The National Research Agenda for Autism Spectrum Disorder: 
*What have Learned and Where are We Headed*

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Children’s Hospital of Philadelphia (CHOP)
Professor, University of Pennsylvania

https://www.centerforautismresearch.org/

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**Disclosure**

I have a potential financial interest in the hardware and computer software to “digitally phenotype” autism. CHOP has a patent pending on this work, and I am listed as one of the inventors.
Lecture Overview

1. Brief Introduction to Autism
2. Clinical Heterogeneity
3. Review research strategy/priorities and Funding
   • National Institute Health (NIH)
   • The Interagency Autism Coordinating Committee
4. Review research progress/findings in select areas
   a. Genetics
   b. Digital Phenotyping for Precision Medicine
   c. Digital Assessment of Social Coordination
   d. Autism Learning Health System
   e. Social Attention & Social Reward Mechanisms: Eye Tracking & Neuroimaging
   f. Developmental Brain Mechanisms: Neuroimaging (babies & toddlers)

Not discussing: services research, intervention research

Center for Autism Research (CAR)

• Founded in 2008
  - Multidisciplinary Collaboration between Clinicians & Scientists in a Dozen different Disciplines
    o Pediatrics    o Psychiatry    o Psychology    o Cognitive Neuroscience
    o Genetics     o Radiology    o Epidemiology    o Neurology
    o Nursing      o Social Work  o Public Health    o Information Sciences
CHOP’s Center for Autism Research

**Tripartite Mission:**
1) Discover Causes of autism at the level of each individual, in order to devise effective treatments (personalized medicine)
2) Train next generation of master clinicians and researchers
3) Create Community Partnerships to provide direct Family Supports (e.g., CAR Roadmap, Next Steps, expert evaluations of 400+ individuals/year) and test novel treatments.

**Guiding Premise:** Outward manifestations of “Autism” are a result of altered brain functions that impede typical learning and development

**Fundamental Goal:** Translation of a biological understanding of causal mechanisms into more effective treatments

**Reality:** Autism is quite varied in its presentation. Hundreds of different causes. Impedes mapping of biology to phenotype. Demands
(a) better quantification of the phenotype (e.g., digital phenotyping)
(b) Identification of subgroups that cohere for biological studies

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**Brief Autism Introduction**

- Laying a foundation for our common understanding of ASD
Autism: Brief History & Overview

- First recognized by Leo Kanner, 1943
  - Congenital in nature (recognized between 2 & 5)
  - Individuals with autism “... have come into the world with an innate inability to form the usual, biologically provided affective contact with other people.”

- Prevalence of Autism Spectrum Disorders (ASD). 1 in 59

- Diagnosable by 18-24 mo., but average age of diagnosis is 4-5 year of age

- No medical treatments for core features
  - Psychopharmacology for behavioral dysregulation (e.g., self injurious); and comorbidities (Anx, ADHD, GI, Sleep)

- Behavioral treatments are the mainstay

- Almost always a life long disability, but symptoms change with age

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DSM 5 Criteria

*Autism Spectrum Disorder* defined by

- signs and symptoms, rather than by etiology or objective markers
- a dyad of problems:

1. Social communication deficits:
   - social-emotional reciprocity (e.g. abnormal social approach & initiation, sharing, turn taking)
   - social nonverbal communication (gesture, expressions, eye contact)
   - developing, understanding and maintaining relationships

2. Restricted interests and repetitive behaviors
   - Motor stereotypies e.g., hand flapping and other mannerisms
   - Insistence on sameness (e.g. adherence to rigid routines)
   - Intense, preoccupying, restricted special interests (e.g. calendars)
     - Become experts on things, not people
     - Suggests differences in reward pathways of the brain
   - Hyper- or hypo-sensory sensitivities
The Debate Over an Autism Cure Turns Hostile

**Disease, Disorder, Individual Difference?**

**Autism Rights Movement:** Don’t “Pathologize” Autism

Autism Rights Movement

Encourages autistic people, their caregivers and society to adopt a position of accepting autism as a variation in functioning rather than a mental disorder to be cured.

**Goals** include:

- a greater acceptance of autistic behaviors
- interventions that focus on coping skills rather becoming more “neurotypical”
- creation of social supports that allow autistic people to socialize on their own terms
- the recognition of the autistic community as a minority group

Wide variety of both support and criticism

A criticism sometimes leveled against autistic activists is that sometimes their views only represent only one segment of the community, e.g., those without intellectual disability

Not all Differences are deficits. Depends on context; e.g., low social motivation, restricted hyper focused interests can be very adaptive.

Need a skills, attributes and challenges based understanding of people, a respect for differences and an emphasis on quality of life.
Prevalence of Diagnosis steadily increasing

![Graph showing autism prevalence since 2000](image)

2018: 1 in 59

166/68 = 2.44

Prevalence of Diagnosis really increasing?

- 1 in 37 boys and 1 in 151 girls
  - Boys:Girls ~ 4:1,
  - Even more boys than girls in IQ range > 70
- Prevalence of Autism Spectrum Disorders (ASD)
  - 1 in 59 or 1.69% (had been 1/68 or 1.47%)
- Explanations for rate increases include
  - Greater detection w/o more cases
    - Driven by greater awareness and more acceptance w/ less stigma
  - Diagnostic swapping
  - Real increase in rate driven by
    - Older parents
    - Environmental factors (e.g., air pollution)
      - IBIS - geocode, heavy metal in baby teeth
      - Other unknown biological causes

Changing Labels

<table>
<thead>
<tr>
<th>U.S. special education student diagnoses per 10,000 students</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual disability</td>
</tr>
<tr>
<td>Autism</td>
</tr>
</tbody>
</table>

Sources: Pennsylvania State University
THE WALL STREET JOURNAL.
Heterogeneity

- variation in clinical manifestations
- variation in underlying biological mechanisms
- Makes things difficult!

Autism X 6
(Discovery Health Documentary)
Autism X 6
(Discovery Health Documentary)

ASD category masks considerable heterogeneity in symptoms
“If you have seen 1 child with autism, you have seen 1 child”

Autism is Not A Single Disorder

ASD as a category masks considerable heterogeneity in symptoms
- “If you have seen 1 child with autism, you have seen 1 child”
- Similar to Intellectual Disability - 100s of similar disorders with 100s of underlying biological risk factors (e.g., genes)

Numerous co-morbidities (50% of cases have 1 or more)
- Anxiety, ADHD, Intellectual Disability
- Seizure Disorder, Sleep Disorder, GI disorders

Comorbidities point to
(a) Pleiotropy (each biological mechanism gives rise to >1 manifestations)
(b) Shared neural system vulnerabilities (e.g., appetitive & aversive motivation/Reward system)

Heterogeneity greatly impedes
- Search for causes (pursuit of personalized medicine )
- Matching cases to best treatment
- Reproducibility of science; many studies fail to replicate

Researchers often fail to characterize our samples along the most important trait dimensions
A manifesto for reproducible science

Marcus R. Munafò, Brian A. Nosek, Dorothy V. M. Bishop, Katherine S. Button, Christopher D. Chambers, Nathalie Percie du Sert, Uri Simonsohn, Eric-Jan Wagenmakers, Jennifer J. Ware and John P. A. Ioannidis

Power failure: why small sample size undermines the reliability of neuroscience

“... it is more likely for a research claim to be false than true.”
- John Ioannides (2005)
ASD Heterogeneity in Severity Reduces Sensitivity To Detect ASD vs. Control Brain Differences

- Novel ASD severity metric: Applied to MRI data set
  - 54 TDCs, 69 ASD

Significant ROI differences for TDC vs. ASD

<table>
<thead>
<tr>
<th>Least Severe</th>
<th>All ASD</th>
<th>Most Severe</th>
</tr>
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</table>

Twice as many brain differences (ASD vs. controls) when eliminating the mildest cases, *despite reduced statistical power to detect differences!*

Tunc et al 2014, *Neuroimage*

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Who Decides on What Research to Fund?

How is it funded?
National Institutes of Health (NIH)

National Board of Health created in 1879
• Congress funds 1st organized, comprehensive, national medical research effort
• Gradually grew with a series of additional laws over the next ~ 70 years
  • Often in response to upsurge in specific communicable diseases:
    • E.g., cholera, yellow fever, the influenza pandemic of 1918.
• 1930, 1938 Land donated & congress appropriated $ funds for first NIH buildings
• 1944. Public Health Service Act consolidated public health activities, providing for post war expansion of current NIH
• 1946. National Mental Health Act passed
• National Heart Institute (1948), National Institute of Mental Health (1949), National Institute of Neurological Diseases (1950), NICHD (1963)
• NIMH is one first four National Institutes (now 27 Institutes in total)
• NIH is part of the Department of Health and Human Services (HHS), Sec. Alex Azar
  https://www.hhs.gov/about/agencies/hhs-agencies-and-offices/index.html

Autism Research Total Funding By Organization

<table>
<thead>
<tr>
<th>Funding Agency/Organization</th>
<th>2015 Funding</th>
<th>Project Count</th>
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<tbody>
<tr>
<td>Federal</td>
<td></td>
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<tr>
<td>National Institutes of Health (NIH)</td>
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<td>500*</td>
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<tr>
<td>Federal</td>
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<tr>
<td>Department of Education (ED)</td>
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<tr>
<td>Federal</td>
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<td>Centers for Disease Control &amp; Prevention (CDC)</td>
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<tr>
<td>Private</td>
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<td>Autism Speaks (AS)</td>
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<td>Federal</td>
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<td>Health Resources and Services Administration (HRSA)</td>
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<td>Federal</td>
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<td>Department of Defense - Army (DoD-Army)</td>
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<td>Federal</td>
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<td>Administration for Community Living (AQL)</td>
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<td>National Science Foundation (NSF)</td>
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<td>Private</td>
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<td>Brain &amp; Behavior Research Foundation (BBRF)</td>
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<td>Agency for Healthcare Research &amp; Quality (AHRQ)</td>
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<tr>
<td>Federal</td>
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<td></td>
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<tr>
<td>Environmental Protection Agency (EPA)</td>
<td>$343,809</td>
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18 federal & private funders

$343 Mil
80% Federal
Budget: NIH Institutes that fund Autism Research

NIH - part of the Dept. Health & Human Services
NIH total Annual Budget: ~ $37 Billion

Nearly all autism funding from 6 Institutes:
1. National Institute of Mental Health (NIMH)
   • Total budget $1.8 B/yr
2. National Institute of Child Health & Human Development (NICHD)
   • Total budget $1.6 B/yr
3. National Institute of Deafness & Other Communication Disorders (NIDCD)
   • Total budget $0.5 B/yr
4. National Institute of Environmental Health Sciences (NIEHS)
   • Total budget $0.8 B/yr
5. National Institute of Neurological Disease & Stroke (NINDS)
   • Total budget $2.2 B/yr

HHS Organizational Chart

NIH is 1 of 11 Admin. Units
NIH Is 3.3% of entire HSS budget
NIHM is 0.16% of HSS budget
Autism Research: 0.03% (across 18 fed & private funders)
National Institute of Mental Health (NIMH)

NIMH composed of 4 Divisions (% of total budget):
- Translational Research: Translate model system research to humans (~35%)
- Neuroscience & Basic Behavioral Science (~35%)
- Services & Intervention Research (~15%)
- AIDS Research (~15%)

2017 NIMH Budget: $1.8 Billion.
Funds support:
- Internal NIH labs
- Extramural research program
  - Trainees
  - Faculty Research Projects

75% of funds allocated each year are to prior commitments, e.g. projects funded in prior years.

2017 NIMH Autism Budget ~ $100 Mil
it would take 50 years for the NIMH Autism investment to match what Tesla spent the last 2 years on its battery making factory - $5 Billion

10 Kinds Research Funded by the NIH

A. Primary Research Focus for NIH Autism Research Grants (NIH PA-16-388):
1. Epidemiology (e.g., risk factors, prevalence, range of expression)
2. Screening, Early Identification, and Diagnosis
3. Genetics
4. Brain Mechanisms
5. Shared Neurobiology of ASD with Related Disorders (e.g., Fragile X syndrome)
6. Cognitive Science (e.g., social attention, theory of mind across the lifespan)
7. Communication Skills
8. Pharmacological/Biological Interventions
9. Psychosocial/Behavioral Interventions
10. Services Research (research on the organization, delivery, coordination and financing of services for persons with ASD and their families)

Grants due/accepted 3 times per year (February, June, October)

~ 75 page Application includes:
Abstract; Specific Aims (1 pg); Research Strategy (12 pages); Biosketches; Budget; Timeline; Facilities & Resources; Equipment; Resource Sharing Plan; Protection of Human Subjects; Inclusion of Women, Children, Minorities.
**Is Funding Equivalent across Disorders?**

**Relationship between DALYS & Funding**

**DALYs:**
- Disability-adjusted life years.
- An aggregate number of years lost to premature mortality & years lost to disability.

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**NIH Research Funding: Grant Reviews**

“Study Section” scores all grants, best scored grants are funded
- Members are Academic & Clinical Experts w/specific expertise
- 3 Reviewers per grant (but all members vote).
- Scored with a 9 point scale: 1 = exceptional; 9 = poor (whole numbers)
  - Overall Impact: The likelihood for a project to exert a sustained, powerful influence on research field(s) involved
  - 5 specific areas

<table>
<thead>
<tr>
<th>A near miss... this SBIR grant has great scores and will probably win on the next try</th>
<th>Deep doo-doo... winning is impossible without a top to bottom overhaul</th>
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<tbody>
<tr>
<td><strong>Scores from 3 reviewers</strong></td>
<td><strong>Scores from 3 reviewers</strong></td>
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<tr>
<td>#1</td>
<td>#2</td>
</tr>
<tr>
<td>Significance</td>
<td>2</td>
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<tr>
<td>Investigator(s)</td>
<td>1</td>
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<tr>
<td>Innovation</td>
<td>3*</td>
</tr>
<tr>
<td>Approach</td>
<td>2</td>
</tr>
<tr>
<td>Environment</td>
<td>1</td>
</tr>
</tbody>
</table>

*Improve these scores to win.
* these scores are disastrous.
NIMH Strategic Plan (2015*)

NIMH - Institute that funds bulk of autism research

Strategic Plan to support “research that transforms the understanding and treatment of mental illnesses, paving the way for prevention, recovery, and cure”

Identify the most important problems and identify areas of traction (science and public health needs), with guidance from the National Advisory Mental Health Council and a diverse set of public stakeholders

Conscious effort to devote budget to both

- Urgent mental health needs
  - Treatment research
  - Services/implementation research
- Longer-term investments in basic research
  - Genomics, neuroscience
  - Environmental factors (e.g., stress, social determinants)

*Previously updated in 2008
NIMH Strategic Plan (2015*):
4 Strategic Objectives

1. Define the Mechanisms of Complex Behaviors (basic science)
   • E.g., Describe the molecules, cells, and neural circuits associated with complex behaviors... DREADDS to manipulate neuronal activity

2. Chart Disorder Trajectories To Determine When, Where, & How to Intervene
   • E.g., Identify clinically useful biomarkers and behavioral indicators that predict change across the trajectory of illness, and treatment effects;

3. Strive for Prevention and Cures
   • E.g., Develop treatments from genomics & neuro- & behavioral discoveries.
   • Develop biomarkers to detect subgroups so that clinical trials don’t include highly heterogeneous groups for whom treatment response may differ.

4. Strengthen the Public Health Impact of NIMH-Supported Research
   • E.g., services research can speed implementation of evidence-based care

*Previously updated in 2008

Autism Centers of Excellence (ACE)
ACE grants fund large collaborative projects or Centers: ~$2 million/year for 5 yrs
• ACE grants can only be submitted once every 5 years

9 or 10 Centers, co-funded by 5 NIH Institutes:
1. UC Davis. Identify clinically meaningful subtypes to aid treatment development
2. Emory. Early development of reciprocal social behavior and autism risk
3. George Wash. U. Longitudinal follow-up study of ASD sex differences
4. Infant Brain Imaging Study. F/u of infants and toddlers into school age to study brain-behavior trajectories and outcomes (ASD, school, mental health)
5. Drexel. Proving that early screening leads to early ID, treatment and improved outcomes
6. FL State U. Studies parent use of Early Social Interaction treatment model
7. UCLA 1. Biological bases of clinical heterogeneity (trajectories, treatment response)
8. Yale. Molecular, cellular, and neural mechanisms, prenatal to childhood
10. UCLA 2. ASD genetics in African Americans and studies of care access
Number of applications increased ~75% since 1998.
Hyper-competitive environment of research funding across NIH.
Destructive effects on innovation and early stage investigators.
**Interagency Autism Coordinating Committee (IACC): A 2nd influencer of Research Funding Priorities**

- **Federal advisory committee** charged with coordinating federal activities concerning autism spectrum disorder (ASD) and providing advice to the Secretary of Health and Human Services (*Alex Azar*) on issues related to autism.


- **Members:** representatives from a wide array of Federal Agencies and Private Foundations, as well as public stakeholders, self-advocates, family members of individuals with ASD, service providers, and researchers.

- **IACC is required to**
  1) Monitor and Report on Federal Program/Agency progress related to ASD
  2) Develop an annual strategic plan for ASD research*
  3) Annual research progress report

* The *IACC Strategic Plan* organizes research priorities around seven general topic areas represented as community-focused “questions.”

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**https://iacc.hhs.gov/**
IACC Strategic Plan: Addresses 7 Questions

1. **How can I Recognize the Signs of ASD, and Why is Early Detection so Important?**
   - E.g., to strengthen the evidence base for the benefits of early detection of ASD; reduce disparities in early detection & access to services; develop tools

2. **What is the Biology Underlying ASD?**
   - Foster research to better understand of early development, molecular and neurodevelopmental mechanisms of ASD and co-occurring conditions

3. **What Causes ASD, and Can Disabling aspects be Prevented or Preempted?**
   - E.g. understand risk (e.g., genes) & resilience factors for ASD across the full spectrum

4. **Which Treatments and Interventions will Help?**
   - Improve medical & behavioral interventions for core and co-occurring symptoms.

5. **What kinds of Services and Supports are Needed to Maximize Quality of Life for People on the Autism Spectrum?**
   - Implement evidence-based interventions in community settings, improve access (and reduce disparities), improve service models.

6. **How can we meet the Needs of People with ASD as into Adulthood?**
   - Development coordinated/integrated services for core & co-occurring conditions to enhance inclusion, independence and quality of life.

7. **How do we Enhance Infrastructure to meet the Needs of the ASD Community?**
   - Expand research & services workforce, accelerate research translation to practice, strengthen ASD surveillance, promote growth & coordination biorepositories
Progress toward IACC Strategic Plan Objectives

Strategic Plan (2016-17) has 78 objectives
- Each 2015 ASD funded project was evaluated with respect to the 78 objectives
- 97% of the 78 objectives in the Strategic Plan were judged to be underway or completed

IACC Reporting of Funding by Question
New vs. Continuing Project $ by Question

Genetics
Research Progress: Genetics

- ASD often Runs in Families
  - Sibling recurrence risk ~ 20%
  - Broader autism phenotype in relatives
    - Parent symptom level predicts child ASD severity ($r^2=20\%$)
- Twin studies suggested very high heritability
  - Twin Concordance
    - Identical Twins (MZ): ~ 70% “concordance”
    - Fraternal Twins (DZ): ~20%
    - Estimated “heritability ranges 37% - 84%”
  - Multifactorial: clear role for non genetic factors

Genomic Heterogeneity

- 500+ genomic risk variants
- Pleiotropy: genetic risk factors for autism are shared across many disorders (e.g. ADHD, schizophrenia, intellectual disorders)

Why Identify Autism “Risk” Genes?

- genetic test
- early prediction
- early intervention
- better outcome?
Why Identify Autism “Risk” Genes?

- Behavior
  - gene therapy
  - genes
- Brain region
  - proteins
- Circuits & Cell/neurons functions
  - molecules
- Pathways
- Proteins/molecules
- drug development
- Disorder mechanism

Genetic Mechanisms

- Steady progress in pin pointing Autism “Risk” Genes
  - Simplex (de novo) vs multiplex (inherited risk genes)
  - Currently 23 “high confidence genes” (genome-wide statistical significance, with independent replication)
  - 42 “strong candidates” (less good replication)
  - Total number of ASD risk genes estimated to be more than 400
  - Common genetic variance: mass accumulation of very small genetic effects.
    - accounts for ~50% of population risk
- Considerable heterogeneity in ASD severity and comorbidities
  - Predicts considerable genomic heterogeneity, suggesting the need for individualized biomedical interventions (precision medicine)
Genetic Syndromes Associated with ASD

Low “penetration”

<table>
<thead>
<tr>
<th>ASD-related syndrome</th>
<th>Associated gene(s)</th>
<th>Proportion with ASD</th>
<th>Proportion ASD with syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1q21 Duplication</td>
<td>Many</td>
<td>50%</td>
<td>~1%</td>
</tr>
<tr>
<td>3p Deletion/duplication</td>
<td>CNTN4</td>
<td>&lt;50%</td>
<td>~1%</td>
</tr>
<tr>
<td>15q Duplication (maternal)</td>
<td>Many (including UBE3A, GARRB3, SNRPN, and SNURF)</td>
<td>High</td>
<td>~1%</td>
</tr>
<tr>
<td>15q13 Deletion</td>
<td>Many (including CHRNA7)</td>
<td>&lt;50%</td>
<td>Unknown</td>
</tr>
<tr>
<td>16p11 Deletion</td>
<td>Many (including SERRD2)</td>
<td>High</td>
<td>~1%</td>
</tr>
<tr>
<td>22q11 Deletion (also VCFS / DGGeorge)</td>
<td>Many (including TRIM and COMT)</td>
<td>15–50%</td>
<td>~1%</td>
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<tr>
<td>Angelman (15q11-13)</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
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<tr>
<td>Beckwith Weidemann (11p15)</td>
<td>Maternal UBE3A</td>
<td>40–40%</td>
<td>~1%</td>
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<tr>
<td>Cortical dysplasia focal epilepsy (7q55-56)</td>
<td>IGF2 and CDKN1C</td>
<td>~7%</td>
<td>Unknown</td>
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<tr>
<td>Cowden/BRSS (11q23)</td>
<td>CNTNAP2</td>
<td>70%</td>
<td>Negligible</td>
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<tr>
<td>Down (trisomy chr.21)</td>
<td>PTEN</td>
<td>20%</td>
<td>&gt;10% with macrocephaly</td>
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<tr>
<td>Fragile X (Xq27)</td>
<td>FMR1</td>
<td>6–15%</td>
<td>Unknown</td>
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<tr>
<td>Potocki-Lupski (1p11)</td>
<td>Many (including RAI1)</td>
<td>~90%</td>
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<td>Smith-Lemli-Opitz (11q13)</td>
<td>DHCR7</td>
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<td>Prader–Willi (15q11-13)</td>
<td>Paternal deletions</td>
<td>20–25%</td>
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<td>Rett (Xq26)</td>
<td>MECP2</td>
<td>N/A</td>
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<td>Timothy (12p13)</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Negligible</td>
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<td>Tuberous sclerosis (9q34 and 16p11)</td>
<td>TSC1, TSC2</td>
<td>20%</td>
<td>~1%</td>
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Pleiotropy: Same Mutation is associated with many different outcomes

Copy Number Variants: Risk Factors for Multiple Neurodevelopmental Disorders

<table>
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<tr>
<th>CNV (Genes)</th>
<th>ASD</th>
<th>ID/DD</th>
<th>SCZ</th>
<th>ADHD</th>
<th>Epilepsy</th>
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<td>2p16.3 (NRXN1)</td>
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ASD: autism spectrum disorders; ID/DD: intellectual disability/developmental delay; SCZ: schizophrenia

Smoller et al 2013, Am J H Genetics, B
### Challenges to developing Treatments from Genetic Discoveries

- Mutations in blood not always representative of those in neurons or all neurons
- Genetic risk factors are often not shared between affected individuals.
  - Necessitates personalized medicine
  - Since ASD is the result of many (genetic & nongenetic) factors, might suggest the need for poly-pharmacy to modulate > 1 biological process in each person
- Neural system specificity – how to prevent a drug from affecting all tissue?
- Developmental specificity – recent data suggest genetic risks are expressed prenatally. How to intervene earlier? What effect will later intervention have?
- Long time horizon until success?
  - Compare to cancer. NCI budget $5,206 Mil vs. $273 Mil for ASD research (19 X more)
  - How to best allocate basic vs. more applied research funding?

### Digital Phenotyping for Precision Medicine
The Precision Medicine Revolution

Medical trials are getting a makeover in a shift poised to deliver major breakthroughs.

Precision needed measuring individual behavioral, cognitive and emotional attributes, not just cells and molecules.

Precision Medicine/Individualized Understanding Requires Precision Measurement

- Quantify everything
- Make sure measures are reliable (reproducible across time & between evaluators)
- Measure with the most finely graded “rulers”

Weight loss example
- Great new weight loss medicine
- 160 lb woman can loose 20 lbs!
- Scale is in 50 lb increments
  - FAIL to See a true tx Effect!!
Electronic Capture of All Observable Behaviors: “Digital Phenotyping”

**ASD** is a behaviorally defined disorder

- understood from descriptions of what the person can do well and cannot do well, or does too much or too little

**Now possible to digitize Every Behavior** that experts observe, without lapses in attention or memory:

1. **Language:**
   - **What we say:** Words chosen (interests, preoccupations), contractions, turn taking
   - **How we say it:** prosody, fundamental frequency, rate, tone, rhythm, volume, stress, intensity, co-articulation (spacing between phonemes/words)

2. **Anxiety/arousal via ECG HR variability, blushing (video detection)**

3. **Motor behavior & coordination:** posture, fine motor skill, gross visuo-motor skill, imitation ability, repetitive behaviors.

4. **Nonverbal Communication**
   - Facial expressions, eye contact, gestures
   - **Social motor coordination:** responsiveness, reciprocity

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**Markerless Gross Motor Capture**

- Repetitive Behaviors
- Atypical gait
- Atypical Kinematics (velocity, acceleration, jerkiness)
- Integration of gesture and speech
- Poor integration of sequential movements (e.g., reach to grasp to eat or place)
- Impaired imitation (praxis)

**Gross Motor delays and difficulties are strongly associated with autism and one of the earliest signs of autism risk, e.g., IBIS**
Movement Path

Adolph et al. 2012. Learning to walk. Thousands of Steps and Dozens of Falls Per Day

- Exploratory behavior
- Coordination, Postural stability
- Social Approach, proximity seeking

Gross Motor Delay Begins at 6 months – One of the Earliest Predictors of Autism

Gross Motor Skill
- e.g., head steady on sit

significant differences at 6, 12 and 24 months
Imitation: A Core Difficulty

Benton Test of Face Recognition

Example Item

N = 518 ASD, 519 TDC, $d = .58$

female > male, $d = .17$

IQ, $d = .55$

Pick 3 that match the person above
Imitation – Big Effect Size

A Common Language Explanation
With a Cohen’s d of 2, 98% of the treatment group will be above the mean of the control group (Cohen’s d, 32% of the two groups will overlap, and there is a 82% chance that a person picked at random from the treatment group will have a higher score than a person picked at random from the control group (probability of superiority). Moreover, in order to

Face Recognition – Medium (Smaller) Effect Size

A Common Language Explanation
With a Cohen’s d of 0.5, 69% of the treatment group will be above the mean of the control group (Cohen’s d). 82% of the two groups will overlap, and there is a 63% chance that a person picked at random from the treatment group will have a higher score than a person picked at random from the control group (probability of superiority). Moreover, in order to have one more favorable outcome in the treatment group compared to the control group we need to treat 6 people. This means that if 100 people go through the treatment, 16.2 more people will have a desirable outcome compared to if they had received the control treatment.
Social Perception: Facial Expression

Wolfe et al. 2008

52 TDC vs. 53 ASD
Age = 11.6, 11.6
FSIQ = 106.0, 106.0
d = .63

New sample
442 ASD, 314 TDC d = .47
Female > male d = .21
IQ, d = .70

Face Immediate Memory
147 ASD, 135 TDC d = .53

Expression Recognition – Medium Effect Size

Cohen’s d: 0.7

75.8 %
72.63 %
68.97 %
4.1

Interpretation

With a Cohen’s d of 0.7, 75% of the treatment group will be above the mean of the control group (Cohen’s d). 73% of the two groups will overlap, and there is a 69% chance that a person picked at random from the treatment group will have a higher score than a person picked at random from the control group (probability of superiority). Moreover, in order to have one more favorable outcome in the treatment group compared to the control group we need to treat 4.1 people. This means that if 100 people go through the treatment, 24.4 more people will have a favorable outcome compared to if they had received the control treatment.
Still not as big as Imitation Effect Sizes

Cohen's d: 2

Interpretation

- **97.72%**
- **31.73%**
- **92.14%**
- **1.48**

A Common Language Explanation

With a Cohen's d of 2, 97.72% of the treatment group will be above the mean of the control group (Cohen's d), 31.73% of the two groups will overlap, and there is a 92.14% chance that a person picked at random from the treatment group will have a higher score than a person picked at random from the control group (probability of superiority). Moreover, in order to have one more favorable outcome in the treatment group compared to the control group we need to treat 1.48 people. This means that if 100 people go through the treatment, 67.7 more people will have a favorable outcome compared to if they had received the control treatment.

Digital Assessment of Social Coordination
Head, Face and Eye Motion Capture

Measuring Dyadic Interactions

Down-Right and Down-Left Eye-Gaze Saccades Respectively

Keith

Brianna

Joint Attention
Social Motor Coordination

All living beings synchronize: birds flock, fish school, bees swarm, humans dance, including the social dance of a coordinated conversation.

There is a natural tendency for social partners to spontaneously and dynamically coordinate their movements (Chartrand, 1999; Garrod, 2004; Hove, 2009; Sonnby-Borgstrom et al., 2003; Wiltermuth, 2009; Riehle 2017; Schmidt 2012; Condon 1974; Nadel 1999):

- Conversational partners’ smiles and limb movements correlated in time
- Develops early in life - 2 month old can differentiate between contingent vs. non-contingent behaviors
- Facilitates: Communication; Empathy; Perspective-taking; Rapport and closeness; Cooperation and helping behavior
- Disruption in natural interpersonal contingencies cause social partners to feel less connected and social interaction to feel more challenging

Social Motor Coordination in ASD

Interpersonal synchrony is diminished in ASD

- For example, less spontaneous rocking chair synchrony with parent (Marsh 2013)
- Less blink synchrony to video of an actor giving a speech (Nakano 2013)
- Less likely to spontaneously match other’s emotional expressions (McIntosh 2000; Beal 2008)
- Well established imitation deficits (Williams 2004; Bernier 2007) (large effect sizes ~ 1 to 2 SDs)

Methods for measuring the timing of behaviors passed back and forth between people during a social interaction have been lacking
Video Measurement of Social Interactions
In natural “get to know you” conversations

• Markerless motion capture of *time synchronized* motor behaviors across dyadic partners
• Automated computer vision analyses; machine learning for categorical and dimensional phenotypic measurement

We Measure 180 “Bases”
Regionally specific independent time series of facial behavior

Bases are localizable and easy to semantically interpret
Bases provide a sparse representation (bases are activated sparsely in time)
Eye Brow Movement and its Basis


Measuring Social Motor Coordination

Patent Pending, Application No. 62/621,762

• Social Motor Coordination: Within narrow time windows, measure cross correlations of all “facial bases” between dyadic partners
  • 180 facial per participant.
  • 4 of the most predictive bases shown here for illustration
• 90% Accurate in diagnosing ASD from 3 min video
  • More accurate than expert clinicians
Simultaneous Coordination of Head Nods

- Simultaneous nodding (closely aligned basis co-activation)

Diagnosing ASD from a 3 minute “Get to know” Conversation

17 ASD, 27 TD, Young adults
Age, sex and IQ matched

- Netflix, Pandora recommendations
- Advertisements on your browser from your Amazon searches
- Many medical applications, including computer vision analyses

The Rise of Artificial Intelligence

AI is better at diagnosing skin cancer than even some of the best human experts
Motor Coordination Analyses

Classification via linear support vector machines (SVMs) in conjunction with feature selection, and fully automatic (nested) leave-one-out cross validation (LOOCV).

SVM chosen because it yields interpretable features (deep learning likely yields higher accuracies)

Social Motor Coordination Results

1. Diagnostic accuracy from a 3 min conversation = 89%.
   - Worked equally well in Caucasian & African American samples
   - No sex differences
   - Significantly better than Human dx judges: 79% accuracy (p<.001)

2. Prediction of Individual Differences within the ASD group
   - Support Vector Regression with leave one out next cross validation (LOOCV) for generalizability of severity prediction
   - r=.57, p=.02 with ASD severity metric (ADOS CSS)
   - Social Affect score r=.65 but RRB r=.00 (discriminant validation)

3. Replication sample: 30 Adolescents, 17 with ASD, 13 TD
   - Tested generalizability: Used Features that predicted adult diagnoses
   - 87% accuracy
   - r=.57, p=.02 with ASD severity metric (ADOS CSS)
   - Correlated significantly with social affect score (.36) but not RRB score (.02)
Behaviors are exquisitely organized representations of neural circuitry activity, i.e. Biomarkers

If you can Quantify them Well

**Diagnosis ASD based on Words used**

20 min speech sample fromADOS

1. N=32 (18 ASD), matched on age (6-14, mean 11.1 in both groups), sex, FSIQ (106, 108)

2. N=100 (65 ASD, 18 mixed clinical 17 TDC) not age or IQ matched
   - 85% AUC using word choice (Parish-Morris et al, 2016b)

**What is the relationships between social motor coordination and acoustic signals?**
Infants later diagnosed with ASD have acoustically distinct cries & cooing

- **4 mo**: fewer complex pitch contours during cooing (Brisson et al., 2014)
- **6 mo**: Higher and more variable F₀ in cries, poorer phonation (Sheinkopf et al., 2012)
- **12 mo**: Less waveform modulation and more dysphonation in cries, compared to TD and DD (Esposito & Venuti, 2009)
- **18 mo**: Higher F₀ (Median Pitch) in cries, compared to TD and DD (Esposito & Venuti, 2010)
- **6 to 24 mo**: F₀ of cries vs. fusses don’t differentiate over time in ASD and HR babies like they do typically (Parish-Morris, 2018)

**Summary**: higher pitched, more poorly phonated, harder for adults to interpret, rated as less typical, and elicit more negative feelings than the cries of typical infants, and thus could disrupt parent-child communication/relationship

*What is the relationships between social motor coordination and acoustic signals?*

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**Digital Phenotyping Promises**

- Reduction in clinic waitlists by allowing remote *Screening & Triage*
- *Shorter* routine care visits/*better* informed care providers
- Earlier, more accurate diagnosis → earlier intervention → *better outcomes*
- Improved *Outcome Measurements* - increased odds of clinical trial success
- Treatment *efficacy monitoring & care management*
- Enhancement of every aspect of behavioral & biological science
  - Every study *depends* on an accurate assessment of the person in the study.
- More precise, lower cost, briefer, automatized assessments in the wild
- Larger scaled studies with enhanced reproducibility
An Autism Learning Health System

CHOP Autism LHS

• LHS promotes *discovery as natural outgrowth of patient care*
• Missed opportunities: ~10,000 individuals with ASD received care at CHOP last year. None participated in research during their ~20,000 clinical visit
• Turns the electronic health record (EHR) into a database
  • For Scientific discovery via pattern analyses/machine learning
  • Help researchers drill down into which patients, with which backgrounds and which disorder characteristics, respond best to specific treatments
  • To improve clinical care, e.g. through “clinical decision support tools”
• *Creates a virtuous cycle of discovery and improved clinical care*
• Requires standardizing clinical reporting in the EHR
• We are combining our LHS with a genomic biorepository
• Rolling out our brief digital phenotyping into clinics
IOM 2007 -2018 Learning Health System

LHS: A Virtuous Cycle

Use new Knowledge to inform Care

Using Al
Social Attention & Social Reward Mechanisms: Eye Tracking & Neuroimaging

Social Attention as a Proxy for Social Motivation
Social Attention, Motivation & Learning

Heat maps: showing looking (fixation) time
Social Perception Deficits: Identity & Expression

Increased brain activity with increased social information

TDC  ASD
Increased Social Node Connectivity with Increased Social Information Professing Demands
TDC> ASD

Herrington et al, under review

Using Technology To Measure Social Perception Of Actual Social Interactions

Mapped with Infra Red Eye Tracking
Lack of Clear Social Preference in ASD early in Life
(Pierce et al. 2010, Arc Gen Psychiatry)

- People |Screen Savers
- Eye tracking (1 min)
- 12-43 mo old ASD, TD, DD

- No correlation with age, DQ or clinical symptoms
- Good specificity, poor sensitivity

Reward Circuitry Abnormalities?

- DSI: social  DGI: geometric

The social motivation theory of autism

- Drive to engage others is a basic human motivation
- Individual/group differences in social motivation
- Diminished Social Interest: one of the earliest & most persistent symptoms in ASD
- Early onset impairments in social motivation deprive the child of adequate social learning experiences
Two Components of “Reward”

- **REWARD**
  - ‘Wanting’ (motivational drive)
    - NAcc
  - ‘Liking’ (consummatory pleasure)
    - vmPFC
Brain Mechanisms: Neuroimaging (babies & toddlers)
A lesson from a boy with autism who was a prodigious Calendar Calculator

IN THE BEGINNING
The Infant Brain Imaging Study (IBIS):

**Aims:**
- Identify early biomarkers
- Insights into fundamental nature of Autism

Sample: 375 **HIGH Risk** Infants
175 **LOW Risk** controls

**CASES:** 4 Kinds

**High risk positive:**
1. Autism ("classic")
2. “Spectrum” (milder)
3. High Risk Negative (normal)
   - family risk but no signs of autism at 24 months
4. Low Risk Negative (normal)
   - No family risk, no signs

NIH Autism Center of Excellence (www.ibis-network.org)

**ASD Symptom Development 6 to 12 months**

- disengagement of attention
- visual tracking
- response to name
- social babbling
- eye contact
- reciprocal social smiling
- social anticipation
- social interest and affect
- response to facial emotion
- imitation
- coordinate eye gaze - action
- reactivity
- transitions
- atypical motor behaviors
- atypical sensory behaviors
- engagement
- social referencing

Autism = Spectrum > HR neg = LR neg
at 12 months

Age (Months)
• significant group x time effect (symptoms unfold)
• significant differences at 12 and 24 months
• autism = spectrum < HR neg = LR (trajectories)
Significantly increased size of the “corpus callosum” starting at 6 months of age.

Delayed Maturation of Specific White Matter Connections (axonal fibers)

15 Fiber pathways evaluated
12 showed delayed maturation
fMRI Connectivity: Synchronous Brain Activity

fMRI Connectivity – synchronous activity
6 Month “Functional Architecture” predicts 24 month ASD diagnosis
Summary of Early Brain Developmental Differences in Babies who go onto have ASD

- Slower white matter maturation 6 to 24 months
- Rapid expansion of cortical brain surface 6 to 12 months
- Excess Cerebral Spinal Fluid 6, 12 & 24 months
- Different Functional Architecture @ 6 months

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THANK YOU!

Center for Autism Research (CAR)