CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center on Birth Defects and Developmental Disabilities

Evidence-Based Evaluation of Genomic and Precision Health Applications

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Centers for Disease Control and Prevention

Disclaimer

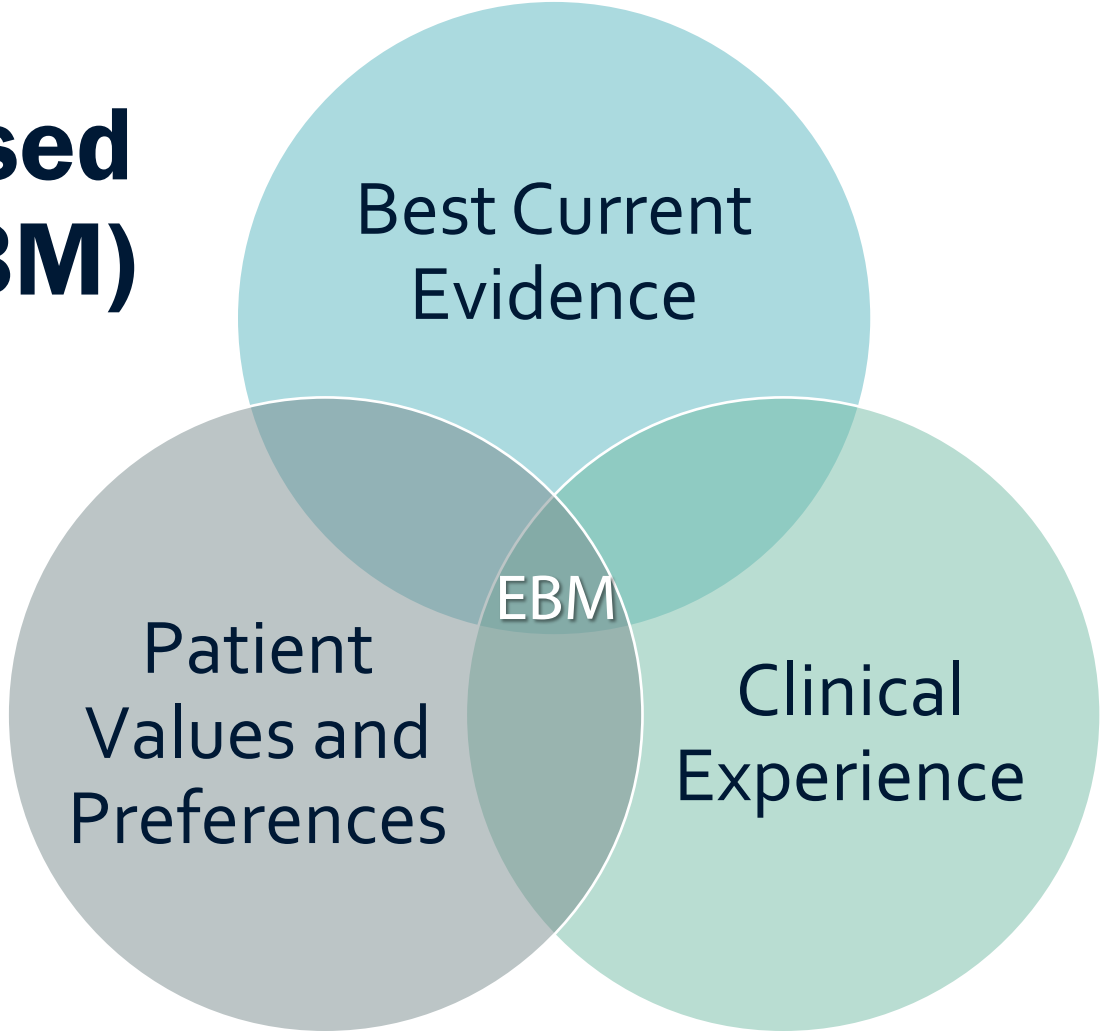
Opinions expressed in this presentation are those of the author and do not reflect the views of the Centers for Disease Control and Prevention, the Department of Health and Human Services, or the United States government.

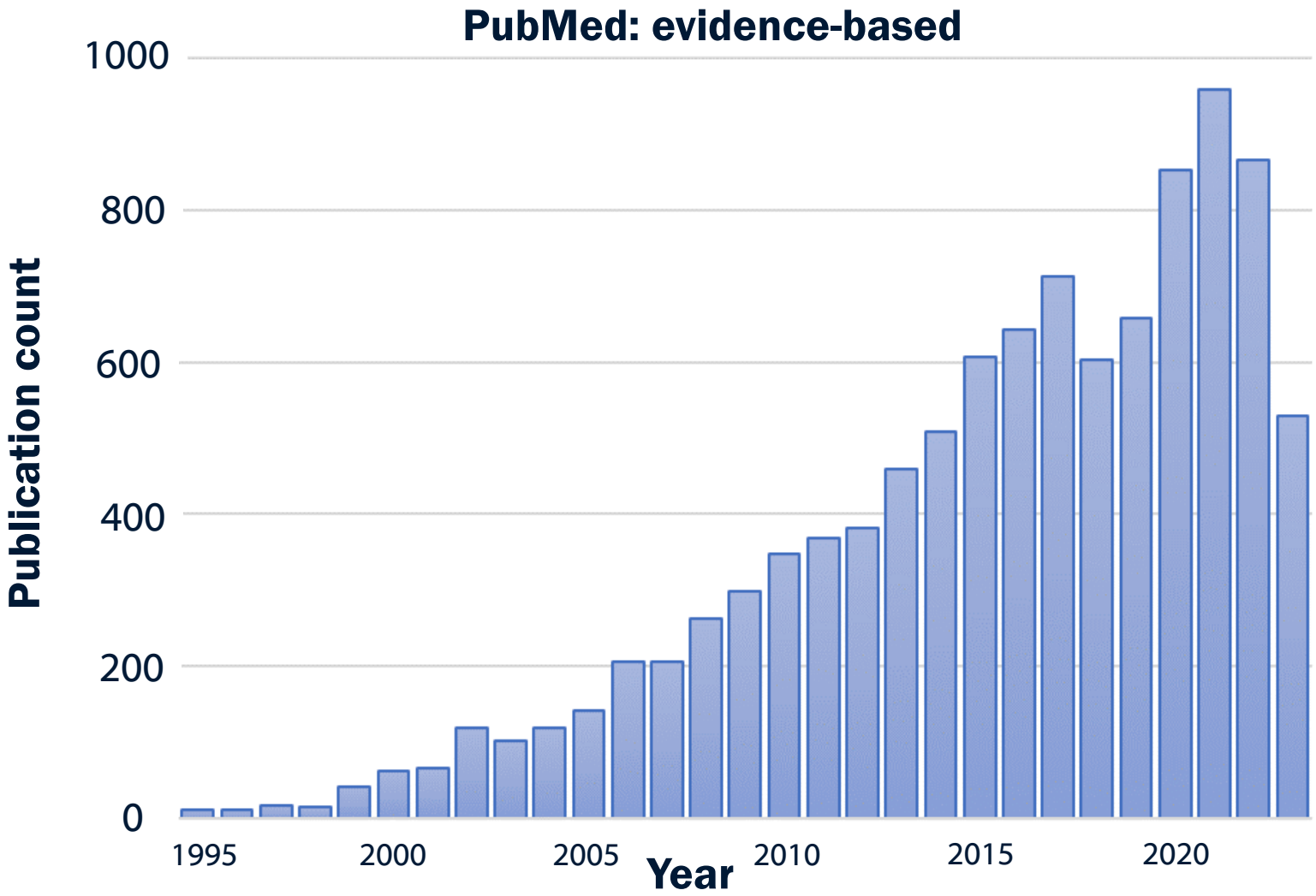
Overview

- Evidence-based genomics and precision health
  - Systematic reviews
  - Guideline development
- Components of genomic test evaluation
  - Analytic and clinical validity
  - Clinical utility
- Some relevant initiatives
  - ACCE model process
  - EGAPP
  - Tier classification of evidence-based guidelines

Evidence-Based Genomics and Precision Health

Evidence-Based Medicine (EBM)

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Publication count
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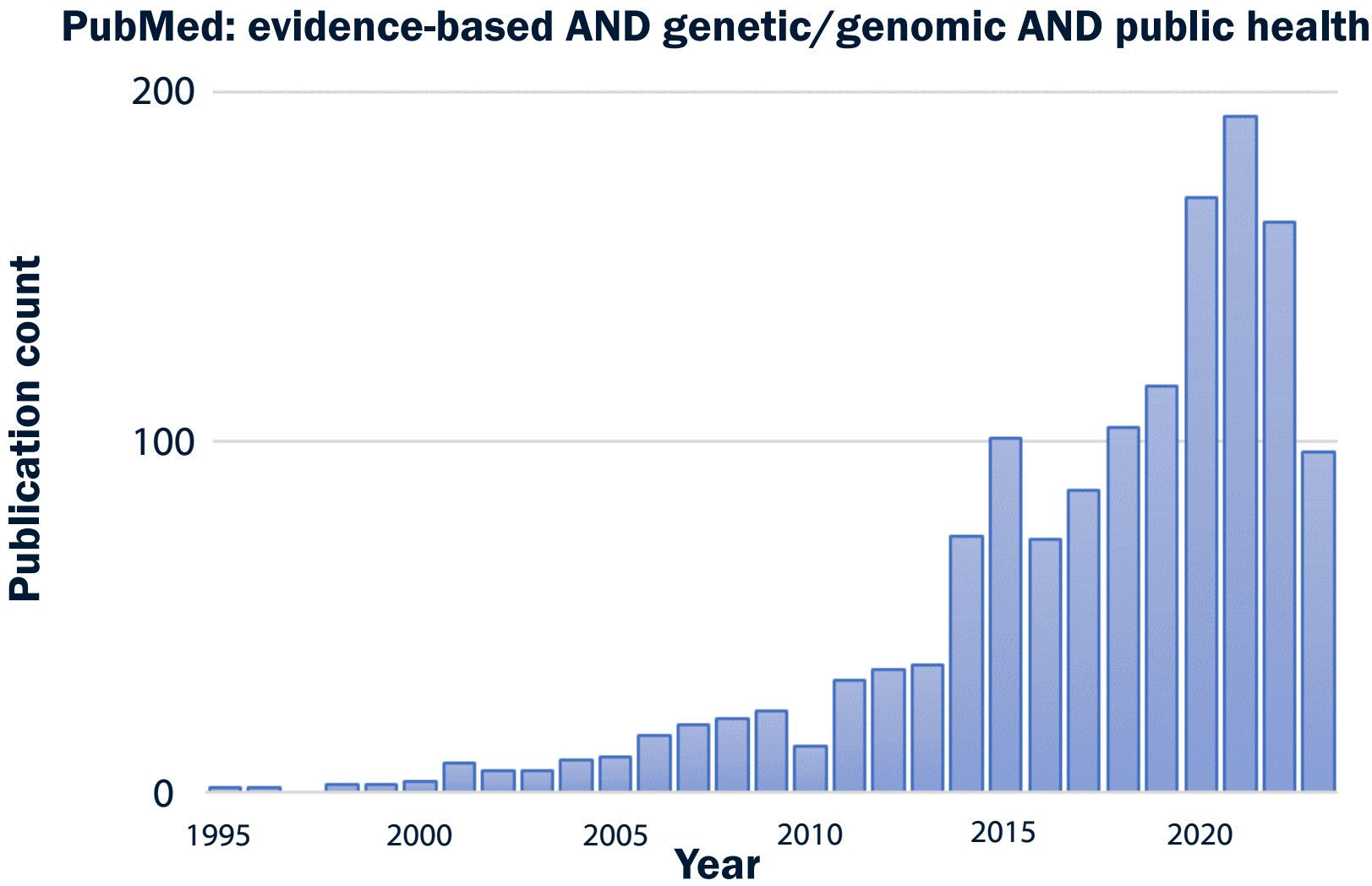
PubMed: evidence-based AND genetic/genomic AND public health
Publication count
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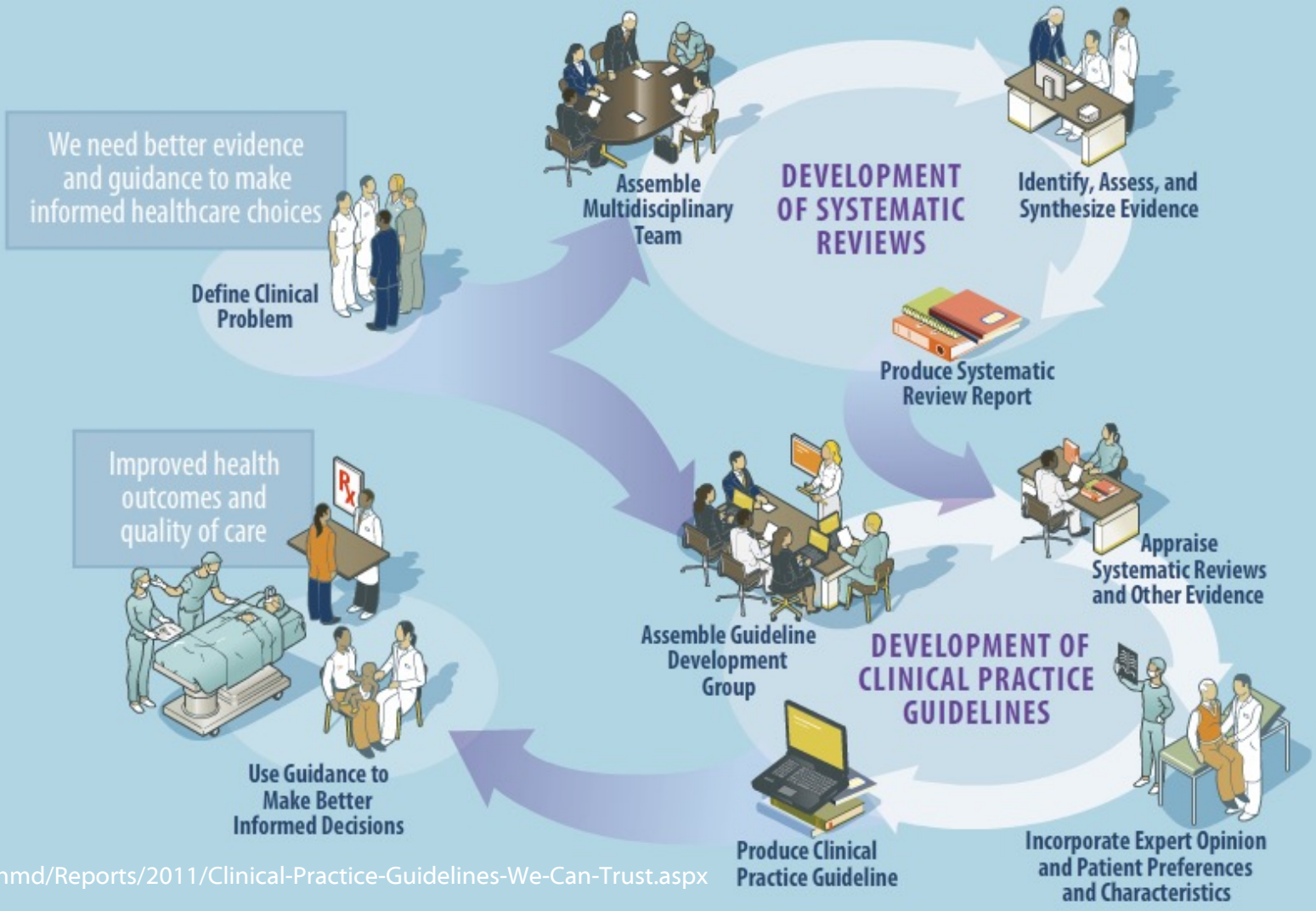
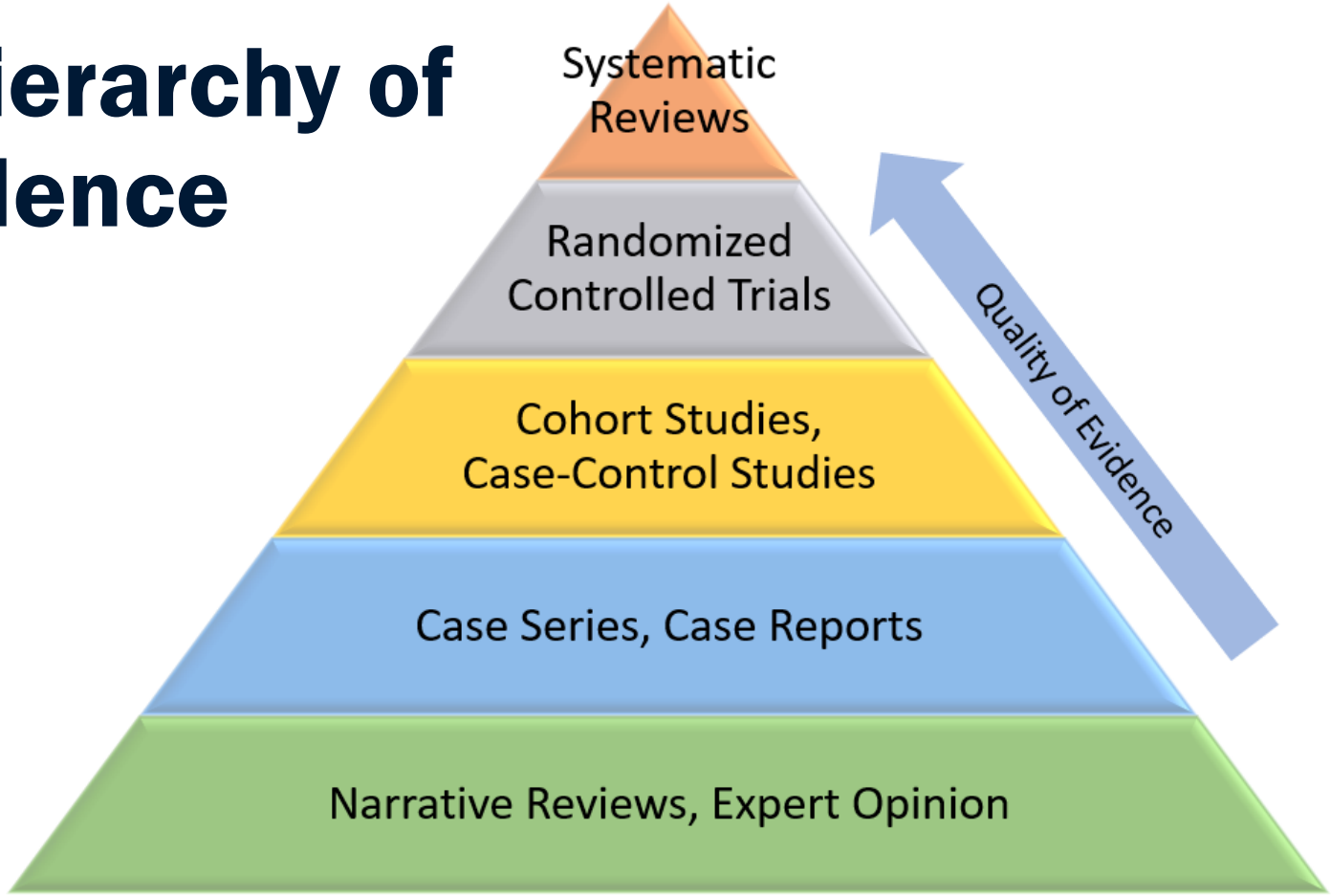
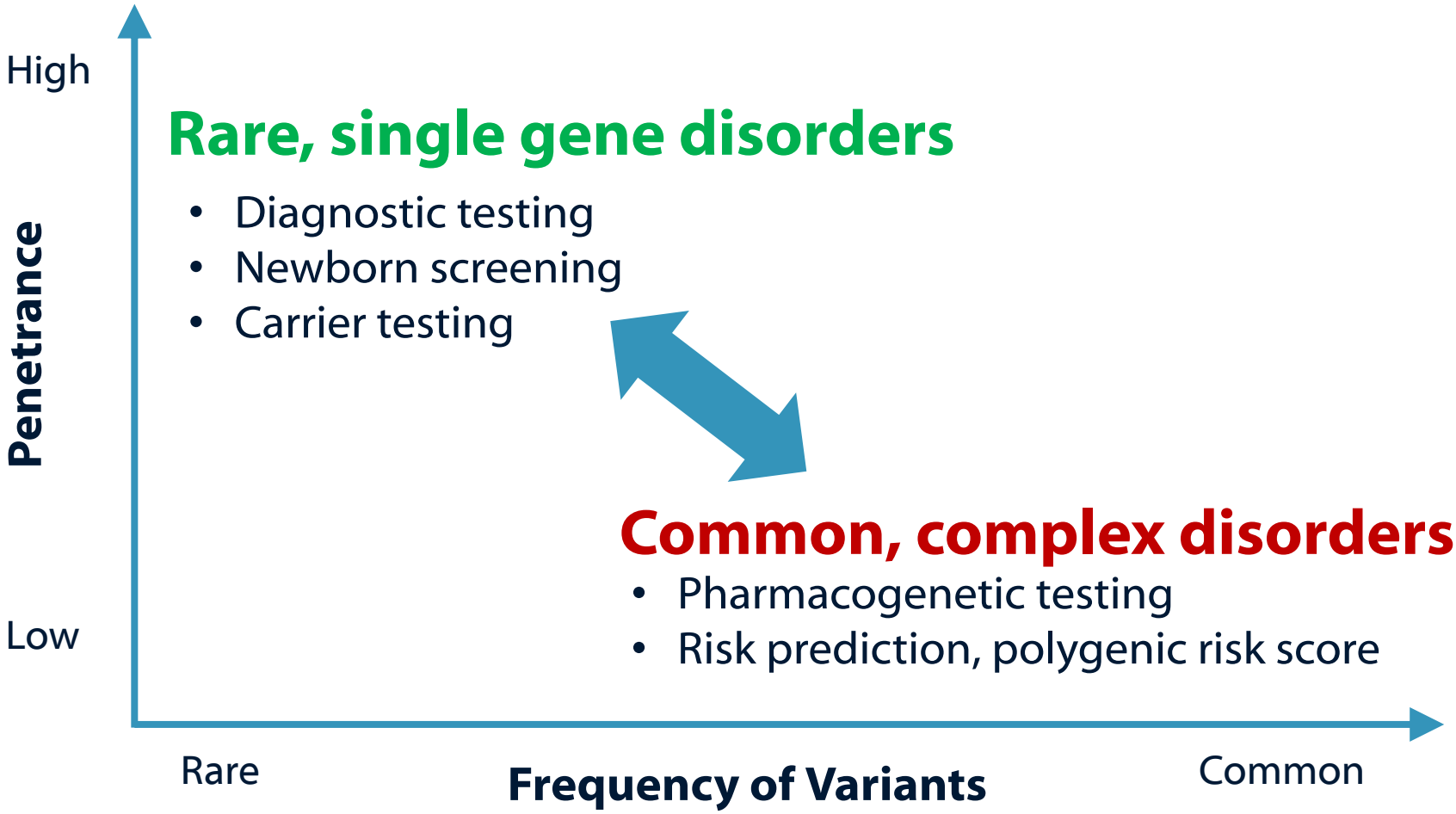


nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx

A Hierarchy of Evidence





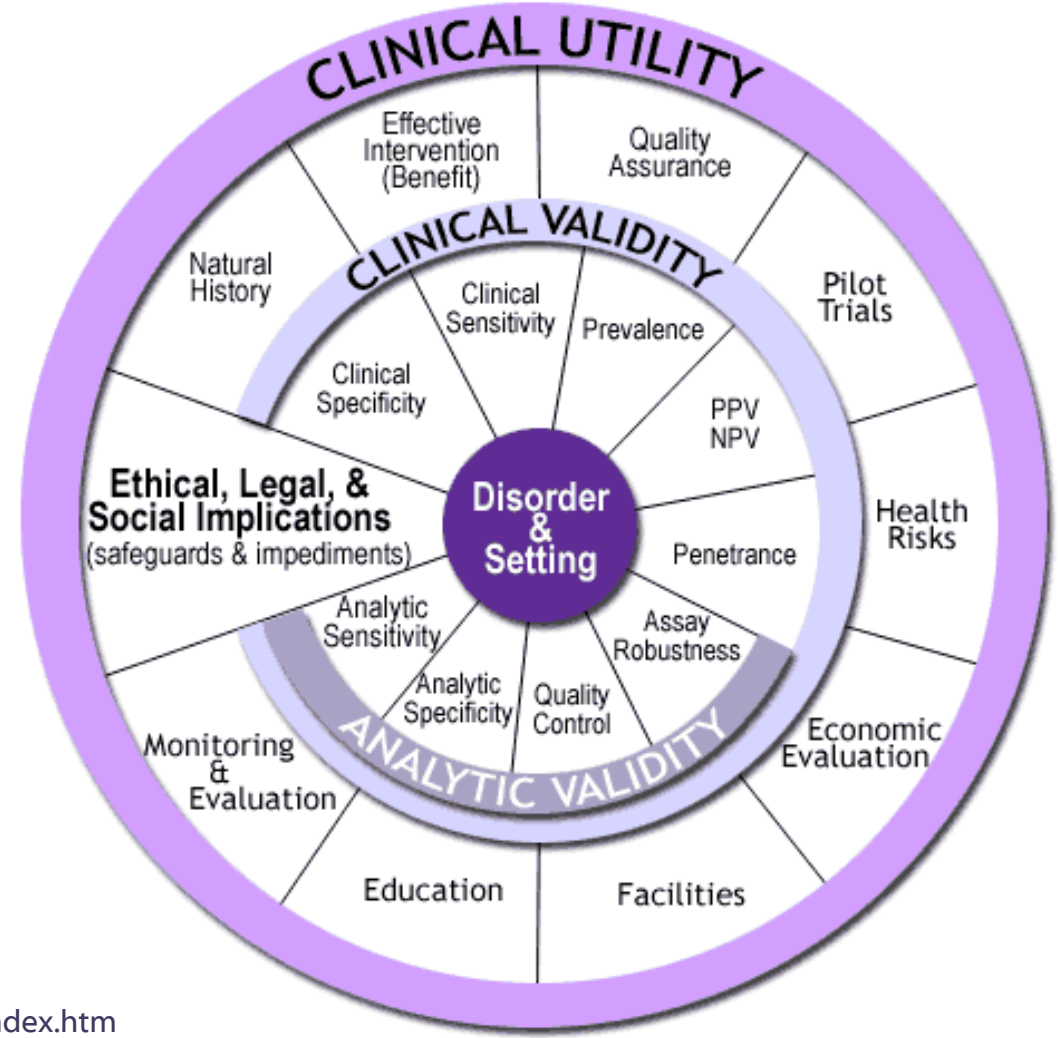
Modified from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2831613/

- **Analytic Validity**
  - How well does a test identify genomic characteristics (e.g., sequence variants, gene expression patterns, etc.) of interest?
- **Clinical Validity**
  - How well does a test identify a clinical disorder or condition of interest?
- **Clinical Utility**
  - Does testing lead to changes in clinical practice (regardless of health outcomes)?
  - Does testing ultimately lead to improved health outcomes?
  - What is the balance of risk vs benefits?

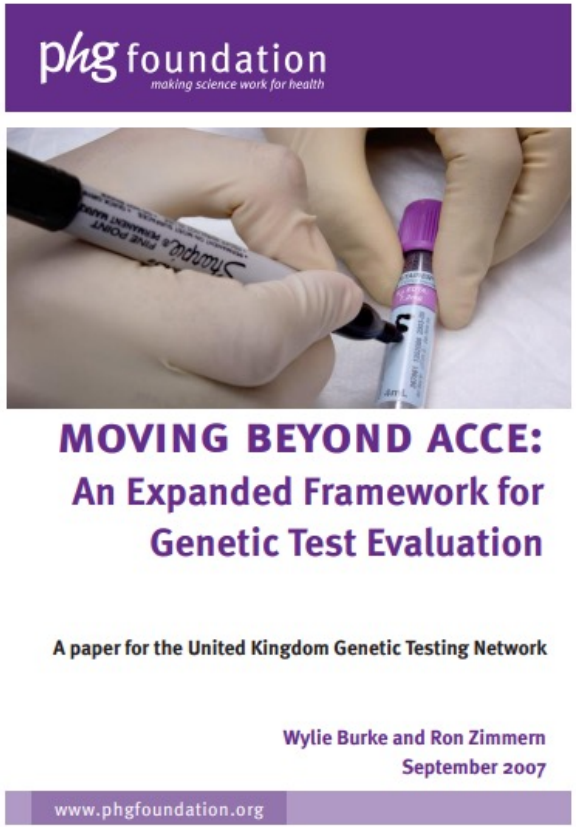
The ACCE Model

ACCE

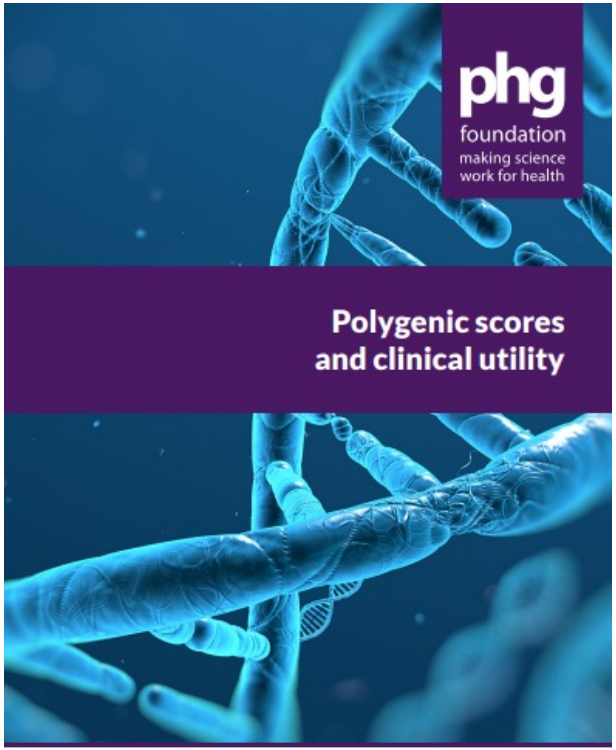
- **A**nalytic validity
- **C**linical validity
- **C**linical utility
- **E**thical, legal and social implications (ELSI)



https://www.cdc.gov/genomics/gtesting/acce/index.htm



2007



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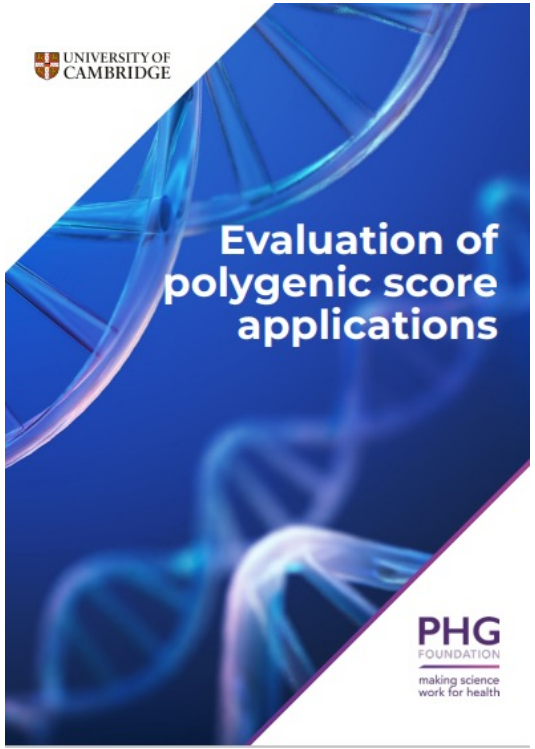
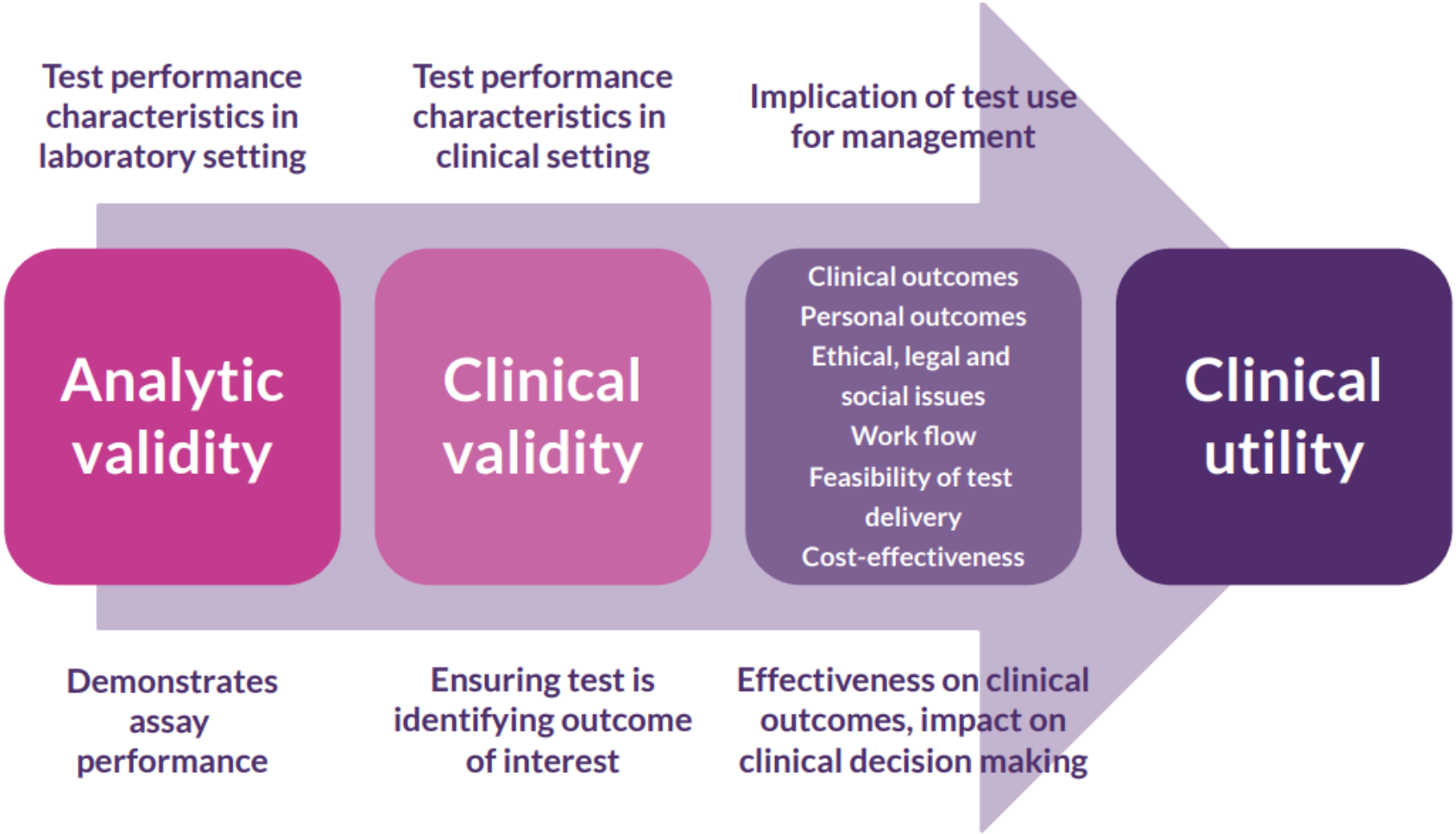


2023

https://www.phgfoundation.org/publications/reports



https://www.phgfoundation.org/report/polygenic-scores-and-clinical-utility

The EGAPP Initiative

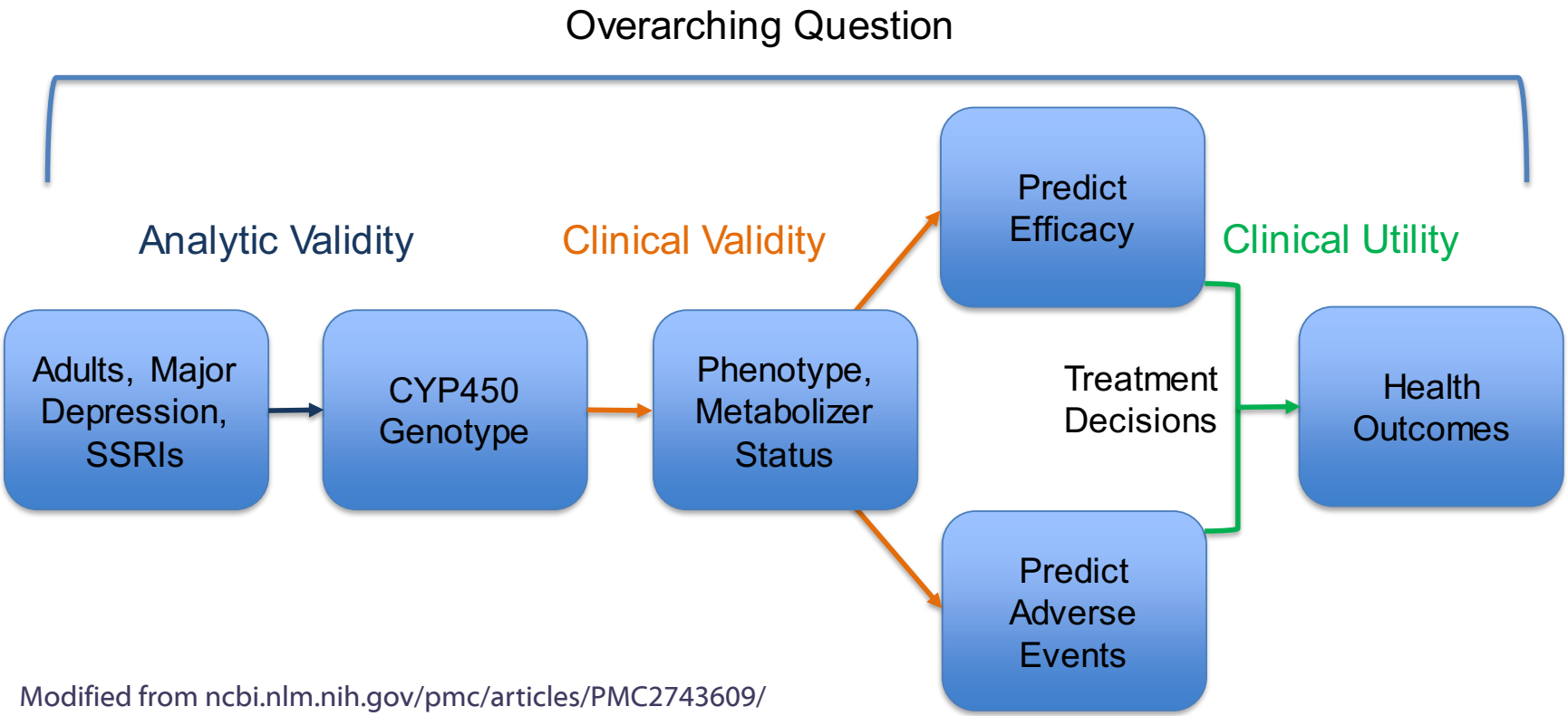
Evaluation of Genomic Applications in Practice and Prevention (EGAPP): Implementation and Evaluation of a Model Approach

The EGAPP initiative was launched by the CDC Office of Public Health Genomics in the fall of 2004. The initiative's goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice. EGAPP also aims to integrate

- Existing recommendations on implementation of genetic tests from professional organizations and advisory committees.
- Knowledge and experience gained from existing processes for evaluation and appraisal (e.g., US Preventive Services Task Force, CDC's Task Force on Community Preventive Services), previous CDC initiatives (e.g., the ACCE process for assembling and analyzing data on genetic tests), and the international health technology assessment experience.

Modified from https://www.cdc.gov/egappreviews/about.html

Analytic Framework



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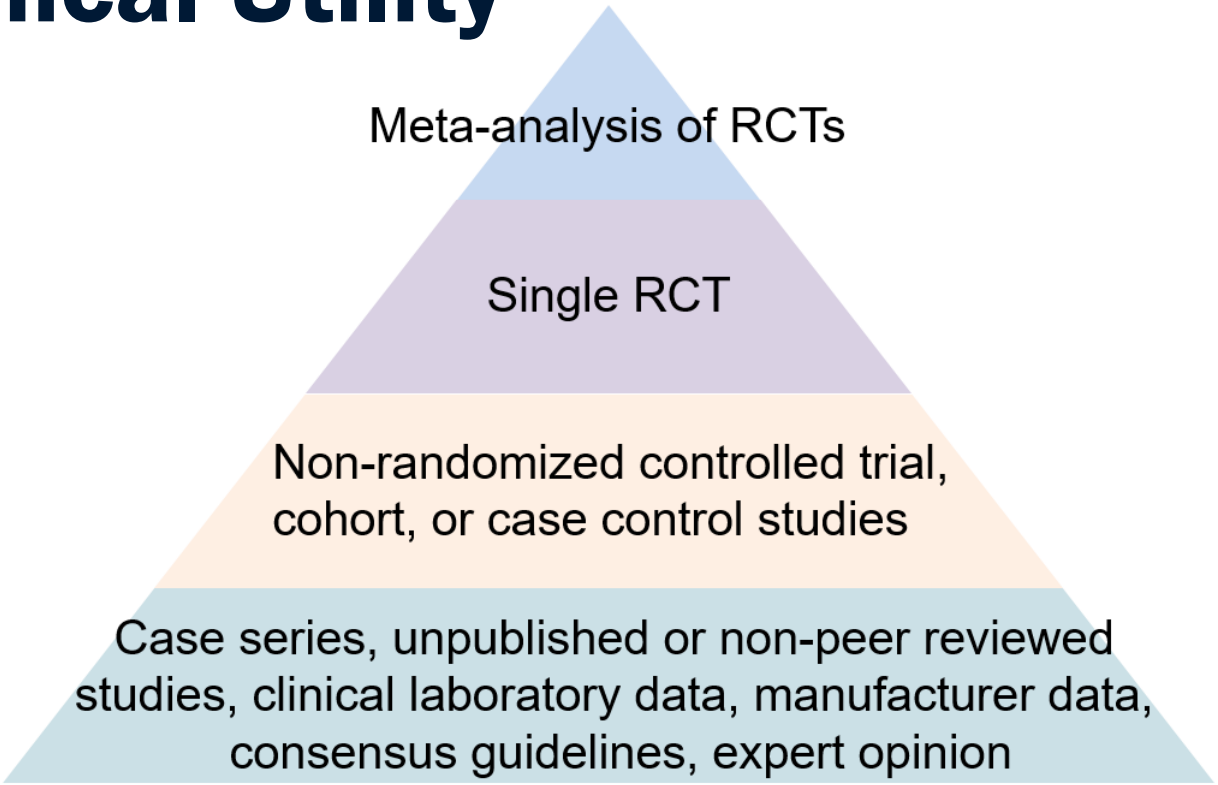
Clinical Utility



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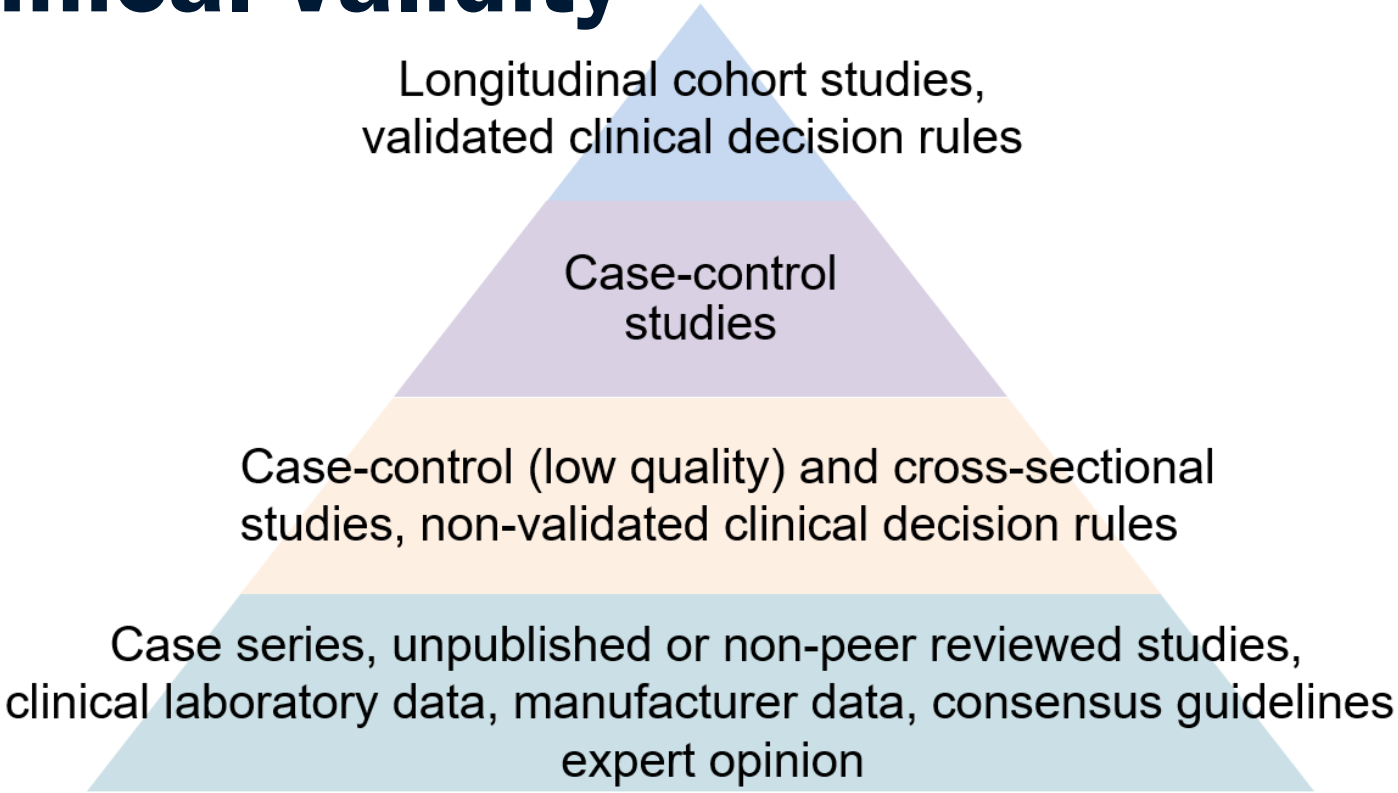
Clinical Validity



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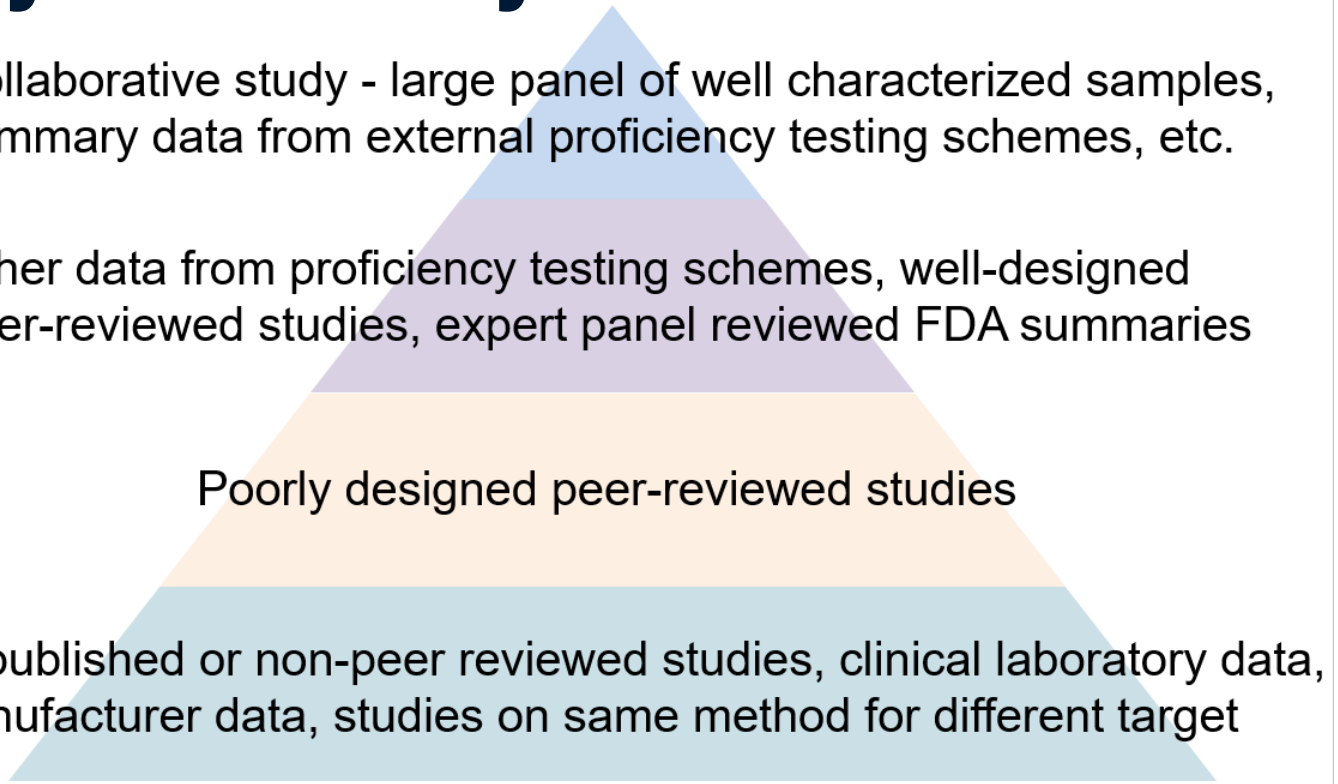
Analytic Validity



Modified from ncbi.nlm.nih.gov/pmc/articles/PMC2743609/
US Food and Drug Administration abbreviated as FDA

Tier-Classified Guidelines Database

Tier-Classified Guidelines Database

Why did we build it?

- ***Challenge:*** *The public and healthcare providers are bombarded with information on genomic tests, many with unproven utility*
- **Opportunity:** Educate providers and the public about potential benefits and harms of genomic tests and the need for evidence

- ***Challenge:*** *There is no widely agreed upon threshold level of evidence for determining whether genomic tests are ready for use*
- **Opportunity:** Develop flexible method(s) for classification of tests by level of evidence to aid in research/evaluation and help define which aspects of evidence should be considered in developing thresholds

Public Health Genomics and Precision Health Knowledge Base (v8.7)

PHGKB

About

Office of Genomics and Precision Public Health

Genomics (A-Z)

Specialized PHGKB

Cancer PHGKB

Diabetes PHGKB

Tier-Classified Guidelines Database

Recommend Tweet Share

Last data update: Jun 20, 2023. (Total: 527 Documents since 2012)

Enter a search term Search All dataset

All All Tier 1 All Tier 2 All Tier 3

https://phgkb.cdc.gov/PHGKB/tierStartPage.action

Classification Criteria

Tier 1

- FDA label requires use of test to inform choice or dose of a drug
- FDA cleared or approved companion diagnostic device
- CMS covers testing
- Clinical practice guidelines based on systematic review supports testing

Tier 2

- FDA label mentions biomarkers
- FDA premarket approval (PMA)
- FDA 510(k) substantially equivalent decision
- CMS coverage with evidence development
- Clinical practice guideline, not based on systematic review, supports use of test
- Clinical practice guideline finds insufficient evidence but does not discourage use of test
- Clinical practice guideline recommends dosage adjustment, but does not address testing

Classification Criteria

Tier 3

- FDA label cautions against use
- CMS decision against coverage
- Clinical practice guideline recommends against use of test
- Clinical practice guideline finds insufficient evidence and discourages use of test

Last data update: Jun 20, 2023. (Total: 527 Documents since 2012)

all Search All dataset

Query Trace: all records[original query]

Publications are indexed with the following 3 tier(s).

Click Continue button after making selection.

Continue Clear

Tier	Number of Publications
☑ 1	164
☐ 2	345
☐ 3	18

Continue Clear

Additional Tools and Resources

ACMG Foundation for Genetic and Genomic Medicine

Better Health Through Genetics™

Evidence Based Guidelines

About the ACMG Evidence-Based Guidelines Program

The Evidence Based Guidelines (EBG) Program is an important joint effort between the ACMG Foundation and ACMG. The EBG Program develops unbiased guidelines in medical genetics and genomics and provides a solid evidence base to demonstrate the clinical utility of genetic or genomic services. ACMG's guidelines help clinicians make informed decisions regarding the use of genetic and genomic testing and aid both government and private health insurers in determining coverage options for new tests and treatments.

https://www.acmgfoundation.org/ebg

NSGC Practice Guidelines

NSGC Practice Guideline Process

The NSGC Practice Guidelines Committee works with authors to produce Evidence-Based Clinical Practice Guidelines through an established guideline process. The **Guideline Development Manual** outlines NSGC's criteria and includes an Appendix with all relevant forms, documents, and background for authors and individuals who submit topic proposals. The Committee also has established criteria for Practice Resource documents, which focus on topics that do not have an evidence-base to meet NSGC's Practice Guideline criteria.

NSGC Practice Guidelines & Practice Resources Information

- **Practice Guideline Development Manual** (revised in 2020)
- **Practice Guideline Development Manual Appendices**
- **The Differences Between a Practice Guideline and Practice Resource**

From https://www.nsgc.org/POLICY/Practice-Guidelines

Advisory Committee on Heritable Disorders in Newborns and Children

About

Meetings

Reports

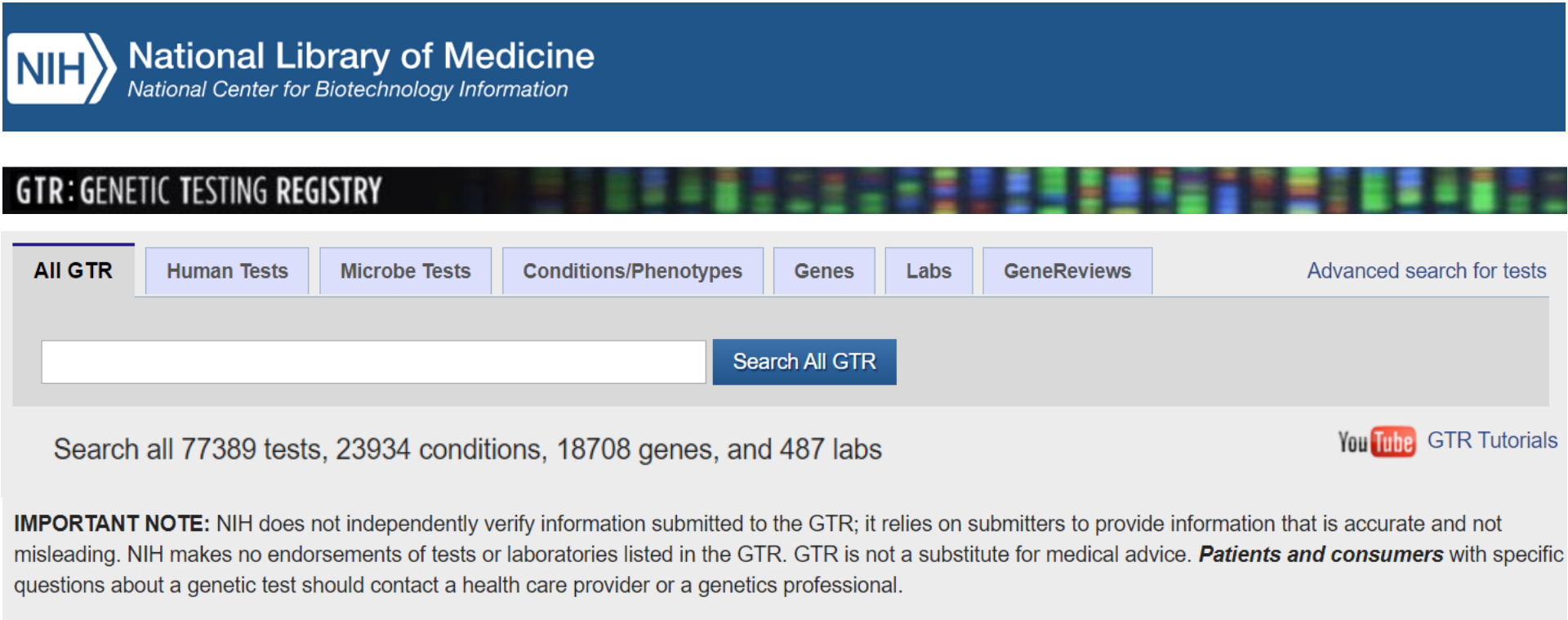
Advisory Committee on Heritable Disorders in Newborns and Children

https://www.hrsa.gov/advisory-committees/heritable-disorders

CPIC Guidelines Genes-Drugs Alleles Publications Meetings Resources Working Groups Members Contact

Search CPIC Website

https://cpicpgx.org/



https://www.ncbi.nlm.nih.gov/gtr/

ClinVar and ClinGen

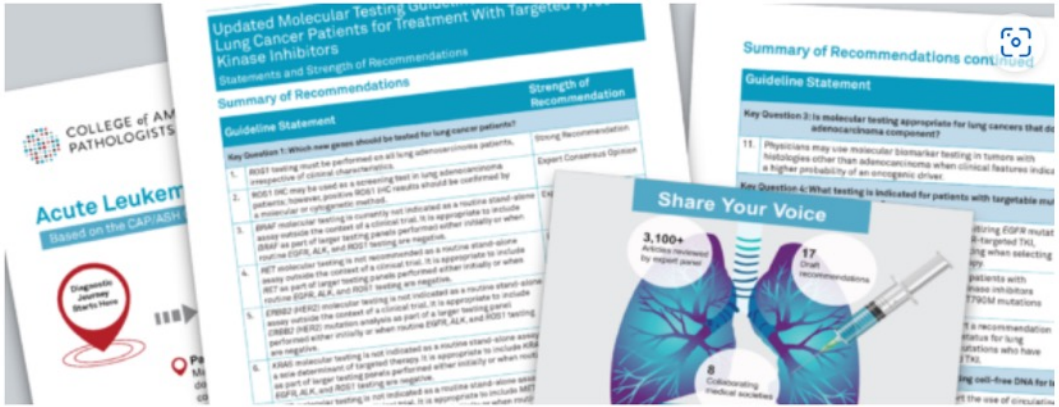
ClinVar is like PubMed for clinical variants

- It is a long term internally funded government archive.
- It collects data about genotype-phenotype relationships from many contributors.
- Each contribution is intellectually attributed to the author, not to ClinVar.
- ClinVar sets the editorial and structural standards for the data, but the intellectual content comes from the author.
- Authors in ClinVar may provide data that disagrees with each other.
- ClinVar contains contributions at many levels: basic reports, as well as authoritative reviews or guidelines. These different levels of report are explicitly flagged and clearly distinguished from each other.

ClinGen is like a scientific journal that publishes reviews

- It may have various funding sources and lifetimes.
- It reviews data about genotype-phenotype relationships, from ClinVar and other sources.
- It has an editorial board that reviews credentials of data sources.
- It publishes reports about specific genotype-disease association topics.
- Each report represents the intellectual effort of the authors and the "journal" staff.
- The report may be available directly from the website in various forms.
- The report will be deposited in ClinVar in a standard form for long-term archiving and for uniform access by users.

https://www.ncbi.nlm.nih.gov/clinvar/docs/clingen/



CAP Guidelines

The CAP Pathology and Laboratory Quality Center for Evidence-based Guidelines, along with our professional partners, advances the practice of pathology and laboratory medicine by bringing evidence-based guidelines and consensus recommendations to the forefront of clinical decision making. Adopting these guidelines helps pathologists and laboratory professionals to provide more effective testing with consistent, high-quality results, and expert interpretations.

Learn more about our guidelines

See the current guidelines

See the upcoming guidelines

https://www.cap.org/protocols-and-guidelines

Practice Guidelines

Clinical Practice Guidelines and Reports

AMP Clinical Practice Guidelines and Reports are developed to be of assistance to laboratory and other health care professionals by providing guidance and recommendations for particular areas of practice. The Guidelines or Report should not be considered inclusive of all proper approaches or methods, or exclusive of others. The Guidelines or Report cannot guarantee any specific outcome, nor do they establish a standard of care. The Guidelines or Report are not intended to dictate the

https://www.amp.org/clinical-practice/practice-guidelines/

Thank You

Dave Dotson

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