Helping Patients Understand the Benefits, Limitations and Uncertainties of Genetic Testing

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March 18, 2025

Oregon Academy of Family Physicians: Lunch and Learn

Synergistic Genomics LLC

About Heather

- Master's degree - Human/Medical Genetics
- Licensed and board certified genetic counselor
- 18 years of clinical genetics experience
- 8 years in insurance, regulatory, and healthcare operations
- 2 years of independent healthcare consulting
- Serves on the AMA-PLA TAG* committee
- Serves on the ACMG** Therapeutics committee

*American Medical Association (AMA) Proprietary Laboratory Analyses (PLA)-Technical Advisory Group (TAG)

** American College of Medical Genetics and Genomics (ACMG)

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Conflicts of Interest

- Owner of Synergistic Genomics, LLC
- Synergistic Genomics, LLC is not affiliated with or supported by any clinical genetic testing laboratory or clinical genetic service

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Agenda

- Clinical Genetics: A Brief History and Basic Review
- Updated Genomic Paradigm
- Benefit of Genomics in Clinical Practice
- Limitations and Risks of Genomics in Clinical Practice
- Clinical Scenarios
- Take Home Points and Action Items

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Very Brief History of Clinical Genetics and Genomics

- 1909: Term “gene” is coined by Wilhelm Johannsen

1859	1866	1944	1953	~2000	~2015
Charles Darwin	Gregor Mendel	Avery, MacLeod..	Watson, Crick…	Human Genome Project	1000 Genomes Project
On The Origin of Species…	“Experiments on Plant Hybridization”	DNA is the basis of heredity	DNA is a double helix	First sequence of the human genome	Study of genome variability

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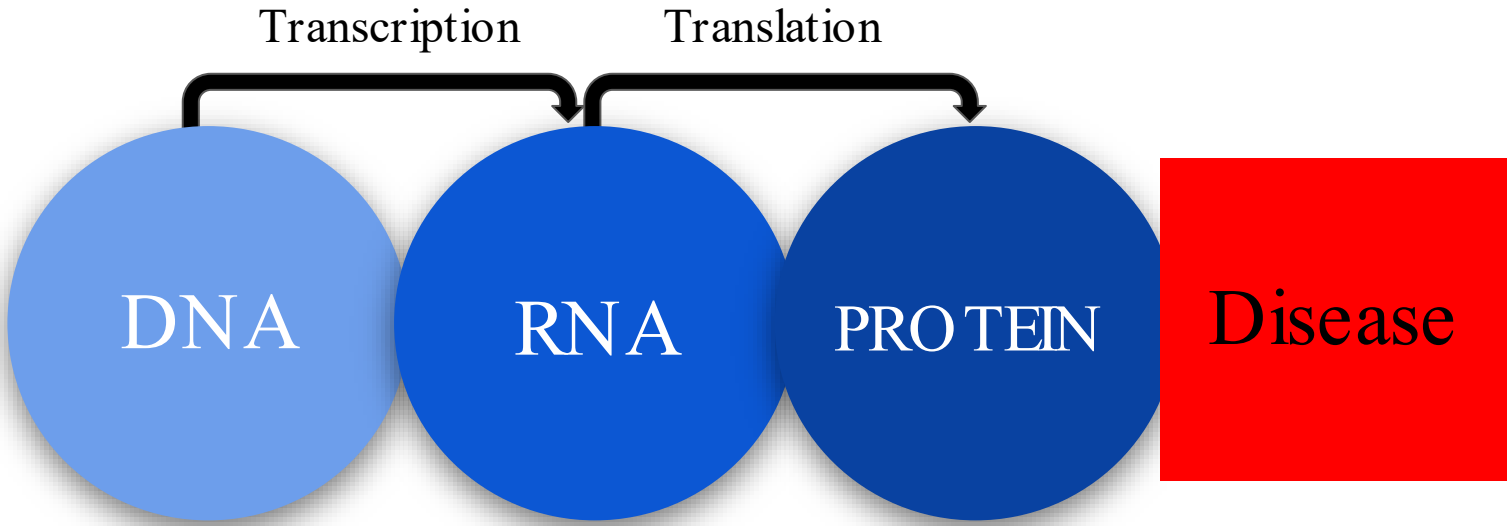
Historic Paradigm: Central Dogma



NHGRI 11.13.24

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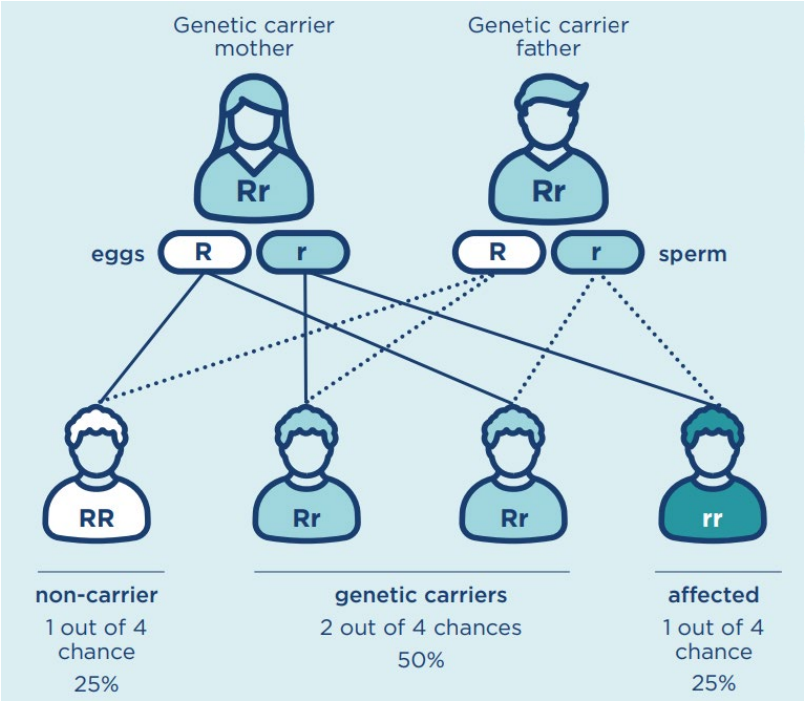
Cystic Fibrosis (CF): Clinicals, Genetics and Inheritar

- Chronic, multiorgan condition
- Autosomal recessive inheritance
- Most common in European populations, but occurs in any population
- Caused by variants in *CFTR* (>2000 variants noted)
- New treatments have improved outcomes, but are *CFTR* variant specific currently



StatPearls: Cystic Fibrosis 8.8.2022

Fact Sheet: Centre for Genetics Education

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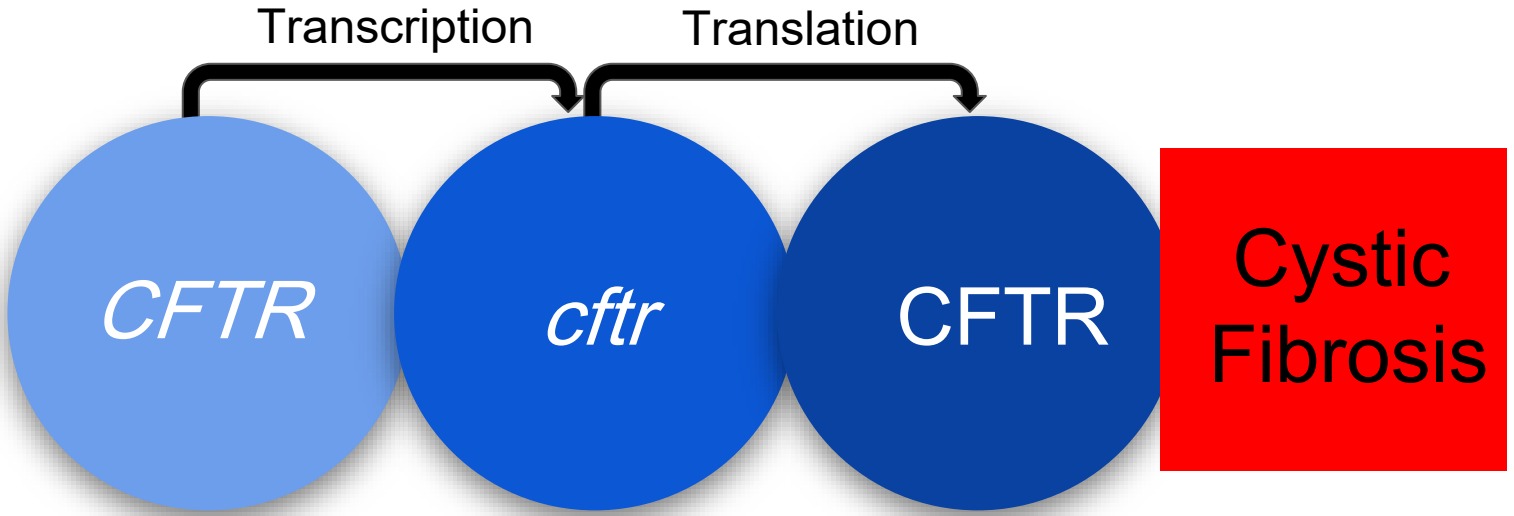
Historic Paradigm: Cystic Fibrosis is *CFTR* in Isolation



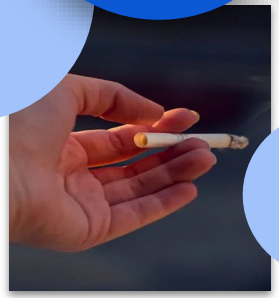
CFTR = DNA
cftr = RNA
CFTR = protein

Updated Paradigm: Integrated Genome & Environment

DNA

RNA

PROTEIN



The unit of input is NOT the gene, it is the GENOME (and transcriptome and proteome).

It's not nature or nurture, it's nature AND nurture.

DNA = Genome
RNA = Transcriptome
Protein = Proteome
= Environmentalome

NHGRI webinar (10.23.24)
Dr. Rasmus G. Winther
Complex Trait Genetics

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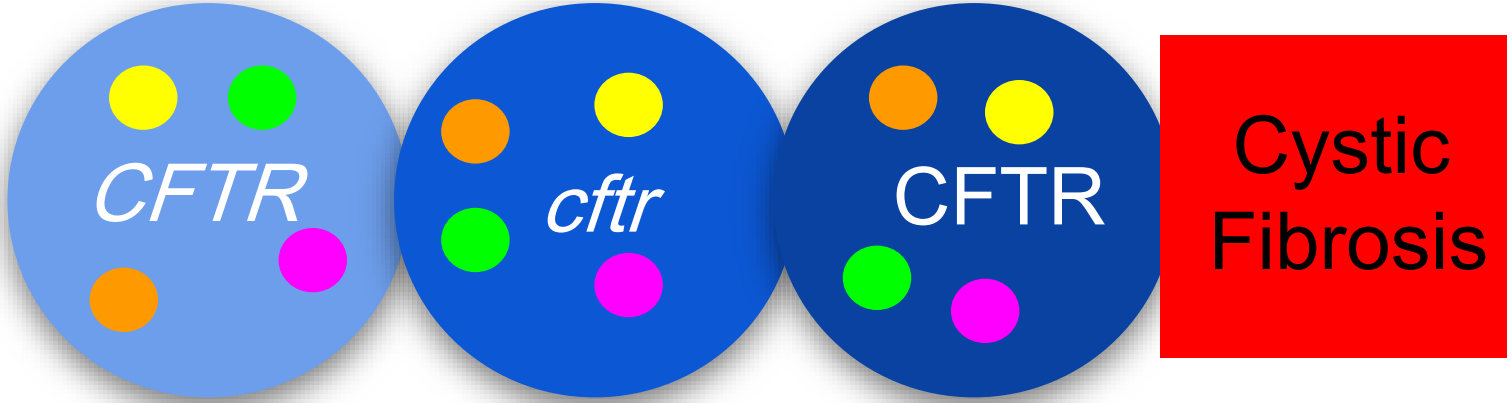
Images from Pexels

Updated Paradigm: Cystic Fibrosis – *CFTR* Integrated



= non-CFTR variation at the DNA, RNA and protein levels

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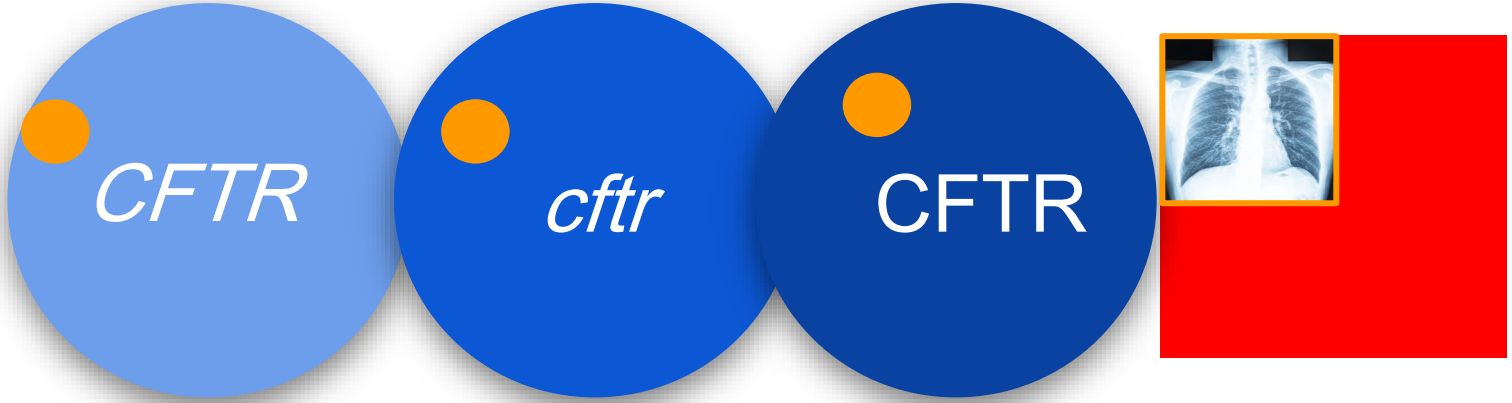
Updated Paradigm: Cystic Fibrosis – Impact on Lungs



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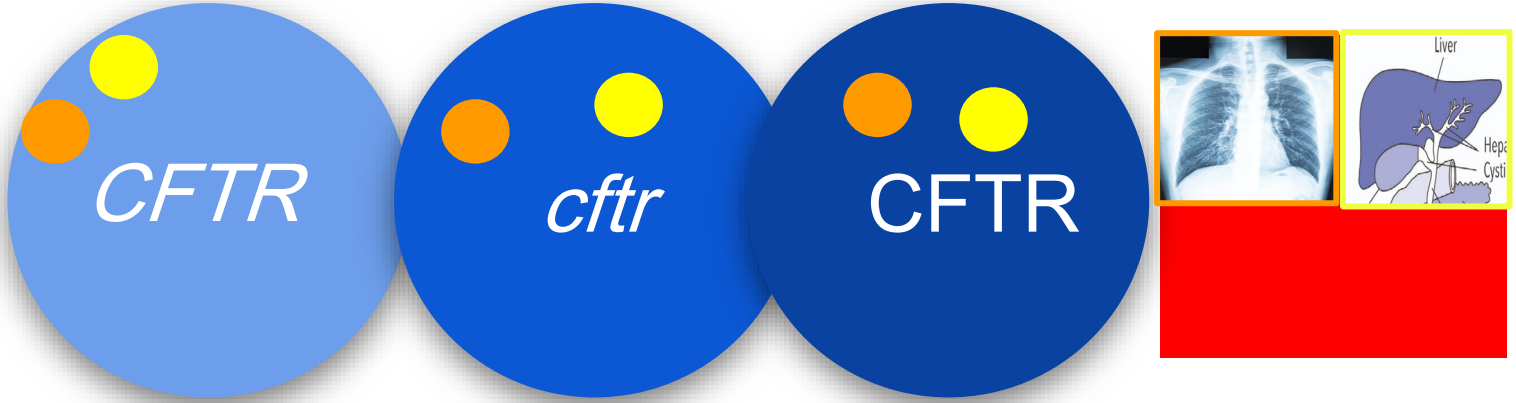
Updated Paradigm: Cystic Fibrosis - Impact on Liver



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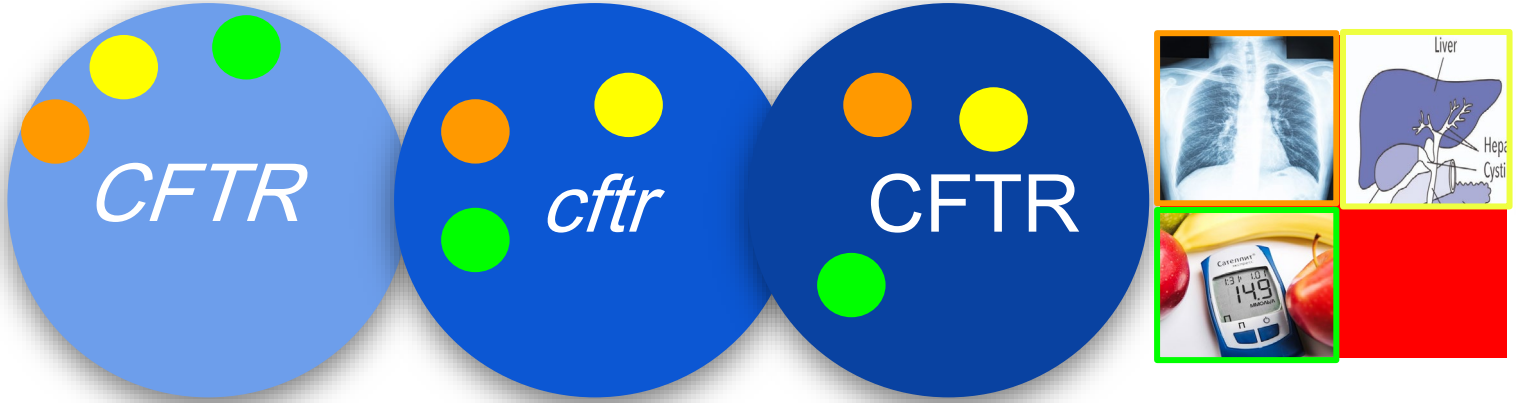
Updated Paradigm: Cystic Fibrosis – Impact on Diabetes



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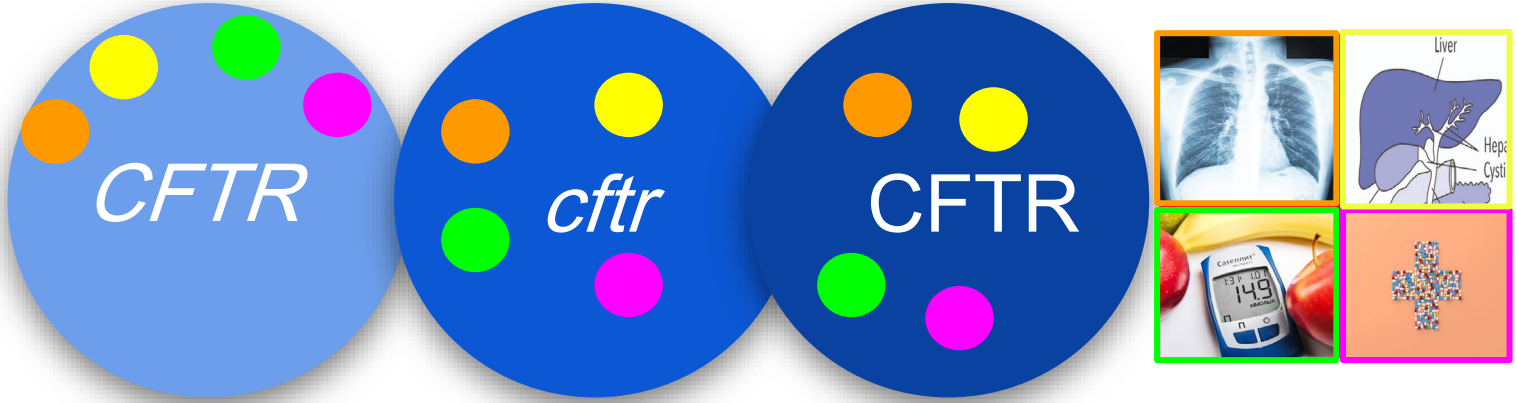
Updated Paradigm: Cystic Fibrosis – Impact on Therapy



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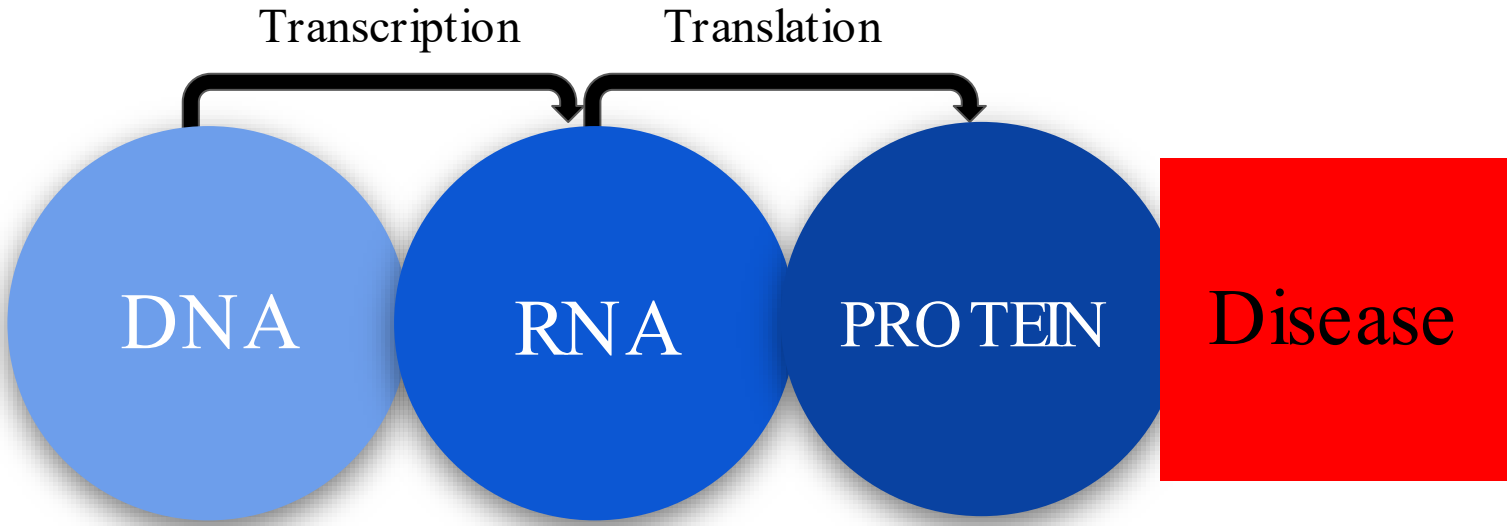
Historic Paradigm: Central Dogma – Outdated Model



Life is not linear.

Updated Paradigm: Accounts for the Complexity of Life

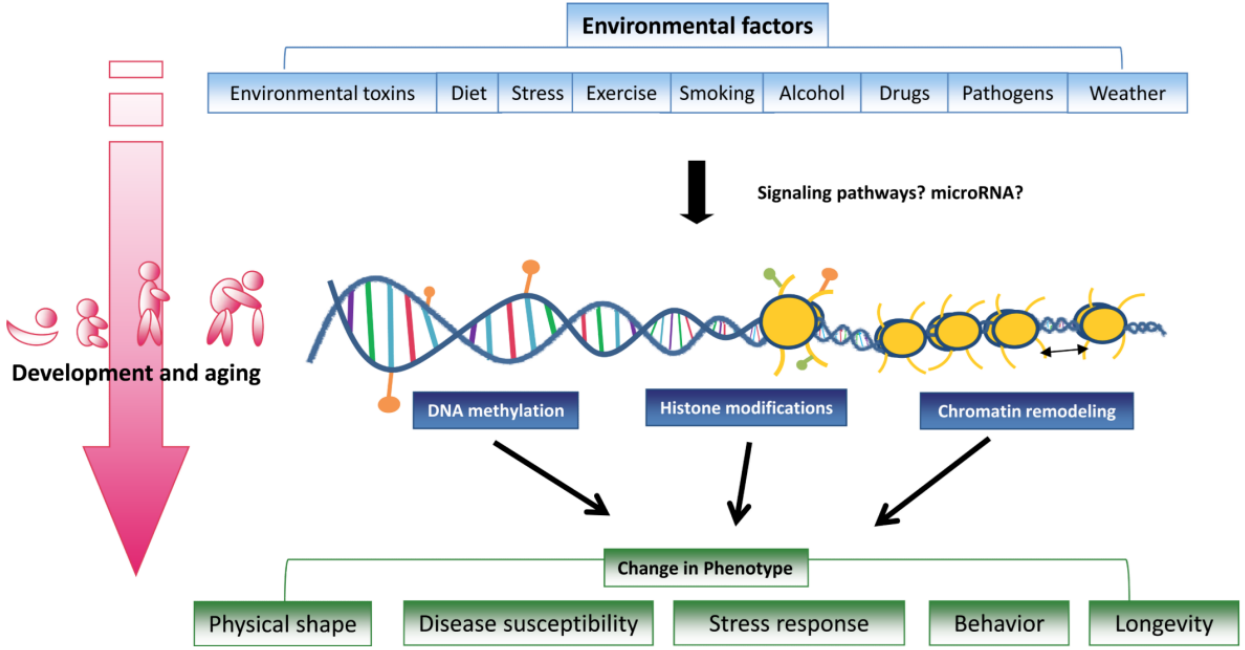


Figure 1.
Epigenetic mechanisms provide the link between environmental factors and phenotypical changes during the whole lifetime.

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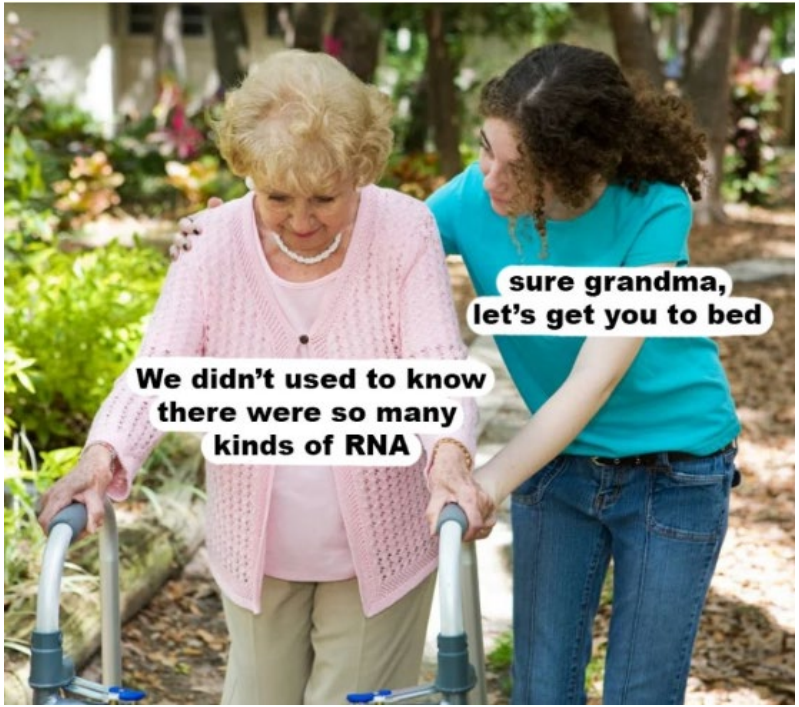
Updated Paradigm: Challenge of Keeping Currer



NHGRI post on LinkedIn

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Breast Cancer: Clinicals, Genetics and Inheritance

- Common cancer in female (XX) individuals (~1 in 8 lifetime risk)
  - Risk factors include age, personal and family history, environment
    - 1 in 1,000 lifetime risk for breast cancer in male (XY) individuals
- Outcome depends on many factors (e.g., stage, biomarker status)
- Improved management has overall reduced morbidity and mortality
- Outcomes are divergent across populations
  - Black females have poorer outcomes than White females
- 5-10% of cases are influenced by a genetic (i.e., germline) predisposition
  - *BRCA1/2*, discovered in the 1990s, correlated with breast cancer risk
  - Other correlated genes have since been identified (e.g., *PALB2*)

StatPearls Breast Cancer 2.25.24

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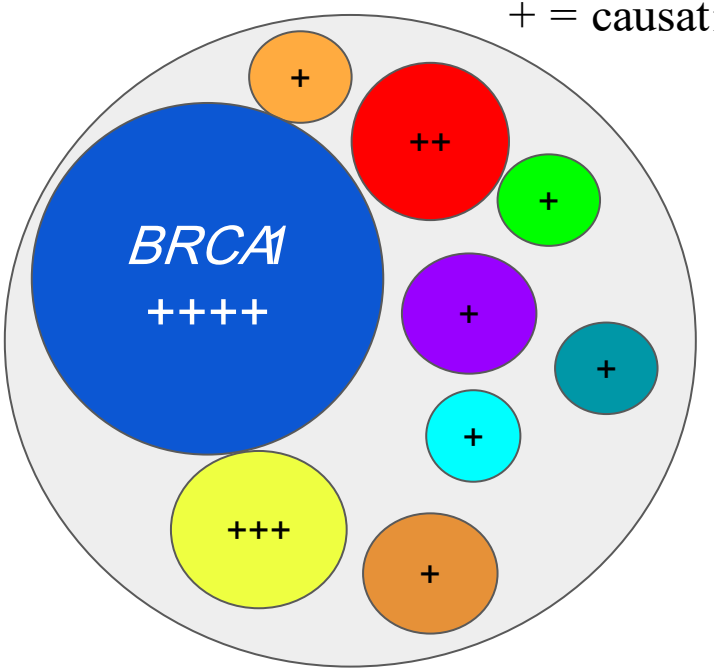
Breast Cancer: Genes, Environment and Populatic

Women with breast cancer

+ = causation



Unmeasured confounding events

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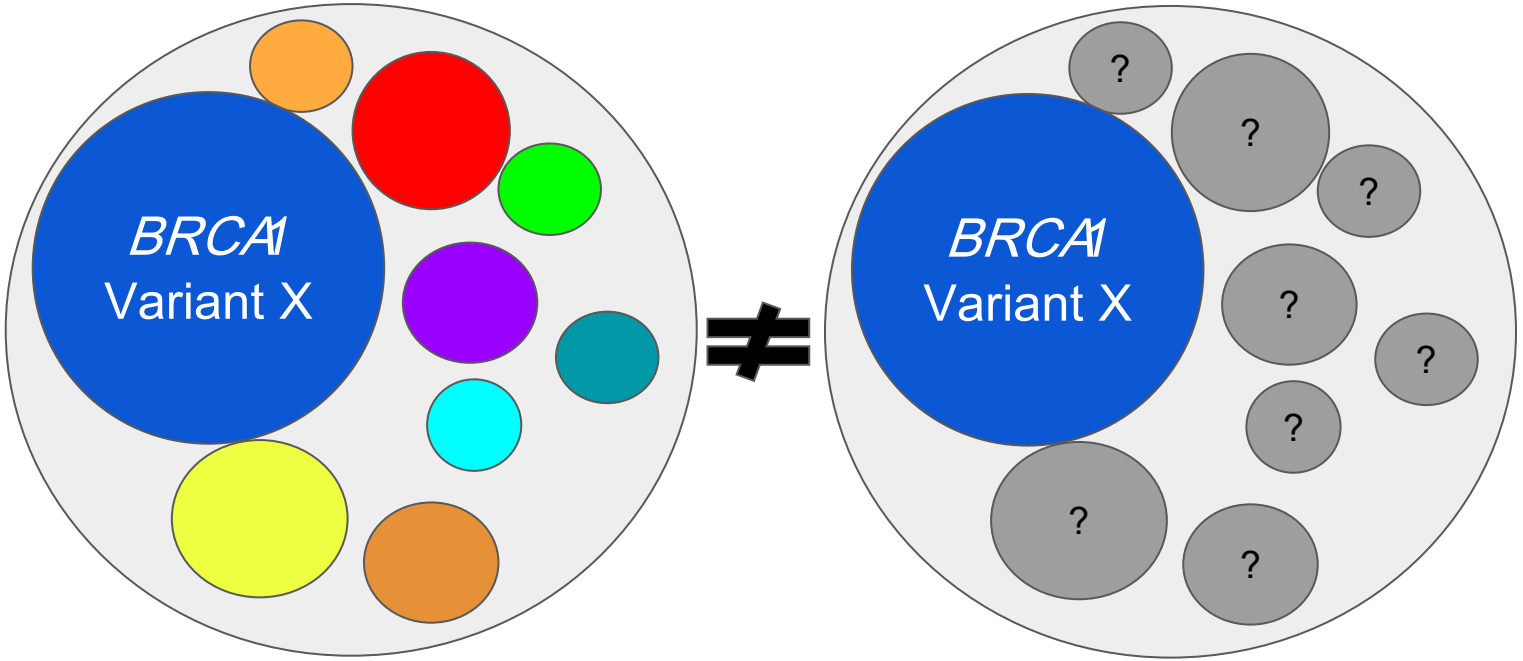
Breast Cancer: Updated Paradigm – Population Matters

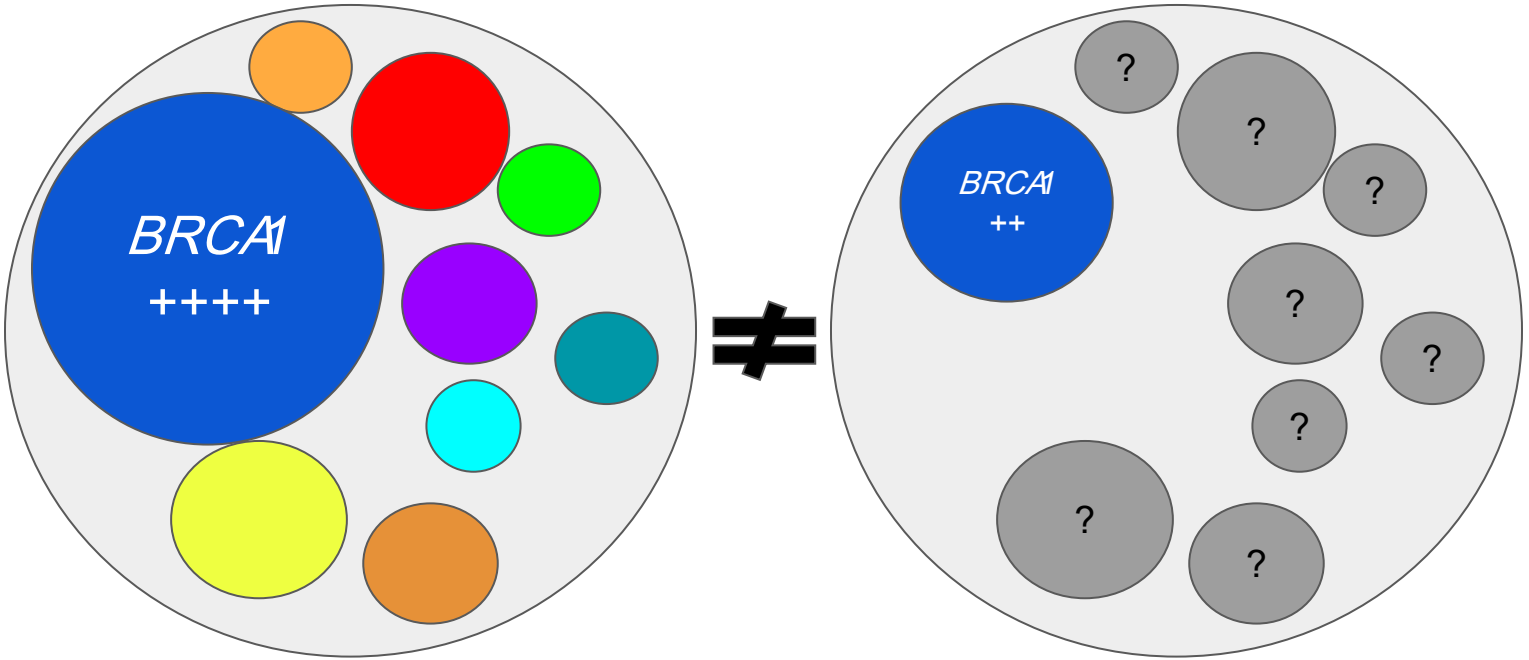


Female with breast cancer

Unselected healthy female

ClinGen AC133

Breast Cancer: Variation at the Gene Level



Protein truncating variant

Missense variant

PMCID: PMC7611105

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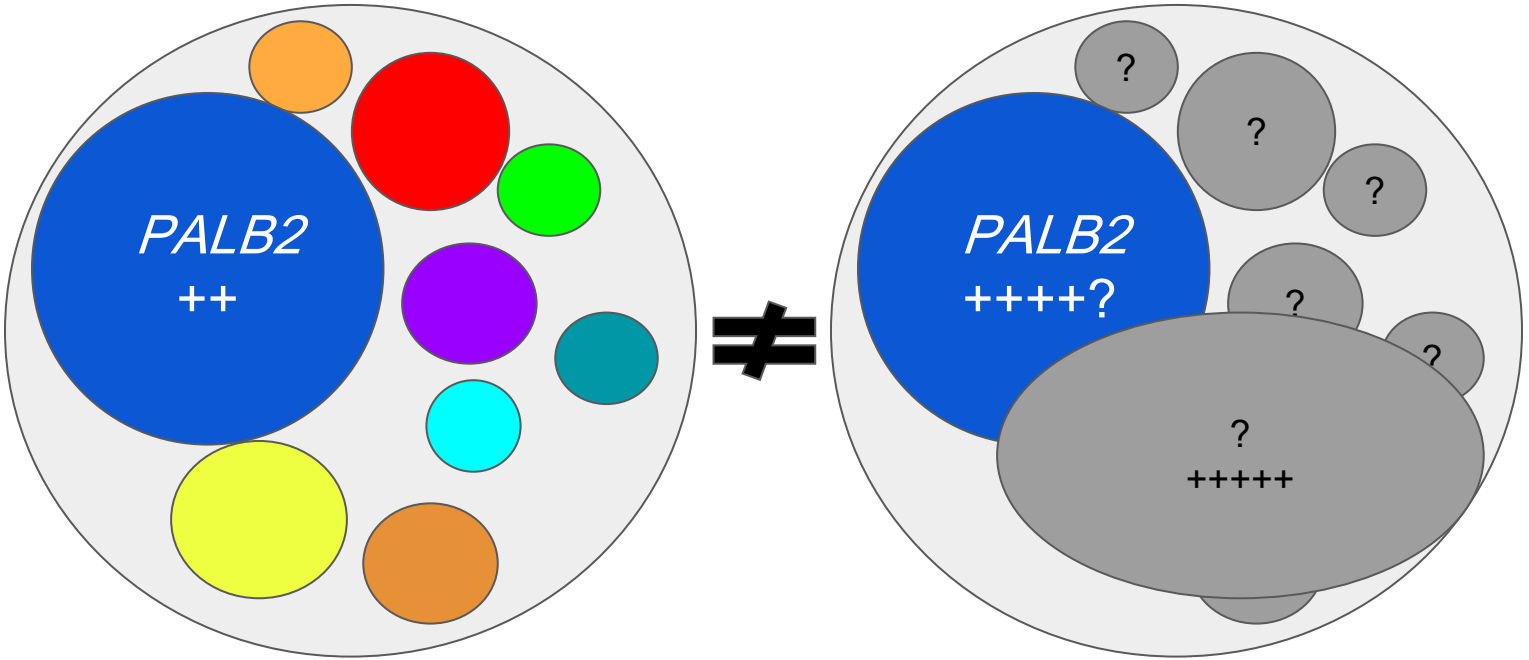
Breast Cancer: Variation by Population (e.g., Ancestry)



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Breast Cancer Summary - *BRCA1*

- Average lifetime risk for female breast cancer from *BRCA1* is 50%
  - 4-fold increase from the general population risk (~1 in 8)
  - Not ~80-100%, as was initially suspected
  - This risk might change as more evidence accumulates
- An individual's lifetime risk for breast cancer due to *BRCA1* varies by personal history, family history, gene/variant, and other factors
  - One size does not fit all
- Genomic result must be interpreted in the clinical context
  - Not doing so risks over or under interpreting the result
- Implications for underrepresented populations in genomic datasets
  - Less genomic data to draw from currently, barrier to interpretation

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Gene vs Genome Contribution to Disease

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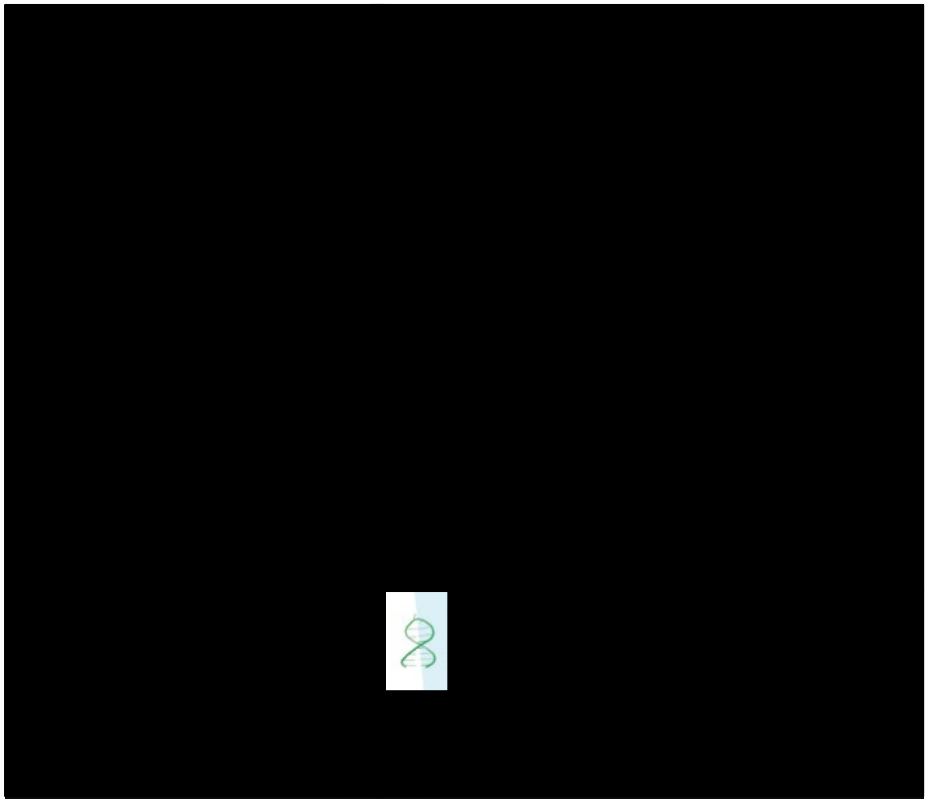
Gene vs Genome Contribution to Disease



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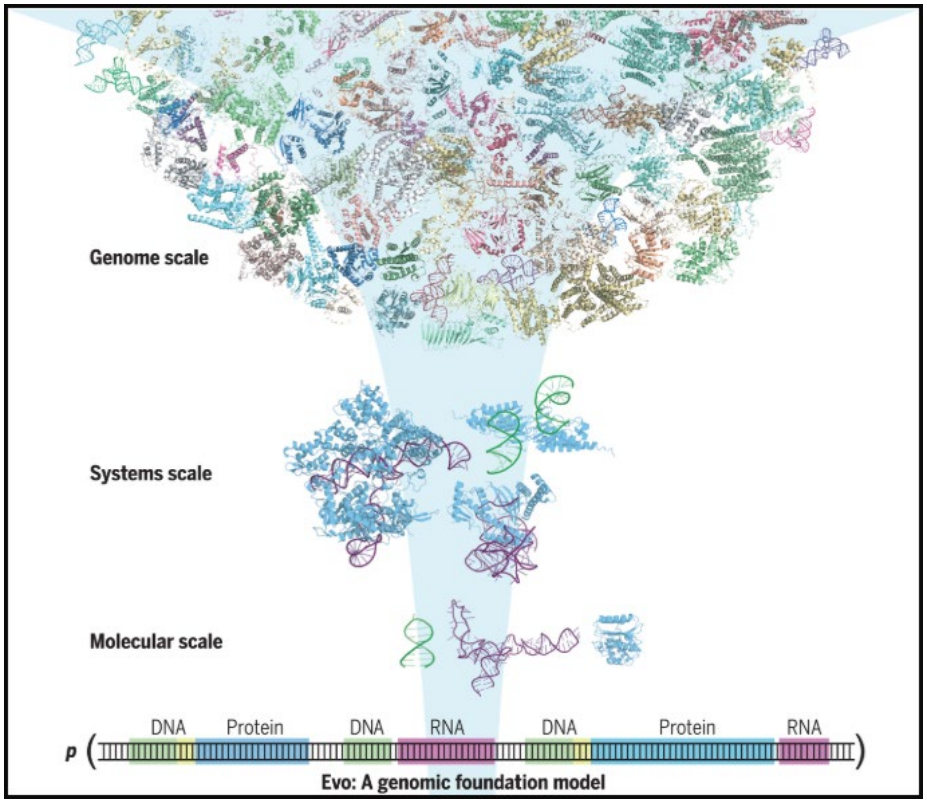
Gene vs Genome Contribution to Disease



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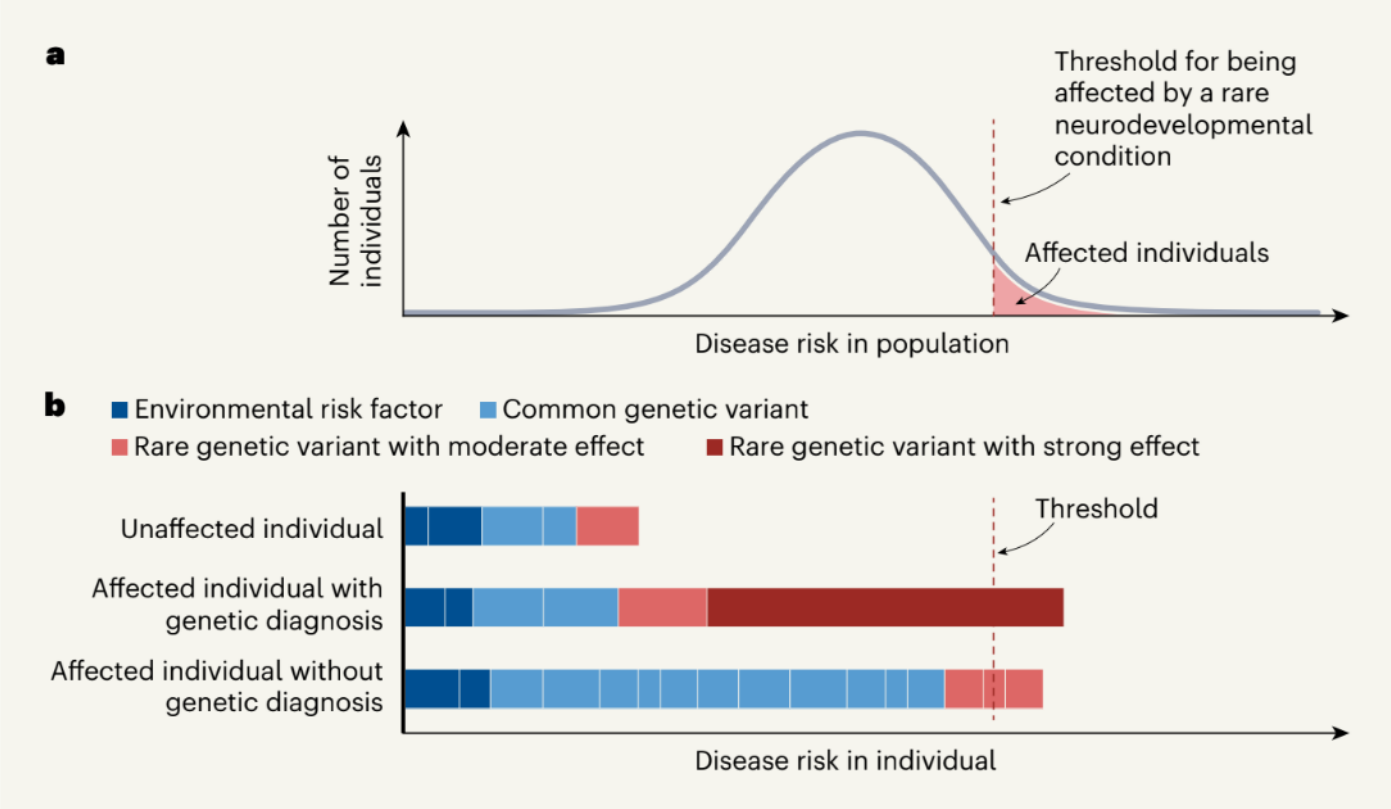
Genomic vs Environmental Contribution to Diseas



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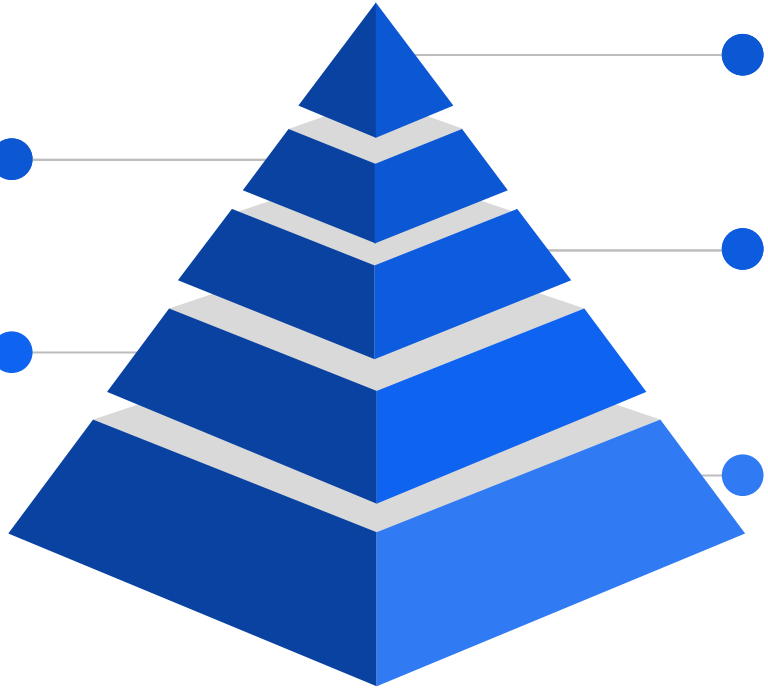
Evidence to Support Precision Medicine - Cystic Fibrosis



Improved diagnosis

CFTR causes cystic fibrosis

Improved outcomes

Clinical picture expands

Cystic fibrosis is defined by severe clinical disease only

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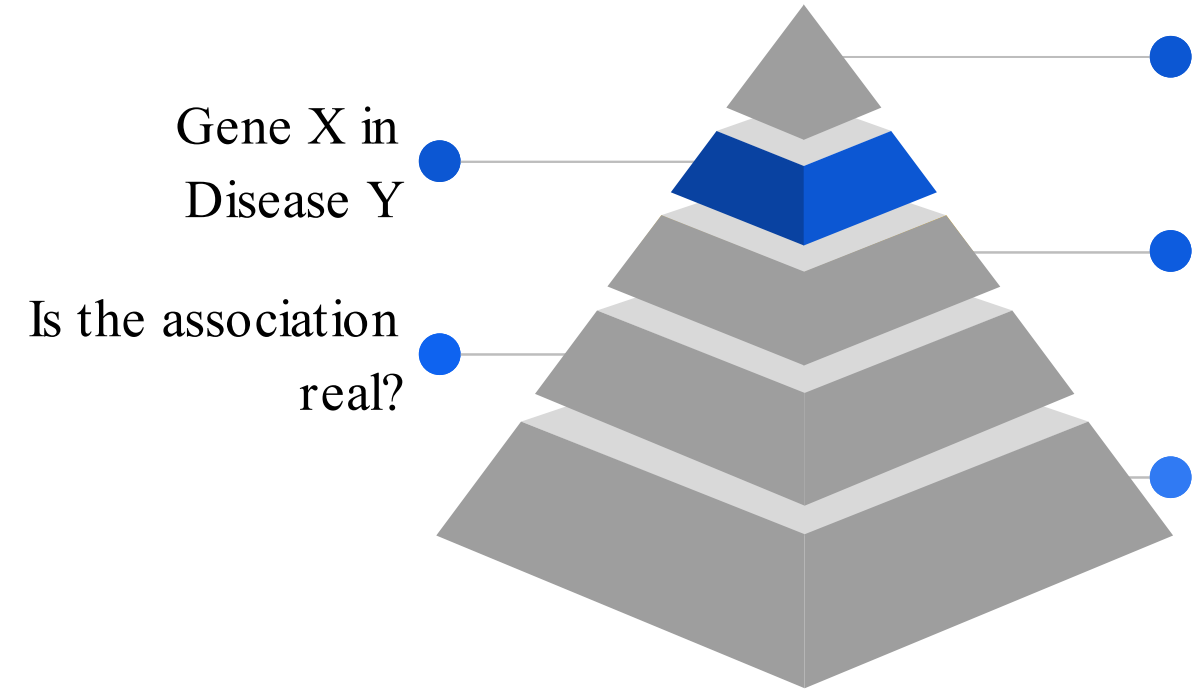
Evidence to Support Precision Medicine – Novel Results



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Translation of Genomics: Clinical Evidence Needed

- Establish gene-disease validity across populations
  - *CFTR* causes cystic fibrosis but not breast cancer, for example
  - Some gene-disease relationships are not well established
- Establish penetrance across populations
  - E.g., power to cause disease varies by disease, gene and population
- Establish intragenic variability across populations
  - Different variants within a gene confer differing risks for disease
  - Some are unknown (e.g., variant of uncertain significance or VUS)
- Establish clinical risk across populations
  - The risk is not for ANY disease, but for specific disease risk
  - Multiple disease risk (e.g., pleiotropy)

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Innovation is Outpacing Education and Clinical Translation

1859	1866	1944	1953	~2003	~2015
Charles Darwin	Gregor Mendel	Avery, MacLeod..	Watson, Crick…	Human Genome Project	1000 Genomes Project
On The Origin of Species	"Experiments on Plant Hybridization"	DNA is the basis of heredity	DNA is a double helix	First sequence of the human genome	Study of genome variability

2004- next-generation sequencing (NGS) clinically available
2013 - Supreme Court: human genes are not patentable

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Next-Generation Sequencing Fueled Explosion of Testing

(not all inclusive)

- Exome and Genome Sequencing
- Transcriptomics
- Methylomics (or epigenomics more generally)
- Liquid Biopsy
- Polygenic Risk Scores
- Gene Expression Profiling
- Multi Cancer Detection (MCD)
  - Also known as multi cancer screening (MCS)

Tests are only as good as the data and structure they are built upon.

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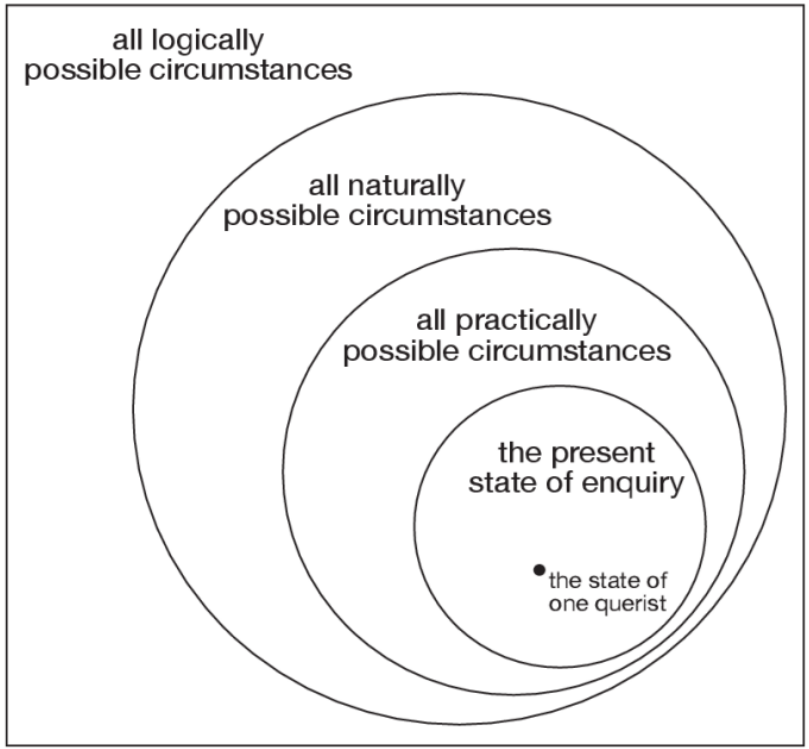
Novel Technologies: A Cautionary Tale

It is increasingly challenging to separate accurate and actionable science from complexity and noise.

Fresh Spectrum

PMID: 39549267

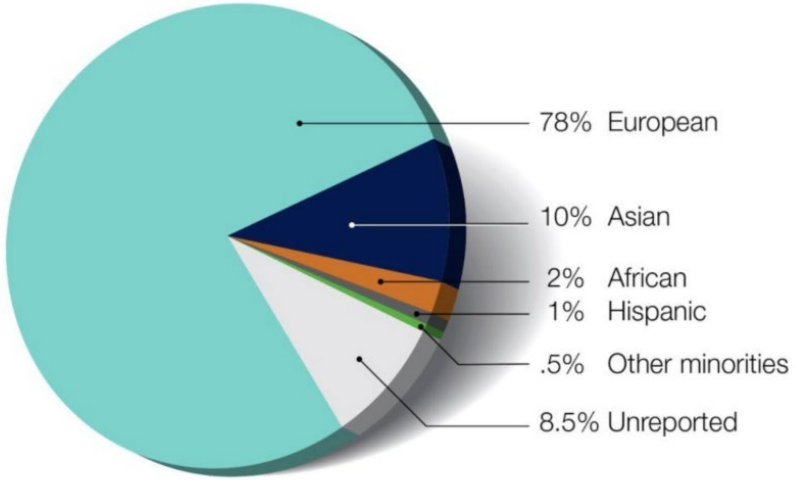
Underdetermination of Theory by Evidence



P.D. Magnus 2003. Underdetermination and the Claims of Science. PhD Thesis in Philosophy. UCSD.

Uncertainties

- We have come a long way, but still have farther to go
- What we don't understand still outpaces what we do
- Challenge: representing all populations in the data



NIH NHGRI

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NHGRI

Market Not Always Aligned with Proven Clinical Benefit

- Results may include more than you expect
  - Once information is in the chart, you can't take it back
- Be mindful of:
  - "Professional Services" offered in addition to the primary test
  - Reporting more than you expected (e.g., polygenic risk score)
  - Preliminary evidence results
  - Opportunistic screening without population level benefit
  - Labs providing clinical management recommendations
    - Laboratory professionals are not clinical professionals
    - Conflict of interest when a genetic professional works for a lab

PMID: 28125084

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Everyone is Looking to You (for everything, I know!)

Library of Congress

"...we can interrogate our patient genomes, and the genomes of organisms and cancers that infect and affect them. But despite all this wonderful technology, diagnosis remains difficult. Every patient is a unique individual in a unique context, a product of both their biology and biography."

- Dr. Andrew Elder (2024)

PMID: 39362674

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Clinical Scenarios

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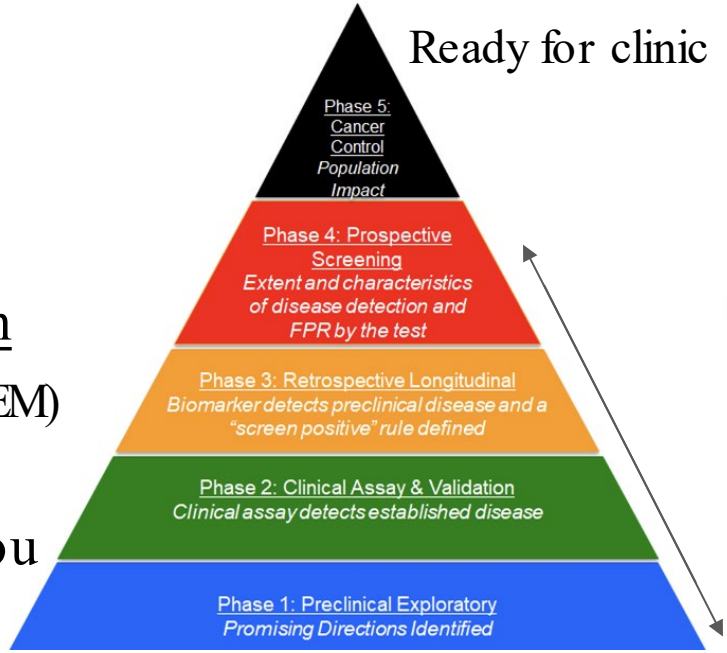
Multi-Cancer Detection/Screening (MCD/S)

- Test to detect cancer signals
  - Many, varied test modalities
- Goal: improve morbidity and mortality due to cancer
- Still in development - unproven clinical validity and utility (NASEM)
  - Vanguard trial (NIH)
- Test performance erodes as you progress from Phase 1 to 5
  - Leading tests only at Phase 4



EDRN website accessed 10.28.24

Multi-Cancer Detection (Screening) - Practical Points

- A negative result DOES NOT mean there is no cancer
  - False negative rates have not been established
  - Routine screening still recommended (e.g., pap smear)
- A positive result DOES NOT mean there is cancer
  - How do you tell a true positive from a false positive?
    - Follow-up needed to clarify (what follow-up is another question)
  - Low/no benefit, high benefit, and “too late” results
    - A positive result isn’t always helpful
- Benefits and harms still under investigation
- Healthy lifestyle changes likely more impactful than screening
- Encourage participation in a clinical trial!!!!

Hereditary Cancer Screening - Practical Points

- Test and gene selection should be based on the specific patient
  - Who to test? By whom?
  - How to test?
- General population screening - more evidence needed
- Opportunistic screening - majority of panel testing currently
  - Lab perspective
    - Add more genes because it is easy to do so
      - More is better
  - Clinical perspective
    - Evidence to support clinical interpretation is often insufficient
      - Does this help or harm?

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Pharmacogenomics - Practical Points

- Addressing the molecular complexity and clinical complexity is a HUGE challenge
- Good evidence for targeted use of pharmacogenetics in select scenarios
  - Quality and accuracy of the test is an important consideration
- Large panel testing is commercially popular, but has issues:
  - Cannot integrate future knowledge into historic results
  - Integration into health systems is challenging
  - Off-target concerns (reproductive risks, *APOE*)

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Take Home Messages

- Clinical genomics is complex, but increasingly mainstream
  - Getting more complex the more we learn
- Genomic results must be interpreted in the clinical context
- Evidence-based genomics leads to improved patient outcomes
  - *BRCA1* high-penetrance variants: breast/ovarian cancer management
- Lack of appreciation of complexity may lead to patient harm
  - Need to understand the test performance characteristics
  - Need to understand the clinical benefit for a specific patient
- Patients are looking to you for guidance
  - **Need for high -quality, unconflicted genomics expertise**
  - **Need for better guidelines and patient education tools**

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Action Items

- Don't be afraid to question a genetic or genomic test result
  - Clinically available tests can vary in quality
  - DTC testing - how do you utilize this information?
- Reassess historic genetic test results for accuracy and impact
  - Knowledge may have changed - impact on clinical guidance
- Think critically about concerning results before acting
  - Genetics is not destiny (Stat News 11.30.23)
- Understand both test level and patient level benefit
- Be aware of the potential for fraud
  - E.g., requests to sign-off on genetic testing not ordered by you

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Needs for Additional Support in Primary Care

- Independent and unconflicted support including:
  - Genomic education
    - Genomic versus conventional screening for cancer, for example
  - Test comparison tools
  - Patient education tools
    - Why genetic testing isn't always beneficial, for example
  - Shared decision making tools
  - Systematic implementation support
  - Improved data sharing

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Thank you!
Questions?

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