Now What Do I Do?

Wendy Chung, MD, PhD
Beth A. Pletcher, MD, FAAP, FACMG
Cecilia M. Rajakaruna, MS, CGC
Beth Tarini, MD, MS, FAAP
Disclosure Slide

• The session presenters have no relevant financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.

• We do not intend to discuss an unapproved/ investigative use of a commercial product/device in our presentation.
Session Objectives

Using a series of clinical cases, presenters will:

• Identify strategies to sustain practices to identify patients at risk for genetic disorders based upon family history
• Review criteria for referral to genetics
• Review how to implement health supervision guidelines for the care of children with genetic disorders.
Family History and Identifying At Risk Individuals

Wendy Chung, MD PhD
Director of Clinical Genetics
Columbia University
Familial Cardiomyopathy
What is the most likely mode of inheritance?

A. Autosomal recessive 25%
B. Autosomal dominant 25%
C. X linked recessive 25%
D. Mitochondrial 25%

★ 15
What is the probability that the patient has inherited the gene for this condition?

A. 0%
B. 25%
C. 50%
D. 100%

[Bar chart showing 25% for each option]
Hypertrophic Cardiomyopathy

- Hypertrophied, non-dilated left ventricle
- Wall thickening of at least 13 mm (normal is typically 10 mm for an adult)
- 25% of patients will have left ventricular outflow tract obstruction
- Other causes of HCM include Athlete’s Heart, aortic stenosis, or hypertension, aging, valvular heart disease
- Prevalence is 1:500
Isolated Hypertrophic Cardiomyopathy

- Incidence of 1/500 adults, most common genetic cardiac disease
- Most common cause of sudden cardiac death in children and adolescents
- Autosomal dominantly inherited, usually
- Family history may not be revealing
- Penetrance varies with age, hypertrophy often not apparent at least until after puberty
  - Requires serial echos
- First symptom may be sudden death
Sarcomere

- Myofibril
- Thick filament
- Thin filament
- Z-disc
- Titin
- M-line
- Z-disc

- Cypher/ZASP
- α-Actinin
- MLP
- Teletethion

- Troponin T
- Troponin I
- Troponin C
- α-Tropomyosin
- Actin
- Ca²⁺

- Myosin-binding protein-C
- Myosin light chain
- β-Myosin heavy chain
# HCM Genes

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene Name</th>
<th>Frequency in patients with HCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td>B Myosin heavy chain</td>
<td>25%-35%</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Cardiac myosin-binding protein C</td>
<td>20%-30%</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Cardiac troponin T</td>
<td>5%-15%</td>
</tr>
<tr>
<td>TNNI3</td>
<td>Cardiac troponin I</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>TPM1</td>
<td>Tropomyosin 1a</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MYL2</td>
<td>Regulatory myosin light chain 2</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>ACTC</td>
<td>A Cardiac actin 1</td>
<td>Rare</td>
</tr>
<tr>
<td>MYL3</td>
<td>Essential myosin light chain 3</td>
<td>Rare</td>
</tr>
<tr>
<td>PRKAG2</td>
<td>Noncatalytic AMP-activated protein kinase gamma 2 (Wolf Parkinson White syndrome)</td>
<td>Rare</td>
</tr>
<tr>
<td>LAMP2</td>
<td>Lysosome-associated membrane protein 2 (Danon disease)</td>
<td>Rare</td>
</tr>
<tr>
<td>GLA</td>
<td>Galactosidease alpha (Fabry)</td>
<td>Rare</td>
</tr>
<tr>
<td>CAV3</td>
<td>Caveolin 3 (Muscular dystrophy)</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTG</td>
<td>Mitochondrial transfer RNA glycine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTI</td>
<td>Mitochondrial transfer RNA isoleucine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTK</td>
<td>Mitochondrial transfer RNA lysine</td>
<td>Rare</td>
</tr>
<tr>
<td>MTTQ</td>
<td>Mitochondrial transfer RNA glutamine</td>
<td>Rare</td>
</tr>
<tr>
<td>TTR</td>
<td>Transthyretin (amyloidosis)</td>
<td>Rare</td>
</tr>
<tr>
<td>TNNC1</td>
<td>Troponin C</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Who should be tested first in the family?

- Asymptomatic child in question
- Mother of child in question
- Deceased cousin
- No one should be tested. They’ll never be able to get insurance if they are tested.
Utility of Susceptibility Testing

• Identify family members at risk
• Distinguish CM from athlete’s heart
• Reproductive planning: increasing demand
• Stratify risk of sudden death to guide ICD placement
Mutation of Cardiac Troponin T Causes Cardiomyopathy

Key

+ = Arg92Gln heterozygote
- = Wild type

Age 37 A&W
Troponin T Mutation Specific Prognosis

Val606Met

Arg92Gln

Survival
Six Year Old Girl
12 Café-au-Lait Spots

Beth A. Pletcher, MD, FAAP, FACMG
Associate Professor of Pediatrics
Rutgers New Jersey Medical School
History

• JM is a 6 year old girl who is new to your practice
• She comes in with her mother for an initial visit and well child check
• Developmentally she is doing well and is currently in first grade with no recognized academic issues
• Exam is significant for 12 discreet café-au-lait spots between 1 and 3 cm in diameter with no other findings
Based on your exam, you recommend the following:

A. Follow-up in one year for her health supervision visit
B. Referral to a dermatologist for the café-au-lait spots
C. Referral to a geneticist for evaluation for neurofibromatosis type 1
D. Send a gene sequencing test for a neurofibromin mutation
E. Perform an MRI of the brain to look for signs of NF1
Follow-up

• JM returns next year and at this time you note that she has one right axillary and multiple left inguinal freckles and the same 12 café-au-lait spots
• She has no subcutaneous or cutaneous lesions
• Family history is negative for anyone with café-au-lait spots or other signs of NF1
• Mom says the teachers have been concerned about JM’s ability to sit still and pay attention in class and suggested the parents ask you to see if she may have a “touch of ADHD”
You now tell the mother that:

A. JM very likely has NF1 and should be followed for this by a specialist

B. JM probably does not have NF1 with such a benign exam and negative family history

C. JM may have ADHD and you will provide the mother with Connor’s scales to have the teachers and parents fill out and return to you

D. JM may have ADHD or ADD and should be seen by a developmental pediatrician

E. You would like to begin a trial of a psychostimulant to see if there is any improvement in JM’s ability to pay attention in class
You Need Two to Diagnose NF1

- 6 or more CALs ≥ 0.5 cm in diameter
- Axillary or inguinal freckles
- Optic nerve glioma
- Lisch (iris) nodules visible on slit-lamp exam
- Neurofibromas (2 regular or 1 plexiform)
- Bone lesion (pseudarthrosis or sphenoid dysplasia)
- Positive family history in a first degree relative
Next Visit

- JM returns for her eight year old health supervision visit
- Mom tells you that JM is doing well in school and is getting extra help in math with resource room services through a federal 504 plan
- JM has been taking a long acting dextroamphetamine/amphetamine 10 mg capsule each morning with improved ability to concentrate in school and on the soccer field
- There is no change in her clinical exam and she is growing well on the growth curve
Based on this update and your exam you tell mom that J M:

A. Should have a brain MRI since she is now old enough to cooperate with the exam

B. Should be seen by a neurologist annually because she has NF1

C. Likely has ADHD that is unrelated to any underlying diagnosis of NF1

D. Is at high risk for scoliosis and should have spinal x-rays

E. Should have formal neurocognitive testing because of her learning difficulties
Mom now tells you that she is about 6 weeks pregnant and wants to know what JM’s diagnosis means for this pregnancy. You tell mom that:

A. There is a 50% chance for NF1 to occur in their next child because this is an autosomal dominant condition

B. Both mom and dad should be checked for Lisch nodules to assess the risks for recurrence

C. Prenatal testing could be done to see if the unborn child inherited a gene mutation for NF1

D. A level 2 ultrasound may be helpful in diagnosing NF1 in an unborn child

E. Neurofibromatosis tends to present in a similar way for individuals in the same family, so mild manifestations would be expected if another child was affected
Facts about NF1

• More than 85% of individuals with NF1 are generally healthy and do not go on to develop serious complications
• The incidence of learning disabilities and ADD/ADHD are quite a bit higher in this population
• Macrocephaly and speech/dev delays are the most common issues in young children
• Optic nerve gliomas are fortunately rare but occur mostly in children under 5 and vision MUST be carefully monitored
• Scoliosis can be rapidly progressive in children with NF1, especially if it is first noted in the pre-adolescent
• Blood pressure should be assessed at each visit and hypertension in a child or teen with NF requires further evaluation for renal artery stenosis or pheochromocytoma
If you were following a child in your practice with confirmed NF1 you would have easy access to:

A. The AAP Committee on Genetics Health Supervision Guidelines for NF1
B. Support group information from either the Children’s Tumor Foundation or NF Inc
C. Information about ongoing NIH research trials for patients with NF1
D. A & B
E. All of the above
Do you currently have a patient or patients in your practice with NF1?

A. Yes for sure
B. No for sure
C. Have a suspicion but no firm diagnosis
D. Not sure at all
For those with a patient with NF1 in your practice, are you:

a. Having the patient followed by a pediatric neurologist
b. Having the patient followed in an NF1 specialty center
c. Monitoring the patient yourself in your practice
d. Following the recommended HSG for NF1 and (A)
e. Following the recommended HSG for NF1 and (B)
The End

Any Questions?
Now What Do I Do... Pediatrician’s Role in Newborn Screening

Cecilia M. Rajakaruna, MS, CGC
Genetic Counselor
University of Louisville
Newborn Screening

- National public health program

- Purpose is to test every newborn for serious but treatable disorders not otherwise apparent at birth
  - Tests are screening tests – not diagnostic
Question

• Newborn screening is a national public health program mandated by
  A. State law
  B. Federal law
Conditions on the NBS

• Core conditions are the conditions that newborn screening is specifically designed to identify.
  – There is a specific and sensitive test available to detect it
  – The health outcomes of the condition are well understood
  – There is an available and effective treatment
  – Identification of the condition could affect the future reproductive decisions of the family
Case “What do I do”

• You receive a call from the newborn screen state lab stating that your new patient has an abnormal newborn screen demonstrating an elevation of the following acylcarnitine species C8, C6, and C10.
What condition on the newborn screen is associated with elevations in acylcarnitine species C8, C6, and C10?

A. Glutaric acidemia type 1 (GA-1)
B. Congenital adrenal hyperplasia (CAH)
C. Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)
D. Phenylketonuria (PKU)
## Case Presentation

- **Review the screen**
  - What are the markers

### Fatty Acid Oxidation Disorder

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Analyte</th>
<th>Results</th>
<th>Cut-off</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCADD</td>
<td>C8</td>
<td>7.63 umol/L</td>
<td>&lt;0.35</td>
<td>Abnormal</td>
</tr>
<tr>
<td></td>
<td>C6</td>
<td>0.95 umol/L</td>
<td>&lt;0.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C10</td>
<td>0.77 umol/L</td>
<td>&lt;0.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C10:1</td>
<td>0.32 umol/L</td>
<td>&lt;0.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C8/C10</td>
<td>9.93</td>
<td>&lt;5.00</td>
<td></td>
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</tbody>
</table>
Case Presentation

• First Places to Visit
  – ACMG ACTSheets

<table>
<thead>
<tr>
<th>FATTY ACID OXIDATION DISORDERS</th>
<th>MCAD</th>
<th>C8;C6;C10</th>
<th>ACT Sheet (PDF, 276K)</th>
<th>Algorithm (PDF, 53K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT 1 deficiency</td>
<td>C0; C0/C16+C18</td>
<td>ACT Sheet (PDF, 275K)</td>
<td>Algorithm (PDF, 67K)</td>
<td></td>
</tr>
<tr>
<td>CPT2 CACT</td>
<td>C16 and/or C13:1</td>
<td>ACT Sheet (PDF, 274K)</td>
<td>Algorithm (PDF, 59K)</td>
<td></td>
</tr>
</tbody>
</table>
Are you using the ACT Sheets when you receive an abnormal newborn screen?

A. Yes
B. No

Yes: 50%
No: 50%

15
Case Presentation

- Star- G Website
- (Parent and Physician Factsheet)
- [http://www.newbornscreening.info/](http://www.newbornscreening.info/)

![Diagram of Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)]
Case Presentation

• Two week old, Caucasian male, with a BW 7lbs 4 oz, BL 20 in. The infant had no complications at birth and was discharged home after 2 days.

• Upon evaluation the infant has had poor weight gain and is not breast feeding well.
Question

• Is poor weight gain, spitting up, and poor feeding normal with infants with MCADD?
  – A. Yes
  – B. No
Is poor weight gain, spitting up, and poor feeding normal with infants with MCADD?

A. Yes

B. No

15

50%  50%
Family History

Episodes of hypoglycemia

Poor wt gain as infant

Poor wt gain as infant

Seizures onset childhood

d. 6 mos

d. SIDS

2 mos

Abnl NBS
Is it odd that there is no family history of MCADD?

A. Yes  
B. No
What is the most striking feature in the family history?

A. Poor weight gain in father and paternal uncle
B. Childhood seizures in mother
C. Infantile death in sister
D. Hypoglycemia in paternal grandmother

25%  25%  25%  25%
MCADD Recommendations

• ACTSheet

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Contact family to inform them of the newborn screening result and ascertain clinical status (poor feeding, vomiting, lethargy).
- Consult with pediatric metabolic specialist.
- Evaluate the newborn (poor feeding, lethargy, hypotonia, hepatomegaly). If signs are present or infant is ill, transport infant to hospital for emergency treatment that would include IV glucose and any further treatment in consultation with the metabolic specialist.
- If infant is normal initiate timely confirmatory/diagnostic testing, as recommended by specialist.
- Educate family about need for infant to avoid fasting and the need for immediate medical attention if the infant even becomes mildly ill (poor feeding, vomiting, or lethargy).
- Report findings to newborn screening program.
Results Confirm MCADD

- Make referral to metabolic geneticist if not already done
- Stress importance of frequent feedings
  - At risk infants need to feed at least every 4 hours
- During times of illness, infant should be monitored closely and sent to the ER for IV fluids if lethargy, poor feeding, or vomiting persist
Meeting with the Geneticist

• Most geneticists are able to see patients with an abnormal newborn screen in a timely fashion

• Review treatment plan
  – Frequent feedings
  – ER Protocol
  – Carnitine supplementation
Team Effort

• The geneticist needs the pediatrician
• Upon illness, families may contact you first.
• Build that relationship
  – Geneticist
  – Genetic Counselor
  – Dietician
Future Pregnancies

• The growing family...what to do about future pregnancies
  – Contact geneticist
  – Make a plan
  – Review inheritance with the family
  – Discuss options for the future pregnancy
  – Flag NBS
Transitioning Children

• Reinforce education of child’s condition to family and child
• Discuss management periodically as it changes over time
• As child gets older, discuss reproductive impact of their condition
Summary

• NBS is an evolving program
  – Utilize resources to help you identify patients at risk for genetic conditions and how to manage them
  – Connect with your geneticist
  – Take an active role in the care of your patient with an abnormal newborn screen
References


Websites
- www.babysfirsttest.org
- www.newbornscreening.info/
Putting it Together for Providers on the Front Lines

Beth Tarini
Assistant Professor of Pediatrics
University of Michigan
Newborn Screening
Help!

• Remember you are not alone
  – ACT sheets, state NBS website
  – Local geneticist/specialist
  – State Newborn Screening Program personnel

• Take advantage of information provided
  – Call NBS program contact number
Look Through Parents’ Eyes

- This is likely to be a shock to parents
  - Baby appears healthy
  - May not remember NBS

- Draw on experience from other clinical situations with abnormal lab tests
  - Abnormal CBC → potential cancer dx
  - Glucosuria → potential diabetes dx

- Parents’ ability to process info impaired
  - Repeat, revisit, ask questions
But the NBS was negative...

• A negative newborn screening result does not always rule out disease
• False negatives occur
• If you suspect a newborn screening disorder, test for it.
Questions/comments for the panel?
Identifying Children with Suspected Genetic Condition
“There is too much to know…”

- STOP & REMEMBER---
  - You are not a geneticist
  - You need to know clinical associations, not genetic mechanisms
  - You can look up detailed information later
What do I need to do?
Continue to ask..

“Could this be genetic?”
Family History

• Take one
• Record information in an accessible place
• Routinely review past information
• If you are unsure about whether there is a genetic risk, contact an expert
Where do I find experts?
Be Creative

• Call your Regional Collaborative

• Call the nearest hospital with pediatric specialists
  – Even if it is in another state

• Use Google
Questions/comments for the panel?