Educational Workshop for the Autism Research Community:

Incorporating Genetic Information into Patient-Centered Outcomes Research

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PCORI (EAIN-3885)

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Welcome!

This workshop was funded through a Patient-Centered Outcomes Research Institute (PCORI) Eugene Washington PCORI Engagement Award (EAIN-3885)

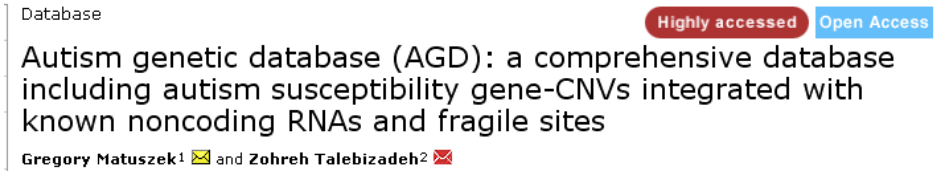
My journey (Genetics to Outcomes)

- I am a research scientist and the main focus of my research work is related to understanding genetics/epigenetics of autism.
- 15 years of experience working on this field as well as having the pleasure of interacting with families, inspired me to see if it is possible to consider patients' perspectives, in addition to scientific facts, when designing genetic research studies.
- That is why in the past 3 years, I invested significant time into learning about outcomes research (i.e., Patient-Centered Outcomes Research-PCOR), hoping to use my research experiences in improving patients' health.

Point of Inspiration

Autism Genetic Database (AGD)

1. Autism susceptibility:
   - genes: > 500
   - CNVs: > 700


Database

Highly accessed Open Access

Autism genetic database (AGD): a comprehensive database including autism susceptibility gene-CNVs integrated with known noncoding RNAs and fragile sites

Gregory Matuszek[1] and Zohreh Talebizadeh[2]

BMC Medical Genetics. 2009

2. Known fragile sites: 120
3. Known human ncRNAs: > 650,000

AUTISM SPEAKS
It's time to listen.

KANSAS CITY AREA LIFE SCIENCES INSTITUTE, INC.

For Research Use Only

Parent Interest?

Why Exploring Outcomes Research?

What I find exciting about research:

1. Thinking outside the box!
2. Exploring new approaches
3. Making genetic research more patient-centered

My PCORI project:

- It is NOT a technical/methodology project.
- It is about:
  - developing a **novel concept** (integrating soft & hard sciences)
  - using **PCORI platform** to improve translational aspects of genetic research questions

Ultimate goal: Use PCORI's engagement methods to incorporate patient perspective/clinical data in developing genetic research questions (improving patient-centeredness of the research questions)

PCORI

Mission:

- advocates for a change in the culture of research from being **researcher-driven** to becoming more **patient-driven**.
- views tangible engagement of patients and other stakeholders as an essential component of the research process to ensure inclusion of patient perspectives in research, leading to improved choice of research questions

PCORI funding portfolio:

1. **Research projects.** support comparative effectiveness research (CER), for example, comparing the effectiveness of two treatments.
2. **Research infrastructures.** In addition to funding CER research projects, PCORI has also invested on building research infrastructures by launching a National Patient-Centered Clinical Research Network, PCORnet.
3. **Engagement projects.** Facilitate partnerships between researchers and stakeholders.

PCORI funding portfolio (as of December 2016)

PCORI has awarded **$1.6 billion** for more than **570 research-related projects** covering a wide range of clinical conditions.

- **Mental health** is among **top priority conditions** with more than 86 funded CER research projects (totaling about $290 million) for conditions such as:
  - depression, substance abuse, schizophrenia/psychotic disorders, bipolar disorder, anxiety disorders, and neurodevelopmental disorders, including autism and ADHD.
  - Of 86 mental health CER studies, 76 (88%) are focused on treatment and the rest are related to other areas, including prevention and screening.
  - The **autism related PCORI projects** (n=13, more than $30 million) are focused on different areas of outcomes research, such as community/stakeholders' engagement, implementation of new evidence-based treatments, improvement of currently existing intervention/treatment options, organizing educational workshops, as well as development/implementation of computerized technology to support decision making and improve outcomes for patients, families, and caregivers.

PCORI investigator input

Kim Smolderen, PhD (UMKC)

Advances in autism genetics research

Autism belongs to a group of disorders known as “autism spectrum disorders” or **ASD** [impairments in social interaction/language/range of interests)

- 1940s: 1st clinical descriptions
- 1980s: the importance of genetic contribution became clear
- 1990s: 1st whole genome linkage study was performed

Autism Genetics Consortiums (repositories)

- 2007: Copy number variations (CNVs)
- 2009: Whole genome association study (GWAS)

- 2012: Whole exome sequencing (WES)
- 2015: Whole genome sequencing (WGS)

} NGS

ASD-Complex genetics

ASD Genes
- **Protein coding**: many genes >500 (n=?)
- **Non-coding:** may have regulatory roles

Environmental factors: non-genetic factors may also contribute
- gene X environment interactions

Novel splice isoforms for NLGN3 and NLGN4 with possible implications in autism

Z Talebizadeh, D Y Lam, M F Theodoro, D C Bittel, G H Lushington, M G Butler

J Med Genet 2006;43:e21 (http://www.jmedgenet.com/cgi/content/full/43/5/e21). doi: 10.1136/jmg.2005.036897

RESEARCH ARTICLES

Feasibility and Relevance of Examining Lymphoblastoid Cell Lines to Study Role of microRNAs in Autism

Zohreh Talebizadeh, Merlin G. Butler, and Mariana F. Theodoro

Environmental Factors

1. prenatal
2. postnatal

AUTISM RESEARCH INSAR

RESEARCH ARTICLE

Maternal Serotonin Transporter Genotype Affects Risk for ASD With Exposure to Prenatal Stress

Patrick M. Hecht, Melissa Hudson, Susan L. Connors, Michael R. Tilley, Xudong Liu, and David Q. Beversdorf

Epigenetics

Gene Regulatory Process

1. alternative splicing
2. non-coding RNAs
3. DNA methylation

ASD-Treatment

- Currently, the treatment of autism involves intensive behavioral/developmental therapy.
  - In some cases medications are used to treat symptoms such as anxiety, inattention, or hyperactivity.

- Despite advancements in the autism research field, there are currently no generally accepted biomarkers or physiologic tests in use to guide treatment.
  - One potential approach to address this issue is to reduce the extent of heterogeneity by subject stratification.

Heterogeneity in ASD

Phenotypic heterogeneity

various degrees of severity and clinical symptoms

inter- and intra-family heterogeneity

– **Male to Female** ratio: 4:1


OPEN ACCESS Freely available online PLOS ONE

A Novel Stratification Method in Linkage Studies to Address Inter- and Intra-Family Heterogeneity in Autism

Zohreh Talebizadeh[1]*, Dan E. Arking[2], Valerie W. Hu[3]


RESOURCE

nature medicine

Whole-genome sequencing of quartet families with autism spectrum disorder

ASD subtyping

– Co-morbidity (macrocephaly)

– Clinical observations

- GI abnormalities
- **Sleep problems**
- Eating behaviors
- **Metabolic disorders**
- **Sensorimotor deficits**


SHORT REPORT

Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline *PTEN* tumour suppressor gene mutations

M G Butler, M J Dasouki, X-P Zhou, Z Talebizadeh, M Brown, T N Takahashi, J H Miles, C H Wang, R Stratton, R Pilarski, C Eng

J Med Genet 2005;**42**:318–321. doi: 10.1136/jmg.2004.024646

Overlap/ Other conditions

Fragile X

ASD biorepositories

- There are several publicly available resources, or biorepositories, dedicated to collecting both genetic and clinical information.
  - **Disease-specific** (AGRE, SSC, MSSNG, IAN)
  - **Disease-independent** (eMERGE, PCORnet)
- The substantial investments made by the research community and participating patients indicate the high level of interest in combined assessment of genetic and clinical data.

- However, patients' contributions to such repositories have been mainly limited to providing clinical data, predefined by approved research protocols, and biomaterials.
- While having this type of clinical data is essential for rigorous statistical analyses, it also poses a **limitation** of not capturing **patient/parents observations and perspectives**.

Parents' concerns and clinical observations

- In addition to the phenotypic information collected for clinical and/or research level diagnosis, ASD subjects often present with other symptoms not covered by these standard assessments:
  - **Parent reports:** eating behaviors and sleep problems
  - **Clinical observations:** neurological symptoms, sensory motor deficit

- These observations (anecdotal evidence) and not considered in many research studies.

- Such evidence is **potentially valuable for research** purposes and should not be overlooked. Currently, there is no systematic platform to gather and process patient/parent perspectives and clinical observations for research use (gap), therefore such critical information is not commonly considered in study designs.

ASD translational research-barriers

Concerns over the need to improve translational aspects of autism research studies, particularly for genetics research, and to engage community members in the research process have been recently noted in the literature and raised by patient advocates.

1. Translational aspects must be identified and incorporated at the study conception phase, instead of adding it at the end of the study, which is the traditional approach in most, if not all, genetic research studies. (Szatmari et al., 2012).

2. A large scale survey conducted in UK investigated the community involvement from both researchers and community members' perspectives. The authors concluded that the autism funding landscape currently does not correlate with the type of questions that people with autism and caregivers would like to be addressed. In order to promote the type of research that makes a meaningful difference in the lives of those affected by autism, it is vital to have a constructive dialogue about research priorities between researchers and the autism community (Pellicano et al., 2014).

Why exploring PCOR?

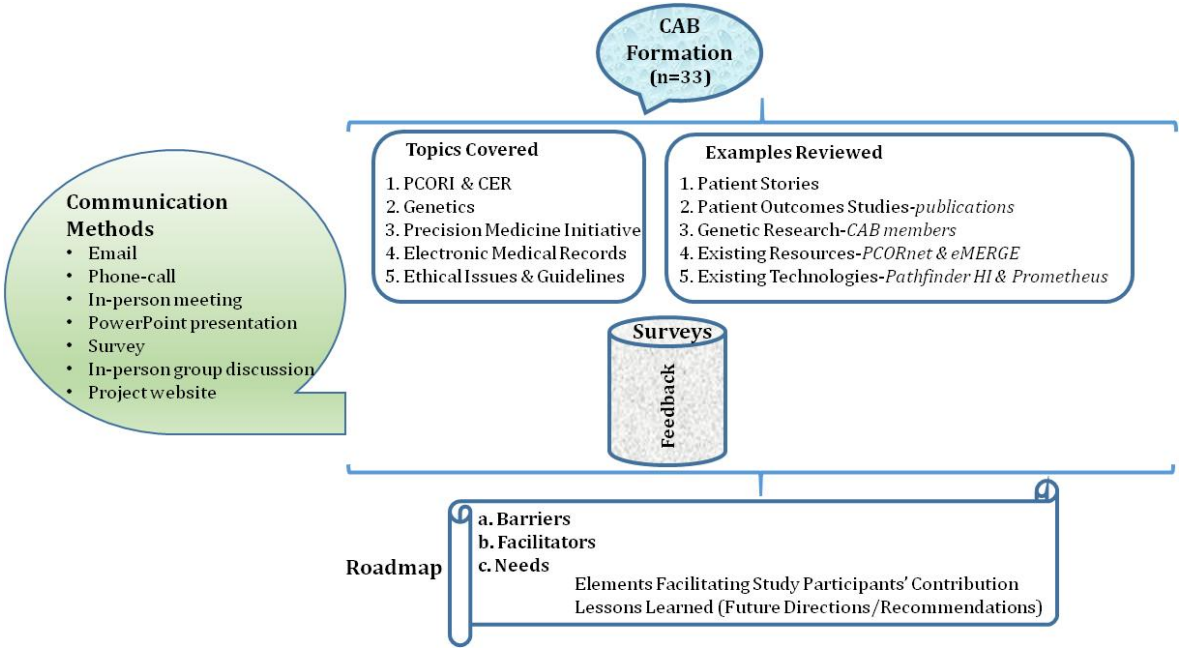
1. Addressing these concerns requires applying a different research approach than what is traditionally being used by the basic research community and is supported by the autism funding agencies.
2. Patient-centeredness and community engagement are key elements of the PCORI mission.

- Thus, we decided to use a PCORI engagement model to promote building a bridge between basic research (i.e., genetics) and translational research (i.e., outcomes).

Autism Genetics and Outcomes (AutGO)

Our project, Autism Genetics and Outcomes (AutGO), consists of two phases (I and II).

- **Phase I (1YEAR): Completed**
  - **Goal:** To assess IF/HOW genetic information may be incorporated in PCOR/CER studies.
  - **Methods:** Focus groups, surveys, online educational materials, in-person group discussions.



Scientist/Physician Stakeholders (n=15)

PCORI Funded Investigators

Kim Smolderen, PhD
Outcomes Research

Jim McClay, MD
Informatics

Monirul Islam, MD, PhD
Epidemiology

John Spertus, MD
Cardiovascular

Angie Myers, MD
Infectious Diseases

Laura Fitzmaurice, MD
Medical Information

Zohreh Talebizadeh, PhD
Genetics
PI

Mark Hoffman, PhD
Informatics

Emily Farrow, PhD
Genetics

Valerie Hu, PhD
Genetics &
Parent Representative

Olivia Veatch, PhD
Genetics

John Lantos, MD
Pediatrics &
Bioethics

Matt McLaughlin, MD
Rehabilitation Medicine

Darcy Weidemann, MD
Nephrology

Ginger Nicol, MD
Psychiatry

Other Stakeholders (n=18)


Seth Bittker


Angie Knackstedt &&
Health Literacy Coordinator


DeeJo Miller


Sheryl Chadwick


Mary Kinart


Jamie Bolen


Mary Anne Hammond

Patient/Parent Representatives


Mark Bryant &
Community leader


Kristen Worden


Broderick Crawford &
Faith Community &
Community Health


Kelly Ranallo &
Community leader &
President, Turner Syndrome
Global Alliance


Paul Law, MD
Founder, Interactive Autism
Network &
Parent Representative


Amy Brower, PhD
American College of
Medical Genetics &
Parent representative

Tayebeh Rezaie, PhD
NCBI-NIH


Ayten Shah
Project Coordinator


Andrea Bradley-Ewing
Community Engaged
Coordinator

Other Stakeholders

Industry Representatives


Jeff Blackwood
CEO, ABPathfinder


Leon Rozenblit, PhD
CEO, Prometheus

Phase-I (AutGO) participants' recommendations

We identified the following tasks that could facilitate implementation of findings from Phase I:

1. Raising Awareness in the Research Community
2. Developing Effective Educational Models
3. **Developing Disease-Specific Examples**
4. Building Multidisciplinary Teams
5. Assessing Existing Resources (biorepositories)

Phase-II AutGO (2 YEARS)

Status: Ongoing

Goal: to develop an engagement/educational model and deliver the message to the autism research community.

Methods:

- Using a combination of focus groups, online educational materials, and semi-structured literature search (inclusion criteria/evaluation metric)
- Developing a research example
  - with input from our multidisciplinary team (including genetics researchers, autism researchers, physicians, parents, and outcomes researchers) we will develop a research hypothesis for autism that fits with both soft (outcomes) and hard (genetics) sciences. Our team will then evaluate the data archived in the existing autism-related (AGRE, SSC, MSSNG, and IAN) and non-disease specific (e.g., eMERGE and PCORnet) genetic/phenotypic resources to identify to what extent they can be used to answer the identified patient-centered genetics research questions, as well as limitations.

Dissemination & feedback from community:

- organizing two workshops:
  [1] Kansas City (introducing AutGO project) (April 2017)
  [2] International Meeting for Autism Research-IMFAR (May 2018)

Another Motivational Point

- AutGO study participants
- Autism research leaders