Understanding Ethical Implications of Genetic Testing and Research

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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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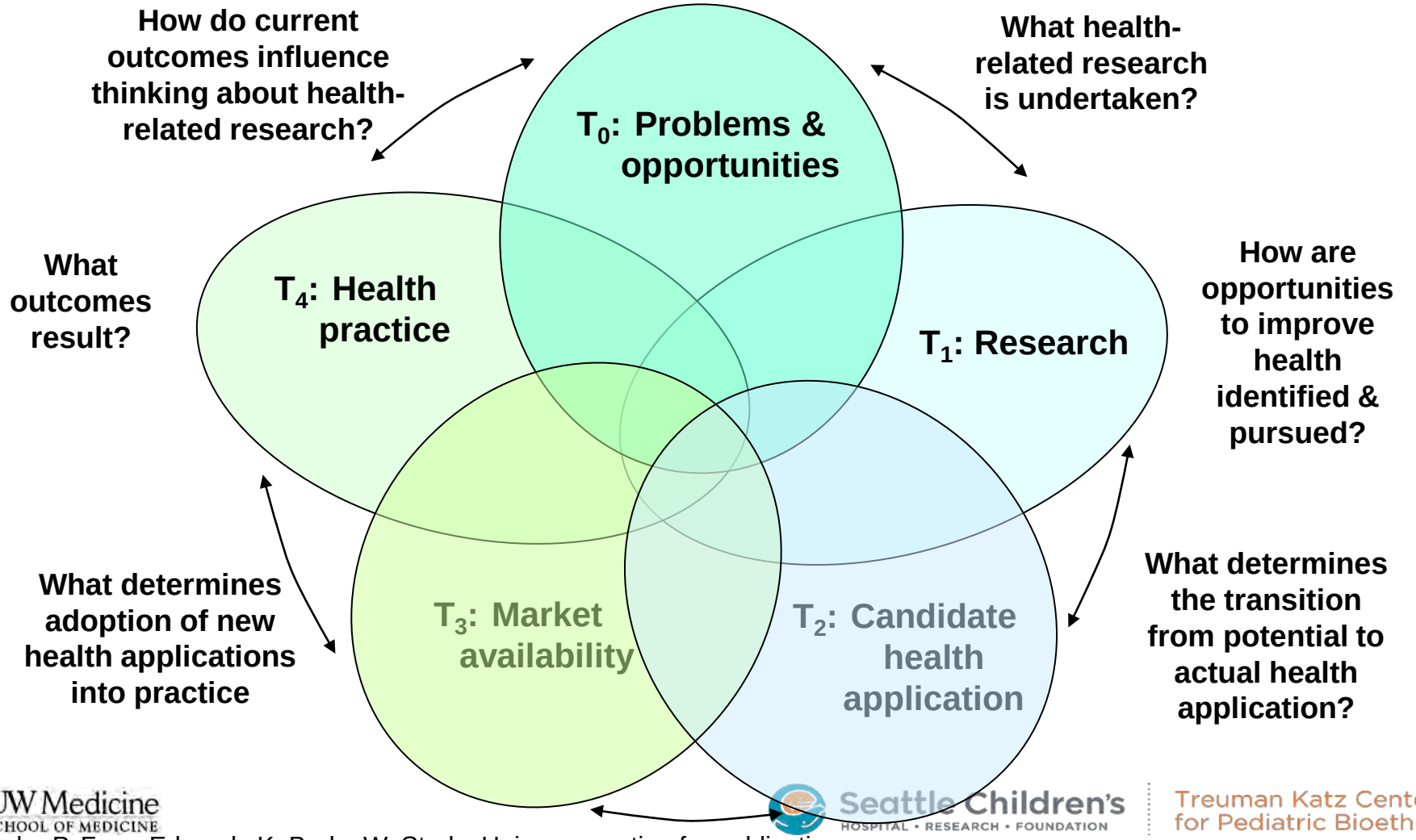
Translational Pathway



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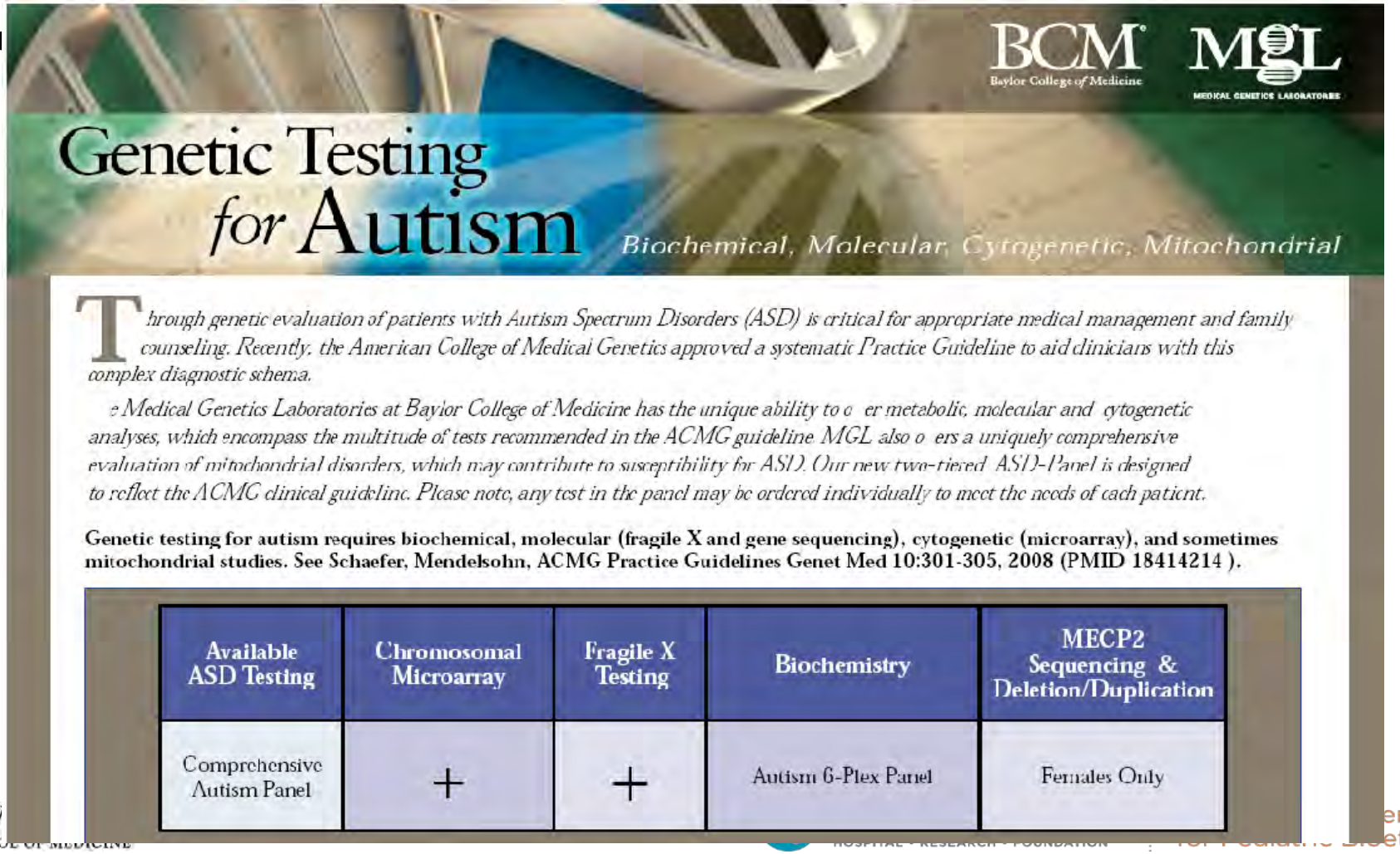
Kuszler P, Fryer-Edwards K, Burke W, Starks H. in preparation for publication.

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

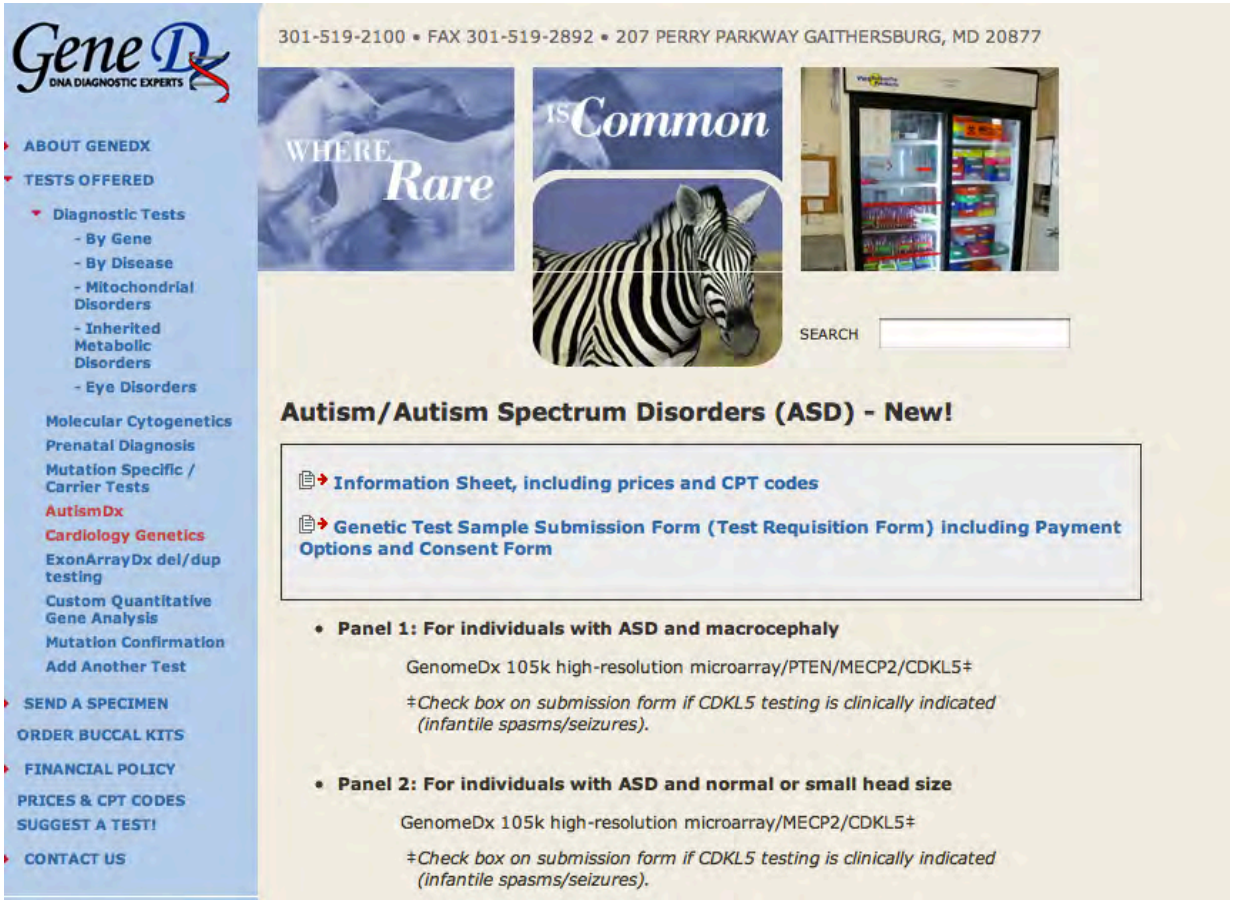
Through genetic evaluation of patients with Autism Spectrum Disorders (ASD) is critical for appropriate medical management and family counseling. Recently, the American College of Medical Genetics approved a systematic Practice Guideline to aid clinicians with this complex diagnostic schema.

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



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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[a]*Autism Consortium, Boston, Massachusetts;* [b]*Department of*

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?

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?

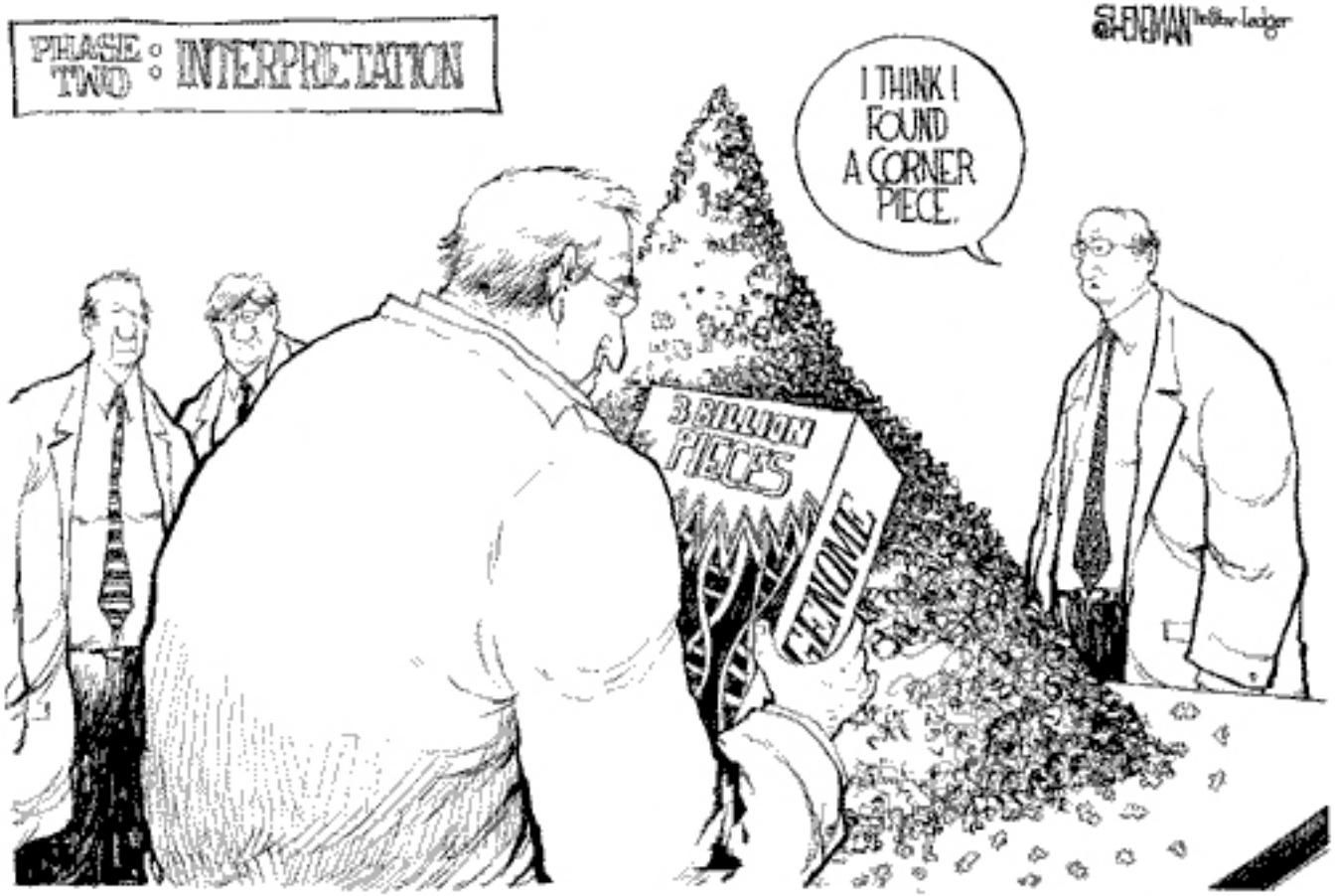
The Promise and Peril of Personalized Genomics

- 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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