Overview of Genetic Testing and Screening

Leah Burke, MD, FAAP, FACMG

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Acknowledgements

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Faculty

Leah Burke, MD, FAAP, FACMG

– Active faculty member in the College of Medicine at the University of Vermont
– Chair of the AAP Section on Genetics and Birth Defects
Dr Burke has no financial relationships or conflicts of interest to disclose relevant to this presentation.
Learning Objectives

1. Differentiate between diagnostic and screening genetic tests and their appropriate use in pediatrics
2. Describe several types of diagnostic genetic testing and their limits and applications
3. Demonstrate how to access current information and resources for genetic testing
Genetic Testing

**Screening** vs **Diagnostic**

**Screening**
- Testing done on a particular population
- Individuals are asymptomatic
- Not designed to diagnose, simply to identify individuals at a higher risk
- May lead to diagnostic tests

**Diagnostic**
- Testing done on individuals
- Individuals are often symptomatic
- Individuals may have had a positive screening test
- May lead to treatment options
Genetic Screening Test Examples

- Family history
- Prenatal screening tests
- Newborn screening tests
- M-CHAT screening test for Autism
Diagnostic Genetic Testing

Karyotype

Microarray

FISH Image
Fluorescence In Situ Hybridization
Karyotype

http://www.nature.com/scitable/content/cells-growing-in-a-tissue-culture-14264811
Chromosome Analysis

Karyotype
Arranging chromosomes in order to facilitate chromosome analysis

- Microscope 100-X mag.
- Digital imaging
- Karyotyping software
Karyotype

Compare the Karyotype to published Idiograms

2p24
2q10
2q34
FISH: Fluorescence in situ Hybridization
FISH: Fluorescence in situ Hybridization
FISH

- You need to know the specific areas for which you are doing the test
- Can be done on either metaphase or interphase chromosomes
- Works best for deletions
Diagnostic Genetic Testing

Karyotype

Microarray

FISH Image

Fluorescence In Situ Hybridization
Whole Genome Microarray
Comparative Genomic Hybridization (CGH)

Reference DNA

Test DNA

Mix

Block repeated sequences

Hybridize

Microarray with oligonucleotides
Whole Genome CGH Microarrays

- 118,000 - 135,000 oligonucleotide probes for detection of copy number variants (CNVs) anywhere in the genome
  - CNVs as small as 500 bp to 15 kb in targeted locations
  - CNVs from 15 kb to the length of an entire chromosome in the rest of the genome

- Some have additional genes associated with neurodevelopmental disorders that are targeted at the exon level to detect intragenic copy number mutations
Whole Genome Oligonucleotide Microarray

Targeted areas of interest

Whole genome coverage

Targeted areas of interest
## Comparison

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Individual FISH test</th>
<th>Whole Genome Microarray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can detect whole chromosome differences, translocations, and large deletions or duplications</td>
<td>Only looks at specific areas for deletions or duplications</td>
<td>Can detect very small duplications or deletions and high level mosaicism</td>
</tr>
</tbody>
</table>
Case #1

• Newborn term infant – born to a G3P3 mom
• Initially had grunting and went to NICU
• Noted to have epicanthal folds, 5th finger clinodactyly, 3-4 syndactyly of the toes and mildly increased nuchal skin
• No clear syndrome diagnosis
• Karyotype sent – and was normal
Case #1: Follow-up

- Hypsarrhythmia dx at 6 months, treated with Keppra without recurrence
- Referred for OT, PT, and speech
- At 13 months is walking and saying Mama and Dada
- Parents note that people keep asking them if he has Down syndrome
- Referred to the Genetics Clinic
Microarray (aCGH) Results

- Found to have a duplication of the terminal end of the long arm of chromosome 21
Reevaluating the Karyotype Results

- The duplicated material was inserted into the short arm of chromosome 21
- The duplicated material had a similar structure to an expanded satellite region
Karyotype
Single Nucleotide Polymorphism (SNP)
Single Nucleotide Polymorphism (SNP)

• Linked SNPs – basis for DNA fingerprinting and identifying position of genes

• Causative genes
  – Disease causing mutations
  – Susceptibility
  – Pharmacogenetics

Genetic Science Learning Center, University of Utah
http://learn.genetics.utah.edu
Whole Genome (CGH) Microarray With SNP Array

Targeted areas of interest

Whole genome coverage

Targeted areas of interest
SNP Arrays added to CGH Microarrays

• Contain all of the oligonucleotide probes to detect copy number variants (CNVs)
• Also contain 66,000 SNP probes throughout the genome
  – Can detect stretches of homozygosity extending 10 Mb or longer.
Whole Genome (CGH) Microarray
With SNP Array

Targeted areas of interest

Whole genome coverage

Targeted areas of interest

Loss of heterozygosity
Loss of Heterozygosity (LOH)

- Cancer – tumor tissue

Oncogene 2008 Vol: 27(35):4788-4797. DOI: 10.1038/onc.2008.113
Loss of Heterozygosity (LOH)

• Cancer – tumor tissue
• Uniparental disomy
  – Usually confined to a particular gene, segment of a chromosome, or chromosome
  – Some syndromes can be caused by uniparental disomy of a particular chromosome or part of a chromosome
    • Beckwith-Wiedemann
    • Prader-Willi
    • Angelman
    • Russell-Silver
Loss of Heterozygosity (LOH)

- Cancer – tumor tissue
- Uniparental disomy
- May uncover consanguinity
  - Usually involves multiple chromosomes
  - Percentage of homozygosity or LOH can indicate the closeness of the relationship of the parents
    - i.e. >25% indicates possible 1st degree relative
Case #2

- Four day old infant is seen for severe intrauterine growth restriction, cleft palate, and unusual facial features
- Whole genome microarray (CGH + SNP) was sent
Case #2

- Microarray results: 645 Mb (23%) of autosomal genomic length
Case #2

Diagram of family tree showing generations with labels: 18 YO, 4 YO, 18 Mo, and NO INFO.
What about prenatal testing?
Whole Genome Oligonucleotide Microarray

Targeted areas of interest

Whole genome coverage

Postnatal Array

Targeted areas of interest

Whole genome coverage

Prenatal Array

Targeted areas of interest

Whole genome coverage
Take Home Points

• Both karyotypes and microarrays pick up missing or added chromosomes (i.e. Down syndrome or Turner syndrome)

• Microarrays pick up smaller deletions and duplications than karyotypes

• Karyotypes pick up translocations, microarrays do not

• Neither pick up sequence changes
Mutation Testing

- Set of common mutations
- Mutation scanning
- Gene sequencing
Genetic Testing

**Screening** vs **Diagnostic**

- Testing done on a particular population
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Newborn Screening

Screening

Diagnostic
Genetic Testing in Newborn Screening

• Initial testing in newborn is verified by reflex genetic testing in some conditions

• Formal informed consent is not usually obtained
Case #3

- A baby born to a G2P1 mother was diagnosed with meconium ileus at birth.
- Sweat chloride testing was positive for CF.
- The couple had had carrier screening for cystic fibrosis (CF) during the pregnancy.
- The mother had been found to have a common CF mutation and the father’s screening test was negative.
Case #3

- Newborn screening test was also positive for CF
- Reflex testing only revealed one mutation, that found in the mother
Testing for Specific or Common Mutations

- The DNA segments of interest are amplified in the patient sample.
- They are then compared to DNA segments with known mutations on a gel electrophoresis.
- Most newborn screening programs use a panel of CF mutations as a reflex test.
Case #3: Follow-Up

• Baby had sequencing done of the whole CF gene and was found to have a second rare mutation
• Father was subsequently tested and found to carry the rare mutation
Case #4

• A newborn infant has a positive newborn screen for cystic fibrosis (CF)
• Newborn screening for CF involves first testing for elevated immunoreactive trypsinogen (IRT), an indicator of pancreatic insufficiency
• When an elevated IRT is found, reflex testing of a panel of CF mutations is done
Case #4

• Reflex genetic testing reveals two different CF mutations
• Both parents had prenatal carrier screening for CF; only the mother was found to be a carrier
• What could this mean?
Case #4: Follow-up

• The parents were retested and only the mother was a carrier
• The implications for paternity were discussed with the couple
Take Home Points: Newborn Screening

• Newborn screening test includes many genetic disorders
• Initial positive screens often reflex to mutation testing that may reveal carrier status or lead to further genetic testing in the baby and the parents
• Pediatricians need to understand the nature of the testing and when to refer for genetic counseling
• Ideally the parents will have discussed the implications of newborn screening testing prior to delivery
Mutation Testing

• Set of common mutations
• Mutation scanning
• Gene sequencing
Sequencing

• The patient DNA is amplified by PCR using non-labeled deoxy nucleotides and fluorescently labeled dideoxy nucleotides

• Each time a labeled dideoxy nucleotide is incorporated, the copying stops leaving segments of various lengths ending in fluorescently labeled nucleotides
Sequencing

Normal Nucleotides: dATP, dTTP, dGTP, dCTP

Fluorescently labeled Dideoxy nucleotides: ddATP, ddTTP, ddGTP, ddCTP

DNA Fragments
Sequencing

• The segments are sorted by size using the colors

• Reported out as wavelengths
Next Generation Sequencing

• A massively parallel sequencing technology in which millions of overlapping “reads” of DNA sequences are done simultaneously
• Creates an enormous amount of data to be analyzed
• Can detect single gene mutations including nonsense, missense, splice-site, and frameshift mutations
• Used in cardiovascular diagnosis and cancer as well as childhood syndromes
Whole Exome Sequencing

• Now being offered clinically
• Parallel sequencing of at least 98% of the coding sequences
• Recommended when all other diagnostic testing has been negative
• Cost is still prohibitive for most situations
• Recommend sequencing the child and both parents together to address changes that are not clear
• Findings must be confirmed using a second method
Variants of Unknown Significance: The Dreaded VUS
Variants of Unknown Significance: The Dreaded VUS

• With aCGH (microarrays) you may get a result which is reported out as of “unknown significance”
• Comparing to parental samples may help
• Looking at the specific change and its possible effect on the resultant protein may help
• Bottom line: parents want to know what it means
• Very important to counsel parents about VUS BEFORE testing
Variants of Unknown Significance: The Dreaded VUS

• With whole genome sequencing or whole exome sequencing, the chance of VUS is even greater

• Bottom line: parents want to know what it means

• Very important to counsel parents about VUS BEFORE testing
Where do you find information on genetic conditions and testing?
Visit the GeneTests booth (#424) at the American Society of Human Genetics (ASHG) meeting in Boston October 23-25.

Tell us how we're doing.
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Tell us how we're doing.
<table>
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<th>Related Disorders</th>
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<tbody>
<tr>
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<td>Noonan Syndrome 1</td>
<td></td>
</tr>
<tr>
<td>KRAS-Related Noonan Syndrome</td>
<td>Noonan Syndrome 3</td>
<td></td>
</tr>
<tr>
<td>SOS1-Related Noonan Syndrome</td>
<td>Noonan Syndrome 4</td>
<td></td>
</tr>
<tr>
<td>RAF1-Related Noonan Syndrome</td>
<td>Noonan Syndrome 5</td>
<td></td>
</tr>
<tr>
<td>NRAS-Related Noonan Syndrome</td>
<td>Noonan Syndrome 6</td>
<td></td>
</tr>
<tr>
<td>BRAF-Related Noonan Syndrome</td>
<td>Noonan Syndrome 7</td>
<td></td>
</tr>
<tr>
<td>MAP2K1-Related Noonan Syndrome</td>
<td>Noonan Syndrome 8</td>
<td></td>
</tr>
<tr>
<td>Noonan Syndrome</td>
<td></td>
<td>Noonan Syndrome 1</td>
</tr>
<tr>
<td>Neurofibromatosis-Noonan Syndrome</td>
<td></td>
<td>NFNS</td>
</tr>
</tbody>
</table>
## Disorder Search

### Results for NOONAN

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<td>Noonan Syndrome</td>
<td>GeneReview, OMIM</td>
<td></td>
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<tr>
<td>Neurofibromatosis- Noonan Syndrome</td>
<td>Tests, OMIM</td>
<td></td>
</tr>
</tbody>
</table>

[Source: www.ncbi.nlm.nih.gov/books/n gene/noonan]
GeneReviews™ [Internet].

Noonan Syndrome
Includes: BRAF-Related Noonan Syndrome, KRAS-Related Noonan Syndrome, MAP2K1-Related Noonan Syndrome, NRAS-Related Noonan Syndrome, PTPN11-Related Noonan Syndrome, RAFT-Related Noonan Syndrome, SOS1-Related Noonan Syndrome

Judith E Allanson, MD and Amy E Roberts, MD.

Author Information
Initial Posting: November 15, 2001; Last Update: August 4, 2011.

Summary
Disease characteristics. Noonan syndrome (NS) is characterized by short stature, congenital heart defect, and developmental delay of variable degree. Other findings can include broad or webbed neck, unusual chest shape with superior pectus carinatum and inferior pectus excavatum, cryptorchidism, characteristic facies, variegated coagulation defects, lymphatic dysplasias, and ocular abnormalities. Although birth length is usually normal, final adult height approaches the lower limit of normal. Congenital heart disease occurs in 60%-80% of individuals. Pulmonary valve stenosis, often with dysplasia, is the most common heart defect and is found in 20%-50% of individuals. Hypertrophic cardiomyopathy, found in 20%-30% of individuals, may be present at birth or develop in infancy or childhood. Other structural defects include atrial and ventricular septal defects, branch pulmonary artery stenosis, and tetralogy of Fallot. Up to one third of affected individuals have mild intellectual disability.
Testing by multigene panel: Multigene panels can be used for the simultaneous analysis of some or all of the genes in the Ras/MAPK pathway associated with Noonan syndrome. These panels vary by methods used and genes included; thus, the ability of a panel to detect a causative mutation or mutations in any given individual with the Noonan syndrome phenotype also varies.

Table 1. Summary of Molecular Genetic Testing Used in Noonan Syndrome (NS)

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Proportion of NS Attributed to Mutations in This Gene</th>
<th>Test Method</th>
<th>Mutations Detected</th>
<th>Test Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTPN11</td>
<td>50%</td>
<td>Sequence analysis / mutation scanning 1, 2, 3</td>
<td>Sequence variants 4</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion / duplication analysis 5</td>
<td>Partial- and whole-gene deletion 6</td>
<td></td>
</tr>
<tr>
<td>SOS1</td>
<td>10%-13%</td>
<td>Sequence analysis / mutation scanning 1, 2, 3</td>
<td>Sequence variants 4</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion / duplication analysis 5</td>
<td>Partial- and whole-gene deletion 6</td>
<td></td>
</tr>
<tr>
<td>RAF1</td>
<td>3%-17%</td>
<td>Sequence analysis 2, 5</td>
<td>Sequence variants 4</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion / duplication analysis 5</td>
<td>Partial- and whole-gene deletion 6</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>&lt;5%</td>
<td>Sequence analysis</td>
<td>Sequence variants 4</td>
<td>Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deletion / duplication analysis 5</td>
<td>Partial- and whole-gene deletion 6</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>4 individuals to date</td>
<td>Sequence analysis</td>
<td>Sequence variants 4</td>
<td>Clinical</td>
</tr>
<tr>
<td>BRAF</td>
<td>&lt;2% 10</td>
<td>Sequence analysis / mutation scanning 1, 2</td>
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<td>MAP2K1</td>
<td>&lt;2% 11</td>
<td>Sequence analysis 2</td>
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</tr>
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</tbody>
</table>

1. Sequence analysis and mutation scanning of the entire gene can have similar detection frequencies; however, detection rates for mutation scanning may vary considerably between laboratories based on specific protocol used.

2. Some laboratories offer sequencing of select exons. Note: The exons sequenced may vary by laboratory. Some laboratories offer a tiered approach to testing; if a mutation is not identified in the selected exons, the remaining exons are sequenced.
Noonan/ Costello/ LEOPARD/ Cardiofaciocutaneous Syndrome(s) (RAS/MAPK Pathway) Multi-Gene Panels - Tests
Disorders

Noonan/ Costello/ LEOPARD/ Cardiofaciocutaneous Syndrome(s) (RAS/MAPK Pathway) Multi-Gene Panels

<table>
<thead>
<tr>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>CeGaT GmbH - Tuebingen, Germany</td>
</tr>
<tr>
<td>Children's Hospital of Philadelphia, Molecular Genetics Laboratory - Philadelphia, PA, USA</td>
</tr>
<tr>
<td>GeneDx - Gaithersburg, MD, USA</td>
</tr>
<tr>
<td>GGA - Galil Genetic Analysis - Kfarren, Israel</td>
</tr>
</tbody>
</table>
negative predictive value

The likelihood that an individual with a negative test result is actually unaffected and/or does not have the particular gene mutation in question

newborn screening

Testing done within days of birth to identify infants at increased risk for a specific genetic disorder so that treatment can begin as soon as possible. When a newborn screening result is positive, further diagnostic testing is usually required to confirm or specify the results and counseling is offered to educate the parents.

Related Terms: diagnostic testing, screening, sensitivity, specificity

nonsense mutation

A single base pair substitution that prematurely codes for a stop in amino acid translation (stop codon)

northern blot

Synonym: northern blotting analysis

The separation of sequences or fragments of RNA, partially digested by endonucleases, on an electrophoretic gel

novel mutation

A distinct gene alteration that has been newly discovered; not the same as a 'new' or 'de novo' mutation

nucleotide

A molecule consisting of a nitrogenous base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate group, and a sugar (deoxyribose in DNA, ribose in RNA). DNA and RNA are polymers of many nucleotides.

null allele

A mutation that results in either no gene product or the absence of function at the phenotypic level

obligate carrier

Synonym: obligate heterozygote

An individual who may be clinically unaffected but who must carry a gene mutation based on analysis of the family history
Disease Example (newborn screening): Phenylketonuria (PKU)

Phenylketonuria (PKU) is the prototype disorder for newborn screening as it occurs at relatively high frequency in some populations (as high as one in 2000 live births). It is easily detectable through assay of phenylalanine concentration in droplets of blood from a newborn heel prick dried on filter paper, and is readily treatable by dietary modification. PKU is an autosomal recessive condition affecting phenylalanine metabolism, usually caused by mutations in the gene for phenylalanine hydroxylase (PAH), which normally converts the amino acid phenylalanine to the amino acid tyrosine. High levels of accumulated phenylalanine and its metabolites damage the developing central nervous system and interfere with brain function causing significant intellectual impairment. Neurological damage can be avoided if the condition is detected early and dietary consumption of phenylalanine is reduced. Screening is usually done before an infant leaves the hospital. Positive results must be confirmed quickly so that dietary modification can be initiated as soon as possible.

Some Clinical Implications

- Newborn screening programs are usually legally mandated and vary from state to state.
- Newborn screening is performed routinely at birth, unless specifically refused by the parents in writing.
- Screening tests are not designed to be diagnostic, but to identify individuals who may be candidates for further diagnostic tests (Clinical Example).
- Many parents do not realize that newborn screening has been done (or which tests were included), even if they signed a consent form when their child was born.
- Education is necessary with positive screening results in order to avoid misunderstandings, anxiety, and discrimination (Clinical Example).

Box

Clinical Examples of Newborn Screening: Sickle cell disease. Dominique is a 26-year-old woman who has had her first child, Leon. Shortly after Leon's two-week check-up, the pediatrician calls Dominique and tells her that one of Leon's newborn screening (more...)
The information on this website remains accessible, but due to the lapse in government funding, the information may not be up to date, and the agency may not be able to respond to inquiries until appropriations are enacted. For updates regarding government operating status see USA.gov.

Display Settings: Summary, 20 per page

Results: 1 to 20 of 80

#615095 - MICROCEPHALY 10, PRIMARY, Autosomal RECESSIVE; MCHP10
1. OMIM: 615095
   Gene summaries Genetic tests Medical literature

#613970 - MENTAL RETARDATION, AUTOSOMAL DOMINANT 6; MRDS
2. OMIM: 613970
   Gene summaries Genetic tests Medical literature

#613717 - TREACHER COLLINS SYNDROME 2; TCS2
3. Cytogenetic locations: 13q12.2
   OMIM: 613717
   Gene summaries Genetic tests Medical literature

#613611 - CHOANAL ATRESIA AND LYM PHEDEMA
4. Cytogenetic locations: 1q32
   OMIM: 613611
   Gene summaries Genetic tests Medical literature
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Results: 1 to 20 of 80

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   OMIM: 615065
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   Gene summaries, Genetic tests, Medical literature

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4. #613611 - CHOANAL ATRESIA AND LYMPHEDEMA
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   OMIM: 613611
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Showing 1 to 2 of 2 tests for 1 condition in 2 labs

- **Treacher Collins Syndrome 2 (POLR1D related)**
  - **Methods:** DNA Sequence analysis of the entire coding region
  - **Analytical Validity:** At least 97%
  - **Lab:** DNA Diagnostic Laboratory at Johns Hopkins Hospital
  - **Directors:**

- **Treacher Collins Syndrome via the POLR1D Gene**
  - **Methods:** DNA Sequence analysis of the entire coding region
  - **Analytical Validity:** As of July 2013, we compared 7.3 megabases of Sanger DNA sequence generated at PreventionGenetics to NextGen sequence generated in other labs. We detected only 4 errors in our Sanger sequences, and these were all due to allele dropout during PCR (>99% accuracy). For Proficiency Testing, both external and internal, in the 9.5 years of our lab operation we have Sanger sequenced roughly 2,000 PCR amplicons (~1 megabase). No errors have been identified (100.00% accuracy).
Due to the lapse in government funding, the information on this website may not be up to date, transactions submitted via the website may not be processed, and the agency may not be able to respond to inquiries until appropriations are enacted.

Updates regarding government operating status and resumption of normal operations can be found at http://www.usa.gov/.
Resources

- http://www.genetests.org/
Questions
Thank you for your participation!

For more information, please contact

Lindsay Wilson
lwilson@aap.org
847/434-7612

www.GeneticsinPrimaryCare.org
Please join us for our next webinar!

Genetic Red Flags in Well-Checks
Faculty: Beth Pletcher, MD, FAAP, FACMG
November 14, 2013
12pm Eastern (11am Central)

https://www2.gotomeeting.com/register/655831986