing a common language, determining common biomarkers/base panel and how do we work with smaller cohorts
3. How best to deal with small n, large p problem
4. Problems with very heterogeneous clinical conditions (such as spinal cord injury) where there may be very differing outcomes based on severity/location of injury that far outweigh effects of environmental exposures
5. Difficult to establish causality with adverse exposures in small populations because unlike beneficial interventions unable to randomize people to adverse exposures.
6. Challenges in studying chronic disease where people may change their exposures after they become ill (e.g. needing to stop work because of illness, moving). Harder to study premorbid exposures.

Potential Solutions:

1. Use of animal or cell models to identify exposures of greatest impact and for more causal studies. Examples:
    a. collect pollution from freeways and then exposome mice to study response to these exposures as well as any interventions
    b. Animal models of spinal cord injury where can randomize groups to exposures (either pre or post injury) to compare effects
    c. Zebrafish models with use of real world mixtures to study complex effects
    d. In systemic autoimmune disease - test tube model stimulates type I interferon/key cytokines in response to toxnet chemicals - looking at type I interferon response
2. Use of Human as the exposure monitor - urine untargeted analysis in these clinical populations - linkages to inhaled exposures
3. Targeted analysis of chemical classes with better hypothesized mechanisms of action
4. Mixture models and statistics - evolving and evolving rapidly - new statistical innovations bring over going to advance a study struggle with more innovative methods - moving forward.
5. There are some advantages to small populations studies - larger studies environmental exposures can be “grayed out” - small cohort from delimited area can better define problem and collect data appropriate to solution. Also clinical populations can have better longitudinal retention than healthy populations.
6. Longitudinal profiling can be an important to address between person variability (which reduces statistical power further in small samples) because individual can

serve as their own control - may work better for chronic conditions where exposures can exacerbate clinical condition or where there are well developed clinical biomarkers that can be followed over time.

OPPORTUNITIES FOR ACTION:

- Question: if disease has history of clusters emerging somewhere in the world – could that lead to be followed to understand effect of exposures (problem may be confounders outweigh environmental exposure effects.) Or occupational studies.
- Longitudinal Cohorts to facilitate using individuals as their own control (works best variations in exposures and disease activity over time)
- Statistical method development address mixtures, small n populations, “causal” modeling methods
- Animal models, pre-animal models to establish important associations/causal mechanisms
- Adding exposome onto existing cohorts/multi-institutional studies
- Combining small cohorts (especially if they have biological samples that could be analyzed for exposures) or pre-step to multi-institutional study.

IMMEDIATE NEXT STEPS:

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Funding can be an issue - hard to have major funding without establishing importance (particular causal relationship with an outcome) , difficult to establish causal relationship with an outcome in small population with clinical heterogeneity, etc. Catch-22 which makes it difficult to obtain funding.

ISSUE #43: Developing and implementing intervention studies in the context of the human exposome

CONVENER(S): Lida Chatzi

PARTICIPANTS: Joeseph Braun, Irva Hertz-Picciotto, Gwen Coleman, Antonia Calafat, Sarra Bridges, Jesse Goodrich, Charles Sneiderman, Srimathi Kannan, Katarina Grafanaki, Peng Gao, Rima Habre, Arcot Rajasekar, Susan Laessig**,** Carmen Chen, Allison Zhang, Lisa Rider, Dakotah Maguire, Elisabeth Cook, Yau Adamu, Bren Ames, Sarah Rock

SUMMARY OF DISCUSSION:

- Does exposomic framework provide the structure for successful intervention trials? Potential strengths of exposome intervention studies.
    - Allows us to incorporate the novel exposure assessment methods outlined in exposomic framework to characterize multiple exposures.
    - Start with a targeted approach – focus on a single exposure for funding opportunities and policy change, but capture more exposures
    - Use of intermediate omics biomarkers (epigenomics, metabolomics, proteomics, RNAseq) as biomarkers of effect. This framework may allow us to link the intervention to biomarker rather than a health outcome (less follow up time, smaller sample size)

- What are the best study designs for exposome intervention studies?
    - Natural Experiments, Personal interventions, Multi-modal intervention, Community-based participatory research (CBPR)

- Important questions to inform study design
    - What are the exposures you are trying to reduce and what are the sources?
    - Which are the drivers of outcome? What are the pathways?
    - How can we look upstream to understand:
        - Is this a feasible intervention long term? (affordable, sustainable, etc.)
        - Are these interventions culturally relevant?
        - Are we targeting the appropriate populations for this intervention? (i.e. those that are susceptible to health effects)

- Questions on study design
    - Do we have to characterize exposures and measure pre- and post-intervention?
    - Do we target those who have been highly exposed?
    - Can we prove that these studies are effective in the long term? Can we push these ideas upstream by integrating GIS/urban planning?

- Ideas
    - Partner with policymakers for intervention studies
    - Use smaller scale study to link intervention to intermediate biomarkers (omics biomarkers, single cell RNA seq), rather than the health outcome
    - Start with a targeted approach – focus on a single exposure for funding opportunities and policy change, but capture more exposures

  - Use systematic reviews and meta-analysis to inform intervention studies on environmental health research.
  - Explore opportunities to conduct exposome research in the context of natural experiments (eg climate change initiative, water filtration for PFAS)

OPPORTUNITIES FOR ACTION:

- NIEHS funding opportunities for intervention studies in the context of exposome research
- Facilitate opportunities for conducting systematic reviews and meta-analyses in the context of environmental health research. Big picture studies, not focused on single exposures.
- Conduct exposomic studies in parallel with current changes in filtration methods, policy changes, and exposure sources

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- You cannot isolate intervention to a single exposure
- Researchers/epidemiologists alone do not have the expertise for intervention and implementation studies – need to collaborate with communities, implementation scientists, and researchers from other fields to conduct this type of research.

ISSUE #44: Innovative clinical systems and models of care aligned with interdisciplinary exposomic interventions and advancing clinical epidemiology designs, particularly in environmental justice communities.

CONVENER(S): Jessica Castner

PARTICIPANTS: Bren Ames

SUMMARY OF DISCUSSION:

Disaster R&D units (similar to disaster medical assistance teams but with an R & D focus) that travel to regions with acute increases in disaster exposures (large scale fire disasters with smoke exposure outside evacuation zone, hurricane-related home flooding, volcanic ash) focused on residents with multiple chronic conditions (occupational exposures often already well addressed, but opportunities to increase there, too) for multi-level harmful exposome reduction intervention testing and novel protective practices in housing modifications, filtration, therapeutics (e.g. considerations for increase doses/frequency of prescribed medications where indicated (inhalers, anti-arrhythmic), novel extremolytes or other EENT/Respiratory protective mucus membrane coating solutions/other therapeutics to interrupt/reduce exposure pathways at the molecular and tissue level.), etc.

Telehealth R&D units with a specialty designation to assess and intervene to reduce harmful exposome conditions for those at risk, in addition to standard care for qualifying multiple chronic conditions with high level of environmental burden (documented occupational exposure with chronic disease sequelae, asthma, migraine with environmental triggers, CHD in high ambient particulate exposure geographies, autoimmune disease, allergy, related mental health conditions, EENT/respiratory irritation linked to environmental exposures, etc.). Leverage screenshots of video-telehealth of patient environment to assess/generate a repository of novel exposome assessment methods that do not add to clinician burden or workflow.

Home visitation R & D units in Justice40 or EJ communities to deliver multi-level harmful exposome reduction interventions and monitoring in addition to usual care for high risk populations (mother-baby, respiratory disease, cardiovascular disease, migraine, known EENT/respiratory irritation linked to low level chemical exposures, etc.).

Extend the EMU concept to mobile clinic/home visitation/telehealth with interventionists/clinicians who provide standard of care/usual episodic and chronic disease care plus expertise in reducing harmful exposome exposures. For example, a specialty primary care clinic or visiting nurses/public health nurses with clinicians certified in harmful exposome reduction interventions.

Evidence based standards, assessments, and regulation/certification on odors and fragrance exposure assessment and standards in clinical environments and models of care.

Better clinical detection and treatment for chemical exposure induced immune responses (or olfactory receptor induced neuro/immune responses) that parallel IgE-mediated immune responses.

EMU or Environmental health care units/environmental health inpatient units – purpose is to provide “clean” place for patients with increased/highest susceptibility (e.g. syndromic experiences aligned with TILT/environmental illness/chemical sensitivity; asthma with chemical triggers common to personal care products/used in health care environment/ autism with environmental trigger linked to odors, digestive problems, food allergies, etc.) to environmental exposures for acute care/short-term and residential therapy alternative site.

Need for clinical guidelines and feasible practices; synthesis of gaps in implementation science of exposome applications in clinical care.

Implementation science of CDC fragrance free policy (laundry/personal care products brought into health care workplace) and other harmful exposome reduction interventions in acute and long term care settings.

Deeper understanding of the exposome conditions and effective interventions in disaster shelters. Interventions to address the special needs of those susceptible to harmful exposome conditions in disaster shelters (allergens, molds, etc.).

OPPORTUNITIES FOR ACTION:

Expand R&D from a single intervention by intervention study to a model of care study and/or multi-level investigation that incorporates the health care delivery system under which harmful exposome reduction interventions are delivered.

Align disaster R&D unit with current disaster response efforts to accelerate advancement in natural disaster/hazard exposure environments.

Utilize intramural clinical unit strengths/environments (and government health care delivery) to model care delivery systems that may scale/translate to private sector.

Align capacity building for clinical delivery models to reduce harmful exposome conditions with current and upcoming efforts to decarbonize the health sector.

IMMEDIATE NEXT STEPS:

High level institute alignment with EPA/DHHS decarbonize health sector initiatives focused on care delivery models, clinician education, metrics, and incentives.

Investigate opportunities at NIH clinical center for EMU as exemplar/model with well characterized policies, operations, and related outcomes. Investigate opportunities in government-sector care (military hospitals, veterans’ affairs hospitals, IHS facilities) to assess for leadership alignment/commitment with need implement/scale EMU. Increase clinician capacity for harmful exposome reduction models of care and implementation science.

Develop partnerships with public health community health worker models to escalate home visitation/telehealth care for those with multiple chronic conditions with a known high environmental-attributable burden of disease – enhance capacity of these public health care delivery systems for harmful exposomic reduction interventions.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Incentives aligned/misaligned with other care priorities or manners in which public health and clinical care delivery is financed and organized. R&D often focuses on intervention by intervention rather than on the delivery system or model of care under which these interventions are organized and delivered – multi-level conceptualizations needed.

ISSUE #45: Decision Support Tools to help physicians incorporate exposomics into patient care

CONVENER(S): David Balshaw

PARTICIPANTS: Krystal Pollitt, Graham Parker, Bob Wright, Shannon Bell, Chris States, Michelle Bennett, Ariana Haidari, Rachel Keith, Hyun Chung, Jessica Castner

SUMMARY OF DISCUSSION:

- Touches on our Return of Results discussion:
    - Applicability of CLIA (particularly with wearables)
    - Actionable levels aren't really a thing we have
- How to interest clinicians in this data in the first place
    - Part of the problem is ego, they understand it and feel that they have been educated there; exposure is hard and a harder sell
    - Get environment into the med school curriculum
        - Engage with the Dean of Admissions who sets the curriculum
        - Engage with LCME, ACGME
    - Relate to what they do understand (diet, pharmaceuticals)
- To engage clinicians it has to be actionable
    - Billable/medicare reimbursable
        - What is the evidence base threshold for medicare?
        - How did Genetic Counseling get in there?
    - Consult with physician on validating the exposure data would be billable (if you found an exposure of concern)
- To add something to a 15 minute Dr. visit need to be really simple to use, and take something away
- Start simple, asthmatics add a indoor/wearable air monitor to understand triggers
- How do we go to emerging contaminants?
    - Clinicians are unwilling to report the uncertain
    - Clinicians are (generally) uncomfortable with a research effort connected to patient care
- Can we identify sources – guide behavior change no/low cost interventions
- Implementation Science/Health Services is very genetics focused, get environment into that space
    - EWG and Silent Spring report back tools
    - cpDat and other databases of what is in products
    - "Exposome Risk Scores" analogous to polygenic risk scores
    - Behavior change is fundamentally hard, particularly when they are entrenched behaviors
- Environmental correlate of a Genetic Counselor
    - Share courses with dieticians, etc.
    - It addresses a liability issue, you have to help people understand their risks
    - Consider the analogy to low penetrance genetic variation and how hard that is in the genetics arena
        - Focus on the most obvious 'high penetrance' exposures
- Clinicians arguing against including Return of Results in IRB approvals

    - Will bend to patient pressure – if 20 patients ask what phthalates do they will find the information
- Divide and conquer – pulmonologists are interested, some neuroscientists are becoming interested start with them
- Get exposure data into the clinical guidelines
- Think of other clinicians than physicians – dieticians (will spend up to an hour with the person), nurse practitioners, physician assistant, genetics counselors
    - They are already geared to 'what can we take off the physicians plate'
    - Poison Control, Occupational health
- Grand Rounds experience with Genetics Counselors are underwhelming and they only have to master one realm; we are so broad it is going to be hard to train them
    - Minimally a master level; PhD might be preferable
    - R25 as a pipeline tool; get the students interested
    - Draw people from related fields like industrial hygiene, genetics, dieticians, etc.
    - Needs communication to hospitals that this is desirable
- Need research on how to detoxify someone
    - Pharmaceutical/nutraceutical intervention trials for environmentally mediated disease
    - Leverage Biobanks from trials with exposomics to identify factors that influence therapy effectiveness
- Where outside of the hospital could this service be useful?
    - Educational arena
    - Community advocacy/EJ/health disparities
    - As a stand alone 'general interest'
    - Disaster Response/Climate Change (huge in the CTSA world right now)
    - Lifestage – perinatal – children - elderly

OPPORTUNITIES FOR ACTION:

- Training Grants for Environmental Counseling and environmental implementation science/R25
    - Biomedical engineering as a problem solving community that we might be able engage with in a population scale public health world
- Expand the PEHSU training to other lifestages
- Identify the 'High Penetrance Toxicants' that in an of themselves are bad (Pb) as opposed to low penetrance where you need a genetic susceptibility or very high exposure
- Need driven by climate change, https://www.nih.gov/sites/default/files/research-training/initiatives/climate-change/20220802-announcement-scholars.pdf
- Commercialization of the exposome (23 and me model)
    - Marketing challenge to build a demand
- Exposure mitigation
    - If you can't move from an area with high exposure what do we do?
    - Cookstove model, the obvious may work but not be accepted, its more complicated
    - Prescriptions for air cleaners, cleaner stoves, air conditioners – healthy homes retrofits
- Leverage Consumer demand – mother-baby exposures

- Leverage Biobanks from trials with exposomics to identify factors that influence therapy effectiveness
    - Also the Atul Butte mining of the Kaiser data
- Find one or two exposures to focus on getting into the clinical guidelines
    - Climate change – air pollution - cardiopulmonary

IMMEDIATE NEXT STEPS:

- Research the process for becoming billable
    - Patient detoxification improves outcomes
- Research process for setting clinical guidelines and work to incorporate more exposure knowledge there
- Research CMMS medical family homes program
- Shift our research toward people who are sick and how to detoxify them

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Our natural tendency to undersell our importance
- Our focus on prevention is limiting, it’s a hard sell, no one funds it
- Psychological barrier to getting environmental health integrated into medical education

ISSUE #46: Integrating adverse health outcomes (ex: respiratory pathologies, cancer, etc) with environmental pollution burdens, and newer sensor technologies

CONVENER(S): Lily Wu

PARTICIPANTS: (1 is a lonely number)

SUMMARY OF DISCUSSION:

Simply put, exposomics has a world of potential – it can bridge knowns with kind-of knowns, and unknowns.

- We know that air pollution, primarily from the burning of fossil fuels produce greenhouse gases, which has resulted in climate change.
- We know humans have many adverse health effects from exposure to chemicals and pollution from different sources in the built and natural environment.
    - Many adverse health outcomes takes a long time to develop (ex: cancer) and cause(s) is/are incredibly challenging to identify.
- We do not necessarily know who, what, when, where, why and how are exposures impact the health of people.

Exposomics (a non-targeted approach) can be bridged with biomonitoring (a targeted approach) and translational sciences ((such as key characteristics, adverse outcome pathways, mode of action, etc.); a semi-targeted approach) to validate answers to complex risk assessment issues.

Cumulative impacts are not addressed by the current standard human health risk assessment.

Very simplified ideas:

- Cumulative impacts = cumulative exposure(s) + cumulative risk (vulnerability)
- Our built environment isn't equitable. Populations in communities with more pollution burdens do not necessarily have access to means for reducing their exposure(s), and risk to adverse outcomes may be higher.
- Individual low cost PM2.5 sensors (such as PurpleAir) and other technologies such as smart phones may help individuals reduce their exposure to poor air quality and track other health metrics.
    - Access to technology and internet infrastructure is not equitable

OPPORTUNITIES FOR ACTION:

- Build multi-disciplinary working relationships
    - Government, academics, and communities in any and all levels of combinations
        - International, national, state, local levels
        - Establish trust
- Share data-widely (transparency)

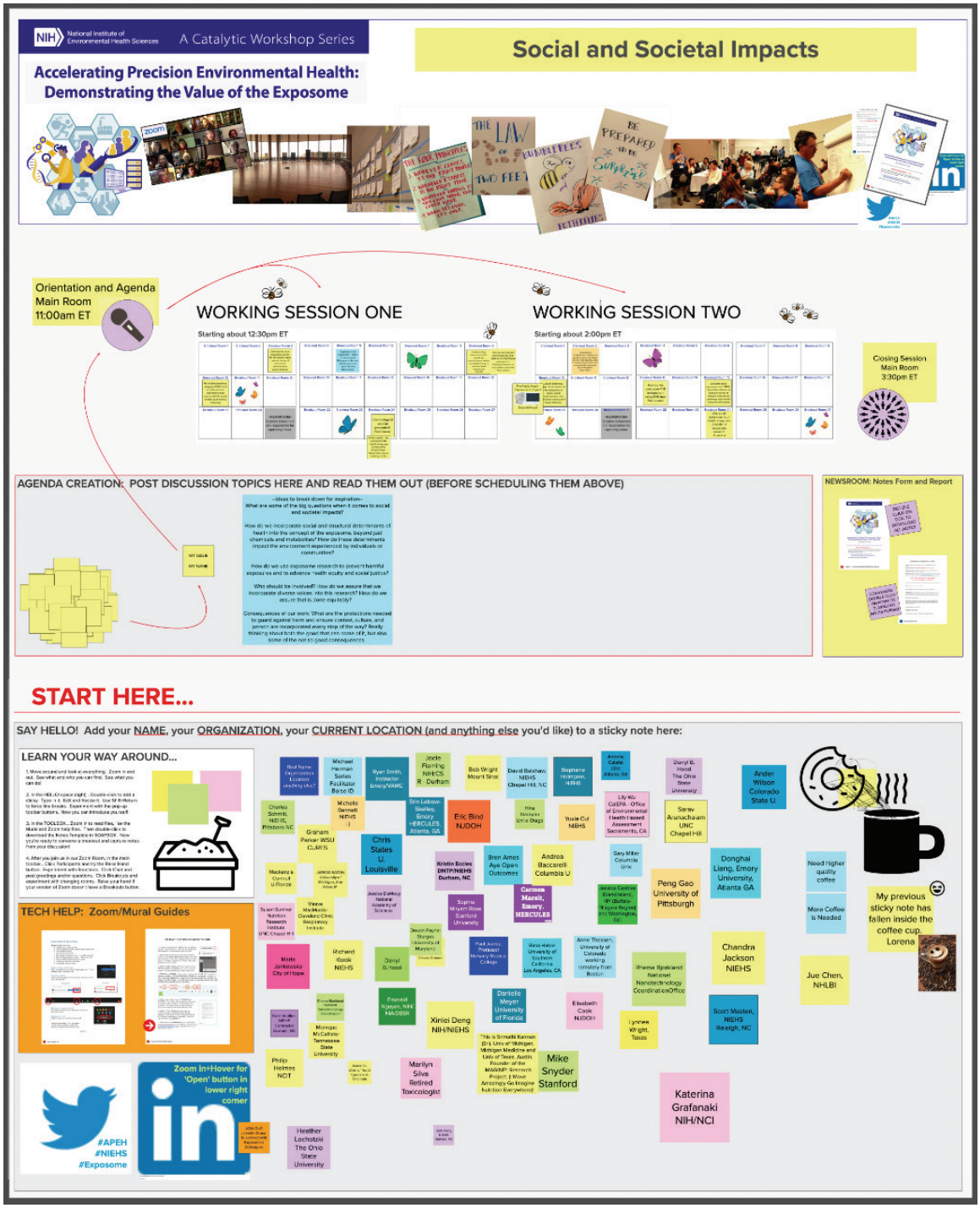
IMMEDIATE NEXT STEPS:

- Share successful examples widely for others to learn from/implement
- Develop shared definitions and goals
    - Definitions should be accessible to different disciplines (scientific, engineering, computational/AI, and translatable to the lay person/public)
- Scientific communication for the general public
    - messaging

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Universally sharable data as its developed
    - Who and where can it be “housed”?
    - How will it be paid for?

VIRTUAL WORKSHOP #4: Social and Societal Impacts



A high-level view of our fourth workshop space, including our agenda and the space we used to create it. Much of the detail won't scale to be easily readable, but it gives some sense of the messy, organic, emergent nature of our work.

ISSUE #47: How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience.

CONVENER(S): Paul Juarez and Lily Wu

PARTICIPANTS: Trevor Penning, Edith Eaton, Hina Narayan, Gary Miller, Katerina Grafanaki, Danielle Meyer, Devon Payne-Sturges, Sarra Bridges, Rhema Bjorkland, Jarrod Eaton, Eric Binc, Kai Zhang, Thurka Sangaramoorthy, Erin Lebow-Skelley, Jessica Castner, Ananya Paria, Caitlin Falk

SUMMARY OF DISCUSSION:

- How is exposomic data going to affect regulation to protect health?
- Correlating geospatial exposures with internal biomarkers; population surveillance studies
- 1 km grid size, geospatial grid size
- Exposomic analysis in policy - not “ready” in the US
- Multigenerational effects of epigenomics
    - Interventional methods/treatments developed from this data?
    - HHEAR
    - Biological pathways

From Erin Lebow-Skelley to Everyone 10:14 AM

- I should add: VERY interested in how we move the science to action and actual change for communities! Policy, intervention, etc. What is needed?
- Macroenvironmental factors, built environment

From Devon Payne-Sturges to Everyone 10:03 AM

Regarding application of exposome data, perhaps would it be helpful for exposome scientists to understand how policy decisions are made

From Michelle Bennett to Everyone 10:13 AM

Human Health Exposure Analysis Resource (HHEAR) provides services to researchers who want to include or expand analyses of environmental exposures in their studies of human health. HHEAR is funded by NIEHS; the National Cancer Institute; the National Heart, Lung, and Blood Institute; and the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) Program.
https://hhearprogram.org/
https://www.niehs.nih.gov/research/supported/exposure/hhear/index.cfm

From Erin Lebow-Skelley to Everyone 10:22 AM

We at HERCULES are definitely interested.

We referenced the public health exposome in our community definition of the exposome - a great framework!!

https://www.frontiersin.org/articles/10.3389/fpubh.2022.842539/full?fbclid=IwAR0B99wMHHh4gS0punIjGs8kCh5eeZBzZKQwxiz63W6EtZnip__GfypHA8s

From Devon Payne-Sturges to Everyone 10:22 AM
There are lots of papers from EU on assessing the impacts of chemical mixtures

From Gary Miller to Everyone 10:23 AM
We do know a lot about exposures that would allow action without a more complete exposomics analysis.

From Erin Lebow-Skelley to Everyone 10:14 AM
I should add: VERY interested in how we move the science to action and actual change for communities! Policy, intervention, etc. What is needed?

From Devon Payne-Sturges to Everyone 10:32 AM
@Jessica, this is what is done for pesticides. However, health effects can occur via multi-MOAs and if we focus only on one, we miss critical effects.

From KATERINA GRAFANAKI to Everyone 10:39 AM
1. Experimental Design of inclusive studies,
2. Systematic Reviews, to identify exposomic exposures and potentially future "emergency"cases,
3. Epigenetic analysis identifying meaningful biomarkers and GEO affected pathways, in order to validate them in the real-world,
4. Public health strategies should be proactive - in the context of policy making,
5. Communicate and educate the public to recognize dangers and report them, in order to create trustworthy "geocoding"

From Erin Lebow-Skelley to Everyone 10:39 AM
We have been gathering the lived experience of local communities in Atlanta using the exposome framework and would love to see more of this incorporated into the science! https://www.frontiersin.org/articles/10.3389/fpubh.2022.842539/full?fbclid=IwAR0B99wMHHh4gS0punIjGs8kCh5eeZBzZKQwxiz63W6EtZnip__GfypHA8s

- Data driven approaches vs. hypothesis driven approaches

OPPORTUNITIES FOR ACTION:

- European regulatory framework and science as a model
- Individual level data compared to community level data (ex: air pollution measures from sensors to regulatory monitors)
- Defining cumulative exposures to affect air pollution reductions
- Risk communications
- Adverse outcome pathways (AOPs) to correlate exposomics
    - Systematic review
    - Translational sciences (key characteristics, mode of action, etc.)
- Regarding application of exposome data, perhaps would it be helpful for exposome scientists to understand how policy decisions are made

IMMEDIATE NEXT STEPS:

- NIEHS investing in the framework for exposomics to affect policy
- Create a roadmap to contextualize exposomics
- Develop a “roadmap” for consistent approach to using exposomics
- Include multidisciplinary sciences (social, biological, data, etc.)
- Take learning lessons from international regulatory scientists
    - Add what works for US

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Integrating cumulative impacts to the lived experience when there are many silos in science, government, etc.
    - How to align the silos?
- Many “moving variables”
    - Study populations provide only a snapshot in time of data

ISSUE #48: Extrapolating/merging SDOH and exposures from alternative data sources (EHR, social media, purchasing histories)

CONVENER(S): Marta Jankowska

PARTICIPANTS: Maeve MacMurdo, Chris States, Yuxia Cui, Kavita Berger, Rima Habre, Rachel Keith, Jessica De Mouy, David Balshaw, Mackenzie Connell, Ariana Haidari, Stephanie Holmgren

SUMMARY OF DISCUSSION:

Issues of interest to the participants:

- Challenge how we can quantify exposure using EMR?
- Naming SDOH, what are they, and then how do we quantify/define them?
- Mechanics of how we pull data out of open datasets. How do we go over PHIs and firewalls – how do we incorporate the multilevel nature/structure of the data into our questions?
- Perhaps there isn't one list of SDOH that we all need to use… how do we do it right and how do we incorporate various definitions?
- How do we do this right with modeling?
- EHR/EMR is so messy and often poor data - how do we use them properly, how do we get a reliable source of data there?
- Interest at NIEHS is how do we cost effectively implement the exposome in very large studies such as All of Us. You must use the data that you have available to the extent that you can, but you don't want garbage in / garbage out. EHR data is all based on procedure and what gets the most money the fastest not based on what is going on with the patient.
- Minimize burden on participants in terms of invasive methods – can we pull in wearables and other methods that don't seem to violate as much of the patient's trust with research.
- Are there certain exposures that are more impacted by SDOH.
- Which covariates do we need in a population? Can we use that to figure out the best ways to measure disparities?

Themes

Triangulation

- Short scales, can we develop better short scales. Can we use these for validation for other information sets? Validation of neighborhood factors… bringing us back to harmonization and validation of neighborhood measures.
- Have ability to ask individuals and compare to more objective geospatial measures.
- Balance of tons of data but dealing with noise and less data but its more specific/accurate. Need individual level validation of how things are perceived.
- If one person uses SVI and compares it to another using CalEnv how do you compare them? These indexes use different data to generate the outcome, and how much variation are you introducing by using various indexes. Nuance at sub levels, might need to use other data sources with higher resolution, other contextually specific datasets. Elements that are cross cutting that may always hold, other factors that vary and are specific to the specific context.
- Technology in research that can help address SDOH, examples food access and diet quality very hard to get good data in low literacy populations. Photo navigation and dietary assessment can provide insight into diet access and food quality. Lots of

opportunity to leverage technology for triangulating data and targeting populations. We have health apps where you can upload health records, but also are monitoring health aspects. Some are terrible and some are improving, what does that mean for gathering data that is more precise? Other countries gathering data on Covid infection, what does that mean for monitoring health? So many tools being developed outside of research contexts, is there a need/opportunity/challenge to use some of that information. 23 and me also gives customers a questionnaire to fill out and try to correlate those answers with the genome sequencing and have established relationships with GSK for making drugs. Have incorporated these questionnaires that ask about everything. Given all this new private sector and tech development, but part of the broader ecosystem, what roles do they play? What data sources can they offer?

- Community perspective – is it the same as what researchers think are important in SDOH? Will it change across communities and regions?
- We need to validate and triangulate our data and information sources, big failing because always left with what exists or someone else collected (at the time, someone else thought important, but maybe not the right question years later)

Burden/privacy

- Looking at PHI, when do they consent, when do they not consent. A lot of data can be pulled without IRB, the most valuable thing is the address + time of exposure. Asking patients to fill out extensive histories takes hours. PHI is a burden, but the participant/patient becomes weary. Answers get less and less accurate as you go down the list.
- Do we need different questions for people of different backgrounds?
- How do tech and apps that play into patient privacy and patient concerns, when people participate in these do they realize the data is being used on these larger scales for research etc.
- People when participating in research studies bounded by IRBs are getting more concerned about their data and samples due to misconduct by larger companies. People are becoming savvier and its impacting patients in a good way.

Definition

- Variation of levels of an SDOH within a population as compared to another population, but we still want to measure it.
- Same question can mean different things – cultural sensitivity. Questions would need to be vetted in focus groups.
- What are things worth looking at – education, income, neighborhood (zip codes and within), housing quality, do we know what is most important?
- Often think about obvious ones (poverty, education) e.g. census data which in of itself is not perfect. For people hardest to reach may not have great data on them. Issues with diversity and cultures/people not reporting race/ethnicity, not finding a category that fits them. May not just be census level that we should be thinking about… in smaller studies we need to be able to have small validation studies (harmonization and representation).
- SDOH boil down to that there are many, and in each neighborhood will vary, and in each community maybe different factors drive disparities. Structural racism may be an underlying confounder for a lot of this. Which one is the most important at the individual, neighborhood level. Generalize based on CT but they are a broad measure and they don’t capture neighborhood level variation.

- Have to start somewhere – decide for the moment what the top 10 are, start collecting the data, and see how it works out and then shift and drop some, add others. Can't get frozen because we aren't collecting it all. Integrate with health outcome/exposure data and start integrating.
- There's a lot on the individual, family, community, neighborhood, larger society level that matters for many of these SDOH's (what is easier to do at scale, might not always be capturing all these levels.)
- Admin boundaries don't necessarily reflect 'real-life' boundaries of how people move and who they interact with and where they access everything they need in their lives etc.. another census data issue

Study design/modeling

- Amount of data is going to vary based on the type of study you are running. Large studies you can make more adjustments, but how do you incorp. into smaller studies and still retain power. Adjustments – accounting for errors, accounting for missing data. Example: how do SDOH alter exposure outcomes, can only do so much can only have so many factors within the analysis based on the population size. Smaller population studies don't have 1000s 10000s people may be harder to account for SDOH. SDOH as a confounder or mediator, only so much that can be done.
- Numbers and sample size – multiple testing? Alternative ways to validate inferences? Some of the thought behind multiple testing may be off base, not applied quite correctly… often measuring different things. In SDOH we are likely measuring different things. Can you find something that corroborates your results? This field will need something like that. Link health outcome with SDOH various definitions, what measures can replicate that inference that aren't quite the same.
- Conflate power with sample size – forget that there is a lot more that gives statistical power e.g., measurement error. Improvements in a study that can give more power than samples size. Can go back to corroboration or triangulation and if you have higher confidence in the measure may increase your power. Is there a limit to where you can include SDOH based on sample size?

OPPORTUNITIES FOR ACTION:

- Advancements in stats methods for small sample sizes. Can pull a bit from economists for stats ideas – looking at the stats themselves versus how we collect the data may help in overcoming hurdles.
- Collaboration – pulling small sample sizes and working across samples to validate (triangulation).
- Harmonize some of the large datasets that are out there for SDOH. Helps with comparing results from various studies.
- Utilizing consumer geared technology in research, partnerships with tech companies/data collection. How to keep data compliant with PHI rules? HIPAA protections are only as good as people are willing/unwilling to share their own data via an app. Legal/security protection for when people volunteer their data to the apps. Taking science to people where they are… opportunity.
- Getting PHI/HIPAA rules changed… much of this data and tech didn't exist when these rules were written.
- Short scales – validation of shorter methods and incorporation of those into EMR for more reliable data collection. EMR quality is an obstacle. But some measures are very standard such as PHQ-9, can we get a standard SDOH measure across the board?

- The genomics community has done a lot of work on reporting results from commercial services and apps can learn from their work.

IMMEDIATE NEXT STEPS:

- More $$$$$$
- Top 10 SDOH <- data driven exercise, like a meta analysis of health outcomes. If you look at the largest studies what data do they have in them already that capture SDOH?

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- More $$$$$$
- Standards for SDOH, question dependent, harmonization/validity of the question.

ISSUE #49: Causal Pathways, teasing out the sequencing of policy, SDOH, and Chemical Exposures

CONVENER(S): David Balshaw, NIEHS, and Darryl Hood, THE OSU

PARTICIPANTS:
Anne Thessen, Kavita Berger, Rachel Keith, Sarra Bridges, Chris States, Marta Jankowska, Jarrod Eaton, Paul Juarez, Hina Narayan, Katerina Grafanaki, Eric Bind, Lorena Baccaglini, Michelle Bennet, Ariana Haidari, Carmen Marsit, Devon Payne-Sturgess, Jodie Fleming

SUMMARY OF DISCUSSION:

- Not independent variables, interdependent, how do we map the causality
- Historically it all starts with policy, redlining, zoning, etc. drives SDOH and Chemical Exposure
- Not only how policy is incorporated and analyzed, also how we use the information to change policy to address EJ and EHD, burden of exposure
- Policy as a tool for public health, education so communities know that they are exposed, identify risks, be proactive. Policy before the problem manifests
- By the time the chemical or SDOH/Policy gets under the skin it has been diluted so much that effect sizes are small. The effects are just as strong as chemicals in the blood, but the data don't show it
- Research in service to the public, make sure we serve the community and enable action
    - Conflict between our research mission and focus and the communities need for action
- Linkage of genomes, phenomes, and exposomes
- Create a database of policies and their impact, difference between having a policy and having it implemented or enforced. Different jurisdiction leads to different effects. Easy to get federal data, more challenging to get state (50 places, inequal access), local is a mess!
- Examine and explore how health outcomes vary in a policy context through land use and ordinances. Policies relating to built environment, social policies (SDOH), and access to health care
- Urban – Rural divide, much different policies because there is much different land use
- Questions
    - Modeling at the census track, on average or at the individual? Individuals who opt in. That dilutes variation as everyone in the CT gets the same value.
        - Work through stakeholders to make sure that they have variation in the zips within the CTs
        - An association can serve as a 'red flag; for a deeper dive locally
        - Can layer clustering, supervised, and Bayesian approaches to drive the associations
        - Does this become offset or enhanced as we get to a larger and more diverse analysis (state-wide or national) and there is more variation because the CT is a smaller unit?

- Analyze all of the data you can get in different ways to draw the inferences and validate (capture uncertainty)? But how do we use it proactively to drive science for policy or policy for science?
- Carmen – wandering across rooms, policy is coming up a lot, question is how do we actually measure policy and it's effects
    - Connections between policies and their interactions? Becomes a challenging feedback loop.
    - Improve through iterations
    - Systems approaches/modeling needed – there will be non-linear relationships at work.
    - Look to fields outside of traditional EHS for examples, look to sociology, philosophy, and history for examples
- Intended versus unintended consequences of policies as you look at unequal implementation across jurisdictions.
    - Look at case studies that look at context with small numbers
    - Help recognize the potential future impacts, help educate the public and the underserved.

OPPORTUNITIES FOR ACTION:

- Need to focus on data-driven rather than hypothesis driven research. Data sets become an issue, need larger more complex data
    - Support acceptance of Discovery Driven research – relies on validation, of data sets, identification of meaningful and informative hazards/risks
- Look at effects across life-course
    - Recognize that new cohorts are hard, but there are some
    - Synthetic cohorts like ECHO
    - Meta and pooled analysis of historical data, need curated databases
- Harmonization/standardization of tools (bioinformatics and modeling tools)
    - How do we bridge the gap between those who are developing the tools and those who need them?
    - Proxy measures may have very different meaning in different communities
- Expansion of PhenX type libraries (ECHO questionnaire of implementable instruments to harmonize the data
- Conflict between our research mission and focus and the communities need for action
    - DOT and DOE are actively trying to work on this, may be lessons learned
    - Enhanced models of CBPR
- Don't focus only on the negative, think of the positive (access to green space, green energy, etc.). Makes it easier to engage in policy change if it is an improvement in health.

IMMEDIATE NEXT STEPS:

- Consensus ontology of environment (EHLC)
    - First priority is convincing the community these are useful so they will be implemented

- Synthesis of existing ontologies or finding the gaps in between as needed? Yes

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Acceptance of data-driven in review specifically
- Standards, Standards, Standards, and getting acceptance of implementation of standards

ISSUE #50: Characterizing exposome and SDOH disparities within and between levels of analysis and causal pathways to health outcomes.

CONVENER(S): Jessica Castner

PARTICIPANTS: Rhema Bjorkland**;** Ariana Haidari; Maeve MacMurdo

SUMMARY OF DISCUSSION:

Indoor air quality measures relative to nanoparticle exposure.

Responsible development of nonotechnology – DEI, ethics, distribution of potentially harmful exposures.

Need to develop indoor exposure measures of nanoparticles. Dosimetry and toxicokinetics/transformation.

Consider the precautionary principle in nanotech manufacture, use, etc. for those with high burden of SDOH risk. Proactively characterize health effects of nanoparticle-formulated household and personal products (e.g. sunscreen, clothing, furniture, adhesives, coatings, computers, electronics, etc.). Health risk assessment and ecological health assessment….methods of modeling and understanding health risks, exposure pathways, body burden, tissue effects.

Ethical, legal, societal implications. Is there a racial identity, educational level, or income strata where nanoparticle personal or household products tend to be purchased/marketed and thus generating a potential SDoH disparity in potentially harmful exposure?

Epigentics – Mexico City cohort data with -omics. Water access, water usage, related to nutrition and meal preparation practices. City or well, consistent running water – water quality.

Waste and recycling stream of the electronic lifecycle (specifically related to nanoparticles) with SDOH and lifecycle assessments.

Climate change impact – prepare for future with changes in clean/quality water access and environmental degradation and environmental justice.

Variation with air pollution is street to street/hyperlocal analysis may be needed with environmental justice geospatial characterization.

Nano waste fate and transport – scale and geographic distribution unknown – need to characterize how far particles travel in air, water, soil as pathways of exposure.

Potential protective factors in SDOH heterogeneity or homogeneity at the larger levels (census, zip code, etc.) – measure of discrimination and societal acceptance in heterogeneity/homogeneity of SDOH at the community level vs. flat measures of the SDoH itself. Consider social support interactions.

Measures of stability/resilience (“exposome risk you know that is stable vs. a new risk”). Housing instability in the health record…. Insurance instability and changes in insurance as an exploratory proxy. Minimize burden on patients. Economic stability at the community level. Unique considerations of climate change risk as disconnected from past generation’s knowledge and coping as a measure of instability.

Need methods with triangulate – big/data population level and link with individual qualitative and outlier case studies. Individual exposure experience, clinical record, exposure worry – tie findings back to understanding within the population level using mixed-methods.

Personal care product choice may provide a counterfactual to the ability to group and attribute to geographic community level determinants…other consumer purchasing choices may as well.

Nutrition, low-income and food insecurity with community turning to subsistence food sources (gardens, fishing, hunting) with additional exposure potential/lack of knowledge about prevention and remediation – particularly around legacy waste that may be displaced/re-emerge into pathway of exposure with climate change—particularly in former manufacturing and low-income neighborhoods/regions.

Link of progression from biomarker of exposure to disease outcome – differences when examining at the individual level or aggregating by geographic or SDoH community.

Dose-response from individual SDOH interaction with chemical exposures vs. integrating contextual/community SDoH.

OPPORTUNITIES FOR ACTION:

Integrate social science, anthropology expertise in risk and risk communication related to nanoparticle characterization for individual and community level exposure characterization.

Adding idea of modeling a non-segregated homogeneity at the community level of what is often considered an SDoH risk as a potential protective factor when the experiences of discrimination linked to that SDoH are lessoned/removed or social support is increased (e.g. lower variability in regional household income, lower variability in regional educational attainment) – or low local/regional disparities even if national or larger scale disparity comparisons exist. Adding considerations for modeling social support across communities with traditionally considered high aggregate but homogeneous SDoH in the exposome-outcome pathway.

IMMEDIATE NEXT STEPS:

Support mixed methods, multi-level discovery of SDoH interactions with chemical exposome and equity interventions.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Precautionary principle needs - as applied to nanoparticle manufacturing/product human lifecycle exposures. Harmonizing individual cohort data for larger comparisons and community-level comparisons. Reducing participant/patient burden in research participation with the many measures/complexities of characterizing exposome and SDoH.

ISSUE #51: Defining the ecto-exposome across the life-course (built, natural, physical and social environment)

CONVENER(S): Darryl B. Hood, THE OSU, and Susan Sumner, UNC Chapel Hill

PARTICIPANTS:

- Bob Wright – Mt Sinai
- Ann Thessen- data science- from ??
- Allison Cook – NCI- epigenetics and connection to exposome- multiple chronic conditions
- Elizabeth Cook – NJ Department of Health
- Carmen Marsit – Rollins School of Public Health and Organizer
- Anayna Paria- NIH population- social and env health study section
- Sri Kannan- UMich- nutrition based effect modification of exposures
- Emerald Nguyen –
- Chandra Jackson-NIEHS epi focused on social and env determinants of sleep health
- Heather Lochotzki – PhD student in the Hood lab- exposures and learning outcomes
- Dave Jett- NINDS- director of neuro exposome and tox
- Monique McAllister- assistant professor at Tenn State Univ- public health exposome and covid related exposures that might effect learning
- Jody Flemming- SRO at CSR- env toxicants
- Donghia Liang- Emory- maternal and child health- and exposures

SUMMARY OF DISCUSSION:

Dr Hood had a case study approach to the topic so the take home points were; How do we learn from what he presented? Is what his group is doing what we need to think about. In terms of what needs to happen nationally? What are some of our other starting points? What can be done in the next year? Is this work just being done in Ohio? Is Ohio building more capacity/foundation than in other states, regions? Is it the hope that at some point we can link everything together.

Overview by Dr. Hood. He began the *Public Health Exposome* discussion from a policy perspective indicating the potential ways in which to explore how health outcomes vary by policy boundaries. There are multiple levels of government that programs and funds sift through before implementation in vulnerable communities. For example, in Ohio there are 24 regional planning councils, 88 counties, and over 1,000 local governments, villages, townships, cities and counties, all of which coalesce into land uses determined by zoning ordinances.

Dr. Hood stressed that is very likely that different levels of government vary in their impact on predicting health outcomes. For example, many local governments were developed during the period of America's suburbanization just after WWII. This was a time when the US Federal Housing Administration rendered those communities with black residents to be a bad investment for governmental loans, shaping the tax structure and local programs in a racialized way that continues to impact how communities experience policies that influence community health.

Conversely, he pointed out that regional councils in cities are a relatively new institutional construct that have attempted to mitigate inequities via programs in transportation, job development, environmental protection, housing, etc. and through local government collaboration. These different levels of governments provide a patchwork of policy environments that work as 'laboratories of democracy' whose variation we might be able to utilize to focus in on as to what levels of government might be most impactful to sustain healthy communities.

Short story from Susan Sumner – Health disparities in food access drives availability of intake of nutrients, and inadequate intakes are associated with perturbations in host metabolism, metabolic individuality, and adverse health outcomes. Genetics, SNPS, and polymorphisms related to nutrient metabolism are key in sex, race, and ethnic disparities in health outcomes, and access to the adequate intakes of key nutrients, and mitigation of poor diet is key.

Bob Wright – Need the overlay maps of local policy – in terms of exposure risk and health outcomes- for example maternal morbidity and health outcomes…and the overlay with policies

Chandra Jackson - Challenges in the policy map as that relates to "what are the route determinant in health disparities" e.g. structural racism etc…

Darryl- Policies and Trajectory of in relationship to health trends/risks

Sri Kannan- How will Emerging biomarkers be incorporated into Exposome research and policy point of view

Darryl Hood - Discussed slide on Strategies for using data to deliver public health and policy

Michelle Bennet asked - How do we learn from what Darryl is doing/has done as we think about what needs to happen nationally? What are our starting points? What can we do in the next year? Is it just in Ohio? Is Ohio building more capacity/foundation thank in other states, regions? Is it the hope that at some point we can link everything together.

Ann Thessen - Are the Paracliques robust in other areas?

Bob Wright- mapping layers of policies vs. chemical and non-chemical stressors should be helpful and a great starting point at the county levels.

Cancer Corridor in Louisiana as an example

Anne Thessen mentions data harmonization needs and how to harmonize data at the national level. OR do we need new Paracliques for new areas?

Darryl- variables are probably right- but paracliques may be different for different areas

Rima Habre – Body burden of many chemicals in a pilot program for the state of NJ- in a cohort of 500. Looking for trends or pockets of high exposure.

Led to discussion on air pollution, sensors, and open air network, etc..

Importance of Validation and performance of sensors.

Allison Cook: Epigenetic changes that link to the exposome and health outcomes

David Jett-needs for more basic research to address the biological plausibility of the exposomics factors impacting health.

Hood provides more focus on extraction and use of data for impacting policy.

OPPORTUNITIES FOR ACTION:

Many but dependent on what NIEHS decides is a priority from these workshops.

IMMEDIATE NEXT STEPS:

To ensure that there is immediate translation **of opportunities for action** from this NIEHS workshop to alignment with the present and future strategic plan.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Traditional thinking and I would like to suggest that everyone go to the NASEM workshop on Children and the environment held just 2-weeks ago and watch it. See link below.

https://mountsinaiexposomics.org/events/exposome-symposium/past-events-es/past-events-exposome-symposium-2022/

ISSUE #52: Fragrance Free Exposome - Allow Environmental Refugees to Access Healthcare and rejoin Society

CONVENER(S): Bren Ames

PARTICIPANTS:

SUMMARY OF DISCUSSION:

Healing and Health-Promoting Environments are crucial for lowering disability barriers and allowing Environmental Refugees to access healthcare without experiencing further harm, to participate in research, and begin to rejoin society. Environmental Refugees are people who have been forced to withdraw from many places, social interactions and services because they are susceptible to, and experience harm from, chemical and electromagnetic emanations that are now ubiquitous,

- Healthy indoor and outdoor environmental quality are critical to the health and well-being of everyone, and particularly for people impacted by environmental access barriers.

- Improving indoor environmental quality makes indoor environments healthier for everyone and more accessible for people with chemical and electrical sensitivities.

- Healthy and accessible environments, at the most elemental level, **must be smoke, pesticide, and fragrance-free with minimal electromagnetic pollution**.

By using the exposome as a framework for organizing and implementing a holistic approach for environmental health as part of healthcare, we can advance both preventive and corrective actions from the individual to regulatory levels.

If we also offer systematic monitoring and evaluation of environmental exposures, biological responses, and the experiences of vulnerable populations within such improved conditions -- we can improve research and understanding of exposome influences on health while making a measureable difference in the lives of many.

The exposome experience lens that environmentally sensitive people offer can inform research, policies and practices that **enhance conditions conducive to wellbeing for all** as we develop and demonstrate paths for positive impact in vulnerable, underserved communities.

OPPORTUNITIES FOR ACTION:

Adapted from the 2015 presentation **"Environmental Refugees: Understanding the Disability Access Needs of Persons with Environmental Sensitivities in Rural America***" by Mary Lamielle, Executive Director, National Center for Environmental Health Strategies, Inc. <ncehs.org>:*

ADOPT AND PRACTICE -- WORKPLACE POLICIES

- No Smoking Policy
- Fragrance-Free Policy
- IPM (Integrated Pest Management) Policy: eliminate conventional pesticides for buildings and grounds; organic or low impact products and practices, if necessary
- Cleaning and Maintenance Policy: promote least toxic/low impact products and practices for cleaning and maintenance; materials and furnishings; remodeling
- Notification Policy
- Vehicle Idling Policy
- Cell Phones and Smart Phones, Wi-Fi, and EMF Shielding Policy

Federal Fragrance-Free Policies

CDC Indoor Environmental Quality Policy, June 2009

Quotes from CDC's Fragrance-Free Policy

"Scented or fragranced products are prohibited at all times in all interior space owned, rented, or leased by CDC." (p. 9)

"Fragrance is not appropriate for a professional work environment, and the use of some products with fragrance may be detrimental to the health of workers with chemical sensitivities, allergies, asthma, and chronic headaches/migraines." (p. 9)

CDC Non-Permissible Products

- Incense, candles, or reed diffusers
- Fragrance-emitting devices of any kind
- Wall-mounted devices, similar to fragrance-emitting devices, that operate automatically or by pushing a button to dispense deodorizers or disinfectants
- Potpourri
- Plug-in or spray air fresheners
- Urinal or toilet blocks
- Other fragranced deodorizer/re-odorizer products

Census Bureau, March 2009
Issued fragrance-free policy and implementing language to protect employees and accommodate disabled workers

Department of Health and Human Services, October 10, 2010
Restricts application of fragranced products at work; exempts fitness centers and day-care centers

List of non-permissible fragranced cleaning and maintenance products identical to CDC Fragrance-Free Policy

FEMA
Blanket purchase agreements (BPAs) for medical supplies require products to be latex and fragrance-free (Source: Getting Real I, September 2010)

U.S. Access Board
2000 Adopts Fragrance-Free Policy for Board Meetings
http://www.access-board.gov/the-board/policies/fragrance-free-environment
2006 “Indoor Environmental Quality Project Report”
http://www.access-board.gov/research/completed-research/indoor-environmental-quality

2010 Opens permanent meeting space designated fragrance-free: all participants refrain from perfume and cologne; unscented personal care products; scent-free cleaning and maintenance (July 2010)

IMMEDIATE NEXT STEPS:

Establish **Cleaner Air Room & Paths of Travel for Healthcare Facilities**

- No smoking
- Fragrance-Free
- Pesticide-Free (Indoors and Outdoors)
- Least Toxic/Risk Cleaning Products
- No Recent Construction or Remodeling Including Carpet Installation
- Cell phones and Wi-Fi turned off
- Ability to turn off or unplug computers and other electrical equipment by occupant or staff
- Ability to turn off fluorescent lighting by occupant or staff
- Ability to adjust temperature and air flow by occupant or staff, or the availability of operable window(s)

http://www.access-board.gov/research/completed-research/indoor-environmental-quality

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Need to support

- OPPORTUNITIES FOR ACTION listed above
- Creation of exposome conditions conducive to near-to-long-term healing and health (**SALUGENESIS**).
- Win-win synergies and outcomes.

ISSUE #53: What social determinants of health should we consider in exposome research?

CONVENER(S): Yuxia Cui

PARTICIPANTS: Susan Sumner, Donghai Liang, Carmen Marsit, Marilyn Silva, Christopher states, lily Wu, Srimathi Kannan, and others

SUMMARY OF DISCUSSION:

Participants shared their own research experiences, where social determinants of health play an important role in the health outcomes observed, and the challenges and opportunities they see as moving forward.

- How to define social determinants of health? How to measure?
- How important we think about social determinants of health?
- There is no one set of social determinants of health for every study to use. It depends on the community/population you study.
- Wildfire, drought, pesticides…California is facing many challenges, these are not only environmental problems, but also social problems
- High exposure to traffic related air pollution in an African American cohort of pregnant women in Atlanta.
- Language barriers and mistrust lead to poor communication and health literacy
- Community engagement, dissemination and return of results are important
- Microbiome at the intersection of nutrition and environmental exposure (obesogens from pesticides exposure)
- Education, poverty, neighborhood factors, structural racism, housing, …
- Sleep is an important factor
- Social context is important for data interpretation

OPPORTUNITIES FOR ACTION:

- Understanding the linkage between disparity in socioeconomic status, food access, and neighborhood factors and nutritional status and how that to different health outcomes. (Social driver – food and nutrition – health disparity).
- In nutritional studies can stratify the data based on race and ethnicity and look at the zip code level factors that impact the results. Nutrition biomarkers have been developed. Results can be returned to the participants and guide intervention.
- This workshop series is a great opportunity. It brings together the diverse expertise. NIEHS should develop a roadmap so a common language can be used for communicating science.

IMMEDIATE NEXT STEPS:

- Community engagement is critical. Engage the community as study partners, not just study subjects for collecting data from.

- Build partnership in general, not only with the communities, but also across federal and state government agencies to allow more broad resource sharing, data access…
- Involvement of youth in developing educational materials, community engagement and intervention
- Final good models and follow (for example, the work in California can be a good model)

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Difficulty in obtaining data on social determinates of health. Lack of transparency in data creates difficulty for researchers to access and sue.
- Lack of reliable statistical methods for analyzing complex social determinants data, which are often interrelated.
- Need shared definition.
- Replicating social study in a different cohort is challenging (or not possible). How to extrapolate?
- Omics data is relevant and important but how to translate that information into something that community can utilize to improve their health

ISSUE #54: Unintentional consequences, making sure we do no harm, not mixing diversity with disparity… How to ensure diverse voices are incorporated? Both community and investigators

CONVENER(S): Rima Habre

PARTICIPANTS: Allison Cook, Graham Parker, Danielle Meyer, Chandra Jackson, Edith Eaton, Bren Ames, Marta Jankowska, Elisabeth Cook

SUMMARY OF DISCUSSION:

When incorporating social determinants of health and thinking about societal impacts in the exposome, in particular in regards to avoiding unintentional consequences and making sure we do no harm, and we make sure to engage and include diverse voices and stakeholders into the discussion, these important themes came out of our discussion.

Beware of averaging out nuance – there have been lots of examples in the literature on public health/medical solutions being developed on one group that is not very diverse or representative, with unintentional consequences. For example, pulse oximeters were largely developed on people with light skin tones and reading biased high for people with darker skin tones, because development of these methods did not consider nuance or variability, see https://www.fda.gov/medical-devices/safety-communications/pulse-oximeter-accuracy-and-limitations-fda-safety-communication

Proposals for campaigns to mitigate racial bias of pulse oximeters (from Albert Donnay as an example)

- Salient examples of unintentional consequences in focusing on one population in our investigations, but we need to institutionalize mandatory health equity lens to all our research processes (from the beginning, plenty of examples of harm or unintended consequences when this was not the case)
- For example, require health equity impact assessments to inform policy evaluations, as we create and apply the exposome these kinds of assessments can help weight or formally assess a project's or study's potential for harm and potential to promote health equity (from a lifecycle of the project lens, not just at the end).

Beware of healthy equity tourism – Because funding is now available or directed at this work, people are entering the field without proper training and understanding of nuance, while experts in this field already exist and have been advocating for and working on these issues for a long time (often from less well resources institutions). This can do way more harm than likely intended, typically coming from more wealthy resourced environments, with higher funding success rates, which risks marginalizing already historically excluded people. This risk can be avoided if collaboration is required between communities being studies and researchers – concept of nothing about me without me (should not allow study of populations without an investigator from that group or population, even if positively intended, can end up creating harm because of preexisting biases that infiltrate research process questions and outcomes, or unintentional labeling, judging, future harm, etc. take example from rules around studies of Native Americans).

- Often times we see **'saviors'** 'rescuers' 'vanguards' wanting to lead/direct/help solve problems in underserved communities with existing bodies of governance already working on solutions. The **'parachute' scientist** here to save the day.. while there is nothing inherently wrong with wanting to be a leader or wanting to help, not really understanding culture/history/anthropology of community, not engaging and listening to local collaborators and stakeholders to intelligently inform the design and implementation of the project and report back/discussions with community can have harmful unintended consequences.
- Internal exposome has been focus so far – now bringing in social impacts and external exposome – can use omics tech to pinpoint which one or more factors matter – link exposure to health outcome – **concern with homogeneous investigators and institutions that are not quite diverse doing most of this work – missing opportunities to bring in all the questions and how to diversify the field and scientists doing the work** – logistically speaking, especially when those interested most coming from less wealthy sourced institutions (how do we institutionalize requirements for diversity)?
- **How do we make sure well-intentioned efforts (monitoring, greening etc.) do not come back to cause harm or impact local communities adversely,** how do we balance that with the need to know what local conditions are like to advocate for improvement? Need for knowledge / data / measurements generally a priority even if might highlight issues that could lead to longer term unintended consequences (eg, property prices in local community being impacted, gentrification, etc.). Balance of having access to tons of data vs more locally curated and relevant data.
- How do we make sure these requirements are not abused or used as shortcuts to checking boxes off (for funding opportunities, for evaluations by funding agencies etc..) and actually forcing/motivating the real work to happen**? Incentivize the process instead of the outcome (guard against gaming the diversity system)** – for example, by requiring community partners be co-authors on paper/community being studied (**nothing about us without us model**), collaborator would have to also benefit from co-authorship and has a say in what goes in it.
    - On requirement to institutionalize this into future exposome effort to enhance the rigor of the science, perhaps we **need new standards for publishing on racism**– see health affairs article: https://www.healthaffairs.org/do/10.1377/forefront.20200630.939347/

- Implementing the processes of inclusion, and avoiding extra checkmark situation, within HERCULES, training to pilot applicants to **reframe research** apps in context of inclusion, reframing things with exposome attributes instead of using race as a shortcut, grouping by race/skin tone is a shortcut, stress and experiences of racism certainly have biological and broader impacts on health – reframe racism and other attributes of exposome instead of shortcut (myth of race) – make it a process rather than a checklist to meet
    - Great examples from community engagement core work in CURES P30 center (Graham Parker)

Empower stakeholders to take more informed interest in exposomics and G x E – thinking about longer term sustainable models, and avoiding unintended consequences, **how will we allow MDs working in a hospital to bill for exposomics issues** – should be talking to lawyers and insurance companies, what will they do with this information? Social entrepreneurship? Genetic counseling precedent? Questions already asked but not fully answered.. crucial to get doctors involved/interested in exposome, and if we can get to a

point to demonstrate the value/cost savings from a billing perspective of incorporating SDOH into exposome and medical records, maybe we can be more effective at prevention and early detection (and move focus away from treatment further upstream).

- **Reimbursement** models for EMR/EHR type of external exposome data, link environmental data (air pollution, temp, etc.) to **claims** data (within privacy requirements) to characterize physical env of individuals – link to biomarker data, with a glimpse to internal – can then make cases with cost benefit analyses of what should be covered by insurance (more comprehensive)

It is also important to focus on biomarkers of healing and positive health and not just mechanisms and disease: Chronic conditions build up slowly over time, get very expensive and matter a lot for health – early biomarkers of damage/increased risk? We can save a lot of money if we find a way to early detect and slow/prevent – make the case and support it.. don't just focus on treating disease after it appears. Current biomedical model not really embracing this philosophy – focus on prevention and creating conditions for healing and health.

- When we identify X person/group as susceptible, insurance consequences, workplace consequences (minimize turnover, etc.), markers of a condition even if not expressed yet can have **adverse consequences in workplace and personal life**.. need creative ways to think about this in exposome framework – create conditions to support healing and health and not just focusing on pathologies after they have happened

How do we establish safe levels of exposure for all, even most vulnerable or sensitive groups? In occupational health safe exposure levels for workers – but we don't apply same logic for preventing chronic diseases as a whole – environmental recommendations not translating to local decision making – eg, recommendations on light pollution, evidence based, identify best practices or expert consensus on various exposures and use to drive change and standards within exposome context – intervene and study impact on health and move needle on biomarkers..

- Can we learn something from long term residential situations with institutionalized individuals (elder care, memory care, etc.) – facilities with environments that are clean enough for people to reside with no further harm.. having better background conditions allows us to understand…
- New infrastructure bill? Implications – requiring neighborhood scale air monitoring not just at fenceline/industrial facilities.. – will require data collection at that scale but we need to do the studies/establish the science to support health protective standards… pinpoint upstream reasons/sources to tackle..
- How to regulate products in a more streamlined way? If introducing product into consumer use, has to be at minimum able to be processed in downstream treatment / biodegradable or separable with existing level of treatment – lifecycle analysis.

OPPORTUNITIES FOR ACTION:

Real-time interventions, how to incorporate in exposome work for societal impact NOW? We can be actionable now. Communities know their issues the best, leverage

technologies to have citizens identify issue in their immediate environment to hold policy/decision makers accountable for addressing them.

- Citizen science approaches are helping incorporate community feedback from conception of idea – to bring to exposome – what are barriers and facilitators for being able to optimally leverage citizen science in context of exposome – eg, air sensors, personal, probably superior to stationary in a non-relevant location? Bring the tools and collecting the data at the right level that matters.

Low hanging fruit perhaps? – **utilize people that are susceptible in research for feedback about exposome conditions that are healthy for them** (**canaries, sentinels..),** if potential for harm to very vulnerable populations maybe hint or early sign that issue is relevant or potentially wider reaching in impact. Not just catering to people who are susceptible but using it as a way to understand / establish conditions that are healthy for all.

- Make sure we don't exclude communities/groups/vulnerable populations or remove barriers to their involvement as equal stakeholders (in all aspects of community including health care)
- Use known levels of thresholds on susceptibility etc. to create baseline acceptable living env for all individuals, currently most socially vulnerable and disenfranchised are living in inhumane conditions (public housing, unhoused, condemned buildings, Flint water crisis).

Social situations could mask environmental/adverse effects – no way to discern effects sometimes when no way to break away from it (no contrast, no other experience) – **baseline burden** can be different or too high sometimes masking or disguising other issues.. psychometrics.. (self-reported data and concerns with perceptions or baselines/experiences etc..). It is challenging to ensure construct validity in assessments that rely only on self-report but also important to triangulate or validate with more objective data that may be more actionable to truly understand nuance.

- When it comes to harmonization of questionnaires and perception questions – the more socially vulnerable the group the more overly burdened, don't want to add **burden**, caution needed.

Conflicts of interest and politics/pressure against revealing/talking about issues – can be a huge unintended consequence – lots of examples of triumphs of environmental success touted when underlying drivers were economics or business related rather than advocacy. Need to ensure we don't move on to the next "win", keep political attention on issues and not cater to conflicts of interest.

- Conflicts of interest can also appear in domains of expertise in healthcare, where vested interests in a disease persisting might trump desire to solve the issues (extreme example but important to consider).

IMMEDIATE NEXT STEPS:

Even if harmonization needs are real and important, first priority must be for ensuring equity and social impact, and capturing different experiences, mixtures, unique considerations and not using broad strokes or generalizations.

Still need to capture unique exposures and contexts that make an exposure relevant (freq, intensity, etc) for a particular group or outcome, even if not as prevalent in other contexts… profiling exposure patterns (across multiple dimensions) and looking at how these vary

across multiple populations/communities etc.. level of variability will not be captured by standard approach/assessment to everyone.

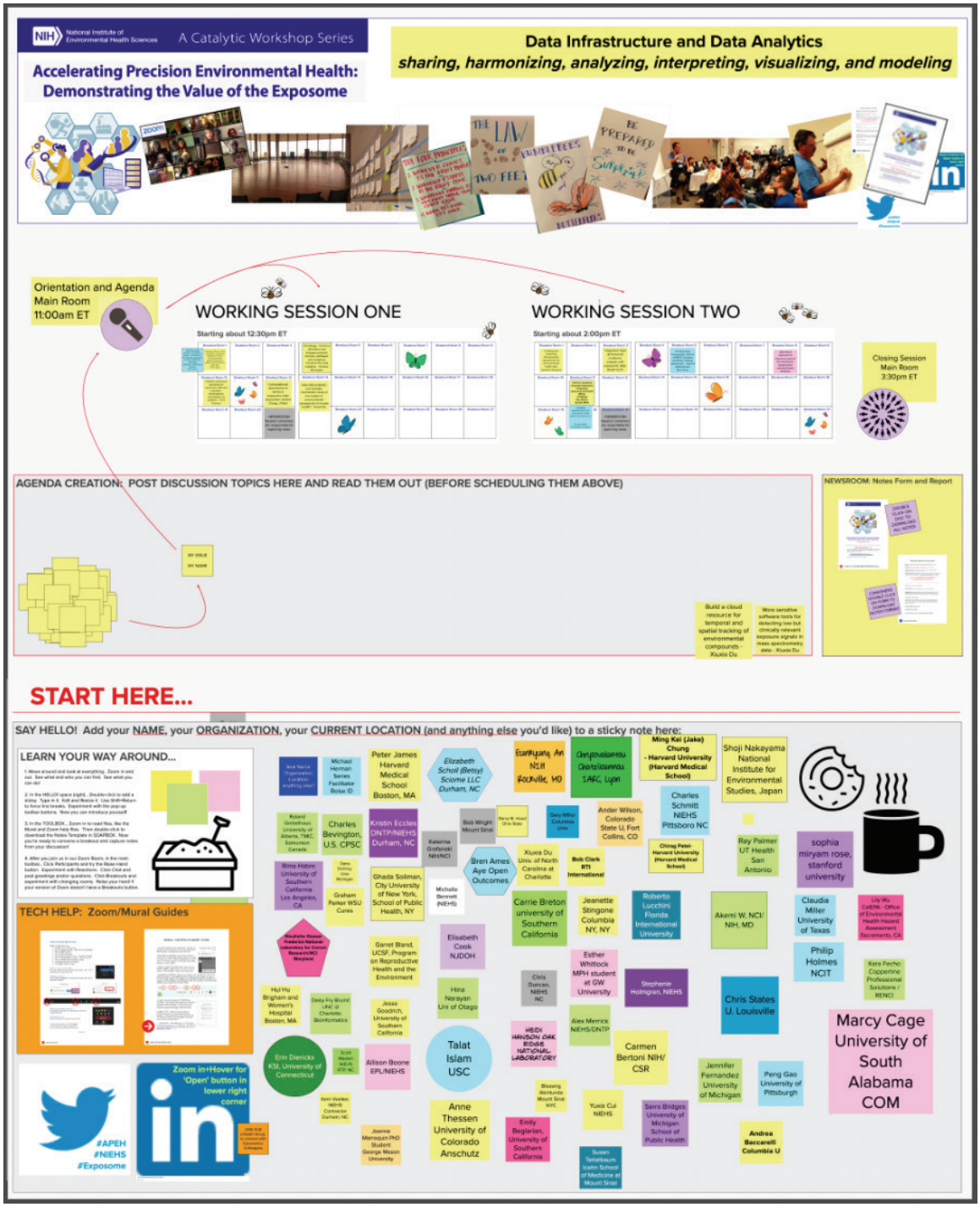
Different social vulnerabilities and biological susceptibility (and buffers/protective factors) will not be captured by standard/broad single approaches/quantifications.

We can actually get there with the exposome, especially linking EMR, SDOH, biomarker data, to get closer to Precision Environmental Health

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

A lot of important specific questions that can get lost in broad general questions, with unintended consequences

VIRTUAL WORKSHOP #5: Data Infrastructure, and Data Analytics



A high-level view of our fifth workshop space, including our agenda and the space we used to create it. Much of the detail won't scale to be easily readable, but it gives some sense of the messy, organic, emergent nature of our work.

ISSUE #55: Managing the Spatial Exposome

CONVENER(S): Peter James

PARTICIPANTS: Charles Schmitt, Dakotah Maguire, Erin Dierickx, Hui Hu, Kavita Berger, Maria Shatz, Yuxia Cui, Bren Ames

SUMMARY OF DISCUSSION:

Many spatial datasets

- Depends on size of datasets. If polygons, pretty small. But rasters can live on a single workstation. But if massive raster, google earth engine
- NIEHS ran into some problems with GEE. GIS team is using a linux package
- Concerned that not all researchers have access to computational resources and storage to deal with these datasets. How do we democratize these data?

Processing these data

Linking data with PHI / geocoded addresses / GPS

- Charles: PHI sat on medical servers. Not set up for high performance computing.
- Looking at DeGAUSS as a model. Essentially a containerized set of code that does exposure estimation. Moves only the spatial data you need while maintaining privacy (low enough spatial resolution to do that)
- Bren: Learning from data formats that were adopted by PIXAR. Had to deal with a lot of big data that is geolinked and changes over time. Streamlining but allowing it to be flexible and applied for lots of different purposes.
- SideFX Houdini. Flexible to tag points or edges with attributes. No limit to what attributes you can attach to a particular entity. Tools for migrating data between platforms and procedural dependencies. Have been able to pull in Google Earth Data.
- Dakotah: Migration process leaves opportunities for error
- Bren: Some tools would have to be developed for simple uses in health field.
- Apprentice version is free. But unclear what enterprise cost is.
- Python compatible
- Charles: Julia as an alternative to R or ArcGIS. Seems to run faster.

Sharing data across institutions (DeGAUSS)

- PJ: we use R.
- PJ: We are using Google Drive to share non-PHI spatial data easily
- Charles: using Google Drive makes sense. Where we've seen issues is with large scale GIS data and producing visual tools. Have to have a server. Using RStudio and have to have a significant server behind that. That becomes a cost.
- Charles: Any thoughts about a cloud-based product? Some clinical data is being made available on the cloud. Pushing heavily for researchers to stay on the cloud. Bring your code up to the cloud to work with that PHI.

- Dakotah: Degrees in geography. At Oak Ridge. Everything is locked down in servers that no one can get to it. Laws and security put in place make it difficult to implement the tech.
- Charles: Once you join GIS data to health data, how identifiable is it? Especially as you add more variables and more spatial data. Can you reverse geocode?
- One thing that shut down their work is releasing PM2.5, which could be re-engineered.

Ethical issues / maintaining privacy

- All of us—Environmental data. They have to deal with it.
- Maria: Hear a lot about risk of reidentification. You need the opportunity and the motivation. Why would a researcher care to identify?

OPPORTUNITIES FOR ACTION:

- Creating secure approaches for cloud computing
- Learning more about Houdini
- Learning more about Julia
- Understand more about reidentification risk
- Consensus on how different IRBs will determine whether geocoded address is PHI

IMMEDIATE NEXT STEPS:

- Look into process of converting R scripts and key algorithms to Houdini
- Cloud computing piece—plan to deal with large scale GIS data to enable computing with PHI data
- Convene legal/ethical, spatial epi folks, and computer scientists to figure out approved approach to storing and analyzing spatial data / PHI
- Communicate with NASA to understand what products are needed/coming on line

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Legal / ethical issues with cloud-computing: can this be solved with more investment / resources from NIH?
- Having data linked with the level of detail that it should be viewed at—that level of detail should be able to be tagged so that we can pull things in that are appropriate

ISSUE #56: Methods to advance "exposome-wide association studies"

CONVENER(S): Chirag J Patel

PARTICIPANTS: Alex Merrick, Alison Montsinger, Ander Wilson, Carrie Breton, Ghada Soliman, Heidi Hanson, Hina Narayan, Jake Chung, Mohamaed Shahriar, Rima Habre, Shoji Nakamura, Yixua Cui, Robert Wright, Lida Chatzi, Gary Miller, Alison Boone, Tim Fennell, Tina Baker, Talat Islam, Diane Kamen, Mike Langston, Jesse Goodrich, Nicolette GM, Alexandra Law, Kristin Eccles, Mike Langston, Kai Zhang, Phillip Holmes, Chris States, Alison Boone, Catherine Pichard

SUMMARY OF DISCUSSION:

- How to translate ExWAS results of complexity to policy?
- How to translate ExWAS results to experimentation?
- That is the optimal study design for ExWAS and how to get to etiology and mitigate biases such as confounding or reverse causality; power and type 1 error? How to communicate these issues as broadly as possible among diverse teams?
- How do we make ExWAS a standard for doing exposome-wide research that would incorporate at type 1 error and study design parameters?
- What measurements to use methods to use, and when, and how to perform exposome-wide analyses?
- How to gauge and QC exposure measurement at scale? How to analyze
- How to recognition for multi-disciplinary studies; how to recognize data producers and harmonizers; how to recognize team membership.

OPPORTUNITIES FOR ACTION:

- ELSI research for exposomic research
- Use of biobanks for exposome research
- Cross-listed educational opportunities for exposomic research; pull in data scientists/CSs
- Develop specific training in epidemiology, study design, biostatistics
- Building repositories and infrastructure for analysis
- Need for standards for analysis for ExWAS approaches
- Evaluation of diverse data sources, such as biobank data to conduct ExWAS
- Prerequisites include: Public data for evaluation of methods, benchmarking papers for evaluation of methods
- A google earth engine model for repositories that bring compute to the data (rather than the other way around) that contain canned methods for reproducible approaches
- Data access and security – how to obfuscate and keep data secure?

IMMEDIATE NEXT STEPS:

Leverage existing tools and mold them for exposomic research, including:

- DeGauss for sandboxed geocoding

- Ontologies for handling of meta-data for exposomic data (e.g., types and measurements of data)
- Compute resources, such as google earth engine
- Analytic pacakges: https://www.bioconductor.org/packages/devel/bioc/vignettes/omicRexposome/inst/doc/exposome_omic_integration.html

Scope out aims for parameters for ELSI-based research (https://www.genome.gov/Funded-Programs-Projects/ELSI-Research-Program-ethical-legal-social-implications#areas)

Older guide: Manrai et al, *ARPH* 2017 https://www.annualreviews.org/doi/10.1146/annurev-publhealth-082516-012737?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Understanding the data:

- Time-course of exposures and their time-dependent phenotypic effects are difficult to capture and may need new paradigms for analysis.

Translation of ExWAS and making exposomic research useful:

- ELSI research for exposomic approaches?
- How to communicate complex findings to stakeholders?
- Incentivization of data harmonization and integration of ‘omic information
- Open data repositories and infrastructure to conduct exposomic reseach

Training and hiring in academia:

- Data consumers vs. producers – how to make it reward multi-team science?
- Where do new faculty fit in?! – universities that consider trans-disciplinary approaches and moving beyond single displicines
- Courses that support data science of the exposome that cover epidemiology, biology/toxicology, computer science at all levels.

Supporting trans-disciplinary research:

- Meta-language about methods – how to we communicate in inter-disciplinary groups? How to incentivize them to speak together?
- Incentivizing long term vs. short term goals: citations that can accrue for datasets and methods

ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data

CONVENER(S): Jeanette Stingone

PARTICIPANTS: Maria Shatz, Anne Thessen, Yuxia Cui, Charles Schmitt, J Christopher States, Rosalind Wright, Stephanie Holmgren, Carrie Breton, Marcy Cage, Charles Bevington, Carmen Chen, Chris Duncan, Susan Teitelbaum, Tim Fennell, Lily Wu, Esther Whitlock, Kara Fecho, and others who joined after…

SUMMARY OF DISCUSSION:

- We need overarching data model with tools and services to translate between repositories

  Enable investigators to continue data culture but adopt and adapt new processes to use data models for translation (Beckett Sterner?-Data Unification Approaches); LinkML and BioLink, KGX (Knowledge Graph exchange) potential tools; Biomedical Data Translator; Software exists for functionality

- Think boldly! Including environmental data in a secure way with point of care data (EHR) and research data, bi-directional; how do we need to adapt data collection/deposition?Need infrastructure for translation to clinical care; Incorporate environment into existing clinical repositories in addition to research repositories

- What data should be deposited? Source-related databases, pathways, biomonitoring, exposed populations-occupation; Discussed during early afternoon breakout on ontologies

- Defining core elements as a community: How do we standardize and capture metadata needed to interpret data? (What was done in experiment)

- Software to be used by data generators needs to be user-friendly, easy and accurate/valid. Can be a real challenge; requires resources and people—Needs to be streamlined

- Devise Templates to Make it Easier for Data Depostion—Would they need to be linked to a BioLink model? (Every column is an element in BioLink model); Requires domain scientists/data generators/data users and semenatic scientists/software developer/modeler
  Example: OECD Templates—go into an online site that can be searched

- Ability to link across repositories key, but then need central repository of repositories. Create a Data Catalog?; Ensure it is all searchable and finable

- Automated solutions are needed; Manual can’t scale

- Connection to education about how to use linked repositories; how to incorporate different domains

- Training needs?: illustrate how difficult it can be to use someone else's data and then justification for need for standardization is clear; how can we be thoughtful about how to show people during training so they don't have to go through it on their own?

- Where are repositories housed? Who maintains them? How are they sustained? Need curators of repositories; Need sustained support; Should NIH maintain all repositories? Needs community input

- How do we work with existing repositories and extant data (e.g. web scraping)? Ideally can link EHS repositories to other domains; Requires expertise to link and use external data-streams to come into existing repositories

- Current academic reward model is a challenge to implementation of repositories and data sharing; Need to recognize team science; sharing data isn't a liability to promotion; Get buy-in from institutions; use existing institutions as models-example MPI grants gives credit to multiple people; Related challenge to junior faculty for data-sharing; need to recognize the valuable contributions of team science; journals acknowledging co-leading and consortial/collaborating authors is another example of policies to change reward model

- Use pathways to link datasets/repositories; AOP frameworks, MOA-translational sciences

- Recognize data-generators/depositors to facilitate community adoption: How are they acknowledged in publications?

  HHEAR Example: Embargo period and DOIs for datasets; provide information on funding etc so its easy to include in acknowledgements and citations

  Give depositors a way to track the use of data; create automated reminders of citations; used to create sharing index; educate journals/reviewers to check that data are cited

  Propriety software (Clariavite-Web of Science) exists to track use of public datasets: indexed datasets and data repositories and connected data to publications; track citations to data; data citation index does allow alerts

- DUA/MOU-something similar on the repository to access data; acknowledge responsibility to cite datasets and repository

- There is existing work in Data citation, versioning, identification that can be useful; From Earth Science community; existing tools to facilitate tracking and recognize contribution of data generators.

- Make data searchable through Google Data Search

- Need to reach audiences outside of EHS, including engineers, computer scientists, policy regulators, EJ communities, etc.; need common language for accessibility

- Cross-referencing abilities needed in a repository

- Existing repositories being used:
  -omics data has repositories and existing standards
  -IPSCR for social sciences

OPPORTUNITIES FOR ACTION:

- Create templates to facilitate standards for data deposition: What would they look like? What data/metadata to include? Need variety of templates depending upon data domain; all templates can be linked to health outcomes and then cross-linked; Define templates by measurement being done?

- Develop and disseminate metrics to value teaming and data sharing in the academic promotion process; Can be done through CTSA, Schools of Public Health, etc; Look to genomics for ideas?

- Push for requirements for deposition of data for publication; That leads to adoption of standards

- White paper to NIEHS/NCBI to support a public repository for EHS data (see obstacle below)

IMMEDIATE NEXT STEPS:

- Look at OECD as a potential model for templates of submitting standardized data/metadata; very siloed so may not fully translate to cross-disciplinary nature of exposome

- Requirements gathering for templates; host conversations with data generators and users

- Catalog existing repositories and the types of data they house; Understand the types of data that do not have a repository that meets standards to know what type of new repository might be needed

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Ownership is a primary obstacle: Should an EHS repository(ies) be publicly supported or owned? Do academic institutions have resources to host such a cross-disciplinary repository? How would they be sustained?

ISSUE #58: Data about exposure to trauma as related to the exposome/epigenetics

CONVENER(S): Esther Whitlock

PARTICIPANTS: Hina Narayan, Sophia Miryam Schussler-Fiorenza Rose, Tina Loos

SUMMARY OF DISCUSSION:

Trauma, especially in early childhood development, affects health throughout the lifetime. Epigenetics studies provide supporting evidence that trauma can be inherited because of DNA methylation and that changes in histone proteins to affect which genes are expressed.
The Socio-Exposome: socio-political factors and inequalities that affect health
"Early environmental quality and life-course mental health effects: The Equal-Life Project" (Irene van Kamp et al, 2022) → a review summarizing other studies about physical, social, and environmental factors affecting the health of children. This review proposed a framework for measuring and analyzing this data, but did not for example describe how the "bullying" measurement would be accomplished. Quantifying "bullying" is difficult despite its importance in the health of children. Other variables may also be difficult to quantify.

"Your zip code matters more than your genetic code" - a saying I heard in grad school; zip codes and conditions can cause a 10 year variance in life expectancy. For example, people living in particularly poor D.C. districts have a shorter average life expectancy than people living in more affluent neighborhoods or counties in the DC/MD/VA area.

Adverse Childhood Experiences and lifelong effect on health
Sophia is an expert in this field!

Need to integrate the data about social factors and physical exposures - for example, areas near poorer communities are more commonly chosen for toxic waste dump locations. Currently, studies about physical exposures and psychological exposures/traumas are rarely combined.

Brief tangent into ethnic disparities and how racial categories are more of a social construct but may be treated as biological categories by medical studies or public health publications, which may be problematic.

Isolation as an exposure during the Covid-19 pandemic?

Ethnic disparities in health outcomes as related to the Covid-19 pandemic

Environmental justice issues

The difficulties in sharing information with other countries, where the data is different, collected differently, definitions are different, cultural definitions of what abuse or trauma constitutes may be different.

SOURCES:

Book "The Body Keeps the Score" by Bessel van der Kolk

Papers that I referenced and shared in the chat box:

Deconstructing the role of the exposome in youth suicidal ideation: Trauma, neighborhood environment, developmental and gender effects | Elsevier Enhanced Reader. (n.d.). https://doi.org/10.1016/j.ynstr.2021.100314

Koch, S., Yoon, L., & Gils, B. (2020). From the Exposome to the Socioexposome in COVID-19 Research—A Call for More Multidisciplinary Research. *JAMA Network Open*, *3*(12), e2032287–e2032287. https://doi.org/10.1001/jamanetworkopen.2020.32287

Senier, L., Brown, P., Shostak, S., & Hanna, B. (2017). The Socio-Exposome: Advancing Exposure Science and Environmental Justice in a Post-Genomic Era. *Environmental sociology*, *3*(2), 107–121. https://doi.org/10.1080/23251042.2016.1220848

van Kamp, I., Persson Waye, K., Kanninen, K., Gulliver, J., Bozzon, A., Psyllidis, A., Boshuizen, H., Selander, J., van den Hazel, P., Brambilla, M., Foraster, M., Julvez, J., Klatte, M., Jeram, S., Lercher, P., Botteldooren, D., Ristovska, G., Kaprio, J., Schreckenberg, D., Hornikx, M., … Bolte, G. (2021). Early environmental quality and life-course mental health effects: The Equal-Life project. *Environmental epidemiology (Philadelphia, Pa.)*, *6*(1), e183. https://doi.org/10.1097/EE9.0000000000000183

OPPORTUNITIES FOR ACTION:

- Foster cross-sector collaboration
- Conduct studies that combine physical factors such as 2.5 particulate matter with the social and emotional factors involved in childhood development and lifelong health ramifications.

IMMEDIATE NEXT STEPS:

- Develop tools for public health departments, researchers, and stakeholder entities to use in collecting data about trauma, psychological factors, and components of the Socioexposome

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Combining different types of data about various categories of exposures that affect health can be difficult. Compatibility and definitions have to correspond
- Interviewing adults about their past can involve recall bias
- Retrospective studies present certain challenges for this and other reasons

ISSUE #59: Exposure Ontologies and Definitions Sources | Pathways | Receptors

CONVENER: Charles Bevington, CPSC

PARTICIPANTS:

- Stephanie Holmgren, NIEHS
- Anne Thessen, University of Colorado Anschutz
- Andrea Baccarelli, Columbia University
- Lily Wu, toxicologist, CalEPA - Office of Environmental Health Hazard Assessment
- Mireya Diaz, Homer Stryker M.D. School of Medicine, WMU
- Esther Whitlock, George Washington University, MPH
- David Balshaw, NIEHS

SUMMARY OF DISCUSSION:

Exposure science is a very diverse field that describes data on sources (i.e., chemicals used in products, chemicals used in industrial processes or tasks), pathways (i.e., near-field emissions or contact in the indoor environment or workplace, far-field emissions to environmental media), and receptors (i.e., intake and uptake into biological matrices of different population groups).

Exposure ontologies and definitions should consider information across the source to receptor continuum.

These exposure ontologies are definitions are agnostic to different regulatory contexts and should be interoperable to answer fit-for-purpose questions related to exposure science in support of exposure assessment.

Examples of existing ontologies and databases are provided below. In addition, discussion centered around specific examples or applications related to this topic.

HHEAR Ontology, https://bioportal.bioontology.org/ontologies/HHEAR#:~:text=The%20Human%20Health%20Exposure%20Analysis,environments%2C%20from%20conception%20through%20adulthood.

Also links to ExO and other major ontologies

Here's ECTO, https://bioportal.bioontology.org/ontologies/ECTO
Exposure model and mixtures. ECTO is build out for monarch initiative. Relatively new ontology. ECTO has value-added content in it. Hosted in Github. Multiple organizations.

PEGS survey- questionnaire data | are you exposed to solvents and do you have hobbies related to solvent exposures. Combination of tasks | occupation | residence and known exposures.

Comparative Toxicogenomics Database (CTD)-Has an existing exposure module ontology database http://ctdbase.org/

CPDAT- EPA Consumer Products Database Assessment Tool,
https://www.epa.gov/chemical-research/chemical-and-products-database-cpdat

Builds off of the - Walmart Database- who voluntarily shared Safety Data Sheets for all their products.

Product ingredients- database from NLM [Household Products Database]-

Household Products Database – https://www.whatsinproducts.com/

This is safety data sheets based.

Information transparency for ingredient sources, consumer product formulations. Suspect screening and non-targeted analysis from environmental and biomonitoring.

Example of types of information for consumer product sources

- Safety Data Sheets
- Experimental product testing (individual studies)
- Experimental product testing compiled by agencies
- Required reporting to government agencies

What can we learn using epigenomics databases for this purpose? How to protect people who are using the database from misinterpreting the database. Lack of understanding on what is in the database and what it is for.

Using the same ontologies that were out there, mapped the space to the studies that were out there. For example, using biomonitoring studies. Bias in chemical coverage of studies that are already out there vs. chemicals that haven't been analyzed yet because studies don't exist.

Relevance to integrating data across. Mixtures, classes, that have similar effects. Example BPA and other similar compounds. Potential benefit of trying to do systematic reviews and determine which chemical classes have similar endpoints, effects, mechanisms, uses, exposures, etc. Adjust one-at-a-time risk assessment paradigm to be quicker/faster. BPA both as used in consumer products and in other sources (background exposures). Needs to be a unifying language to define common sources, pathways, across disciplines.

RE unifying language - see EHLC
https://www.niehs.nih.gov/research/programs/ehlc/index.cfm

Databases from NIOSH- occupational exposure | occupational sources and occupational diseases connected through occupational surveillance by companies and or HHEs from NIOSH

Health risks associated with occupational industries (extractive such as coal mining). Even with epi data is available, that data is difficult to use proactively because it is looking for associations that have already happened.

Example- comparison of agricultural workers and residents living in or near pesticide applications. Need to know more about sources (pesticides).

Scale of reporting for who is exposed (occupational and non-occupational) Federal, State, County/Local databases. Thinking about definitions of how to define who is exposed. While there are databases of workers, there are not similar databases for other exposed population groups.

OPPORTUNITIES FOR ACTION:

- Cross-sector collaboration to provide safer occupational opportunities and adjustments for at-risk people, both employees and people who live in the area where exposures are significant. Developing terms to communicate across sectors.
- Centering the people at risk in the process of developing solutions instead of having a top-down approach

- Development of “common language” for the multidisciplinary sciences that are necessary for complex data sets (ex: data science such as Github, -omics data, toxicology “jargon”, exposure sciences, etc.)

    - Connecting these conversations with EJ screening tools and the language used for the public

- ELC- environmental health language collaborative - https://www.niehs.nih.gov/research/programs/ehlc/index.cfm. Sign up for email listserv at https://list.nih.gov/cgi-bin/wa.exe?SUBED1=EHSCOMMONLANGUAGE&A=1 Community driven approach to harmonize environmental health. Resource catalog which includes ontologies, vocabulary, This is in progress/working initiative. Main focus is around -use cases- Four use cases are currently in process. Is there a minimum information template that we can encourage common reporting, retrieval of information?
- https://public.tableau.com/app/profile/ntp.visuals/viz/EHSOntologyResources/EHSOntologyResources

IMMEDIATE NEXT STEPS:

- Develop an inventory of available exposure science ontologies- databases that cover exposure sources, pathways, and/or receptors and see which data fields that have in them.

- Crosswalk the ELC initiative with available data sources and databases.

- Encourage more participation in ELC. Sign-up- List-serve for ELC. Workshop coming up in the next couple of months.

- https://www.niehs.nih.gov/research/programs/ehlc/index.cfm

- Possible participation in voluntary standards development organizations once definitions- ontologies are defined to show applications

- Development on implementation plan to build on this series of workshops. (Near-term and longer-term next steps both need to be developed).

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Permanent funding for the entity(-ies) that will house databases that will be developed, integrating the existing databases, and incorporating data from past sources (ex: ToxNet) that are no longer used.

- Increasing participation and building consensus around harmonized definitions and ontologies related to exposure science.

ISSUE #60: Integrated High Dimensional Multiomic Analysis with Exposomics Data

CONVENER(S): David Conti

PARTICIPANTS: Jesse Goodrich, Rima Habre, David Balshaw, Graham Parker, Elizabeth Scholl, Robert Clark, Heidi Hanson, Alex Merrick, Lida Chatzi, Chada Soliman, Ghada Soliman, Garret Bland, Ander Wildon, Carmen Chen, Mireya Diaz, Jingxuan He, Charles Schmitt, Blessing Akintunde, Chirag Patel, Darryl Hood, Shoji Nakayama, Hina Narayan, Michael Snyder, Srimathi Kannan

SUMMARY OF DISCUSSION:

- Ideas of multiomics are different if you come from a population science vs. biological background
- For analysis, we can think about exposomics as a “new” version of omics
- Integrating environmental factors with omics is tricky
- Going a bit further- how to we put together a mediation type framework with exposomics, multiomics, and an outcome?
    - One option is to run all possible mediation models
- Discussion focused on different options for multiomics
    - Early vs. late integration approaches for omics analysis
        - Clustering, dimensionality reduction, etc.
    - Mediation approaches for exposomics and multiomics
    - There is not a best approach
- Common processing is important
- There is lots of variability in the different approaches, and deciding which to use is difficult, this compounds when you add additional omics.
- Pathway level results are a good way to compare results across studies
- For regulators: dose response or mechanisms of response are important
- Discussion of unsupervised vs. supervised approaches in exposomics
- Incorporating biological knowledge into the analysis is important but difficult

Questions:

- How do we leverage the biology to understand these approaches?
- How do we deal with missing values in exposomics- using imputation?
- Standardizing techniques, how do we compare between different studies?
    - One idea is that we can use lots of different approaches and narrow down once you start to get consistent results
- When you start to talk about “multiomic signatures”- how do you compare? If the goal is biological meaning, (ie, exposure → multiomic signatures), then the outcome is usually pathways, which is probably going to be robust to different analytic approaches.
- Multiomics is good for hypothesis generating, how do we then test these hypotheses?
    - Validation cohorts can help
- How do we quantify variability at each step of a multiomics analysis pipeline?
- How do you think about temporality in multiomics analysis? Ie, temporal dynamics.

- Windows of susceptibility- how would you look at windows of susceptibility with multiomics?
- Possibility of having a certified lab that can rerun analysis using a standardized analysis protocol?
    - For example- NIST can provide common samples that other people can use.
- Artificial intelligence approaches for multiomics?
    - There have been a lot of examples of success in other fields (ie, image processing)
    - Not many people are invested in how to take their shiny new method and help to be able to interpret these in a data science approach.
- Prediction frameworks vs. causation framework- how worried should we be about collinearity? More complex methods can deal with this pretty well.
- Thinking about leveraging large genetic databases where you have germline genetics- can we inform exposomics studies with this data?
    - For example- methods can be used to impute gene expression or metabolomics which can be implemented in exposomics studies

OPPORTUNITIES FOR ACTION:

- Developing robust pipelines for different multiomic analysis
- If you have a standardized lab, you can have a single protocol for data processing
- Bringing teams together from different backgrounds has the potential to push the field forward
- Create a journal club or other way of communication where people can share experience with new methods in the field of exposomics.

IMMEDIATE NEXT STEPS:

- Develop a set of samples for standardization and normalization - can be used by all studies to measure data (e.g. metabolomics), which can then be used to compare across studies for standardization and comparison of methods that are run on those samples
    - This will allow for standardization or benchmarking of different analysis approaches for multiomic data analysis approaches

ISSUE #61: Towards consensus standards for exposome data and metadata: development, coordination, and adoption.

CONVENER(S): Chris Duncan, NIEHS

PARTICIPANTS:

Susan Teitelbaum, ISMMS
Jeanette Stingone, Columbia Univ.
Christopher States, Univ. of Louisville
Darryl Hood, OSU
Esther Whitlock, George Washington University
Maria Shatz, NIEHS
Rosalind Wright, ISMMS

SUMMARY OF DISCUSSION:

Questions posed to initiate discussion:

- **Big question:** How can we move as a global community towards consensus standards for exposome data and metadata? What will it take to get to consensus, community-driven data standards?
- **Key technical/organizational aspects?** What are (or how do we identify) key metadata and schema needed to make diverse exposomics data interoperable and AI/ML-ready? How to best assemble teams to develop/extend/adapt standard terminologies, controlled vocabularies, ontologies, common data elements, minimal information standards, and related schemas and workflows that link together semantic meaning and data?
- **Social aspects and coordination?** Data and use cases relevant to the exposome are highly diverse. How to coordinate and engage the relevant persons, scientific/community groups, and organizations? How to do this without creating silos?
- **Adoption?** How to promote adoption of existing (or new) standards that are applicable to the exposome? What are anticipated barriers to adoption?
- **Gaps?** What are the current gaps and obstacles (for instance, infrastructure limitations)?

Discussion Notes:

- Example of ongoing work in this area:
  - EHLC Data Harmonization use case – ongoing group of 8 people. This group is talking about what ontologies, terminologies can/should be used.
- There is a spectrum of complexity in knowledge organization/representation ranging from term lists to ontologies?
  - Ontologies may not be needed in all types of use cases – labeling via standardized terminologies may be sufficient to achieve some goals.
  - However, we eventually need ontologies to support reasoning, and need buy in here.

    - Consider modular approaches with a range of term complexities – e.g. labeling → reasoning
- Discussion on the collection of standard measures (such as through resources such as the PhenX toolkit, etc.)
    - Consider existing resources such as PhenX:
        - Concept of bringing together many knowledge experts/domains – picking a handful of questions (standard measures) to be validated for standard assessment in questionnaires
    - How are they being utilized and could we leverage parallel type efforts?
    - There is benefit of using the same questions/measures across experiments, however the depth of validated questions is a challenge. Can be challenging to get the depth we need with respect to personal characteristics, exposures, etc.
    - Ideally we would all measure in the same way, but this may not feasible (difficult to convince scientists to do this).
- Perhaps we need a toolkit for metadata – focused on how we tag data, rather than telling people how to collect the data
    - Need to collect the minimal amount of information that can be tagged in the same way
    - Need a repository of all that metadata that could focus on findability of studies as a first step.
- Discussion on examples of metadata repositories
    - There is no central encyclopedia of epidemiology studies
    - The NIH biocaddie effort didn't seem to work for what you wanted it to do, issues with usability.
    - Sustainability is a big issue – these efforts are not often maintained.
- There has to be a bridge in place (e.g. Cedar metadata templates, online template forms) with behind the scenes the metadata gets translated into sematic enabled schemas
- Discussion on the social aspects of standards development
    - Most data/semantic scientists don't understand environmental health.
        - Further, it is difficult to find individuals with these skill sets (e.g., data science, semantic/ontology, curation, computer science, etc.). Competition from industry.
    - There is a need for standards, but not everyone needs to be an ontologist (there are different levels, fit for purpose).
- For the social aspects, it is important to assemble cross-disciplinary teams together (e.g, with environmental health scientists, data scientists, ontologists as part of a team)
    - Examples of these types of teams and training include:
        - NIH Data Science Innovation Labs
        - Cross-disciplinary training as part of K (career development) awards to gain appreciation and deep exposure to other domains (in either direction data science <-> biomedical)
        - Immersion at the grad student level– with courses during biomedical training curriculum that lead students to be predisposed to understanding the value of data curation. (Ex. ODSS AI/ML-readiness T32 supplements). This can lead to skills such as – git, using command terminal, etc. Need to incorporate data standards, semantics, etc. into education.
- Discussion on new Data Management and Sharing (DMS) Plan requirement in January
    - Investigators can include funds for DMS in grant budgets

    - However, without an encyclopedia of recommended metadata tags, harmonized tagging of data will be difficult to implement.
        - Barrier – there are many different ontologies, some of which have the same terms in different ontologies. Need expert determination of terms that meet minimum criteria along with providing documentation/guidelines, trainings and workshops to help researchers understand what to do.
        - These decisions need to be worked out before we expect people to use standard terms and ontologies.
        - Need to avoid reinvention of the wheel.
- How to make decisions on standard terminologies? How to bridge the gaps between an expert panel determination and broad understanding/buy-in from a larger user-base?
    - Expert working groups/expert panels work well for making decisions on standard terms. These groups should include external consultations as needed.
    - It is difficult, historically, to make these decisions in larger groups.
    - Mandates will increase the interest here.
    - Getting key stakeholders to buy in through requirements for trainings and tagging in training grants and centers.
- Need software to make data curation easier. If you could make an easy online template to facilitate this, would make adoption easier.
    - Need to work in parallel with software teams.
    - Fundamental point – the easier and more obvious the tool and process are, the better the use/adoption. Using these tools will open eyes and will be useful from educational perspective.
- Doing simple things like metadata templates are logical first steps (but may not be super exciting to computer scientists, at first).
    - Team should include … domain experts (e.g., epidemiologists trained specifically in the domain and that understand sources of bias; software developers; data managers (who understand how to store, retrieve data).
- One issue that is coming up is that our computational discussions, may be jumping ahead of infrastructure. Need to solve the infrastructure issues.
- Important to look at parallel fields/examples:
    - Parallels to genomics
        - For standards in genomics, leaders in the area need to come together and establish standards for recording data
            - E.g., Calling genes with the same names.
        - Need central repositories
        - Need to engage journals, requirements will help
        - Regarding the parallel to genomics data, there are challenges with the ‘messiness’ of exposomics-related data. Different measures frequently utilized. Many complexities.
        - How did the genomics community make these decisions?
            - Brute force – leaders in the field to make the decisions
                - Who? Journals, institutions, symposia series organizers …
        - Example: GeneCards – central website that brings together all these things. Exposome needs something similar.
        - Here, our task at hand is to define the ontologies and define the “bins to be filled” for exposomics. Not a requirement that every dataset

have every element, but when you do have data elements mapping to the exposome, they need to fit in a defined/curated bin.
    - Another parallel with biomarkers.
        - Tried this within HHEAR. Templates for labs to report assay results. Automated processing of data which is coming in an expected format.
        - Difficulties in getting the labs initially to reach agreement, but were eventually able to agree.
        - Defined accepted HHEAR analyte codes. i.e., when you see 'BPA' you know what it means.
            - Even some exposure biomarker kits that are being commercialized … adds complexities.
- Standards areas that may need attention:
    - Chemicals: CAS numbers, ChEBI, etc. (there are existing crosswalks) more complex when looking at isomers, branching, etc.
        - Include tags/structured field for chemicals that were examined when submitting data or publications. Adopt software from other fields.
    - Geospatial based on Latitude and Longitude.
    - Public Health: Compatibility across sectors, and breaking down silos – for environmental health we use data collected by public health departments, need to engage these groups.
    - Clinical Health Records: Incompatible systems for EHRs
        - Want to avoid this issue for the exposome!
        - Collaboration across fields is needed!

OPPORTUNITIES FOR ACTION:

- Develop and publish opinion pieces or other guideline documents to guide the field for a domain area. Be bold.
    - Example: could put out list of biomarker analyte codes (etc.) in EHP for community adoption, as an opinion piece with a supplementary table
    - Should be linked to a github repository with accompanying code,
    - Group should include several key community stakeholders.
    - Expert working groups/expert panels work well for making decisions on standard terms.
    - Could have leaders in different domain areas follow this same pipeline.
- We need a toolkit for metadata – focused on how we tag/curate data
    - Includes specifications for the minimal amount of information
    - Information is tagged in the same way
    - Need a repository of all that metadata that could focus on findability of studies as a first step.
- To facilitate adoption, we need software to make data curation easier. If you could make an easy online template to facilitate this, would make adoption easier.
    - There has to be a bridge in place (e.g. Cedar metadata templates, online template forms) with behind the scenes the metadata gets translated into sematic enabled schemas
- It is important to assemble cross-disciplinary teams together (e.g, with environmental health scientists, data scientists, ontologists as part of a team) in the above efforts.

IMMEDIATE NEXT STEPS:

- Development of metadata templates are logical first steps
- Major stakeholders to gather to discuss foundational issues in prep for developing guidelines.
- Find and share functional examples of data curation (e.g. mapping of HHEAR studies to the HHEAR ontology). For example, take a traditional epidemiology study, show tagging of the variables, and what is behind the curtain. Plus, we need to show the potential – towards empowering knowledge graphs, reasoning algorithms.
    - Finding someone who volunteers data for think tank to map study to an ontology/set of ontologies. Build from there. Include documentation, video tutorials of the process.
    - Who else is doing this? What are other good examples? Who has gone the next step?
- Think about how do we get stakeholders, other ICs, etc. to buy in?
- Action. Not just talking. Do something to get the ball rolling to make this a reality.
- Look into leveraging the EHLC use case groups. Develop pipelines to move from 'data' to 'reasoning over data'. We know what has to be done, and this involves mapping terms, extending ontologies (only if that term does not exist in an ontology). This is doable but not always easy.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- One issue that is coming up is that our computational discussions, may be jumping ahead of infrastructure. Need to solve the infrastructure issues.
- Silos are big obstacles.
- Context is needed for datasets to facilitate understanding, interpretation, and data reuse – Need extensive metadata with standardized terms.
- Need a mechanism for agreement on ontologies/vocabularies/standardized terms.
    - How to get together stakeholders?
- How to enforce standards?
    - If centralized repositories are established, the standards can be enforced upon data submission.
    - Once you have a repository, can start enforcing some of this?
- How do you federate across systems?

ISSUE #62: Validated Tools for Integrating Health Effects and Exposures

CONVENER(S): Raymond Palmer, Claudia Miller

PARTICIPANTS: Sarra Bridges, Elisabeth Cook, Lily Wu, Shoji Nakayama, Srimathi Kannan

SUMMARY OF DISCUSSION:

Integrating exposures with health effects is an ongoing challenge for environmental scientists, doctors, medical researchers, policymakers, and the public. Validated tools are available, one of which has been used by researchers and clinicians in over a dozen countries to screen patients and assess chemical susceptibility and intolerances.

The Brief Environmental Exposure and Sensitivity Inventory (BREESI), the Quick Environmental Exposure and Sensitivity Inventory (QEESI) and Symptom Star, and the Exposure History are all available free of charge on line.

For clinical and epidemiological studies, the 3-question BREESI screens for chemical, food, and drug intolerances. If any one of the 3 BREESI items is answered affirmatively, then the more detailed 50-item QEESI should be administered. The QEESI has four scales: Symptom Severity, Chemical Intolerance, Other Intolerances (including foods), and Life Impact. The scales are comprised of 10 items each, with 0-10 ratings for symptom severity, yielding total scale scores of 0-100. There is also a Masking Index, which assesses ongoing exposures (e.g., use of tobacco, alcoholic beverages, caffeine, pesticides, fragrances) that may affect a person's ability to recognize chemical triggers.

What is unique about the QEESI is that it was derived from experiences of patients who reported becoming ill following well-characterized exposure events, including pesticides, remodeling/new construction, the Gulf War, and breast implants. Other studies have used the QEESI to identify chemically intolerant individuals in various groups such as people with addictions, autism (children of chemically intolerant mothers have three times the risk of developing autism, and 2.3 times the risk of developing ADHD), and women requiring C-sections (40% vs.7%).

In our most recent survey of 10,000 U.S. adults, 20% met QEESI criteria for chemical intolerance.

For a more thorough discussion of the development and use of the QEESI, watch Dr. Miller's presentation at the recent MicrobiomeFirst Summit. You will see how the QEESI Symptom Star can be used to illustrate changes in symptoms over time pre- and post- an exposure event (e.g., mold), and after remediation or medical intervention.

OPPORTUNITIES FOR ACTION and/or IMMEDIATE NEXT STEPS:

We would like to see NIEHS, other environmental agencies, and consultants use these validated tools and publish their findings.
These tools should be incorporated into the virtual meeting focused on TILT recommended in Issue #13.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Support is needed from the private sector and/or foundations that fund research and outreach on: autism, ADHD, military veterans (including burn pit-exposed soldiers), 9/11 survivors, pesticide/environmental activists, and groups representing chronic medical and mental illnesses such as Parkinson's, chronic fatigue syndrome, fibromyalgia, ALS, depression, long-haul COVID-19, autoimmune diseases and allergies.

ISSUE #63: How data analytics can facilitate mechanistic study of the impact of environmental compounds on human health?

CONVENER(S): Xiuxia Du

PARTICIPANTS: Garret Bland, Allison Boone, Sarra Bridges, Daisy Brumit, Robert Clark, Yuxia Cui, Sophia Miryam Schussler-Fiorenza Rose, Peng Gao, Ryland Giebelhaus, Philip Holmes, Srimathi Kannan, Graham Parker, Charles Schmitt, Michael Snyder, Susan Sumner, Lily Wu

SUMMARY OF DISCUSSION:

The session started with the following three topics to get the discussion started:

- Link environmental compounds with metabolic pathways and diseases
- Predict biotransformations of environmental compounds in human
- Build a cloud resource of environmental compounds, their biotransformations, and mass spectra

During the discussion, more data analytics needs were raised including the following:

- Link co-exposure (including drug, food, pesticide etc) with microbiome and genetics
- Genes x Environment, how to do the data analytics to understand how they work together to affect health
- One compound might hit multiple targets. How to consider the combinatorial effects? Need new machine learning methods such as deep learning and natural language processing to carryout enrichment analysis
- Use time course data to discover causal effects
- Understanding how genetic polymorphisms link to the metabotypes and health outcomes will be key to development of intervention strategies.
- Need for data harmonization
- Need formulized goals and to encourage regular conversations between labs
- In addition to mass, there is a strong need for MS/MS and MS^n to help narrow compound candidates in compound annotations due to the enormous chemical space in exposure analysis
- How to address the global issues in associating exposure with health outcomes at the epidemiological level studies? Linear correlation is far from enough. Can surrogate markers be used to predict downstream outcomes? Need to understand the synergistic effects of the exposures.
- How to leverage all of the cell and animal model research to inform human subject analysis?
- Need to lean more on animal models to estimate and evaluate human data to speed up studies
- Determine correlations with GWAS
- Build a cloud resource for temporal and spatial tracking of environmental compounds
- Semi-targeted approach is also very important, in addition to targeted and untargeted methods.

OPPORTUNITIES FOR ACTION:

- Build good databases for exposomics
- Harmonization of data sets (e.g., NHANES, Metabolomics Workbench, MetaboLights, All of US and the Nutrition for Precision Health study)
- Integration of multi-omics data
- Machine learning and co-exposures for improving enrichment analysis
- Retention time prediction applied to environmental research
- Use model system data for interpretation of clinical and cohort studies.

IMMEDIATE NEXT STEPS:

- Compound identification and annotation. If biologists do not know what compound a signal corresponds to, they do not know how to use the data. It is especially important to know what exogenous compounds are involved.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

- Raw data with no ID or annotations is an obstacle for some researchers. It would be good to provide good annotation for other researchers who don't know how to do this.

ISSUE #64: Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis

CONVENER: Bren Ames

PARTICIPANTS: Katerina Grafanaki

SUMMARY OF DISCUSSION & OPPORTUNITIES FOR ACTION:

Issue Overview:

- **xOMICS universe**: Let's broaden our 'omics vision and framework to be flexible and inclusive so that we can embrace unlimited perspectives and explore and critically examine the full xpectrum of possibilities. Explicitly include salugenesis (beneficial influences, mechanisms and pathways to healing) – and pay attention to biological responses that emerge in exceptional exposome conditions. Put big data into context – where in the xomics universe? Tag attributes, including Level of Detail (LOD) – by tissue domain, level within organism, development stage... Use LOD to view xomics universe w/o getting overwhelmed with detail. Gradually draw the links as evidence is produced, and have the weight of evidence become more recognizable. Also important to prune away assumptions that are not reliable, faulty.

- **XOP**: A specific start would be to expand the Adverse Outcome Pathway (**AOP**) **framework to** the full (spectrum) of **Xpectrum of Outcome Pathways –** (**XOP**). Look beyond pathogenesis and adverse outcomes. *There is **no need to wait** for a full understanding of the pathophysiology of chronic conditions before we should act to prevent them and find pathways to recovery and healing. ~ quote from…?(forgot)*

- We are all part of an uncontrolled exposome experiment. See Fig 7. Chronic Health Disorders that have increased 2-100 times since the 1980s

- One way to unravel exposome influences on chronic complex conditions to inform prevention and interventions -- would be to create exposome conditions conducive for beneficial outcomes, along with the capacity to measure improvements in exposome quality and biological responses.
    - Environmental control and reduction of exposures to known triggers are essential for both treatment of susceptible people and chronic conditions
        - Healthcare & occupational access & reasonable accommodations
        - Respite from triggers, treatment and recovery.
        - See ISSUE#37 notes for more a detailed discussion of
            - Providing healthy and accessible environments for healthcare facilities and practices ('First, Do No Harm'). **Standard baseline exposome quality that is smoke, pesticide, and fragrance-free with minimal electromagnetic pollution**.
            - **EMUs** – with exceptional exposome conditions and exposome quality testing capacity for Clinical & Research purposes.

    - Needed for research and to guide clinical recommendations, patient choices/lifestyles

- Minimize confounders by reducing, controlling and measuring exposures (IAQ, food & water quality, personal care products (PCPs), PPE, treatment and therapy devices); biological response attributes; and links.
- Measure Patient/Resident/Participant responses to improved Exposome conditions.
- Seek to answer: What chronic conditions improve in beneficial-to-exceptional exposome conditions?

- Pay attention to biomarkers that may indicate healing, health. Look beyond pathology. Clarify biomarker limitations, context, including whether indicators of beneficial-to-salugenic processes, pathways.

Two specific examples of research, prevention and clinical intervention solutions that we may be overlooking because of our over-tight focus on pathogenesis, adverse outcomes, disease diagnosis, symptom suppression:

1. Dr. Robert K. Naviaux's model is a framework that pulls together a lot of pieces (that tend to be examined in separate silos) – supports putting mounting evidence into context, with a broad spectrum of vision – spanning from the human Cell Danger Response (CDR) to a multi-stage Healing Cycle, with:

    - roles for multiple forms and functions of mitochondria, extracellular ATP (eATP), oxygen availability and oxidative shielding in the human cell danger response (CDR):
    -

"All cells mount a coordinated defense when threatened. This causes disease if it persists after the threat is gone." – Hypothesis: that chronic diseases are organ-selective manifestations of persistent activation of the CDR.
"The core pathways of the CDR were coordinated and regulated by eATP in over a dozen chronic illnesses."
"It turns out that you cannot have inflammation without a change in mitochondrial function."

    - plausible mechanisms for healing pathways, those being blocked at gateways in chronic disease, treatments to support removing obstacles at healing cycle gateways (guided by metabolomics) and nurture processes towards healing and health – salugenesis.

    - Also recognizes that we have to create a healthy exposome for salugenesis.

- **Video Link** to Naviaux lecture at NIH. CDR and Healing Cycle intro with focus on CFS, time stamped: 55:00 to 1:28:15 min.

2. Another example demonstrating the need to pay attention to when biomarkers and exposures may be beneficial OR adverse, depending on the situation and tissue: ***in some circumstances CO is protective.** Also, interpretation issues.

    - A collection of PubMed references compiled by Albert Donnay, Consulting Toxicologist, Donnay Detoxicology, LLC on the topic: NCBI Collection - COP and hyperventilation

    - **Mitigate under-recognition of chronic low-level CO poisoning**, which:

  - impairs oxygenation of tissue, any organ may be affected, with the brain, heart and lungs being most sensitive to the effects of CO
  - may vary considerably over time as they wax and wane in response to not just exogenous CO exposures but also in response to any chronically stressful stimuli
  - such stimuli induce HO-1 to breakdown heme proteins into CO (**endogenous CO**)

- **Commonalities between COVID-19 morbidity and mortality and chronic CO cases** – "both are reported in the literature to present with extremely low oxygen saturation and hyperventilation." **COVID-19 morbidity and mortality caused by endogenous carbon monoxide poisoning, with recommendations for testing and treatment**, Preprint DOI: 10.31219/osf.io/uvj42 (Donnay, 2020).

  - Appeals to clinicians -- to **start testing CO levels in COVID-19 patients** and to **stop** monitoring oxygen saturation with conventional pulse oximeters that **overestimate oxygen saturation** by the sum of carboxyhemoglobin and methemoglobin
  - ***in some circumstances CO is protective**: "most studies of endogenous CO interpret its close positive correlation with these acute conditions as protective, with some going so far as to recommend treating ARDS with inhaled CO."
  - Offers recommendations for **testing endogenous CO poisoning in COVID-19 cases using devices** approved by the US Food and Drug Administration **that can distinguish CO coming from the lungs, arteries, veins, and average of all tissues**, unlike current protocols for CO poisoning that only measure CO in arteries or veins but not both.
  - Reviews FDA-approved **treatments that may help COVID-19 patients with endogenous CO poisoning**. These include zinc-based drugs that lower the rate of endogenous CO production by inhibiting HO-1, and drug-free devices and methods that reduce the total body burden of CO after exogenous CO poisoning.

Katerina Grafanaki: Agree with the need to pay more attention to mitochondria.
We need a more holistic approach and more involvement, collaboration of the general population with/in healthcare/research. Must be pro-active, prevent adverse exposures and impacts.

First step: education, awareness. Help people recognize what they are exposed to
Often, people are exposed, yet don't know. They may recognize a symptom, but are not seeing the connection with exposures. (Masked)

Usually it is the vulnerable individuals who recognize connections. They are often the ones who develop diseases. Others, who are more resilient don't get it. This contributes to empathy and response gaps/lags in the general population and within healthcare.

The ones who realize the connections and that something is going wrong – need to report it.
E.g., COVID-19 cases were happening long before it spread to pandemic levels.
Be alert. Record what is happening.
The best doctor to their disease is the patient. The patient knows best what is going wrong, and what needs to be done to fix it.

Susceptible people can help us recognize signals in the noise. And help prioritize.

People are sometimes suspicious and hesitant to report and share about their situations. Need a way to establish trust. To understand that it is not happening to just them. Remove barriers so that people will get involved. They need to become available for research, collaboration. Need them to describe what they are experiencing.

We need people to report situations sooner, even anonymously, to get to the beginning of the problem, and intervene to mitigate the exposure earlier

Suggest creating/supporting an EXPOSOME TASK FORCE WEBSITE/HELPLINE where people can:

- Report exposure situations
  - to a trustworthy, non-politicized, non-occupationally-linked, caring support service
  - without being bullied or facing (workplace & other) retribution
- Find trustworthy information about what they can do.

IMMEDIATE NEXT STEPS:

- **Begin** by broadening the perspectives and pursuit of research and healthcare to **include beneficial influences, and salugenic mechanisms and pathways to healing** – beyond the adverse and pathogenic.
- Explicitly expand our frameworks, vision, funding, measurements and interpretations to include the full **xOmics universe** and **XOPs**.
- Create oases with beneficial exposome conditions – healthcare, research and residential settings
- Implement policies and practices that deliver standard baseline exposome quality in healthcare. See ISSUE#37 for more about
  - Providing healthy and accessible environments for healthcare facilities and practices (‘First, Do No Harm’). **Standard baseline exposome quality that is smoke, pesticide, and fragrance-free with minimal electromagnetic pollution**.
  - **EMUs** – with exceptional exposome conditions and exposome quality testing capacity for Clinical & Research purposes, and access for susceptible people.

OBVIOUS OBSTACLES and/or SUPPORT NEEDS IDENTIFIED:

Gaps: If we don’t pay attention to beneficial influences, and create exposome conditions conducive for preventing AOPs and nurturing salugenic pathways – we cannot expect beneficial outcomes.

Masking: People and their healthcare providers often overlook adverse environmental influences when those exposures are ubiquitous, and when they have no opportunity to experience healthy conditions for comparison and unmasking. The patterns and links of cause and effect are obscured. Challenge distinguishing 'typical' and 'healthy'.

Support an Exposome Task Force Website/Helpline that is responsive, yet also holistic and pro-active to prevent adverse exposures and impacts.

Support X-OMICS and XOP (Xpectrum of Outcome Pathways) frameworks that are flexible and inclusive enough to embrace and explore salugenesis (beneficial influences, mechanisms and pathways to healing) -- including prevention and mitigation of chronic conditions in exceptional exposome conditions.

- Start with Cleaner Air Oases

Seek, study, iteratively develop and broaden access to exposome conditions conducive for healing and resilient health beyond isolated oases and EMUs. Create (micro-to-macro) terrain that nurtures and regenerates a diverse, beneficial microbiome, unblocks healing pathways and supports resilient metabolic processes.

- Pay attention to & learn from patient experience. Weight of evidence should consider experience, not be limited to RCTs
- Life, liberty and the pursuit of salugenesis!?

Advance non-invasive Breathomics in general; and more accurate, more granular, less biased CO and Oxygenation measurements, assumptions and interpretations, specifically.

- **Promptly Evaluate Role of Carbon Monoxide in COVID-19 morbidity and mortality**, testing & treatment, including commonalities with chronic CO cases – both are reported in the literature to present with extremely low oxygen saturation and hyperventilation. Start testing CO levels in COVID-19 patients.
- Require devices to be accurate for people of all skin tones. **Mitigate skin tone biases** built into pulse-ox devices.
- Mitigate under-recognition of chronic low-level CO poisoning, situations when CO is protective, overestimation of oxygen saturation (biased and oversimplified devices).

Advance understanding of metabolic features and stages of the **Cell Danger Response (CDR) biology**– including multiple forms and functions of mitochondria, eATP, oxygen availability, oxidative shielding, **interruptions in the Healing Cycle in chronic conditions, and unblocking the Healing Cycl**e…NaviauxLab publications.

PRIORITIZATION WORKSHOP

Now What? Identifying Priorities, Connections and Immediate Next Steps

Thank you for all of your learning and contribution! These proceedings contain all the notes, from each of the five workshops, addressing more than 60 individual issues and opportunities, for demonstrating the value of the exposome and accelerating precision environmental health. [*This form went to all participants after the fifth workshop*.]

- **Please read and review all the notes** – especially those sessions that you've not seen or participated in. Then make a list of the issues that you think are most important – for yourself, your work and the larger field – the issues that deserve the most immediate attention, resources and action – the issues you're most excited about. Note the ISSUE #, not page numbers, when identifying your top priorities.

- **Make a form on paper (like the one below) to make "voting" quick and easy**. You'll have 40 votes to allocate to the issues you think are most important, urgent and exciting. *This isn't about picking winners and losers, it's about noticing energy, alignment, and readiness.*

- **Allocate your "votes" based on the importance of the ideas (substance) and the energy you have for each one – NOT on the quality of the notes taken**. There will be plenty of time later to work out the details and make things pretty.

- **Major Themes or Clusters?** As you read, notice any themes or clusters around which we might organize our work. These will be useful in discussions after the voting.

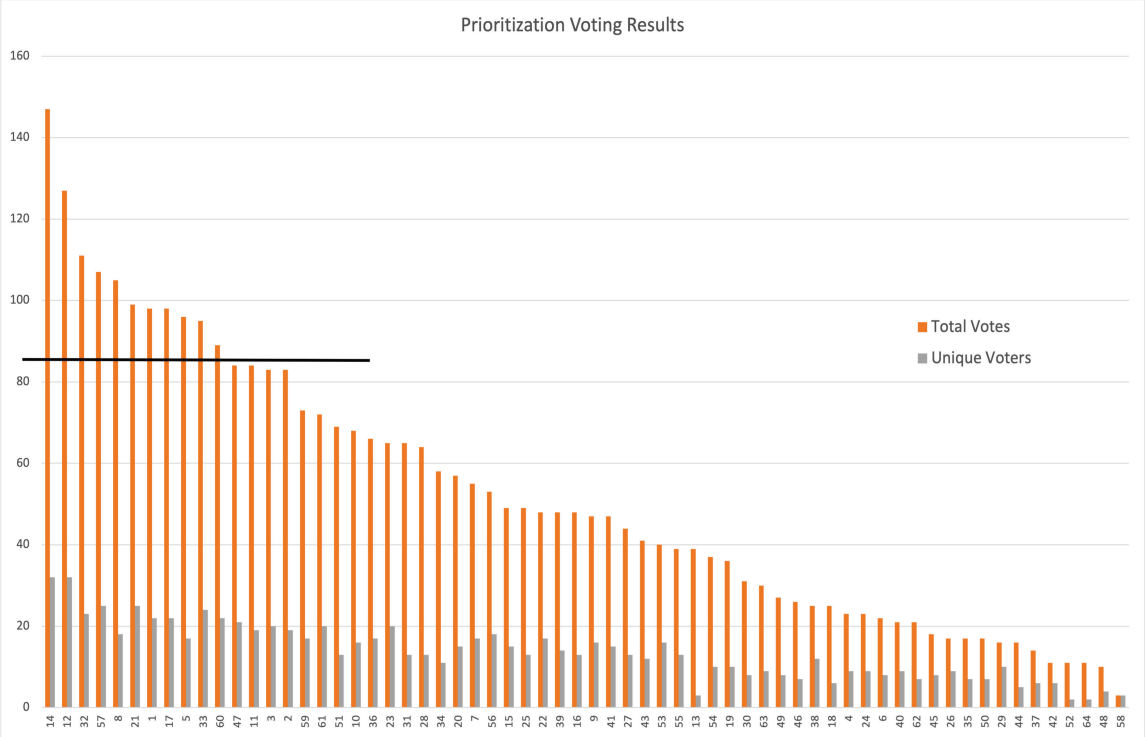
On Wednesday, August 31st, we'll finish our review and you'll enter your "votes" to create a rough prioritization of the issues**.** Then we'll have one last round of working sessions, focused on a short list of top priorities, to connect related issues and identify immediate next steps.

	Issue Number	*How Many Votes to Give Each One? (sample distribution for 36 votes)*
Most Important Issue:	_____	_____ (8)
2nd	_____	_____ (7)
3rd	_____	_____ (6)
4th	_____	_____ (5)
5th	_____	_____ (4)
6th	_____	_____ (3)
7th	_____	_____ (2)
8th	_____	_____ (1)

more if you like, up to a total of 40 votes…

Any Major Themes or Groups of Issues?

Chart of Voting Results: Total Votes and Unique Voters for All Issues



This chart shows the distribution of votes and unique voters across all issues. The black line shows the top ten "cut." Here are those top issues:

ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome

ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility

ISSUE #32: Harmonizing exposome data across studies

ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data

ISSUE #8: Epigenetics and the Exposome / Exposome and Cellular 'endpoints' (adducts (e.g. DNA, protein), epigenetics, mutations – what, how, why / Epitranscriptomics

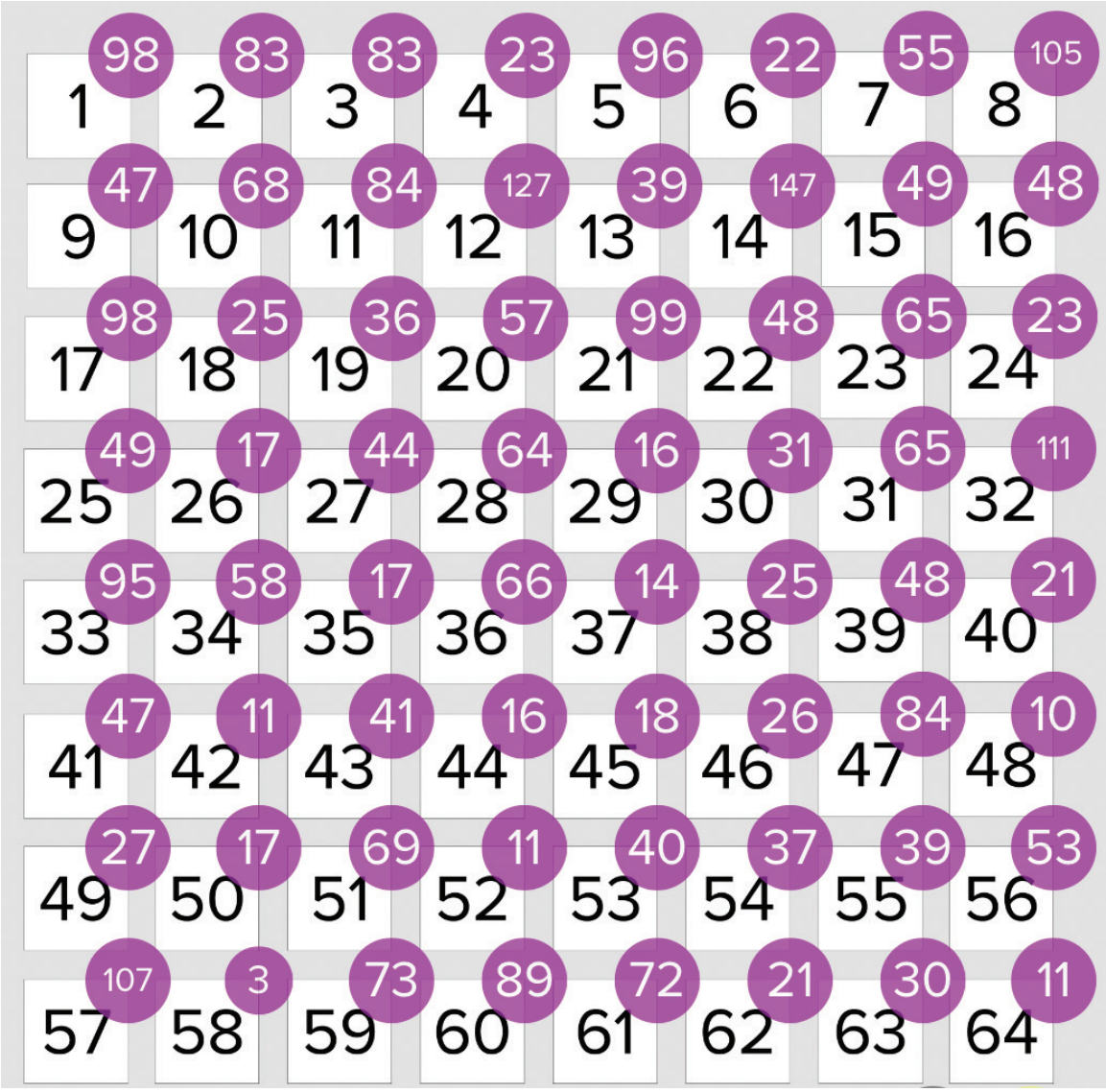
ISSUE #21: Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments

ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi-dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics

ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes

ISSUE #5: Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues

ISSUE #33: Merging data from existing longitudinal studies



Issue numbers shown in black and white squares, vote totals shown in purple circles.

Table of Raw Voting Data and Connections Between Issues

This table shows all issues, in order of total votes received. The issues that received the most votes are shown in YELLOW.

In each issue-numbered COLUMN, dark green cells show which issues were identified as related to each “top” issue.

Blank ROWS show where some issues have yet to be incorporated into any of the top issue clusters.

For the first ten rows, the light green box fills shows where the relationship was only flagged from one of the two issues. (e.g. those working on Issue #14 listed Issue #12, but the #12 group didn’t identify #14 as related.

This map is just the beginning of surfacing the connections between issues and sorting issues into strategic clusters for action.

Additionally, it might be useful to tag issues with the five workshop themes, to be able to see theme coverage and cross-cutting issues.

Finally, the following pages are the notes from very short breakout working sessions that focused on each of the top ten issues.

Unique Voters	Total Votes	ISSUES	14	12	32	57	8	21	1	17	5	33
32	147	**14**										
32	127	**12**										
23	111	**32**										
25	107	**57**										
18	105	**8**										
25	99	**21**										
22	98	**1**										
22	98	**17**										
17	96	**5**										
24	95	**33**										
22	89	60										
21	84	47										
19	84	11										
20	83	3										
19	83	2										
17	73	59										
20	72	61										
13	69	51										
16	68	10										
17	66	36										
20	65	23										
13	65	31										
13	64	28										
11	58	34										
15	57	20										
17	55	7										
18	53	56										
15	49	15										
13	49	25										
17	48	22										
14	48	39										
13	48	16										
16	47	9										
15	47	41										
13	44	27										
12	41	43										
16	40	53										
13	39	55										
3	39	13										
10	37	54										
10	36	19										
8	31	30										
9	30	63										
8	27	49										
7	26	46										
12	25	38										
6	25	18										
9	23	4										
9	23	24										
8	22	6										
9	21	40										
7	21	62										
8	18	45										
9	17	26										
7	17	35										
7	17	50										
10	16	29										
5	16	44										
6	14	37										
6	11	42										
2	11	52										
2	11	64										
4	10	48										
3	3	58										

ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome

ASSOCIATED ISSUES:

- ISSUE #61: Towards consensus standards for exposome data and metadata: development, coordination, and adoption
- ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility
- ISSUE #32: Harmonizing exposome data across studies
- ISSUE #40: Reporting Standards Replication
- ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Need to collect appropriate metadata
2. Need standards across all data types (Get NIST involved); Chemical and Biological standards; reference sample standards
3. Particulate and other monitors (are they calibrated?)
4. What should we be measuring?
5. Establishing common databases
6. Define the appropriate measruing window.

IMMEDIATE NEXT STEPS / PERSONAL:

1. Form working groups

ISSUE #12: Data sharing in exposomics

ASSOCIATED ISSUES:

- ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data
- ISSUE #32: Harmonizing exposome data across studies
- ISSUE #22: Creative solutions for scaling exposomic research to the population scale
- ISSUE #29: Exposome on a shoestring: Making the exposome accessible for community based research
- ISSUE #40: Reporting Standards Replication

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. incentivize data sharing and reuse
2. incentivize submission of documentation to ensure data is understandable to reuse
3. centralized repo for data to be submitted using minimum common data standard
4. training for data generators to submit to repositories
5. funding to support data transformation and upload to repos

IMMEDIATE NEXT STEPS / PERSONAL:

1. identify vendors who are "FAIR at source" to enable readily uploadable to other systems.
2. focus on making own research data FAIR.

ISSUE #32: Harmonizing exposome data across studies

ASSOCIATED ISSUES:

- ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi- dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics
- ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility
- ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes
- ISSUE #23: Maximizing value from biobanked samples
- ISSUE #33: Merging data from existing longitudinal studies
- ISSUE #40: Reporting Standards Replication
- ISSUE #47: How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience
- ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data
- ISSUE #59: Exposure Ontologies and Definitions Sources | Pathways | Receptors
- ISSUE #60: Integrated High Dimensional Multiomic Analysis with Exposomics Data
- ISSUE #61: Towards consensus standards for exposome data and metadata: development, coordination, and adoption
- ISSUE #62: Validated Tools for Integrating Health Effects and Exposures
- ISSUE #64: Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Development of common data elements / forms e.g. PHENX
2. Data dictionariesexsiting, are available and in machine readable formats.
3. Guidelines for metadata
4. Determining consensus definitions of terminologies

5. MIAME - minimal information requirements for studies , tools and assays
6. Harmonization data across data repositories (HHEAR, Metabolomics workbench, Metabolite, Allof US, UK BioBank, Million Vets, etc)

7. Develop software/methods to interpret/harmonize across databases (across database where you bring softwware to data/data under tight control)

8. Standards for what is considered sufficently statistical harmonized fpr meta or mega analyses.. Adjusting for study and batch.

9. Develop standardized data format.

10. Harmonization of different tools that measure the same thing.

11. Develop centralized repositories or make existing ones interoperate.

12. Catalogue of existing databases and their contents.

13. Standardize data acquisition to make data harmonization easier.

IMMEDIATE NEXT STEPS / PERSONAL:

1. For working groups to address specific topics.

ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data

ASSOCIATED ISSUES:

- ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi- dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics
- ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility
- ISSUE #32: Harmonizing exposome data across studies
- ISSUE #33: Merging data from existing longitudinal studies
- ISSUE #55: Managing the Spatial Exposome
- ISSUE #59: Exposure Ontologies and Definitions Sources | Pathways | Receptors
- ISSUE #60: Integrated High Dimensional Multiomic Analysis with Exposomics Data
- ISSUE #61: Towards consensus standards for exposome data and metadata: development, coordination, and adoption

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Look at OECD as a potential model for templates of submitting standardized data/metadata; very siloed so may not fully translate to cross-disciplinary nature of exposome
    i. Requirements gathering for templates; host conversations with data generators and users
    ii. Catalog existing repositories and the types of data they house; Understand the types of data that do not have a repository that meets standards to know what type of new repository might be needed
2. Cross-NIH/federal agencies on integration of databases/repositories to avoid duplication and ease access
3. Provide platform for discussing/solving unique issues of exposomic data that need to be addressed in repositories (see personal issue below; related to curation and autocorrelation)
4. Develop canonical questions/test-cases for interoperability across repositories Resources? NIH-led initiatives- can we participate in current activities with exposome relevent repositories?

5. More transdisciplinray education on how to work on transdisciplinary teams, necessary for integration of data and repositories (Bring together domain scientists and informatics/computer scientists)

6. Need to consider sustainability models! Both money and effort

7. Create community of practitioners to foster communication/problem-solving; Take advantage of professional societies?

IMMEDIATE NEXT STEPS / PERSONAL:

1. Individuals can contribute repositories they use; Helps toward achieving catalog; provide community input on priority for needs/gaps

2. Use data/metadata standards in our own work

3. Champion the use of data/metadata standards to the broader community; hold activities within our own insitutions to communicate value

4. Reach out to complementary scientists (eg EHS--> comp sci) and encourage participation in transdisciplinary efforts and community of practitioners

5. Organize symposia at annual meetings; ISEE/ISES/SER/ACE/AIMA/ AGU/ESRI etc to communicate existence, value and tools for use of repositories/templates; communicate needs of exposome data like spatial that may not be covered

6. Communicate to those with educational components to create materials around standards/repositories (example Superfund Research Program)

7. Contribute key challenges for exposome data (curation, autocorrelation) for analysis and use of the data

ISSUE #8 Epigenetics and the Exposome

ASSOCIATED ISSUES:

- ISSUE #9: Integrating exposure over time, with long lived markers such as DNA and protein adducts
- ISSUE #25: Exposure Epigenetics, multi-omics at GxE interface, inter-individual variations
- ISSUE #51: Defining the ecto-exposome across the life-course (built, natural, physical and social environment)

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Epigenetics and adductomics as indicator of exposure. What is the state of adductomics?
2. How does a marker relate to exposure, health issues and disease?
3. Need for long term markers of exposure.

IMMEDIATE NEXT STEPS / PERSONAL:

ISSUE #21: Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments.

ASSOCIATED ISSUES:

- ISSUE #29: Exposome on a shoestring: Making the exposome accessible for community based research
- ISSUE #43: Developing and implementing intervention studies in the context of the human exposome
- ISSUE #39: Issues in building inclusive and representative populations for exposome studies
- ISSUE #11: Underrepresented areas of the exposome: social (social determinants of health) environment, context, and behavior
- ISSUE #47: How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience
- ISSUE #54: Unintentional consequences, making sure we do no harm, not mixing diversity with disparity... How to ensure diverse voices are incorporated? Both community and investigators
- ISSUE #45: Decision Support Tools to help physicians incorporate exposomics into patient care
- ISSUE #30: Identifying - then protecting, the most vulnerable
- ISSUE #44: Innovative clinical systems and models of care aligned with interdisciplinary exposomic interventions and advancing clinical epidemiology designs, particularly in environmental justice communities
- ISSUE #22: Creative solutions for scaling exposomic research to the population scale
- ISSUE #2: Diversity and the exposome
- ISSUE #38: Communicating aspects of exposome research/impacts of exposome with the general public
- ISSUE #18: EXPOSOME as a FRAMEWORK that focuses on identifying OPTIMAL CONDITIONS for HEALTH and HEALING
- ISSUE #27: The Disease Exposome: Effects on Treatment and Disease Progression

- ISSUE #37: Occupational Health: Beneficial Exposome Conditions for Healthcare Services

- ISSUE #52: Fragrance Free Exposome - Allow Environmental Refugees to Access Healthcare and rejoin Society

- ISSUE #54: Unintentional consequences, making sure we do no harm, not mixing diversity with disparity... How to ensure diverse voices are incorporated? Both community and investigators

- ISSUE #64: Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis

Also Related:

- Integrating mixed models using indicators of SDOH along with exposure data and environmental data for decision making including regulatory decisions. Cumulative impact assessment.
- Resource/compilation of modeling approaches across disciplines (Literature Review, Web/Github resource)
- Data resources/hub
- Temporal/Spatial Congruency and synchronicity
- Life course modeling, sensitive periods and challenges and designs
- Need: Statistical methods/collaboration statisticians
- Dietary Exposome: engaging more fully with FDA- developing data might be more applicable to agent based modeling/recipe files to break down into components - facilitate identifying contaminants, etc.

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Next steps idea (community): Scale and expand evidence-based interventions (like green and healthy home visitation programs) to more fully address harmful exposome assessment/mitigation in EJ communities. (https://www.greenandhealthyhomes.org/)

2. high level alignment of mixtures that are harmful and how to put into policy

3. set standards for air, food and water quality for healthcare facilities and services. See #37.

4. use exposome to show what works (effects of policies) (policy and interventions at different levels) ; communities selected aren't necessarily the same community profile

5. evaluating and establishing policy on biomarkers; lack opportunity of cumulative exposure of rapid metabolites; how to match science and policy to create policy

6. integrate in vitro and animal models, pathways, adverse effects (translational sciences) to connect to newer human exposome studies that are harder to replicate and valid; be able to intervene on the exposure

7. climate change as a hazards particularly as disasters, which is unfair distribution - look at EJ / impacted communities to focus on disaster resilience/ prepardness and public health interventions specific to vulnerabilities

8. recognize what needs/exposure levels are, needs to be accessible technologies and low costs, keep in mind accessible of technology

9. consider BREATHOMICS devices, noninvasive, can be low cost, some direct reading.

10. building relationship with communities and have relationships with communities

11. interventions - difficulties of being cost effectiveness (for example in avoiding phalathes and parabens; can be quite difficult and expensive); work on community level for interventions - easier to ask school to change food that kids eat than individual families (individual, community, state/fed intervention)

12. need for technologies / better tools to measure mixtures, then can help frame interventions/policy

13. science of what caused particular health outcome can be rather difficult, (for example - DES - diethylstilbestrol and women's children or their grandchildren having reproductive harm from their mother/grandmother's exposure); difficult to pull out those effects and outcomes

14. use of materials / distrust around biobank samples especially in particular communities that have already been treated unfairly (encourage biobanking for diverse communities? And use of existing biobanks/ encourage participation, and trust)

15. alignment of what is happened across exposures

16. create places where we improve and measure exposome conditions along with biological responses (esp. metabolomics); can show how improved exposome affects healing/health/wellbeing; broad study with individuals across the spectrum (BREADTH) of chronic conditions, and also include slices with DEPTH, prioritizing individuals susceptible to exposome impacts/sensitive to exposures, who are perceptive about the links between triggers and effects to better understand connections and guide study iteration. Build successful case studies that yield improvement of symptoms & outcomes. Begin with clean air oases, fragrance free policies/practices, iterate to include food (quality nutrition, nutrient dense, pesticide/contaminant sparse), water and other conditions. See #37 #52, #64. Chronic care residential facilities (cognitive dysfunction, other), may be good places for piloting such studies and healthcare delivery improvements.

17. address disparities introduced by inaccurate, biased fingertip pulse-ox devices. See #64.

18. consider Dr. John Molot, (2014 book) 12,000 Canaries Can't Be Wrong: What's Making Us Sick and What We Can Do about It, See #37.

ISSUE #17: Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes

Mostly Interdisciplinary methods development needs

#1 Use GIS methods to link (Lat/long)- i.e. exposure biomarkers, molecular biomarker, phenotypes, questionnaire data, water quality, etc)

#2 Address temporality of all meausers

#3 address different levels of resolution- say 600 meter squared vs zip code levels.

#4 how to map proteomics and othe romic measures- i.e. take biomarkers at individual level to a population and spatial level. Needs methods development.

#5 address special populations- nursing home, pregnancy- Study and learn from susceptible people -- who are often more perceptive about links between exposures, effects and outcomes.

#6 Study design: what are they? observational vs interventions. Studies, heavy on metabolomics, that create beneficial exposome conditions for populations - eg., at a residential care facility (improve air quality, personal care products, food - nutrition quality, water quality, etc). and study improvements in exposome conditions, biological responses/ effects and outcomes

#7 Use of NHANES as model for doing this with biomarkers (confidential data site)

ASSOCIATED ISSUES:

- ISSUE #64: Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis
- ISSUE #3: Using GIS/Geospatial methods to better define and quantify the Exposome, Indoor air pollution, and light at night
- ISSUE #55: Managing the Spatial Exposome
- ISSUE #12: Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility
- ISSUE #15: Strategies for scaling and diversifying the external exposome measurements (citizen initiatives?)
- ISSUE #47: How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience

- ISSUE #57: Creating and sustaining interoperable data repositories for environmental health data

- ISSUE #14: The need to establish standardized and robust approaches for biomonitoring of the human exposome

- ISSUE #32: Harmonizing exposome data across studies

- ISSUE #39: Issues in building inclusive and representative populations for exposome studies

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Form Interdisciplinary Teams to merge geospatial data with omics and other biomarker data to address needed methods

2. Teams to address study design issues (critical windows/life stage), diseases, geography (rural vs urban), Social determinants of health/SES

3. How to identify studies that have exemplary data to begin methods development. i.e. omic biomakres and address

4. How to create a data base that address this- i.e. create a platfrom that combines all exisitng datasets e.g. MRbase as an example

5. Can we use more granular data (i.e. peronsal monitors) to refine remote sensing data

IMMEDIATE NEXT STEPS / PERSONAL:

ISSUE #1: From Collection to Action: Use of AI/ML for harmonizing and analyzing multi- dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics

Nothing reported from this issue/breakout, but this issue is noted in #32 and #57.

ISSUE #5: Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues

ASSOCIATED ISSUES:

- ISSUE #11 Underrepresented areas of the exposome
- ISSUE #48 Extrapolating/merging SDOH
- ISSUE #41 Mining EHR
- ISSUE #39 Issues in building inclusive and representative populations
- ISSUE #60: Integrated High dimensional multiomic analysis with exposomics data

- ?ISSUE #62 Validated Tools
- ?ISSUE #63 Data analyltics facilitating mechanistic study of environmental compounds

- ISSUE #33 Merging data from longitudinal studies
- (ISSUE #35 Accelerated design, ISSUE #7 time, critical windows)

- Spatial Factors, Modeling Issues
- ISSUE #3, #51, #55, #47
- (ISSUE #53: what social determinants should we consider)
- ISSUE #10 : dietary exposome
- ISSUE #4: integrating cauasal approaches
- ISSUE #49: Causal Pathways teasing out sequencing of policy SDOH and Chemical Exposures
- ISSUE #50: Characterizing exposome and SDOH disparities within and between levels of analysis and causal pathways to health outcomes

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

IMMEDIATE NEXT STEPS / PERSONAL:

ISSUE #33: Merging data from existing longitudinal studies

ASSOCIATED ISSUES:

(none reported)

IMMEDIATE NEXT STEPS / ORGANIZATIONAL:

1. Create guidelines for specimen collection, lab protocols, etc.
2. Benefits of historical cohorts vs new cohorts to conduct exposome research
3. Harmonization protocols for existing US exposome studies o Idea: collaborate to write small papers on harmonization
4. NIEHS funding opportunities for data harmonization and data analysis in existing longitudinal cohort studies

IMMEDIATE NEXT STEPS / PERSONAL:

The Way Forward: Themes for Demonstrating the Value of the Exposome

After the Workshop Series was completed, all of the issues were sorted into five working themes for advancing and demonstrating the value of the exposome. That sorting took into account the content of issues, the voting results (votes and unique voters), and the associations identified between all of the issues.

The following pages present all of the issues, sorted into these five new themes. A few issues didn't seem to fit squarely in any one theme, but they are not unimportant and should not be left behind.

All of these issues, notes, emergent working themes (each with two discussion topics) were then taken as the starting point for a virtual, three-day summit meeting. In that meeting, a smaller group worked to further detail and refine the themes and then begin to develop a number of concrete integrations, to actively demonstrate the value of the exposome.

Theme #1: What to measure (when, why)?

Topic 1: What should we measure in population studies?

Topic 2: Use animal and in vitro models to prioritize measurements in human

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
5	ISSUE #8	Epigenetics and the Exposome / Exposome and Cellular 'endpoints' (adducts (e.g. DNA, protein), epigenetics, mutations – what, how, why / Epitranscriptomics	105	18
12	ISSUE #11	Underrepresented areas of the exposome: social (social determinants of health) environment, context, and behavio	84	21
14	ISSUE #2	Diversity and the exposome	83	20
18	ISSUE #51	Defining the ecto-exposome across the life-course (built, natural, physical and social environment)	69	13
19	ISSUE #10	Dietary exposome	68	16
23	ISSUE #28	Functional exposomics	64	13
24	ISSUE #34	Indoor Air	58	11
26	ISSUE #7	Time and critical windows for the exposome	55	17
34	ISSUE #41	Mining the Electronic Health Record for Exposomics Research	47	15
37	ISSUE #53	What social determinants of health should we consider in exposome research?	40	16
41	ISSUE #19	Multiple Exposures	36	10
50	ISSUE #6	All About Drinking Water	22	8
64	ISSUE #58	Data about exposure to trauma as related to the exposome/epigenetics	3	3

.

Theme #2: How to measure (methods)?

Topic 1: Standardize and scale up exposome measurements

Topic 2: Map the exposome

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
1	ISSUE #14	The need to establish standardized and robust approaches for biomonitoring of the human exposome	147	32
8	ISSUE #17	Everything, Everywhere All at once: Unifying exposome maps to include exposure and molecular biomarkers and phenotypes	98	22
15	ISSUE #3	Using GIS/Geospatial methods to better define and quantify the Exposome, Indoor air pollution, and light at night	83	19
21	ISSUE #23	Maximizing value from biobanked samples	65	20
28	ISSUE #15	Strategies for scaling and diversifying the external exposome measurements (citizen initiatives?)	49	15
32	ISSUE #39	Issues in building inclusive and representative populations for exposome studies	48	13
33	ISSUE #9	Integrating exposure over time, with long lived markers such as DNA and protein adducts	47	16
52	ISSUE #62	Validated Tools for Integrating Health Effects and Exposures	21	7
54	ISSUE #26	Exposure co-variance matrix and Linkage Disequilibrium	17	9
55	ISSUE #35	Fast but not Furious: A Case for Accelerated Longitudinal Designs for Exposomics	17	7
63	ISSUE #48	Extrapolating/merging SDOH and exposures from alternative data sources (EHR, social media, purchasing histories)	10	4

Theme #3: Share and harmonize (data standards, ontologies, …)
Topic 1: Harmonize data across studies (both epi and basic biology)
Topic 2: Create and sustain interoperable data repositories

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
2	ISSUE #12	Data sharing in exposomics: databases, metadata, encouraging data sharing, and reporting responsibility	127	32
3	ISSUE #32	Harmonizing exposome data across studies	111	23
4	ISSUE #57	Creating and sustaining interoperable data repositories for environmental health data	107	25
10	ISSUE #33	Merging data from existing longitudinal studies	95	24
16	ISSUE #59	Exposure Ontologies and Definitions Sources | Pathways | Receptors	73	17
17	ISSUE #61	Towards consensus standards for exposome data and metadata: development, coordination, and adoption.	72	20
31	ISSUE #22	Creative solutions for scaling exposomic research to the population scale	48	14
39	ISSUE #55	Managing the Spatial Exposome	39	3
51	ISSUE #40	Reporting Standards Replication	21	9

Theme #4: Integrate, analyze, and interpret

Topic 1: Use AI/ML for integration of high dimensional multiomics data with disparate exposure and health outcome datatypes

Topic 2: Incorporate social, chemical and biological knowledge into exposomics for biological plausibility and causal pathways

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
7	ISSUE #1	From Collection to Action: Use of AI/ML for harmonizing and analyzing multi- dimensional exposome data + CyberInfrastructure to identify associations with health outcomes + operationalizing exposomics	98	22
9	ISSUE #5	Simultaneous modeling interpretation of environmental chemical exposome, psychosocial adversity and social determinants of health, diet, activity, and others – with a focus on data issues	96	17
11	ISSUE #60	Integrated High Dimensional Multiomic Analysis with Exposomics Data	89	22
13	ISSUE #47	How do you spatially and temporally align data on environmental exposures to biological response and health outcomes + Implementing exposomics into regulation, environmental justice, cumulative impacts, and the lived experience.	84	19
20	ISSUE #36	EWAS and GWAS similarities, Exposome wide association studies, Epigenomic association studies, GWAS-traditional	66	17
27	ISSUE #56	Methods to advance “exposome-wide association studies”	53	18
29	ISSUE #25	Exposure Epigenetics, multi-omics at GxE interface, inter-individual variations	49	13
43	ISSUE #63	How data analytics can facilitate mechanistic study of the impact of environmental compounds on human health?	30	9
44	ISSUE #49	Causal Pathways, teasing out the sequencing of policy, SDOH, and Chemical Exposures	27	8
45	ISSUE #46	Integrating adverse health outcomes (ex: respire-tory pathologies, cancer, etc) with environ-mental pollution burdens, and newer sensor technologies	26	7
49	ISSUE #24	Modeling and Prediction in Gene x Environment	23	9
48	ISSUE #4	Integrating Causal Inference Approaches	23	9
56	ISSUE #50	Characterizing exposome and SDOH disparities within and between levels of analysis and causal pathways to health outcomes	17	7

Theme #5: Translate and impact

Topic 1: Use exposomics to address health disparity and improve public health

Topic 2: Use exposomics individualized intervention and prevention

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
6	ISSUE #21	Making the exposome relevant to public health interventions and policy & Addressing disparities by intervening on the social and physical environments	99	25
22	ISSUE #31	Maternal Exposome & implications for health outcomes	65	13
25	ISSUE #20	Extrapolating human exposures to internal doses/exposures and then to animal and in vitro models for mechanistic studies	57	15
30	ISSUE #16	Personal interventions/report back and personalized risk models (multiple topics combined)	48	17
35	ISSUE #27	The Disease Exposome: Effects on Treatment and Disease Progression	44	13
36	ISSUE #43	Developing and implementing intervention studies in the context of the human exposome	41	12
38	ISSUE #13	Toxicant-induced Loss of Tolerance (TILT) and Mast Cell Sensitization	39	13
46	ISSUE #18	EXPOSOME as a FRAMEWORK that focuses on identifying OPTIMAL CONDITIONS for HEALTH and HEALING	25	12
47	ISSUE #38	Communicating aspects of exposome research/impacts of exposome with the general public	25	6
53	ISSUE #45	Decision Support Tools to help physicians incorporate exposomics into patient care	18	8
59	ISSUE #37	Beneficial Exposome Conditions for Health Research and Healthcare Services -- First, Do No Harm!	14	6
61	ISSUE #52	Fragrance Free Exposome - Allow Environmental Refugees to Access Healthcare and rejoin Society	11	2
62	ISSUE #64	Full Xpectrum Frameworks - XOPs & xOMICS including beneficial, healing, salugenesis -- beyond pathogenesis	11	2
60	ISSUE #42	Studying Effects of Exposures in Small Clinical Populations	11	6

Other Important Issues

The following issues do not necessarily fall in a specific theme but are important considerations for conducting exposomics research.

Rank	Issue #	Issue Title	Vote Counts	Unique Voters
40	ISSUE #54	Unintentional consequences, making sure we do no harm, not mixing diversity with disparity… How to ensure diverse voices are incorporated? Both community and investigators	37	10
42	ISSUE #30	Identifying - then protecting, the most vulnerable	31	8
57	ISSUE #29	Exposome on a shoestring: Making the exposome accessible for community based research	16	10
58	ISSUE #44	Innovative clinical systems and models of care aligned with interdisciplinary exposomic interventions and advancing clinical epidemiology designs, particularly in environmental justice communities	16	5