National Cancer Institute

Overdiagnosis in Genetic Screening: Implications for Primary Care Providers

(genetic information and how you act on it)

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Preventing Overdiagnosis 2017

Quebec City, Canada - August 17, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

- I have no conflict of interest.

PREVENTING OVERDIAGNOSIS

Winding back the harms of too much medicine

Genetics ⟷ **Disease Overdiagnosis (Cancer)**

PREVENTING OVERDIAGNOSIS
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2016

Risk

Genetics ⟷ **Disease Overdiagnosis (Cancer)**

↓

Probability

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

↓

Sources of

Uncertainty

[riskiness]

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

PREVENTING OVERDIAGNOSIS
Winding back the harms of too much medicine

2017

Genetics ⟷ **Disease Overdiagnosis (Cancer)**

↓

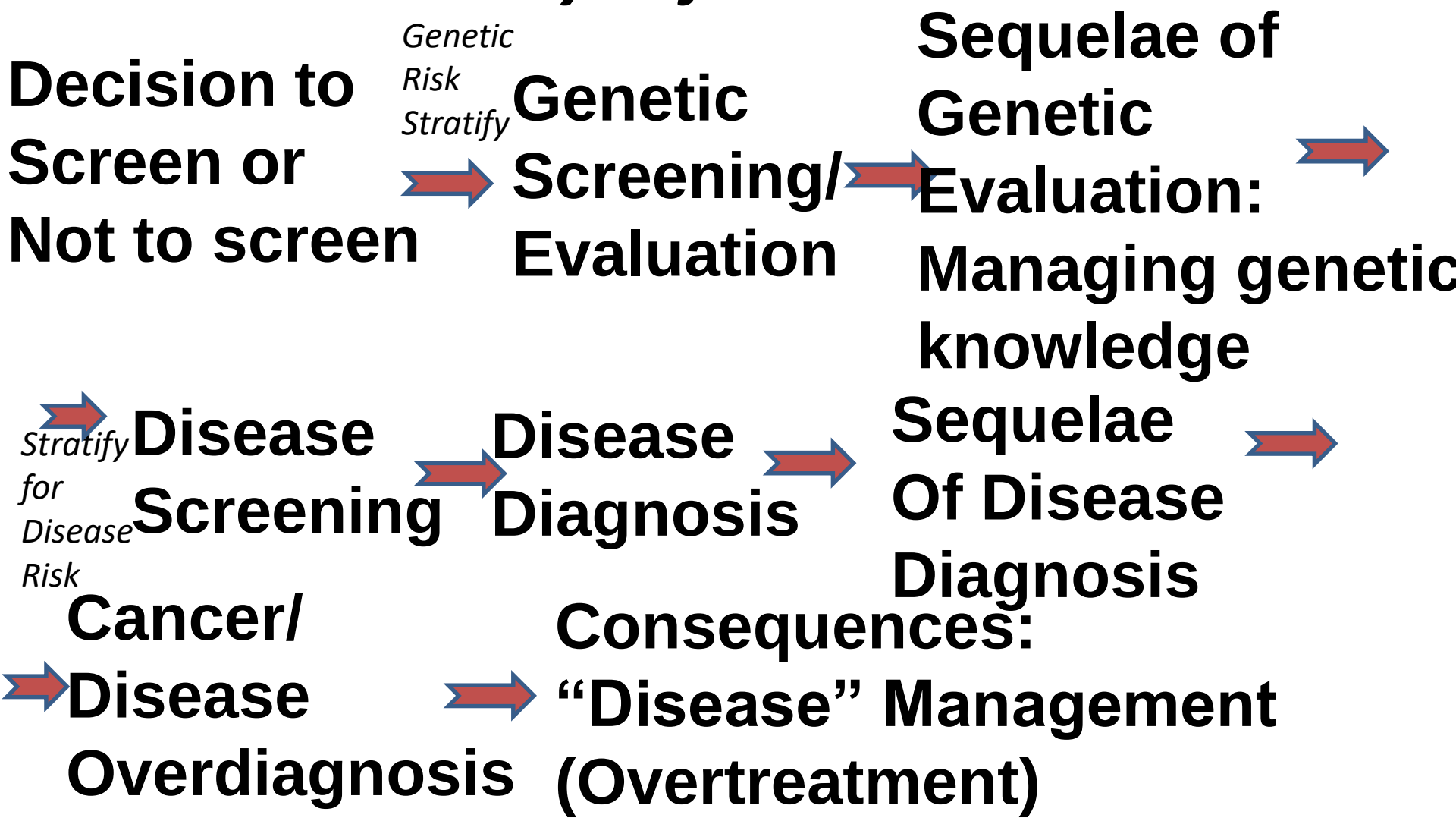
Uncertainty

…in the context of

Primary Care

Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

analytic framework:



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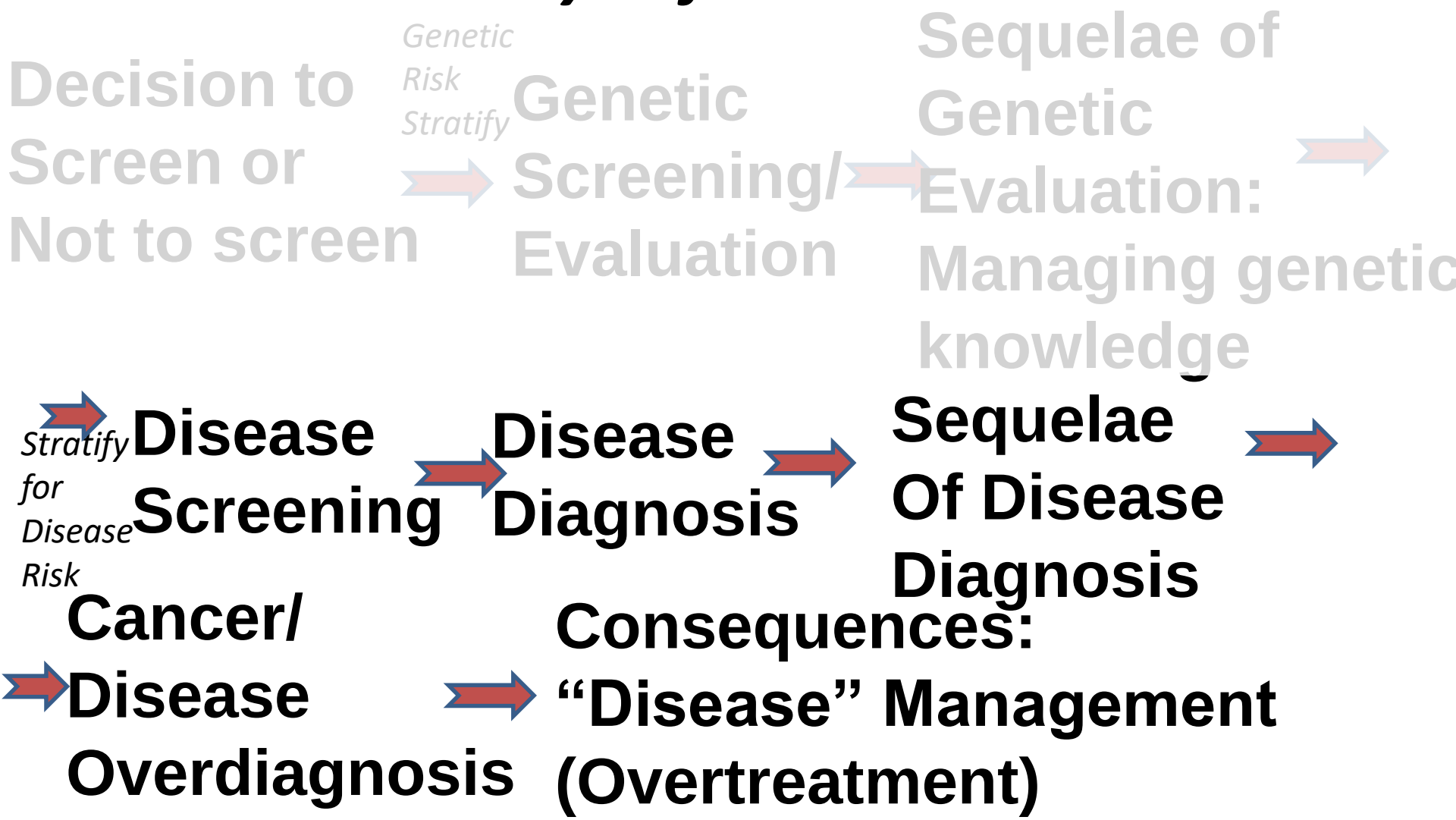

Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

analytic framework:

Decision to Screen or Not to screen

Genetic Risk Stratify

Genetic Screening/ Evaluation

Sequelae of Genetic Evaluation: Managing genetic knowledge

Stratify for Disease Risk

Disease Screening

Disease Diagnosis

Sequelae Of Disease Diagnosis

Cancer/ Disease Overdiagnosis

Consequences: "Disease" Management (Overtreatment)

Assessment of Genetic Risk, Cancer Risk and Cancer Diagnosis

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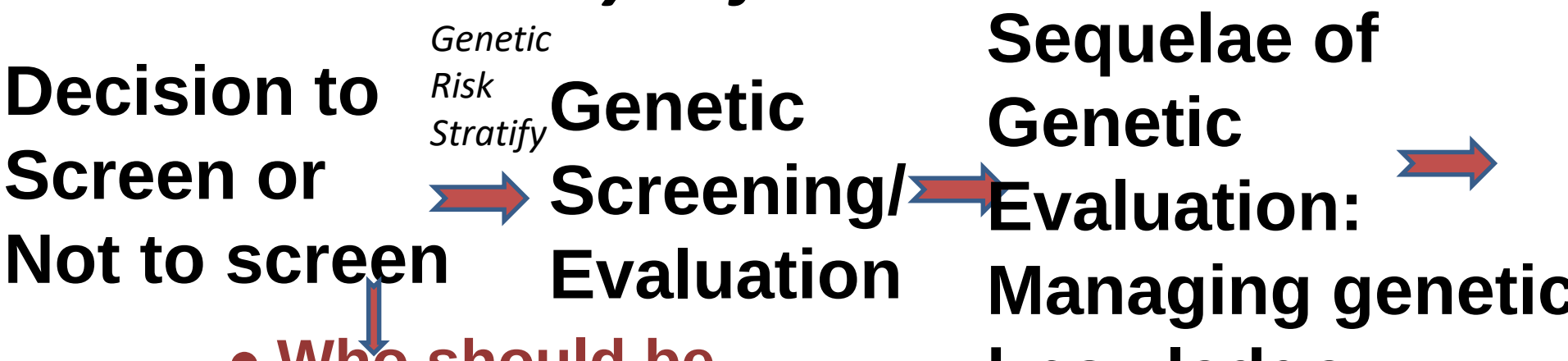

- **Who should be (genetically) tested?**
  - Use "demographic" assessment= strong family history, etc. *versus* population-based screening
  - Candidates for testing:
    - individual with disease/cancer
    - healthy relatives of person with cancer

First encounter with "uncertainty": Whom should I test?

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- **Who should be (genetically) tested?**
- **What test should be used?**
  - Single gene testing
  - Gene-panel based testing
  - Whole genome sequencing

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- **Who should be (genetically) tested?**
- **What test should be used?**
- **Managing uncertainty**
  - -Incomplete Penetrance
  - -Variants of Uncertain Significance (VUS)

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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:
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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**
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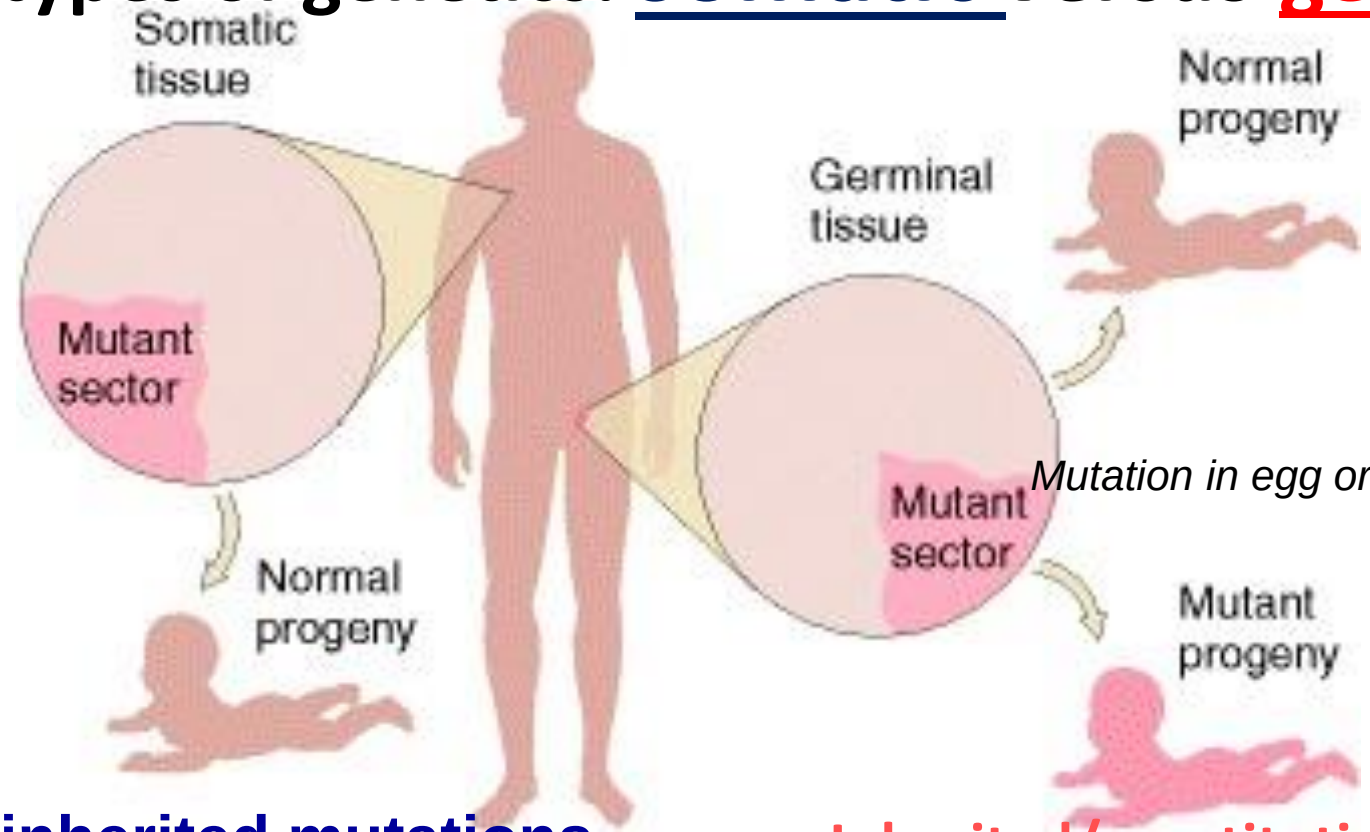
Definitions

2 types of genetics: somatic *versus* germline



New York: W. H. Freeman; 2000.ISBN-10: 0-7167-3520-2

Non-inherited mutations – "Sporadic"

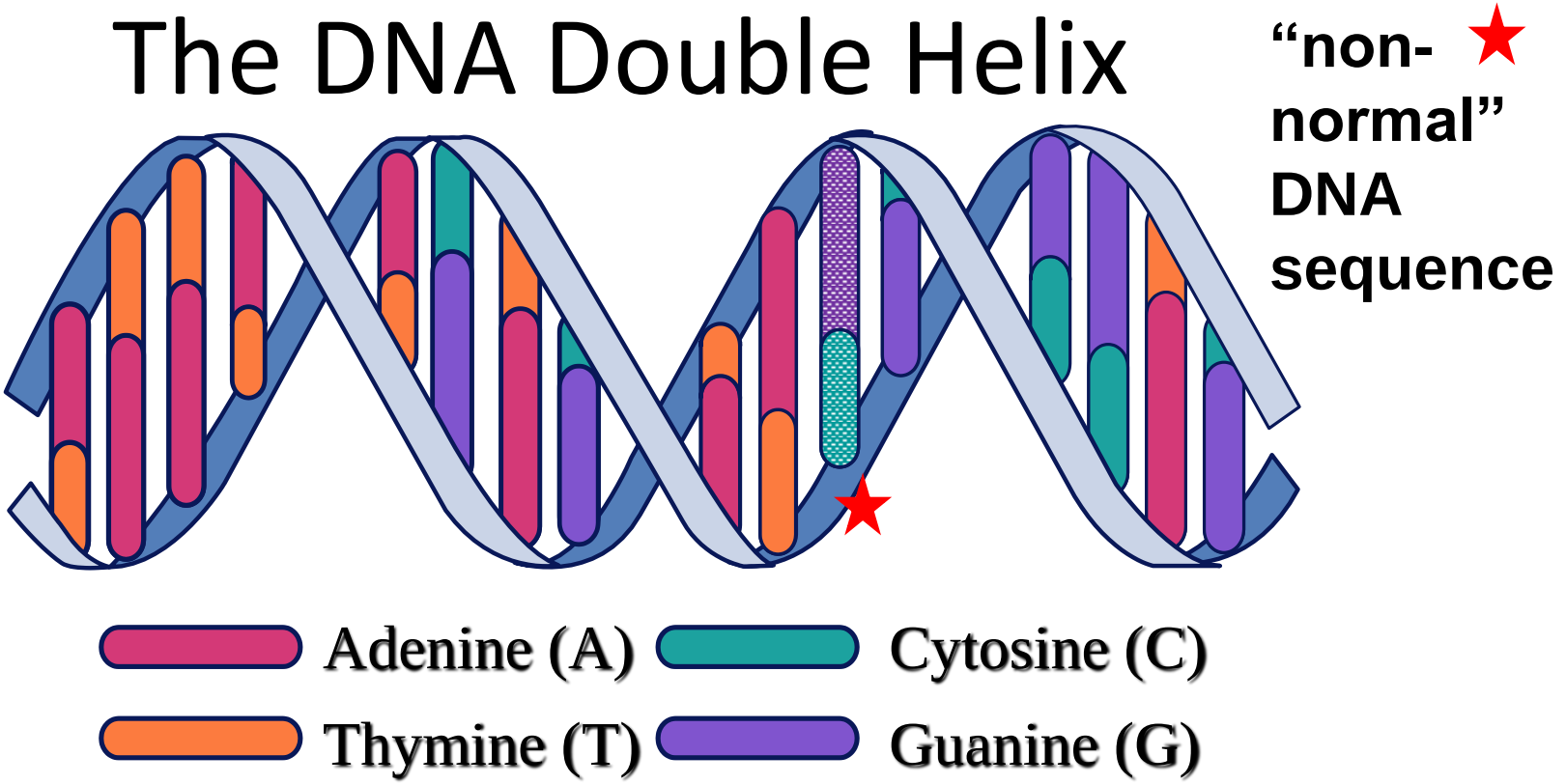
- in only one cell or organ- NOT in eggs or sperm
- Not inherited
- *somatic genetics:* *passed on cell to cell*

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



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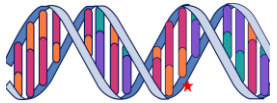
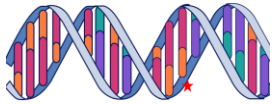


- **Mutation** = any alteration/change in the base-pair sequence of genetic material:
  - **Disease-causing**
  - **Neutral/benign**
  - **"adaptive"**

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

Definitions



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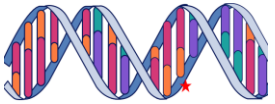

- **Variant** = an alternative version to the usual/ most commonly found base-pair sequence in a gene
- **Polymorphism** = common variations/variants, observed in **≥ 1%** of the population (which population?)

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

Science 293:594, July27,2001

[http://www.biochem.northwestern.edu/holmgren/Glossary/Definitions/Def-G/genetic_polymorphism.html]

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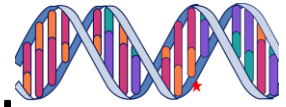

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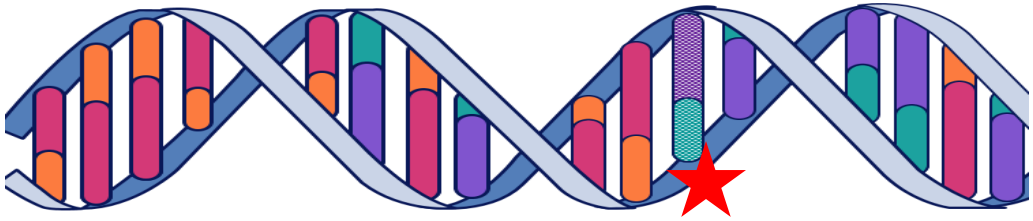


Definitions: How does DNA fit into the picture?

gene* = *piece of DNA, inherited

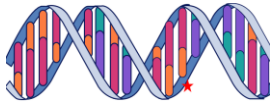
The DNA Double Helix

"non-★ normal" DNA sequence

All changes in DNA sequence are NOT equal !

Not all changes affect the function of the gene product.

Definitions



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Eccles…ENIGMA 2015

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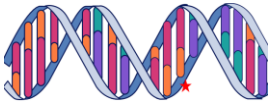

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Kang 2016 J Am Coll Radiol

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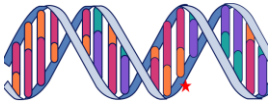

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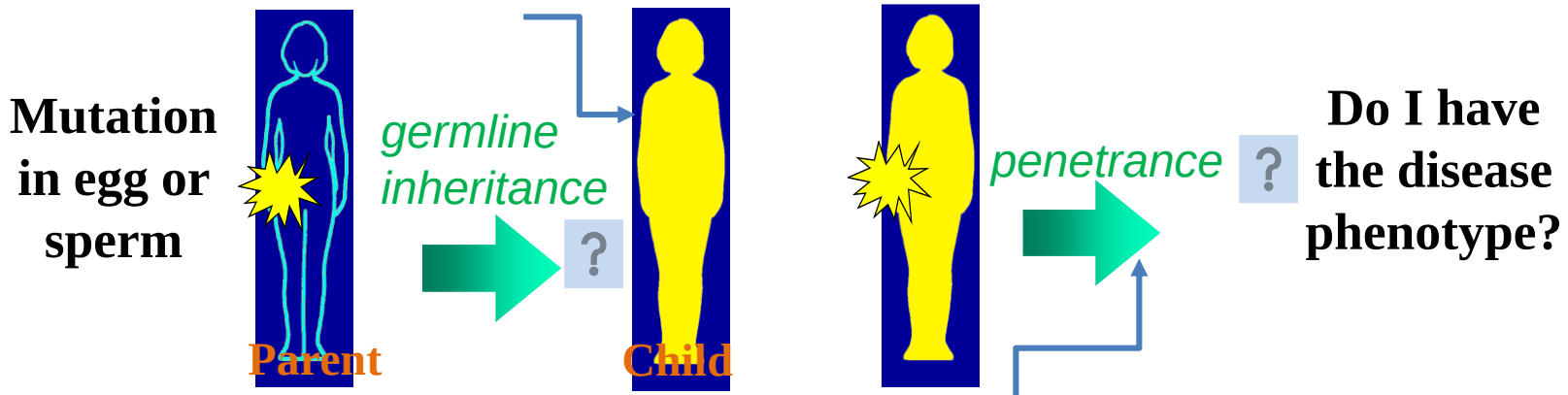
- **Penetrance** = proportion of individuals w/a given variant who express the trait/disease/phenotype

Definitions: Risk / Probability in Genetics

- Probability of <u>inheriting</u> a deleterious variant.



- <u>Penetrance</u> – 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. ⟶ <u>Uncertainty</u>

The danger is people see genetic variants as disease – and they are not disease!

<u>Primary Care Provider</u> must be able to communicate this…

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-Screening; risk algorithms

●Who should be (genetically) tested?

Primary Care Provider

-Single gene testing
-Gene-panel based testing
-Massively parallel sequencing
-Whole genome sequencing,
-Whole exome sequencing

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

Primary Care Provider

●Interpreting genetic results

-Massive amounts of data
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●Managing uncertainty

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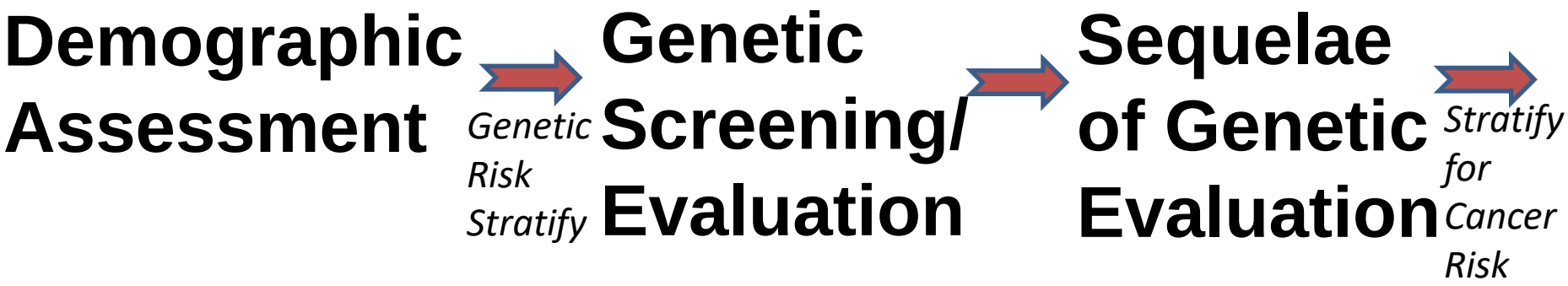

Uncertainty and challenges to Primary Care Provider emerge at all stages of Genetic Testing