Open Translational Science in Schizophrenia

Harvard Catalyst Workshop
March 24, 2015
Fostering Use of the Janssen Clinical Trial Data

• The goal of this project is to foster collaborations around Janssen’s CT data and advance the science around its use
  – This project will use Janssen CT with other publicly funded data about schizophrenia

• Open translational science holds promise in the study of complex problems including human illnesses
  – No one group has all the answers
  – This pilot project will help us determine the benefits of open-science collaborations for schizophrenia
Data Sources

• Janssen CTs in schizophrenia and related disorders:
  – 17 clinical trials
    • Publicly available through YODA*

• Publicly-funded research: Schizophrenia*
  – Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)
  – Neurodevelopmental Genomics (CHOP)
  – Molecular genetics
  – Exome sequencing
  – Methylation

* Note: Investigators must meet the data access and use requirements of all data holders.
Disciplines and Data: Beyond the Usual

Schizophrenia: natural history, subtypes, etiology

Design/Analysis Methods

Rx Efficacy

Rx Safety
Why Schizophrenia

- Severe disabling brain disorder that impacts about 1% of adults, with usual onset in teens and 20s with lifelong impact
- The disorder usually associated with hallucinations and delusions
- The disorder impacts all areas of brain functioning including social interactions, motivation, cognition, emotions, and senses.
Why now

- All medications have similar mechanism of action and only improve some symptoms with minimal impact on disability
- Medications with novel mechanisms of action have failed in late stage clinical trials
- Traditional sub-types have been eliminated
- Increasing recognition that the illness is genetically heterogeneous with over 108 loci identified in a recent paper
- Realization that it is not a single disorder but likely there are multiple illnesses (schizophrenias)
What the field needs

• New ways of thinking about the illness, particularly from people with different expertise

• Need to think of new ways of finding subtypes or phases of the illness that may have different outcomes, response to existing medications, predisposition to adverse events, or may be more responsive to new mechanisms of action
What is paliperidone

- Atypical antipsychotic
- Active metabolite of risperidone, one of the earliest atypical antipsychotic medications
- Available in both an extended release oral form (paliperidone ER) and long-acting injectable (paliperidone palmitate)
- Effective in treating the acute symptoms of schizophrenia as well as preventing relapse
- Primary mechanisms of action is dopamine (D2) and serotonin (5HT₂) receptor antagonist
17 Paliperidone Trials

**Disorders**
- Schizophrenia
- Schizoaffective Disorder
- Bipolar Disorder

**Therapies**
- Primary: Paliperidone ER
- Paliperidone palmitate
- Placebo
- Additional: Risperidone, Quetiapine, Olanzapine, Lithium, Valproate

**Outcomes**
- Symptoms (PANSS, HAMD, CGI-S, YMRS)
- Functional (PSP)
- Time-to-Relapse
- Adverse events

**Design Elements**
- Most studies are acute, randomized, double-blind, placebo controlled.
- Others include relapse prevention, active comparator, and open designs
Two common study designs

Acute

Relapse Prevention
The real voyage of discovery consists not in seeking new landscapes, but in having new eyes.

" Marcel Proust

OUR MISSION

The Yale University Open Data Access (YODA) Project’s mission is to advocate for the responsible sharing of clinical research data, open science, and research transparency. The Project is committed to supporting research focused on improving the health of patients and informing science and public health. The YODA Project can only improve with your feedback. Please share your comments and ideas.

CONTACT US

OUR MODEL

The YODA Project seeks mutually beneficial partnerships with Data Holders, promoting independence, responsible conduct of research, good stewardship of data, and the generation of knowledge in the best interest of society. To participate, each Data Holder must transfer full jurisdiction over data access to the YODA Project.

LEARN MORE

REQUEST DATA

Are you ready to request data? 112 trials are currently available to request as of February 13, 2015.

GET STARTED
## Proposed NCBI dbGaP and Other Public Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
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<tr>
<td>Genome-Wide Association Study of Schizophrenia (GAIN)</td>
<td>Case-control</td>
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<tr>
<td>Molecular Genetics of Schizophrenia -nonGAIN Sample (MGS-nonGAIN)</td>
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<td>Sweden-Schizophrenia Population-Based Case-Control Exome Sequencing</td>
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<td>Whole Genome Profiling to Detect Schizophrenia Methylation Markers</td>
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<td>Neurodevelopmental Genomics: Trajectories of Complex Phenotypes</td>
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<tr>
<td>Clinical Antipsychotic Trials of Intervention Effectiveness</td>
<td>Trial</td>
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Proposed NIMH: CATIE

- The primary purpose of the CATIE study was to provide information to guide the everyday treatment of people with schizophrenia. The goal of phase 2 of CATIE was to provide guidance for doctors and patients facing the dilemma of choosing which antipsychotic medication to try next if the first antipsychotic medication was not satisfactory.
Epidemiology

NIH OPTICS Project Data: NCBI - dbGaP

Preview Site

dbGaP Collection: Open Translational Science in Schizophrenia (OPTICS)

dbGaP Study Accession: phs000887.v1.p1

Show BioProject list

Study Description

Schizophrenia is a chronic, severe, disabling brain disorder that affects approximately 1% of the population worldwide. Epidemiologic studies have clearly demonstrated that genetics play a strong role in etiology, but the inheritance is very complex. Innovative analytic approaches and creative ways of combining disparate data sets will be necessary for making breakthroughs in identifying causal pathways and ultimately new drug targets.

This dbGaP collection consists of all genetic studies of schizophrenia available in dbGaP that have been consented for general research use. The goal is to facilitate identification of datasets with related scientific content in order to expedite the application process and ascertainment of datasets of interest for increased scientific discovery.

The Open Translational Science in Schizophrenia (OPTICS) Project, was launched by Janssen Research & Development, LLC, part of the Janssen Pharmaceutical Companies of Johnson & Johnson, to create a new forum for collaborative analysis of Janssen's schizophrenia clinical trial data and other publicly available data about schizophrenia with the goal of creating new models for conducting research. The OPTICS project is one part of a larger effort at Janssen and other Johnson & Johnson research companies to share clinical trials data to enhance public health and advance science and medicine. Qualified investigators and physicians may apply for access to anonymized clinical trials data from Janssen, for more information please visit https://sites.google.com/site/opticsichizophrenia/.

- Study Type: Collection
- Number of study subjects that have individual level data available through Authorized Access: 0

Publicly Available Data (Public ftp)

Note to previewer: A web link to an ftp site will appear on this page when this study is released to the public.

Selected publications

There are no selected publications related to this study.

Diseases/Traits Related to Study (MESH terms)
How It Works

Investigators applying to participate in OPTICS:

• Agree to conduct research toward at least 1 project goal:
  – Therapeutic safety, efficacy
  – Disease understanding (e.g. subtypes, course)
  – Analytic and design methods for disparate data types

• Apply for access to OPTICS Project data resources:
  – YODA & dbGaP/NIMH
  – Must meet data holder Data Use Agreements

• Goal: Integration of CT and other data about schizophrenia
Summary

• Open science holds promise in the study of complex problems including psychiatric illnesses
  – No one group has all the answers
  – This pilot project will help us determine the benefits of open-science collaborations for schizophrenia

• Despite current medications and scientific advances, schizophrenia continues to be a debilitating, costly illness
  – Collaborative projects such as this have the potential to examine schizophrenia in a manner that may spur the development of novel interventions

• This project will allow us to evaluate a model to establish collaborations involving CT and advancing the science around its use
For more information:

Optics Website

https://sites.google.com/site/opticsschizophrenia/
Thank You!
Proposed NCBI dbGaP: GAIN, non-GAIN

Genome-Wide Association Study of Schizophrenia (GAIN)

Case-Control: N=4,591

- The goal of the study is to find susceptibility genes for schizophrenia.
- Probands must have a consensus best-estimate DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) diagnosis of SZ (schizophrenia) or of schizoaffective disorder with at least six months' duration of the "A" criteria for schizophrenia.

Molecular Genetics of Schizophrenia - nonGAIN Sample (MGS_nonGAIN)

- Case-Control: N=2,868
- Cases met criteria for schizophrenia (SCZ) or schizoaffective disorder (SA) per the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) for all three collections (SGI, MGS1, and MGS2) comprising these cases
- Both: Affymetrix 6.0
Proposed dbGaP: Exome sequencing

- **Sweden-Schizophrenia Population-Based Case-Control Exome Sequencing**

- Case-Control, N=5090

- In order to create a comprehensive catalogue of low frequency or rare coding variation in individuals with psychiatric disease and to build a foundation for future genetic studies of schizophrenia and bipolar disorder, we have obtained whole exome DNA sequence from a population-based schizophrenia and bipolar disorder Swedish case-control cohort.
Proposed dbGaP: Methylation

- Whole Genome Profiling to Detect Schizophrenia Methylation Markers
- Case-control, N=1459
- The aim of this study was to detect DNA methylation (5meC) profiles in whole blood associated with SCZ. The sample consisted of schizophrenia cases and controls selected from national population registers in Sweden.
- Average 32.4 million high quality reads
Proposed dbGaP: CHOP

- **Neurodevelopmental Genomics: Trajectories of Complex Phenotypes**
- Cohort Age 8-21, N=8741

This study is a collaboration between the Center for Applied Genomics (CAG) at Children's Hospital of Philadelphia (CHOP) and the Brain Behavior Laboratory at the University of Pennsylvania (Penn).

The cohort consists of youths aged 8-21 years who consulted the CHOP network and volunteered to participate in genomic studies of complex pediatric disorders. All participants underwent clinical assessment, including a neuropsychiatric structured interview and review of electronic medical records. They were also administered a neuroscience based computerized neurocognitive battery (CNB) and a subsample underwent neuroimaging.