Overdiagnosis in Genetic Screening: Implications for Primary Care Providers
(genetic information and how you act on it)

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• I have no conflict of interest.
Genetics

Disease (Cancer)

Overdiagnosis
Disease (Cancer)

Genetics

Risk

Probability

Sources of Uncertainty

[...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]
Genetics

Uncertainty
...in the context of
Primary Care

Disease (Cancer)

2017
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

*analytic framework:*

- Decision to Screen or Not to screen
- Genetic Risk Stratify
- Genetic Screening/Evaluation
- Disease Screening
- Disease Diagnosis
- Consequences: "Disease" Management (Overdiagnosis)
- Sequelae of Disease Diagnosis
- Sequelae of Genetic Evaluation: Managing genetic knowledge

Cancer/Disease Overdiagnosis
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

Decision to Screen or Not to screen → Genetic Risk Stratify → Genetic Screening/Evaluation → Sequelae of Genetic Evaluation: Managing genetic knowledge

Genetic Risk Stratify → Disease Screening → Disease Diagnosis → Sequelae Of Disease Diagnosis

Cancer/Disease Overdiagnosis → Disease Screening → Disease Diagnosis → “Disease” Management (Overtreatment)
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

- **Decision to Screen or Not to Screen**
  - Who should be (genetically) tested?
    - Use “demographic” assessment = strong family history, etc. versus population-based screening
    - Candidates for testing:
      - individual with disease/cancer
      - healthy relatives of person with cancer

- **Genetic Risk**
  - Stratify

- **Genetic Screening/Evaluation**

- **Sequelae of Genetic Evaluation**
  - Managing genetic knowledge

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

**analytic framework:**

**Decision to Screen or Not to screen**
- Who should be (genetically) tested?

**Genetic Risk Stratify**

**Genetic Screening/Evaluation**
- What test should be used?
  - Single gene testing
  - Gene-panel based testing
  - Whole genome sequencing

**Sequelae of Genetic Evaluation:**
- Managing genetic knowledge

**Consequences:**
- Disease Management (Overtreatment)

**Overdiagnosis**
- Disease for Risk

Cancer/Disease

Sequelae Of Disease Diagnosis

Who should be (genetically) tested?
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

**Decision to screen or Not to screen**
- Who should be (genetically) tested?

**Genetic Risk Stratify**
- What test should be used?

**Genetic Screening/Evaluation**

**Sequelae of Genetic Evaluation:**
- Managing genetic knowledge
  - Managing uncertainty
    - Incomplete Penetrance
    - Variants of Uncertain Significance (VUS)

**Consequences:**
- Disease Management (Overtreatment)

Disease Diagnosis

Disease Overdiagnosis
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**Analytic Framework:**

- **Decision to Screen or Not to Screen**
- **Genetic Risk Stratify**
- **Genetic Screening/Evaluation**
- **Sequelae of Genetic Evaluation:**
  - Managing genetic knowledge
  - Disease Management
  - Primary Care Provider
    - Direct to Consumer/DTC vs Primary Care recommendations
    - Screening: risk algorithms
    - Use “demographic” assessment = strong family history, etc. *versus* population-based screening
    - Candidates for testing:
      - individual with disease/cancer
      - healthy relatives of person with cancer

- **Primary Care Provider**
  - Single gene testing
  - Gene-panel based testing
  - Whole genome sequencing

- **Primary Care Provider**
  - Interpreting genetic results
    - Massive amounts of data
    - Incidental findings
    - Managing care based on genetics
  - Managing uncertainty
    - Incomplete Penetrance
    - Variants of Uncertain Significance (VUS)
Definitions
2 types of genetics: **somatic** versus **germline**

- **Non-inherited mutations** – “Sporadic”
  - in only one cell or organ
  - NOT in eggs or sperm
  - Not inherited
  - **somatic genetics**: passed on cell to cell

- **Inherited/constitutional/germline mutations** – “Hereditary”
  - in all cells in offspring
  - inherited
  - cause cancer cluster—family
  - **germ line genetics**: passed on parent to child

Definitions: How does DNA fit into the picture?

*gene* = *piece of DNA, inherited*

The DNA Double Helix

“non-normal” DNA sequence

- Adenine (A)
- Cytosine (C)
- Thymine (T)
- Guanine (G)
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
Definitions

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• **Variant** = an alternative version to the usual/most commonly found base-pair sequence in a gene

• **Polymorphism** = common variations/variants, observed in ≥ 1% of the population (which population?)

  polymorphisms are **germline**, i.e. inherited, mutations that are **frequent** in a population

*Science 293:594, July 27, 2001*

Definitions

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- **Variant** = an alternative version to the usual/most commonly found base-pair sequence in a gene
- **Polymorphism** = common variations/variants, observed in ≥ 1% of the population (which population?)
- **Single nucleotide variant** = change in a single base
- **SNP/single nucleotide polymorphism** = the variant is ~ frequently observed in a population
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 product.”
Definitions

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• **VUS/variant of uncertain significance** = not frequent in population; not classified as pathogenic - not enough data available to make a classification
Definitions

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• **Incidental findings** = findings not related to the specific reason a test was ordered - $\sim$analogous to “incidental” findings on imaging tests

Kang 2016 J Am Coll Radiol
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• **Penetrance** = proportion of individuals w/a given variant who express the trait/disease/phenotype
Definitions: Risk / Probability in Genetics

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

- **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!

Primary Care Provider must be able to communicate this...
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

- **Decision to screen or Not to screen**

  - Primary Care Provider
    - Direct to Consumer/DTC vs Primary Care recommendations
    - Screening: risk algorithms
    - Who should be (genetically) tested?

- **Genetic Risk Stratify**

  - Genetic Screening/Evaluation
    - Primary Care Provider
      - Single gene testing
      - Gene-panel based testing
      - Massively parallel sequencing
      - Whole genome sequencing
      - Whole exome sequencing
      - Interpreting genetic results
      - Analytic validity

  - Managing uncertainty
    - Incomplete Penetrance
    - Variants of Uncertain Significance (VUS)

- **Sequelae of Genetic Evaluation:**

  - Managing genetic knowledge
    - Consequences: Disease Management (Overtreatment)

  - Primary Care Provider
    - DTC vs Primary Care recommendations
    - Screening: risk algorithms
    - Who should be (genetically) tested?

  - How reliable is the actual laboratory test? (analytic validity)

  - Interpreting genetic results
    - Massive amounts of data
    - Incidental findings
    - Managing care based on genetics

  - Managing uncertainty
    - Incomplete Penetrance
    - Variants of Uncertain Significance (VUS)
Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

**analytic framework:**

Demographic Assessment → Genetic Screening/Evaluation → Sequelae of Genetic Evaluation

Uncertainty and challenges to Primary Care Provider emerge at all stages of Genetic Testing

Consequences: Disease Management (Overdiagnosis, etc.)