Towards precision medicine for people with intellectual and developmental disabilities (IDD)

1. People with IDD and their families have led the way toward precision medicine.
2. Now, continued help is needed to reach this goal.
People with IDD

...with short stature and specific facial traits

1866
People with IDD

...with short stature and specific facial traits

1866

1959

1960

Etiologic–based diagnosis

1930s
Full trisomy 21: 95%
Mosaic trisomy 21: 1%
Translocation: 4%

Etiologic-based diagnosis

Mechanistic-based diagnosis
Error in egg
Error in sperm

People with IDD
...with short stature and specific facial traits

1866
People with IDD …with X-linked inheritance pattern and no obvious clinical traits

Lerke 1969

Turner 1970s

...with X-linked inheritance pattern, macroorchidism, cytogenetic marker X

Lubs 1969; Sutherland 1977
People with IDD

...with X-linked inheritance pattern and no obvious clinical traits

Lerke 1969

Turner 1970s

...with X-linked inheritance pattern, macro-orchidism, cytogenetic marker X

Etiologic-based: CGG expanded repeat disorder—fragile X syndrome

Lubs 1969; Sutherland 1977

Ostra, Warren, Nelson 1991
But what now? Are we done? Have we reached the goal of precision medicine?

- Down syndrome
- Birth defects
  - Cognition and behavior
    - Seizures
    - Language
    - Autism
  - Drug response
- Alzheimer disease and aging
- Fragile X syndrome
What contributes the variation in clinical outcomes?
One Strategy:
Compare the “extremes” of a specific clinical outcome among those with the same genetic disorder

Environmental factors

Genetic factors

Identify affected biological pathways

Develop interventions that target imbalance
Environmental factors

Genetic factors

Identify affected biological pathways

Develop interventions that target imbalance
Setting the foundation for DS360:
A Genotype/Phenotype project to move towards precision medicine for people with Down syndrome

2873 families
- 988 cell lines
- 520 DNA samples

T21: Non-disjunction

NICHD
NHLBI

DS cognition project
Exploring cognitive variation in people with Down syndrome

DS heart project
People with Down syndrome helping to cure congenital heart disease in all people

LuMind

Stephanie Sherman, Ph.D.
Roger Reeves, Ph.D.
Examples of contributions from DS360 to the research community

- Test-retest studies (Edgin et al. 2017)
- T21RS Clinical and Developmental Committee:
  - Creation of a core battery
  - Data harmonization
- Genomic data to DS-cancer studies
- Cognitive data to examine adverse effects of cancer treatment
- Cell lines to examine genomic stability
Potential avenues of expansion of DS360

- **Merging with existing cohorts—examples:**
  - LonDownS (Strydom)
  - Univ of Geneva (Antanorakis)
  - Human Trisome Project (Espinosa)
  - LeJeune Foundation
  - ...

- **Using existing infrastructures and services:**
  - NIH DS-Connect®
  - NHLBI Pediatric Cardiac Genomics Consortium (PCGC)
  - NIH-supported Clinical and Translational Science Institutes

- **Working with T21RS to create an international consortium**
DS-Connect® is a powerful resource where people with Down syndrome and their families can:

- Connect with researchers and health care providers.
- Express interest in participating in certain clinical studies on Down Syndrome, including studies of new medications and other treatments.
- Take confidential health-related surveys. These surveys are aimed at better understanding of the health of people with Down Syndrome across their lifespans.

Informeación en español

What is DS-Connect®: The Down Syndrome Registry?

Registration Goal

Goal: 10000
Current: 3734

Download the Flyer
DS-Connect®: Facilitate Clinical Research

Explore and analyze de-identified natural history data

<table>
<thead>
<tr>
<th>Answer</th>
<th>Number of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2121</td>
</tr>
<tr>
<td>Yes, surgery for a congenital heart defect in the first year of life</td>
<td>667</td>
</tr>
<tr>
<td>Yes, surgery for a congenital heart defect after the first year of life</td>
<td>213</td>
</tr>
<tr>
<td>Cardiac surgery for other reason later in life</td>
<td>36</td>
</tr>
<tr>
<td>Unsure</td>
<td>8</td>
</tr>
</tbody>
</table>

Bar chart showing the distribution of responses to "Has the participant ever had any cardiac or heart surgery? (Select all that apply.)"
DS-Connect®: Facilitate Clinical Research

Explore and analyze de-identified natural history data
- Initial Health Questionnaire
- Sleep Questionnaire
- Heart Questionnaire
- Prenatal and Birth History
- Skeletal Questionnaire
- Gastrointestinal Questionnaire
- Development Questionnaire
- Adulthood Questionnaire
- Diabetes Questionnaire
- Celiac Disease Questionnaire
- Thyroid Questionnaire
- Men’s Health Questionnaire
- Women’s Health Questionnaire
- Leukemia Questionnaire

Advise and help recruit for approved studies
- Sleep issues
- Feeding issues
- Thyroid screening
- Alzheimer dx and aging (ABC-DS)
- Obesity and diabetes
- Motor and balance
- Gynecological issues
- Language
- Autism spectrum disorder
- Transition to adult care service
- Wayfinding
- Use of nutritional supplements
- Opinions of medical research

Sujata Bardhan, PhD
Melissa Parisi, MD, PhD
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• **Working with T21RS to create an international consortium**
Kimberly M. Huber, Ph.D., University of Texas Southwestern Medical Center
Joel D. Richter, Ph.D., University of Massachusetts Medical School
Stephen T. Warren, Ph.D., Emory University
Centers for Collaborative Research in Fragile X

FX-MOD: Modifiers of Fragile X-Associated Disorders

...tracking down genes that interact with FMR1

People with FXS

No seizures

Seizures

Environmental factors

Genetic factors

Identify affected biological pathways

Develop interventions that target imbalance
Fragile X syndrome

Collaborative Biomarker Research Project
Towards precision medicine for people with intellectual and developmental disabilities (IDD)