Genomic Sequencing in Research and Clinical Care

A Primer and Overview of Ethical Issues

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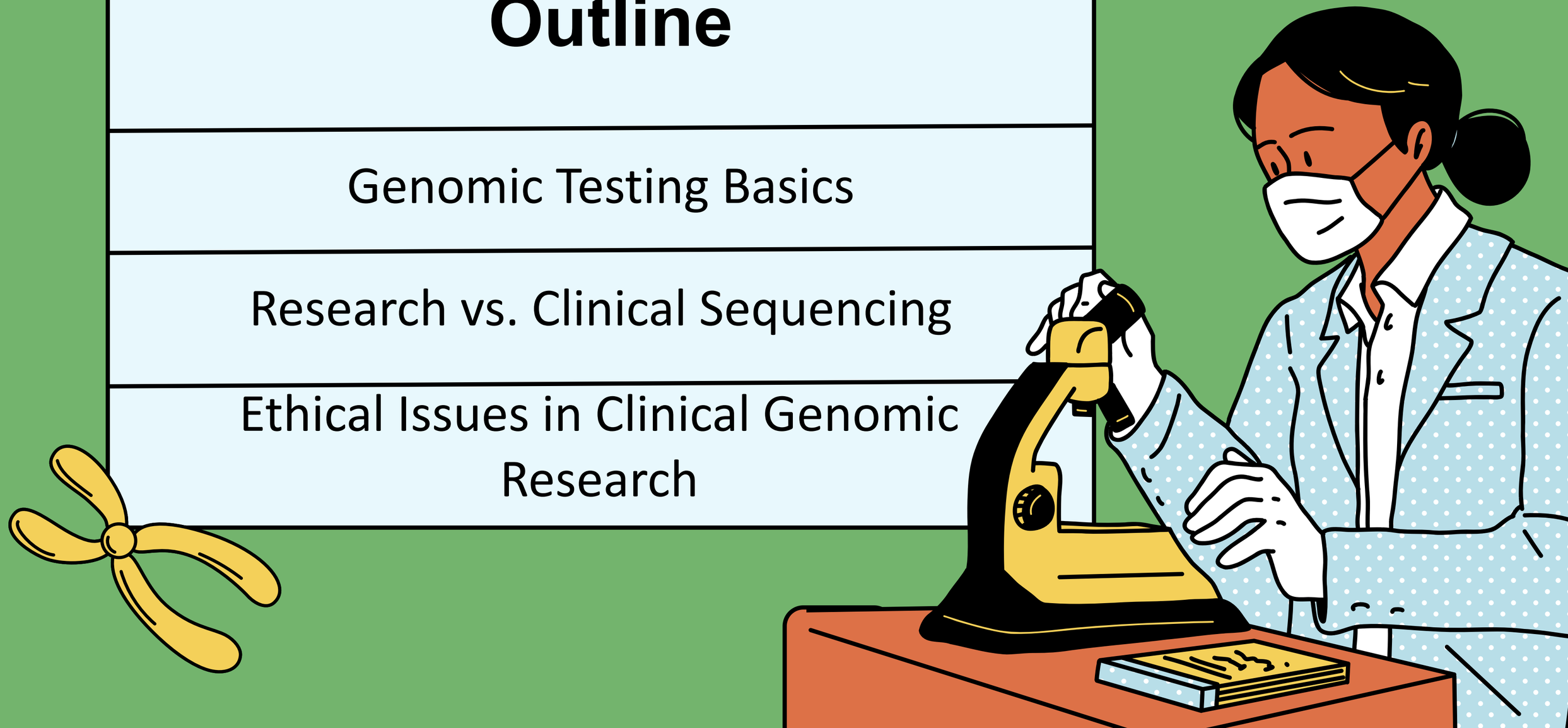
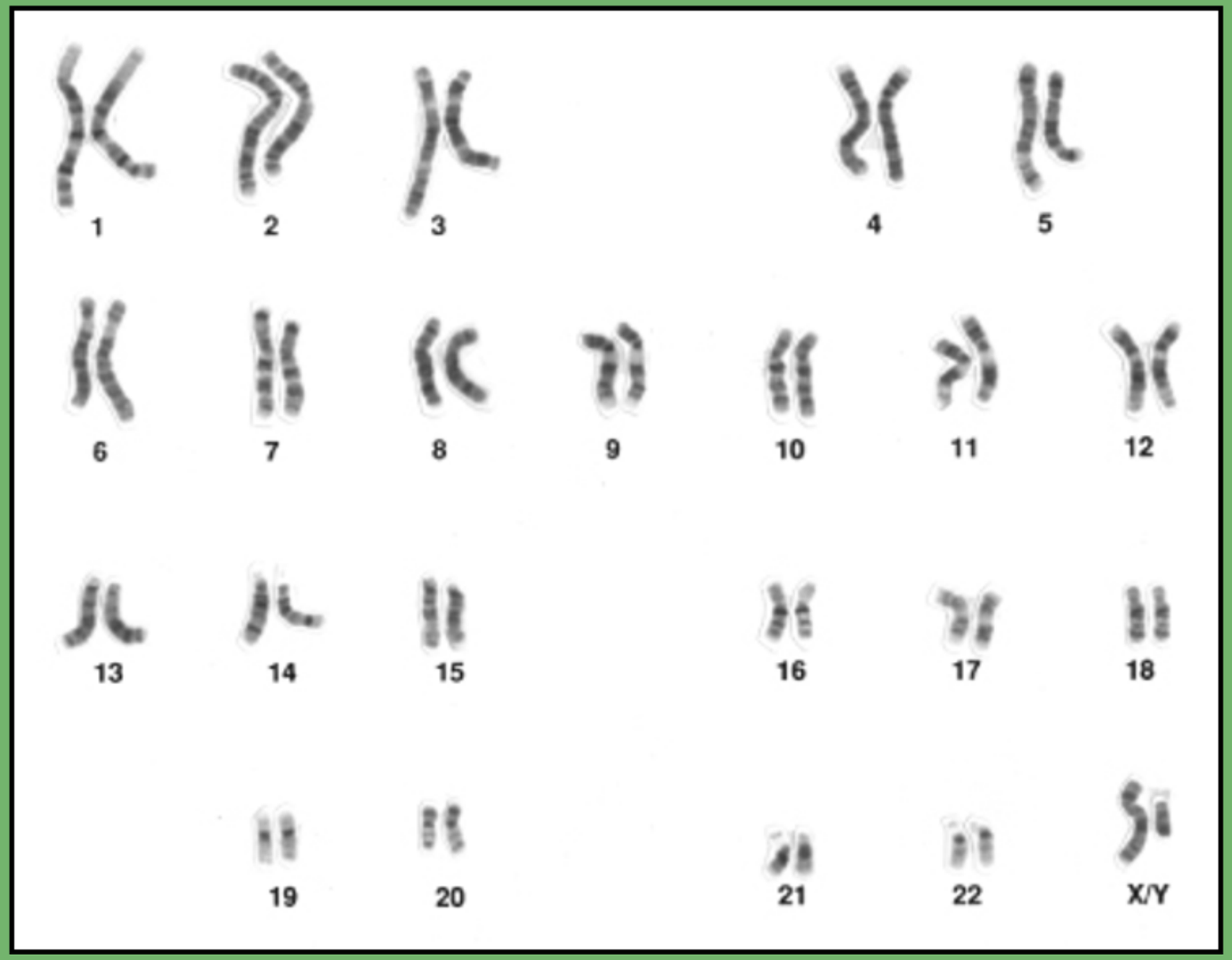
Outline

Genomic Testing Basics

Research vs. Clinical Sequencing

Ethical Issues in Clinical Genomic Research





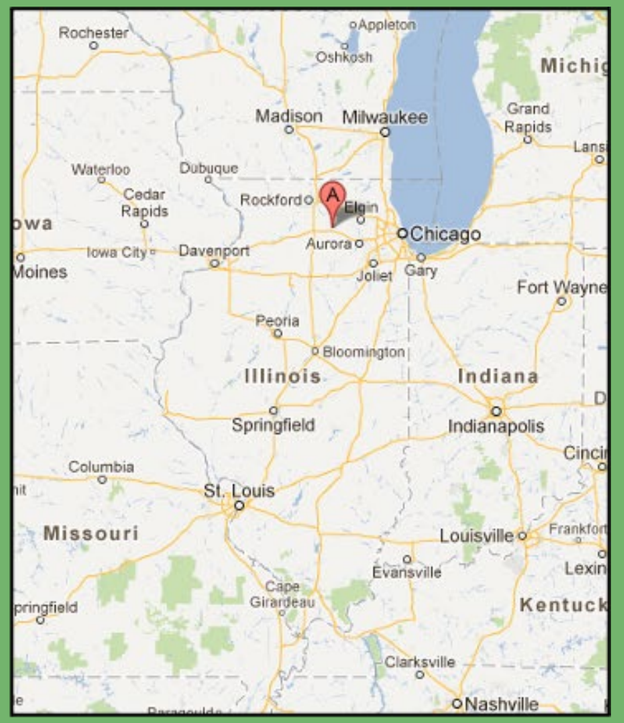
GENOME:

3 billion DNA letters

~25,000 genes

2,500 genetic tests


Google
united states
Canada
United States
Mexico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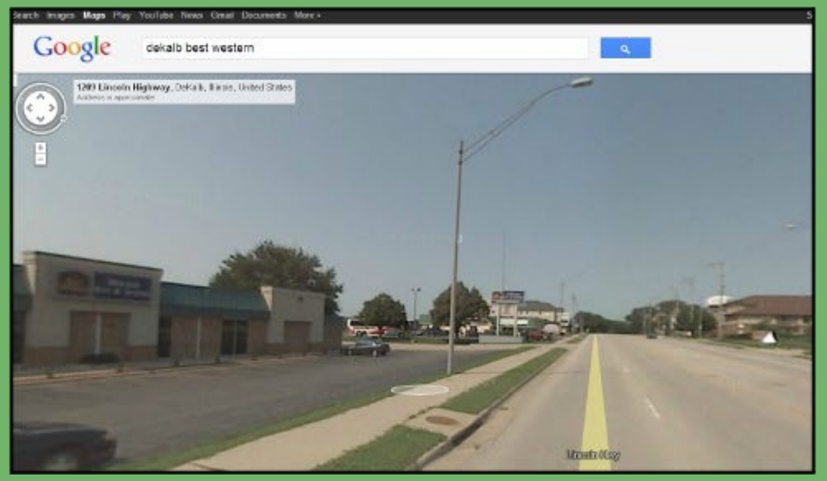
Clarksville
Nashville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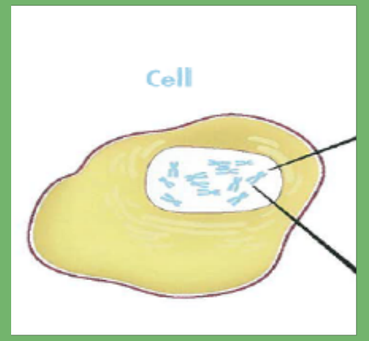

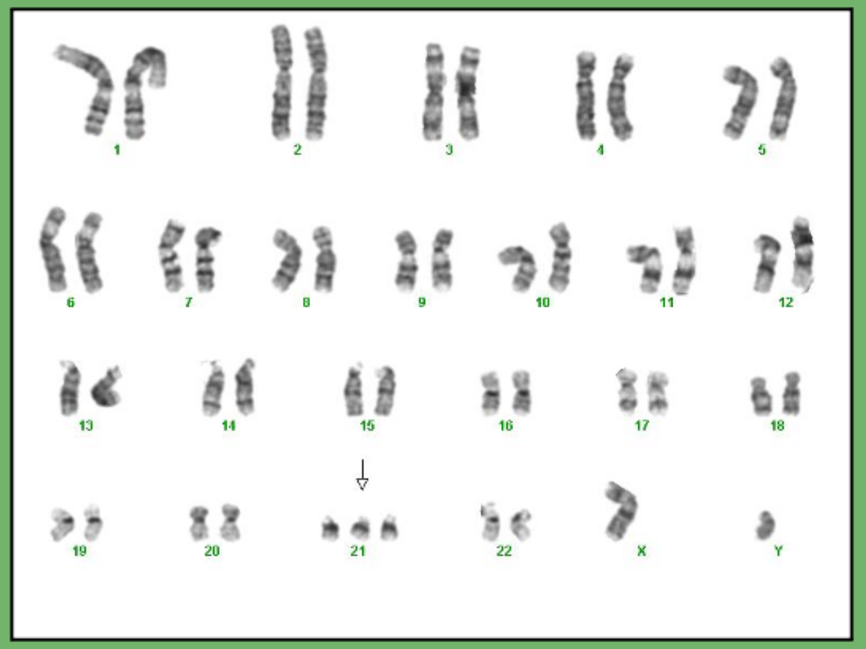

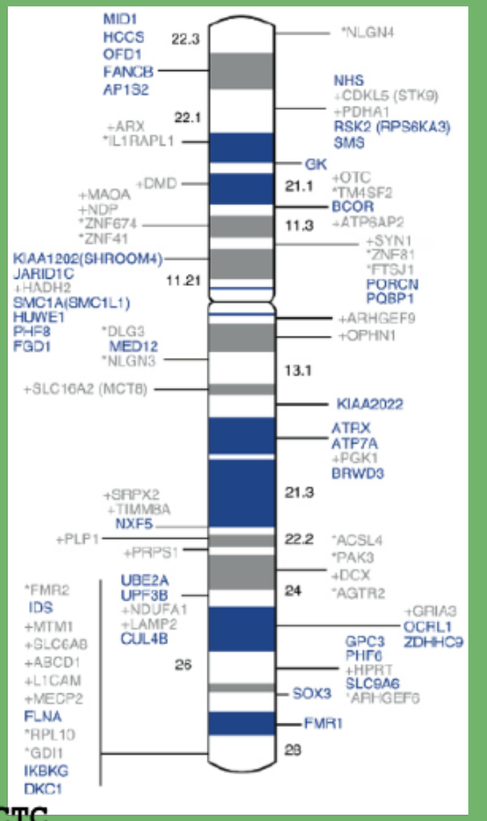

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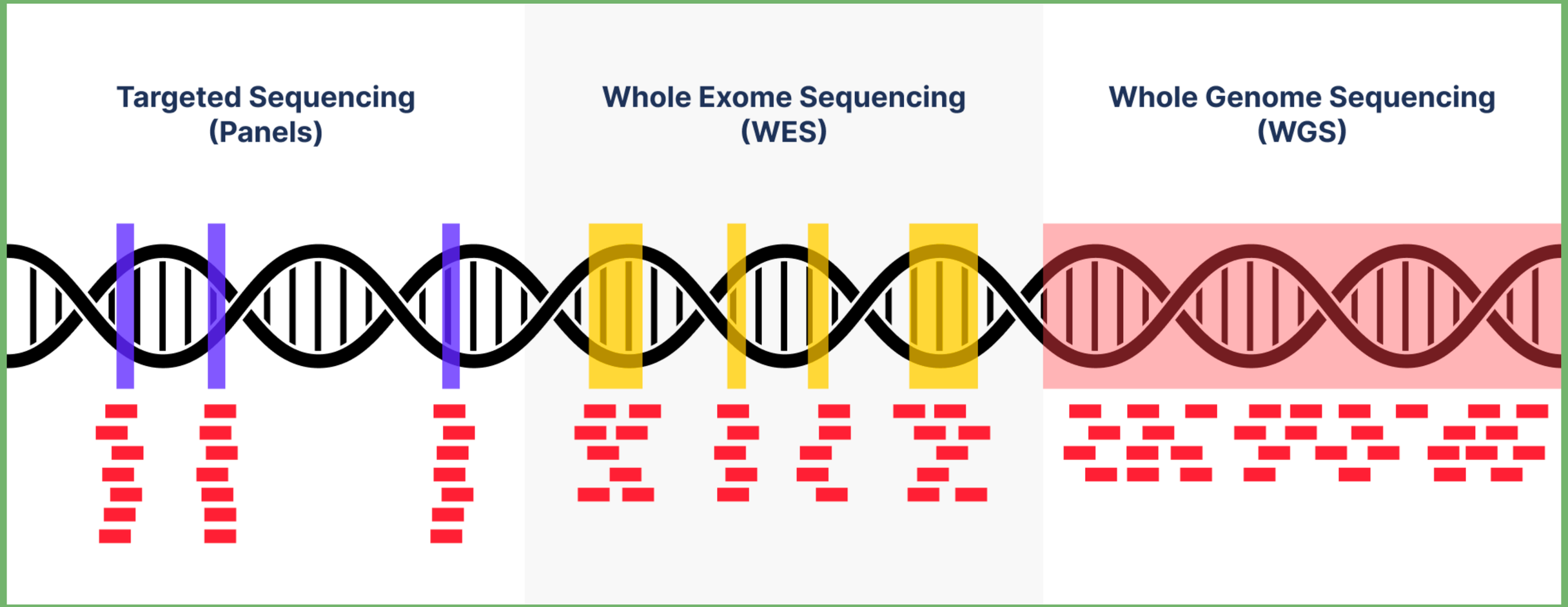


Image credit: 3billion.io/blog

Tumor Testing strategies

- Tumor-only
- Paired normal and tumor

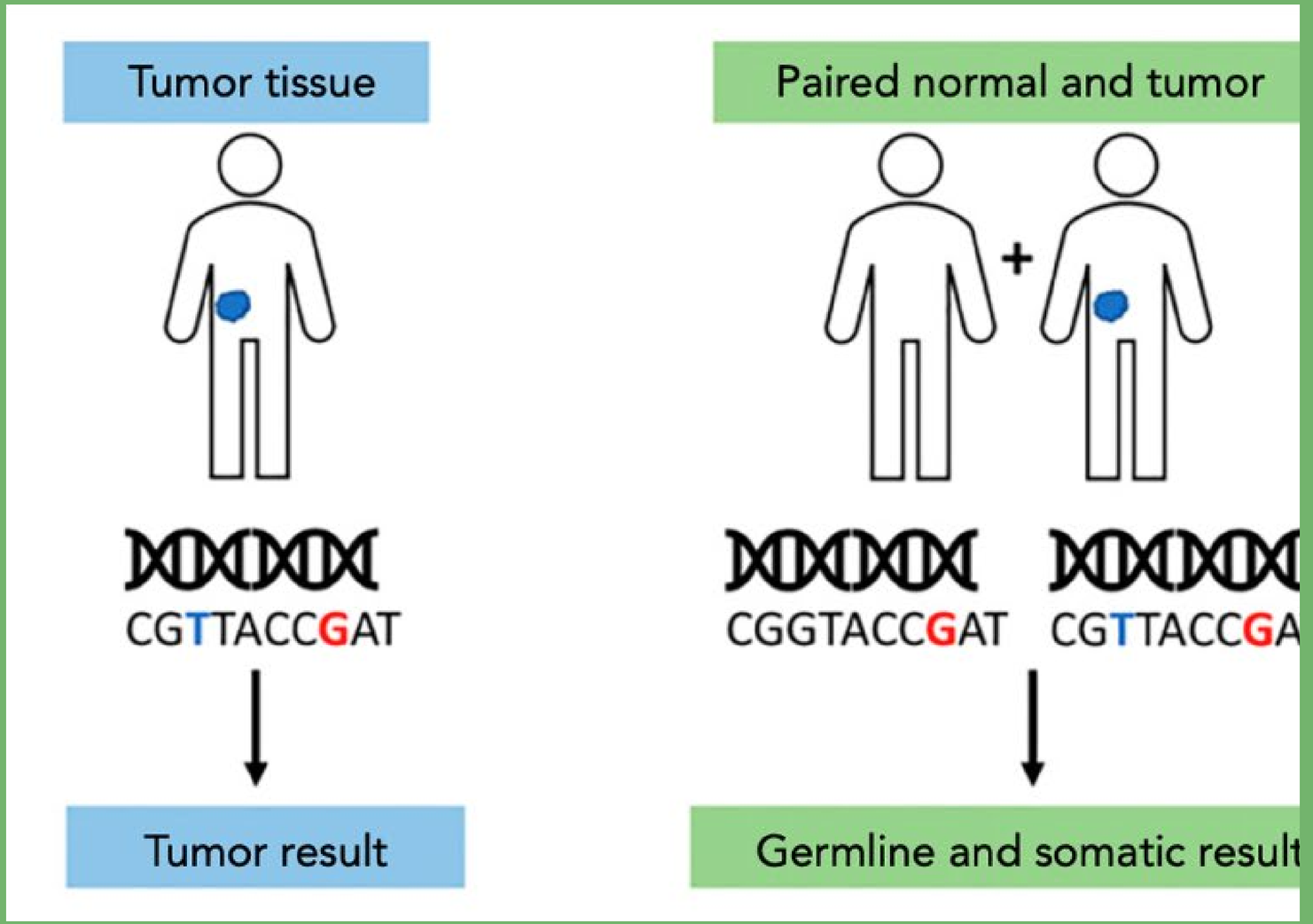


Image credit: Yu & Stadler 2021


PHASE TWO: INTERPRETATION
SHERMAN Hollow Ledger
I THINK I FOUND A CORNER PIECE.
3 BILLION PIECES
GENOME

Clinical sequencing

ACMG STANDARDS AND GUIDELINES | Genetics inMedicine

Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology

Sue Richards, PhD[1], Nazneen Aziz, PhD[2,16], Sherri Bale, PhD[3], David Bick, MD[4], Soma Das, PhD[5], Julie Gastier-Foster, PhD[6,7,8], Wayne W. Grody, MD, PhD[9,10,11], Madhuri Hegde, PhD[12], Elaine Lyon, PhD[13], Elaine Spector, PhD[14], Karl Voelkerding, MD[13] and Heidi L. Rehm, PhD[15]; on behalf of the ACMG Laboratory Quality Assurance Committee

Clinical Laboratory Improvements Amendments

ACMG PRACTICE GUIDELINES | Genetics inMedicine

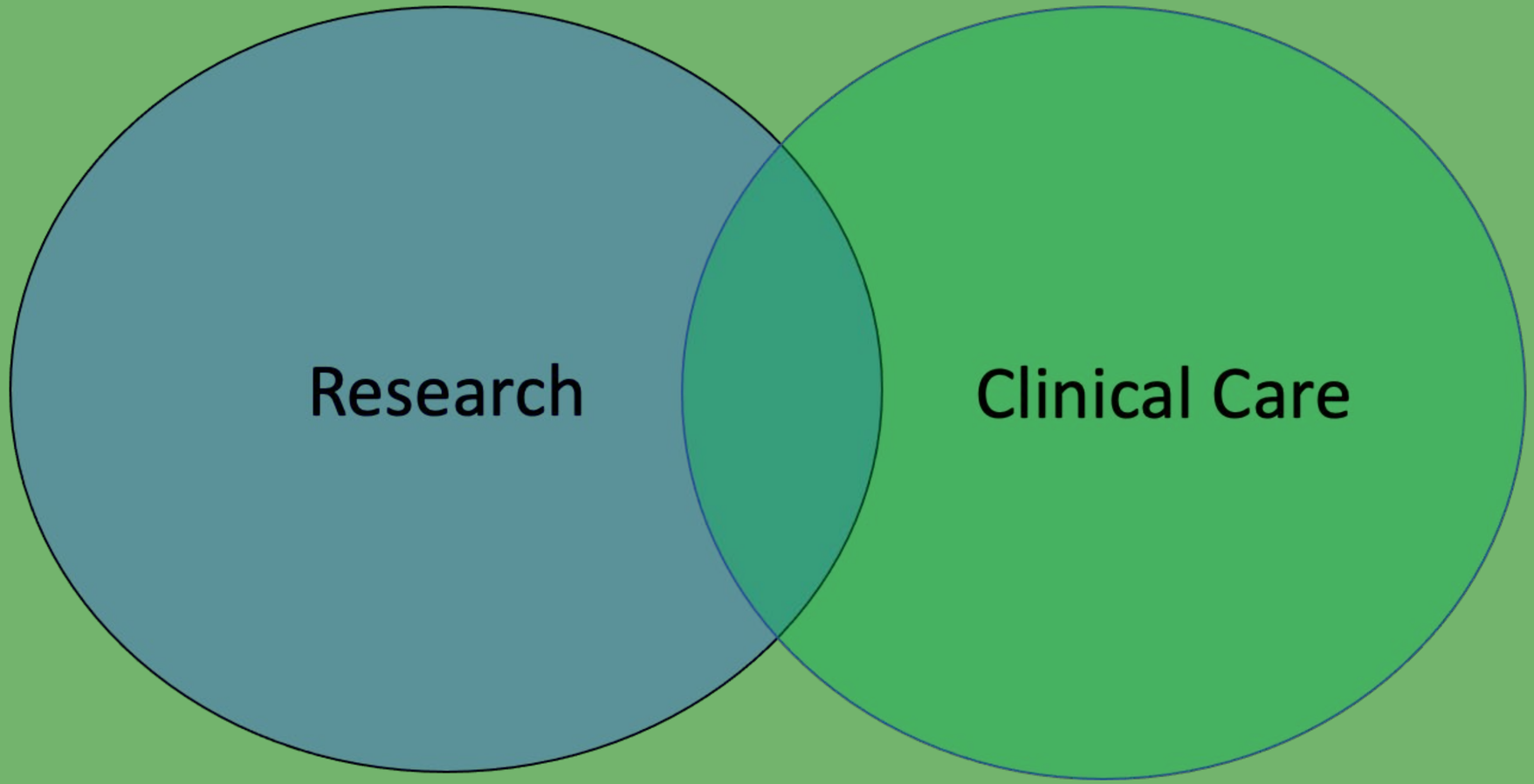
ACMG clinical laboratory standards for next-generation sequencing

Heidi L. Rehm, PhD[1,2], Sherri J. Bale, PhD[3], Pinar Bayrak-Toydemir, MD, PhD[4], Jonathan S. Berg, MD[5], Kerry K. Brown, PhD[6], Joshua L. Deignan, PhD[7], Michael J. Friez, PhD[8], Birgit H. Funke, PhD[1,2], Madhuri R. Hegde, PhD[9] and Elaine Lyon, PhD[4]; for the Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee

Research sequencing

Image credit: IGN.com

NIH Clinical Center - Overlapping Worlds



SUMMARY

- Genetic and genomic testing comes in all shapes and sizes
- Testing can be very targeted or very broad
- Testing can detect both inherited and acquired genetic variations
- There are stricter quality, validity, and reliability standards in the clinical realm than there are in research

OVERVIEW OF ETHICAL ISSUES

- All these issues pertain to both research and clinical care
- HOW we reason through the solutions varies depending on the purpose of testing

Informed consent

- Goal of informed consent : to respect persons as autonomous, voluntary participants in research

- 3 elements: information, comprehension, and voluntariness. Is supposed to be a process not a document

- Many genome studies have unspecified future aims, broad data-sharing policies, and ongoing uncertainties about privacy protections

Elements of informed consent for genomic research

Genomic research data may:

- Be stored, used and shared broadly and indefinitely.
- Inform individuals about susceptibility to a broad range of conditions (some of which are unexpected given personal or family history).
- Carry with them risks that are uncertain or unclear.
- Be reinterpreted and change in relevance over time.
- Raise privacy concerns (in part because of the risk of re-identification).
- Be relevant for family members and reproductive decision-making.

Source: https://www.genome.gov/about-genomics/policy-issues/Informed-Consent

Testing Minors for Adult-Onset Genetic Conditions

Does the child want this information?

What are the parent preferences?

How are the child's interests being promoted or set back by sharing this?

(Gillam et al 2022)

Policy guidance

Professional Society	Guideline Date	Guidance
European Society of Human Genetics	2009	Pre-symptomatic and predictive genetic testing of minors for conditions with adult-onset is only acceptable if preventive actions can be initiated before adulthood
National Society of Genetic Counselors	2018	Encourages deferring pre-symptomatic and predictive testing in children and young people who cannot yet make a mature decision. Decision should be made with the assent of the minor when possible.
American Association of Pathologists/American College of Human Genetics and Genomics	2013	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
American Society of Human Genetics	2015	Testing for carrier status and adult-onset conditions should be deferred, with exceptions for adolescents who meet certain standards of competence, voluntariness, etc. Facilitating predictive or pre-dispositional testing of children for adult-onset conditions can be justified in certain circumstances.

“The right to an open future”

Image credit: @magann

Critiques

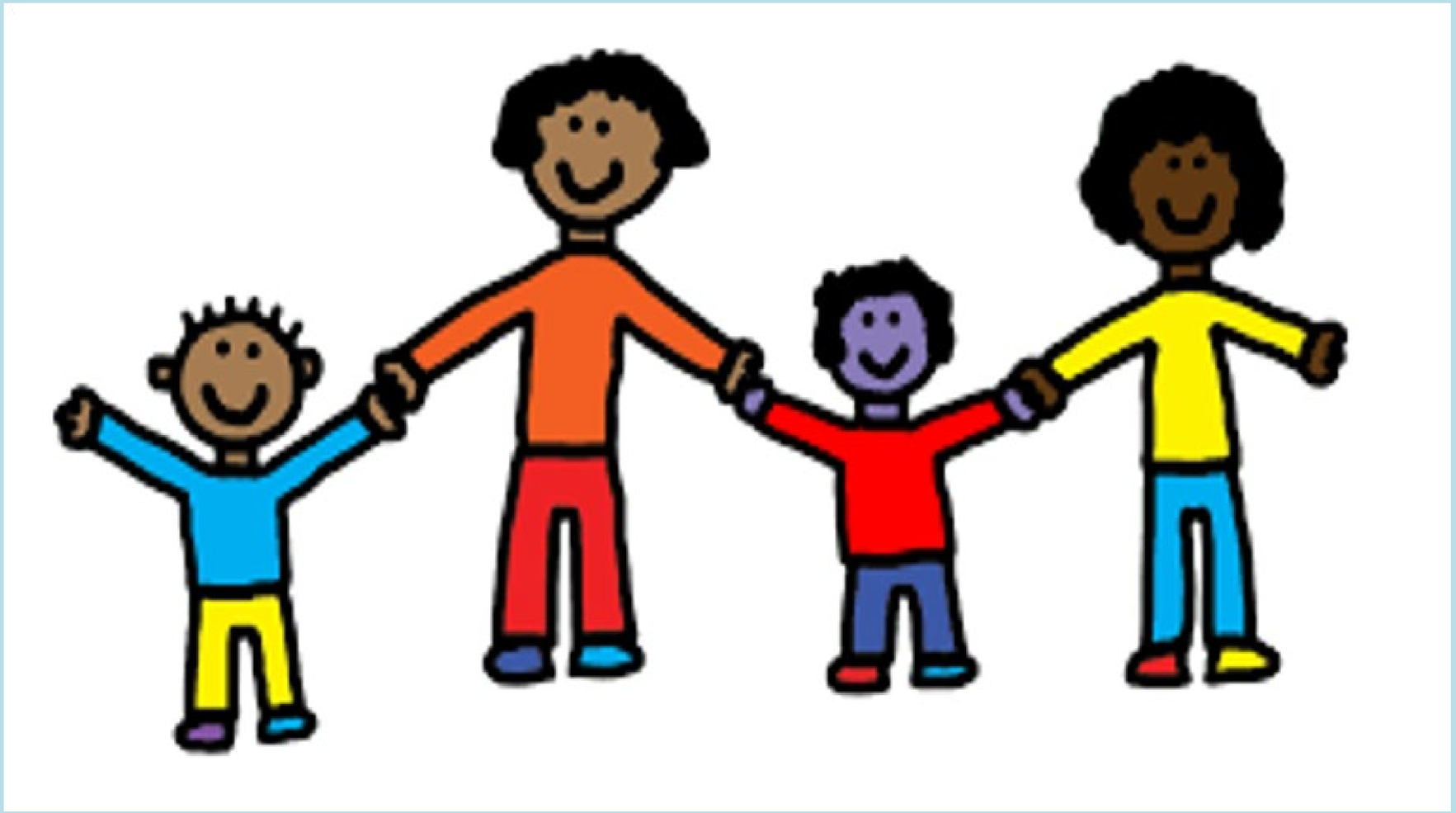
- What is an “open future”?
- Relies on an essentialist understanding of genetics
- Delaying testing is also a decision that affects the child
- Children clearly have an interest in preserving some future decisional autonomy, but is it a right?

Garrett et al. Genetics in Medicine 2019

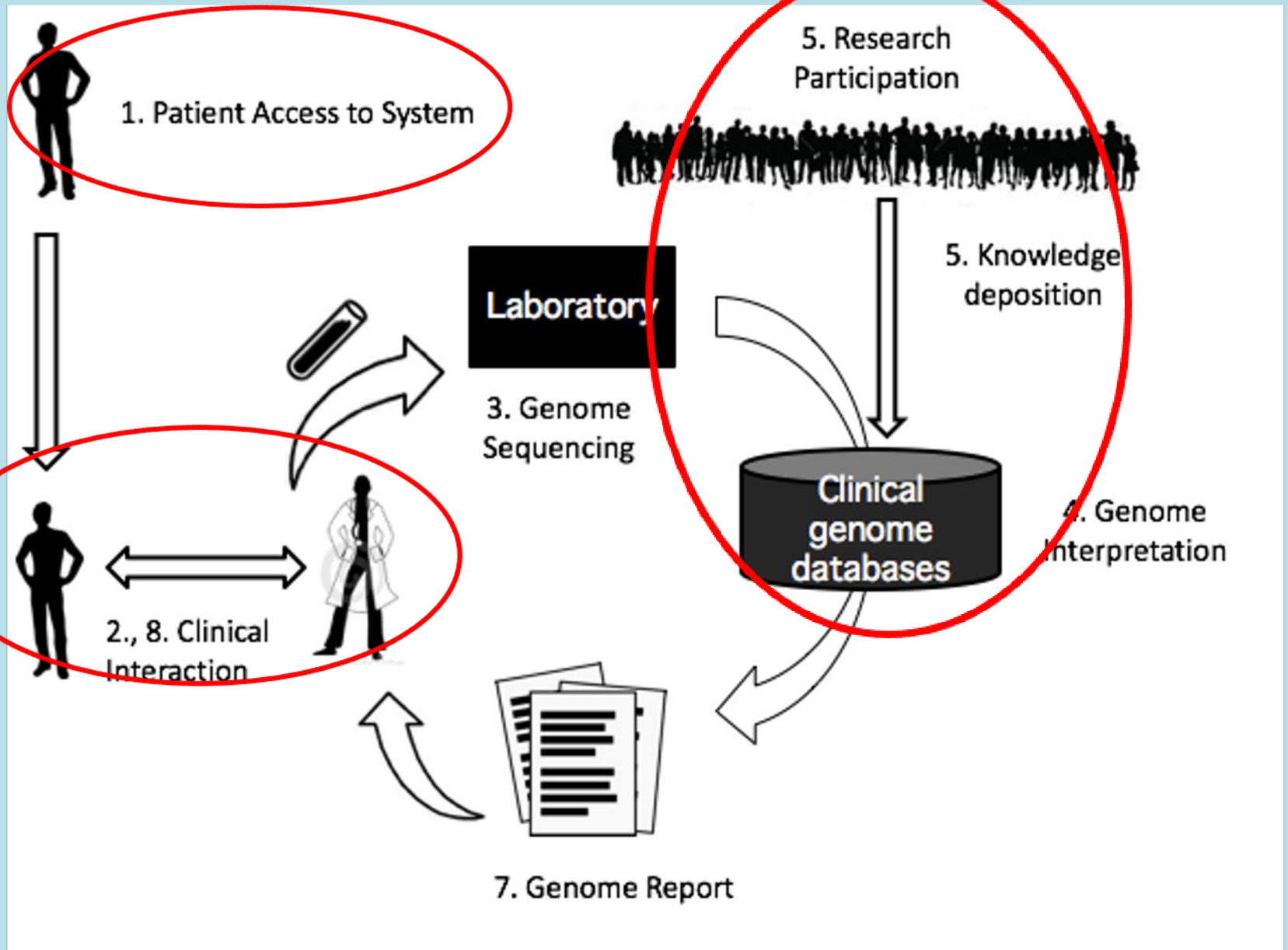
What are the interests of children?

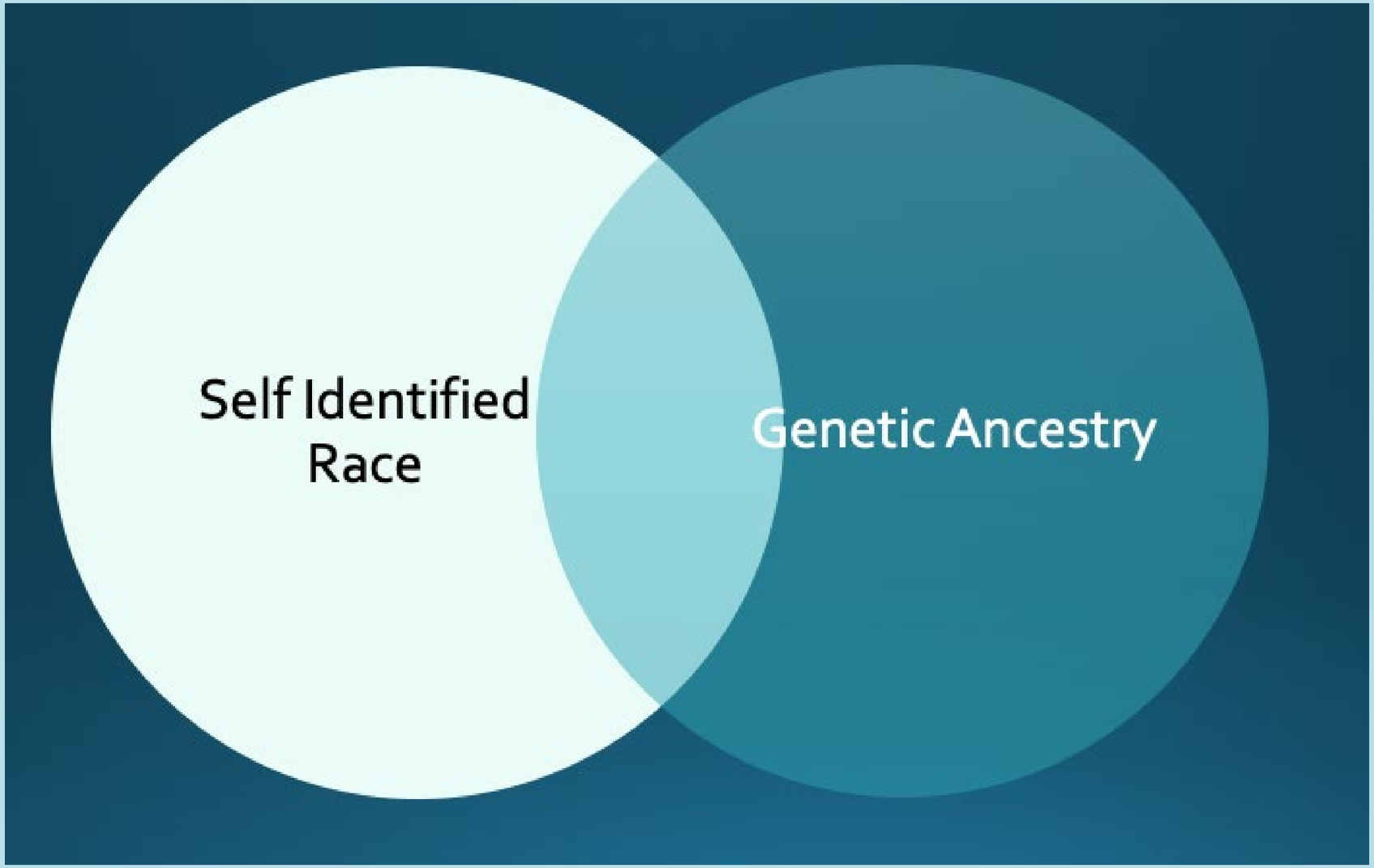
1	**Life:** To live and to anticipate a life of normal human length.
2	**Health and health care:** To have good health and protection from pain, injury, and illness. To have access to medical care.
3	**Basic needs:** To have an adequate standard of living, especially to be adequately nourished and sheltered.
4	**Protection from neglect and abuse:** To be protected from physical or mental abuse, neglect, exploitation, and exposure to dangerous environments. To be secure that they will be safe and cared for.
5	**Emotional development:** To experience emotion and have appropriate emotional development.
6	**Play and pleasure:** To play, rest, and enjoy recreational activities. To have pleasurable experiences.
7	**Education and cognitive development:** To have an education that includes information from diverse sources. To have the ability to learn, think, imagine, and reason.
8	**Expression and communication:** To have the ability to express themselves and to communicate thoughts and feelings.
9	**Interaction:** To interact with and care for others and the world around them. To have secure, empathetic, intimate, and consistent relationships with others.
10	**Parental relationship:** To know and interact with their parents.
11	**Identity:** To have an identity and connection to their culture. To be protected from discrimination.
12	**Sense of self:** To have a sense of self, self-worth, and self-respect.
13	**Autonomy:** To have the ability to influence the course of their lives. To act intentionally and with self discipline. To reflect on the direction and meaning of their lives. *To have "future autonomy" protected by having future options and opportunities kept open.*

Should we also consider benefits to families?



Lack of representation in genomic datasets




Self Identified
Race
Genetic Ancestry

Finding Risks, Not Answers, in Gene Tests

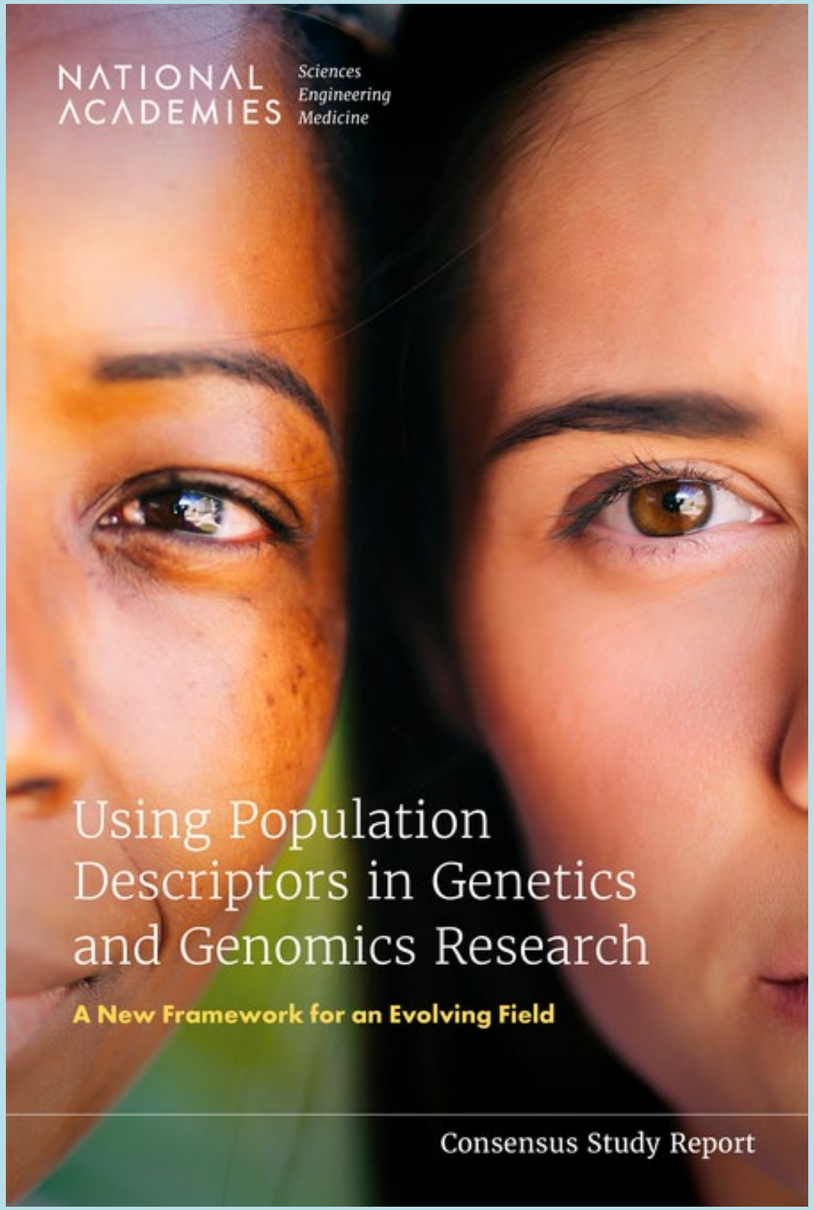
By DENISE GRADY and ANDREW POLLACK SEPT. 22, 2014

Jennifer was 39 and perfectly healthy, but her grandmother had died young from breast cancer, so she decided to be tested for mutations in two genes known to increase risk for the disease.

When a genetic counselor offered additional tests for 20 other genes linked to various cancers, Jennifer said yes. The more information, the better, she thought.

The results, she said, were "surreal." She did not have mutations in the breast cancer genes, but did have one linked to a high risk of stomach cancer. In people with a family history of the disease, that mutation is considered so risky that patients who are not even sick are often advised to have their stomachs removed. But no one knows what

Tamika Matthews has had breast and thyroid cancer, and had genetic screening. She is concerned her son may be at risk. Chester Higgins Jr./The New York Times


NATIONAL ACADEMIES
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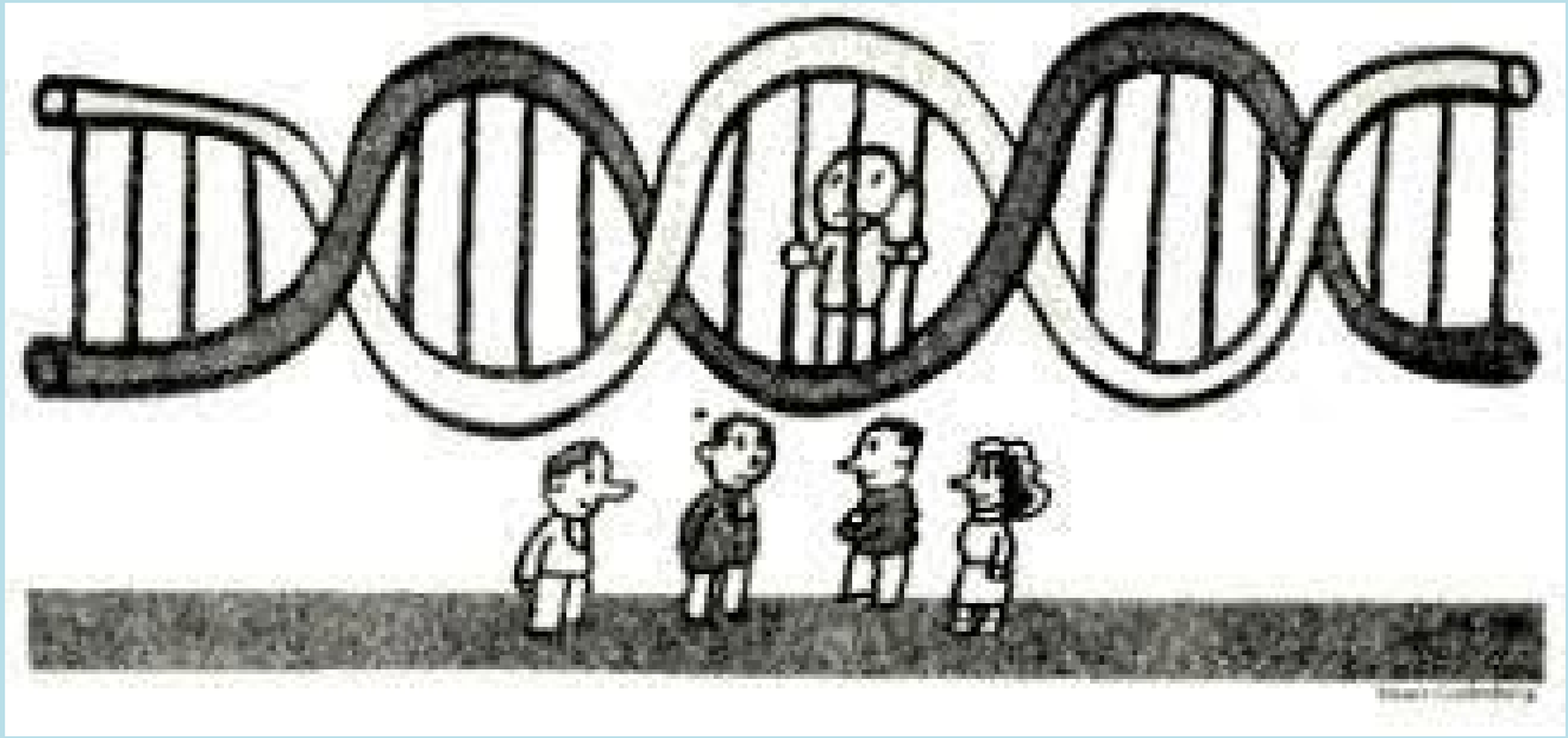
A New Framework for an Evolving Field
Consensus Study Report


All of Us

Genetic Discrimination



Source: Wired Magazine

Genetic Information Non -Discrimination Act of 2008

Strengths

- Health insurers may not use genetic info to determine insurance eligibility, coverage, or premiums.
- Health insurers cannot require genetic testing.
- “Genetic info” includes family medical history, manifest disease in family members, and information regarding individuals' and family members' genetic tests.

Limitations

- Does not cover disability or long -term care insurance
- Military CAN use genetic info to make employment decisions
- Does not cover symptomatic people
- Does not prohibit insurers from asking for genetic info as part of employee wellness programs

A Life Insurer's Perspective

"The ethics around genetic testing and results are complex, particularly when tests reveal conditions that were not anticipated or expected. Nonetheless, legal frameworks should be constructed around the basis of symmetry of knowledge. If insurers are denied relevant data that is easily available to insured parties, it will become increasingly unviable to underwrite certain products. That would not only be a game changer for the industry – if life insurance becomes less available, the wider implications for societies and economies could also be considerable."

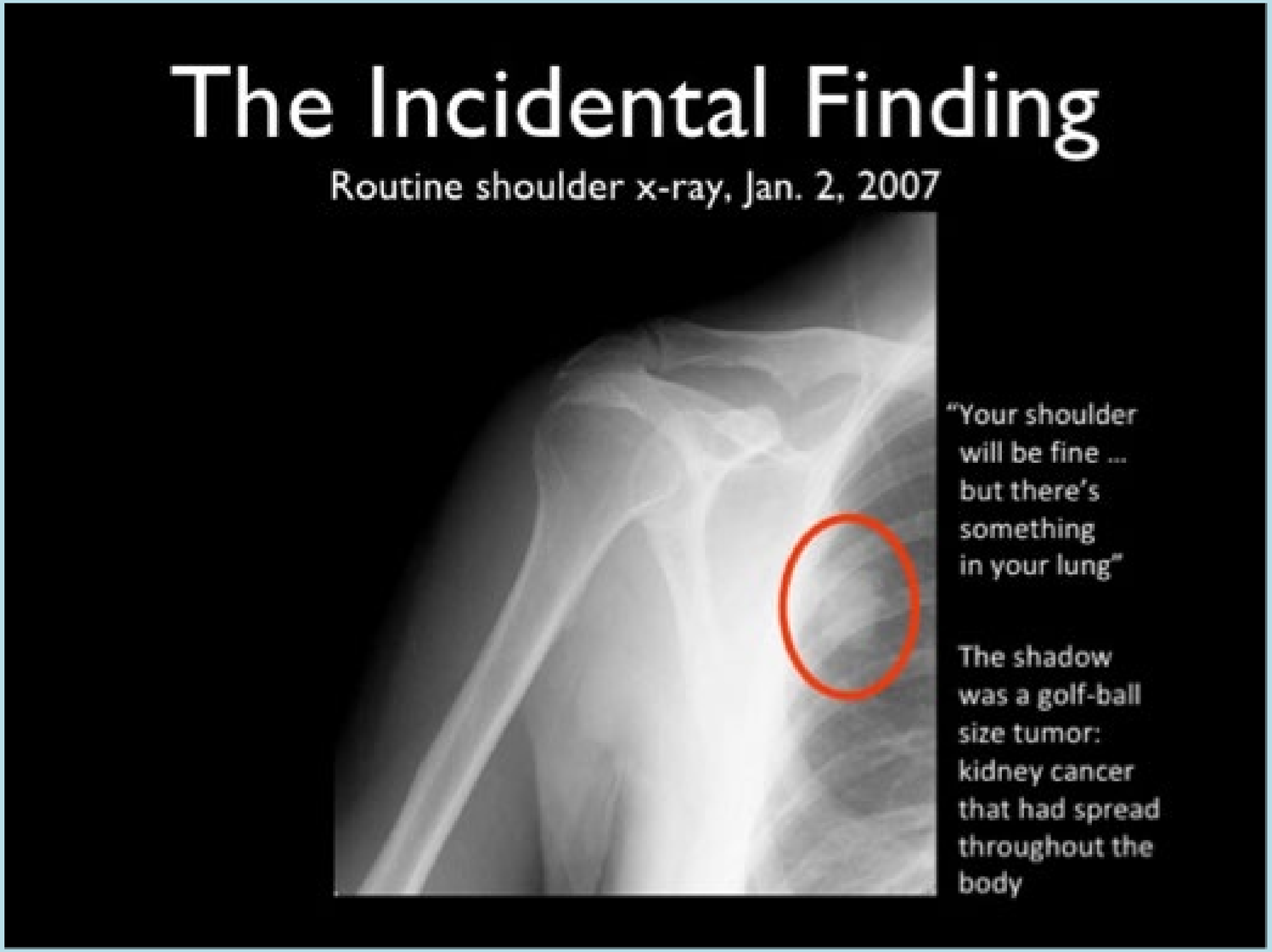
Source: SwissRe, 2017

Return of genomic research results

Primary findings

- Are related to the research question being asked
- Usually are related to a patient’s clinical symptoms
- Can still be surprising if the condition you’re studying is not well understood

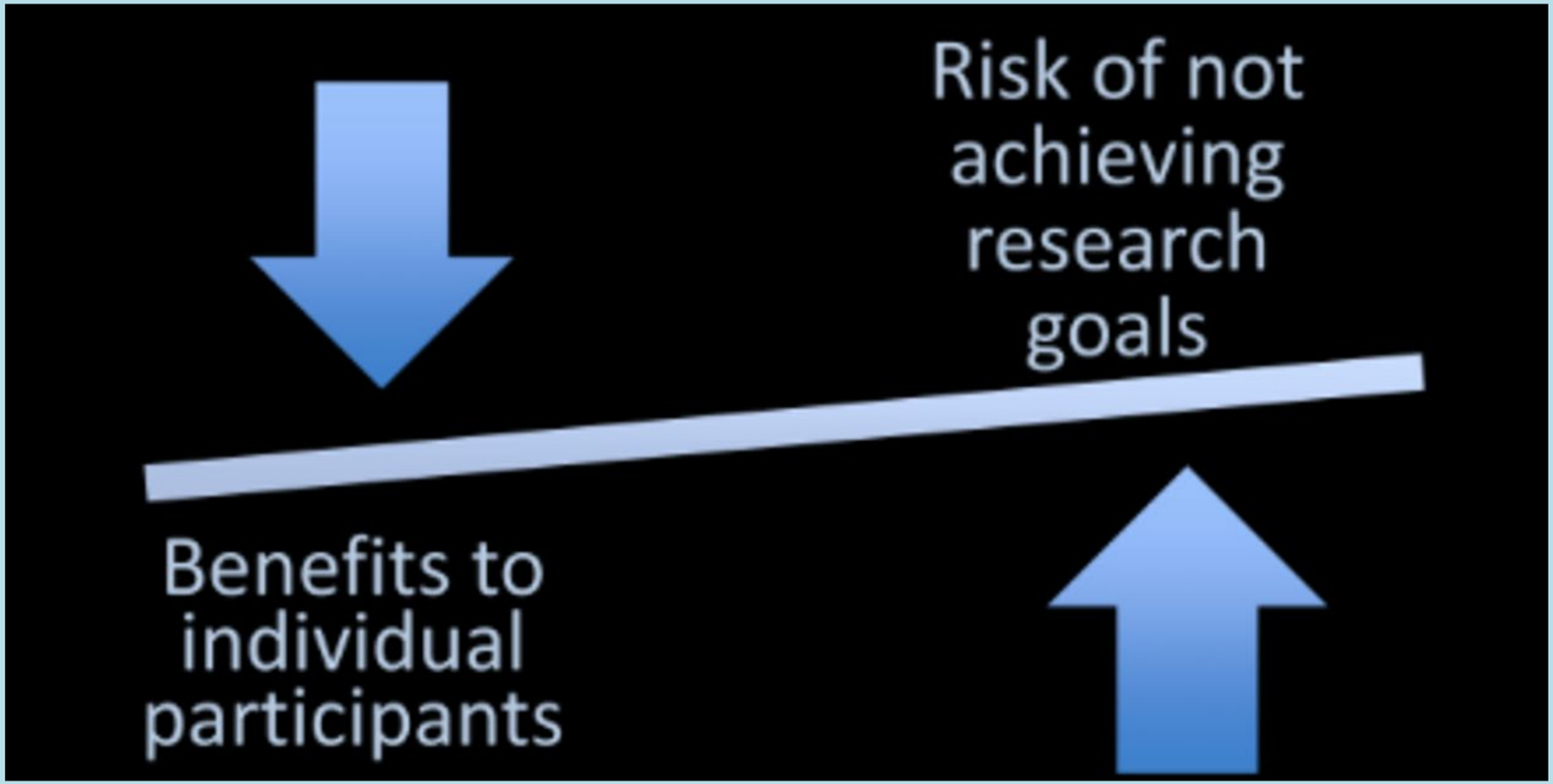
Incidental and Secondary Findings



Examples

- A child diagnosed with an autosomal recessive condition whose father is not a carrier for that condition - raising the possibility of undisclosed non -paternity
- An adopted child who has genome -wide testing to indentify the cause of a rare condition, revealing that she was the product of an incestuous relationship
- A patient whose tumor is sequenced and evidence of a hereditary cancer syndrome is found
- A research participant who enrolls in a study of people with Fragile X syndrome actually finds out they were misdiagnosed and have Friedrich's Ataxia with unexplained autism
- A pregnant woman who is enrolled in a study using maternal blood to detect fetal anomalies and is incidentally diagnosed with early -stage cancer
- A research participant enrolled in a study that aims to discover new genes that cause immune system problems and who is found to have a genetic variant that predisposes them to sudden cardiac death

In a research setting, we must consider...




Thank You!
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