The Integration of Genomics into Acute Care Psychiatry

Precision Medicine on the Inpatient Child and Adolescent Psychiatry Service

UC San Diego/Rady Children’s Autism Research and Practice Seminar

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No Conflicts of Interest to Disclose
Overview

I. Genetics of Autism and Other Neurodevelopmental Disorders

II. Genetic Testing in Child and Adolescent Psychiatry: An Inpatient Experience

III. Genetic Testing Implementation at RCHSD and RCIGM
I. Genetics of Autism and Other Neurodevelopmental Disorders
Neurodevelopmental Disorders (NDDs)

**Autism Spectrum Disorders**
- Social communication deficits
- Restrictive and repetitive behaviors, interests, activities

**Global Developmental Delay**
- Not reaching developmental milestones on time
- <5 years old

**Intellectual Disability**
- Deficits in intellectual and adaptive functioning

(…and ADHD, Schizophrenia, Tourette Syndrome…)
Neurodevelopmental Disorders Are Largely Genetic Disorders

Bourgeron. Nat Rev Neurosc. 2015
Human Genetic Variation Can Be Classified Multiple Ways

**Frequency**
- Common
- Rare

**Inheritance**
- Inherited
- De Novo

**Location**
- Intronic (Regulatory)
- Exonic/Intragenic (Gene Coding)

**Size**
- SNV 1bp
- Indel 1-1000bp
- CNV >1000bp
Rare, De Novo, Intragenic Variants May Have Largest *Individual* Contribution to Genetic Risk for NDDs
Pathogenic Copy Number Variants Are Detected in 15-20% of Individuals with NDDs

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>ASD penetrance* (rate of ASD in carriers; %)</th>
<th>Neuropsychiatric pleiotropy‡ (associated neuropsychiatric phenotypes)</th>
<th>Somatic pleiotropy‡ (associated somatic phenotypes)</th>
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<td>8 (REF. 129)</td>
<td>ID¹⁹, ADHD¹⁹, schizophrenia¹⁹, hydrocephalus¹⁹, heart defect¹⁹, eye abnormalities¹⁹, short stature¹⁹, epilepsy¹⁹</td>
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<td>Epilepsy¹⁹, macrocephaly¹⁹, brachycephaly¹⁹, dilatation of ascending aorta¹⁹¹⁹¹⁹, patent ductus arteriosus¹⁹¹⁹, chronic obstruction¹⁹, kidney abnormalities¹⁹¹⁹</td>
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</tbody>
</table>

Consensus Statement: Chromosomal Microarray Is a First-Tier Clinical Diagnostic Test for Individuals with Developmental Disabilities or Congenital Anomalies

The American Journal of Human Genetics 86, 749–764, May 14, 2010

Vorstman et al. Nat Rev Genet. 2017
Over 100 Genes Are Now Associated with ASD and NDDs through Whole Exome Sequencing (SNVs)

<table>
<thead>
<tr>
<th>ASD predominant (ASDₚ) 53 genes</th>
<th>ASD &amp; NDD (ASDₙD) 49 genes</th>
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<tr>
<td>ASH1L</td>
<td>ADNP</td>
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<td>TM9SF4</td>
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<td>UBR1</td>
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</table>

Gene expression regulation 58 genes

Neuronal communication 24 genes

Cytoskeleton 9 genes

Other 11 genes

36% Diagnostic Yield

Why Do We Order Genetic Tests for NDDs?

✓ Answer the question “why?”
  • Diagnostic clarity (End the diagnostic odyssey)
  • Increase empowerment
✓ Allow for medical monitoring and prognosis
✓ Provide reproductive counseling
✓ Guide medical and psychiatric care
✓ Connect families with community support
✓ Allow families to partake in advocacy
✓ Identify relevant research studies to families
We are Failing to Act on these Guidelines

Daniel Moreno-De-Luca, MD, MSc
Brian C. Kavanaugh, PsyD
Carrie R. Best, MPH
Stephen J. Sheinkopf, PhD
Chanika Phornphutkul, MD
Eric M. Morrow, MD, PhD

JAMA Psychiatry  September 2020  Volume 77, Number 9
II. Genetic Testing in Child and Adolescent Psychiatry: An Inpatient Experience
Why Genetic Testing on an Inpatient CAP Service? It All Began as a Fellow…

- **Clinical observation**: many very sick children with NDDs on our service with no history of genetic testing
  - Ex: 10yo M with mild ID, severe TS, ADHD, OCD, and situs inversus

- Number of patients with NDDs on our inpatient service in 2016: **125**

- Number of patients who received **any** genetic testing on our inpatient service in 2016: **2**
Multi-level Support and Buy-in are Vital

Mark DeAntonio  
Inpatient Child Psychiatry

Mike Enenbach  

Sheryl Kataoka  
Training Director

Julian Martinez  
Medical Genetics

Naghmeh Dorrani  
Genetic Counseling

Hane Lee  
Bioinformatics
What Should a Psychiatrist Know About Genetics?:
Review and Recommendations From the Residency Education Committee of the
International Society of Psychiatric Genetics

John I. Nurnberger Jr, MD,PhD\textsuperscript{a,*}, Jehannine Austin, PhD\textsuperscript{b}, Wade H. Berrettini, MD,PhD\textsuperscript{c},
Aaron D. Besterman, MD\textsuperscript{d}, Lynn E. DeLisi, MD\textsuperscript{e}, Dorothy E. Grice, MD\textsuperscript{f}, James L. Kennedy,
MD\textsuperscript{g}, Daniel Moreno-De-Luca, MD\textsuperscript{h}, James B. Potash, MD,MPH\textsuperscript{i}, David A. Ross, MD,PhD\textsuperscript{j},
Thomas G. Schulze, MD\textsuperscript{k}, and Gwyneth Zai, MD,PhD\textsuperscript{g}

J Clin Psychiatry 80:1, January/February 2019

✓ Understand
✓ Counsel
✓ Consent
✓ Order
✓ Return Results
✓ Consult
✓ Refer
Genetic Testing Indications

**Absolute Indications**
- Intellectual Disability
- Developmental Delay
- Autism Spectrum Disorders
- Childhood-Onset Schizophrenia

**Relative Indications**
- Childhood Epilepsy
- Severe Psychopathology + Congenital Malformations
- High family burden of severe psychopathology
Inpatient Genetic Testing Study

UCLA Inpatient CAP Services
Standard Care

Pre-intervention  12 MONTHS

Genetics Education to Inpatient Psychiatry Trainees

Post-intervention  19 MONTHS

Retrospective Chart Review
Results of Retrospective Analysis

Eligible Patient Overview
- 125 patients pre-education,
- 197 patients post-education
- Age Range: 6-17yo
- Male: 78.3%
- Tested: ID: 39.1%, ASD 69.6%, COS 8.7%

Genetic Testing Rates
- Pre-Intervention: 2/125 (1.6%)
- Post-Intervention: 21/197 (10.7%)

Diagnostic Yield (FX: 18, CMA: 23, WES: 6)
- Pathogenic/Likely Pathogenic: 1/23 (4.3%)
- Variant of Unknown Significance: 8/23 (34.8%)

The Feasibility and Outcomes of Genetic Testing for Autism and Neurodevelopmental Disorders on an Inpatient Child and Adolescent Psychiatry Service

Aaron D. Besterman, Joshua Sadik, Michael J. Enenbach, Fabiola Quintero-Rivera, Mark DeAntonio, and Julian A. Martinez-Agosto

Interpreting and Addressing Low Yield

• Small sample size
• “Unexpected” phenotype (Impulse Control Disorders)
• Poorly studied patient population (High VUS rate)
• High common variant contribution (family history)
• Only ¼ of patients received WES
Outpatient Follow-up Was a Challenge

- Lost to Follow-up: 43.5%
- Medical Genetics: 30.4%
- Genetic Psychiatry: 13.0%
- Not Indicated: 13.0%
Unexpected Benefit to Inpatient Testing

- 39.1% of patients who received testing on inpatient were URMs
- 7.7% of patients who received testing elsewhere were URMs

Inpatient testing has the potential to increase access to genetic services for URMs
III. Genetic Testing Implementation in Child Psychiatry at RCHSD and RCIGM
RCIGM Performs Whole Genome Sequencing (WGS), Which Can Detect Most Variants of Interest for NDD Diagnoses

<table>
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<th>Frequency</th>
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</table>
Rapid WGS Is Ideal for an Acute Care Setting

Rapid Whole-Genome Sequencing for Genetic Disease Diagnosis in Neonatal Intensive Care Units

Carol Jean Saunders, Neil Andrew Miller, Sarah Elizabeth Soden, Darrell Lee Dinwiddie, Aaron Noll, Noor Abu Alnadi, Neveen Andrews, Melanie LeAnn Patterson, Lisa Ann Krivohlavek, Joel Fellis, Sean Humphray, Peter Saffrey, Zoya Kingsbury, Jacqueline Claire Weir, Jason Betley, Russell James Grocock, Elliott Harrison Margulies, Emily Gwendolyn Farrow, Michael Artman, Nicole Pauline Safina, Joshua Erin Petrikin, Kevin Peter Hall, Stephen Francis Kingsmore

Turn around time in 3-7 days!

Average length of stay for psychiatry inpatient: 3-7 days!
**RCHSD and RCIGM Provide a Unique Environment for Success**

### Traditional Barriers to Genetic Testing for NDDs
1. **Diagnostic Odyssey**
   - Step-wise outpatient testing/authorization
   - Many visits, many years
2. Outpatient facilities are not equipped to provide blood draws for patients with severe agitation
3. Underrepresented minorities may have less access to genetic services for NDDs
4. High loss to follow-up with standard “slow” testing approaches
5. Difficult to access team of professionals with expertise in psychiatry + genetics to use results to inform clinical care

### Inpatient rWGS Solution
1. Can detect most variants of interest in 1 test
2. Trained, professional staff can safely draw blood samples
3. Any child who gets admitted and is eligible can get genetic testing as part of their medical work-up
4. Minimize loss to follow-up with rapid turnaround time
5. Explore impact of genetic test result on clinical care with input from RCIGM collaborators
Genomics can Guide Precision Psychiatric Care for Some Patients with NDDs

• **Smith-Magenis Syndrome**
  • 17p11.2 deletion or RAI1 mutation with inverted melatonin secretion and sleep cycle
  • Treat with morning beta-blocker and evening melatonin

• **15q13.3 deletion syndrome**
  • ID syndrome with severe aggression and deleted α7NChR
  • Reduced aggression and psychotropic burden with galantamine
Additional Potential Benefits of rWGS on Inpatient CAP Service

• Improve family experience of hospitalization (e.g. everything is being done) and understanding of child’s illness

• Prepare for dissemination into less acute areas of psychiatry and other indications (e.g. schizophrenia – diagnostic yield 5-10%)

• Educate psychiatry trainees in genomic medicine
Prospective, Observational Hybrid Clinical Effectiveness/Implementation Study

- 50 Inpatients with ID+/-ASD
- Baseline Assessment + rWGS
  - Day 1
- Day 7 of Hospitalization
  - rWGS Results Returned
- Discharge Assessment
- 1 Month Post-Discharge Follow-up

Assessments
- Neuropsychological patient assessments
- Parental Experience
- Clinician Experience
- Implementation outcomes
  - Acceptability
  - Appropriateness
  - Feasibility
  - Cost

- ✓ Diagnostic (CNVs, SNVs, INDELs)
Thank You!

**UCLA**
- Families!
- Julian Martinez
- Mark DeAntonio
- Michael Enenbach

**RCHSD/RCIGM**
- Stephen Kingsmore
- Charlotte Hobbs
- Nicole Stadnick
- Greg Aarons

**Funding and Support**
- T32 UCLA Intercampus Medical Genetics Training Program
- Savant Fellowship in Developmental Neurogenetics
- AACAP Junior Investigator Award
- UCLA CART and IDDRC
- RCIGM