Assessing the Economics of Genomic Medicine

Case 1: Clinician Perspective

July 17, 2012

Institute of Medicine of the National Academies
Roundtable on Translating Genomic-Based Research for Health

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Model 1

- **Targeted mutation detection using individual or panels of tests (current standard of care).**
- **Will include detection of variants of unknown significance.**

What I would want to know: Current Standard of Care

- Complete Family History
- Offer carrier screening in the preconception period
  - Best time for couples to consider the results of testing and plan for pregnancy
  - Some insurers will not cover carrier screening unless a woman is pregnant
- Carrier screening to be offered:
  - Ashkenazi Jewish Genetic Diseases
    - ACOG recommends 9 conditions
    - Philanthropic programs are currently offering 19 conditions (which includes cystic fibrosis) – approximately 1 in 4 AJ's found to be a carrier of at least one condition
    - Note: enzyme testing and not DNA should be offered for other high risk groups (Irish ancestry)
  - Consider Fragile X syndrome (personal or family history of autism spectrum disorder or intellectual disability)
  - Consider Spinal Muscular Atrophy
    - ACOG recommends offering to women with a family history
    - ACMG recommends offering to all women
- How could we assist her with quitting smoking?

Ashkenazi Jewish Genetic Conditions

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ASHKENAZI JEWISH SCREENING PANEL, 18 GENETIC DISEASES

Disorder	Carrier Frequency*	Clinical Characteristics, if affected with the disease
Cystic fibrosis	1 in 26	Causes severe pulmonary and gastrointestinal disease and affects fertility. Intelligence is normal.
Canavan disease	1 in 57	Presents with severe neurological insufficiencies in infancy, seizures, and failure to reach milestones.
Familial dysautonomia	1 in 30	Characterized by abnormal functioning of the nervous system causing decreased sensitivity to pain, abnormal regulation of body temperature, unstable blood pressure, and gastrointestinal abnormalities.
Tay-Sachs disease	1 in 30	Causes progressive deterioration in brain function, leading to mental retardation, blindness, seizures, and paralysis.
Bloom syndrome	1 in 100	Causes poor growth, immune dysfunction, characteristic facial rash, and high risk for developing various cancers. Intellect is usually normal.
Fanconi Anemia Group C	1 in 89	Causes deficient bone development and bone marrow function associated with heart, kidney, and limb abnormalities. There is an increased risk for cancer, especially leukemia. Bone marrow transplantation may reduce the symptoms.
Gaucher disease Type I	1 in 15	Variable presentation of symptoms, including fatique, enlarged liver and spleen, bone pain and fractures, and easy bruising. Onset may not be until age 45, or may not be detected at all. Enzyme replacement therapy is available for treatment.
Mucolipidosis type IV	1 in 122	Presents with profound mental retardation and blindness.
Neimann-Pick disease type A	1 in 90	Causes poor growth, liver enlargement, and mental retardation.

* The carrier frequency is the proportion of people in the population who are carriers of the disease. Bloom syndrome, for example, has a carrier frequency of 1 in 100. This means that out of 100 Ashkenazi Jewish individuals, on average, one person will be a carrier for Bloom syndrome and 99 will not be carriers.

Ashkenazi Jewish Genetic Conditions

Disorder	Carrier Frequency*	Clinical Characteristics, if affected with the disease
Glycogen storage disease type 1A	1 in 71	Leads to severe low blood sugar, which can result in irreversible neurological damage if untreated. Dietary intervention is necessary to avoid symptoms.
Maple syrup urine disease	1 in 81	Causes mental retardation, seizures, and characteristic odor in urine if not treated properly. Dietary intervention is important to avoid symptoms.
Familial hyperinsulinism	1 in 66	Causes dangerously low blood sugar levels, starting any time between neonatal period and 5 years of age. If untreated, causes irreversible brain damage.
Dihydrolipoamide dehydrogenase deficiency	1 in 96	Presents with persistent lactic acidosis, with episodes of vomiting and abdominal pain, neurological impairment, cortical blindness, and coma.
Nemaline myopathy	1 in 149	Leads to progressive weakness and poor muscle tone in face, neck, and limbs. Interferes with normal breathing, mobility, and feeding.
Usher syndrome type IF	1 in 141	Causes profound hearing loss at birth, progressive vision problems, and loss of balance.
Usher syndrome type III	1 in 107	Causes progressive hearing and vision loss, but balance is not usually affected.
Joubert Syndrome	1 in 92	Causes hypotonia, abnormal rapid breathing, rotary nystagmus, variable developmental delay.
Walker-Warburg syndrome	1 in 149	Presents with congenital muscular dystrophy, brain and eye malformations, seizures, and blindness.

Aside from the conditions which are common in the Ashkenazi Jewish population, there are additional conditions which may warrant testing due to their high carrier frequency in *all* populations:

Spinal Muscular Atrophy (SMA)	Causes progressive muscle weakness and atrophy, poor weight gain, spinal curvature and joint contractures. Presentation varies and lifespan may be limited. Inherited in an autosomal recessive manner. The carrier frequency is 1 in 41 in the general population.
Fragile X syndrome	Most common cause of mental retardation in boys. Approximately 1 in 250 women are carriers of the fragile X premuation. Unlike all the other conditions mentioned, fragile X is inherited in an X-linked manner. This means that if a female is a carrier, each of her sons has a ½ chance of being affected and each of her daughters has a ½ chance of being a carrier. Traditionally, carriers of genetic diseases show no effects of having a mutation. However, female premutation carriers are at risk for premature ovarian failure, and males with premutations are at risk for fragile X associated tremor/ataxia syndrome.

A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery

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We have attempted to quantify the most up-to-date estimate of the association between cigarette smoking by the mother and preterm delivery. Studies were selected for inclusion in this review if they were prospective, reported data stratified across at least two levels of maternal smoking, and defined preterm delivery on the basis of gestational age. In a meta-analysis we combined results from multiple studies that reported on preterm delivery and maternal smoking during pregnancy. Pooled odds ratios were computed for various strata of smoking intensity with the Mantel-Haenszel fixed-effects model. Twenty studies met all inclusion criteria and were included in meta-analysis. The pooled point estimate from 20 prospective studies on any maternal smoking versus no maternal smoking was 1.27 (95% confidence interval, 1.21-1.33). Subgroup analyses stratifying maternal smoking on number of cigarettes per day suggest a dose-response relationship at low to moderate levels of smoking, which was not further increased at high levels of smoking. A nonsignificant level of publication bias appears to exist in the smoking–preterm delivery literature. Cigarette smoking is a preventable risk factor that is associated with preterm delivery. Consistent results across many study populations and research designs and evidence of a dose-response relationship support its causal role in preterm delivery. (Am J Obstet Gynecol 2000;182:465-72.)

Cost of Hospitalization for Preterm and Low Birth Weight Infants in the United States

Rebecca B. Russell, Nancy S. Green, Claudia A. Steiner, Susan Meikle, Jennifer L. Howse, Karalee Poschman, Todd Dias, Lisa Potetz, Michael J. Davidoff, Karla Damus and Joann R. Petrini

Pediatrics 2007;120;e1
DOI: 10.1542/peds.2006-2386

ABSTRACT

OBJECTIVE. The objective of this study was to estimate national hospital costs for infant admissions that are associated with preterm birth/low birth weight.

METHODS. Infant (<1 year) hospital discharge data, including delivery, transfers, and readmissions, were analyzed by using the 2001 Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project. The Nationwide Inpatient Sample is a 20% sample of US hospitals weighted to approximately >35 million hospital discharges nationwide. Hospital costs, based on weighted cost-to-charge ratios, and lengths of stay were calculated for preterm/low birth weight infants, uncomplicated newborns, and all other infant hospitalizations and assessed by degree of prematurity, major complications, and expected payer.

RESULTS. In 2001, 8% (384 200) of all 4.6 million infant stays nationwide included a diagnosis of preterm birth/low birth weight. Costs for these preterm/low birth weight admissions totaled $5.8 billion, representing 47% of the costs for all infant hospitalizations and 27% for all pediatric stays. Preterm/low birth weight infant stays averaged $15 100, with a mean length of stay of 12.9 days versus $600 and 1.9 days for uncomplicated newborns. Costs were highest for extremely preterm infants (<28 weeks' gestation/birth weight <1000 g), averaging $65 600, and for specific respiratory-related complications. However, two thirds of total hospitalization costs for preterm birth/low birth weight were for the substantial number of infants who were not extremely preterm. Of all preterm/low birth weight infant stays, 50% identified private/commercial insurance as the expected payer, and 42% designated Medicaid.

CONCLUSIONS. Costs per infant hospitalization were highest for extremely preterm infants, although the larger number of moderately preterm/low birth weight infants contributed more to the overall costs. Preterm/low birth weight infants in the United States account for half of infant hospitalization costs and one quarter of pediatric costs, suggesting that major infant and pediatric cost savings could be realized by preventing preterm birth.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-2386

doi:10.1542/peds.2006-2386

The contents and conclusions in this article are those of the authors; no statement should be construed as an official position of the agencies of the authors or those acknowledged.

Key Words
prematurity, newborns, infants, hospital costs, low birth weight, morbidities

Abbreviations
LBW—low birth weight
LOS—length of stay
NIS—Nationwide Inpatient Sample
HCUP—Healthcare Cost and Utilization Project
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
CTC—cost-to-charge ratio
RDS—respiratory distress syndrome
BPD— bronchopulmonary dysplasia
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis

Accepted for publication Jan 25, 2007

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics

Challenges to Workflow, Education & Support

- If a woman is identified to carry a mutation, next step requires the partner be tested. Often partners cannot be tested if they:
  - Are out of the country for work
  - Are overseas in the military
  - Are incarcerated
  - Are not insured and cannot pay for the testing

- In instances where partners are not available for testing, we often observe:
  - Increased anxiety
  - Money is spent
  - Health outcomes are not improved

- Variants of Uncertain Significance (VOUS)
  - Present significant challenges in the preconception and prenatal period
  - Despite the uncertain significance, couples need to make decisions
  - Extremely difficult counseling scenarios – time consuming and anxiety provoking

Actions I Would Take

- Focus on informing patient of availability of testing options and supporting autonomy in her decision making

- Offer partner testing for Tay Sachs:
  - Let's say he is AJ and he is negative for Tay Sachs mutation
    - Residual risk for him to be a carrier = 1/560
  - Should also offer enzyme assay (will miss 11% of AJ carriers if enzyme is not done)
    - Will bring residual risk of him being a carrier down to 1/1451

- Residual risk to the fetus needs to be reported to the couple
  - Mutation testing plus enzyme assay: 1 x 1/1451 x ¼ = 1 / 5804
  - Mutation testing alone: 1 x 1/560 x ¼ = 1/2240

- If they are both carriers, provide counseling:
  - PGD / IVF is an option but may be too expensive for some couples
  - Couples will face very difficult decisions regarding pregnancy termination
  - Some couples will choose to have an affected baby

Model 2

- **Whole genome sequencing with provision of data relevant only to the current clinical situation and a handful of high-effect sized “actionable variants.”**
- **Will include detection of variants of unknown significance.**

What I would Want to Know (In addition to Model 1)

- Expanded panel of carrier conditions, such as is currently offered by Counsyl
  - Over 100 conditions
  - Varying disease prevalence
  - Sensitivity and specificity of the testing for each condition varies widely
- Prothrombin gene mutation +
  - Also look at Factor V Leiden
- Cytochrome P450s and risk for preterm birth and low birthweight
- Would the patient be interested in BRCA1 and BRCA2 mutation testing?

Full Disease List

= Testing for this disease recommended to be offered by ACOG
ACOG = Testing for this disease recommended to be offered by ACMG
ACMG

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 V Leiden Thrombophilia
*HFE-Associated Hereditary Hemochromatosis
Homocystinuria Caused by Cystathionine Beta-Synthase Defic
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
*MTHFR Deficiency
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

Factor XI Deficiency

Familial Dysautonomia ACMG ACOG

Familial Mediterranean Fever

Fanconi Anemia Type C ACMG

**Fragile X Syndrome

Galactosemia

Gaucher Disease ACMG

GJB2-Related DFNB 1 Nonsyndromic Hearing Loss and Deafness

*Glucose-6-Phosphate Dehydrogenase Deficiency

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

* - Only included if requested by the ordering physician.

** - Only included if requested by the ordering physician. Requires a blood sample.

PROP1-Related Combined Pituitary Hormone Deficiency

*Prothrombin Thrombophilia

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

Prothrombin Heterozygote

Table 1. Risk of Venous Thromboembolism With Different Thrombophilias

	Prevalence in General Population (%)	VTE Risk per Pregnancy *(No History)* (%)	VTE Risk per Pregnancy *(Previous VTE)* (%)	Percentage of All VTE	References
Factor V Leiden heterozygote	1–15	<0.3	10	40	1–4
Factor V Leiden homozygote	<1	1.5	17	2	1–4
Prothrombin gene heterozygote	2–5	<0.5	>10	17	1–4
Prothrombin gene homozygote	<1	2.8	>17	0.5	1–4
Factor V Leiden/prothrombin double heterozygote	0.01	4.7	>20	1–3	1–4
Antithrombin III activity (<60%)	0.02	3–7	40	1	1, 5, 6
Protein C activity (<50%)	0.2–0.4	0.1–0.8	4–17	14	1, 5, 7
Protein S free antigen (<55%)	0.03–0.13	0.1	0–22	3	1, 8–10

Abbreviation: VTE, venous thromboembolism.

ACOG Practice Bulletin 124, September 2011

Maternal Cigarette Smoking, Metabolic Gene Polymorphism, and Infant Birth Weight

Smoking	CYP1A1	GSTT1	#	Gestation, Week β (SE)	P value
Never	AA	Present	251	Referent	
Never	AA	Absent	72	0.9 (0.4)	.03
Never	Aa/aa	Present	182	0.2 (0.3)	.46
Never	Aa/aa	Absent	62	0.2 (0.5)	.64
Continuous	AA	Present	58	-0.4 (0.5)	.40
Continuous	AA	Absent	177	0.3 (0.8)	.75
Continuous	Aa/aa	Present	38	-0.01 (0.6)	.99
Continuous	Aa/aa	Absent	11	-5.2 (1.0)	<.001
Test of interaction Crude				-5.5 (1.0)	<.001
Test of interaction Adjusted				-5.4 (1.0)	<.001

Conclusions: Maternal CYP1A1 and GSTT1 genotypes modified the association between maternal cigarette smoking and infant birth weight, suggesting an interaction between metabolic genes and cigarette smoking.

Wang et al. JAMA. 2002;287:195-202.

Challenges to Workflow, Education & Support

- Sensitivity and Specificity of tests for various conditions on panel vary widely
- Some of the conditions are very rare.
  - Where can adequate information about the natural history of the conditions be accessed (NORD?)
  - Who can provide counseling to families?
- Counsyl is currently not accepting NY State Medicaid so not affordable for some women (even at $350)
  - Challenge to equity and potential to widen disparities
- Would the fact that she is at increased risk for clotting due to a prothrombin gene mutation, or potentially at increased risk for adverse pregnancy outcome based on cytochrome P450s, motivate her to quit smoking?
- More VOUS will present more counseling challenges and anxiety

Actions I Would Take

- Consider hematology work up -
  - Antithrombin, protein c and protein s deficiency
  - Fasting homocysteine level

- Consider anticoagulation early in pregnancy, although there are no clear guidelines for management of these patients, particularly in the absence of any prior event

- Continue to emphasize smoking cessation

Model 3

- **Whole genome sequencing with provision of data relevant to the current clinical situation as well as other potentially significant secondary findings using the current best available data for interpretation.**
- **This will include lower effect size variants.**
- **Will include detection of variants of unknown significance.**

What I would Want to Know (In addition to Model 1 and 2)

Would the patient be interested in knowing about APOE4 homozygosity?

Would family history suggest any other potential risks?

- **Colon cancer – Lynch?**
- **Diabetes?**

Challenges to Workflow, Education & Support

- The patient may experience anxiety, depression, hopelessness, etc after learning about her APOE4
- She may choose not to have children and yet may never develop Alzheimers
- More VOUS will present more counseling challenges and anxiety

Actions I Would Take

- Discuss test results with patient and advise her of increased risk based on test results
- Refer her to appropriate specialists for consultation
- Continue to emphasize smoking cessation

Question for Consideration

- In pregnancy specifically ... What is an improved health outcome?
  - Informed decision making?
  - Fewer affected infants?

Thank you for your attention!

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