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

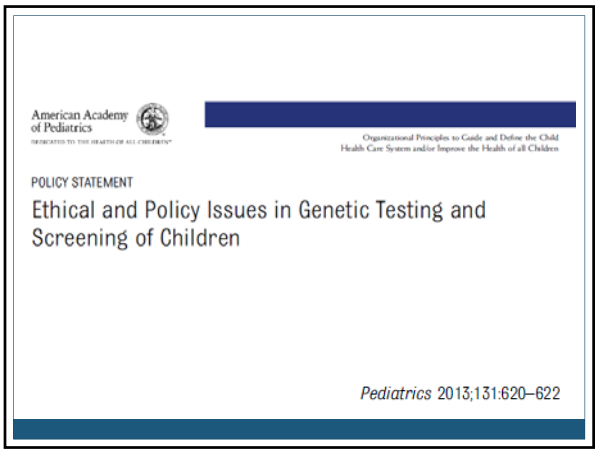
- **Beneficence**: Do good
  - Act in the best interest of the child
- **Non-malfeasance**: Do no harm
  - Action when not indicated or failure to act when required may both cause harm
- **Autonomy**: Respect for the individual to make their own decisions
  - Children will become adults one day
  - Should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



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.

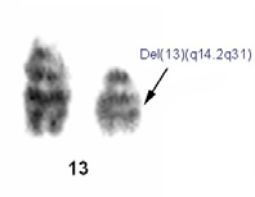
Diagnostic Testing in Minors

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 assoiciated 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
- *RB1* the retinoblastoma gene is located at 13q14.2
  - *First 'hit'*
  - *Extremely high risk for bilateral retinoblstoma 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

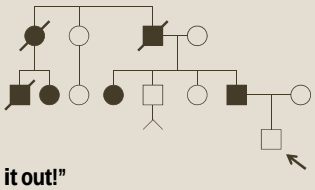
CASE TWO

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?

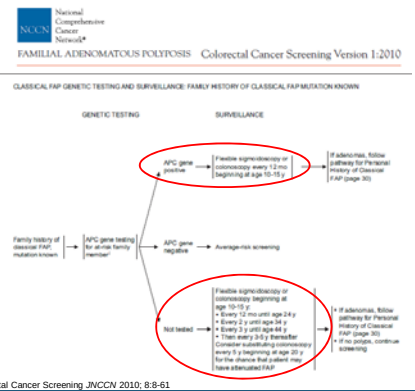
- Consider a differential diagnosis
  - Prioritize: What would kill - what requires immediate treatment to prevent complications- what would recur - everything else
- Where to find information
  - Internet
  - GeneReviews
  - OMIM
  - Telephone call(s)
- What additional information would be helpful
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



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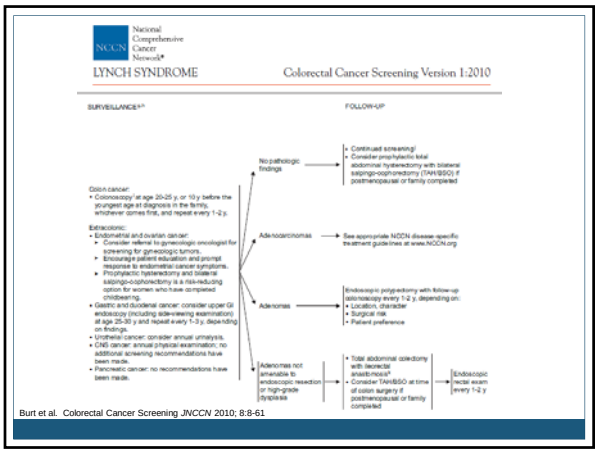

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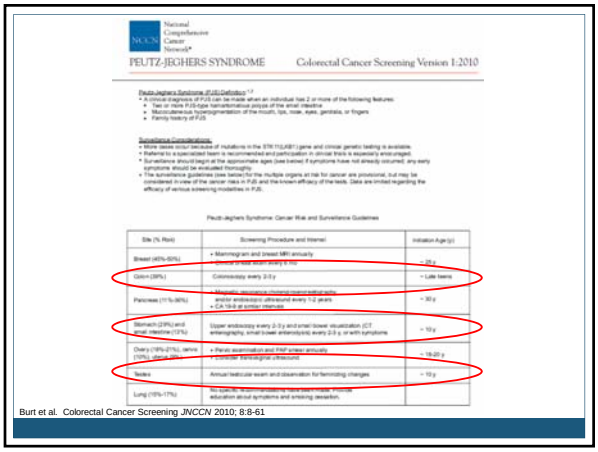

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Pre-symptomatic Genetic Testing

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?
- 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

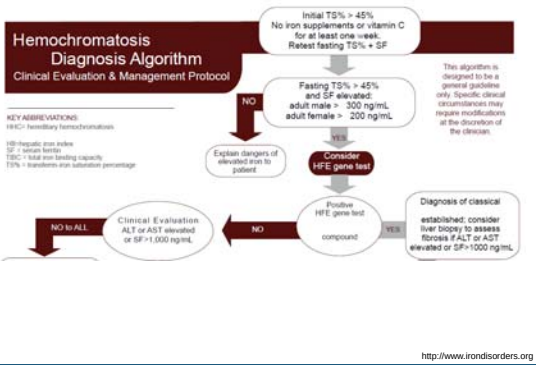
- Discuss options with family
  - Genetics referral for further discussion
  - Consider pre-symptomatic testing vs clinical surveillance
- Genetic testing is an option
  - Only if an affected individual has had testing and it is informative (ie this infant's father should have testing initially)
  - 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

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- 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

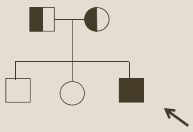
CASE TWO	CASE THREE
• YES • There are risk of disease in childhood • Interventions in childhood are recommended	• NO • No interventions in childhood are necessary

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 Subcommittee 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 DNAcarrier testing: NO
  - There are no health benefits of knowing carrier stats in childhood
  - Recognition that this may happen as a result of NBS (not the reason for NBS)

Diagnostic Testing in Minors

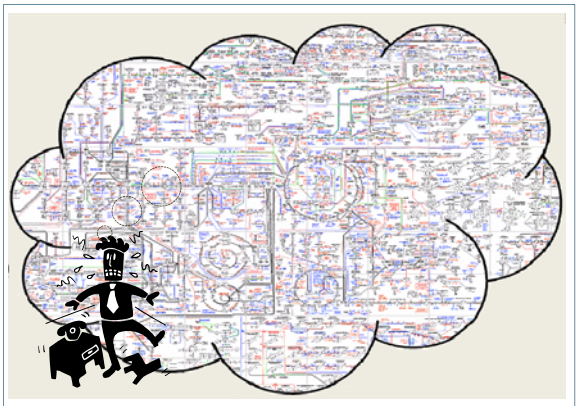
DIAGNOSTIC TESTING

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.[4]

- 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

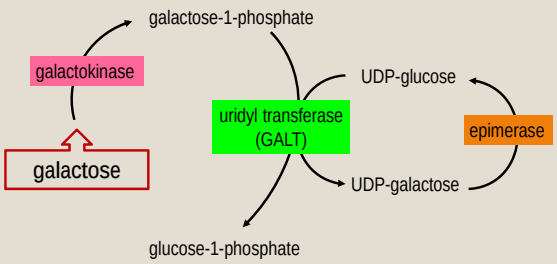
- Read the report
  - Verify patient demographics
  - Review testing information (dates, times etc)
- Identify the analyte/condition of concern
- Review the recommendations
  - Pending results (secondary markers)
  - Repeat screen
  - Diagnostic testing
  - Other actions

CASE FIVE

Infant A	Infant B
• Total galactose 20mg/dl ○ Normal < 14 mg/dl • Uridyltransferase activity 1 ○ Normal is 2 or 3, +enzyme ○ Qualitative (not quantitative) result	• Total galactose 15 mg/dl ○ Normal < 14 mg/dl • Uridyl tramsferase activity 1 ○ Normal is 2 or 3, +enzyme ○ Qualitative (not quantitative) result

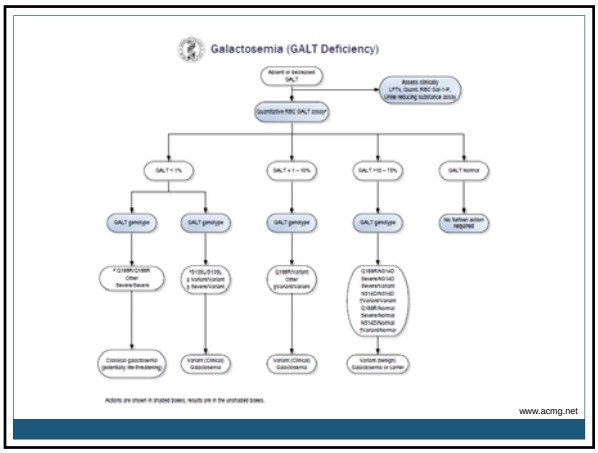
Interpretation: galactosemia until proven otherwise

Elevated galactose: Galactosemia



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

• Total galactose 20mg/dl
• Uridyltransferase activity 1
• Repeat NBS
  ○ Total galactose >24
  ○ GALT 0
• DNA: Q188R/Q188R
	• Total galactose 15 mg/dl
	• Uridyltramsferase activity 1
	• Repeat NBS
	  ○ Total galactose 7
	  ○ GALT 1
	• DNA: N314D/Q188R

Diagnosis: Classical galactosemia	*Diagnosis: Duarte galactosemia*

CASE FIVE

Infant A	Infant B
• Galactose restricted diet for life • At risk for speech delays, possible cognitive delays • Ovarian failure	• No diet restriction • No known long-term complications
Diagnosis: Classical galactosemia	*Diagnosis: Duarte galactosemia*

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

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 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:

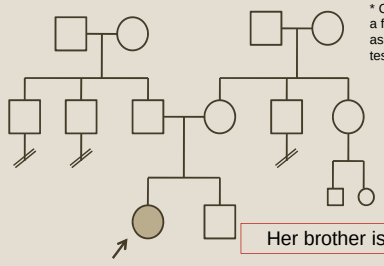
Likely unrelated to her developmental issues

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

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

- This is not *routine* carrier testing

Presymptomatic testing of minor for an adult onset disorder

PREDICTIVE GENETIC TESTING

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.

- 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