NATIONAL HUMAN GENOME RESEARCH INSTITUTE Division of Intramural Research

Genomics in Maternal Child Health

Barbara Bowles Biesecker, M.S., Ph.D., CGC
Social and Behavioral Research Branch, NHGRI, NIH

Societal Values in Predicting Genetic Risk

Market Based Economy

Lack of Health Care System

Technologies

Individual Freedom

Pre-conceptual Counseling

Interpretation of family history

Recurrent loss of male fetuses

Assessment of maternal health risks

Woman with dwarfing syndrome

Ethnic based carrier screening

Ashkenazi Jewish

Genetic Counseling

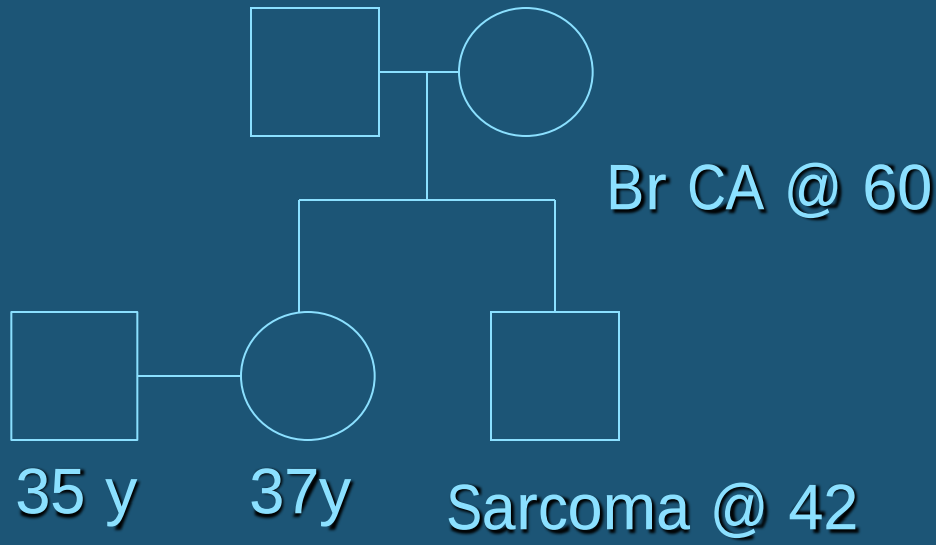
Genetic counseling is the process… that integrates:

- *Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence*
- *Education about inheritance, testing, management, prevention, resources and research*
- *Counseling to promote informed choices and adaptation to the risk or condition*

Resta, et al, *Am J Med Genet* 2006

Clinical Case

Ashkenazi Jewish



Age related risk of aneuploidy
Ethnic carrier screening
Risk of rare cancer syndrome

Ethnicity Based Carrier Screening

Ethnic Group	Disease	Carrier Frequency
Ashkenazi Jewish	Canavan Disease	1 in 40 (2.5%)
	Tay Sachs Disease	1 in 30 (3%)
	Cystic Fibrosis	1 in 25-29 (4%)
	Familial Dysautonomia	1 in 30 32 (3%)
African American / West Africa	Sickle Cell Anemia	1 in 6 – 12 (8 - 16%)
	Other Hemoglobinopathies	1 in 30 – 75 (up to 3%)
European Caucasians	Cystic Fibrosis	1 in 25 - 29 (4%)
Mediterranean / South Asian	Beta Thalassemia	1 in 20 - 30 (3 - 5%)
SE Asian (Laos, Vietnam, Thailand)	Alpha Thalassemia	1 in 20 (5%)
	Beta Thalassemia	1 in 30 (3%)

My Family Health Portrait

A tool from the Surgeon General

Using *My Family Health Portrait* you can:
Enter your family health history.
Print your family health history to share with family or your health care worker.
Save your family health history so you can update it over time.

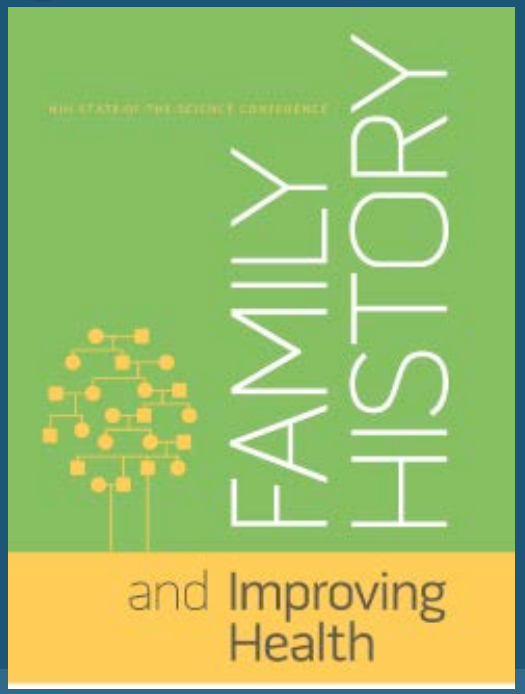
Talking with your health care worker about your family health history can help you stay healthy!

U.S. Department of Health & Human Services • National Institutes of Health

NIH Consensus Development Program

NIH State-of-the-Science Conference: Family History and Improving Health

August 24-26, 2009
Bethesda, Maryland



Prenatal Screening/Testing

To identify those at highest risk

To confirm diagnoses among those at highest risk

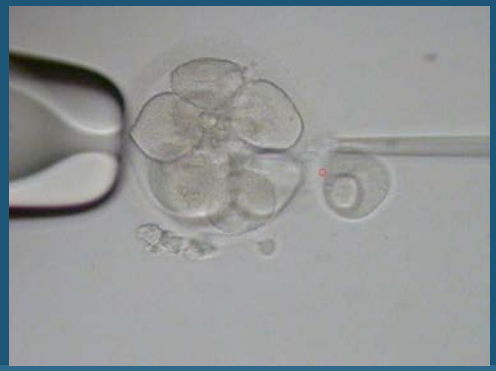
To ensure informed choice and freedom in decision-making about continuing or terminating an affected fetus

Contemporary Tests

Screening:

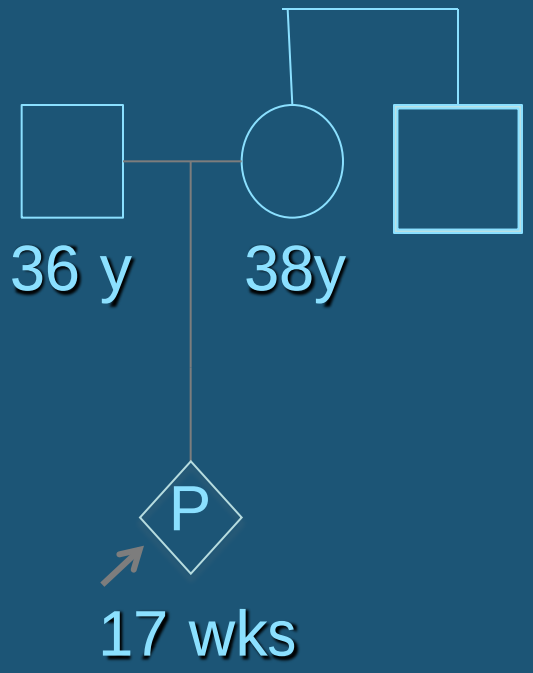
- *Family history*
- *Ultrasound*
- *First trimester screen*
- *Second trimester-Tri or quad screen*

Diagnostic:



- *Amniocentesis*
- *Chorionic villus sampling*
- *Pre-implantation genetic diagnosis*

Clinical Case



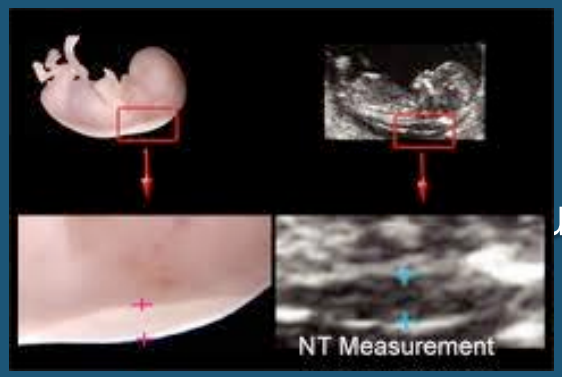
Risk Factor	Est. risk for Down Syndrome
Age related risk	1:189
Quad screen results	Increased to 1:52
Nuchal Fold 6.2 mm	1:50 - 1:10

1st Trimester Screening: Nuchal Translucency ++

Nuchal translucency is combined with hCG and PAPP-A to estimate risks for Trisomies 21, 18 and 13

About 85 out of every 100 affected fetuses will be identified

About 5% of normal pregnancies will receive a positive result



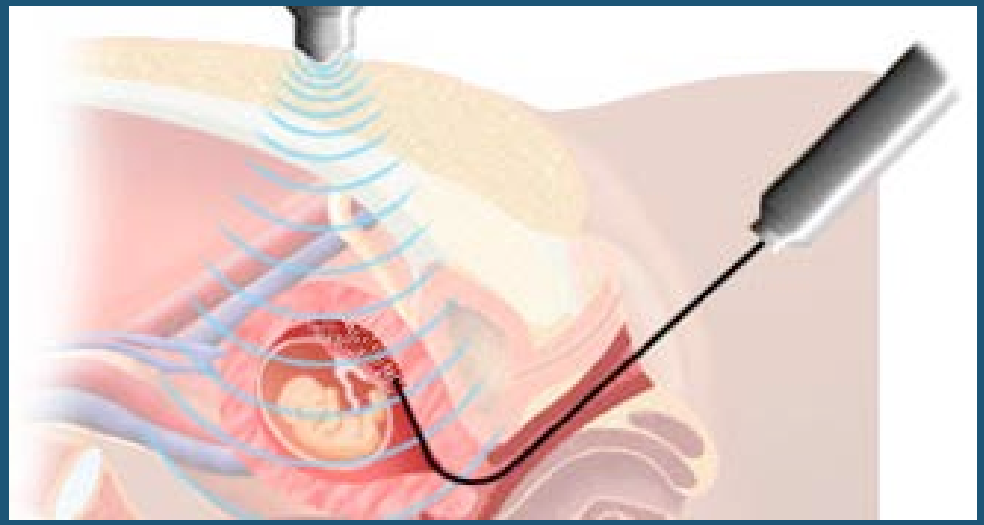
A positive test means that there is a 1/100 to 1/300 chance of the
us being affected

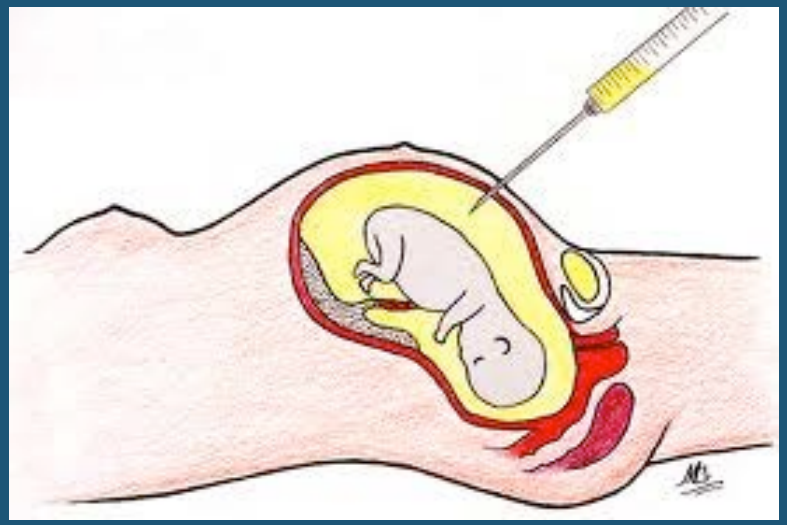
2nd Trimester Screening: Triple or Quad Screen

Condition	MSAFP	uE3	hCG
Neural Tube Defect	Increased	Normal	Normal
Trisomy 21	Low	Low	Increased
Trisomy 18	Low	Low	Low
Multiple Gestation	Increased	Normal	Increased
Fetal Demise	Increased	Low	Low

Invasive Prenatal Testing

Karyotype or molecular testing





Pre-implantation Genetic Diagnosis

Karyotype or molecular testing

Option for parents known to be at significant risk for passing on a chromosome or single gene disorder

Involves genetic interrogation of the embryo

Down Syndrome-Trisomy 21







Latest Prenatal Screening/Testing Approaches

Universal carrier screening

- Costs less than ethnic based screening

Prenatal microarray analysis

- Identifies small deletions/duplications

Non-invasive prenatal testing

- Identification of high or low risk of Trisomy 21

Prenatal whole genome sequencing

Universal Carrier Screening

Not specific to ethnicities, family history

Results returned in 2-3 weeks

Requires a physician or genetic counselor to order test

Out of pocket cost: $349

Conditions on Universal Screen

ABCC8-Related Hyperinsulinism
Achromatopsia
Alkaptonuria
Alpha-1 Antitrypsin Deficiency
Alpha-Mannosidosis
Andermann Syndrome
ARSACS
Aspartylglycosaminuria
Ataxia With Vitamin E Deficiency
Ataxia-Telangiectasia
Autosomal Recessive Polycystic Kidney Disease
Bardet-Biedl Syndrome, BBS1-Related
Bardet-Biedl Syndrome, BBS10-Related
Beta Thalassemia ACOG
Biotinidase Deficiency
Bloom Syndrome ACMG
Canavan Disease ACMG ACOG
Carnitine Palmitoyltransferase IA Deficiency
Carnitine Palmitoyltransferase II Deficiency
Cartilage-Hair Hypoplasia
Choroideremia
Citrullinemia Type 1
CLN3-Related Neuronal Ceroid Lipofuscinosis
CLN5-Related Neuronal Ceroid Lipofuscinosis
Cohen Syndrome
Congenital Disorder of Glycosylation Type Ia
Congenital Disorder of Glycosylation Type Ib
Congenital Finnish Nephrosis
Costeff Optic Atrophy Syndrome
Cystic Fibrosis ACMG ACOG
Cystinosis
D-Bifunctional Protein Deficiency
Factor XI Deficiency
Familial Dysautonomia ACMG ACOG
Familial Mediterranean Fever
Fanconi Anemia Type C ACMG
Galactosemia
Gaucher Disease ACMG
GJB2-Related DFNB 1 Nonsyndromic Hearing Loss & Deafness
Glutaric Acidemia Type 1
Glycogen Storage Disease Type Ia
Glycogen Storage Disease Type Ib
Glycogen Storage Disease Type III
Glycogen Storage Disease Type V
GRACILE Syndrome
Hereditary Fructose Intolerance
Hereditary Thymine-Uraciluria
Herlitz Junctional Epidermolysis Bullosa, LAMA3-Related
Herlitz Junctional Epidermolysis Bullosa, LAMB3-Related
Herlitz Junctional Epidermolysis Bullosa, LAMC2-Related
Hexosaminidase A Deficiency
Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency
Hurler Syndrome
Hypophosphatasia, Autosomal Recessive
Inclusion Body Myopathy 2
Isovaleric Acidemia
Joubert Syndrome 2
Krabbe Disease
Limb-Girdle Muscular Dystrophy Type 2D
Limb-Girdle Muscular Dystrophy Type 2E
Lipoamide Dehydrogenase Deficiency
Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency
Maple Syrup Urine Disease Type 1B
Medium Chain Acyl-CoA Dehydrogenase Deficiency
Megalencephalic Leukoencephalopathy With Subcortical Cysts
Metachromatic Leukodystrophy
Mucolipidosis IV ACMG
Muscle-Eye-Brain Disease
NEB-Related Nemaline Myopathy
Niemann-Pick Disease Type C
Niemann-Pick Disease, SMPD1-Associated ACMG
Nijmegen Breakage Syndrome
Northern Epilepsy
Pendred Syndrome
PEX1-Related Zellweger Syndrome Spectrum
Phenylalanine Hydroxylase Deficiency
Polyglandular Autoimmune Syndrome Type 1
Pompe Disease
PPT1-Related Neuronal Ceroid Lipofuscinosis
Primary Carnitine Deficiency
Primary Hyperoxaluria Type 1
Primary Hyperoxaluria Type 2
PROP1-Related Combined Pituitary Hormone Deficiency
Pseudocholinesterase Deficiency
Pycnodysostosis
Rhizomelic Chondrodysplasia Punctata Type 1
Salla Disease
Segawa Syndrome
Short Chain Acyl-CoA Dehydrogenase Deficiency
Sickle Cell Disease ACOG
Sjogren-Larsson Syndrome
Smith-Lemli-Opitz Syndrome
Spinal Muscular Atrophy ACMG
Steroid-Resistant Nephrotic Syndrome
Sulfate Transporter-Related Osteochondrodysplasia
Tay-Sachs Disease ACMG ACOG
TPP1-Related Neuronal Ceroid Lipofuscinosis
Tyrosinemia Type I
Usher Syndrome Type 1F
Usher Syndrome Type 3
Very Long Chain Acyl-CoA Dehydrogenase Deficiency
Wilson Disease
X-Linked Juvenile Retinoschisis

Microarray Analysis

1.5 x 10^3 cells

RNA prep

Total RNA

(10–50 ng)

oligo(dT)

cDNA

cDNA microarrays

cDNA libraries

TTGGGACATTCCGTAATCCGATG

CCGTGCTTATGCTAACCTTGAAAT

TTGGGACATT
CCGTAATCCG
ATGCGTAATAT
GGCGTAAGAA
AATGCCGATTT

EST sequencing

High-throughput gene expression analysis

Prenatal Microarray Testing

Detects copy number variants that can detect micro-deletions and micro-duplications

2% are CNVs of unknown significance

Often limited cases in the literature to predict variable expressivity and penetrance

Can be a significant degree of uncertainty to guide decisions about whether to continue a pregnancy

Validation Studies

NIH funded validation study done on >4000 samples from routine amniocentesis or CVS

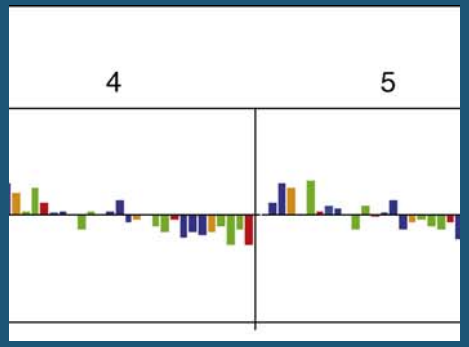
CMA detected additional genetic abnormalities in about one out of every 70 fetal samples that had a normal karyotype

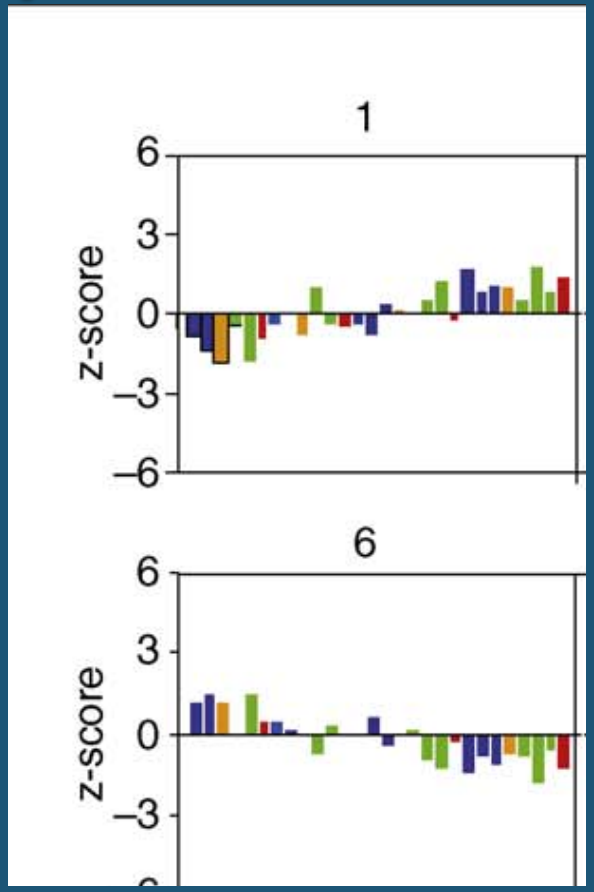
When a birth defect was imaged by ultrasound, CMA found additional important genetic information in six percent of cases.

Wapner et al in press

Non-Invasive Prenatal Diagnosis for Trisomy 21

Pregnancies with Trisomy 21 have a higher percentage of chromosome 21 fragments (*> 3 SD*) than that of euploid pregnancies (*within ± 3 SD*)
z-score > ± 3 = 99% chance





Lo *et al. Lancet,* 1998
Chiu *et al. Trends in Genetics,* 2009

Non-Invasive Prenatal Diagnosis

1696 Singleton Pregnancies Undergoing Invasive Testing

Gestational Age < 15 weeks
105 Down Syndrome Cases
735 Euploid {7:1 match}

Gestational Age ≥ 15weeks
107 Down Syndrome Cases
749 Euploid {7:1 match}

NIPD	Proportion	Sample Estimate (%)	95% CI
DS Detection Rate	209/212	98.6	96.0-99.0
False Positive Rate	3/1471	0.2	0.1-0.6
Failure Rate	13/1696	0.8	---

Palomaki et al. *Genet. Med.*, 2011

Clinical Implementation of NIPD

Only offered to women at high risk

Considered an advanced screening test – not diagnostic

Turnaround time

- 8-10 days

How are results are reported?

- Test (+) or Test (-)
  - Modified risk not reported in results
- Those who test (+) are recommended to follow-up with invasive testing prior to termination of pregnancy

Cost

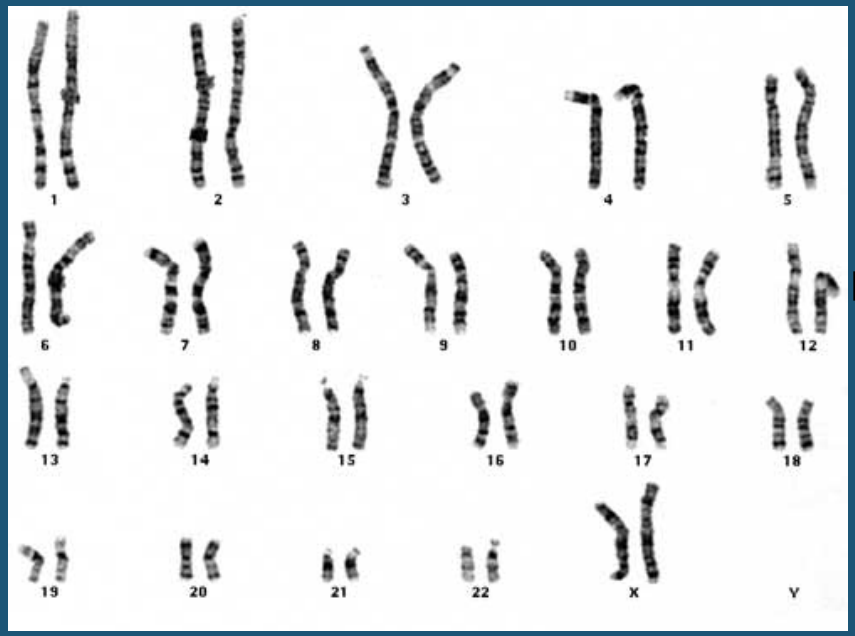
- Insured = $235 Uninsured = $1,900

Non-Invasive Prenatal Testing in Comparison

Screening or Diagnostic Test	Detection Rate for DS	False Positive Rate	Routine Test Window (wks gest)	Procedure-related Risk to Pregnancy
1st Trimester Screen (Serum + Ultrasound Measurements)	95%	5%	9-13	None
2nd Trimester Quad Screen	70-80%	5%	14-22	None
Chorionic Villus Sampling	> 99%	---	10-13	1:175
Amniocentesis	> 99%	---	16-20	1:300
NIPD	98.6%	0.2%	7-20	None

Palomaki et al. *Genet Med* 2011

From Chromosomes to Sequencing



http://blog.goldenhelix.com/?p=822

Bio-ethical Considerations

Do we devalue the lives of those affected with genetic conditions by offering testing?

Is the unstated intention to promote the termination of affected fetuses?

Where do testing options leave those who choose not to use them?

How do those women with fewer resources avail themselves of the options?

Newborn Screening

- PKU screening
- Expanded into a panel of at least 29 conditions
- Discussion of whole genome sequencing

Universal Newborn Screening

Groups of disorders	Incidence
Amino acid disorders (5)	1:20,000-1:500,000
Fatty acid oxidation disorders (5)	1:15,000-1:100,000
Hemoglobinopathies (3)	1:5,000-1:50,000
Organic acid disorders (9)	1:75,000-1:300,000
Endocrine disorders (2)	1:5,000-1:25,000
Other (4)	1:5,000-1:75,000

Bio-ethical Cautions

HASTINGS CENTER REPORT July/August 2012

Prenatal Whole Genome Sequencing: *Just Because We Can, Should We?*

by GREER DONLEY, SARA CHANDROS HULL, and BENJAMIN E. BERKMAN

JAMA February 1, 2012

The Ethical Hazards and Programmatic Challenges of Genomic Newborn Screening

by AARON GOLDENBERG, and RICHARD SHARP

Policy Considerations

Do we sufficiently inform parents about NBS?

Should we be testing for rare conditions for which there is no treatment?

Should there be a uniform criteria upheld for deciding whether to add new tests?

If whole genome sequencing is introduced how should results for adult onset conditions be handled?

Social Science Investigations of Prenatal Testing

Informed choice in making health related decisions

Predictors of decisions to undergo testing

Interventions to enhance informed choice and satisfaction

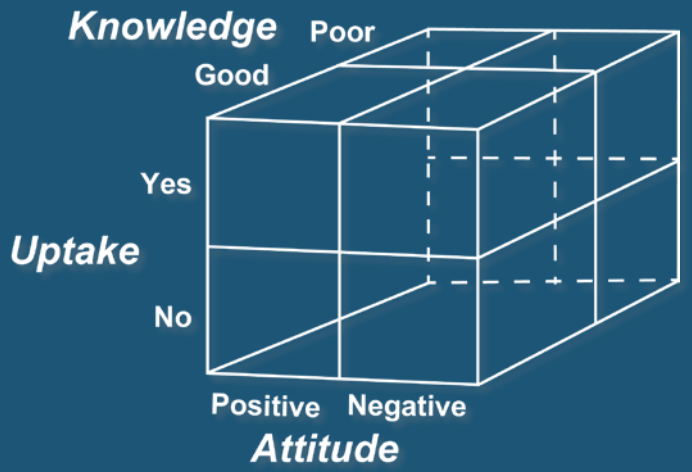
Assessment of Genetic Counseling Practice

Central thesis-informed choice should be a primary metric by which genetic counseling is evaluated

Informed choice-one made with sufficient understanding of relevant information, consistent with one's attitudes toward the object of the decision

Uninformed choices, as seen in prenatal screening,
are associated with decisional conflict and regret

Dormandy et al, *Psych Health* 2006



Michie et al, *Pt Educ Couns* 2002

Ambivalence in Prenatal Testing Decisions

When making a health-related decision, attitudes are a strong predictor of the outcome

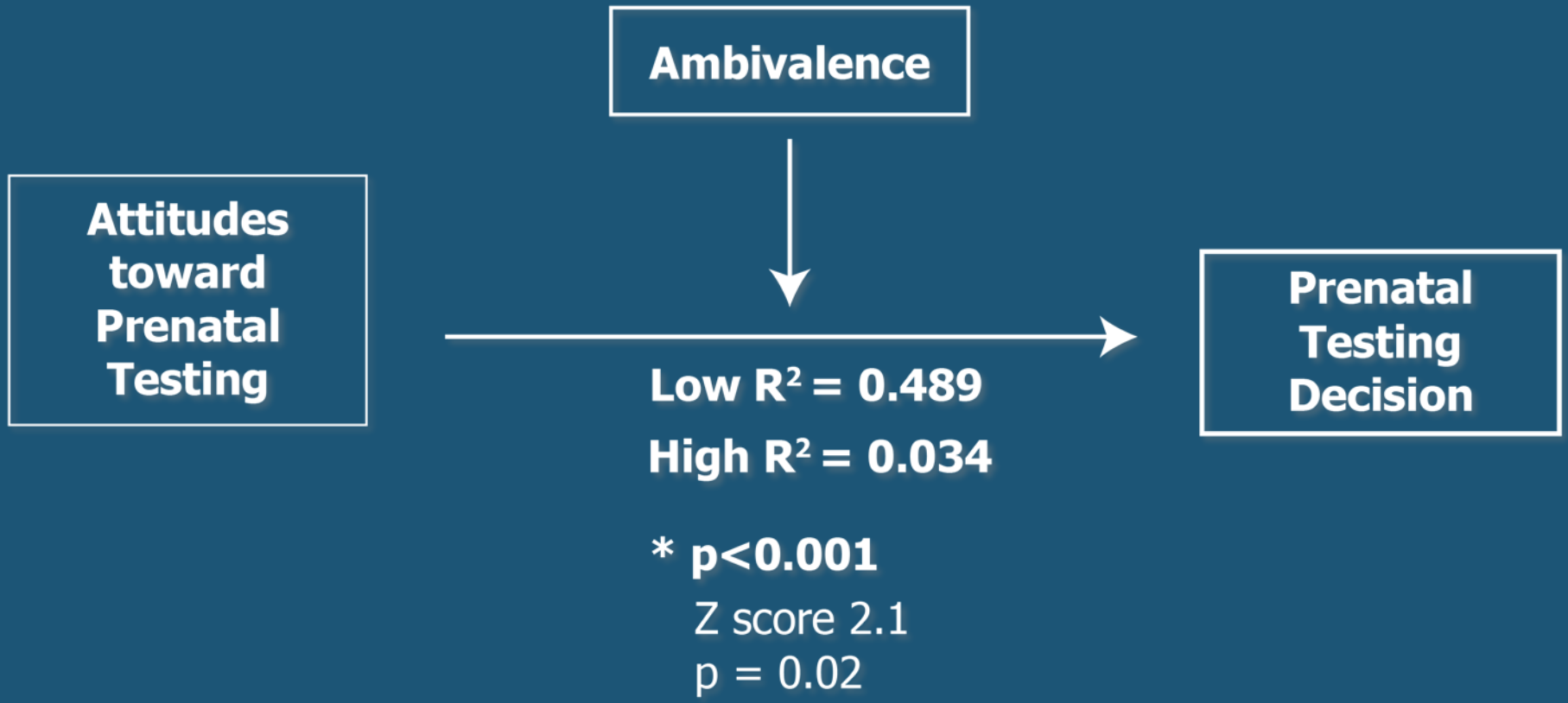
Ambivalence defined as having conflicting thoughts or feelings about prenatal testing

Prenatal genetic counseling clients often have ambivalence about undergoing prenatal testing

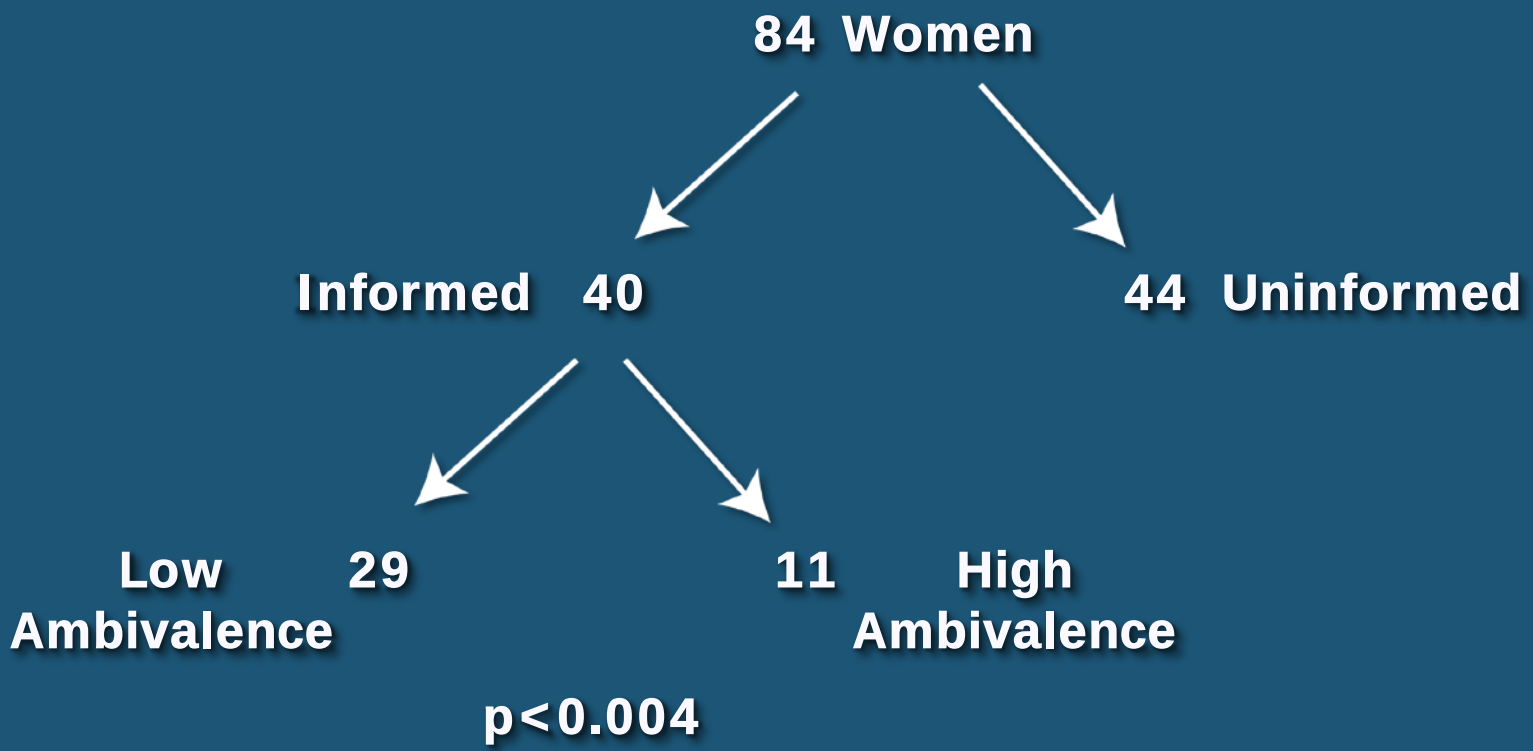
Ambivalence has been associated with uninformed choice in prenatal screening decisions

Sapp, J et al *Prenat Diag* 2009

Ambivalence in Prenatal Testing Decisions



Informed Choice in Prenatal Testing Decisions



Patient Interest and Expected Uptake of Non-Invasive Prenatal Testing

Single most important factor in decision about NIPD
- Elimination of miscarriage risk (75%)
- Accuracy of results (13%)

Interest in NIPD
- Very interested (56.4%)
- Somewhat interested (15.5%)

Preference for NIPD or current diagnostic tests
- Prefer NIPD but follow-up positive results with CVS/amnio (33.6%)
- Prefer NIPD and would use for decisions about pregnancy (30.6%)
- Prefer CVS/Amnio only (3.6%)

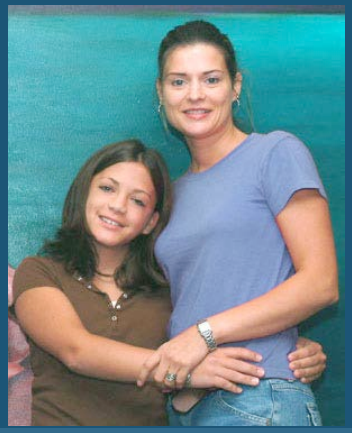
Likelihood to terminate an affected pregnancy based on NIPD
- Likely (33.9%)
- Unsure (33.0%)
- Not Likely (33.0%)

Tischler et al. *Prenat Diagn* 2011

In Summary

- Onslaught of new tests with insufficient evidence to set practice standards
- The volume of information learned can be vast but there are limits on our ability to interpret it and use it
- Need for new clinical paradigms and education of providers

Turner syndrome 46, XO



Summer Reading
Top 10 NYT Book Review 2011