Overdiagnosis in Genetic Screening: Uncertainty

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Genetics

Disease
Overdiagnosis
(Cancer)
Genetics

Risk

Probability

Sources of Uncertainty

Disease Overdiagnosis (Cancer)

[...probability and uncertainty are not quite the same thing...]

[riskiness]

[Uncertainty is caused by information that is yet to come because it is about a future cancer risk...
Dean 2016 Soc Sci & Med]
Disease Overdiagnosis

Screening → subterranean “reservoir” of subclinical lesions.

Uncertainty: Clinical implications?

“Overdiagnosis” in Genetic screening

Don’t see genetic variants unless we actively screen: variants = subterranean “reservoir”

Uncertainty: Clinical implications? Is phenotypic disease/cancer guaranteed?
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

*analytic framework:*

1. Demographic Assessment
2. Genetic Risk Assessment
3. Genetic Screening/Evaluation
4. Cancer Diagnosis
5. Cancer/Disease Overdiagnosis
6. Consequences: “Disease” Management (Overtreatment, etc.)
7. Sequelae of Cancer Diagnosis
8. Sequelae of Genetic Evaluation
9. Stratify for Cancer Risk
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**Analytic Framework:**

1. **Demographic Assessment** → **Genetic Screening/Evaluation** → **Sequelae of Genetic Evaluation** → **Stratify for Cancer Risk** → **Consequences: “Disease” Management (Overtreatment, etc.)**

   - **Cancer Screening** → **Cancer Diagnosis** → **Sequelae of Cancer Diagnosis**
   - **Cancer/Disease Overdiagnosis**
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

analytic framework:

Demographic Assessment → Genetic Screening/Genetic Risk Stratify Evaluation → Sequelae of Genetic Evaluation → Cancer Screening → Cancer Diagnosis → Sequelae of Cancer Diagnosis → Cancer/Disease Overdiagnosis → Consequences: “Disease” Management (Overtreatment, etc.).
Definitions

2 types of genetics: **somatic** versus **germline**
Definitions: Cancer Arises From Gene Mutations

-Inherited/ Constitutional/ Germline Genetics

Inherited mutations – “Hereditary”

- Present in all cells
- Inherited
- Cause cancer cluster-family
- **germ line genetics** = passed on parent to child

- In egg or sperm

- Parent

- Child

- All cells affected in offspring

-Somatic Genetics

Non-inherited mutations – “Sporadic”

- In only one cell or organ
- Not in eggs or sperm
- Not inherited
- **somatic genetics** = passed on cell to cell

- Parent
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Parent
Mutation in egg or sperm

Child
All cells affected in offspring

- Somatic Genetics

Non-inherited mutations – “Sporadic”
- In only one cell or organ-
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- **somatic genetics** = passed on cell to cell
Definitions: How does DNA fit into the picture?

*gene* = piece of DNA, inherited

The DNA Double Helix

“normal” DNA sequence

- Adenine (A)
- Cytosine (C)
- Thymine (T)
- Guanine (G)
Definitions: How does DNA fit into the picture?

*gene* = piece of DNA, inherited

The DNA Double Helix

“All changes in DNA sequence are NOT equal! Not all changes affect the function of the gene.”
Definitions

• **Mutation** = any alteration/change in the base-pair sequence of genetic material:
  – Disease-causing
  – Neutral/benign
  – “adaptive”

• **Mutation** = ~ variant thought to be pathogenic – deleterious mutation
Definitions

• **Mutation** = any alteration in the base-pair sequence of genetic material

• **Variant** = an alternative version to the usual/ most commonly found base-pair sequence in a gene
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• **Polymorphism** = common variations/variants, observed in ≥ 1% of the population (which population?)

  polymorphisms are [germline](http://www.biochem.northwestern.edu/holmgren/Glossary/Definitions/Def-G/genetic_polymorphism.html), i.e. inherited, mutations that are frequent in a population
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• **Single nucleotide variant** = change in a single base

• **SNP/single nucleotide polymorphism** = the variant is ~ frequently observed in a population
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• **VUS/variant of uncertain significance** = not frequent in pop.; not classified as pathogenic; not enough data available to make a classification
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• **Incidental findings** = findings not related to the specific reason a test was ordered - ~analogous to “incidental” findings on imaging tests

Kang 2016 J Am Coll Radiol
Definitions: Risk / Probability in Genetics

• Probability of **inheriting** a deleterious variant.

- Mutation in egg or sperm
- **germline inheritance**
- Parent

- Child
- **penetrance**
- Do I have the disease phenotype?

• **Penetrance** – just because I have a deleterious mutation doesn’t mean I have 100% chance of getting the disease. Penetrance has its own element of probability. → **Uncertainty**

The danger is people see genetic variants as disease – and they are not disease!
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

Who should be (genetically) tested?

- Use “demographic” assessment=strong family history, etc. *versus* population-based screening

Candidates for testing:
- individual **with cancer**
- **healthy relatives** of person with cancer

*First encounter with “uncertainty”: Whom should I test?*
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

*analytic framework:*

Demographic Assessment $\rightarrow$ Genetic Screening/Evaluation $\rightarrow$ Sequelae of Genetic Evaluation

Who should be (genetically) tested?

- We will use *BRCA1* and *BRCA2* genes/mutations/variants as examples: hereditary breast/ovarian cancer=HBOC
Why did we select BRCA1 & BRCA2 as examples?

- Most common inherited cause of breast & ovarian cancer: 5-10% of all breast cancers; ~14%-16% of all ovarian cancers
- Well studied, many women tested for genetic mutations – many deleterious mutations found in these 2 genes

![BRCA and Cancer Table]

30-60% by age 60 versus 3% in gen pop & ~16%-31% of familial BCs = BRCA+
**BRCA1 & BRCA2: the Basics**

**BRCA1**
- Chromosome 17q21.1
- 80 kb genomic DNA
- 24 exons
- 1863 amino acids

**BRCA2**
- Chromosome 13q12.3
- 80 kb genomic DNA
- 27 exons
- 3418 amino acids
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

*analytic framework:*

- **Demographic Assessment**
  - Who should be (genetically) tested?

- **Genetic Screening/Evaluation**
  - Genetic Risk Stratification
  - How reliable is the actual laboratory test? (analytic validity)
  - Gene panel testing; massively parallel sequencing/next gen sequencing (whole genome sequencing, whole exon sequencing), etc.

- **Sequelae of Genetic Evaluation**
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

1. **Demographic Assessment**
2. **Genetic Screening/Evaluation**
3. **Sequelae of Genetic Evaluation**

**Genetic finding** *(BRCA1/2)*

**What kind of findings can I expect?**

Spectrum of findings: deleterious ↔ benign
Genetic Screening/Evaluation Result:

How reliable is the “pathogenic” classification of VUS?

concern: misclassification of benign variants as pathogenic
Genetic Misdiagnoses and the Potential for Health Disparities

Arjun K. Manrai, Ph.D., Birgit H. Funke, Ph.D., Heidi L. Rehm, Ph.D., Morten S. Olesen, Ph.D., Bradley A. Maron, M.D., Peter Szolovits, Ph.D., David M. Margulies, M.D., Joseph Loscalzo, M.D., Ph.D., and Isaac S. Kohane, M.D., Ph.D.

ABSTRACT

BACKGROUND
For more than a decade, risk stratification for hypertrophic cardiomyopathy has been enhanced by targeted genetic testing. Using sequencing results, clinicians routinely assess the risk of hypertrophic cardiomyopathy in a patient’s relatives and diagnose the condition in patients who have ambiguous clinical presentations. However, the benefits of genetic testing come with the risk that variants may be misclassified.

VUS concern: misclassification of benign variants as pathogenic

NYT Thurs Aug. 18, 2016
VUS concern: misclassification of benign variants as pathogenic

- Patient/cardiomyopathy with a variant.
  - Variant was previously considered causal
  - But, is the variant really the cause of the cardiomyopathy? Is it pathogenic?

- Must select appropriate control (healthy) population against which to compare patients with cardiomyopathy (cases)
Misclassification of benign variants as pathogenic: using the wrong control population

General population controls
Mostly white controls

Ancestry-matched controls
AA controls
Misclassification of benign variants as pathogenic: using the wrong control population

- **General population controls**
  - Other people (family members) get tested → variant found

- **Ancestry-matched controls**

Are these folks at risk of cardiomyopathy?

Use this

Patient/cardio-myopathy with variant

AA controls
Misclassification of benign variants as pathogenic: using the wrong control population

General population controls
- Other people (family members)
  - get tested
  → variant found

Ancestry-matched controls
- Use this

In many cases (esp. VUS) genetic over/misdiagnosis can lead to genetic-induced overtreatment

Are these folks at risk of cardiomyopathy?
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RESULTS

Multiple patients, all of whom were of African or unspecified ancestry, received positive reports, with variants misclassified as pathogenic on the basis of the understanding at the time of testing. Subsequently, all reported variants were re-categorized as benign. The mutations that were most common in the general population were significantly more common among black Americans than among white Americans (P<0.001). Simulations showed that the inclusion of even small numbers of black Americans in control cohorts probably would have prevented these misclassifications. We identified methodologic shortcomings that contributed to these errors in the medical literature.

CONCLUSIONS

The misclassification of benign variants as pathogenic that we found in our study shows the need for sequencing the genomes of diverse populations, both in asymptomatic controls and the tested patient population. These results expand on current guidelines, which recommend the use of ancestry-matched controls to interpret variants. As additional populations of different ancestry backgrounds are sequenced, we expect variant reclassifications to increase, particularly for ancestry groups that have historically been less well studied. (Funded by the National In...
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- Demographic Assessment
- Genetic Screening/Evaluation
- Sequelae of Genetic Evaluation
- Genetic finding *(BRCA1/2)*
- Spectrum of findings: deleterious ↔ benign
- Clinical management
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**Analytic Framework:**

Demographic Assessment ➔ Genetic Screening/Evaluation ➔ Sequelae of Genetic Evaluation ➔ Stratify for Cancer Risk

Uncertainty emerges at all stages of Genetic Testing