Phase-II AutGO (2 YEARS)

Status: Ongoing

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

Methods:

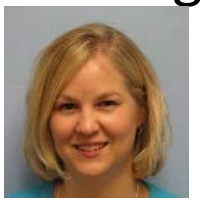
- Using a combination of focus groups, online educational materials, and semi-structured literature search (inclusion criteria/evaluation metric)
- Developing a research example
  - with input from our multidisciplinary team (including genetics researchers, autism researchers, physicians, parents, and 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)

Autism & obesity

Despite suggestive links between autism & obesity, including:



1. a higher prevalence of obesity in autism (24%) compared with controls (17%)
2. association of maternal obesity and risk of autism in offspring
3. association of chromosome 16p11 with both autism & obesity

it is not clear if obesity is co-occurring with autism

Drug side effect: antipsychotic induced weight gain (AIWG)?

AIWG genetic risk factors (pharmacogenomics)

Can J Psychiatry. 2014 Feb;59(2):76-88.

Pharmacogenetics of antipsychotics.

Brandl EJ, Kennedy JL, Müller DJ.

Abstract

OBJECTIVE: During the past decades, increasing efforts have been invested in studies to unravel the influence of genetic factors on antipsychotic (AP) dosage, treatment response, and occurrence of adverse effects. These studies aimed to improve clinical care by predicting outcome of treatment with APs and thus allowing for individualized treatment strategies. We highlight most important findings

Pharmacogenomics. 2013 Dec;14(16):2067-83. doi: 10.2217/pgs.13.207.

Genetics of antipsychotic-induced weight gain: update and current perspectives.

Kao AC[1], Müller DJ.

Author information

Abstract

Pharmacogenomics J. 2016 Aug;16(4):352-6. doi: 10.1038/tpj.2015.59. Epub 2015 Sep 1.

Genome-wide association study on antipsychotic-induced weight gain in the CATIE sample.

Brandl EJ[1,2], Tiwari AK[1], Zai CC[1,3], Nurmi EL[4], Chowdhury NI[1], Arenovich T[1], Sanches M[1], Goncalves VF[1,3], Shen JJ[5], Lieberman JA[6], Meltzer HY[7], Kennedy JL[1,3], Müller DJ[1,3].

Curr Psychiatry Rep. 2014 Oct;16(10):473. doi: 10.1007/s11920-014-0473-9.

Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed.

Shams TA[1], Müller DJ.

Research approach

- 1. Question (direct approach):
  - What is the underlying mechanism of obesity in autism (i.e., genes involved)?
- 2. Alternate question (indirect approach):
  - Is obesity in autism associated with known AIWG susceptibility SNPs?
  - Compare AIWG SNP profile in:
    - individuals with autism who are obese
    - individuals with autism who are NOT obese

Pharmacogenomics literature

AIWG SNPs list

N >100

- If the prevalence of AIWG associated SNPs in obese and non-obese subjects is comparable, it implies that AIWG cannot be the only reason for the observed higher rate of obesity in autism.

Simons Foundation (SSC data)

2000 families (parents, 1 affected & 1 unaffected siblings)

Affected siblings

- **obese**
- **Non-obese**

No statistical differences

Unaffected siblings

- **obese**
- **Non-obese**

No statistical differences

BMI

AIWG SNPs
N=100

Medication Use

One SNP showed sig difference in obese group/ independent of medication use

Gene associated with metabolic disorders

Autism & Obesity

Basic Science

Approach 1

Direct

Underlying mechanism

Advantage:

1. Gene identification
2. Understanding etiology of obesity

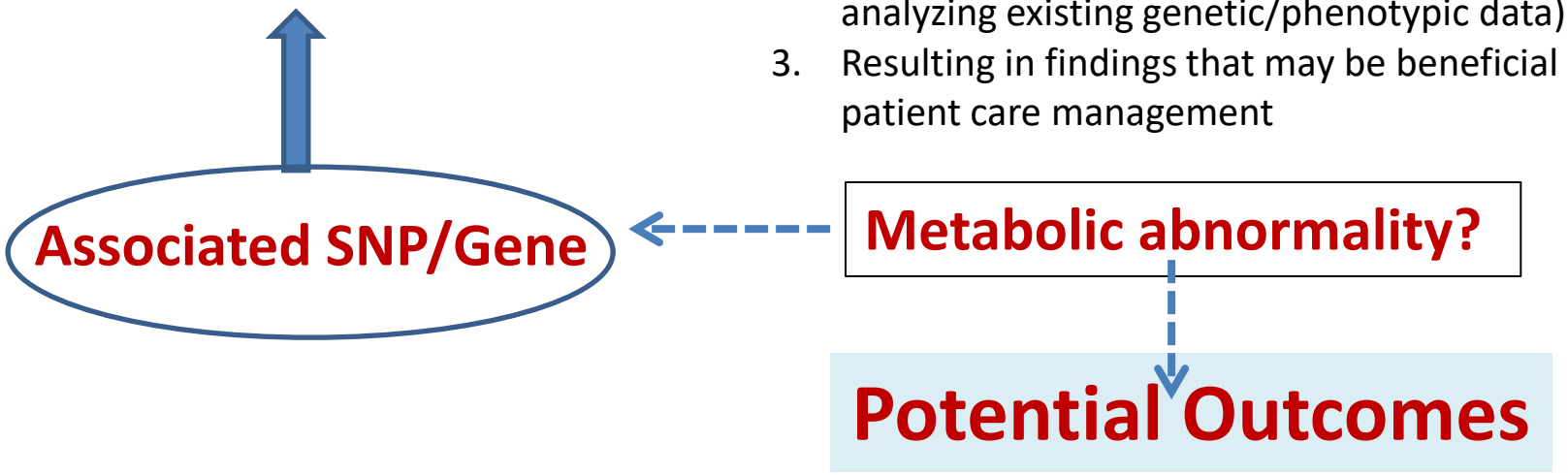
Approach 2

Indirect

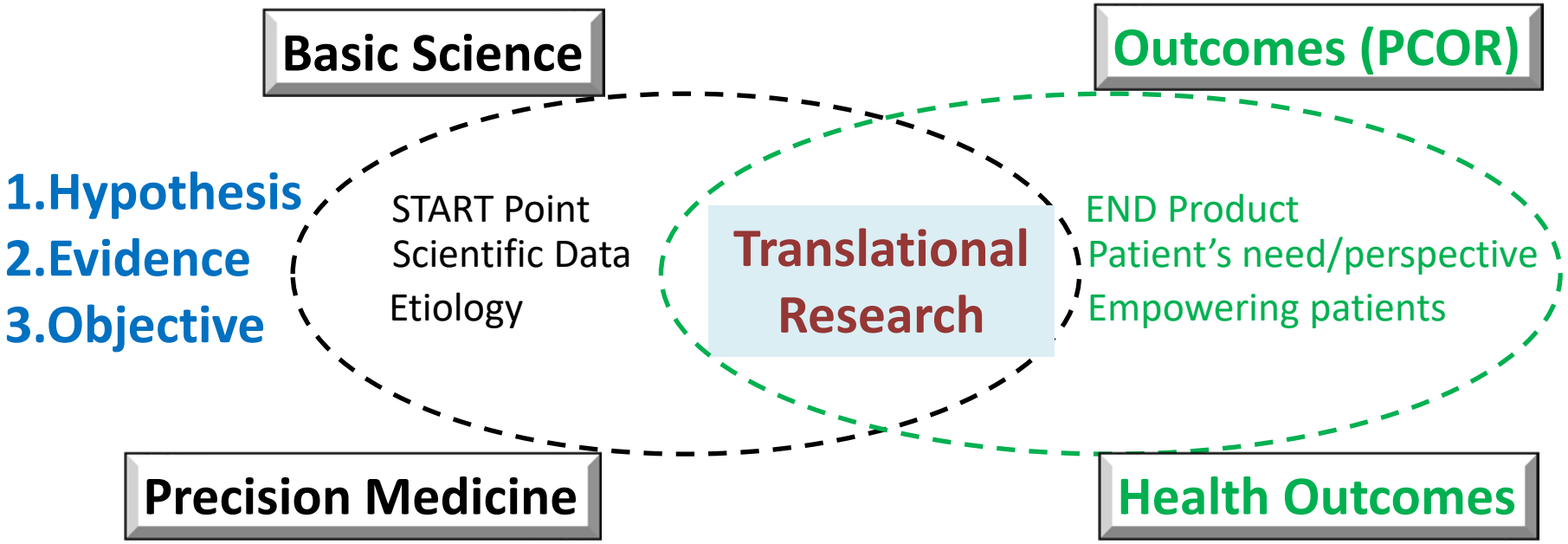
Evaluate association with a drug-side effect

Advantage:

1. Utilizing pharmacogenomics findings (AIWG SNPs)
2. Less expensive (retrospective study & re-analyzing existing genetic/phenotypic data)
3. Resulting in findings that may be beneficial in patient care management



Differences & Similarities



Autism genetics research ⇢

Parent/patient perspectives
Clinical observations

AutGO
(PCORI Project)

Personal Perspective

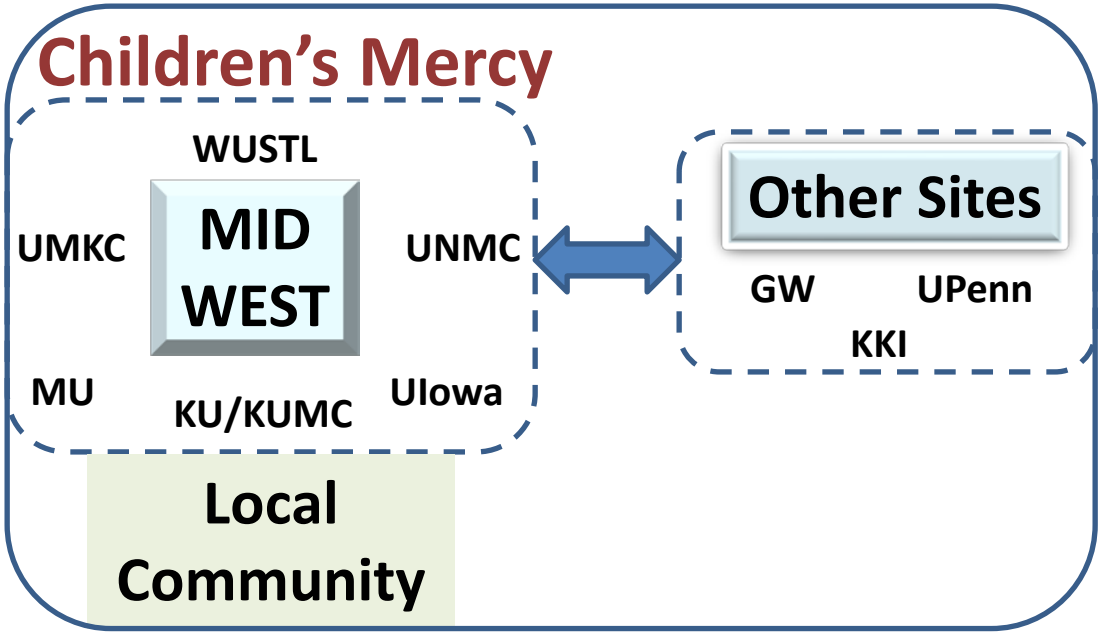
(development of the AutGO project)

- **Unique experience (evolving process)**

1. Involves developing a new integrative concept (no existing model)
2. Identifying/linking existing resources/expertise to address a concern raised by patient advocates and noted by research community using the PCORI platform
3. High demand for PI engagement
4. Extremely time consuming (professional sacrifice), BUT rewarding experience

- **Extensive learning curve**
  - ✓ Sharing our team experiences: paper/workshop
  - ✓ Future researchers do not need to go through the same time consuming process

Concluding Remarks



Autism Foundations
Community Leaders
Scientific Community

CONCEPT DEVELOPMENT

Taking the message to the autism research community

DISSEMINATION

Thank You!

- We welcome your feedback & thoughts
  - Workshop evaluation survey
  - Project website
    - **Phase-I:** public access
    - **Phase-II:** ongoing

Acknowledgments

- PCORI (Contract #s EAIN-2419, EAIN-3885)
- AutGO Study Participants
- Autism Parent Advocates

Project Coordinator: Ayten Shah, BSN

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Michele Kilo, MD
Mark Hoffman, PhD
John Lantos, MD
Laura Fitzmaurice, MD

Community Leaders:

Keith Gary, PhD (KCALSI)
John Spertus, MD (UMKC)
Russ Waitman, PhD (KUMC)
John Constantino, MD (WUSTL)
Kelly Ranallo (RareKC)

Motivational point

- To open up a dialogue for finding practical ways to take into consideration patients/parents perspectives when designing genetic research studies.

- To create a hybrid concept by integrating the two disciplines (i.e., outcomes and genetics).