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2011 NIH WORKSHOP: ETHICAL, LEGAL AND SOCIAL IMPLICATIONS OF AUTISM RESEARCH

DATE

SEPTEMBER 26, 2011

8:30 AM – 5:00 PM

Overview of ELSI

Mildred Cho, PhD
Stanford Center for Biomedical Ethics

Ethical, Legal and Social Implications of Autism Research Workshop
September 26, 2011

Genesis of “ELSI”

genome.gov
National Human Genome Research Institute
National Institutes of Health

SEARCH

Research Funding | Research at NHGRI | Health | Education | Issues in Genetics | Newsroom | Careers & Training | About | For You

Home › Research Funding › DER Funded Programs › **ELSI Research Program**

DER Funded Programs

- Centers of Excellence in Genomic Science
- DER Program Staff
- ELSI Research Program

ELSI Research Program

The Ethical, Legal and Social Implications (ELSI) Research Program

ELSI Research Program : ELSI Planning and Evaluation History : ELSI Abstracts and Activities Database : ELSI Grant Publications and Products : ELSI Program Reports

See Also:

Grants Home

Office of Policy,

genomics.energy.gov

Human Genome Project Information . Genomic Science Program . DOE Microbial Genomics . home

Human Genome Project Information

About the HGP | Ethical / Legal Issues | Medicine | Education | Gene Gateway | Research Archive

Sequence Databases | Landmark Papers | Sequence Insights | Related Projects

Ethical, Legal, and Social Issues Research

Lessons learned

- Privacy, discrimination
- Psychosocial impact of genetic testing
- Attitudes towards and uptake of genetic testing
- Community engagement

ELSI issues: Research

- Informed consent
- Privacy and confidentiality
- Data sharing and use
- Recruitment and diversity
- Fair distribution of benefits

ELSI issues: Health care

- Fairness in and access to services
- Effectiveness and cost-effectiveness
- Informed consent
- Communication
- Health disparities

ELSI issues: Societal

- Concepts of risk and benefit
- Distinction between research and clinical practice
- Concepts of health and disease
- Implications for reductionism, determinism, free will, individual responsibility
- Understanding of relationships among humans and between humans and non-humans

ELSI issues: Legal, regulatory & policy

- Intellectual property
- Regulation of genetic testing
- Ownership and liability of biobanked samples
- Impact of genetic non-discrimination legislation
- Use of genetics in non-medical settings

Criteria for ethical research

- Scientific or social value
- Scientific validity
- Fair subject selection
- Favorable risk:benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled participants

- *Emanuel et al. 2000 JAMA 283:2701*

Independent review

- Current review based on:
  - Recognition of conflict of interest
  - Power differential
- IRBs formed to mitigate conflict of interest
- Relationship between researchers and participants has changed
  - Funding
  - Research design
  - Access to research materials and data
  - Ownership

Independent review

- ASD vs ADHD funding and COI
  - 31% of articles on ADHD vs 6% on autism in PubMed had a disclosed COI
  - 10% for-profit funders of ADHD research vs 1% of autism research

Scientific or social value

- What are the benefits of the research?
- Who decides what constitutes benefit?

neurotypical Normal is a cycle on a washing machine.

What is the standard that identifies one person as whole and capable and another as disabled and broken?

neurodiversity.com

Neurotypical Issues

See also: **Abuse** **Bullying** **Psychological Defense Mechanisms** **Discrimination** **Sociopathology**

Offering a mix of humorous and drop-dead serious examinations of states of mind often characterized as "normal."

Scientific or social value

- Oxytocin study
  - Enhancement
  - Medicalization of normal behavior
- Prenatal genetic testing
  - Prenatal genetic counseling patients indicated desire to use prenatal testing for:
    - 75% for “mental retardation”
    - 13% for “superior intelligence”
    - *Hathaway et al. 2009*

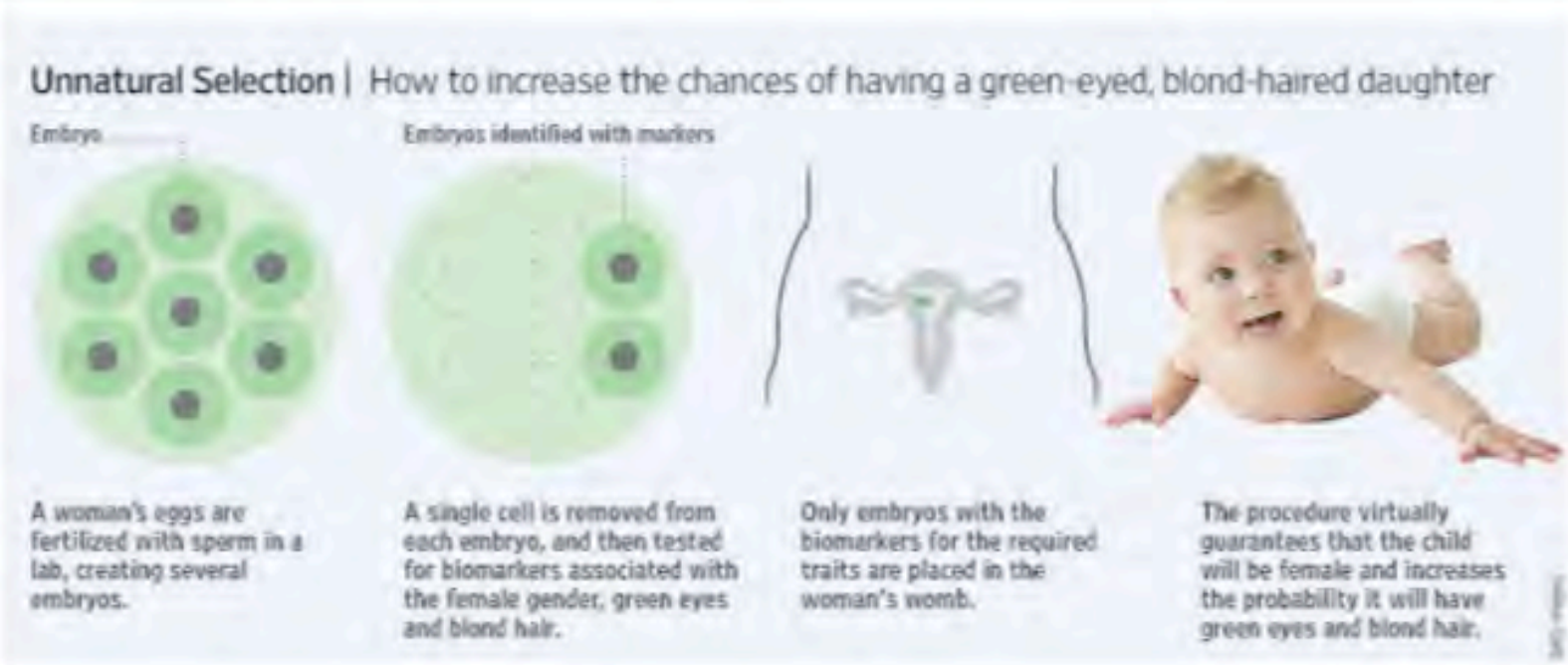
THE WALL STREET JOURNAL.
WSJ.com

FEBRUARY 12, 2009
CURRENTS

A Baby, Please. Blond, Freckles -- Hold the Colic

Laboratory Techniques That Screen for Diseases in Embryos Are Now Being Offered to Create Designer Children

By GAUTAM NAIK



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welcome | ancestry | health | how it works | store

Measures of Intelligence - Sample Report

» view all sample reports

Preliminary Research report on 1 reported marker.

Example Data

About Measures of Intelligence

Though genetics clearly plays a role, the relative significance of nature and nurture in determining a person's intelligence is highly controversial. Even the nature of intelligence and the validity of tools used to measure it are subject to great debate. While some aspects of intelligence – such as mathematical ability – lend themselves to standardized testing, others are much more difficult to quantify. Recent studies estimate that in early childhood about 25 - 40% of individual variation in measurable intelligence can be attributed to genetics. In adults, this number increases to about 80%.

visit the store

try a demo

- IQ (intelligence quotient)
- EQ (emotional quotient)
- Athletic Abilities
- Character
- Health
- Environmental Sensitivity
- Artistic Creativity
- Addiction Susceptibility

It is the Best Gift for My Child,
I Want To Get The Report Now >>

(1) Character

1 Optimism Gene
2 Risk Taking Gene
3 Sociable Gene
5 Persistence Gene
6 Shyness Gene
8 Composure Gene
9. Split Personality Gene
11 Depression Gene
12 Impulsive Gene
13 Attentiveness/Focused Gene
15 Mould-abiltiy/Adaptability Gene

(2) Intelligence (IQ)

19 Creative Gene
21 Analytical/Thinking Gene
23 Comprehension Gene
25 Memory Gene
26 Intelligence Gene

(3) Emotion (EQ)

28 Affectionate Gene
29 Faithfulness/Loyalty Gene
30 Passion/Enthusiasm Gene
31 Propensity for Teenage Romance Gene
34 Sensitivity/Sentimentality Gene

(4) Artistic Gene

35 Performing Gene
37 Musical Gene
38 Drawing Gene
40 Dancing Gene
42 Linguistic/Literature Gene

(5) Sport

44 Endurance Gene
46 Explosive Power Gene
49 Technique/Skill Gene

(6) Environment

49 Sensitivity to Second-Hand Smoke Gene
51 Insensitivity to Second-Hand Smoke Gene

(7) Health

51 Myopia Gene
55 Obesity Gene
57 General Wellness Gene

(8) Addiction

59 General Addiction/Obsession (Internet, Games, TV)
61 Self Detoxifying Gene
63 Alcoholism Gene
65 Smoking Gene
67 Anti Intoxication Gene
68 Alcohol Intoxication Gene

Question 1

- What is needed to heighten awareness of ELSI issues, and approaches to address those issues, in the autism research community?

Developing methods to integrate community values into research

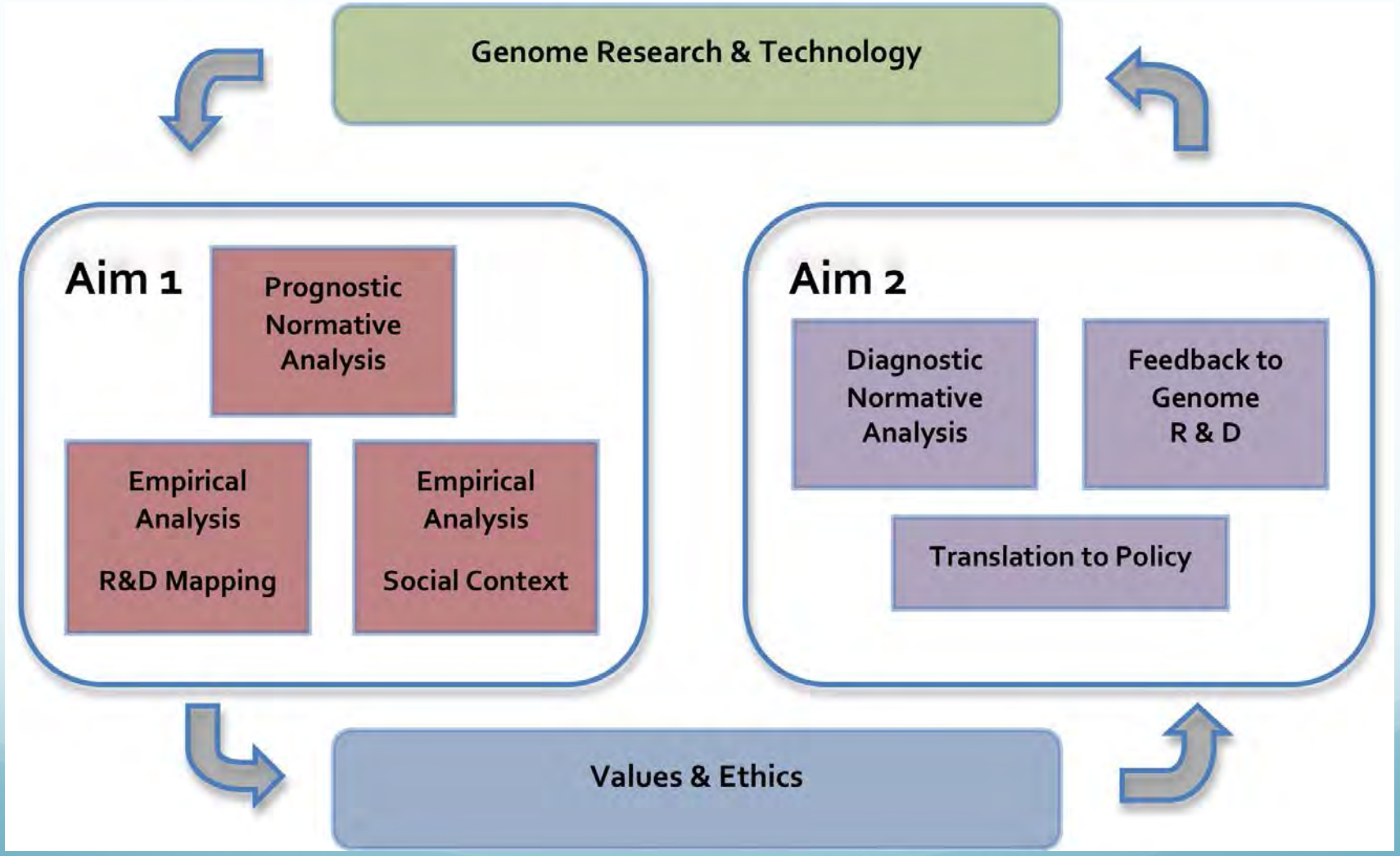
Question 2

- What ELSI issues in autism require targeted research?

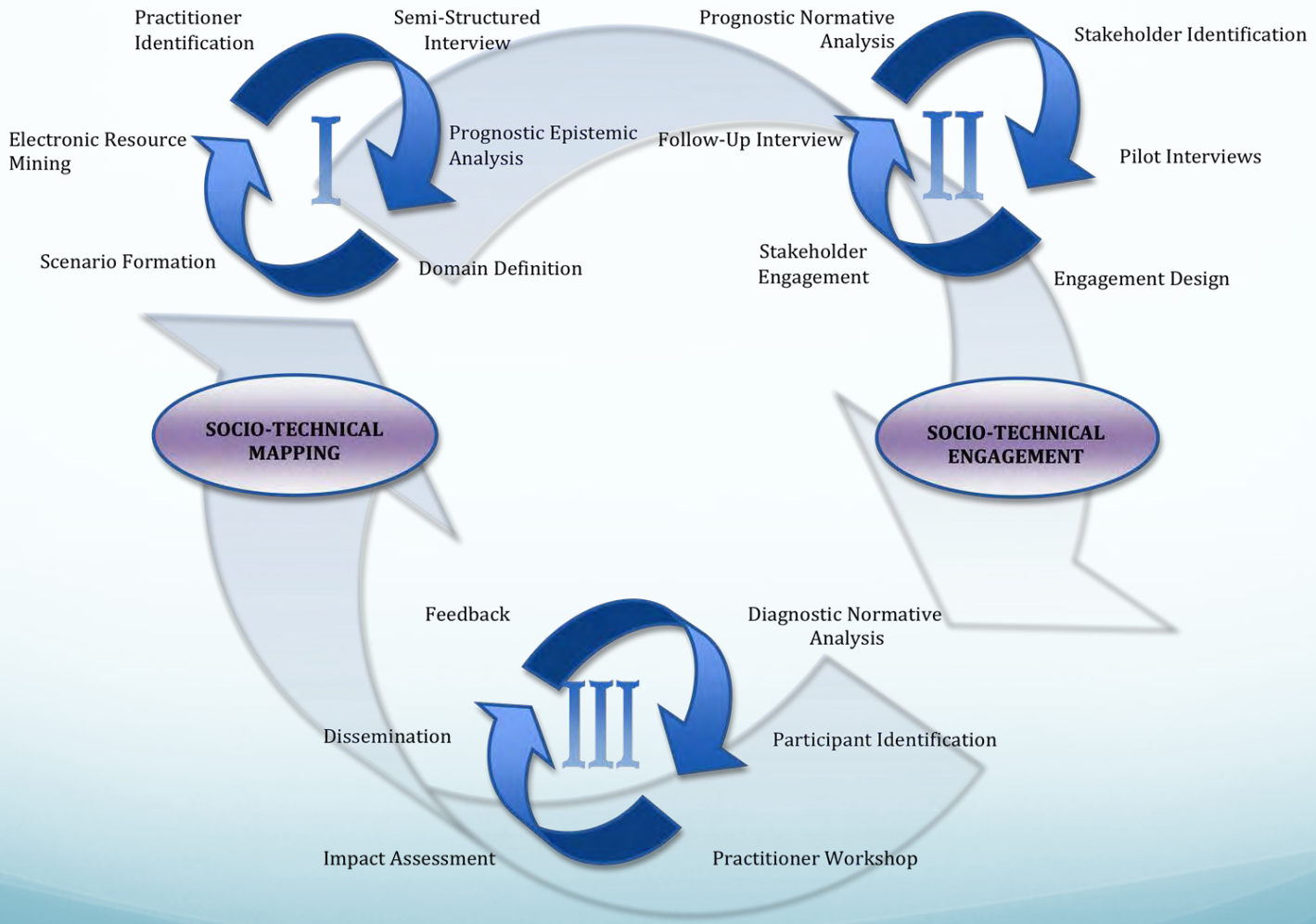
Assessing perceptions of benefit from research

Evaluating ethical and scientific impact of changing relationship between researchers, participants and autism community on research

CIRGE Research Program



INVEST model



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Institute of Education
University of London

Bridging Autism, Science and Society in the UK

Dr Liz Pellicano
Centre for Research in Autism and Education
www.ioe.ac.uk

impact of the “new autism sciences”

guardian.co.uk

News | Sport | Comment | Culture | Business | Money | Life & style

News > Society > Autism

Is autism screening close to reality?

Call for ethics debate as tests in womb could allow termination of pregnancies

Sarah Boseley, health editor
The Guardian, Monday 12 January 2009
Article history

New research published today will bring prenatal testing for autism significantly closer, prompting experts to call for a national debate about the consequences of screening for the disorder in the womb and allowing women to terminate babies with the condition.

The breakthrough study by Cambridge University's autism research centre has followed 235 children from birth to the age of eight. It found that high levels of testosterone in the amniotic fluid of pregnant women was linked to autistic traits, such as a lack of sociability and verbal skills, in their children by the time they are eight.

impact of the “new autism sciences”

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15-minute brain scan developed by British scientists could spot child autism earlier

By JENNY HOPE
Last updated at 9:55 AM on 11th August 2010

“It could help to alleviate the need for the emotional, time consuming and expensive diagnostic process which ASD patients and families currently have to endure”

Dr Christine Ecker

Lead researcher

MRC Medical Research Council

NEWS & PUBLICATIONS

Autism in adults diagnosed by quick, new brain scan

Tuesday 10 August, 2010

Scientists funded by the Medical Research Council (MRC) have developed a pioneering new method of diagnosing autism in adults. For the first time, a quick brain scan that takes just 15 minutes can identify adults with autism with over 90% accuracy. The method could lead to the screening for autism spectrum disorders in children in the future.

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Autism, Ethics and Society

10am – 5:30pm, 28th June 2010 · Anatomy J.Z. Young Lecture Theatre · University College London

http://www.ucl.ac.uk/cpjh/autism

public challenges to the "new autism sciences"

1. should we be pursuing a "cure for autism" and striving for a single "normal" developmental pathway?
2. does this have different implications for individuals who are so-called "high-functioning" and "low-functioning"?
3. who should be asked to make these decisions? scientists, parents, or autistic people?
4. is there any way of resolving disagreements?

who should get a say?

some researchers have suggested that clearly stating one's research goals at the outset should itself foster ethically responsible scientific pursuits ... **but claiming neutrality is not enough**

scientists must recognise that (a) science is not completely impartial, especially in the context of such highly charged issues; (b) the research they carry out and report has non-neutral implications for directly concerned parties; and (c) they must listen to, and learn from, non-scientists

who should get a say?

parents have a unique experience about the onset and development of their child ... and people with autism have direct experience of what it is like to be autistic → each has access to a "special kind of knowledge"

this "experience-based expertise" is vital but it needs to be combined with, rather than to replace, that of the scientific researcher

we need constructive dialogue

Three preconditions to engagement:

1. disagreement is inevitable and must be recognized

2. many concerned parties are currently excluded from decision-making or are dramatically under-represented

3. not all participants are equally affected by the impact of the new sciences of autism

three concrete suggestions from the UK conference

1. extensive quantitative and qualitative research is required on the attitudes of autistic people and parents and carers to the new sciences of autism and their application

2. proper participatory decision-making processes are required in all areas of research and policy on autism

3. researchers should recognise that such engagement as an essential part of the research process

conclusion

the new sciences of autism have generated much excitement both within and beyond the research community

... but this excitement is tempered by significant social and ethical concern

the way forward involves fostering “inter-dependence”, crafting new mechanisms of participation and dialogue to build a bridge between scientists and the broader autism community

many thanks to ...

Larry Arnold
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Geraldine Dawson
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Francesca Happé
Wendy Lawson
Laurent Mottron
Dinah Murray
Sarah Parsons
Kate Plaisted-Grant
Emily Simonoff
Allison Shefcyk
Sandy Starr
Marc Stears
Simon Wallace
Jonathan Wolff

Autistica, UK
Centre for Research in Autism and Education (CRAE)
Centre for Philosophy, Justice and Health, UCL

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ETHICAL ISSUES IN AUTISM RESEARCH

JOHN ELDER ROBISON

NIH

SEPT 26, 2011

ABOUT ME

I am a 54-year-old with Asperger's who is employed and reasonably integrated into society. I was diagnosed at 40.

I write about autism issues and speak internationally

I have a large online community that is actively discussing autism issues

My 21-year-old son also has Asperger's

I serve on various autism science and treatment review boards including Autism Speaks, INSAR, NIH, CDC and several universities

My books *Look Me in the Eye* and *Be Different* have been translated into over 20 languages and are sold in over 60 countries.

There is no such thing as a spokesman for the autism community.

The opinions expressed today are strictly my own.

ABOUT AUTISM

Autism is a spectrum disorder. People with autism can be broadly divided into three groups:

1 - People with non-verbal communication impairment, but good ability to speak and understand language. I will call this the Asperger group.

2 - People with more generalized communication impairment including significant language challenges. I will call this the autism group.

3 - People with generalized communication challenges and significant co-morbid conditions. I will call this the severe autism group.

The degree to which a child is disabled by autism depends in large measure upon the severity of their autistic impairment.

By the time autistic children become adults they will have developed coping skills which mask some of their autistic disability

COMMUNITY - SELF ADVOCATES

The degree to which an adult is disabled by autism is determined by many factors the most important of which is general IQ. People with higher IQ are better able to develop and implement coping strategies to mask disability.

As adults, many of us “look and sound normal,” yet we struggle disproportionally with relationships and jobs. Our opinions are often shaped by repeated social failure.

In the autism world, we talk a lot about self-advocacy. However, the only autistic people able to self-advocate (in meaningful numbers) are those least impaired. There are some noteworthy exceptions online, where the typed mode of communication levels the playing field for those who do not speak.

That tends to bias the self-advocate’s discussion toward issues relevant to the Asperger population to the exclusion of more severely impacted individuals.

Self advocates tend to focus on work, relationships, and independent living.

COMMUNITY - PARENTS

The most vocal parents tend to be those with severely impacted children, but there are active parents with children at all points on the spectrum.

Most active parents have children 5-15 years old.

Parents tend to focus on basic social skills, and successful progress through school.

Ideally, parents and children share a generalized goal of happy, healthy, productive and independent lives. Since parents and children are unique individuals, each affected differently by autism, they may have differing views of how the autistic person should conduct his life, even though the general goal is the same. That's especially true when the autistic person is older.

COMMUNITY - SCIENTISTS

Until quite recently the major emphasis in autism science was in genetics and other low-level work. Valuable as that work is, most of it has no quality of life impact for autistic individuals living today.

Geneticists and biologists may tend to focus on severe autism because its effects can be modeled in animals. There are no animal models for Asperger's.

We need to draw researchers from many other disciplines into autism research.

Medical researchers must keep their ethical obligation to today's autistic population in mind.

HOW AUTISM AFFECTS US

Autism is at its heart a communication disorder. One practical manifestation of that is that autistic people have an inherent difficulty recognizing and accepting other points of view.

There is a tendency to feel "my way is the only way."

We may also believe "I have trouble with x, so x is the primary problem to be solved by autism scientists."

Organizing our thoughts and keeping ourselves focused and on track can be tremendously challenging. When we fail at that, our lives feel out of control. The result – fear and anxiety.

HOW AUTISM AFFECTS US

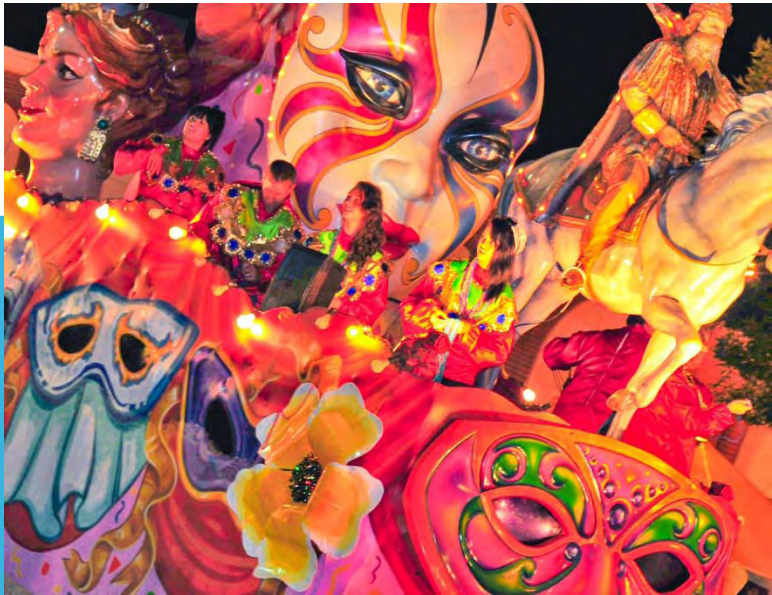
Autistic people have difficulty interpreting signals from other people. We may not recognize sarcasm, or we may be easily misled. Our logical interpretation of a situation may be totally different from other people's emotional assessment, leaving us "in the wrong." The result – fear and anxiety.

The principal emotion felt by autistic people is fear. When you have difficulty understanding the world around you, it is natural to be fearful. Autism limits our ability to understand certain dynamics. We may withdraw, or defend ourselves by becoming angry and aggressive. That can shape our engagement with the world in counterproductive ways.

HOW AUTISM AFFECTS US

Many autistic people also suffer from organization and focus issues (ADHD), anxiety, and depression.

Our social challenges lead to frequent and sometimes continuous social failure. This translates into unwanted isolation, generalized loneliness, failure to form and sustain romantic relationships, and failure to get and keep a job. The result – depression, anger, withdrawal.



RESEARCHERS – KNOW YOUR CUSTOMER!

Autism researchers must remember that their ultimate responsibility is to the autistic individuals, not their parents or guardians. In the end, everyone involved in autism research should be working toward the goal of improving quality of life and remediating disability for those on the spectrum.

The older a severely autistic person is, the more likely his own wants and needs are to be at odds with those of his guardians.

A less impaired autistic person may have no desire to change his behavior while those around him express strong desire for change.

This reality offers the potential for ethical conflict with autistic research subjects, when the research involves the possibility of cognitive changes.

THE “OTHER PERSON” IN AUTISM

Substantially all current autism research is directed toward improving quality of life for the autistic individuals.

Should we be funding research into quality of life issues for families and caregivers?

There is a great deal of guilt, frustration, and anger among parents. Should we be looking at ways to moderate those destructive feelings?

ETHICS OF INFORMED CONSENT

When experimental therapies or treatments change cognitive function there is the possibility that effects will go well beyond what researchers envision. For example, if a subject does better recognizing faces on a screen, his success interacting in the real world may be changed, with unforeseeable results.

How do we present this when obtaining consent?

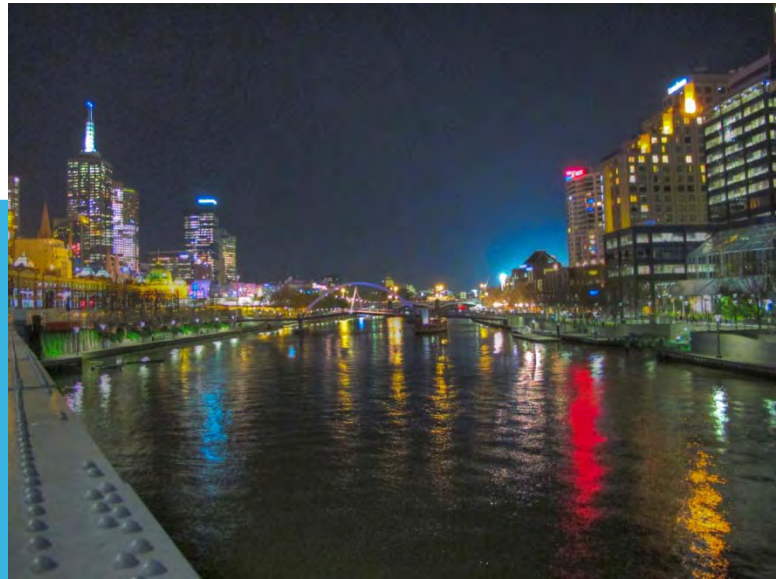
Is it risk or opportunity?

ETHICAL ISSUES – ADULT STUDIES

It's common for studies to say, "Looking for research subjects with an autism or Asperger diagnosis . . ."

That's fine when working with school age children

What happens when we study middle aged adults, most of whom never got a formal diagnosis?



ETHICS OF DIAGNOSIS

For children, diagnosis is usually necessary to gain access to critical services. For adults, an opposite situation may prevail. A diagnosis may subject adults to higher insurance rates, exclusion from employment, etc.

An on the record diagnosis may be a godsend for parents of a child, but a curse for autistic adults who are trying to make their own way.

If diagnosis is done as part of a study, should it become part of the medical record?

Should adults be able to keep an autism diagnosis private? (not in record)

Should adults be entitled to counseling; how to handle diagnosis?

EUGENICS – THE SELF ADVOCATE'S FEAR

The perceived threat – genetic testing will lead to the deliberate elimination of autistic people.

Scientists say prenatal testing will facilitate early intervention, with potentially dramatic results.

Critics fear pregnant women will get a test and decide on an abortion instead of prolonged and possibly unsuccessful treatment of a "broken" baby.

I believe the development of genetic autism tests is inevitable. What can we do to prepare for that day?

We can develop statistics for the effectiveness of intervention. That will be a key decision making tool for parents.

We can begin a campaign to educate the public; show that abortion is not the only reason for tests.

THE FUTURE OF AUTISM

The real threat today – new studies show parents with one autistic child are far more likely to have additional children with autism. Parents with autism and one autistic child are at even greater risk. That news will have significant family planning impact.

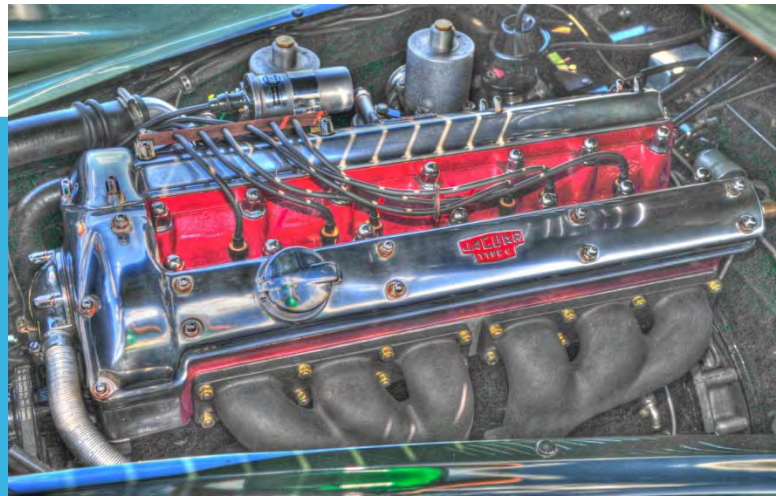
As recently as five years ago autism was described as a rare, random event. Parents with one autistic child often went on to have more children.

Today, in light of current studies, many parents stop having children altogether.

With no genetic testing, just knowledge of family history, we can identify certain groups whose odds of having more autistic children are high

Genetic testing will allow us a higher degree of confidence in making predictions.

What can/should we do with this knowledge?

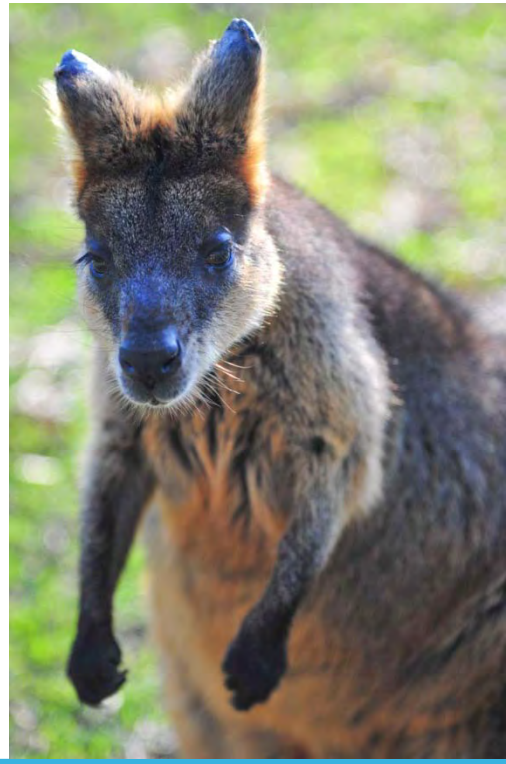


THANKS FOR LISTENING

I invite you to continue this discussion in my online communities:

www.facebook.com/JohnElderRobison

Jerobison.blogspot.com



My speaking schedule is online at:

Johnelderrobison.blogspot.com

Understanding Ethical Implications of Genetic Testing and Research

Holly K. Tabor, Ph.D.
Assistant Professor
Treuman Katz Center for Pediatric Bioethics, Seattle Children's Hospital
Division of Bioethics, Department of Pediatrics, University of Washington
September 26, 2011

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for Pediatric Bioethics

Outline

- What do people do with genetic risk information?
- The story of accelerated translation of microarray genetic testing and autism
- Future directions and research questions

My perspective

- Trained in genetics, epidemiology and ethics
- Funding from NHGRI, NHLBI
- Research on ethical issues in genetic research on complex traits (including autism) and in exome and whole genome sequencing
- Mother of two boys, one with autism

What do people do with genetic risk information?

Find Explanation

- Why me? Why my child?
- Why your child and not my child?
- Cultivate a sense of control and understanding
  - “If I only do this, then my child will not get autism.”
  - “It is/is not my fault that my child has autism.”
  - “You can’t fight the genome.”

Find Meaning

- "Meaning is not something you stumble across, like the answer to a riddle or the prize in a treasure hunt. **Meaning is something you build into your life.** You build it out of your own past, out of your affections and loyalties, out of the experience of humankind as it is passed on to you, out of your own talent and understanding, out of the things you believe in, out of the things and people you love, out of the values for which you are willing to sacrifice something."

-John Gardner

Find Direction and Guidance

- Treatment
- Therapy
- Prevention
- Identity
- Community

Microarray Testing for Autism: A Story of Accelerated Translation

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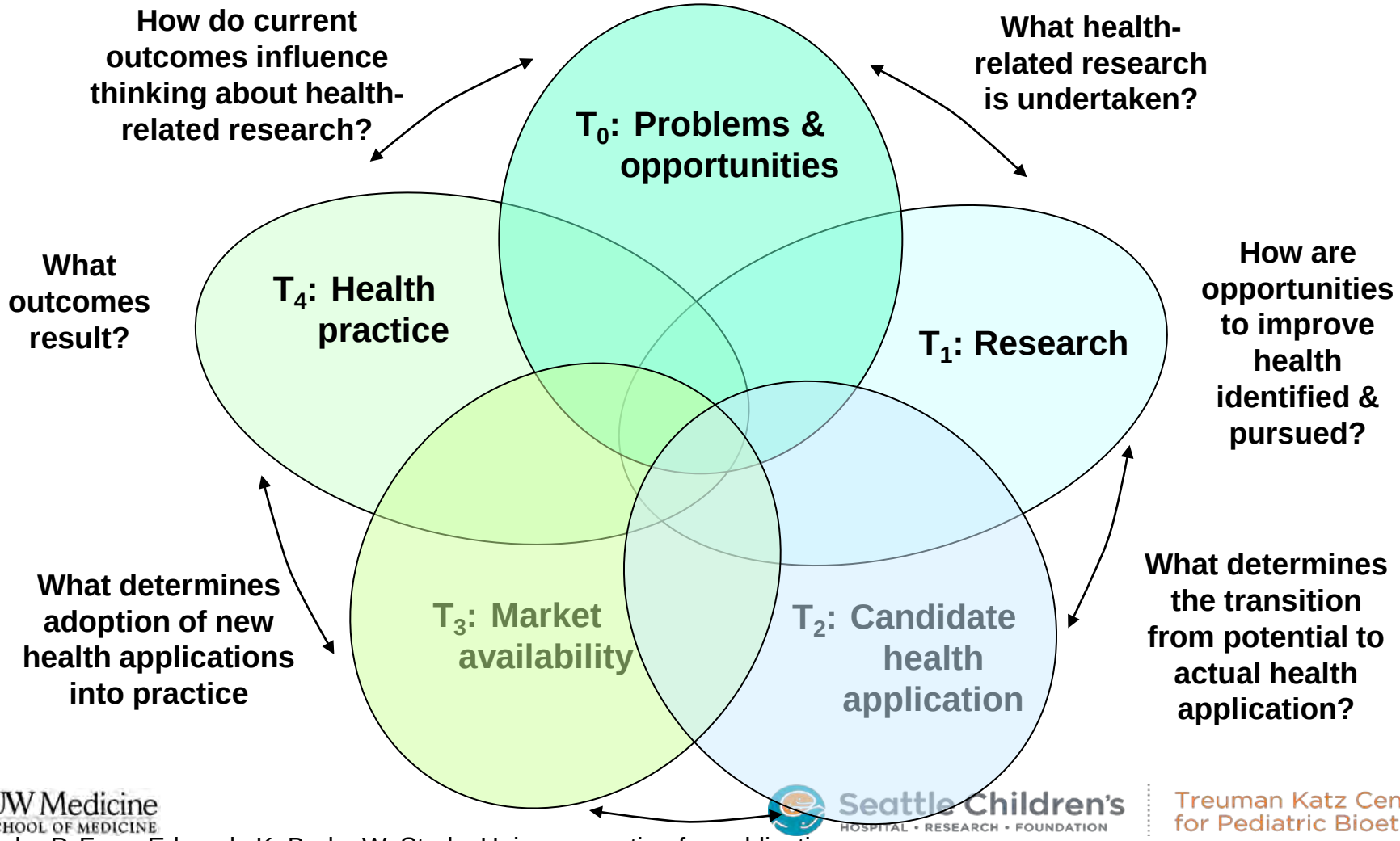
Translational Pathway



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Kuszler P, Fryer-Edwards K, Burke W, Starks H. in preparation for publication.

T_1: Research

Are CNVs associated with, or do they cause autism?

- Apply array CGH and GWAS to existing autism genetic databases and studies
- Results published primarily in 2007 and 2008 in articles by several groups using several different samples and techniques

T_3: Market Availability

BCM Baylor College of Medicine

MGL MEDICAL GENETICS LABORATORIES

Genetic Testing *for* Autism

Biochemical, Molecular, Cytogenetic, Mitochondrial

Through genetic evaluation of patients with Autism Spectrum Disorders (ASD) is critical for appropriate medical management and family counseling. Recently, the American College of Medical Genetics approved a systematic Practice Guideline to aid clinicians with this complex diagnostic schema.

e Medical Genetics Laboratories at Baylor College of Medicine has the unique ability to o er metabolic, molecular and cytogenetic analyses, which encompass the multitude of tests recommended in the ACMG guideline. MGL also o ers a uniquely comprehensive evaluation of mitochondrial disorders, which may contribute to susceptibility for ASD. Our new two-tiered ASD-Panel is designed to reflect the ACMG clinical guideline. Please note, any test in the panel may be ordered individually to meet the needs of each patient.

Genetic testing for autism requires biochemical, molecular (fragile X and gene sequencing), cytogenetic (microarray), and sometimes mitochondrial studies. See Schaefer, Mendelsohn, ACMG Practice Guidelines Genet Med 10:301-305, 2008 (PMID 18414214).

Available ASD Testing	Chromosomal Microarray	Fragile X Testing	Biochemistry	MECP2 Sequencing & Deletion/Duplication
Comprehensive Autism Panel	+	+	Autism 6-Plex Panel	Females Only

T_3: Market Availability

GeneDx
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    - By Disease
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    - Inherited Metabolic Disorders
    - Eye Disorders
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  - Prenatal Diagnosis
  - Mutation Specific / Carrier Tests
  - AutismDx
  - Cardiology Genetics
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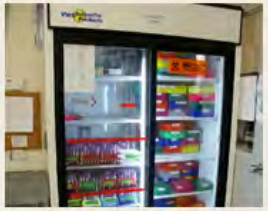

SEARCH

Autism/Autism Spectrum Disorders (ASD) - New!

Information Sheet, including prices and CPT codes

Genetic Test Sample Submission Form (Test Requisition Form) including Payment Options and Consent Form

- **Panel 1: For individuals with ASD and macrocephaly**

  GenomeDx 105k high-resolution microarray/PTEN/MECP2/CDKL5‡

  ‡Check box on submission form if CDKL5 testing is clinically indicated (infantile spasms/seizures).

- **Panel 2: For individuals with ASD and normal or small head size**

  GenomeDx 105k high-resolution microarray/MECP2/CDKL5‡

  ‡Check box on submission form if CDKL5 testing is clinically indicated (infantile spasms/seizures).

T_4: Health Practice

How should tests be used in a clinical setting?

ACMG Guidelines, April 2008

- "Defining the etiology of an ASD can be of great benefit to the parent and family. Information gained from an identified etiology can help with family counseling, medical management, preventive health strategies, and empowerment of the family."

T_4: Health Practice

ACMG Guidelines, April 2008

- "A genetic consultation should be offered to all persons and families with ASDs. Evaluations should be considered for any individual along the full autism spectrum."

T_4: Health Practice

But what does this really mean?

- family counseling
  - What can we say about recurrence risks?
- medical management
  - How will these children be managed differently?
- preventive health strategies
  - Early intervention? What data is needed?
- empowerment of the family
  - To do what? What if the information is wrong?

Pediatrics April 2010

Clinical Genetic Testing for Patients With Autism Spectrum Disorders

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WHAT'S KNOWN ON THIS SUBJECT: Multiple lines of evidence indicate a strong genetic contribution to ASD. Current guidelines for clinical genetic testing recommend a G-banded karyotype to detect chromosomal abnormalities and fragile X DNA testing, but guidelines for CMA have not been established.

WHAT THIS STUDY ADDS: We present here clinical genetic test results, including karyotype, fragile X testing, and CMA, and discuss the implications for clinical care for a large cohort of patients with ASD.

abstract

BACKGROUND: Multiple lines of evidence indicate a strong genetic contribution to autism spectrum disorders (ASDs). Current guidelines for clinical genetic testing recommend a G-banded karyotype to detect

CONCLUSIONS: CMA had the highest detection rate among clinically available genetic tests for patients with ASD. Interpretation of microarray data is complicated by the presence of both novel and recurrent copy-number variants of unknown significance. Despite these limitations, CMA should be considered as part of the initial diagnostic evaluation of patients with ASD. *Pediatrics* 2010;125:e727–e735

Genetic Testing for Autism

Pre array:

- Very limited patient population with other comorbidities (seizures, facial dysmorphologies, significant intellectual disability
- "Ruling out" syndromes: Fragile X, Chromosome 15, Rett's Syndrome
- Yield: 8.3% (Adbul-Rahman and Hudgins, 2006)
- Offered by geneticists

Post array:

- First line diagnostic test of all children with autism
- Yield: 7-8% (but many novel and of uncertain significance) (Shen 2010)
- Many results are non-specifc to ASD
- Offered by nongeneticists and geneticists

What does bioethics add?

A different point of view is simply the view
from a place where you're not.

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What is driving this paradigm shift?

"The concept of genetically based health care is intuitively appealing, but these potential harms underscore the need for a more comprehensive view of the translational process. Without objective measures of outcomes, developers run the risk of creating genetic tests that do more harm than good."

-Burke et al., *Am J Bioeth*. 2008 March ; 8(3): 54–W

Focus on Translation

- Who is this going to help and how?
- Who will have access? Who will not?
- How might this be misinterpreted and how?
- How important is this to communicate vs translate?
  - How can each be achieved?
- What should parents do with this information?

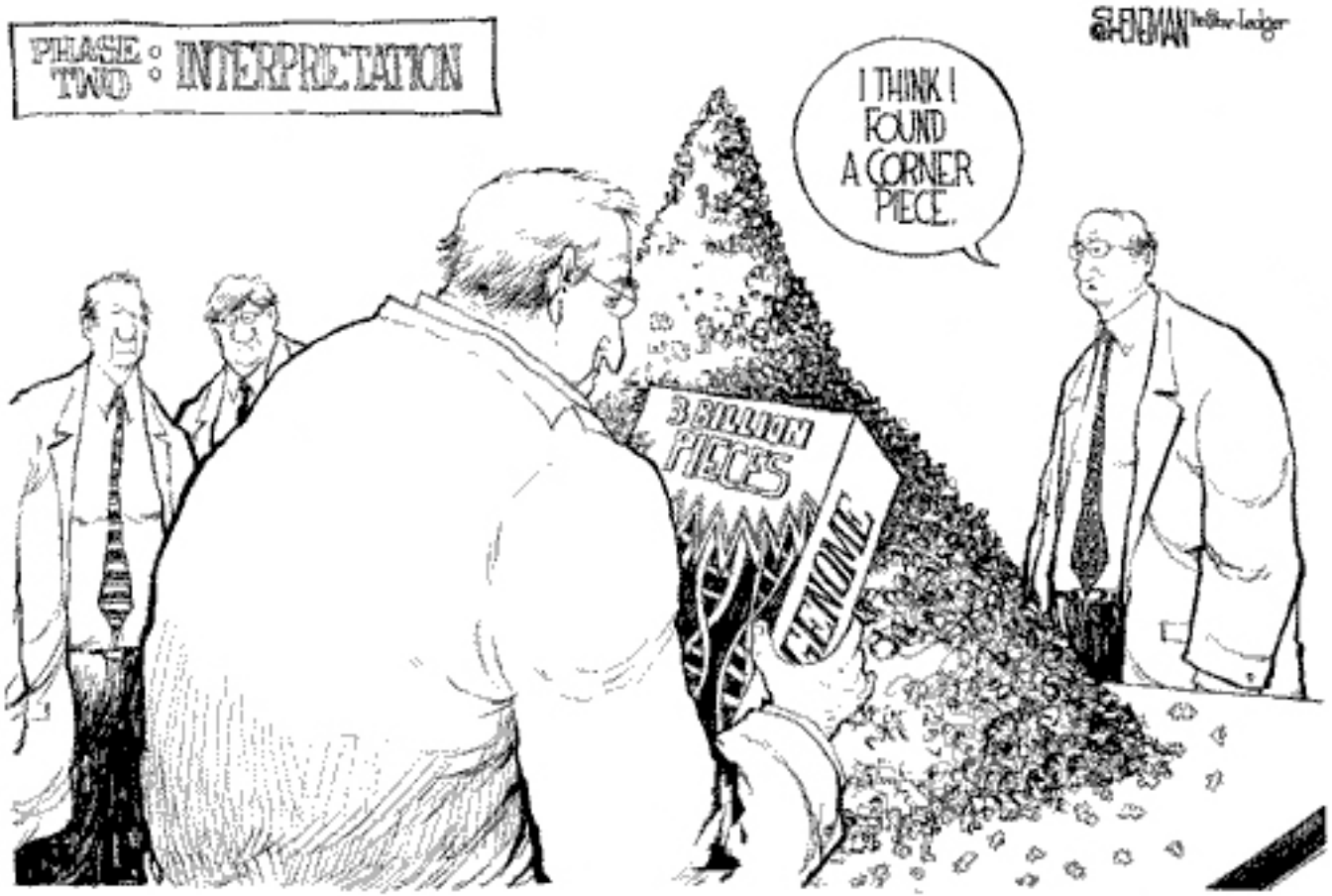
The Promise and Peril of Personalized Genomics

- Genetics as deterministic, explanatory, scientific
  - As opposed to uncertain, unscientific, based on hype (e.g. vaccines)
  - But “you can’t fight the genome!”
- Genetics as finding meaning
  - Role of guilt and blame
- Genetics as finding direction and guidance
  - Do genetic results change diagnosis or treatment?
  - Can/should they affect reproductive planning?
- How much are we driven by doing what we can, in the absence of other, or better, alternatives?

Research Questions/Priorities

- How should genetic testing be incorporated into evaluation of ASD? What criteria should be used for clinical validity and utility? Should it be paid for by insurance? Medicaid?
- What are the translational benefits of genetic testing of autism? What are the possible risks? How can families use the information to help their children?
- Why do parents seek out genetic testing for ASD? Why do they refuse it? How do they react to and use genetic risk information?
- What role does genetic risk information play in potentially increasing stigma, or decreasing access to services for people with ASD?
- How are competing etiological models for autism (genetic and environmental) translated into public perceptions and clinical guidelines for autism diagnosis, treatment and prevention?

It’s Complicated



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for Pediatric Bioethics

Ethical issues in etiological and biological research into autism

Jason Scott Robert, PhD

Franca Oreffice Dean's Distinguished Professor in the Life Sciences *and* Lincoln Professor of Ethics in Biotechnology and Medicine

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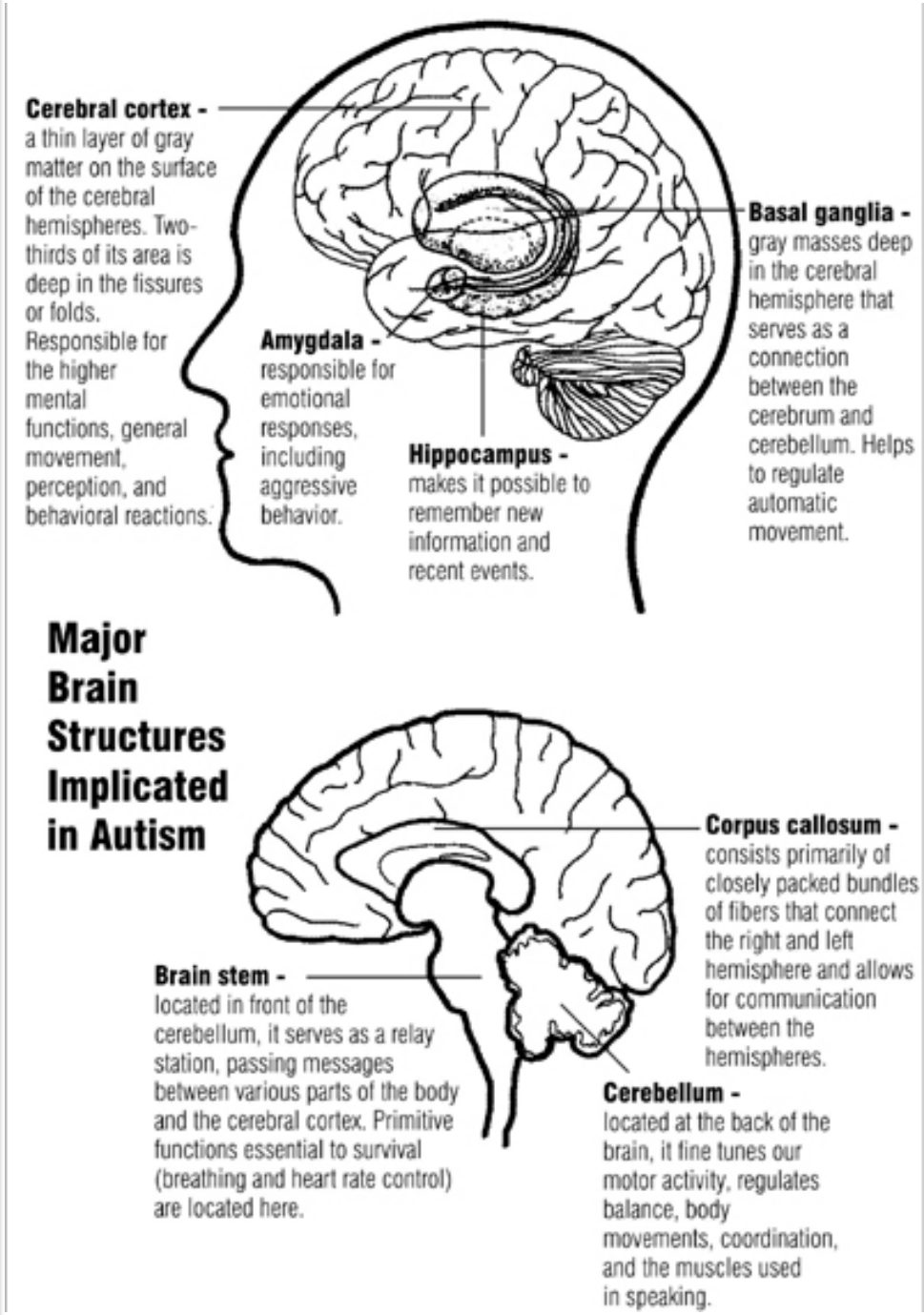
Center for Biology and Society, School of Life Sciences*, and *Consortium for Science, Policy, and Outcomes



ASD etiology

- Multiple brain regions have been implicated
- Multiple genes / gene variants have been implicated
- Diathesis—stressor explanatory models abound, from relative simple to terrifically complex, multi-factorial ones

http://www.nimh.nih.gov/health/publications/autism/complete-index.shtml

What causes autism?

- Parenting?
- Genes?
- Vaccines?

- Genetic diatheses challenged by generic and/or specific environmental stressors?
- Non-genetic diatheses challenged by generic and/or specific environmental stressors?

“Autism’s puzzle”

“Autism's Puzzle” by Pamela Weintraub

Experience Life

October 2011

http://experiencelifemag.com/issues/october-2011/wellness/autisms-puzzle.php

The heterogeneous biologies of autism

"The heterogeneous biologies underlying autism may conceivably converge onto the autism profile via multiple mechanisms that all somehow perturb brain connectivity. Studying the interplay between the biology of intermediary mechanisms on the one hand and processing and connectivity abnormalities on the other may illuminate relevant final common pathways and contribute to focusing the search for treatment targets in this biologically and etiologically heterogeneous behavioral syndrome."

Herbert, M. 2005. Autism: A brain disorder, or a disorder that affects the brain? *Clinical Neuropsychiatry* 2: 354-379.

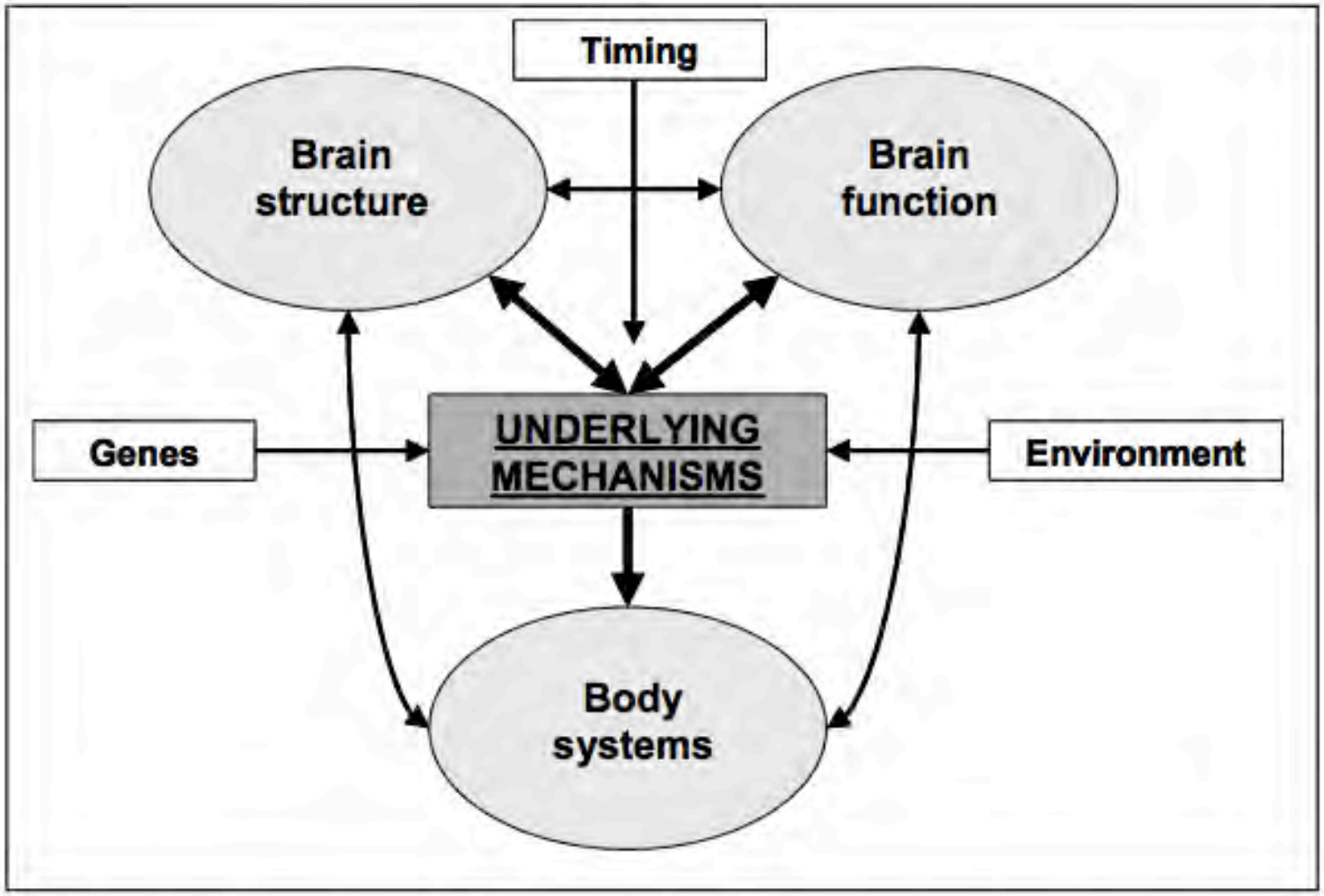


Figure 2. *Common underlying mechanisms, influenced by genes and environments in specific developmental windows, may underlie phenotypic features at multiple levels of the organism.*

Herbert, M. 2005. Autism: A brain disorder, or a disorder that affects the brain? *Clinical Neuropsychiatry* 2: 354-379.

A systems approach to autism

"If we can elucidate the genomic, proteomic [proteins expressed by specific genes] and metabolic differences associated with subtypes of ASD, then we can develop therapies targeted at correcting these imbalances. The ultimate goal is not just treating visible symptoms but actually rebalancing biochemistry — in fact, altering genetic expression — to prevent autism from developing at all," says [Lawrence] Rosen [MD, currently Director of the Whole Child Center in Oradell NJ].

As cited in: Weintraub, P. 2011. Autism's puzzle. *Experience Life* (October), online at http://experiencelifemag.com/issues/october-2011/wellness/autisms-puzzle.php.

Outstanding challenges

- The research agenda
  - Legacy of blame and mistrust
  - Etiological mayhem and phenotypic heterogeneity
- The research enterprise
  - Recruitment, especially given phenotypic heterogeneity
  - Observation of natural history of gXe interactions *vs*. intervention to prevent (further) harm
- The results of research
  - Operationalizing results to make a difference for kids, families
  - Toxic torts on the horizon (genetic susceptibility to specific environmental insults + specific environmental insult = tort claim, even if the environmental insult is not usually causally involved in the phenotype)

Starting at the very beginning: Toward "science with impact"

- Credibility – science produced with integrity: good technical data, sound methods, reasonable analysis, responsible argument, and acknowledgement of limitations of any given study
- Legitimacy/transparency – sensitivity to divergent values among stakeholders, unbiased and fair analysis (especially of opposing views); applies to research agenda setting and knowledge production
- Salience – usefulness to a range of stakeholders, achieved through asking and answering meaningful questions in a way that may inform eventual application in clinical, policy, or other contexts

D.W. Cash *et al. PNAS* (2003)

AUTISM, HISTORY, AND THE COMMUNICATION OF SCIENTIFIC FINDINGS IN ERAS OF UNCERTAINTY AND CONTROVERSY

Michael Yudell, PhD, MPH
Associate Professor, Drexel University School of Public Health

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Why Autism, Risk Communication & Ethics?

- There are few studies and papers examining Risk communication & ethical issues unique to ASDs
- Areas of need include:
  - The communication of environmental, genetic, and GxE risks to diverse stakeholders
  - communicating potential harms from autism research to parents, patients, and the public
  - Autism & culturally sensitive genetic counseling
  - the communication of genetic test results and their uncertainty

History, Ethics, and Risk Communication

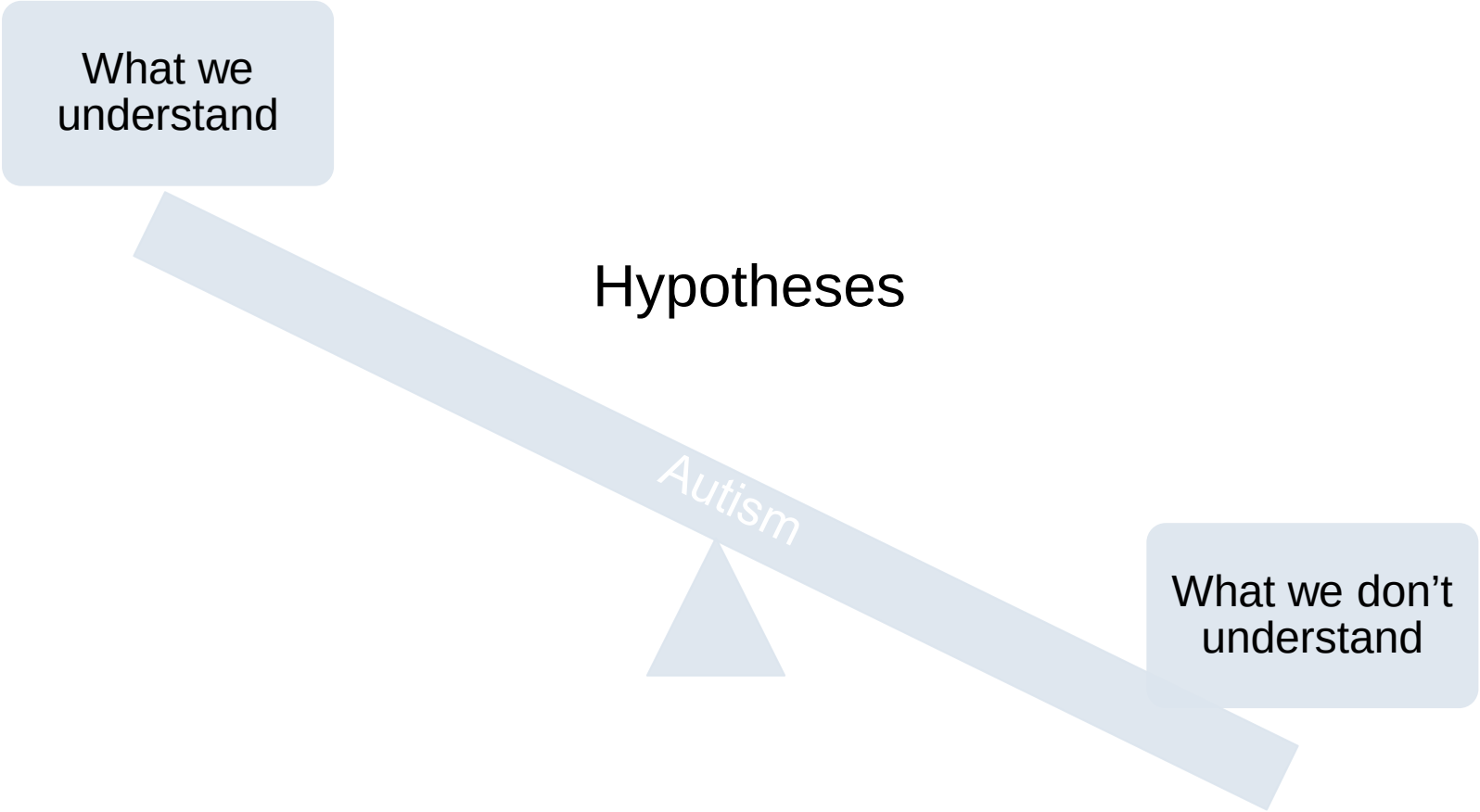
- Historical controversies in autism demand research in this area
  - Debates over autism etiology have raged for more than sixty years
  - These debates and controversies have shaped the behavior of all stakeholders, both historically and present day
  - Recent debates about autism and vaccination have polarized many ASD stakeholders

Autism and Risk Communication Failures

+ Mothers =

AUTISM

Challenges of Autism Risk Communication



Risk Communication Challenges

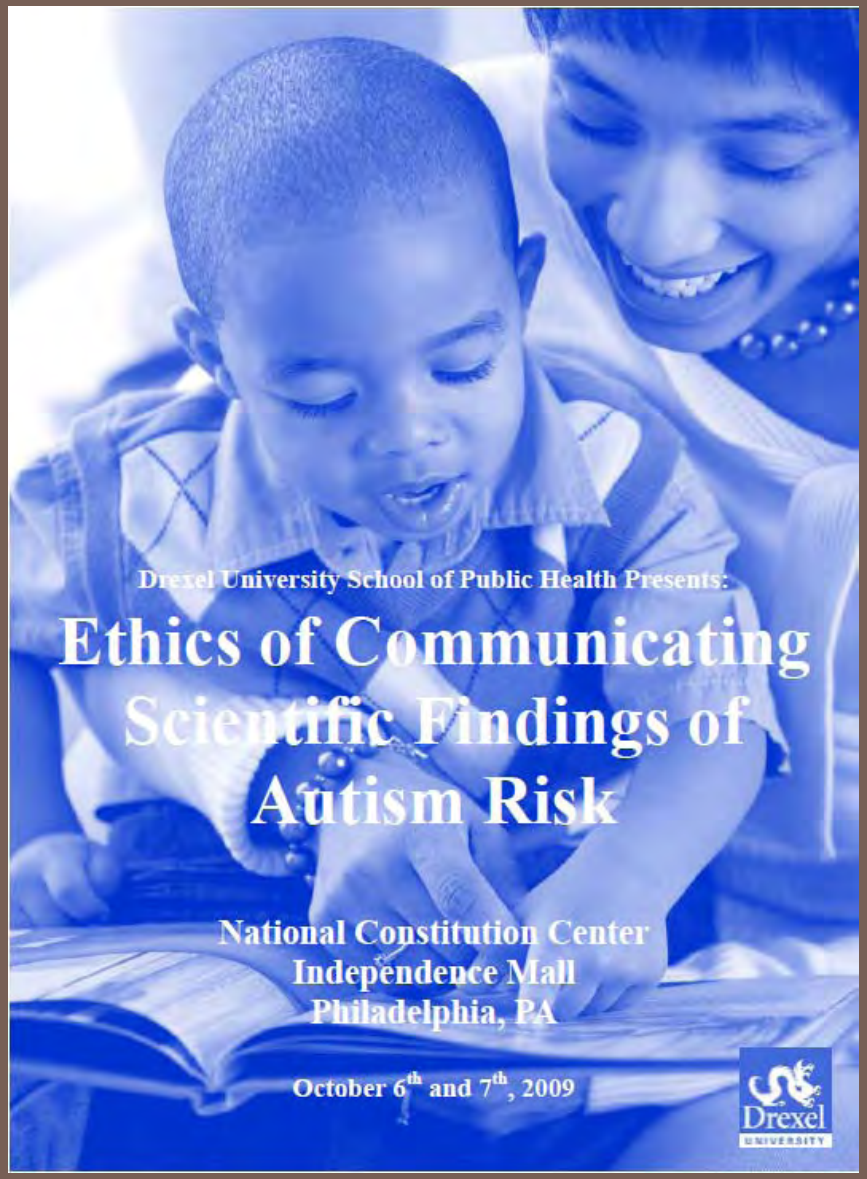
- Environmental Risk Factors
  - Uncertainty of evidence
  - Causal contribution
  - Avoidability
  - Responsibility
  - Risks and benefits
  - Stigma
  - Guilt

Risk Communication Challenges

- Genetic Risk Factors
  - Determinism
  - identity
  - Early detection and treatment?
  - Eugenics
  - Genetic counseling
  - Clinical relevance?
    - Rare variant, large risk
  - Stigma

Risk Communication Challenges

- Complex Causation → G x E
  - In addition to environmental and genetic challenges…
    - Numeracy
    - Not 1, but 2 or more causes
    - Communicating attributable risks



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Stakeholder Participation

- Susan Axelrod, MA, Pennsylvania Department of Education
- Evon L. Bergey, MSW, LCSW, Magellan Health Services Newtown Care Management Center
- Laura Bono, SafeMinds & National Autism Assoication
- Louis Z. Cooper, MD, College of Physicians and Surgeons of Columbia University & National Network for Immunization Information
- Bernard Courtieu, DVM, MBA, IntegraGen
- Lisa A. Croen, PhD, Kaiser Permanente
- Geraldine Dawson, PhD, University of North Carolina at Chapel Hill & Autism Speaks
- Peter Doehring, PhD, Children's Hospital of Philadelphia
- Baruch Fischhoff, Howard Heinz University & Carnegie Mellon University
- Lynn Goldman, MD, MPH, John Hopkins University Bloomberg School of Public Health
- Richard Grinker, PhD, George Washington University
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- Vidya Bhushan Gupta, MD, MPH, New York Medical College & AAP
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- Cathy Melfi, Maternity Care Coalition in Philadelphia

Clinicians & Service Providers

- Require risk communication by professional organizations as part of continuing education requirements
- Develop risk communication “tool kits” for distribution to providers through various channels
- Improve content and resources supporting these efforts by emphasizing communication styles that “meet families where they are”
- Train professionals on how to best communicate risk information in the face of scientific uncertainty
- Prepare professionals to address emerging risk factors as they move into the public consciousness
- Establish a centralized resource, which compiles up-to-date evidence related to autism risk factors and is “vetted” by a broad range of stakeholders.
- Address the glaring need for families to understand more complex ideas about risk by including access to understandable information in the centralized resource

Researchers & the Media

- Train autism scientists to handle the media by having them work closely with university press officers
- Develop a media tool kit for scientists to assist in dealing with the mainstream press
- Develop clear guidelines for reporting preliminary findings
- Support graduate training in risk communication with a particular focus on performing it accurately & ethically
- Include a separate allowance in grant awards for the funding of the dissemination of research findings

Tailoring Risk Messages

- Present information on websites in an accurate, clear manner that conveys respect and encourages affected individuals and their families to explore their questions with trusted professionals
- Provide opportunities for voicing opinions, sharing feelings, offering different points of view, and asking questions either through webinars, town hall meetings, or social networks
- Provide a mechanism for direct one-on-one contact when possible
- Assist in improving the public's understanding of new findings by providing clear accurate interpretations, answering questions with accurate information, and allowing researchers the opportunity to post directly in articles or blogs.

Dissemination of Research Results

- Develop protocols and approaches for the evaluation and possible return of results for autism studies including returning aggregate results when more appropriate
- Consider the clinical validity and utility of possible results as well as what they will possibly used for by recipients before their return
- Avoid the creation or amplification of therapeutic misconception in the return of results when addressing the purpose of research with participants
- Create guidelines for return of results in autism research by involving multiple stakeholders in the autism community, including affected individuals, their families, and advocacy groups. This could include the establishment of a national autism ethics advisory board
- Perform research into how study participants actually interpret and use research results to fill the lack of empirical data in this area

Themes in Autism Risk Communication

- Uncertainty (in the face of certainty)
  - Communication of scientific findings, return of results
- Risk salience (prioritizing risk)
- Controversy
  - Vulnerable populations
- Blame (from parents to clinicians to science and medicine)
  - vulnerable populations, return of results
- Distrust
  - Access & barriers to care, culturally sensitive
- Health disparities
  - Justice, vulnerable populations, access & barriers to care

ELSI Issues Related to ASD Screening and Diagnosis Research

- Ethical issues in the conduct and uptake of ASD screening research-**Lonnie Zwaigenbaum, M.D.**
- Identifying and communicating meaningful genetic results used in ASD screening and diagnosis-**Fiona Miller, Ph.D.**
- Lessons from newborn screening for Fragile X syndrome-**Don Bailey, Ph.D.**
- Ethical issues in adult diagnosis – **Catherine Lord, Ph.D.**

Ethical issues in the conduct and uptake of ASD screening research

Lonnie Zwaigenbaum MD FRCPC
Department of Pediatrics, University of Alberta

Ethical, Legal and Societal Implications of Autism Research

NIH Workshop, Bethesda, MD

September 26th, 2011

Context

- **Post-natal** (generally 18-30 months)
- **Symptomatic**- ASD-related behaviors as measured by parental questionnaires and/or clinical observation
- **Universal vs. targeted** ('first-level' versus 'second-level' screening)
- **Current practice parameters: e.g., AAP**

American Academy of Pediatrics

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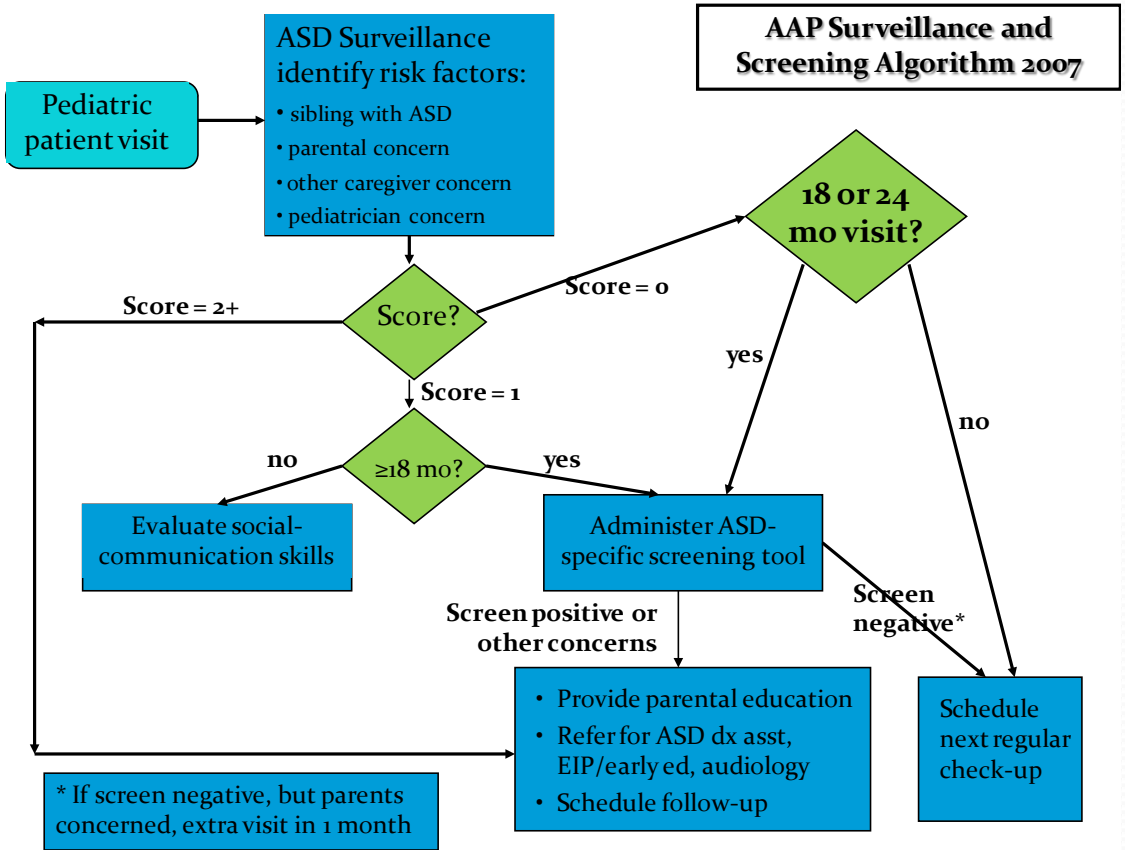
CLINICAL REPORT

Identification and Evaluation of Children With Autism Spectrum Disorders

Guidance for the Clinician in Rendering Pediatric Care

Chris Plauché Johnson, MD, MEd, Scott M. Myers, MD, and the Council on Children With Disabilities

Oct, 2007



- **Monitor for early signs of ASD at each visit**
- **Universal screening for ASD at 18 and 24 months**
- **E.g., M-CHAT, ITC**

Important ethical and societal issues

- **Beneficence vs. Nonmaleficence**
  - Benefits and risks
  - Individuals, autism community, society
  - Criteria for uptake into 'best practice', public policy
- **Evaluation of ASD screening**
  - What determines optimal balance of sensitivity and specificity?
  - Focus on individual classification vs. clinically meaningful endpoints
- **Broader health care perspective**
  - Importance of system capacity – but what drives what?

Criteria for 'screening effectiveness' in health care (proposed by Cadman et al, 1984; cited by Al Quabandi, Gorter & Rosenbaum, 2011)

- **Is a valid screening test available?**
- **Has the effectiveness of the screening program been established in a randomized controlled trial**
  - Implicit is the identification of meaningful end-points
- **Are there efficacious treatments and/or preventative strategies?**
- **Will the screening program reach a high proportion of the persons for whom it was intended?**
- **Will those with positive screens follow-up with further assessment and intervention?**
- **Can the health care system adequately respond?**

Letter to the editor, Pediatrics: Dawson, Fein, Rogers, Zwaigenbaum

(http://pediatrics.aappublications.org/content/early/2011/06/08/peds.2010-1881/reply#pediatrics_el_51471)

- "In conclusion, while Al-Qabandi et al. pose important questions that should be considered prior to the implementation of a community screening program for any health condition, we disagree with the conclusions drawn regarding the availability of accurate autism screening tools, the evidence base for effective early intervention, and the feasibility of care provision for children with ASD identified through early screening…"

Are there valid ASD screening tests?

- **CHAT** – important contributions, but insufficient sensitivity to have utility as 1st or 2nd level screen
- **M-CHAT and ITC** – recent community level data support use as 1st level screen as part of overall early detection strategy (also M-CHAT as 2nd level screen)
- **STAT** – utility as 2nd level screen
- **SCQ** – some utility as 2nd level screen in clinical samples, poorer sensitivity/specificity for < 4-year-olds
- The **ESAT** experience: education and engagement may be as important as screening...

Are there effective interventions for children with early ASD diagnoses?

- **ESDM Clinical Trial (Dawson et al., 2010)**
- 18-30-month-old toddlers with ASD (n=48)
- Randomized to 24 months of:
  - ESDM (20 hr/wk, plus parent sessions and other community interventions)
  - 'Assess and monitor' (include community interventions – about 10 hr/wk)
- ESDM group showed marked improvements:
  - Advances in language and cognitive skills
  - Tendency to shift to milder diagnostic subtype

Are there controlled clinical trials of ASD screening?

- **Oosterling et al. (2010)**
  - Evaluated ASD screen (ESAT) as part of an overall early detection *strategy*
  - Compared changes in age of diagnosis in two regions with similar demographics and service structure, one of which had the novel strategy implemented
  - Strategy consisted of training for (and interaction between) professionals and front-line workers, 2nd level screening with the ESAT (<36 months), establishment of an enhanced multi-disciplinary diagnostic team
  - Mean age of diagnosis dropped from age 7 to about age 5 in 'experimental region'; stable at age 7 in 'control region'
  - Previous research suggests ESAT has limited sensitivity and classification accuracy; yet the overall strategy was effective!

Will the screening program reach a high proportion of children for whom it was intended? Will those with positive screens follow-up with further assessment and intervention?

- **Data are somewhat mixed**
- e.g., Pierce et al., 2011; 'One-year Well Baby Check-up'
  - Efficiacy study (i.e., ideal circumstances) – well-engaged pediatricians, streamlined access to expert diagnostic assessment and intervention in research context
  - 1319 of 10479 (13%) of 1-year-olds failed ITC screen
    - Only 346 (26%) were referred
    - Only 184 were seen in follow-up (53% of those who were referred, or 28% of those with positive screens)
- Loss to follow-up also noted in M-CHAT research

How do we study the potential benefits and risks of ASD screening?

- **From whose perspective?**
  - **Individual child:** What is the impact of being correctly identified as having ASD? Or incorrectly identified as having ASD (or as not having ASD)?
  - **Research and advocacy community:** Can we identify, diagnose and treat ASD earlier? Can we improve long-term outcomes for children (and families)?
  - **Societal:** What are the resource and opportunity costs and benefits, both short- and long-term? Does ASD screening strain or build system capacity?

Challenges in ASD diagnosis in children under age 2 years (Zwaigenbaum et al., *Pediatrics* 2009)

- **Limited clinical experience and research evidence base for reliability/stability**
  - Minimal data outside of highly specialized tertiary care setting
- **Minimum cognitive level needed to assess critical developmental domains;** e.g., joint attention behaviors
- **'Fuzzy boundaries' between ASD and other developmental impairments**
- **However, experience to date in 'baby sib' samples suggests stability of early diagnosis is high, but sensitivity is fairly low**

Priorities in ASD Screening Research: Through an ELSI Lens

- **Family experience related to ASD screening**
  - Communication of findings
  - Navigating the system after a positive screen
  - Impacts of misclassification
    - Importance of longer term follow-up
  - Impacts of earlier detection
- **ASD Screening *Effectiveness***
  - ASD screening as part of overall early detection *strategy*
  - Focus on short- and long-term meaningful outcomes
- **Setting ethical standards for early detection and screening research**
  - e.g., 'infant sibling' research

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Many wonderful children and families!

Health Policy, Management & Evaluation
UNIVERSITY OF TORONTO

Identifying and communicating meaningful genetic results in ASD diagnosis & screening

Fiona A. Miller, PhD

Associate Professor, HPME

Joint Centre for Bioethics

September 26, 2011

HPME

www.hpme.utoronto.ca

Overview

- Genetic research results in ASD
  - Placing genetic information in context
  - Considering the nature of the information
  - Obligations to provide updated information?

  - Genetics in clinical diagnosis
  - Population screening – a role for genetics?

Complex research context …

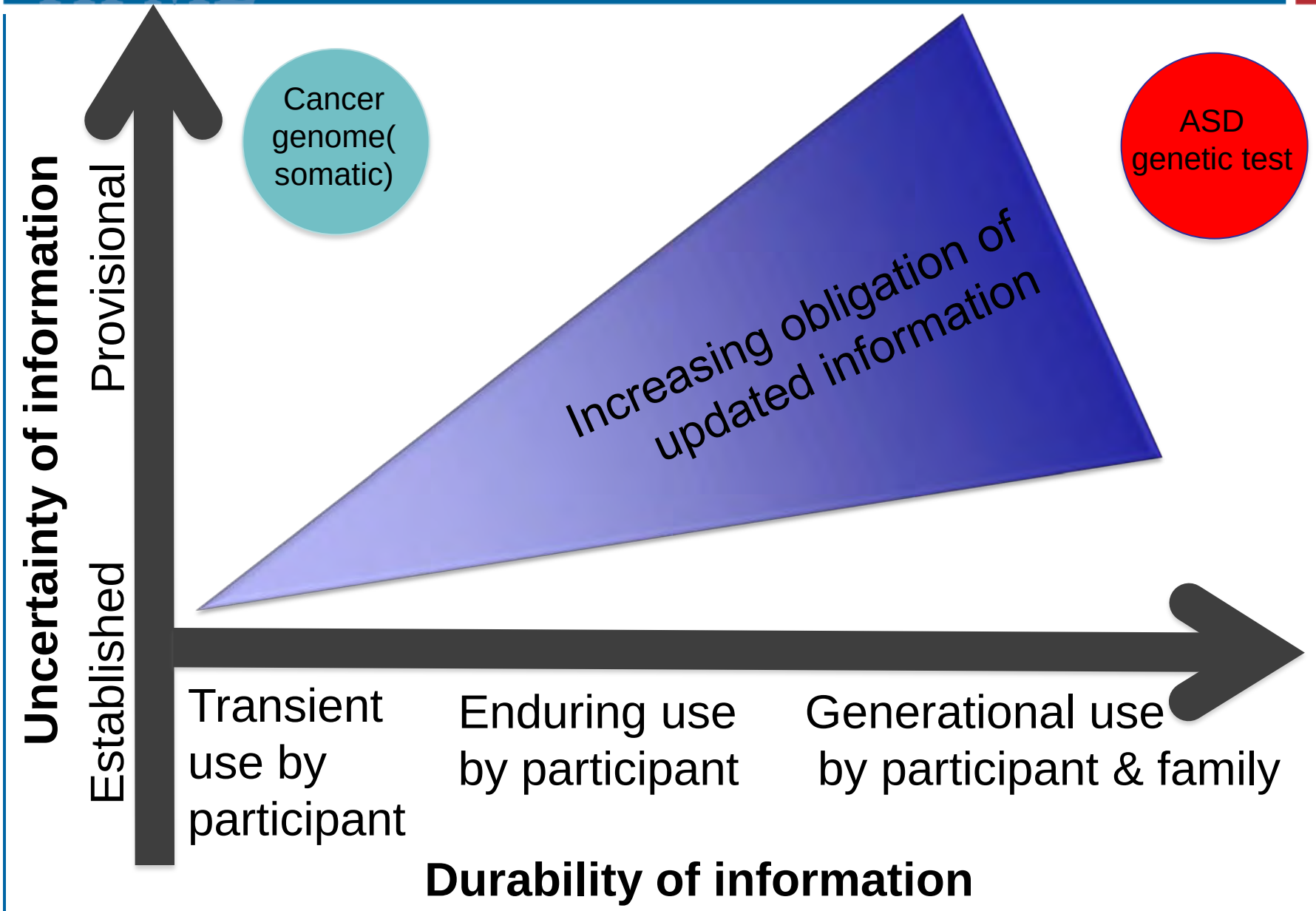
- Families with ASD diagnosis need care/info
  - Uncertainty of ASD
- Research can be a resource
  - Access to specialists
  - Access to diagnostic assessments
  - Access to information

ASD genetic results: meaning

- … are a relatively small part of overall needs
- Meaningful information would be valued
  - Instrumental value (extrinsic):
    - Reproductive risk
    - Personalized treatment
  - Non-instrumental value (intrinsic):
    - Understanding ‘why?’
    - Seeking legitimacy – a ‘real’ disorder

ASD genetic results: reporting

- Researchers' judgments to report …
  - Informed by science
  - Informed by values
  - Informed by interests
  - Informed by disciplinary norms/ epistemological assumptions
  - Informed by ontological assumptions


Uncertainty of information
Provisional
Established
Cancer genome(somatic)
ASD genetic test
Increasing obligation of updated information
Transient use by participant
Enduring use by participant
Generational use by participant & family
Durability of information

In sum …

- Genetic research serves many needs
  - For information
  - For care

  → Genetic information is a part, and not the whole
- Genetic information in ASD
  - Is highly provisional
  - Is highly durable

  → Obligation of information update

Overview

- Genetic research results in ASD
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  - Genetics in clinical diagnosis
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ARTICLE

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

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Genetics in clinical diagnosis

- As in research context
  - To explain causation in idiopathic cases

  →Durable information
- As in research context
  - Complex professional judgments

  →Provisional information

→ Obligation of updated information

Population screening – genetics?

- No current role for genetic testing
- But, likely to be complex addition
  - May increase diagnosis/ overdiagnosis challenge
- CF NBS instructive
  - CFTR vs. other biomarkers in pre-symptomatic diagnosis
  - The problem of “borderline” babies

- "Screening differs from routine clinical care because the process is initiated by the state or professionals, not by patients or parents. … In the context of screening, it is not appropriate for professionals or the state to initiate contact with the public unless there is very strong evidence that available treatments are effective."

Draft for Consultation

NHS

Screening for Autism Spectrum Disorders in Children below the age of 5 years

A draft report for the UK National Screening Committee

Dr Martin Allaby
Dr Mohit Sharma

4 July 2011

ASD and ELSI

- Avoid unnecessary exceptionalism
  - There are differences but also similarities
  - Evidence standards for common, not ultra-rare, disease
- Research on genetic tests in ASD
  - Comparing receipt to non-receipt of genetic info (interpretation and use in context)
  - Updated information: when required; how provided; how paid for

Many thanks

Parents and researchers who have provided information and insight

Robin Hayeems, PhD, HPME
Colleagues in the AGP
Genome Canada

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Lessons Learned From Newborn Screening for Fragile X Syndrome

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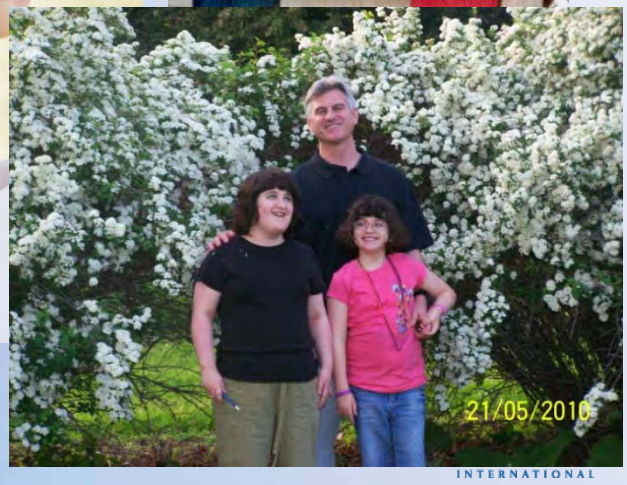
RTI International is a trade name of Research Triangle Institute.

Major points

- Fragile X syndrome (FXS) and autism both suffer from an early diagnosis problem
- Although very different conditions, there is some overlap in phenotype
- Because FXS is a single-gene disorder with an accurate diagnostic test, a definitive early diagnosis is possible
- This will likely never be the case in autism (a single definitive biomarker), but there will be an increasing number of biomarkers identified that are associated with elevated risk for autism
- Some of the ethical, legal, and social issues that have arisen in our FX newborn screening work may have some relevance for autism

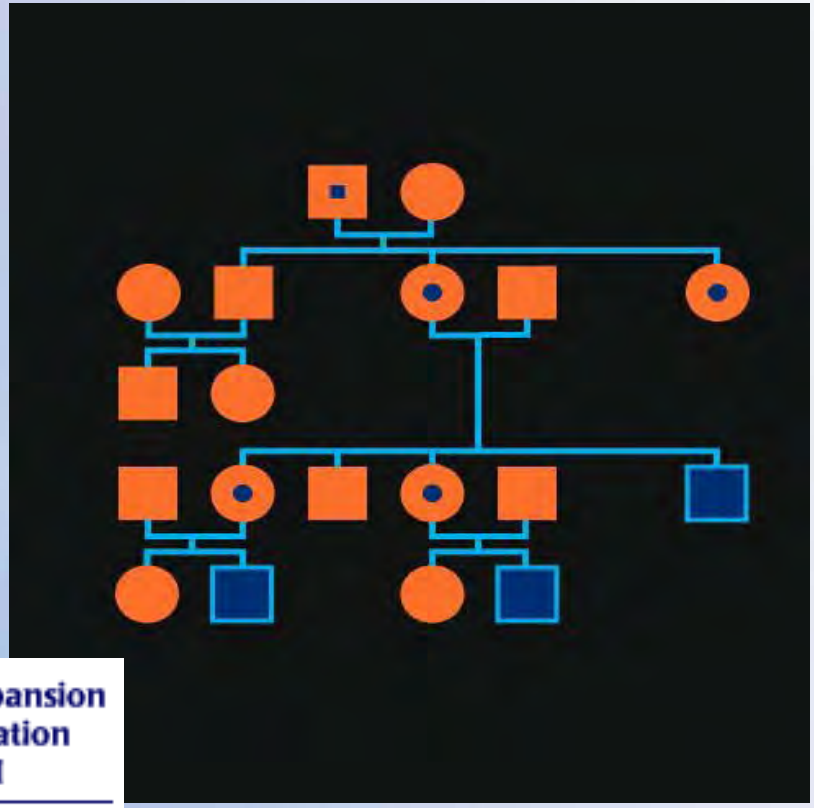
What is fragile X syndrome?

- Most common inherited form of intellectual disability (@1:4000)
- Males and females affected, males more severe
- Many individuals with FXS also meet the diagnostic criteria for autism (35-60%)



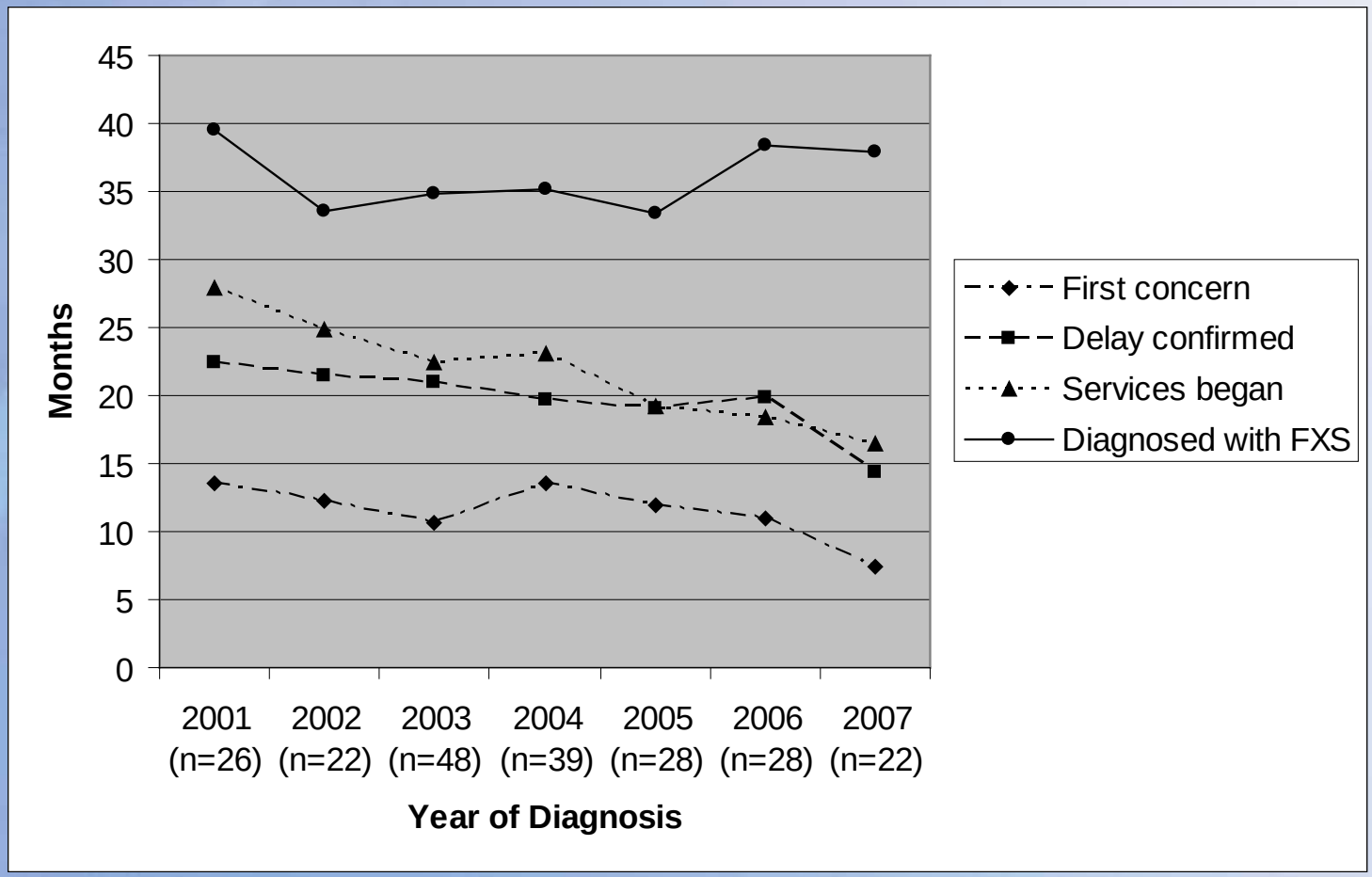
How is fragile X syndrome inherited?

- A single-gene disorder passed down through carrier parents
- Unstable CGG triplet repeats with increasing risk of expansion in subsequent generations



Number of Repeats in Mother's Pre-mutation	Chance of Expansion to Full Mutation in Child
56 - 59	<1.0%
60 - 69	17%
70 - 79	71%
80 - 89	82%
90 -199	99%

No change in the age of diagnosis of FXS
(Bailey et al., 2009, *Pediatrics*)



Promoting earlier identification will be hard

- Lack of clear phenotype, especially in the early years
- Differences in severity between males and females
- Moving from a diagnosis of “developmental delay” or “autism” to genetic testing and the FX diagnosis

Projected best case scenario if relying on developmental screening as “point of entry”

- 9-month developmental screening identifies some males (probably a lot fewer females) with FXS as infants “at-risk” for delay
- Infants are referred for follow up developmental evaluations (1-3 months?)
- A majority (but not 100%) of males will show definite delays in a full evaluation at 12 months
- Those with significant delays would be referred for genetic testing
- Best case scenario for all of this is 16-18 months for a diagnosis of boys

So, what about newborn screening?

- All states have NBS to test babies for important but non-obvious health conditions
- Bloodspots obtained before the baby leaves the hospital
- Spots sent to a state or regional laboratory for quick analyses
- Positive results are returned for diagnostic confirmation and treatment
- States decide which conditions to screen
- Most screening is mandatory

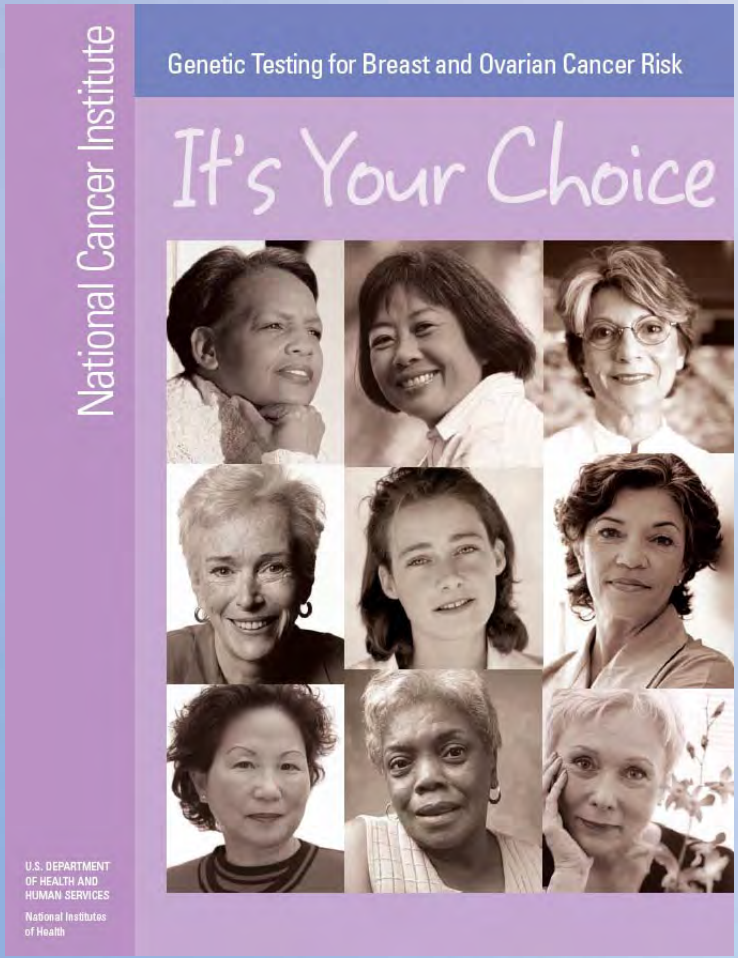
FXS could be identified through newborn screening, but….

- There is no medical treatment currently available that must be provided early
- A DNA-based screening test would identify carriers
- The test is too expensive for population screening
- There are late-onset conditions associated with a subset of carriers (FX-POI and FXTAS, + ???)
- Given these concerns, FXS would not meet current NBS criteria
- BUT….
  - The test is getting cheaper
  - Parent advocates are pushing for earlier identification
  - New pharmacological treatment possibilities are on the horizon

We must envision a future of whole genome sequencing or some variation thereof at birth

- Many rare conditions will be identified
- Most will not have biomedical treatments
- Conditions will be pre-symptomatic and some will be normal
- Information may be increasingly “probabilistic” rather than certain disease – ***this will almost certainly be the case with autism***

The autism scenario might be more similar to BRACA1 or APOE genetic testing than to FX testing



Newborn screening for FXS evokes a number of ELSI concerns that may also apply to autism

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STATE-OF-THE-ART REVIEW ARTICLE

Ethical, Legal, and Social Concerns About Expanded Newborn Screening: Fragile X Syndrome as a Prototype for Emerging Issues

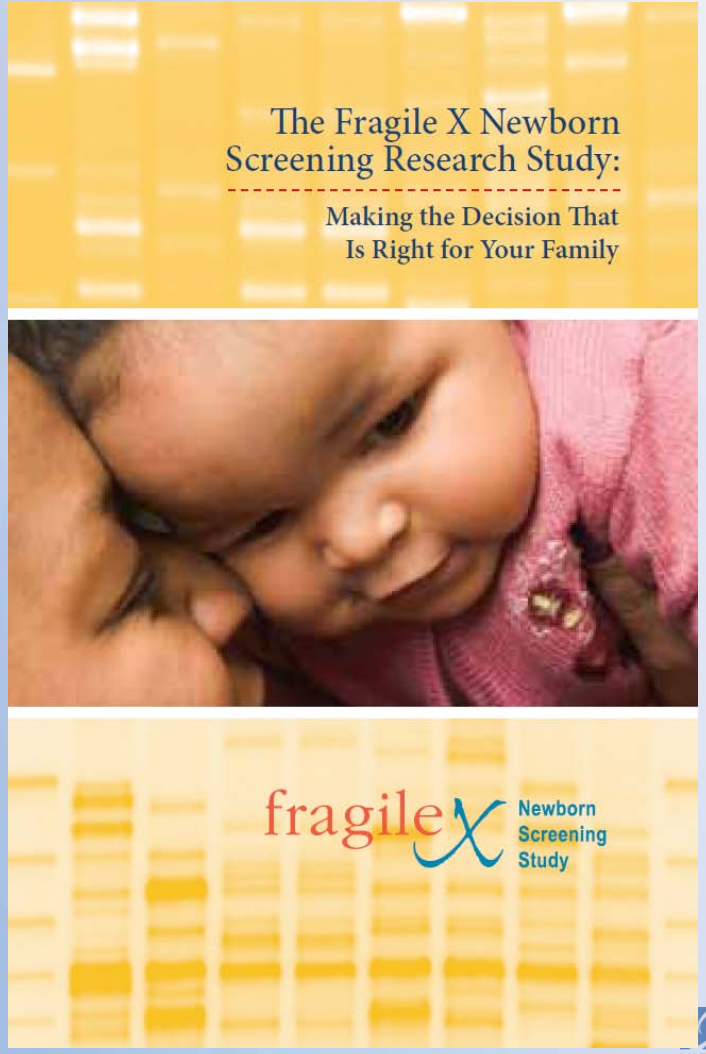
Donald B. Bailey, Jr, PhD[a], Debra Skinner, PhD[b], Arlene M. Davis, JD[c], Ian Whitmarsh, PhD[b], Cynthia Powell, MD[d]

Concerns about NBS for fragile X

- Early identification of an “untreatable” condition could lead to heightened anxiety about parenting, oversensitivity to development, alterations in parenting, or disrupted bonding

Concerns about NBS for fragile X

- FX screening should be voluntary. But the consent process could overwhelm parents, burden hospitals, and reduce participation in the core screening program



Concerns about NBS for fragile X

- Screening will identify some children who are or appear to be normal, or are only mildly affected

Concerns about NBS for fragile X

- Screening could overwhelm an already limited capacity for genetic counseling and comprehensive care

Concerns about NBS for fragile X

- If carrier status (or in the case of autism, genetic risk) is disclosed, it could increase the likelihood of harm, including negative self-concept, societal stigmatization, and insurance or employment discrimination

Concerns about NBS for fragile X

- Screening would implicate or suggest risk in extended family members, raising ethical and legal issues (since they never consented to screening), creating a communication burden for parents or expanding the scope of physician responsibility

Questions asked by families of children identified with pre-symptomatic conditions

- What is my child's "condition?"
- What are the chances that my child will exhibit any aspects of the syndromes associated with his or her genetic variation?
- Should I seek preventive services or wait until a problem becomes apparent?
- How often should he or she be checked?
- Should we have more children, and would they possibly be affected?
- Should we tell other family members, friends, or teachers?
- When and what should we tell our child about his or her "condition?"

Conclusions

- Both the hopes and concerns about NBS for FXS are valid, but we do not have sufficient data to estimate the magnitude of each
- Many of these concerns could apply to autism, especially as genes or other biomarkers emerge as “predictors” of elevated autism risk
- Anticipatory research is needed to be prepared for such a scenario.

FX Screening Pilot Study

- We are currently conducting a pilot FX newborn screening project
- The screening test detects carriers and children with FXS
- Because of all of these concerns, we framed the study as the social science equivalent of a Phase 1 Clinical Trial
  - Treatment is the information
  - One goal is to determine uptake rate (do people want to know this information?)
  - A second goal is to identify any “adverse events”
    - Postpartum depression
    - Altered parent-child relationships
  - A third goal is to study early development, especially of carriers

Funding support

- NICHD (Intellectual and Developmental Disabilities Branch
- NHGRI (Ethical, Legal, and Social Implications Program)
- CDC (National Center on Birth Defects and Developmental Disabilities
- DHHS (Maternal and Child Health Bureau)
- U.S. Dept of Education (Office of Special Education Programs)

Diagnosis of Autism Spectrum Disorders in Adults: Ethical Issues

Catherine Lord
Department of Psychiatry
Weill-Cornell Medical College

General issues

- Shared with other developmental disabilities and psychiatric disorders
- Uniqueness
  - Tremendous heterogeneity
    - Needs, challenges and abilities
    - Trajectories
    - Family resources and involvement
  - Strengths and difficulties associated with ASD
  - Access to services as children; falling between the cracks as adults
- Absence or very limited research

A “success” story for ASD research

Being an adult participant in research as part of an ASD sample

- Informed consent
  - Current IRB process acts against rationality
    - Issues with language level, guardianship and amount of information (not specific to ASD)
  - Transparency of the purpose of the research (e.g., neuroimaging)
- Coercion vs. fair reimbursement
- Privacy
  - Getting a valid history and context

Having a diagnosis or not

- For ASD
  - Autism, PDD-NOS, Asperger Syndrome
  - Various specific genetic conditions
  - (Fragile X, Rett, 16p 11.2 deletions)
  - Intellectual disability
  - Psychiatric disorder

Appropriate behavioral measures

- Direct observation
  - Limitations of the Autism Diagnostic Observation Schedule (ADOS: module 4)
  - Adapted ADOS (for nonverbal, minimally verbal or not quite fluent adolescents and adults)
  - TTAP (vocational measure)
- Self-report
- Caregiver reports
  - ADI-R – algorithm and current
  - Adult SRS
  - Vineland Adaptive Behavior Scales
  - Other adaptive measures and psychiatric measures

Accuracy of diagnostic measures

- Difficulties in specificity
  - Add in ADOS data
- Difficulties in sensitivity
  - Psychiatric measures
  - ADOS

Unique considerations with individuals seeking first ASD diagnoses as adults

- Specificity of self-referrals is very low
  - People seek diagnoses because of personal crises
    - Job related
    - Financial
    - Relationships (marriages, parents, step-parents, siblings)
    - Problems with the law
- Do we want to be very careful about not missing diagnoses

Self-advocacy

- New directions to address ethical issues
  - Inclusion of individuals with ASD on research advisory boards
  - Representativeness of individuals and how recruit
- Standard ways to decide consent and whether to share information and how and when to include families
- Shared databases

What is Autism?

Diagnoses
Where are we now?
Where are we going? (calibration, DSM V, trajectories)

Autism is more than the sum of its parts

- So many people are trying so hard to change trajectories
- Autism is not all that is problematic for many families and individuals (comorbidities including language delay, intellectual disabilities and other psychological disorders)
- There are many things we can do to help

Heading in the right direction and working together

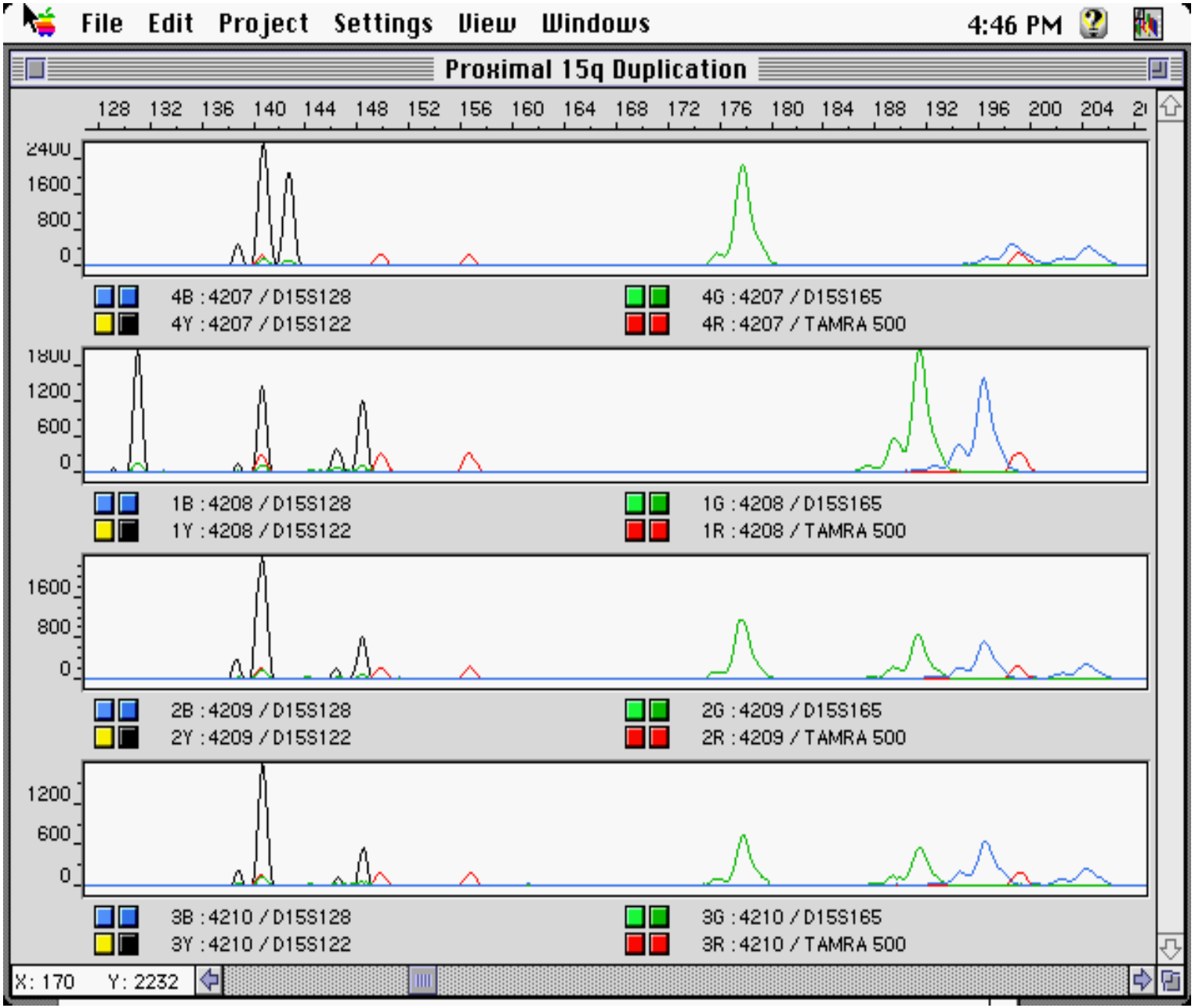
Ethical issues in genetic risk factor research

Edwin Cook M.D.

University of Illinois College of Medicine

15q11-q13 Maternal Duplication

- Initial goal – map common variants across 15q11-q13 and especially GABA-A gene cluster related to anxiety and epilepsy in autism
- 1995 – consent form had no mention of clinically meaningful findings because frankly not anticipated to have individually meaningful factors
- Then and now, view was that autism etiology was multifactorial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3Y : 4210 / D15S122
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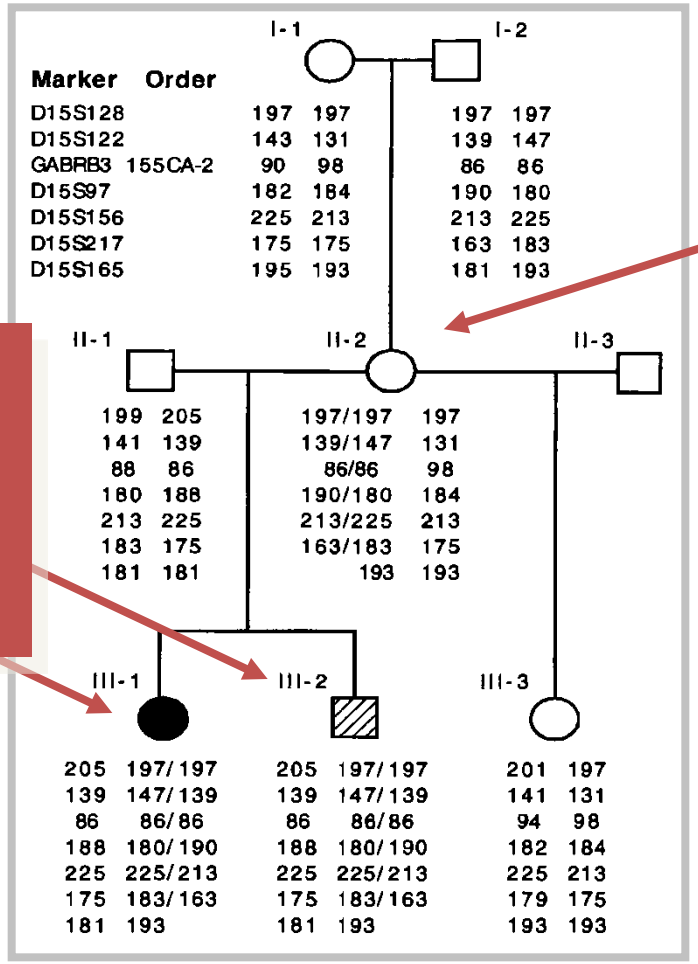
15q11-q13 Duplication—Parent of Origin Effect/ 2. Pre-conceptual risk



15q11-q13 dupe from father–no effect

15q11-q13 dupe from mother–autism or Asperger's syndrome

- Bolton and colleagues confirm increased risk for developmental disorders with maternal compared with paternal 15q11-q13 duplication*

*Bolton PF et al. *Am J Med Genet.* 2001;105:675-685.

15q11-q13 Duplication Pre-conceptual Counselling

- Later approached by mother who requested prenatal counseling and would not have become pregnant without the knowledge from fetal testing
- 20% risk for ASD (baby sibs paper in Pediatrics) to 33% after two affected, is 50% risk that much of a difference to a given parent ? – concern was about suffering of her child, not intellectual disability
- No duplication found from chorionic villus sampling (CVS) – parent was unsure what she would have done if duplication had been present
- In this case, the opportunity to know the risk is likely substantially reduced (but <u>not</u> zero)
- Other risks unaffected or paradoxically may have increased
  - e.g. possibly some risks related to having more group social interaction (e.g. drug abuse)

Implications for Identification of Strongly Implicated Findings

- IDEAs, now dup 15q alliance (http://www.idic15.org/)
- Considerable support, among parents and those with dup 15q11-q13 ranging from children to adults
- Identification of risk for sudden unexpected death
- Another ethical concern – duty to warn the group of a pharmacogenetic risk ?

Pros and Cons in the Balance

- Insufficient data – rate of sudden unexpected death higher but about level of refractory epilepsy (but occurring in mostly controlled epilepsy)
- Association with GABA-A agonists in death during sleep which may be associated with failure to restore respiration after seizure or deep sleep
- However, may have been on GABA-A agonists due to their epilepsy – exception – single dose of Ambien and death that night

Sudden Death Statement for Physicians

- Most primary care physicians would have only one patient
- Provided for families to take to their physicians with explicit instructions only to make changes in consultation with their physicians
- Obsessive document (probably so much so interfered with the communication)
- Outcome – sudden unexpected death rate has reduced (but is this the fall of a rare event)

Simons Foundation Approach

- Over 2500 children with ASD and unaffected siblings
- Highest odds ratio is threshold at which 5% of those with ASD have a CNV and 1% of unaffected siblings
- However, which of the 5% at that threshold are likely pathogenic CNVs
- Expert team relying highly on rapidly developing databases such as ISCA database

“Clinical significance”

- For an example of 10 flagged for review, 2 or 3 are undisputed and probably don’t need reference to a database
- About half are uncertain pending additional data although in many cases, the data are sufficient to show modest odds ratio
- About 2 or 3 are likely not “clinically relevant”

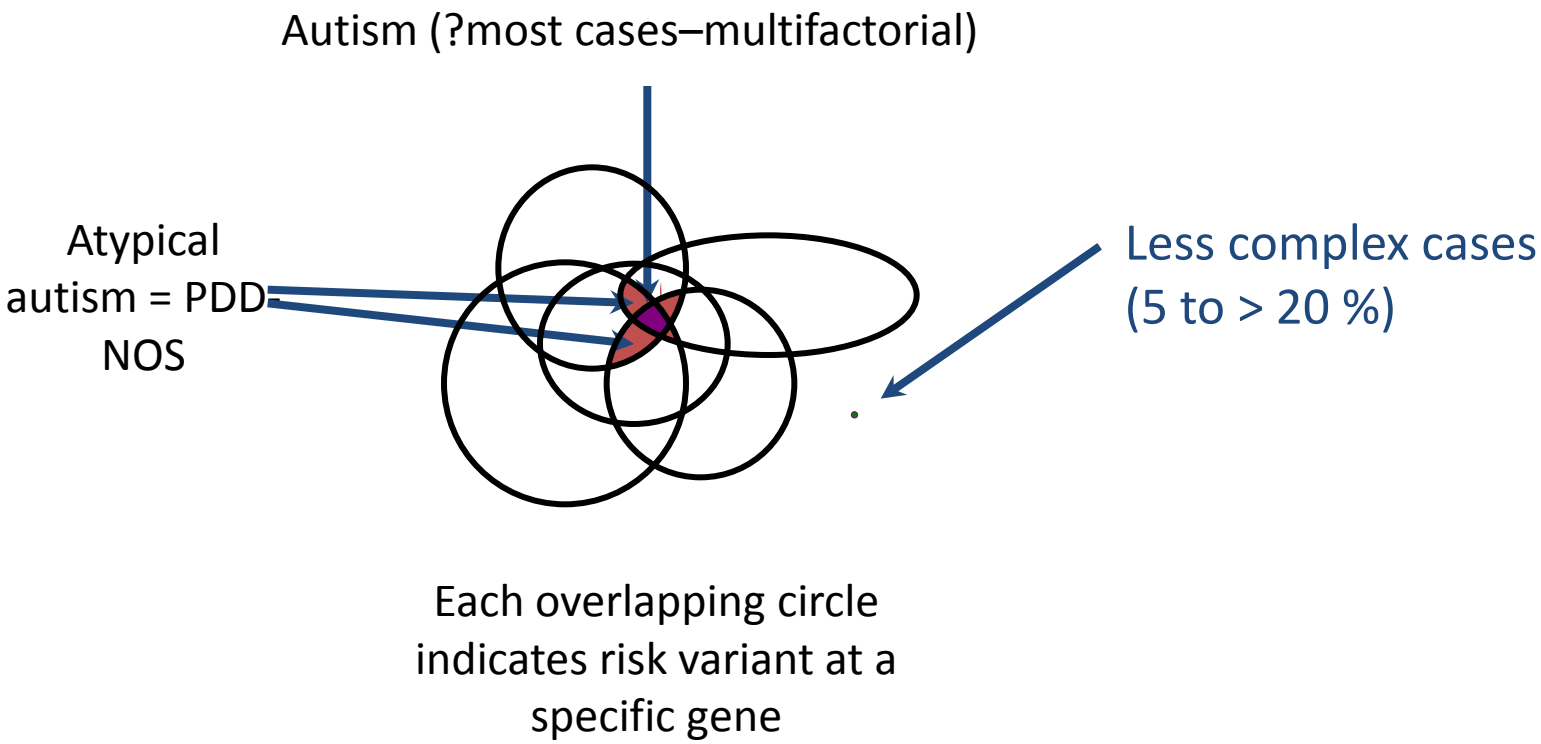
What may be predicted ?

- 16p11.2 duplication and deletion (need to have the precise genetic coordinates and map being used – e.g. hg18 vs. hg19)
- Highly significant risk factor for ASD
- However, if someone was identified early in development with such a deletion the range of outcome could be from obesity without LD to ASD & ID to schizophrenia
- Therefore specific predictions are often limited and are stronger for ID for some findings than for ASD

Language

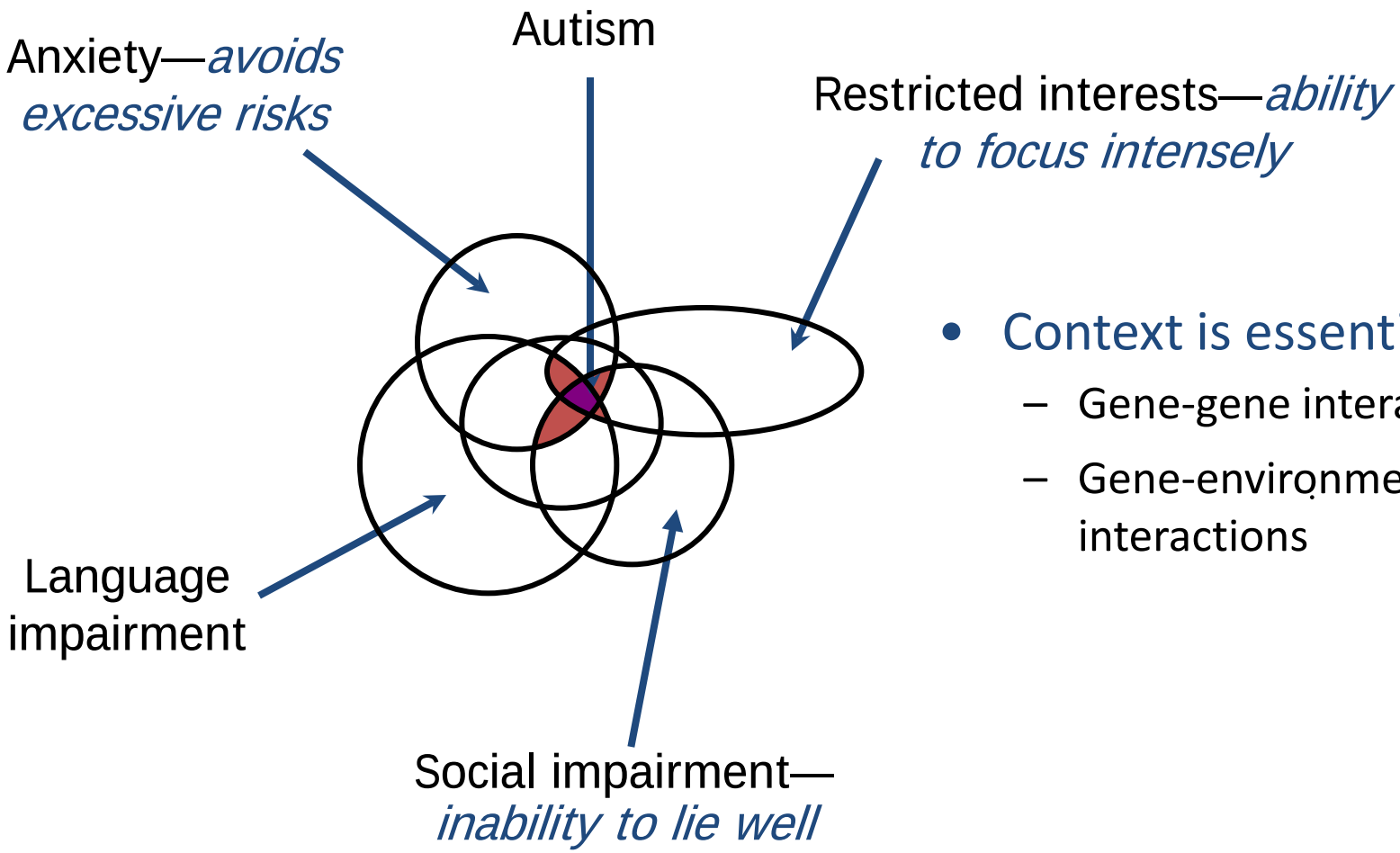
- Most of ASD explained by complex interplay of common genetic and environmental variants and chance
- A very complex multivariate equation
- That equation includes stronger effects but often not present and don’t affect risk
- Almost none of the variants are ASD specific
- Strongly implicated used in the AGP-CNV paper by Pinto and colleagues, 2010, NOT CAUSAL

Genetic Model of Autism



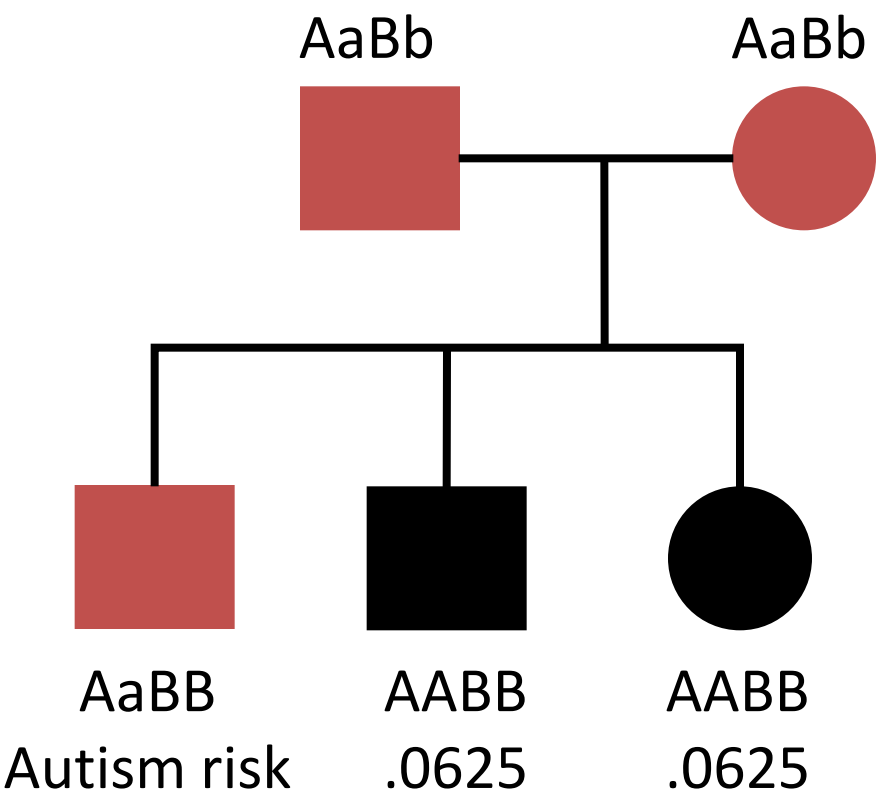
Most likely model is that the “less complex” cases represent situations where the chromosomal or single gene variant is equivalent to a number of smaller effect risk variants

Beneficial Effects of Risk Variants?



- Context is essential
  - Gene-gene interactions
  - Gene-environment interactions

Multiplicative Recessive Genetic Disorder Model—2 Interacting Recessive Loci



- A,B risk alleles; a,b protective alleles
- If A and B equally common and population prevalence is 1:500
- Frequency of A and B 21% each
- At least 1 “risk” allele: 61% of population
- Double-carriers 15% of population

Genetic Knowledge & Autism Ethics & Policy

- Insurance discrimination
  - All are at risk for common, developmental neurobiological, and other medical disorders
  - Risk for one illness may decrease risk for others and/or be associated with strengths
- Respect for persons with autism is vital aspect of humanity
- Provision of appropriate education, behavioral intervention, pharmacological management, quality adult placements, family and community supports are essential (but not ubiquitous)

Implications of Genetics of Autism

- Genetic etiology doesn’t reduce need for habilitation, education, or any other non-genetic treatment
- Idea is to help empower patient and families
- Inherited risk genes for most diseases likely shared partly by all, has implications for parent blaming (Stop parent blaming, but parental guilt is not an easy thing to stop)

Why genetics remains relevant to ASD

- Predictions of ASD or severity of any given ASD-related dimension based on genetics will be limited in vast majority of cases (multiple protective and risk genetic variants and multiple environmental protective and risk factors)

- Point of genetics:
  - 1) develop new treatments by understanding pathophysiology and developing paths to new interventions (e.g. FRAXA to Seaside trials) or preventative strategies (can we find another PKU?)
  - 2) help to choose available treatments

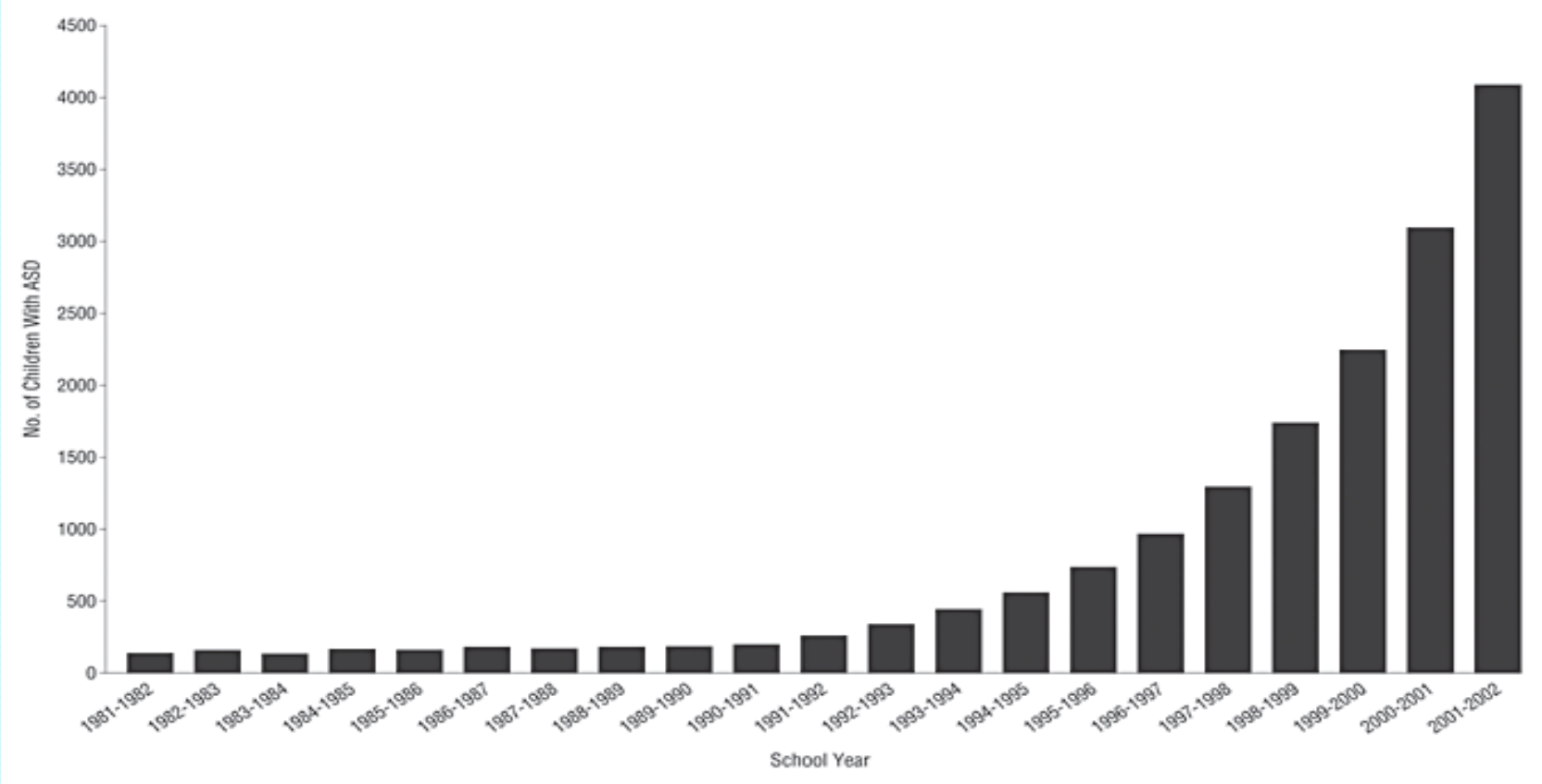
Politics, Prevalence, and the Public Interest

Some Historical Notes

Jeffrey P. Brosco MD PhD
Mailman Center for Child Development
Department of Pediatrics
University of Miami

What Do You See?

Number of children classified as having an autism spectrum disorder (ASD) special educational disability in Minnesota from 1981-1982 through 2001-2002



Gurney, et al. Arch Pediatr 2003;157:622-627.

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3 Statements and a Question

1. Data on the prevalence of a condition are often used in political statements.
2. Data on prevalence have (and should have?) consequences for public resources.
3. Prevalence is calculated in a specific political environment. Which influences which? (Empirical research question)

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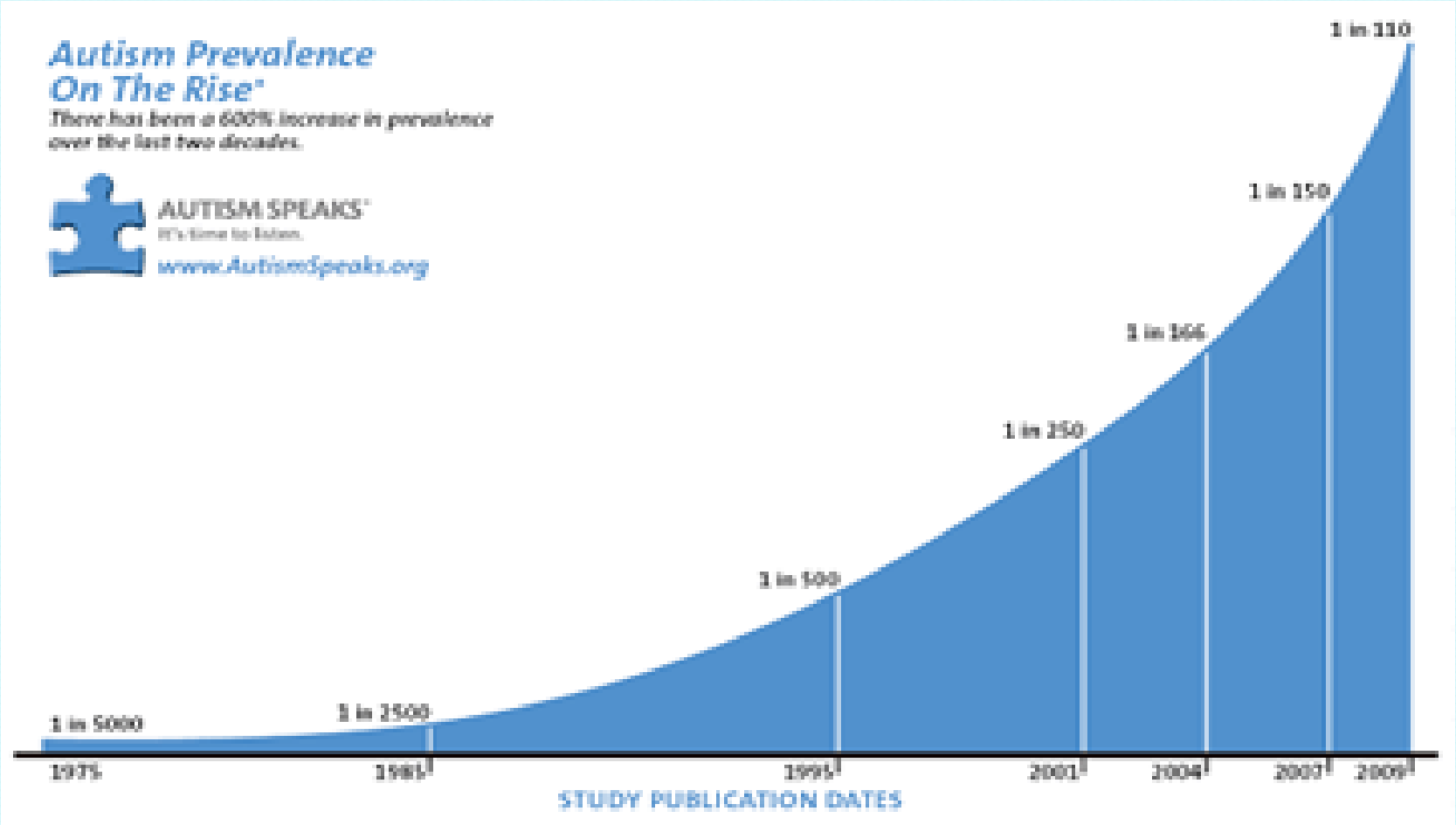
Infant Mortality (US Bureau of Statistics)

Death is a Social Disease (Wm Coleman, 1982)

- Public health statistics has origins in early 1800s France and Great Britain
- Morbidity and mortality linked to social class, environment, etc.
- Since at least the early 1800s, prevalence estimates reflected well-being of a specific location/community
- Early 1900s in US and Europe: infant mortality rate was interpreted as a measure of economic, political, and moral well-being of a community (Brosco, Pediatrics 1999)

Autism Speaks: 2009 Top Research



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1% of children have an ASD

- Different approaches lead to different estimates (e.g. case definition, case finding)
- **As near as we can tell, it's around 1%**
  - Kogan, 2009 - parent report
    - 1/91
  - CDC-ADDM Network, 2009 – record review
    - 1/110

Chronic Conditions of Childhood

Prevalence (per 100)

Learning disability	6.8
ADHD	5.9
Intellectual dis. (MR)	1.5
Autism	**1.0**
Hearing loss	0.4
Visual loss	0.4
Cerebral Palsy	0.3
Down Syndrome	0.15
Allergies	9.6
Recurrent OM	8.3
Asthma	7.2
Diabetes	0.1
Sickle cell	0.1
Kidney transplant	0.002

Is there an epidemic of autism?

- - 15% of children in the US have a developmental/behavioral disorder
  - ADHD, Reading disorder, Depression
- > 20% of children in the US live below the Federal Poverty Line
- 30-40% of children do NOT graduate high school on time

Autism is a Public Policy Challenge

- AAP/Bright Futures recommends that pediatric health providers **formally** screen all children for ASDs at 18 and 24 months
- Children who screen positive should be referred for assessment and early intervention (Part C of IDEA)

Implications of Universal Screening

- Best screening tool available is MCHAT
  - Specificity 93-99%
- Using the MCHAT will yield approximately 10-20 “false positives” for every “true positive”
- In Florida, e.g., Part C/Early Intervention may get as many as **10,000 new referrals** per year
  - Personnel/resources not available to help families who are referred with positive screen

Costs of Autism in Florida

- Screening for ASDs is an "unfunded mandate"
  - $2000 - $3000/physician
- Cost to Part C/EI if autism assessments
  - $1-2 million per year
- Cost of providing treatment 25 hrs/week
  - $55 million per year for 1500 children
  - Total budget now for Part C/EI
    - $48 million/year for 37,000 children

3 Statements and a Question

1. Data on the prevalence of a condition are often used in political statements.
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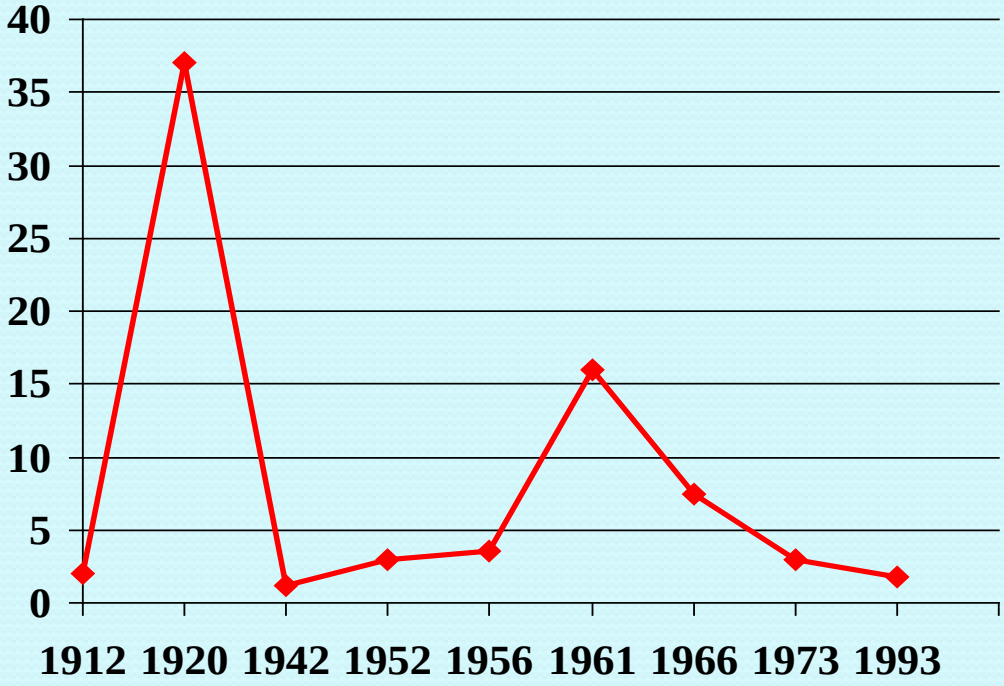
Prevalence of Intellectual Disability

Per 100 population



Brosco, More Than the Names Have Changed , 2008

Why Such Dramatic Variation?

- "Real" change in prevalence of intellectual disability? Unlikely.
- Change in methods of estimating prevalence
  - Case ascertainment
  - Population shifts
  - **Case definition**

Conditions of the Decade

- 1950s – Polio
- 1960s – Mental retardation
- 1970s – Physical disability
- 1980s – ADHD
- 1990s – Learning disabilities
- 2000s – Autism

Conclusion: "ELSI" Issues

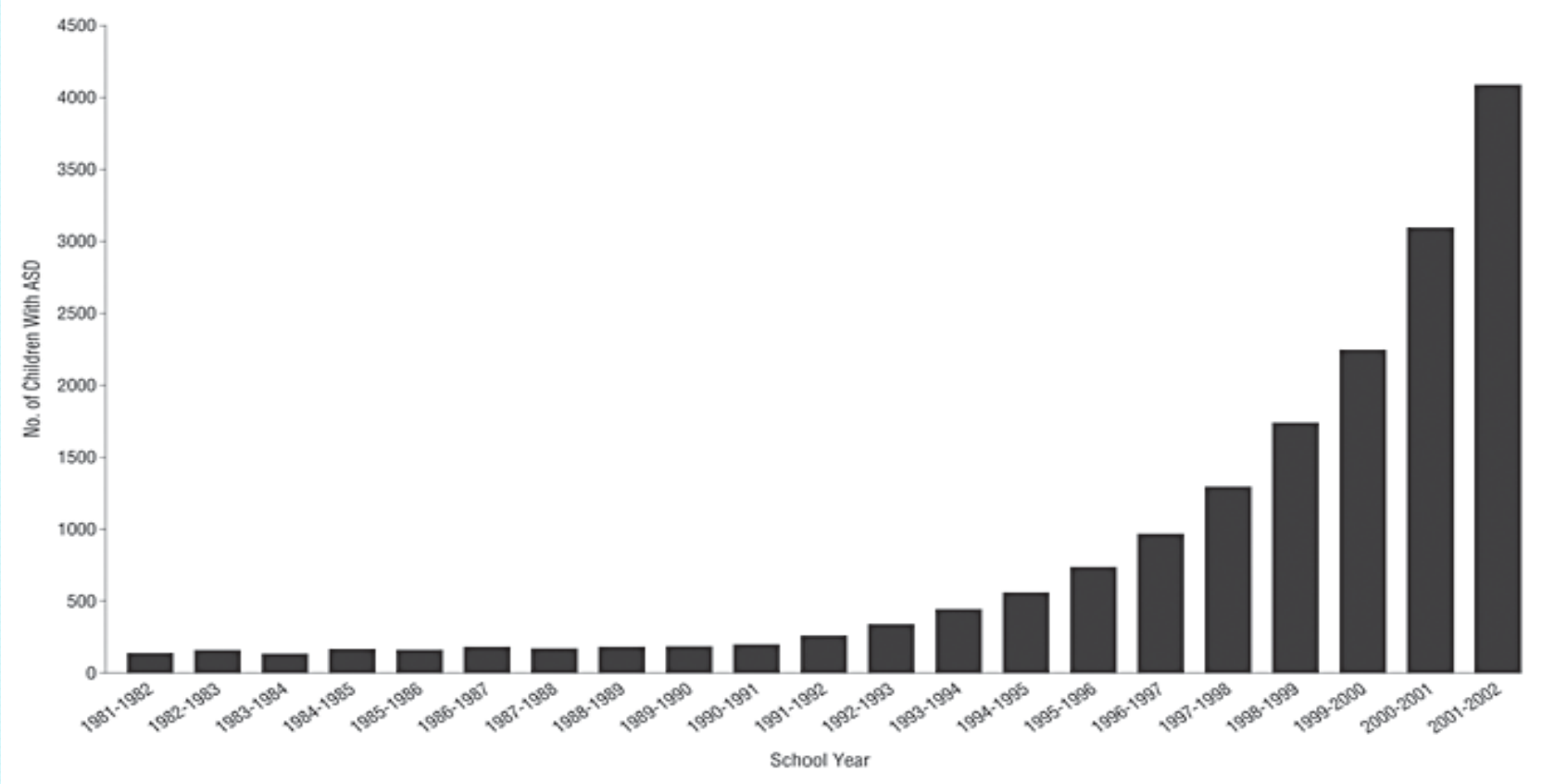
- At certain moments in time, estimates of prevalence are political statements
- Prevalence of a condition should be one component in deciding public policy
- Historical record suggests that "social-political milieu" influences estimates of prevalence in ways that researchers likely don't recognize
- Advocacy groups/individual families historically can have great power in deciding policy
- Autism has much in common with other NDD

Bonus Slides

Has the number of children with autism increased since 1980?

Why is this important?

Number of children classified as having an autism spectrum disorder (ASD) special educational disability in Minnesota from 1981-1982 through 2001-2002



Gurney, J. G. et al. Arch Pediatr Adolesc Med 2003;157:622-627.

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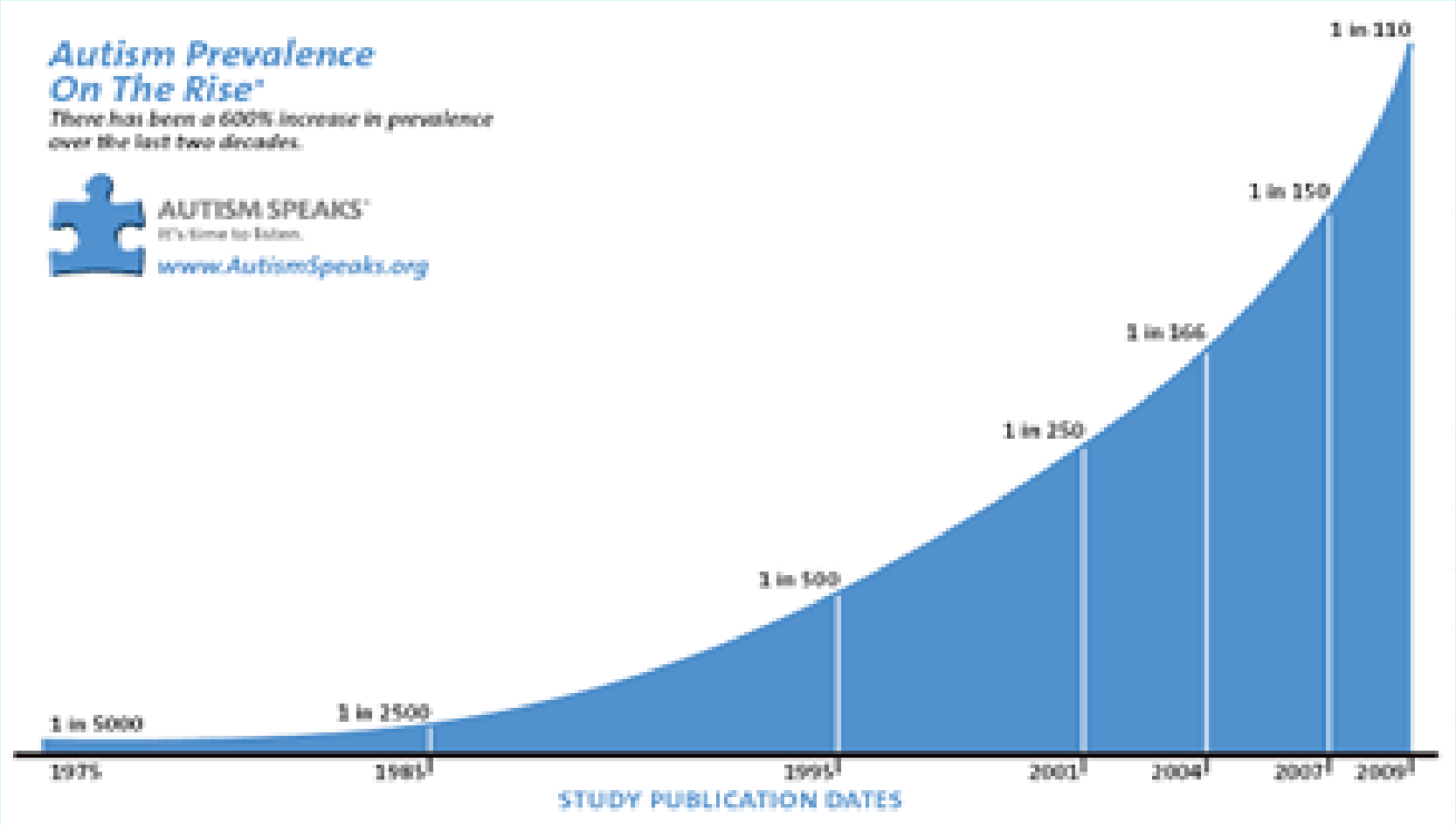
Autism Speaks: 2009 Top Research



Increase in Population-Based studies?

- Consistent in studies in US, Europe, Japan, etc.
  - Note: low prevalence condition
  - Nearly all studies used different case definition and/or methods of finding

DSM III (1980): Infantile Autism

A. Onset before 30 months of age
B. Pervasive lack of responsiveness to other people
C. Gross deficits in language development
D. If speech is present, peculiar speech patterns such as immediate and delayed echolalia, metaphorical language, pronominal reversal.
E. Bizarre responses to various aspects of the environment, e.g., resistance to change, peculiar interest in or attachments to animate or inanimate objects

DSM III-R (1987): Autistic Disorder

- “spectrum disorder”
- diagnostic triad
  - “qualitative impairment in reciprocal social interaction”
  - “impairment in communication and imaginative activity”
  - “markedly restricted repertoire of activities and interests”

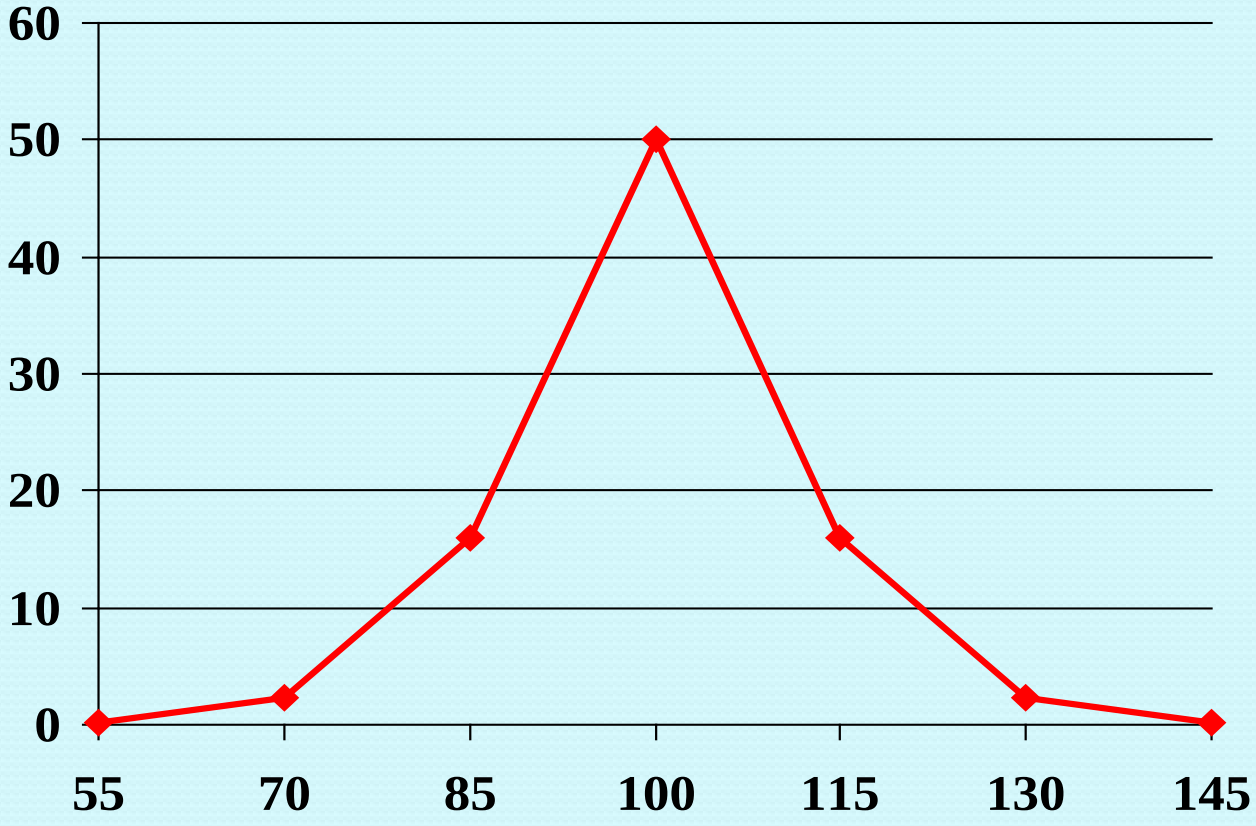
DSM III-R (1987): Autistic Disorder

- "No mode of communication, such as: communicative babbling, facial expression, gesture, mime, or spoken language"
- "No or abnormal seeking of comfort at times of distress"
- "Absence of imaginative activity, such as play-acting of adult roles, fantasy character or animals; lack of interest in stories about imaginary events"

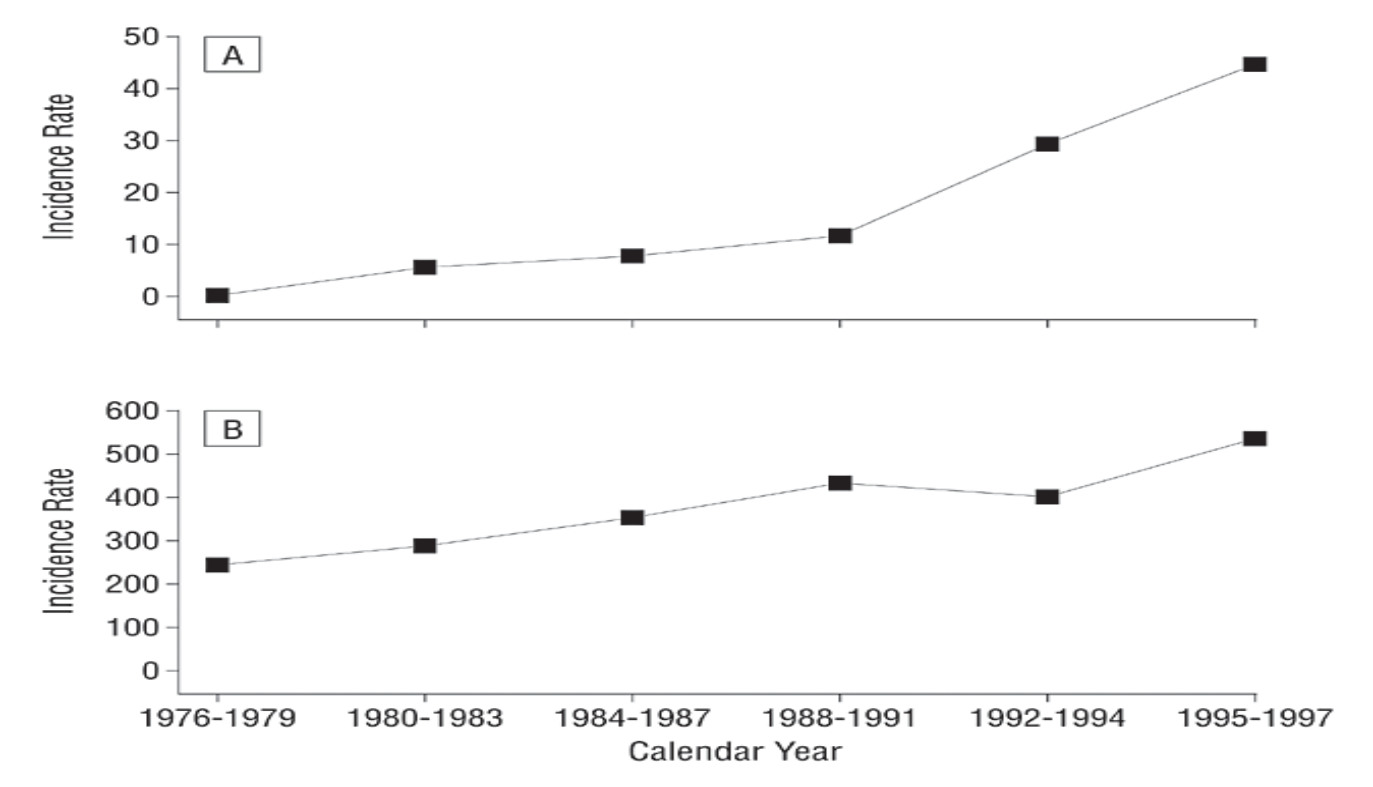
DSM-IV (1994) Autistic Disorder

- "In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation"
- "Failure to develop peer relationships appropriate to developmental level"
- "Lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level"

DSM Since 1980: Changing "Cut-off" for Defining Autism



Overall age- and sex-adjusted incidence per 100 000 children by period of research-identified autism (A) and all other clinical diagnoses of developmental, neurologic, and psychiatric disorders (B) among residents of Olmsted County, Minnesota, between 1976 and 1997



Barbaresi, W. J. et al. Arch Pediatr Adolesc Med 2005;159:37-44.

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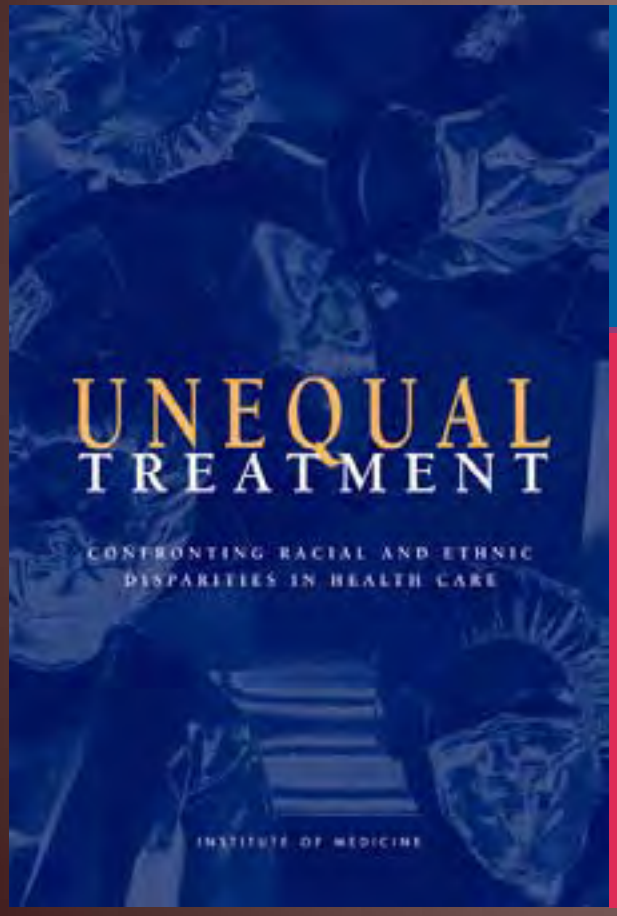
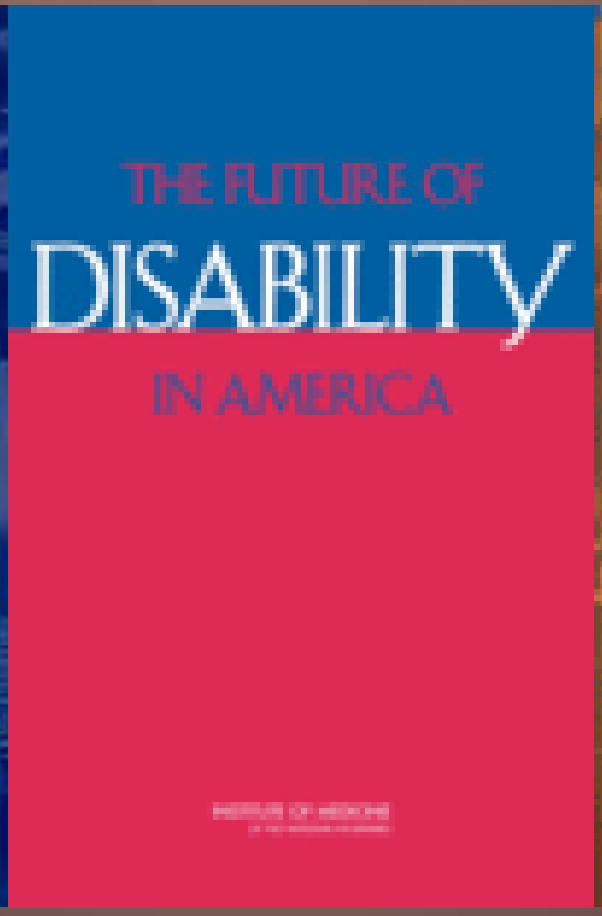
Effective Partnering with the Autistic Self-Advocacy Community to Advance Intervention and Services Research

Christina Nicolaidis, MD, MPH
Associate Professor, Oregon Health & Science University
Co-Director, Academic Autistic Spectrum Partnership In Research and Education (AASPIRE)

But We Don't


UNEQUAL
TREATMENT
CONFRONTING RACIAL AND ETHNIC
DISPARITIES IN HEALTH CARE
INSTITUTE OF MEDICINE


THE FUTURE OF
DISABILITY
IN AMERICA

RESPONSIBLE
RESEARCH
A Systems
Approach to
Protecting
Research
Participants

Minority Communities' Frustrations

- Misalignment of research priorities
- Lack of inclusion in the research process
- Inadequate informed consent
- Threats to study validity
- Dehumanizing , stigmatizing language
- Use of findings to advance agendas that oppose community values

→ Low participation rates, poor science, questionable impact, continued disparities

Autistic Self Advocates' Frustrations

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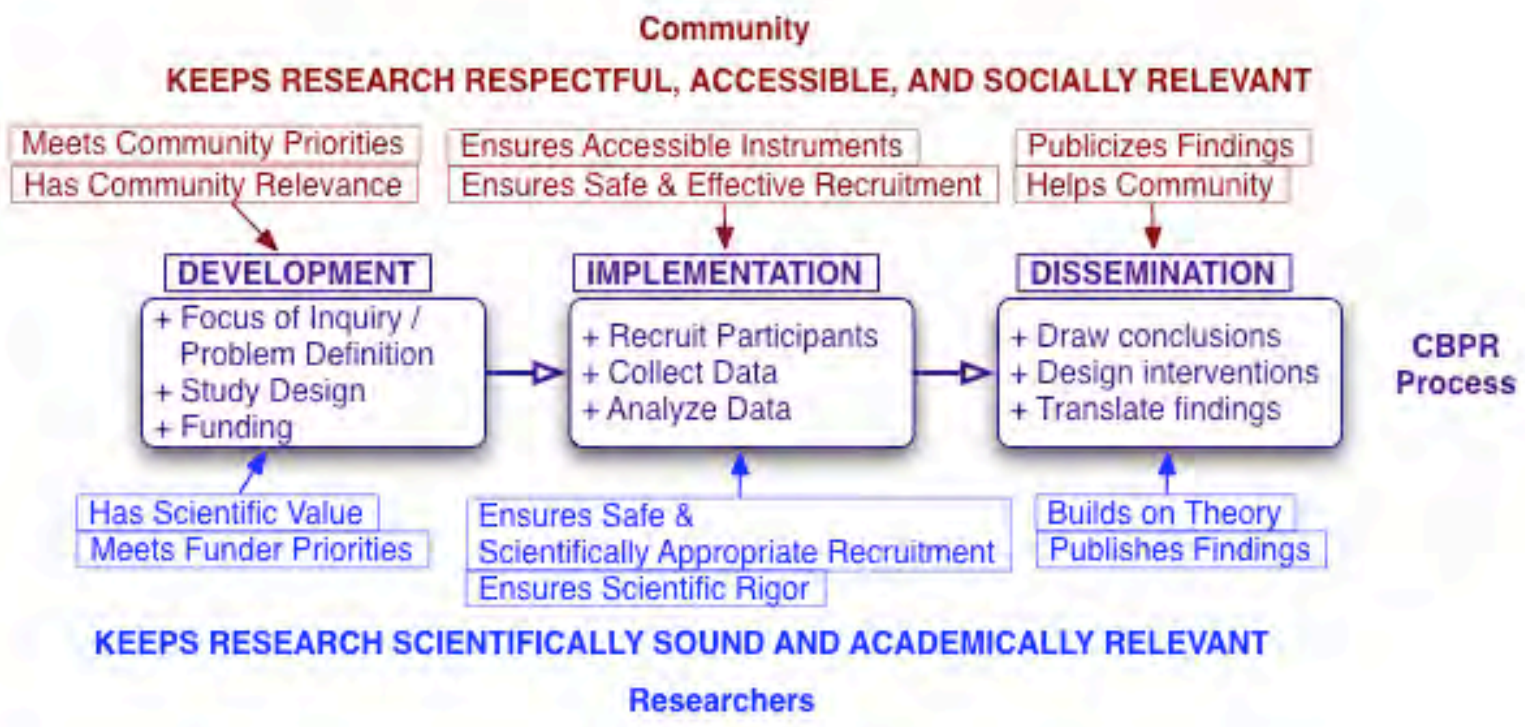
DITTO

Community-Based Participatory Research

- Response to problems of traditional research
- An APPROACH, not a method
- One of many forms of community-engaged or participatory research
- Equal partnership between academics and community members
- Can be used with quantitative or qualitative methods
- Not only for intervention or services research

Community-Based Participatory Research



Nicolaidis et al, PCHP, 2011

Unique Challenges in Autism

- Who is “the community”?
  - Self-advocates, family members, professionals?
- What if the community is geographically dispersed?
- How does one implement CBPR with partners whose disability is defined by atypical social interactions and communication?

Who is the Community?

- Autistic self-advocacy community
  - Own culture, support systems, leaders, shared values, social spaces, events, organizations, terminology…
- Community of family members and professionals
- Similar pattern as LGBT and Deaf communities

Who is the Community?

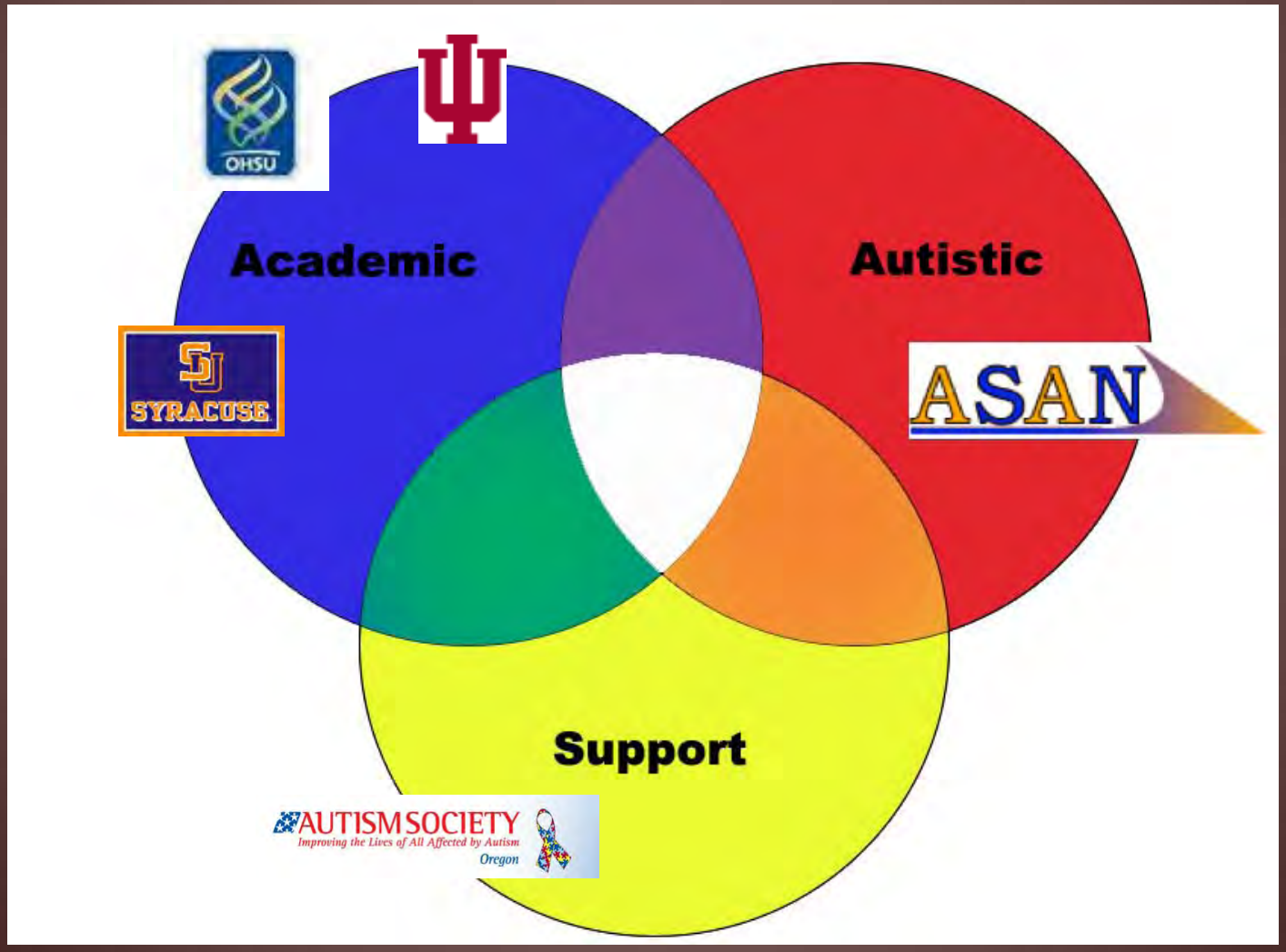
- Values and priorities can at times be in opposition
  - Search for a “cure”, blaming vaccines, emphasis on “devastating” effect on families, potentially dehumanizing or harmful messages
- Desire for research to improve quality of life
  - improving healthcare, decreasing violence and bullying, increasing access to alternative communication, disproving false stereotypes, increasing employment opportunities

AASPIRE

Mission:

- To encourage the inclusion of people on the autistic spectrum in matters which directly affect them.
- To include adults on the autistic spectrum as equal partners in research about autism.
- To answer research questions which are considered relevant by the autistic community.
- To use research findings to effect positive change for people on the spectrum.

AASPIRE's Overlapping Communities



AASPIRE Projects

- Healthcare disparities study
- Internet, community, and wellbeing study
- Tools to improve primary care services
- Collaborations with other groups:
  - Registration system for online studies committed to inclusion, respect, accessibility, and community relevance (the Gateway Project)
  - Partnering to Address Violence in People with Developmental Disabilities

Ensuring Equal Partnership

- Academic and autistic Co-PIs
- Very wide range of skills and needs
- Preference for text-based communication
- “Translation” of science jargon / concepts
- Great attention to process
  - Strict agendas, structured email formats, process for reaching consensus, clear expectations
- Need for great flexibility
  - Multiple formats for providing input
  - Individualized supports and accommodations

Effects on Research Materials

- Informed consent materials
- Prefaces to add specificity
- Hotlinks for confusing or ambiguous terms
- Wording changes to increase clarity
- Consistent pronouns (1st or 2nd person)
- Graphics for response options
- Comment boxes
- ASL, read-out-loud options
- Cognitive interviewing, internal consistency

Conclusions

- It is possible and desirable to use a CBPR approach with autistic self-advocates
  - True community, capable of working as equal partners
- True inclusion requires significant attention to infrastructure and processes to equalize power and avoid tokenism
- Participatory approaches have the potential to address ethical challenges, enhance science, and improve outcomes

Future Challenges

- Inclusion of autistic self-advocates with minimal spoken and written communication
- Greater use of participatory approaches over entire range of autism research
- Quality health services for adults on the spectrum
- Adequate funding / alignment of research agendas

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For More Information

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GEORGE WARREN BROWN SCHOOL of Social Work

Dilemmas of Omission in Services Research about Adults with an AS

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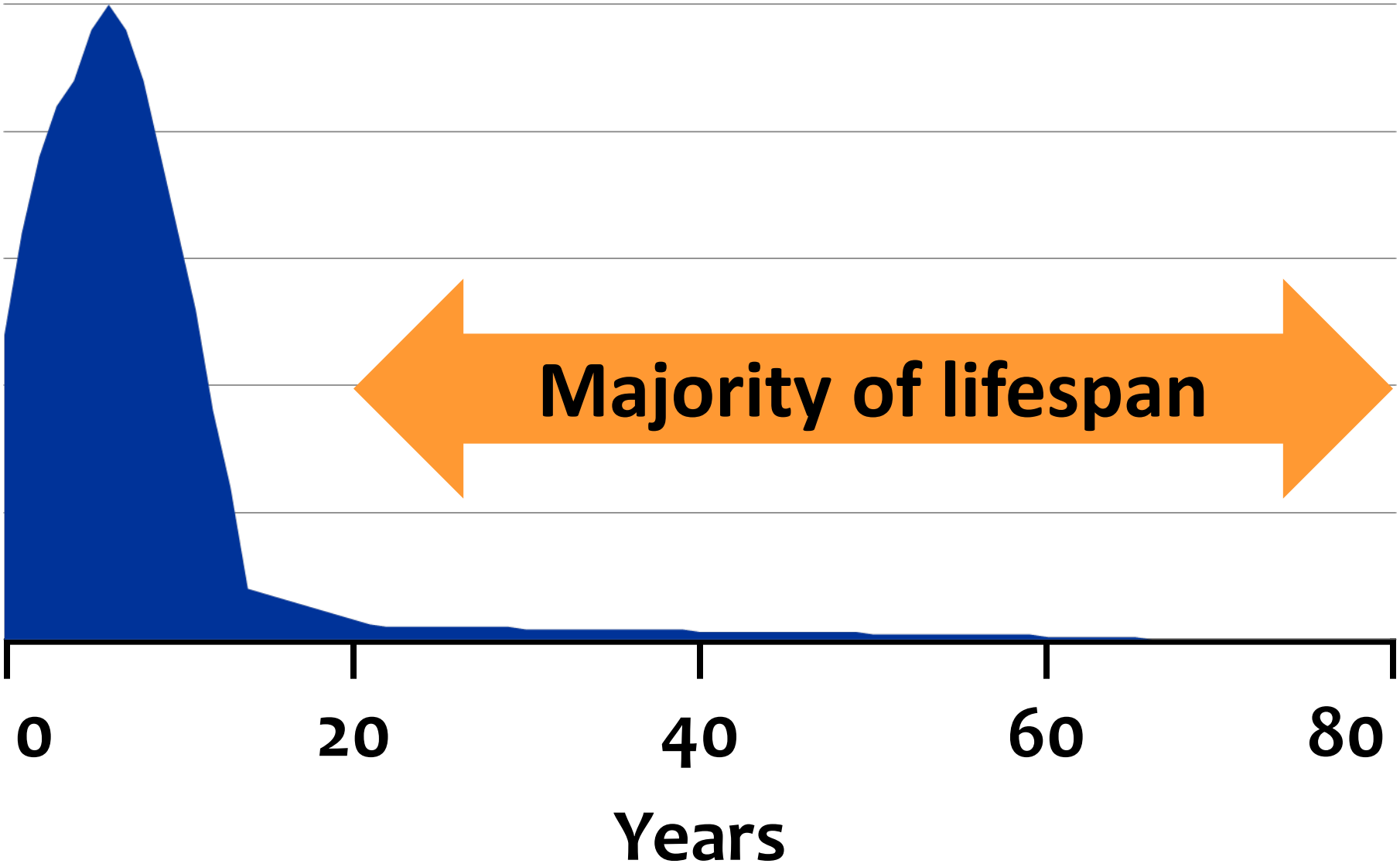
Washington University in St. Louis

Ethical and Social Implications of…

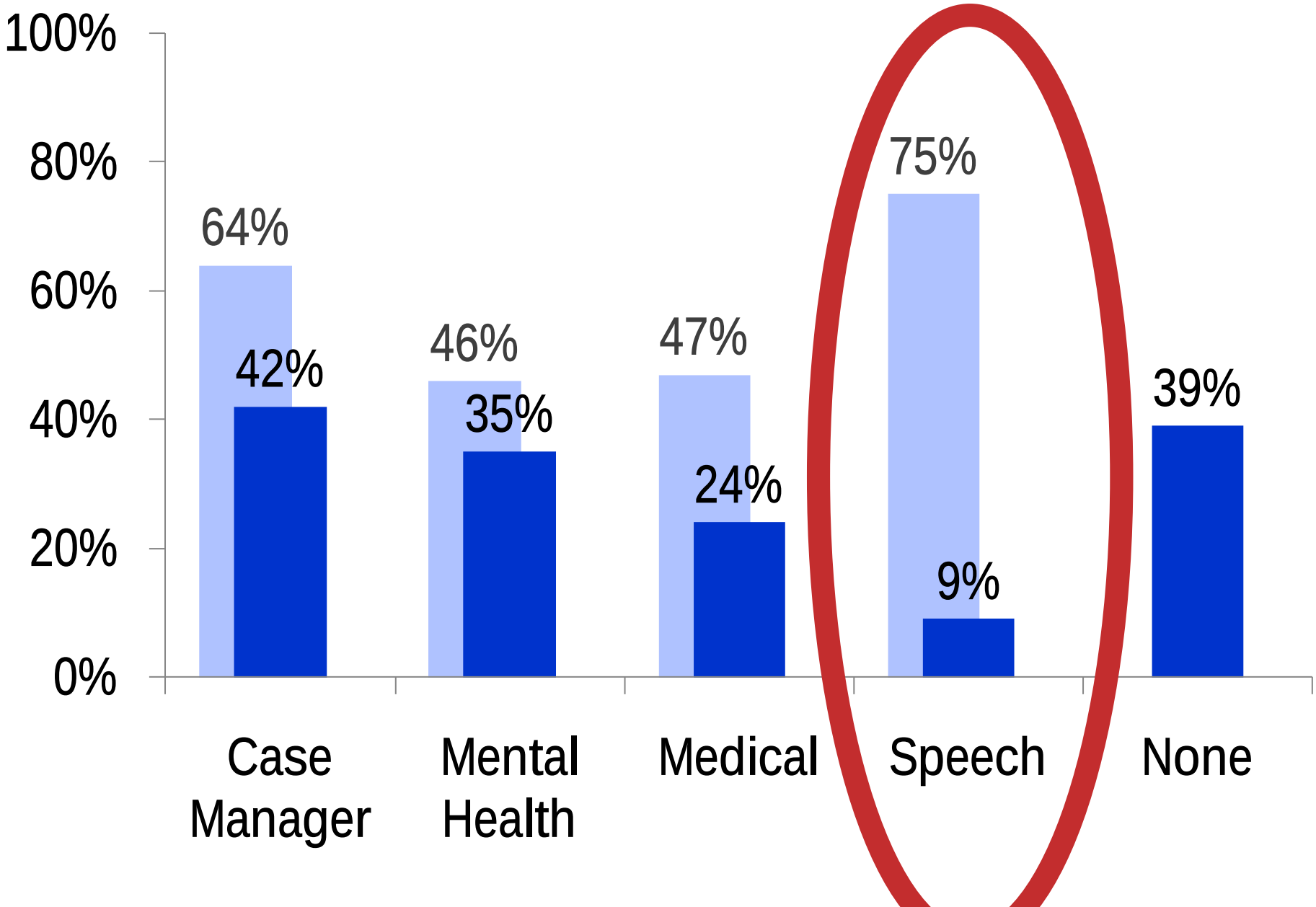
- **Understudied stage of life**
- **Understudied populations**
- **Underreporting of study details**
- **Under-explored questions**

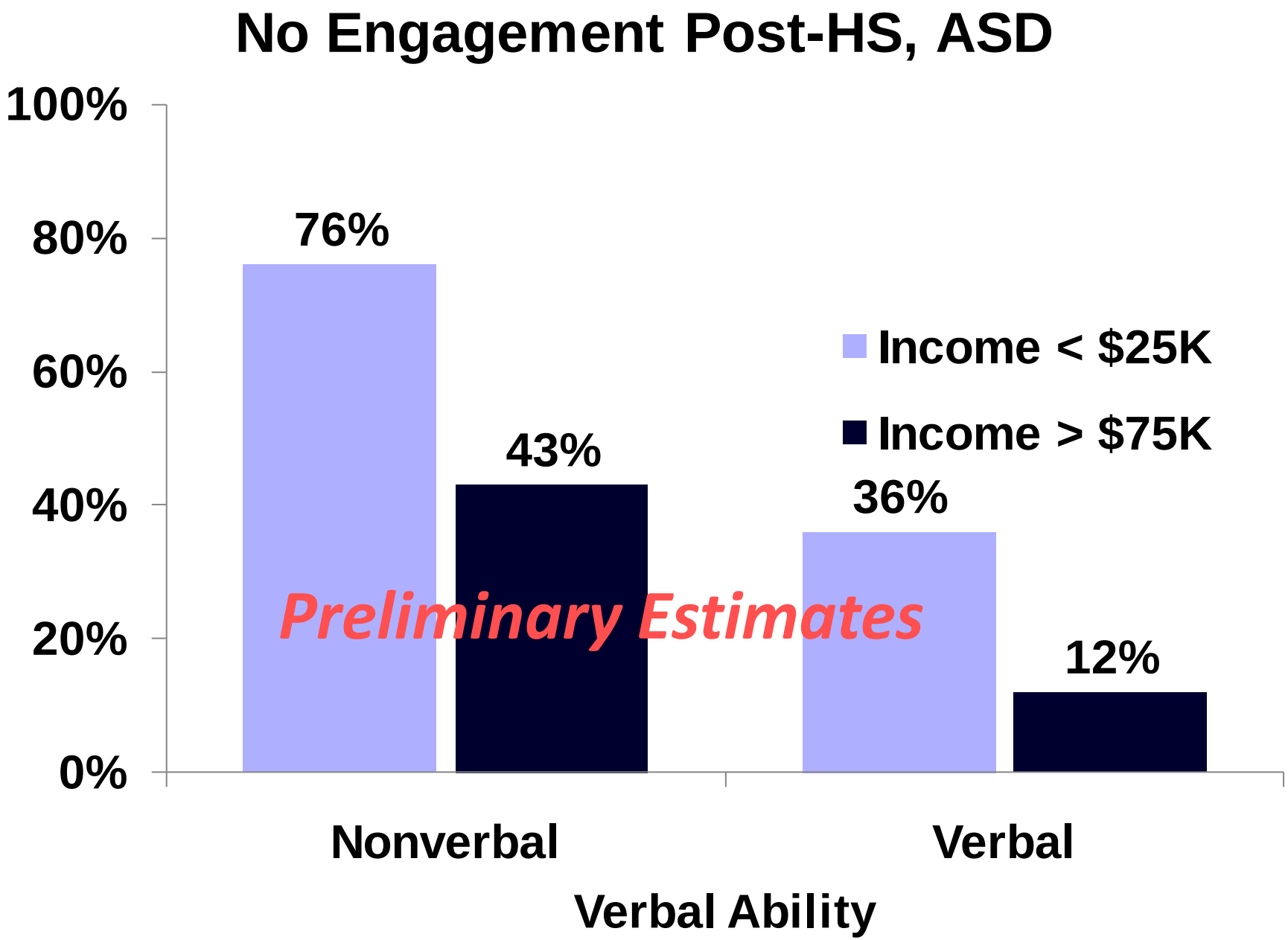
Understudied stage of life



Post-High School "Services Cliff"

In- vs. Post-HS Service Receipt




No Engagement Post-HS, ASD
100%
80%
60%
40%
20%
0%
76%
43%
36%
12%
Income < $25K
Income > $75K
Preliminary Estimates
Nonverbal
Verbal
Verbal Ability

Understudied Populations

- 2-way link between poverty and intellectual disability (ID)
  - Contributes to ID risk
  - ID as risk factor for poverty
- Race emerging as correlate of reduced service access in our research with national data

Underreporting of Study Details

- **Forthcoming lit. review**
  - **23 studies from 2000-2010**
  - **Mean N: 14**
  - **Mostly convenience samples**
  - **Inconsistent reporting of**
    - Sampling, recruitment, criteria
    - ASD heterogeneity
    - Income, race, ethnicity

Under-explored Questions

- **Efficiency**
  - **Global economic recession and declining resources VS.**
  - **Growing population in need of help**

- **Community and Social Context**
  - **WHO ICF & developmental models emphasize person X environment**
  - **Not purely an individual level problem to fix**

Research Opportunities

- Reframe adulthood as intrinsically worth studying
- Raise the bar re. external validity
- Adhere to editorial standards
- Study:
  - Efficiency
  - Community factors
  - Measurement based care

Core Discussion Questions

1. What ELSI issues are common to research in autism and other complex disorders?

2. Are there lessons learned from ELSI research in other neurodevelopmental disorders or other complex genetic conditions that can be applied to autism?

3. What ELSI issues are unique to autism research?

4. What is needed to heighten awareness of ELSI issues, and approaches to address those issues, in the autism research community?

5. What ELSI issues in autism require targeted research?

Acknowledgments:

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