

**Genetic Testing in Practice
Ethics and Guidelines**

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Disclosure Statement

I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity

Role of the Primary Care Physician

- Identification of individuals and families who require additional investigation
 - Modes of inheritance
 - What tests might be indicated
 - What would/do results mean
- Communication of genetic information to facilitate informed decision making
- Management of family dynamics

Ethics in Genetic Testing of Children

- **Beneficence: Do good**
 - Act in the best interest of the child
- **Non-maleficance: Do no harm**
 - Action when not indicated or failure to act when required may both cause harm
- **Autonomy: Respect for the individual to make their own decisions**
 - Children will become adults one day
 - Should not over-ride their ultimate autonomy

OBJECTIVES

- **Examine clinical situations where genetic testing is indicated**
 - Diagnostic testing
 - Presymptomatic testing
 - Medical management
- **Examine clinical situations where genetic testing is not indicated**
 - Presymptomatic testing
 - Carrier testing
- **Investigate resources to identify genetic testing options**
- **Review ELSI, consent, financial and insurance issues**

Types of Genetic Testing

- **Diagnostic testing:** used to establish or confirm a suspected clinical diagnosis
 - prognostication
- **Presymptomatic testing:** testing performed on an asymptomatic at-risk individual
- **Carrier testing:** used to determine whether an individual is at risk for passing on a genetic change
- **Family testing:** testing involving several family members (affected and unaffected) to determine if a documented genetic change is clinically significant

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

POLICY STATEMENT
Ethical and Policy Issues in Genetic Testing and Screening of Children

Pediatrics 2013;131:620-622

CASE ONE • Diagnostic testing

CASE TWO • Pre-symptomatic testing

CASE THREE • Pre-symptomatic testing

CASE FOUR • Carrier testing

CASE FIVE • Diagnostic testing

CASE SIX • All together now.....

CASE ONE

THE MOTHER OF A 9 MONTH OLD INFANT IS CONCERNED ABOUT HIS GROWTH AND DEVELOPMENT WHICH ARE ALL SIGNIFICANTLY DELAYED. YOU ARE CONCERNED HE MAY HAVE A CHROMOSOME ABNORMALITY AND ORDER A KARYOTYPE.

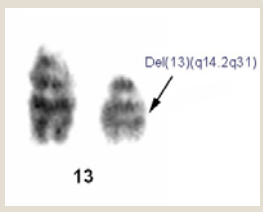
Diagnostic Testing in Minors

DIAGNOSTIC TESTING

3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally and when appropriate, the assent of the child should be obtained.⁴

- How does the AAP/ACMG position statement apply?
- Chromosome analysis to diagnose a suspected abnormality: YES
 - Diagnostic evaluation
 - Genotype/phenotype implications
 - ✦ Treatments
 - ✦ Prognosis
 - ✦ Recurrence risks

46, XY del(13)(q14.2q31)



- Chromosome abnormality associated with MR/ID, growth delay
- DIAGNOSIS
- Referred for early intervention services

46, XY del(13)(q14.2q31)

- 6 months later he is diagnosed with bilateral retinoblastoma
- *RBI* the retinoblastoma gene is located at 13q14.2
 - First 'hit'
 - Extremely high risk for bilateral retinoblastoma and associated treatment related sarcomas

- A 'diagnosis' might not be the only information from genetic testing
- Need to become informed of what other information might result
 - Additional medical issues
 - Limited medical information
 - "other" issues

CASE TWO

AT A TWO MONTH WELL CHILD CHECK THE MOTHER OF YOUR PATIENT MENTIONS THAT SHE IS MORE RELAXED NOW THAT HER BOYFRIEND HAS HAD HIS SURGERY. SHE INFORMS YOU THAT HE HAD COLON CANCER, "LIKE HIS WHOLE FAMILY", AND REMEMBERS BEING TOLD THAT HIS CHILDREN MIGHT BE AT RISK.

WHAT DO YOU DO?

What do you do?

- Additional family history: pedigree
 - Affected family members
 - Inheritance pattern
 - Autosomal dominant

"When in doubt, write it out!"

What do you do?

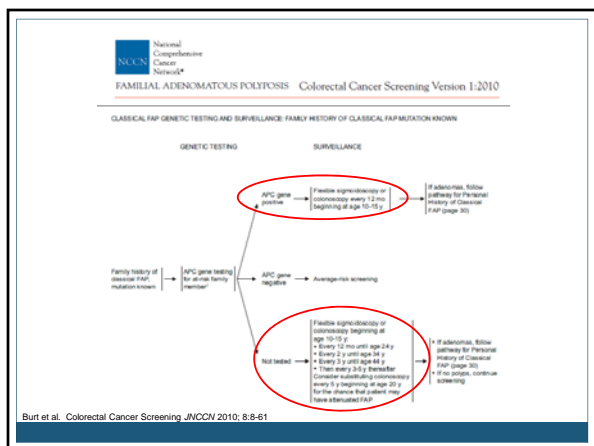
- Consider a differential diagnosis
 - Prioritize: What would kill - what requires immediate treatment to prevent complications- what would recur - everything else
- Where to find information
 - Internet
 - GeneReviews
 - OMIM
 - Telephone call(s)
- What additional information would be helpful
 - More medical details

What do you do?

- **Additional family history**
 - Autosomal dominant
- **Differential diagnosis**
 - Familial adenomatous polyposis
 - Lynch Syndrome/HNPCC
 - Peutz-Jeghers syndrome
- **Clinical Options**
 - Clinical surveillance
 - Pre-symptomatic genetic testing

What are the options?

- **Clinical surveillance**
 - National Guidelines Clearinghouse (<http://guideline.gov/>)
 - ✦ Burt et al. Colorectal Cancer Screening *JNCCN* 2010; 8:8-61.
 - GeneReviews (www.genereviews.org)
- **Pre-symptomatic genetic testing**
 - GeneReviews, no longer updates laboratory information
 - NIH Genetic Testing Registry (www.ncbi.nlm.nih.gov/gtr/)



National Comprehensive Cancer Network
LYNCH SYNDROME Colorectal Cancer Screening Version 1-2010

SURVEILLANCE** **FOLLOW-UP***

Distal cancer:

- Colonoscopy at age 25-29 y. or 10 y before the youngest age at diagnosis if the benefit, however distant first, and repeat every 1-2 y.

Etiologic:

- Etiological and variant cancer
- Consider referral to geriatric oncologist for screening for geriatric cancer
- Encourage patient education and prompt response to endometrial cancer symptoms
- Prophylactic hysterectomy and bilateral salpingo-oophorectomy is a risk-reducing option for women who have completed childbearing
- Gastric and duodenal cancer: consider upper GI endoscopy (including side-viewing examinations) at age 25-30 y and repeat every 1-3 y, depending on findings
- Urinary cancer: consider annual urinalysis
- GI and other annual physical examinations: no additional screening recommendations have been made
- Pancreatic cancer: no recommendations have been made

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    graph LR
      NoPath[No pathologic findings] --> CS[Continued screening]
      CS --> C1[Consider prophylactic total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) if postmenopausal or family completed]
      Adeno[Adenocarcinomas] --> F1[See appropriate NCCN disease-specific treatment guidelines at www.NCCN.org]
      Adeno --> F2[Endoscopy in conjunction with follow-up colonoscopy every 1-2 y, depending on: Location, character, Surgical risk, Patient preference]
      Adeno --> F3[Table abdominal cavity with distal endoscopy]
      F3 --> F3a[Consider TAH/BSO at time of colon surgery if postmenopausal or family completed]
      F3 --> F3b[Endoscopic review every 1-2 y]
      Adeno --> F4[Adenomas not amenable to endoscopic resection or high-grade dysplasia]
  
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Burt et al. Colorectal Cancer Screening JNCCN 2010; 8:8-61

National Comprehensive Cancer Network
FELTZ-JEGHERS SYNDROME Colorectal Cancer Screening Version 1-2010

Felzt-Jeghers Syndrome (FJJS) Definition 1*

- Presence of FJJS can be made when an individual has 2 or more of the following features:
 - The or more FJJS-type hamartomatous polyps of the small intestine
 - Microscopic hyperplasia of the mouth, lab, nose, vagin, genitalia, or fingers
 - Family history of FJJS

Screening Considerations:

- While the overall rate of mutation in the SMAD4 gene and clinical genetic testing is variable
- Referral to a specialist team is recommended and participation in clinical trials is strongly encouraged
- Survival advantage of the asymptomatic upper gastrointestinal tract has not clearly occurred; any early symptoms should be evaluated thoroughly
- The surveillance guidelines were based on the multiple organs at risk for cancer risk potential, but may be considered in view of the cancer risk in FJJS and the known efficacy of the tests. Data are underpinning the efficacy of various screening modalities in FJJS.

Disease (Risk)	Screening Procedure and Interval	Initiation Age(s)
Breast (10%-20%)	Mammogram and breast MRI annually + Ultrasound every 6 mo	18 y
Colon (10%)	Colonoscopy every 2-3 y	16-18 years
Pancreas (11%-16%)	Annual endoscopic ultrasonography (EUS) plus CA-19-9 or other marker	18 y
Stomach (20%-25%) and Esophagus (15%)	Upper endoscopy every 2-3 y and lower bowel visualization (CT enterography, small bowel enteroscopy) every 2-3 y or with symptoms	16 y
Chyle (10%-17%) (small intestine) (15%-20%)	Physical examination and MRI enteroclysis + Consider pathological alterations	16-20 y
Small Intestine (10%-15%)	Annual histologic exam and observation for alarming changes	16 y
Lung (10%-17%)	Low-dose CT scan + Consider endoscopic surveillance + Education about symptoms and smoking cessation	

Burt et al. Colorectal Cancer Screening JNCCN 2010; 8:8-61

Pre-symptomatic Genetic Testing

PREDICTIVE GENETIC TESTING

- Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
- Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.

- How does the AAP/ACMG position statement apply?
- FAP and PJS: YES
 - There are risks for development of complications in childhood
 - Clinical surveillance should begin in childhood
- HNPCC: NO (maybe)
 - Earliest age at onset

Outcome

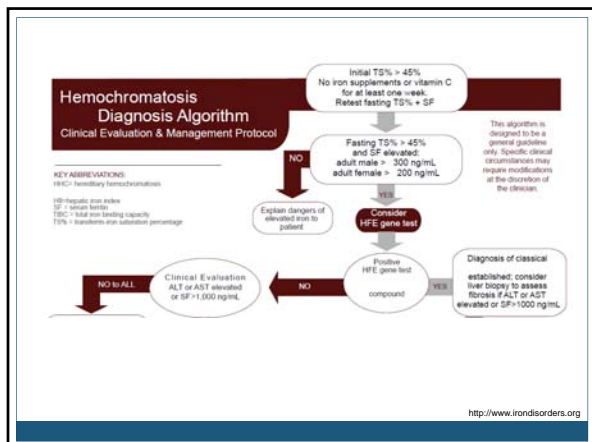
- **Discuss options with family**
 - Genetics referral for further discussion
 - Consider pre-symptomatic testing vs clinical surveillance
- **Genetic testing is an option**
 - Only if an affected individual has had testing and it is informative (ie this infant's father should have testing initially)
 - If testing is un-informative or if an affected individual is not available for testing, must proceed with clinical surveillance

CASE THREE

THE MOTHER OF A 5 YEAR OLD BOY AND AN 8 YEAR OLD GIRL IN YOUR PRACTICE INFORM YOU THAT HER FATHER, WHO HAS MULTIPLE MEDICAL PROBLEMS, WAS RECENTLY DIAGNOSED WITH HEMOCHROMATOSIS. MOM HAS BEEN TOLD THAT THIS IS A GENETIC CONDITION AND WANTS TO HAVE HER CHILDREN TESTED.

What is hemochromatosis?

- **Autosomal recessive disorder of iron metabolism resulting in storage of excessive iron over time**
- **Onset of symptoms in adulthood (usually >30 years)**
 - Hepatosplenomegaly > cirrhosis > HCCa
 - Arthritis, cardiomyopathy, DM, hyperpigmentation
- **Treatment: phlebotomy**
- **Screening:**
 - Serum ferritin, transferrin saturation
- **DNA testing: available**



DNA testing in hemochromatosis

- **HFE gene allele frequency**
 - p. C282Y (c.845G>A) : 4% Caucasian population
 - p. H63D (c. 187C>G): 25% Caucasian population
- **HFE in affected individuals**
 - 80% homozygous p.C282Y
 - 5% compound heterozygotes
 - 15% other mutations and combinations
- **Variable penetrance**
 - Of individuals C282Y/C282Y only 15-20% of males will be symptomatic, only 5% of females (50% biochemical evidence of iron overload)

Pre-symptomatic Genetic Testing

PREDICTIVE GENETIC TESTING

8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.
9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.

- **How does the AAP/ACMG position statement apply?**
- **Hemochromatosis: NO**
 - There are no risks for development of complications in childhood
 - There are no interventions to be made in childhood to reduce risks

Outcome

- **Discuss options with family**
 - Genetics referral for mother to review disease and natural history
 - No role for testing children
- **Clinical surveillance is an option for mom**
 - Could consider iron studies in the children
- **Genetic testing is an option for mom**
 - Only if an affected individual has had testing and it is informative (ie will require knowledge of her father's test results)

Presymptomatic testing in childhood for an adult onset condition

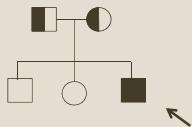
CASE TWO	CASE THREE
<ul style="list-style-type: none"> • YES • There are risk of disease in childhood • Interventions in childhood are recommended 	<ul style="list-style-type: none"> • NO • No interventions in childhood are necessary

CASE FOUR

ONE OF YOUR PATIENTS HAS BEEN DIAGNOSED WITH CYSTIC FIBROSIS. DURING HIS EVALUATION HE WAS FOUND TO HAVE TWO COPIES OF THE COMMON ΔF508 MUTATION. HIS MOTHER IS CONCERNED THAT HIS OLDER SIBLINGS COULD ALSO HAVE CF AND REQUESTS TESTING.

What do you know about CF?

- **Autosomal recessive disorder**
 - 1/30 carrier frequency in Caucasians
 - Parents of your patients are obligate carriers
 - Siblings of your patient have a 1/4 chance of being affected
 - Unaffected siblings have a 2/3 chance of being carriers



What do you know about CF?

- **Autosomal recessive disorder**
 - Siblings are at-risk for being carriers or affected
- **Testing options**
 - Sweat chloride : Gold standard, Diagnostic
 - DNA testing widely available
 - Prenatal carrier screening
 - Supportive, but not diagnostic
 - Newborn screening (all 50 states)
 - Various methods including IRT and DNA

Prenatal Carrier Screening for CF

- **ACOG and ACMG recommend CF carrier screening to all couples considering pregnancy**
- **Universal screening panel of 23 mutations**
- **Detection rates vary by ethnicity**
 - Caucasian 1/25 carrier frequency; 88% detection rate
 - A Jewish 1/24 carrier frequency; 94% detection rate
 - A American 1/61 carrier frequency; 64% detection rate
 - Hispanic 1/58 carrier frequency; 72% detection rate
 - Asian American 1/94 carrier frequency; 49% detection rate

Technical Standards and Guidelines for CFTR Mutation Testing
Approved by the Board of Directors of the American College of Medical Genetics October 26, 2002. Genetics in Medicine 2002;3 (5).
Reviewed and Revised: 2005 by the Molecular Subcommittees of the Laboratory Quality Assurance Committee

Newborn Screening for CF

- Performed in all 50 states
 - www.babiesfirsttest.org
- Various methods
 - IRT (immunoreactive trypsinogen)
 - DNA: several different options, state dependent
- Depending on where and when the other children were born they may have been screened
 - May or may not have had DNA testing performed as part of the screen, state dependent
 - May or may not have been reported (carrier status state dependent)

Carrier Genetic Testing in Minors

CARRIER TESTING
6. The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The

- How does the AAP/ACMG position statement apply?
- CF DNA carrier testing: NO
 - There are no health benefits of knowing carrier status in childhood
 - Recognition that this may happen as a result of NBS (not the reason for NBS)

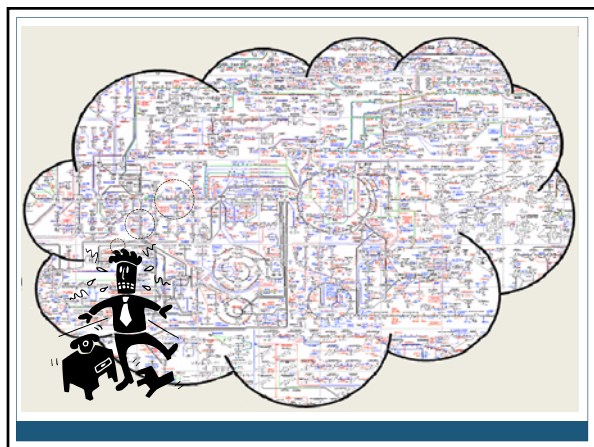
Diagnostic Testing in Minors

DIAGNOSTIC TESTING
3. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally and when appropriate, the assent of the child should be obtained.*

- How does the AAP/ACMG position statement apply?
- CF DNA testing as first line: NO
 - There is a more appropriate clinical test available
- CF DNA as confirmatory testing: YES
 - In general, may provide genotype/phenotype information that is useful for management

CASE FIVE

YOU HAVE RECEIVED A CALL FROM YOUR STATE NEWBORN SCREENING COORDINATOR THAT A NEW INFANT IN YOUR PRACTICE HAS AN ELEVATED GALACTOSE.

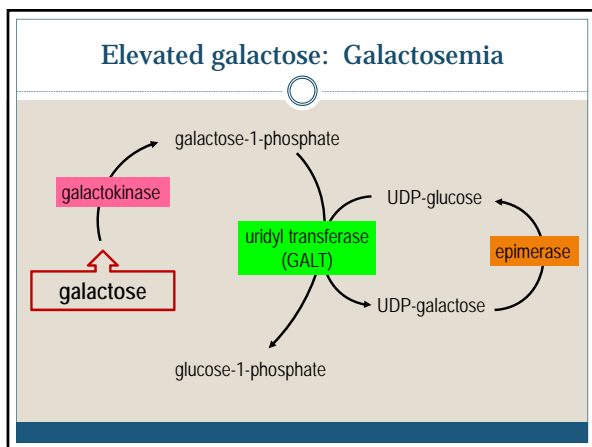


Do Not Panic

- **Read the report**
 - Verify patient demographics
 - Review testing information (dates, times etc)
- **Identify the analyte/condition of concern**
- **Review the recommendations**
 - Pending results (secondary markers)
 - Repeat screen
 - Diagnostic testing
 - Other actions

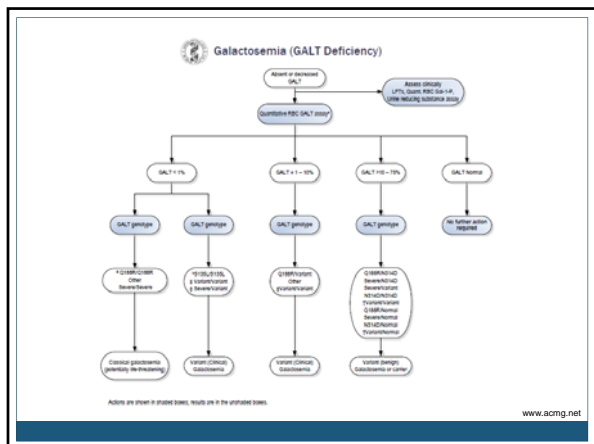
CASE FIVE

Infant A	Infant B
<ul style="list-style-type: none"> • Total galactose 20mg/dl <ul style="list-style-type: none"> ○ Normal < 14 mg/dl • Uridyltransferase activity 1 <ul style="list-style-type: none"> ○ Normal is 2 or 3, +enzyme ○ Qualitative (not quantitative) result 	<ul style="list-style-type: none"> • Total galactose 15 mg/dl <ul style="list-style-type: none"> ○ Normal < 14 mg/dl • Uridyl transferase activity 1 <ul style="list-style-type: none"> ○ Normal is 2 or 3, +enzyme ○ Qualitative (not quantitative) result
<p><i>Interpretation: galactosemia until proven otherwise</i></p>	



What information do you need?

- ACMG ACT sheets (www.acmg.net)
 - Eminence and evidence based guidelines
 - Provides an ACT sheet and diagnostic algorithm for each NBS disorder
 - ✦ Organized by type of disorder
 - ✦ Categorized by analyte: need to know how your state does testing



CASE FIVE

Infant A	Infant B
<ul style="list-style-type: none"> • Total galactose 20mg/dl • Uridyltransferase activity 1 • Repeat NBS <ul style="list-style-type: none"> ○ Total galactose >24 ○ GALT 0 • DNA: Q188R/Q188R <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> <p><i>Diagnosis:</i> Classical galactosemia</p> </div>	<ul style="list-style-type: none"> • Total galactose 15 mg/dl • Uridyltransferase activity 1 • Repeat NBS <ul style="list-style-type: none"> ○ Total galactose 7 ○ GALT 1 • DNA: N314D/Q188R <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> <p><i>Diagnosis:</i> Duarte galactosemia</p> </div>

CASE FIVE

Infant A	Infant B
<ul style="list-style-type: none"> • Galactose restricted diet for life • At risk for speech delays, possible cognitive delays • Ovarian failure <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> <p><i>Diagnosis:</i> Classical galactosemia</p> </div>	<ul style="list-style-type: none"> • No diet restriction • No known long-term complications <div style="border: 1px solid black; padding: 5px; margin-top: 5px;"> <p><i>Diagnosis:</i> Duarte galactosemia</p> </div>

CASE SIX: the final exam.....

YOU ARE RE-EVALUATING A 16 YEAR OLD GIRL WITH MILD MENTAL RETARDATION. SHE HAS HAD PRIOR GENETIC TESTING INCLUDING A KARYOTYPE AND FRAGILE X TESTING. MOM ASKS ABOUT NEWER TESTING OPTIONS AND YOU DISCUSS MICROARRAY TESTING (aCGH).

Diagnostic Testing in Minors

DIAGNOSTIC TESTING

5. In a child with symptoms of a genetic condition, the rationale for genetic testing is similar to that of other medical diagnostic evaluations. Parents or guardians should be informed about the risks and benefits of testing, and their permission should be obtained. Ideally and when appropriate, the assent of the child should be obtained.⁴

- How does the AAP/ACMG position statement apply?
- Chromosome microarray for evaluation of MR/ID: YES
 - Diagnostic evaluation
 - Genotype/phenotype implications
 - Treatments
 - Prognosis
 - Recurrence risks

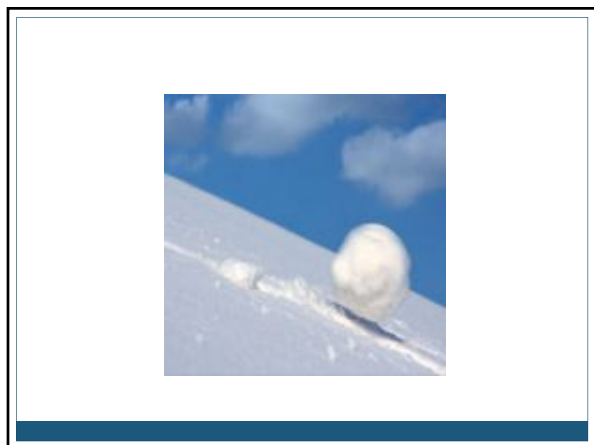
Result: variant of uncertain significance

- arr Xp21.1 x1 102 Kb deletion
- Deletions vs. Duplications
 - Deletions less tolerated than duplication
- Known syndrome? No
- Size? Small (~100Kb)
- Where? X chromosome, in a girl

CONCLUSION:
Likely unrelated to her developmental issues

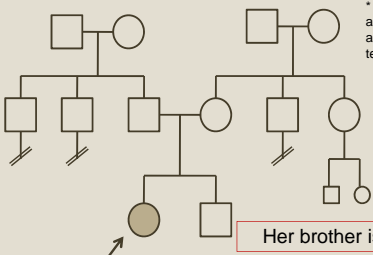
Where to go for additional information

- Read the test result report
 - Good clinical labs provide significant information and possibly references
- Published literature (possibly)
- Genome browsers
 - Associated with various commercial labs (open access)
 - Search by chromosome locus, basepairs, breakpoints
- OMIM Gene Map (<http://omim.org>)
 - Search by chromosome, specific locus, disease



The problem....

The deletion is located "in proximity to the *DMD* gene*"....



* Code for: we cannot report a finding in a patented gene as we cannot legally perform testing involving that gene

Her brother is 30 months old

The problem...

- **If this deletion is truly within the DMD gene**
 - Is your patient a carrier for DMD?
 - If so, your patient is at-risk for *DMD* associated cardiomyopathy
- **If this deletion was inherited from the mother**
 - Her brother has a 50% risk of having inherited DMD and is too young to show symptoms
 - Mother is at-risk for *DMD* associated cardiomyopathy
- **Now what should you do?**

The issues....

- **Sister: Carrier testing of a minor**
- **Sister: Presymptomatic testing of minor for an adult onset disorder**
- **Brother: Presymptomatic genetic testing of a minor for a childhood onset disorder**
 - Not diagnostic as he has no symptoms
- **Mother: Presymptomatic testing of an adult for an adult onset disorder**
 - not an issue if appropriate pre-test genetic counseling is provided

The sister....

Carrier testing of a minor	Presymptomatic testing of minor for an adult onset disorder
<p>CARRIER TESTING</p> <p>6. The AAP and ACMG do not support routine carrier testing in minors when such testing does not provide health benefits in childhood. The</p> <ul style="list-style-type: none"> • This is not <i>routine</i> carrier testing 	<p>PREDICTIVE GENETIC TESTING</p> <p>9. Predictive genetic testing for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality. An exception might be made for families for whom diagnostic uncertainty poses a significant psychosocial burden, particularly when an adolescent and his or her parents concur in their interest in predictive testing.</p> <ul style="list-style-type: none"> • Focus on the intent of testing

The brother.....

- **Brother: Presymptomatic genetic testing of a minor for a childhood onset disorder**
 - Not diagnostic as he has no symptoms

PREDICTIVE GENETIC TESTING
8. Parents or guardians may authorize predictive genetic testing for asymptomatic children at risk of childhood-onset conditions. Ideally, the assent of the child should be obtained.

- **Other diagnostic testing options are available**

The issues....

- Carrier testing of a minor vs Presymptomatic testing of minor for an adult onset disorder
- Presymptomatic genetic testing of a minor for a childhood onset disorder
- *Need to determine what situation takes precedence*

What is the real question?

Does the brother have DMD?

Does the brother have DMD?

- **NO: CK is elevated, but not necessarily consistent with DMD**
- **What ultimately happened....**
 - Sister did have DMD sequencing: identified as a carrier
 - Mother did not want to know her status
 - Unintentional disclosure issues discussed
 - Brother was found to not be affected by DNA
 - Mom's status is not known

SUMMARY

- Multiple different reasons for genetic testing
- Applicability of testing may depend on many factors
- What is acceptable in one situation may not be in another

- DO GOOD
- DO NO HARM

ELSI: Ethical, legal and social issues

- Ethical issues involve the entire family
 - Disclosure/non-disclosure
- Legal issues
 - Genetic Information Nondiscrimination Act (GINA) 2008
 - Prevents discrimination by health insurance and employers based on genetic information
 - Does not cover life, disability or long-term care insurance
- Social issues are myriad
 - Autonomy, especially adolescents
 - Family dynamics (blended, foster/adoptive)
 - Financial burden

Financial Issues

- There are no 'general' policies that allow determination of coverage of Genetic testing
- Each insurer creates their own Policy
 - Different insurance products ('policies') from the same company may be very different
- Coverage is determined by the employer (and what policy they purchase), not the insurance company
- Driven by money: genetic testing is expensive

Pitfalls

- Only cover testing if the diagnosis is known (ie cancer genetic testing)
- Only cover diagnostic testing (diagnosis not known)
- Recurrence risk is not a commonly justifiable reason for testing
- Watch when carrier testing is allowed (pregnancy)
- Must benefit the insured

CONCLUSIONS

- In many clinical situations, genetic testing is necessary for patient care
 - Diagnostic testing
 - Presymptomatic testing
 - Medical management
- There are situations, especially in Pediatrics, where genetic testing is not ethically appropriate nor medically necessary
 - Presymptomatic testing
 - Carrier testing
- Remember ELSI, consent, financial and insurance issues
