The Continuum of Care: From Research to Practice.

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Objectives: By the end of the session, participant should be:

- Able to discuss how Autism is unique?
  - GENETICALLY: Hundreds of mini syndromes looking like “autism”
    - How integrative genomics: connecting genes to brain function will allow development of novel therapeutics
  - Clinical phenotype and outcome studies
    - Siblings of children with ASD and the earliest signs
    - Trajectories of development
    - Lived Experiences of families

- Aware of needs in Research
  - Intervention: one size does not fit all
    - But generic approaches to enhance early brain development may enrich brain function for all children and ongoing support to enhance economic health and wealth of nations
  - Systems research to inform policy on developing a true continuum of care
What is Autism?

• How is it different from any other Developmental Disorder?
Spectrum: Dimensions of Impairment

Intelligence
Social Anxiety
Use of Language
Form of Language
Insistence on sameness
Stickiness/rigidity
Sensorimotor

Social Communication

Narrow interests including sensory and repetitive motor behaviors and mannerisms.

Lorna Wing, 1980
Georgiadis, Szatmari et al, 2012
DSM 5 Criteria for ASD.

※ All of the following symptoms describing persistent deficits in social communication/interaction across contexts, not accounted for by general developmental delays, must be met:

- Problems reciprocating social or emotional interaction, including difficulty establishing or maintaining back-and-forth conversations and interactions, inability to initiate an interaction, and problems with shared attention or sharing of emotions and interests with others.

- Severe problems maintaining relationships — ranges from lack of interest in other people to difficulties in pretend play and engaging in age-appropriate social activities, and problems adjusting to different social expectations.

- Nonverbal communication problems such as abnormal eye contact, posture, facial expressions, tone of voice and gestures, as well as an inability to understand these.
Two of the four symptoms related to restricted and repetitive behavior need to be present:
- Stereotyped or repetitive speech, motor movements or use of objects.
- Excessive adherence to routines, ritualized patterns of verbal or nonverbal behavior, or excessive resistance to change.
- Highly restricted interests that are abnormal in intensity or focus.
- Hyper or hypo reactivity to sensory input or unusual interest in sensory aspects of the environment.

Symptoms must be present in early childhood but may not become fully manifest until social demands exceed capacities. Symptoms need to be functionally impairing and not better described by another DSM-5 diagnosis.

Symptom severity for each of the two areas of diagnostic criteria is now defined. It is based on the level of support required for those symptoms and reflects the impact of co-occurring specifiers such as intellectual disabilities, language impairment, medical diagnoses and other behavioral health diagnoses.
Is Aetiology Genetic??

• Evidence?
Highly-penetrance risk gene/CNV for ASD
No single gene accounts for >1% of autism

<table>
<thead>
<tr>
<th>Identified from ASD research</th>
<th>P-value; Odds Ratio (95% CI)</th>
<th>In other neuro-psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. (del)16p11.2</td>
<td>2.0x10^{-10}; 9.5 (5.2-17.4)</td>
<td>SCZ, BPD, ADHD, ID</td>
</tr>
<tr>
<td>2. (del)NRXN1</td>
<td>4.9x10^{-19}; 15.6 (7.6-32.1)</td>
<td>SCZ, BPD, ADHD, ID</td>
</tr>
<tr>
<td>3. *(del)PTCHD1-DDX53</td>
<td>1.2x10^{-5}; ∞ (5.89-∞)</td>
<td>ID</td>
</tr>
<tr>
<td>4. (dup)7q11.23</td>
<td>8.0x10^{-4}; 30.7 (3.4-275.1)</td>
<td>SCZ</td>
</tr>
<tr>
<td>5. (dup)1q21.1</td>
<td>3.6x10^{-5}; 8.0 (3.5-18.4)</td>
<td>SCZ, BPD, ADHD, ID</td>
</tr>
<tr>
<td>6. SHANK1-SHANK3</td>
<td>9.0x10^{-3}; ∞ (1.76-∞)</td>
<td>Social anxiety?</td>
</tr>
<tr>
<td>others</td>
<td>others</td>
<td>+++</td>
</tr>
</tbody>
</table>

*X-chromosome; female carriers

Drugmakers dance with autism

Sarah Webb, 2011

• Novel therapeutics: Focus on morbidities not hope for cure or eradication
Genotype the Phenotype

Dysmorphology & anthropometry

Medical Co-morbidities
- epilepsy
- congenital anomalies
- brain malformations

Cognitive/Behavioural Profile
- IQ
- Language
- Adaptive level
- Attention
- Hyperactivity
- Executive function

Autism phenotype
- social affect
- repetitive behaviour
- aggression/irritability
- regression
Phenotype the Genotype

Dysmorphology & anthropometry
- Neuroimaging Studies

Medical Co-morbidities
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Gene Identification, but, more importantly, find the proteins that effect gene expression making focussed therapy possible. Novel therapeutic development, then tested in animal models, then ready for clinical trials.
Genotype enabling clinical diagnosis

- Average age is ~4.5 years, but optimal age of intervention much earlier

- Families experience ‘Diagnostic Odyssey’ and can go years without focussed management plan

- Many medical co-morbidities (e.g. seizures, gastrointestinal, sleep)

del(16p11.2) Based on AJHG 2008; Nature 2011
GAPS: Implications of New Genetic Findings

• >1,000 clinical microarrays run in Ontario/yr
• Thousands of families with ASD will have their genome sequenced in the next few years...will we find the other 80%??
• Are health systems ready for huge numbers of families who will request and receive often uncertain information?
  – Genetic counselling services already overwhelmed
• Do we understand ethical issues involved for individuals themselves as well as affected and unaffected family members?
Nurture interacting with Nature!

- Epigenetic factors effecting gene expression
  - Fertility?
  - Parental age
  - Environmental exposures...in order to know what to avoid
    - Toxins, pesticides, medication
Concurrent Research

• Sibling Studies

• Developmental Trajectories Studies

• Lived Experiences of Mothers, Fathers and Individuals with ASD...qualitative interviews, home visits, Delphi panels and Questionnaires
Research with Siblings of Children with ASD

- Informs specialized diagnostic assessment

- Design and evaluation of effective interventions

- Assess adequacy of system capacity to support each step
  - Early recognition of risk status
  - Access to early intervention
Autism Spectrum Disorders and Infancy’s Earliest Signs:

Insights from Studies of High-risk infants
ASD in toddlers

• Visual attention
• Social-communication/language
  • Play interests and behavior
  • Motor skills and behavior
VISUAL ATTENTION
SOCIAL COMMUNICATION/LANGUAGE
ASD RED FLAGS AT 12 MONTHS

- Social referencing (54%)
- Social babbling (44%)
- Reactivity (42%)
- Orient to name (41%)
  - Atypical motor behaviour (38%)
  - Social interest/ affect (37%)
  - Eye contact (28%)
  - Insistence (27%)
  - Sensory (24%)
  - Motor control (14%)

\(^1\text{ASD-Sibs}>\text{Non-ASD-Sibs and controls; } p<.05\)
PLAY INTERESTS AND BEHAVIOURS
MOTOR SKILLS AND BEHAVIOURS
ASD Symptom trajectories

- Difficult to identify behavioral differences specific to ASD at 6 months
  - Reduced motor control at 6 months associated with ASD within high-risk group
  - Sibs as a group > social-communication challenges than low-risk controls
- Differences emerge between 6 and 12 months
  - Eye gaze, social interest/affect, reactivity, atypical motor and sensory behaviors
- Caveat: differences more subtle in children less severely affected and Aspergers; detected later
Reactivity and Temperament

NeuroDevNet in fourth year of operation is piloting the use of a sensor to track physiological responses in an effort to understand temperamental differences among siblings and controls
Very Very Early Intervention Study: 
Social ABC’s:  Bryson and Brian, 
        funded by Autism Speaks

• Principles of Pivotal Response Therapy (R. and L. Koegel, 
  C.Kasari):
  – Capitalize on child’s motivation
  – Follow child’s lead
  – Capture child’s attention
  – Provide clear (communication) opportunities
  – Intersperse easier and harder tasks
  – Reinforce all good (communication) attempts
  – Natural, immediate and contingent reinforcement
When see red flags, need to be able to act!

– Best evidence to date:

  • Dawson, G. Randomized controlled trial for toddlers with autism: The Early Start Denver Model. Pediatrics 125:No 1 Jan. 2010

– Preventative Intervention Needed
Dimensional approach

• Alternative approach to categorical

• Defines the disorder empirically on dimensions ranging from:

  mild impairment  severe
Play

- Reduced imitation of actions
- Reduced interest in social play
- Repetitive actions with toys
  - e.g., spinning, rolling
- Prolonged/intense visual examination of toys and other objects

Bryson et al., 2007; Ozonoff et al., 2008; Wetherby et al., 2006; 2007; Zwaigenbaum et al., 2005
PEDIATRICS, SEPTEMBER 1, 2011

1. Ozonoff et al.
2. Recurrence risk for ASD: Baby Siblings Research Consortium Study.
4. Overall recurrence risk 18.4%;
   - 25.9% in boys, 9.6% in girls.


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Abstract

OBJECTIVE: The recurrence risk of autism spectrum disorders (ASD) is estimated to be between 3% and 10%, but previous research was limited by small sample sizes and biases related to ascertainment, reporting, and stoppage factors. This study used prospective methods to obtain an updated estimate of sibling recurrence risk for ASD.

METHODS: A prospective longitudinal study of infants at risk for ASD was conducted by a multisite international network, the Baby Siblings Research Consortium. Infants (n = 664) with an older biological sibling with ASD were followed from early in life to 36 months, when they were classified as having or not having ASD. An ASD classification required surpassing the cutoff of the Autism Diagnostic Observation Schedule and receiving a clinical diagnosis from an expert clinician.

RESULTS: A total of 18.7% of the infants developed ASD. Infant gender and the presence of >1 older affected sibling were significant predictors of ASD outcome, and there was an almost threefold increase in risk for male subjects and an additional twofold increase in risk if there was >1 older affected sibling. The age of the infant at study enrollment, the gender and functioning level of the infant's older sibling, and other demographic factors did not predict ASD outcome.

CONCLUSIONS: The sibling recurrence rate of ASD is higher than suggested by previous estimates. The size of the current sample and prospective nature of data collection minimized many limitations of previous studies of sibling recurrence. Clinical implications, including genetic counseling, are discussed.

18.7% Recurrence Risk, 28% in Boys, 8% in Girls
Pathways in ASD

A longitudinal study of how children with ASD grow and develop
Main Objectives

- To describe how children with ASD grow and develop
- To describe how the level of family stress changes over time
- To identify child, family, school, and community (including services) factors that might predict or influence development of children with ASD (and their families)
Unique Aspects

- This is not an investigator initiated project
- Question(s), design and measures influenced by input from parents, clinicians, and policy makers
- Feedback to/from these stakeholders prior to publication of major papers in peer reviewed journals
- Also evaluating the whole process of researcher-parent-policymaker interaction through the research process
Multisite Design

Consecutive series of children 2-4 years of age with a diagnosis of ASD within a geographic region

Canada
N=400

Policy Study

Montreal  Halifax  Hamilton  Vancouver  Edmonton
Ecological and Multilevel

- Community
- School
- Services
- Family
- Child
Early summary of ongoing gaps in Canadian system.  Szatmari, 2013

• There is too long a gap from age when parents see concerns and get diagnosis.

• A “Gap” is present before a “Disorder” can be recognized; evidence based interventions are needed PRIOR to diagnosis. Evaluation of delivery of this generic approach to early intervention will benefit all children, typical development and with any Developmental Disorder.

• Not all children progress at the same rate; therefore intervention needs to be flexible and a variety of interventions need to be developed and evaluated. There is increasing heterogeneity in developmental trajectories over time. This means that interventions must be available across the life span for those that do not progress as rapidly as others.

  Improvement in one developmental domain does not ensure a similar rate of progress in another and does not predict family stress (need comprehensive interventions which include strengthening family’s capacity to deal with stress)
LIVED EXPERIENCES OF MOTHERS, FATHERS AND INDIVIDUALS WITH ASD...
Lived Experience of Autism

• Qualitative interviews with mother and fathers, home observations, Delphi panels, questionnaires and direct assessment of affected individuals ages 3-25y.
Study Sample

- 85 mothers of a child with autism
- Couples/parenting dyads
- Sample stratified:
  - preschool-age children (<5 years)
  - elementary school-age children (5–12)
  - high school-age youth (13–17)
  - youth transitioning to adulthood (18-25)
Experiences

• Love and loss/sadness
• Confusion, anxiety, fear $\Rightarrow$ confidence
• Appreciation for the victories
• Gratitude, but yet…
• Limited choices and opportunities
• Absorption of care in day- and night-time hours
• Exhaustion
• Decreased social contact
• Shifts over time
Shifts over Time

“In the beginning it hurts and it upsets you…you want to fix it, because you think it’s broken. And then as you live it, you come to realize it’s just part of who the person is. And then you know, you have to accept it and live with it, and just try to do your best.”
Gaps in Systems of Care and Society

• Listening to parents: Families have to completely reorganize around transition periods.
• Society lacks knowledge re how to best support families in cost effective ways. Needs vary.
• Inclusive, person/family-focused, coordinated services needed to decrease stress; family involvement may help to find economically feasible systems.
• Shifts over time – transitions most difficult
• Transition from adolescent to adult life least informed by research and often most traumatic
Gaps in family and genetic studies

• Counselling re recurrence risk
  – Is it as high in community sample vs high risk sample?
  – How to predict severity prenatally?
• Specificity for autism....some with ID, LD, language problems and ADHD, anxiety etc
• Overlaps with other neuropsychiatric disorders
• Personallized approaches to intervention
• Family support re stressors and economics
Biggest Gap: Continuity of Care

- Child
- Family
- Services
- School
- Community
Next steps: Addressing the Gaps

• **Preventative Intervention after Early Identification:**
  – *Focussed, effective* intervention techniques in place before diagnosis is possible...by *one* year of age! Need careful outcome evaluation.
  – *Eclectic “personallized” intervention* at each developmental stage to reduce morbidity and minimize crisis intervention only

• **Family stress** and **economic implications** of living with autism and other neurodevelopmental disorders must be understood and supported, including some of the highest risk families who are already affected by neurodevelopmental disorders by virtue of having parents and/or other siblings affected
Summary: Key Word is Integration!

Genetics: Hundreds of mini syndromes involving autism

• **Integrative genomics**: connecting genes to brain function to allow development of **novel therapeutics**

• **Ethics of sharing novel information with uncertain implications needs urgent study**

Intervention and Outcome Research Gaps

Preventative Intervention:

• generic approaches to enhance early brain development may enrich brain function for all children....and enhance economic health and wealth of nations

**Ongoing Individuallyzed intervention** for specific Disorders developed in concert with well defined outcome evaluation re Individual, the family and health and economic delivery systems

**FAMILY EXPERIENCE AND ECONOMIC IMPLICATIONS of ineffective or insufficient Intervention from infant to adult**
Investigators

- Dr. Peter Szatmari (CAMH, Hospital for Sick Children, University of Toronto)
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- Dr. Eric Fombonne (Oregon Health & Science University)
- Dr. Pat Mirenda (University of British Columbia)
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- Dr. Charlotte Waddell (Simon Fraser University)
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Selected Publications

Investigating phenotypic heterogeneity in children with autism spectrum disorder: A factor mixture modeling approach (Georgiades et al., 2013)

Influence of reporting effects on the association between maternal depression and child autism spectrum disorder behaviors (Bennett et al., 2012) *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 53*(1), 89-96.

Comparing early language development in monolingual- and bilingual-exposed young children with autism spectrum disorders (Ohashi et al., 2012)

Phenotypic overlap between core diagnostic features and emotional/behavioral problems in preschool children with autism spectrum disorder (Georgiades et al., 2010)

Using the Preschool Language Scale-IV to characterize language in preschoolers with ASD (Volden et al., 2012)