Genetic Testing: Current Concepts for Underwriters

Reviewed by Bill Rooney MD
VP/Medical Director
Introduction: Bill Rooney, MD

- Vice President and Medical Director for SCOR Global Life Americas
- Board certified in Family Medicine.
- Bachelors and M.D. degrees from the University of Missouri-Kansas City
- Masters of Business Administration from Benedictine College
Welcome & Webinar Guidelines

1. Phones will be locked during the presentation
2. Please submit questions by using the question “?” function to type in your question
3. Question & Answers will be discussed at the end (time permitting)
4. Your comments are important to us; please complete the survey at the end of the webinar
Agenda

Genetic Basics
- Genetic discoveries
- A library full of genes
- Classifying genetic disorders

Testing

Looking at 3 diseases from a genetic point of view
- Huntington Disease
- Hypertrophic Cardiomyopathy
- BRCA Associated Cancers

Role of Genes in Disease --- Important concepts
A 44 year old female has a strong family history of cancer

- Mother: Breast—Dx 49 y/o
- M GM: Ovarian—Dx 62 y/o
- M Uncle x 2: Prostate—Dx 53 and 58 y/o

BRCA testing done in 2001 reported to be “negative.”

- Her 45 y/o sister was very recently diagnosed with breast cancer
- Her sister’s BRCA 1 testing is positive

What are the considerations in this case?
Selective breeding for agriculture and domesticated animals had occurred since the beginning of civilization.

Charles Darwin published “On the Origin of Species” in 1859. He described transmission of variable factors in detail. Natural selection according to the law of survival of the fittest.

Gregor Johann Mendel in 1865 worked with garden peas and made some fundamental observations.
Mendel’s laws

First assume tallness is a dominant trait in pea plants.  
**Tallness = T  Short = t**

Law of segregation:  
Crossing pure-bred tall (T-T) and pure-bred short (t-t)  
• Results in all of the offspring inheriting  
  • T from one parent  
  • t from the other.  
• All will have T-t code
Mendel’s laws

**Law of dominance:**
- One factor in a pair of traits dominates the other unless both factors in the pair are recessive
- All of the T-t codes will be tall
- Crossing two first generation hybrids (Genotype T-t; Phenotype “Tall”) results in:
  - Tall and short offspring
  - ¾ are tall and ¼ are short in large numbers but the laws of chance apply
  - There are no moderately tall offspring
  - Proof that the short gene was passed down despite all of the first generation offspring being tall

**Law of independent assortment:**
Separate genes for separate traits are passed independently of each other
20th century

Chromosomes

Mitosis

Parent cell

DNA replicates

2 daughter cells

Melosis

Parent cell

DNA replicates

2 daughter cells

4 daughter cells
Watson and Crick in 1953 unraveled the DNA structure

DNA when compared to a ladder has:

- The backbone of a polymer of sugar and phosphate groups
- The steps consisting of 4 nucleobases:
  - Adenine
  - Thymine
  - Cytosine
  - Guanine
- A and T always combine and C and G always combine
- A, C, T, and G are the blueprint for all life forms on the planet

Human DNA
Sequence matters!

Take one of these strands and stretch it.
Sequence matters!

Polymer of sugar and phosphate groups

Nucleobases
- Adenine
- Thymine
- Cytosine
- Guanine

Deletions

Insertions

Switches

Repeats
Sequence matters! Exons and Introns
Abnormal mRNA

Abnormal Protein

Protein function:
- Cell Structure
- Cell Function
- Cell Regulation

Examples of Protein function:
- Antibodies
- Enzymes
- Structural component
- Transport

Sequence Does Matter!
1990
The NIH, the Dept. of Energy, and an international team launched the Human Genome Project.

- Effort to sequence the human genome.
- All data freely available on the internet.

2003
Researchers completed the project.
**Human Genome Project**

Cost for sequencing a human genome

- **2004** ~$28,800,000
- **2014** ~$1,000

*Topol, Eric Individualized Medicine from Prewomb to Tomb. Cell 157 March 27, 2014*

**Human Genome Project Results**

- 2000 genetic tests for human conditions
- 350 biotechnology products in clinical trials
- >1800 disease genes discovered

*NIH.gov Accessed 8/26/2015*
Human DNA

An Analogy

3 billion letters
Nucleotide Base Pairs

With 23,000 books
Genes

23 shelves
Chromosomes

ATCGATCGATCGATCG ATCGATCGATCGATCG
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Human Genome

- TOTAL GENOME
- Coding region

Non-coding region
RNA
Regulatory DNA
Introns
???
Human Genetic Variability

TOTAL GENOME

0.1% x 3 billion = 3 MILLION

ACTGAGTCCGT

913-421-3456

0.1%

4%

Timeline of discoveries

- Darwin 1859
- Mendel 1865

1850

- Human Genome Project
  - Started 1990
  - Completed 2003

Watson and Crick 1953

1953

- BRCA 1 gene discovered 1994
- BRCA 2 gene discovered 1995
- Huntington genetic basis discovered 1993

1993

- BRCA 1/2 testing became clinically available 1996

1996

- BRCA “rearrangement panel” 2002
- BRCA test enhanced with large genomic rearrangements 2006

2006

- Today August 31st, 2016
Chromosomes

The human genome is DNA organized as 23 chromosomes including 22 autosomes (named 1-22), and one sex chromosome (either X or Y). Humans are diploid, with each somatic cell consisting of two sets of 23 chromosomes, one paternally inherited (blue) and one maternally inherited (pink). The Y chromosome is necessarily paternally inherited. The mitochondrial genome (mt) is derived solely from mitochondria in the ova and therefore exhibits exclusive matrilineal inheritance.
## Diseases We Will Discuss Today

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>TNNT2 gene</td>
<td>1q32</td>
</tr>
<tr>
<td>Huntington Disease</td>
<td>HTT gene</td>
<td>4p16.3</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>MYBPC3 gene</td>
<td>11p11.2</td>
</tr>
<tr>
<td>Hypertrophic Cardiomyopathy</td>
<td>TNNI3 gene</td>
<td>19q13.4</td>
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<tr>
<td>BRCA 1 gene</td>
<td></td>
<td>17q21</td>
</tr>
<tr>
<td>BRCA 2 gene</td>
<td></td>
<td>13q12.3</td>
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<tr>
<td>Among Others</td>
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Genetic Disorders

- A specific gene variant causing a disease
- Variations in the DNA from:
  - A mutation in one gene
    - Single nucleotide polymorphisms (SNP’s)
    - Insertions/deletions
    - Triplet-repeat expansion
  - Multiple mutations in many genes
  - Deletion or addition of an entire chromosome

Categories

- Chromosomal Diseases
- Monogenic Disorders
- Mitochondrial Disorders
- Polygenic disorders
1) Chromosomal Diseases

- An entire chromosome (or large segment) is missing or duplicated
- Typically result from an error in cell division following meiosis or mitosis in the germ cell

EXAMPLE
Down Syndrome (Trisomy 21)
- 3 copies of chromosome 21 instead of the usual 2 copies
2) Monogenic Disorders

Autosomal Recessive

- A small modification in a single gene
- When on an autosome the inheritance obeys Mendelian laws

Autosomal Recessive Genes

- Disease in homozygous genotypes
- No disease in heterozygous genotypes

EXAMPLE

- Sickle Cell Anemia
- Cystic Fibrosis

Thalassaemia
Familial dyslipidemias
Haemophilia
Familial Alzheimer’s Disease
Tay Sachs Disease
Huntington’s Disease
Marfan Syndrome
Ehlers-Danlos Syndrome
Retinoblastoma
Neurogenic muscular atrophies
Muscle dystrophy-Duchenne
MODY
Familial Hemiplegic Migraine
Long QT (Romano-Ward)
Long QT (Jervell and Lange-Nielsen)
Monogenic Disorders
Autosomal Recessive

Monogenic Diseases

Autosomal Recessive Inheritance

No disease BUT is a carrier

No disease BUT is a carrier

Abnormal gene

No Disease and is NOT a carrier

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Monogenic Diseases

- A small modification in a single gene
- When on an autosome the inheritance obeys Mendelian laws

Autosomal Dominant Genes

- Disease in homozygous genotypes
- Disease in heterozygous genotypes

EXAMPLE

Huntington’s Disease

~7,000 known Mendelian diseases
Topol, Eric Individualized Medicine from Prewomb to Tomb.
Cell 157 March 27, 2014
Making this whole topic more complex is...

Variable expressivity
- Age
- Mutation type
- Genetic heterogeneity
- Environmental exposure
- Genetic modifiers
- Parent-of-origin effects (i.e. Prader-Willi Syndrome)
- Sex-limited expression (i.e. male pattern baldness)
- Anticipation
- Mosaicism

Penetrance
- Full
- Incomplete
- Variable

Abnormal gene
The X chromosome can also be involved in genetic disorders

Example: Hemophilia
3) Mitochondrial Diseases

- Mitochondrial inheritance
- Always maternal inheritance
- Small number of genes (37) found in the mitochondria (Involved in oxidative phosphorylation).
- Rare disorders which can manifest themselves in many ways
  - Muscular weakness
  - Dementia
  - Heart disease
  - Poor growth
  - Hearing and visual problems

Cell Structure

- Cilia
- Lysosome
- Centrioles
- Microtubules
- Golgi apparatus
- Smooth endoplasmic reticulum
- Rough endoplasmic reticulum
- Mitochondrion
- Cytoplasm
- Nucleolus
- Chromatin
- Ribosomes
- Nuclear membrane

https://upload.wikimedia.org/wikipedia/commons/1/10/Illu_cell_structure.jpg
Downloaded 8/3/16 from Bing "free to modify, share, and use commercially"
4) Polygenic Diseases

- Multi-factorial ("Complex Disorders")
  - Mutations in multiple genes
  - Frequently associated with environmental causes

- Large twin and adoption studies indicate genetic variation accounts for 25-50% of the risk. The rest is environmental in cause.

- Examples include DM, CAD, asthma, manic depression, schizophrenia, and hypertension
CAD has >50 genetic risk variants discovered.

- Only 15 of the 50 genetic variants work through known risk factors (hyperlipidemia, hypertension etc.).

Currently traditional risk factors identify risk for CAD better than genetic testing.
Complex Disorders—We need to think of it in this way

Genes + Environment + Behavior = Risk

Example:
A MMP-12 variant can impact COPD but is dependent on cigarette smoke exposure

Hunninghake, Gary et al. MMP 12, Lung Function, and COPD in High-Risk Populations. NEJM, Dec 16, 2009 NEJM.org. Retrieved 8/30/16
## Characteristics of a good test

<table>
<thead>
<tr>
<th>Characteristics of a good test</th>
<th>Genetic testing</th>
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</thead>
<tbody>
<tr>
<td>100 % Sensitive</td>
<td>Varies</td>
</tr>
<tr>
<td>100% Specific</td>
<td></td>
</tr>
<tr>
<td>Inexpensive</td>
<td>No</td>
</tr>
<tr>
<td>Accurate and reproducible</td>
<td>Typically</td>
</tr>
<tr>
<td>Ordering person has a thorough understanding of the test</td>
<td>Varies</td>
</tr>
<tr>
<td>Tested individual can easily understand the results</td>
<td>Varies</td>
</tr>
<tr>
<td>Established testing protocol/process with little modification or changes anticipated</td>
<td>Not typically</td>
</tr>
<tr>
<td>Abnormalities point to one and only one disorder</td>
<td>Not typically</td>
</tr>
<tr>
<td>Always actionable</td>
<td>No</td>
</tr>
<tr>
<td>Always one test for each disorder</td>
<td>No</td>
</tr>
<tr>
<td>Results are always yes or no</td>
<td>No</td>
</tr>
</tbody>
</table>

The genetic test was done and was negative.
## Test Results

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Variant previously associated as cause of the disorder</td>
</tr>
<tr>
<td>Likely Pathogenic</td>
<td>Variant expected to cause the disorder</td>
</tr>
<tr>
<td>Variants of uncertain significance</td>
<td>Variant that might be causative</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Variant probably not causative</td>
</tr>
<tr>
<td>Benign</td>
<td>Variant recognized as neutral</td>
</tr>
</tbody>
</table>
Genetic Testing

TYPES

- Perinatal screening
  - Preimplantation
  - Prenatal testing
  - Fetal DNA
  - Newborn screening
- Carrier Testing
  - Pre-symptomatic predictive testing
- Diagnostic testing
- Pharmacogenetic testing

TESTS

- Currently testing available for >1,000 conditions
- ~10% increase in genetic test availability each year
- >200 genetic tests clinically available to detect cancers.

Biochemical testing
- Analytes/Protein analysis/Enzyme assays

DNA analysis
- Real-time PCR
  Small number of genes tested
- High-density DNA array testing
  Analyze for 1,000,000 gene variants
- Highly efficient DNA sequencing techniques
  (next generation sequencing)
  Entire human genome
Genetic Testing---Who to test?

Family member with known disease

Unaffected individual

Test for that specific mutation in family members

Mutation found

Increased chance for inconclusive results

If test is negative, is it:

• Because that gene is not mutated in the family??

or

• The mutation does exist in the family but the tested person doesn’t have it??
Clinical Validity and Clinical Utility

Clinical Validity: The ability of a genetic test to predict a phenotype

- APC gene: Familial adenomatous polyposis (~ 100%)
- APOE e4/e4: Alzheimer disease (~ 30%)

Clinical Utility: The impact of the genetic test on clinical care

- Huntington
- BRCA

Minimal Significant
## Testing

<table>
<thead>
<tr>
<th>Ethical, legal and psychosocial concerns</th>
<th>Fears of genetic discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical utility and validity concerns</td>
<td>Family dynamics</td>
</tr>
<tr>
<td>Small families/Adopted individuals</td>
<td>Lack of patient and physician knowledge</td>
</tr>
<tr>
<td>Availability of counseling</td>
<td>Fear of false positive, false negatives, and variants of uncertain significance</td>
</tr>
<tr>
<td>Expense</td>
<td>Incidental findings</td>
</tr>
</tbody>
</table>

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**Study\(^1\):**
- 387 patients seen in a GI clinic with FH compatible with Lynch Syndrome
- 17% were referred for genetic counseling/testing

---

Utilization of pretest counseling

October 2015 study in JAMA Oncology

- 3874 BRCA-tested women completed a questionnaire (out of 11,159 consecutively tested, insured women)
- 5.3% tested positive
- 16.4% did not meet testing criteria
- 36.8% received pretesting genetic counseling
  - The most common reported reason for no counseling was lack of clinician recommendation
“From Prewomb to Tomb”
Huntington disease

Description:
- Progressive neuro degenerative disorder

Components of the disorder:
- Choreiform movements
- Psychiatric manifestations
- Dementia
- Weight loss and cachexia

Presentation and course
- Typically presents in middle age
- Progressive over the ensuing 10-20 years

Cure:
- None

Treatment:
- Symptomatic only
- No disease modifying treatment is available
Huntington disease—the genetics component

- Repeat expansion mutation

**Diagram:**

- Original DNA code for an amino acid sequence.
- DNA bases: CATT CAC CAG GTA ATC CAT GCT A
- Amino acid sequence: His Ser Gln Val Ile Met Leu...
- Repeated trinucleotide (CAG).
- Repeated trinucleotide adds a string of glutamines (Gln) to the protein.
Huntington disease—Genetics testing

Testing can be done prenatally (amniocentesis or chorionic villi sampling) or by a blood sample in a child/adult

Genetic testing is ~:
- 98.8% sensitive
- 100% specific

Testing
- ~15% of those with a FH of HD complete testing
- ~1% of those tested experience a:
  - Psychiatric hospitalization
  - Suicide attempt
  - Suicide (Only those with HD symptoms in one study\textsuperscript{1})
- Those testing negative are prone to depression at times as well

\textsuperscript{1} Almqvist EW et al. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after Predictive testing for Huntington disease. Am J Hum Genet. 1999;64; 1293.
Hypertrophic Cardiomyopathy

Description:
- Heart muscle disorder caused in 60-70% of the cases by mutations in sarcomere genes that encode proteins involved in contractility.

Components of the disorder:
- LVH involving various morphologies
- Various clinical manifestations and mortality concerns

Presentation and course
- Typically presents in puberty or early childhood with gradually increasing LVH.
- Course:
  - Most—benign
  - Some—Sudden death or CHF.

Cure:
- None

Treatment:
- Medications (Beta blockers, Calcium channel blockers, Disopyramide)
- Surgical septal myectomy or alcohol septal ablation
Hypertrophic Cardiomyopathy

Inherited:
- Autosomal-dominant pattern
- Variable expressivity and age-related penetrance

Type of genetic abnormality:
- Mutation in one of at least 15 known genes
- >1500 mutations known
- Most are missense mutations involving a single normal amino acid replacement

Testing
- Frequently done on a probabilistic basis instead of a yes or no answer.
- Frequently testing results in a “variant of uncertain significance”
- ~50% of patients with HCM have no mutation identified—considered inconclusive.

Dilated cardiomyopathy is even more complicated.
- >30 genes
- Some transmitted in autosomal dominant way.
- Some transmitted in autosomal recessive, X-linked, and mitochondrial way.
Proband = first affected family member seeking attention for a genetic disorder

Clinical screening for family members

Genetic Testing---Who to test?

Family member genotyping frequently done

Positive test = Need for surveillance and imaging

Mutation found

Test for that specific mutation in family members

If test is negative, is it:
- Because that gene is not mutated in the family??
- Or
- The mutation does exist in the family but the tested person doesn’t have it??

U5: fected individual

Increased chance for inconclusive results
BRCA 1 and 2

Description:

- BRCA genes
  - Suppress tumor development
  - Make proteins which helps repair DNA

Components of the disorder:

- BRCA genes make proteins which help repair DNA molecules.
- Mutations are associated with an increased cancer risk:
  - **Breast**
    - BRCA 1: Women: ~55-70% risk by age 70  Male: ~1%
    - BRCA 2: Women: ~45-70% risk by age 70  Male: ~8%
  - **Ovarian**
    - BRCA 1: ~40%
    - BRCA 2: ~15%
  - **Prostate**
  - **Pancreas**
  - **Stomach**
  - **Others**


Global Life
BRCA 1 and 2

Presentation and course

- Same mutation in same family
  - Different types of cancers
  - Different ages of onset

- Gene-gene interactions
  - Gene-environment and hormonal factors are felt to account for this variability

- Mutation location matters
  - Central region gene mutations
    - increase the chance of ovarian cancer
    - lowers the risk of breast cancer compared to other loci

- Penetrance
  - Dependent on other changes in other genes (SNP’s).
  - SNP determinations are not currently built into genetic testing.

Cure:
- None

Treatment:
- Close surveillance
- Chemoprevention (eg Tamoxifen)
- Risk-reducing surgery
Inherited:
- Autosomal-dominant pattern
- Highly (but not completely) penetrant

Type of genetic abnormality:
- BRCA 1 gene – Chromosome 17 region 2 band 1 from base pair 41,196,321 to 41,277,500
- BRCA 2 gene – Chromosome 13 at position 12.3
- 100’s of different types of mutations in the gene.
  - Deleterious mutations
  - Suspected deleterious
  - Variant of unknown significance

Factors associated with increased chance for BRCA1 or BRCA2 harmful mutation:
- Breast cancer diagnosed prior to 50 y/o
- Bilateral breast cancer
- Both breast and ovarian cancer in the same woman or same family
- Multiple breast cancers
- Male breast cancer in the family
- Ashkenazi Jewish ethnicity

## BRCA genetic testing

### Testing

Testing has changed several times through the years

The test is not 100% sensitive or specific

The test can return as:

- Positive
- Negative
  - Known mutation in family member ("True negative")
  - Uninformative negative
- Variant of uncertain significance

### "Variant of Uncertain Significance" test result rate

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Result Rate</th>
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<tbody>
<tr>
<td>BRCA 1 and 2 test</td>
<td>2.1%</td>
</tr>
<tr>
<td>6 Gene testing</td>
<td>7.6%</td>
</tr>
<tr>
<td>14-19 gene testing</td>
<td>20-25%</td>
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<tr>
<td>25 gene testing</td>
<td>42%</td>
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Approximate values

Concept:
“Finding a mutated gene doesn’t necessarily help”

- Gene found $\rightarrow$ Disease happens
- Gene not found $\rightarrow$ Disease absent

Ideally, this would be the case 100% of the time for predictive purposes. But....not so fast.
Concept:
“Each Test Has It’s Own Characteristics”

Genetic testing = Blood testing = Radiologic testing

- Sed Rate
- CEA
- Blood sugar
- PSA
- CPK
- EKG

- Sensitivity
- Specificity
- Clinical Validity
- Clinical Utility
Concept: “Spectrum”

Genetic

100%

PKU

Huntington

CAD

BRCA associated Breast CA

Scurvy

DM

Environment

100%
Diseases can be a combo of one or more genes, one or more behaviors, and one or more environmental factors, with both good and harmful effects.
Epigenetics: Methylation example

Epigenetics:
The study of how environmental factors impact gene expression.

Instead of gene sequence disturbances the impact of epigenetics is with turning off or on how cells read the genes

Methyl group added to the DNA base cytosine at CpG sites

Accessed 9/29/15 (Bing listed as “Free to modify, share, and use commercially”)
The role of genes in diseases can be associated with prevention, early detection, disease modification analysis as well as treatment. This knowledge can have a significant impact on mortality.
In Summary

Most of the major advances in Genetics have occurred relatively recently.

Each genetic test has a unique clinical validity and clinical utility.

Genetic testing results are very similar to other tests we deal with daily.

Genetics plays a role in thousands of diseases.

Genetics, environment, and behaviors frequently interact to impact diseases.

In Summary

Most of the major advances in Genetics have occurred relatively recently.

Each genetic test has a unique clinical validity and clinical utility.

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Genetics plays a role in thousands of diseases.

Genetics, environment, and behaviors frequently interact to impact diseases.

Timeline of discoveries

“If I have seen further, it is by standing on the shoulders of giants.” — Sir Isaac Newton –1700

Darwin 1859
Mendel 1865
Frederick Miescher discovered DNA 1869
Oswald Avery DNA ID’d as heritable material 1943
Watson and Crick 1953
Human Genome Project Start 1990 Complete 2003

Clinical Validity and Clinical Utility

Concept: “Each Test Has It’s Own Characteristics”

Concept: “Spectrum”

PKU
Huntington
CAD
BRCA associated Breast CA
Sclrvy
DM

100%

Genetic

Environment

100%
A 44 year old female has a strong family history of cancer

- Mother: Breast - Dx 49 y/o
- M GM: Ovarian - Dx 62 y/o
- M Uncle x 2: Prostate - Dx 53 and 58 y/o

BRCA testing done in 2001 reported to be "negative."

- Her 45 y/o sister actually was very recently diagnosed with breast cancer
- Her sister’s BRCA 1 testing is positive

What are the considerations in this case?

GeneMutación

Genetic Testing---Who to test?

- Family member with known disease
- Unaffected individual
- Increased chance for inconclusive results

Mutation found

Test for that specific mutation in family members

If test is negative, is it:

- Because that gene is not mutated in the family??
- The mutation does exist in the family but the tested person doesn’t have it??

Global Life
The incidence of cancer in humans and elephants.

Risk of dying from cancer

~20% for humans

~5% for elephants

Copies (2 alleles) of TP53 (tumor protein) gene

1 allele present in Li-Fraumeni Syndrome

Lifetime risk of cancer close to 100% for elephants

Questions

????????????????????????????????

Reviewed by:
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VP/Medical Director
Genetic Basics

Genetic discoveries
A library full of genes
Classifying genetic disorders

Testing

Looking at 3 diseases from a genetic point of view
- Huntington Disease
- Hypertrophic Cardiomyopathy
- BRCA Associated Cancers

Role of Genes in Disease --- Important concepts

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