Prenatal genetic screening: Beyond chromosome abnormalities

Owen Phillips, MD, MPH

Disclosures

- None

Objectives

1. What should ‘screening’ for single genes disorders look like for practitioners

2. Controversies

3. New developments in Screening for Single Gene defects: cfDNA

3-4 % of all babies are born with a major birth defect

1. Chromosome abnormalities (Down syndrome, Turner syndrome)

2. Single gene defects (CF, SMA, sickle cell disease)

3. Structural abnormalities (polygenic/multifactorial: cleft lip or CHD)

(About 50% of birth defects have an unknown or uncertain cause)

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Single Gene Disorders

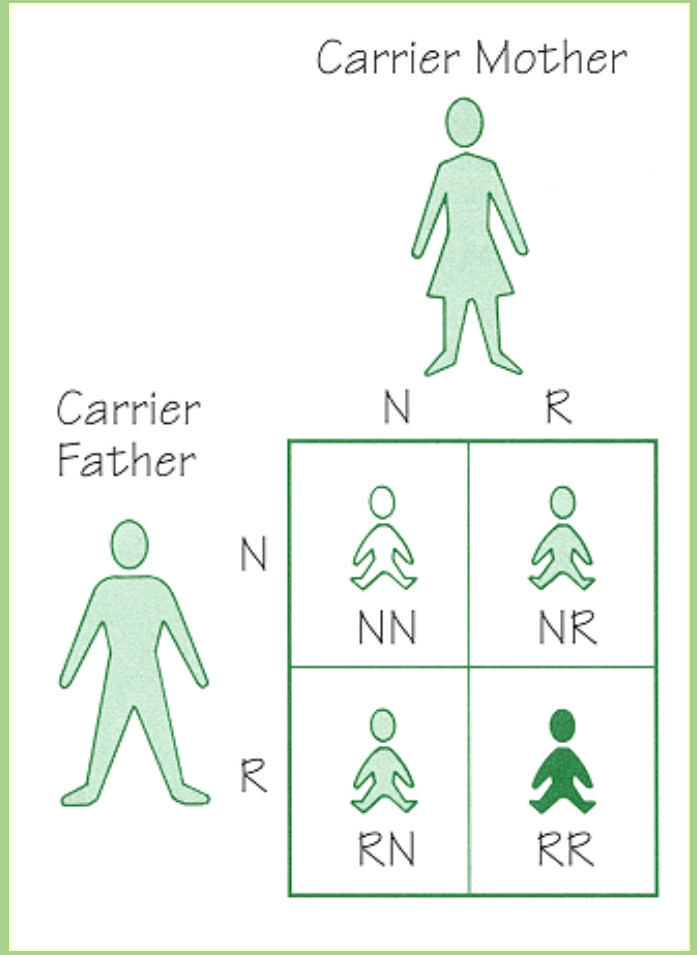
Autosomal Recessive Disorders: EX: CF, Sickle cell, SMA

X-linked: EX: Hemophilia, DMD, Fragile X

Autosomal Dominant: EX: Marfan’s, Huntington’s, NF

Most Single Gene Defects: Autosomal Recessive Inheritance

- If both parents are carriers of the same genetic condition (R)…
- 25% chance of child being affected (RR)
- 50% chance of child being carrier (NR-like parents)
- 25% chance of child not affected nor carrier (NN)



Risk example

- Risk of carriership of CF in European population is 1/25.

1/25 X 1/25 X 1/4= 1/2500

If one member of couple is found to be a carrier

1 X 1/25 X 1/4 = 1/100

If both are found to be carriers

1 X 1 X 1/4 = 1/4

Facts about single gene defects:

- More than 1300 recessively-inherited genetic disorders
- Affecting 30/10,000 children
- Mendelian disorders account for ~20% of infant mortality
- Genetic disease is the single most common cause of hospitalizations in pediatric hospitals

Recommendations for the OBGYN:

Need to have a system to ask about family history of genetic disease: ACOG form, patient check list

Those at high risk for disorders need referral for genetic counseling

- Positive Family history
- Positive screens

Screening for carriership in the low-risk population (for recessive or X-linked): General OBGYN office

What is the point of carrier screening?

"To facilitate reproductive choices for those found to be at high risk for having a child with a serious genetic disease"

1. Education
2. Pregnancy termination
3. Preimplantation genetic diagnosis
4. *Possible treatments*
5. Regardless of ancestry: increases equity and reduces stigmatization
6. Should be done preconceptionally

European Society of Human Genetics; Henneman, et al. *European Journal of Human Genetics* (2016)

This conversation has moved us:

From specific: panels targeting specific communities (as is currently recommended)

To expanded: screening of all individuals regardless of ancestry

Because we can!

Argument against expanding was cost-

- Not anymore: microarrays and NGS as inexpensive as panels

Historical perspective on screening for genetic disease

- Family history of genetic disease: Pedigrees, testing with linkage analysis to see whom else in family is at risk for carrying gene

- Recognizing high-risk populations based on ethnicity
  - African descent: sickle cell and other hemoglobinopathies
  - Greek/Mediterranean: beta thalassemias
  - Asian descent: alpha and beta thalassemias
  - Ashkenazic Jews: disorders resulting from founder effect and isolated population genetics

The American College of
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WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

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Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Stephanie Romero, MD; Britton Rink, MD; Joseph R. Biggio Jr, MD; and Devereux N. Saller Jr, MD.

Carrier Screening in the Age of Genomic Medicine

Screening paradigms endorsed by ACOG

ACOG Committee Opinion 690, 2017: strategies for carrier screening

Suggests ethnicity-specific, panethnic, and expanded carrier screening are all acceptable strategies

Each provider or practice should establish a standard approach offered to all patients

Screening paradigms endorsed by ACOG
ACOG Committee Opinion 690, 2017: strategies for carrier screening

- Regardless of screening strategy, all patients who are pregnant or considering pregnancy should be offered:
  - Screening for CF and SMA
  - CBC/MCV (or hemoglobin electrophoresis) for screening for hemoglobinopathies
  - Fragile X syndrome pre-mutation screening should be offered to women with a family history suggestive of FX or a personal history of premature ovarian failure

- Additional screening may be offered based on family history and ethnicity

Carrier Frequencies Based on Ethnic Origin

Population	Condition	Carrier Frequency
African-American	Sickle Cell Cystic Fibrosis Beta-Thalassemia	1 in 10 1 in 65 1 in 75
Ashkenazi Jewish	Gaucher disease Cystic Fibrosis Tay-Sachs disease Dysautonomia Canavan disease	1 in 15 1 in 26 – 1 in 29 1 in 30 1 in 32 1 in 40
Asian	Alpha-Thalassemia Beta-Thalassemia	1 in 20 1 in 50
European American	Cystic Fibrosis	1 in 25 - 1 in 29
French Canadian, Cajun, Irish	Tay Sachs disease	1 in 30 1 in 50
Hispanic	Cystic Fibrosis Beta-Thalassemia	1 in 46 1 in 30 - 1 in 50
Mediterranean	Beta-Thalassemia Cystic Fibrosis Sickle Cell	1 in 25 1 in 29 1 in 40

Arguments for expanding carrier screening beyond ethnicity

The majority of affected children with genetic disease are born to couples with none of the risk factors

People do not know their ethnicity

Individuals of mixed ethnicities

Expanding carrier screening: More rationale

- About 100 of the 1300 diseases have a prevalence of >1/100,000 (EX: PKU 1/10,000; CF- 1/2500; SS- 1/350)
- 1-2% of all couples are at risk for having an affected child
- Success of Tay-Sachs screening to reduce incidence

Pan-ethnic screening

- Screening all patients for those disorders at increased frequency in various ethnic groups
- Rationale
  - Individuals of mixed ethnicities
  - New genetic technologies: Allows for a panel
  - CF, SMA type 1, hemoglobinopathies
  - Ashkenazic Jews should have a panel as well
  - (Fragile X, only with a positive history)

Cystic Fibrosis

- ACOG 2011 guideline, ACMG 2004 guideline (reaffirmed 2013 and 2017)

- It is “important that CF screening continues to be offered to women of reproductive age”

  - For couples in which one or both partners has a known family history of CF, genetic counseling should be performed to identify if CFTR mutation analysis in the affected relative is available

CF counseling points

- Metabolic disorder, chronic illness affecting lungs, pancreas and in boys, fertility
- Children do not look abnormal. No DD/ID
- Average age of death 30
- Death usually by pulmonary infections
- Variable presentation with genotype/phenotype correlation

- Better treatments
- Genetic treatments (cures) on horizon

Spinal Muscular Atrophy Type 1

- Devastating disorder. Start to lose muscular milestones at 6 Mos. Death by age 3-5 y/o.
- Now new genetic treatments

- Carrier rates in the general population estimated 1/40 to 1/60

- ACOG 2017
  - Carrier screening should be offered to all couples regardless of race or ethnicity “because SMA is present in all populations”

Hemoglobinopathies

- Hemoglobinopathy screening includes screening for sickle cell trait and for alpha- and beta-thalassemias
- CBC (MCV <70). Hemoglobin electrophoresis
- Sorts out qualitatively and can call who is a carrier
- For prenatal diagnosis, must know variant or mutation in the gene

Fragile X carrier screening

- Carrier frequency: 1/250 women
- X-linked disorder
- DD/ID on the order of Down syndrome

- If has a family history of Fragile X (maternal side)

Undiagnosed DD/ID in boys

Premature ovarian insufficiency

Ataxia in older men

Autism

Low threshhold

Genetics inMedicine | ORIGINAL RESEARCH ARTICLE

Open

An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals

Gabriel A. Lazarin, MS[1], Imran S. Haque, PhD[1], Shivani Nazareth, MS[1], Kevin Iori, BS[1], A. Scott Patterson, MA[1], Jessica L. Jacobson, MD[1,2], John R. Marshall, MD[1,3], William K. Seltzer, PhD, FACMG[1], Pasquale Patrizio, MD[4], Eric A. Evans, PhD[1] and Balaji S. Srinivasan, PhD[1,5,6]

- This study found a large number of carriers outside the ethnic groups that are generally associated with particular diseases
- For example, African Americans are the target population for sickle cell disease, but almost 39% of carrier for sickle cell disease were not of African American descent
- Similarly, for many other conditions including TSD -- 40% of carriers were not Jewish
- This data suggests consideration should be given to the idea of a more universal screening panel rather than targeting screening based on ethnicity

GIM 2013: 178-186.

Acceptable strategies for genetic screening

A. Ethno-specific

B. Panethnic

C. Expanded carrier screening

Expanded with microarray technologies
Cheaper

Which diseases ?

- Natural history of disorder is well-characterized and causes early death and/or severe impairment
- Carrier frequency high enough to warrant testing
- Test should be technically and clinically validated
- Reasonable genotype/phenotype correlation
- Interventions should be available

Ram, Klugman, 2010

ACOG/ACMG joint statement: Which diseases?

Edwards, et al *Obstet Gynecol*, 2015

A health problem that encompasses one or more of the following:

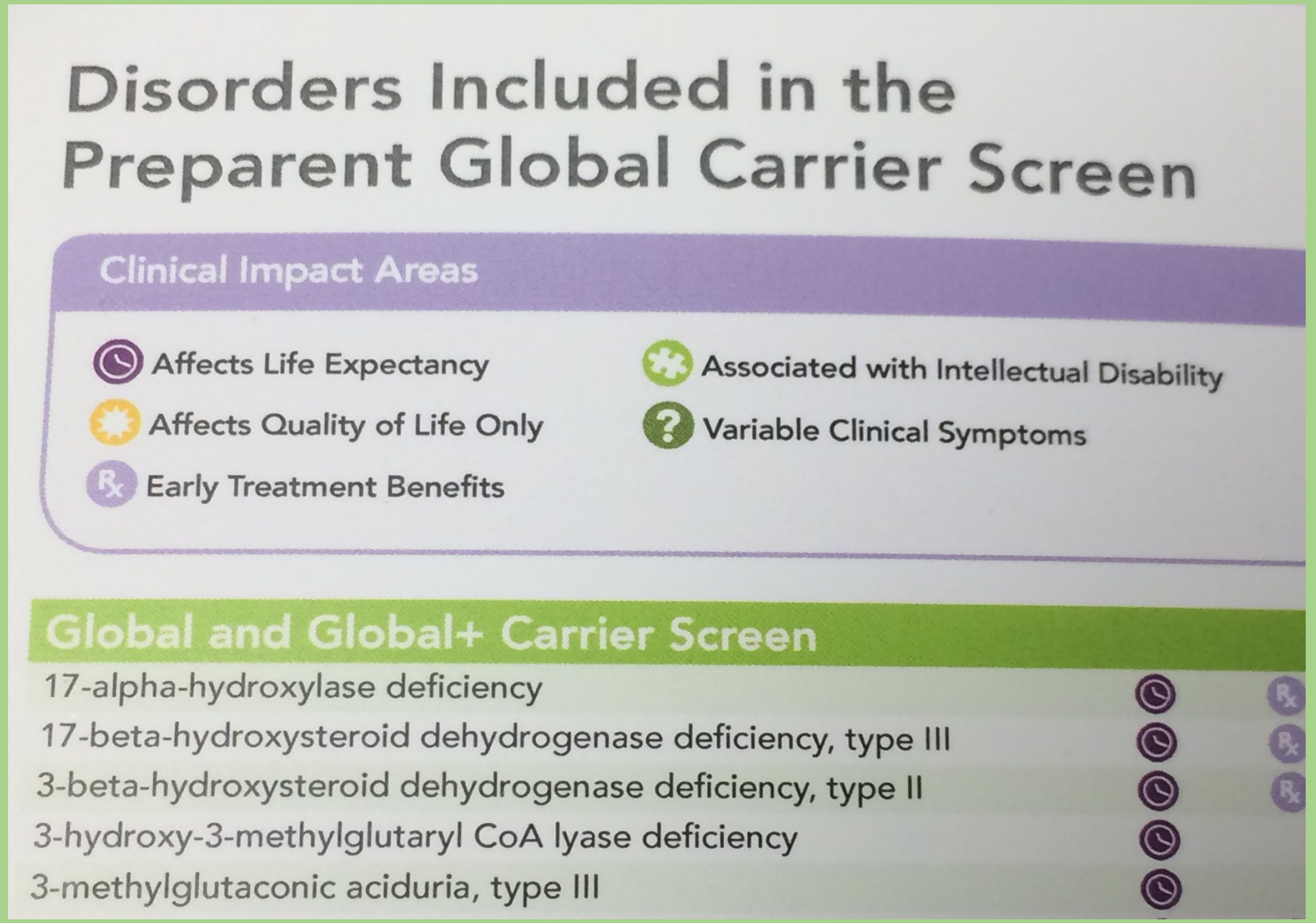
a. Cognitive disability.
b. Need for surgical or medical intervention
c. Effect on quality of life.
d. Conditions for which a prenatal diagnosis may result in:

- Prenatal intervention to improve perinatal outcome and immediate care of the neonate.
- Delivery management to optimize newborn and infant outcomes such as immediate, specialized neonatal care.
- Prenatal education of parents regarding special needs care after birth; this often may be accomplished most effectively before birth.

Expanded carrier screening

- Progenity: 240 diseases
- Pathway Genomics – Carrier DNA Insight - >70 diseases
- GenPath: “Inherigen” – 167 diseases
- Integrated Genetics – InheriTest - 90+; 500+
- ARUP Laboratories: “100-Plus”
- Natera: Horizon 4, 27, 106, 137, 274….

Progenity



Disorders Included in the Preparent Global Carrier Screen

Clinical Impact Areas

- Affects Life Expectancy
- Affects Quality of Life Only
- Early Treatment Benefits
- Associated with Intellectual Disability
- Variable Clinical Symptoms

Global and Global+ Carrier Screen

17-alpha-hydroxylase deficiency	✓	✓
17-beta-hydroxysteroid dehydrogenase deficiency, type III	✓	✓
3-beta-hydroxysteroid dehydrogenase deficiency, type II	✓	✓
3-hydroxy-3-methylglutaryl CoA lyase deficiency	✓	
3-methylglutaconic aciduria, type III	✓	

Maple syrup
Medium-chain acyl-CoA dehydrogenase
MEDNIK syndrome
Metachromatic leukodystrophy
Methylmalonic aciduria, cblA type
Methylmalonic aciduria, cblB type
Methylmalonic aciduria, cblC type
Methylmalonic aciduria, *MUT*-related
Mitochondrial complex IV deficiency
Mitochondrial myopathy and sideroblas
Mucolipidosis type IV
Mucolipidosis, type II/III alpha/beta
Mucopolysaccharidosis, type I (Hurler s
Mucopolysaccharidosis, type II (Hunter
Mucopolysaccharidosis, type IIIC
Mucopolysaccharidosis, type VI
Mulibrey nanism

Controversies: Perspectives from genetics professionals

Cho et al, Human Reproduction. 2013

- Genetics professionals believe current ECS products have major limitations and are not ready for routine use in reproductive healthcare.

- Although ECS products have been marketed as improved versions of traditional carrier screening, genetics professionals in this study felt they would present significant interpretive challenges.

- ECS products depart from standards of care in medical genetics and reproductive healthcare and would introduce a host of difficult patient counseling challenges.

Controversies: Genetics services

Referrals to Genetics Services to counsel post-test with positive results

- A screening panel of 108 disorders identified 24% of individuals as carriers for at least one variant
- 19,000 samples from GeneDx: 26% had a recessive mutation
- 2700 samples from Baylor: 50% had one mutation; 12% had 2

“ Capacity of health care system to deal with counselling should be properly evaluated”

Potential Disadvantages of Expanded Screening

- Carrier rates are high, necessitating follow up screening on partners in a high percentage of cases
- Limits the pool of egg and sperm donors
- Who provides counseling for this type of testing?
  - Most OBGYNs not equipped (knowledge or time)
  - Not enough genetic counselors
  - Available but will insurance companies pay for it
  - Counseling couples in the office about process
  - Different companies offer different panels

From BCBS

- When Carrier Testing for Genetic Disease is covered: Carrier screening for genetic diseases is considered medically necessary when one of the following criteria is met: • One or both individuals have a first- or second-degree relative who is affected OR • One individual is known to be a carrier OR • One or both individuals are members of a population known to have a carrier rate that exceeds a threshold

- Expanded carrier screening panels are considered to be not medically necessary

What to do if carrier parent is identified

- Partner SHOULD have the most accurate test for just that gene.

- Most accurate is sequencing the gene (not another screen)

- Cost?
- Insurance may pay
- Detection rate of screen
- Consider residual risk

Residual risk

- No test (even gene sequencing) detects 100% of variants.
- **If empiric risk of being a carrier is 1/50 and test detects 90% variants then residual risk of being a carrier = 1/50 X 1/10 or 1/500**
- **Risk of offspring if mom is a carrier and partner is negative**
- **1 X 1/500 X ¼= 1/2000**

What we do-

- Family history for ethnicity, history of genetic disease, high-risk factors for Fragile X

Plus, CF, SMA, hemoglobin electrophoresis

- If patient is positive, partner should have testing
  - Can refer or test partner

- If partner negative: residual risk
- If partner positive: refer

Cell free DNA for single-gene diseases

- Fetal DNA in maternal circulation (screens for chromosome abn.)
- For single gene defects: amplify all DNA and look for ratios (‘enhanced haplotype dosage analysis’)

- Easier with autosomal dominant and X-linked recessive genes

- But possible for autosomal recessive (One copy of the gene (Mom is a carrier) or two (Mom and fetus are carriers) or three (Mom is a carrier and fetus is affected)

CcfNA examples in current literature

RH disease: Mom is RH negative (D-). If D gene is present, it is from the fetus. Therefore fetus is RH+ and Mom needs Rhogam.

Skeletal dysplasias (achondroplasia, thanatophoric dwarfism etc.) are most often new mutations

Findings seen on ultrasound- ccfDNA identifies genetic abnormality.

A panel associated with advanced paternal age.

ACOG Practice Advisory, September 2023

- This technology is clinically available and being marketed
- Not sufficient data to provide information regarding accuracy in the general population.
- Single-gene cell-free DNA screening is not currently recommended in pregnancy