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THE PEDIATRIC JOURNEY

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APPROACH TO CHRONIC COUGH IN CHILDREN: AN UPDATE!

ENDY A. DOMINGUEZ SILVEYRA MD FAAP,
Assistant Professor of Pediatrics
Texas Tech Pediatric Pulmonary Medicine Clinic Office: 915-215-5700 Fax: 915-215-8697

Cough is the most common reason why patients acutely seek medical consult with primary care physician in the United Sates.

Chronic cough in children 14 years and younger is defined as a daily cough lasting four or more weeks. It may result in miss school days, multiple physician visit, and place them at risk to adverse effects from inappropriate use of medications, and impairment of their quality of life.

The normal cough mechanism can be simplified into the afferent, central and efferent pathways. An intact cough mechanism it is essential to maintain respiratory health and enhance mucociliary clearance.

Specific cough is defined as cough that is attributable to an underlying cause, while non-specific cough does not have any identifiable cause. It will be most likely dry and without specific cough pointers.

When there is an upregulation or downregulation of the cough, it is considered pathologic. The most common cause of upregulation of the cough (increased cough) is due to respiratory infection. Virus in particular can enhance cough sensitivity, and therefore perpetuating the cough cycle.

Downregulation of the cough reflex (ineffective cough) is secondary to an abnormal afferent neural pathway due to neurodevelopmental abnormalities, placing the patient at risk for salient aspiration and chronic lung disease. These type of cough are seen in tracheostomy or vocal cord palsy, muscular dystrophy or chest wall abnormalities, tracheomalacia or bronchomalacia.

In 2017, the American College of Chest Physician (ACCP) published CHEST guidelines for evaluation of chronic cough in children 14 years old and younger.

There are four general goals for the diagnostic approach.

1. *Does the child have an underlying chronic lung disease that requires further investigations and/or referral?*

2. *Are therapies/medications indicated?*

3. *Are there modifiable factors that exacerbate the cough, such as exposure to tobacco smoke?*

4. *What is the psychosocial impact of the cough on the child and family (e.g., quality of life and function), and what are their expectations for treatment and outcomes?*

Answering these questions require a systematic approach to evaluation, management decisions, and follow-up. Initial work-up consisting of a focused history, physical examination, chest radiography, and spirometry, looking for clues "specific cough pointers" that will help to diagnose the underlying disease. It is important to assess the cough characteristics, like sound and patter, dry vs wet, is the cough during the day or night.

A focused history is recommended to look for key clinical features that predict a specific cause of cough. Social history, psychobehavioral context and triggers of the cough should be explored. As well of the past medical history, neonatal history, recurrent infections, and environmental exposures.

Physical examination can give specific pointer for example; poor growth may be suggestive of chronic illness, eczema or allergic shiners are suggestive of atopic diseases, evidence of a recent rash raises the possibility of a triggering viral infection, or impetigo, which is more common in patients with an immune deficiency, extremities with clubbing or cyanosis, can be a signs of a chronic lung disease.

Chest Inspection, like symmetry vs deformity, use of accessory muscles, breathing pattern. Chest percussion to look for signs of hyperinflation or dullness. Chest auscultation to look for intensity, asymmetry vs symmetry of the breathing sounds, is there wheezing (Polyphonic vs Monophonic), stridor, or crackles.

Chest x ray may show findings like hyperinflation, bilateral peribonchial markings or focal infiltrates, atelectatic process, or even lung masses. Spirometry is an important tool where can be observe low airway obstructive patterns with or without hyperactivity, restrictive patterns, intra or extrathoracic fixed obstruction, among other patterns.

The ACCP summary of recommendations for children aged ≤ 14 years with chronic cough are as follows:

1. *Chronic cough is defined as the presence of daily cough of at least 4 weeks in duration.*

2. *An assessment of the effect of cough on the child and the family be undertaken as part of the clinical consultation.*

3. *To use pediatric-specific cough management protocols or algorithms.*

4. *Use a systematic approach (such as using a validated guideline) to determine the cause of the cough.*

5. *Based on the management or testing algorithm on cough characteristics and the associated clinical history, such as using specific cough pointers like presence of productive/wet cough.*

6. *Based on the management on the etiology of the cough. An empirical approach aimed at treating upper airway cough syndrome due to a rhinosinus condition, gastroesophageal reflux disease, and/or asthma should not be used unless other features consistent with these conditions are present.*

7. *If an empirical trial is used based on features consistent with a hypothesized diagnosis, the trial should be of a defined limited duration in order to confirm or refute the hypothesized diagnosis.*

8. *Undertake chest radiograph and, when age appropriate, spirometry (pre- and post-β2 agonist).*

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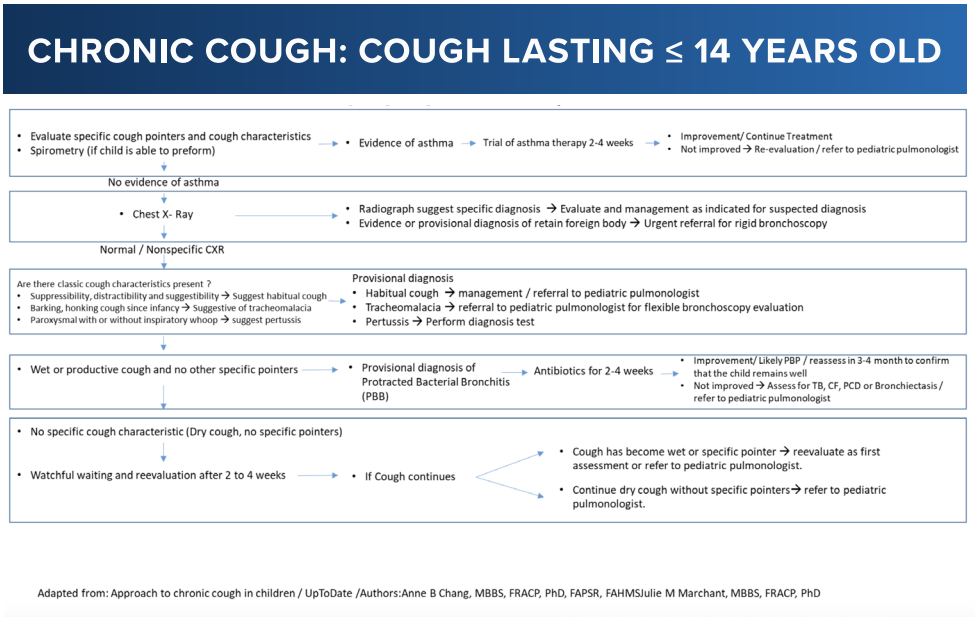
9. *Evaluate for Bordetella pertussis infection when pertussis is clinically suspected.*

10. *Not routinely performing additional tests (e.g., skin prick test, Mantoux, bronchoscopy, chest CT); these should be individualized and undertaken in accordance with the clinical setting.*

11. *For children aged > 6 years and ≤ 14 years with chronic cough and asthma clinically suspected, is suggest that a test for airway hyper responsiveness (AHR) be considered.*

References
Irwin RS. Introduction to the diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129:25S.
Chang AB, Oppenheimer JJ, Weinberger MM, et al. Use of Management Pathways or Algorithms in Children With Chronic Cough: CHEST Guideline and Expert Panel Report. Chest 2017; 151:875.



Adapted from: Approach to chronic cough in children / UpToDate /Authors:Anne B Chang, MBBS, FRACP, PhD, FAPSR, FAHMSJulie M Marchant, MBBS, FRACP, PhD

GENETIC TESTING STRATEGIES IN PEDIATRICS

BY: DANIEL BUSTAMANTE, MD (Pathology) and **ZOE TULLIUS** (Neonatology)

Genetics is one of the most rapidly expanding areas in medicine. The young field has grown immensely since it was discovered that human cells typically have 46 chromosomes in 1956 to next generation sequencing that has been used over the last decade. Trying to figure out which genetic testing strategy will aid in the diagnosis and treatment of our pediatric patients feels a bit like trying to order off the vast menu at the Cheesecake Factory. The goal of this article is to give the non-geneticist a brief overview of normal genetic structure, mutations, and descriptions of some the testing modalities we might use in day-to-day practice.

Our 23 chromosome pairs (22 autosomal pairs and 1 sex pair) consist of double-stranded DNA complexed with histone proteins. Each contains 2 long arms (q), 2 short arms (p), one centromere, and multiple telomeres. Chromosomal numerical abnormalities, especially autosomal ones, contribute significantly to genetic disease. DNA sequence itself can be altered in various ways, both benign and pathologic, including changes in actual sequence, change in amount of given sequence (copy number variation), and change in position (inversion/translocation). These all can occur both in constitutional genetic disease as well as in oncogenesis. As pediatricians, we often struggle to choose the most appropriate test for the diagnosis of a genetic disorder – when do we do a karyotype vs. microarray? when would a FISH be the right test? when is it appropriate to use whole exome sequencing? Here, we'll discuss specific testing strategies, starting with karyotype.

Karyotype requires living cells to divide in culture during which metaphases are examined. Each pair of chromosomes is G-banded, divided into regions, bands, and sub-bands, and organized numerically. Karyotype can detect large deletions or duplications (resolution >5-10 Mb in size) and chromosomal rearrangements that are not associated with a net gain or loss in genetic material but that can cause disease by splitting genes. The major utility of a karyotype is to identify aneuploidy and translocations. Clinically, it can be used in oncology to help diagnose neoplastic disease, determine prognosis, and guide specific treatment. In constitutional disorders, such as in a newborn with multiple congenital anomalies or dysmorphism, karyotype is best used when a critical aneuploidy, such as Down syndrome, Trisomy 13 or 18, or Turner syndrome, is highly suspected or there is known family history of chromosomal rearrangement.

Chromosomal microarray (CMA) is a molecular cytogenetic method used to analyze genomic copy number variants (CNVs). Both types, array-based comparative genomic hybridization and single nucleotide polymorphism-based chrom somal microarray, detect genomic deletions, duplications, and amplifications, while the latter can also detect copy neutral changes, including loss of heterozygosity and uniparental disomy. CMA is done using artificial probes that cover the whole genome. Test DNA and control DNA, labeled with different dyes, are hybridized to a DNA chip. The signal intensities are

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compared. CMA cannot detect point mutations, low-level mosaicism, or balanced chromosomal rearrangements. A normal CMA indicates there are no known clinically significant CNVs or only known benign ones, while abnormal results indicate a CNV within a known, clinically relevant region or of the established size or gene content to be considered pathogenic. CNVs of unknown clinical significance are also common.

CMA can be used for diagnosis and prognosis in the oncology world. In general pediatrics, it is first line in the evaluation of multiple congenital anomalies (not obviously related to an aneuploidy syndrome), including complex congenital heart disease, in the evaluation of autism spectrum disorder, and in the evaluation of nonsyndromic intellectual disability/developmental delay. If it does not yield a diagnosis, it may be helpful to add a karyotype, seeking a balanced translocation, or to proceed to more targeted testing or parental CMA testing.

Fluorescence in situ hybridization (FISH) uses a fluorescently-labeled probe specific to a certain DNA target sequence. FISH can detect microdeletions and microduplications, the location of a segment of interest on a chromosome, and chromosomal rearrangements. FISH and other targeted testing strategies, such as standard PCR or PCR variants, which exponentially amplify target sequences of DNA, must only be used when, clinically, there is a specific diagnosis, gene/region, or group of genes in mind. For example, there is a widely available FISH probe used for the diagnosis of DiGeorge syndrome. With a specific diagnosis in mind, it may be helpful to contact a pathologist to aid in the choice of which testing methodology would be the most appropriate and available.

Finally, whole exome sequencing sequences all coding regions of the genome using massively parallel sequencing techniques. It is becoming more popular, even as a first-line diagnostic tool, as the cost and turn around times decrease. It is successful in finding a diagnosis 25-40% of the time and can be used where there has been prior extensive negative testing or in an unusual presentation of a disorder. Its use may provide for treatment, prognosis, and family planning, but there is also the possible consequence of finding something pathologic not originally sought or finding something incidental of unknown significance. For these reasons, though it has large diagnostic capabilities, it is recommended that it only be used in consultation with a geneticist and with the provision of good pretest counseling.

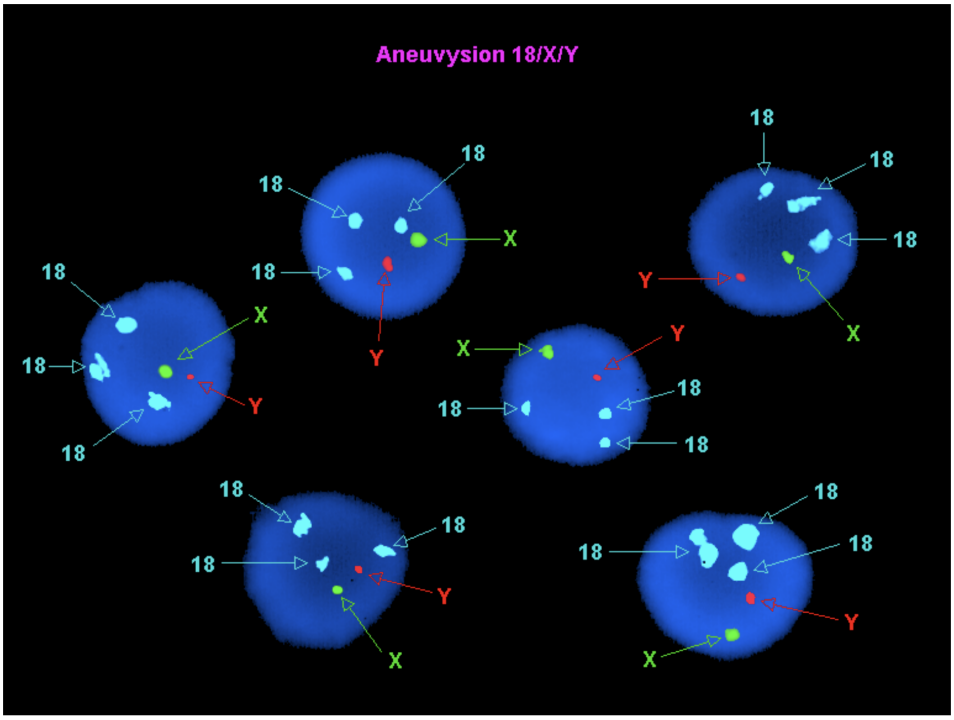
Though this covered a limited number of genetic testing techniques, it will hopefully prove useful in the work up of pediatric patients by highlighting clinical situations in which certain testing might be used. When in doubt, it may be useful to consult with a pathologist (or a geneticist if available) about the most appropriate and available testing strategies.

Diagnostic Test	Indication	Cost*	Turn Around Time*
Karyotype	Suspected aneuploidy, known family history of chromosomal rearrangement	$200-$390	10 days – 4 weeks
Chromosomal Microarray	Test of choice for multiple congenital anomalies, complex congenital heart disease, nonsyndromic developmental delay, autism	$1500-$1750	12 days – 6 weeks
FISH# (or other targeted tests)	Suspected known syndrome, genetic mutation (or set of mutations)	$225-$360	5 days - 2 weeks
Whole Exome Sequencing	Negative prior testing, unusual presentation of disorder, known consanguinity with unknown disorder	Up to $10,000**	2 - 4 weeks

*Dependent on laboratory used

**Cost rapidly changing – some labs quote prices as low as $1000

#Cost and turnaround time apply to FISH



FISH Trisomy 18

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2020 PEDIATRIC GRAND ROUNDS

The First & Third Wednesday of Every Month

Breakfast: 7:30-8 a.m. Grand Rounds: 8-9 a.m.
Academic Education Center (AEC), 2nd Floor, 4800 Alberta Avenue

FEBRUARY 19, 2020	Pediatric Kidney Transplant Introduction: Dr. Villanos	Daniel Ranch, MD UT Health San Antonio
MARCH 4, 2020	Chronic Kidney Disease Cardiovascular Health Introduction: Dr. Khin	Isa F. Ashoor, MD Children's New Orleans
APRIL 1, 2020	Cardiology Introduction: Dr. Maldonado	Ryan Butts, MD UT Southwestern Medical Center
APRIL 15, 2020	Urology Introduction: Dr. Gutierrez	Blake Palmer, MD Cook Children's Hospital
MAY 6, 2020	Urology Introduction: Dr. Gutierrez	"Bradley Fuhrman, MD Texas Tech University HSC El Paso
MAY 20, 2020	Emergency Medicine Introduction: Dr. Maldonado	"Jeff Avner, MD Maimonides Medical Center
JUNE 3, 2020	Emergency Medicine Introduction: Dr. Maldonado	Francis Idada, MD El Paso Children's Hospital
JUNE 17, 2020	Pediatric Gastroenterology Introduction: Dr. Maiyegun	Aldo Maspons, MD El Paso, Texas