PROPHET TOOLBOX FACTSHEET#2

JUNE 2025

UNDERSTANDING CLINICAL UTILITY IN PERSONALIZED PREVENTION

PROPHET

a PeRsOnalized Prevention roadmap for the future HEalThcare

What is Clinical Utility ?

Clinical utility refers to the usefulness and value of a health-related practice or test in improving patient outcomes or healthcare decisions. When it comes to predictive tests used in personalized medicine, including genetic and other omics-based tests, clinical utility refers to the likelihood that it provides information that is of value to the person being tested to identify if an effective intervention or preventive strategy is required. There is no single definition of clinical utility, as it varies by perspective and use case.

Indeed, although the concept of clinical utility is often associated with improvements in health outcomes, it should not be equated solely with the clinical effectiveness of a medical intervention—such as a predictive genetic or omic test in our case—but rather encompasses ten distinct dimensions, as described by Pitini et al. and its update:

1. **Analytic validity:** How accurately and reliably the test measures the genotype of interest
2. **Clinical validity:** The ability to detect or predict the associated disorder
3. **Clinical efficacy:** A measurable change in symptoms, overall health, ability to function, quality of life, or survival outcomes of patients
4. **Personal value:** The indirect health-related and other nonmedical benefits to the individual of having the information
5. **Acceptability:** The test's conformity to the wishes, desires, and expectations of patients and their families

6. **Feasibility:** Sustainability of the intervention and the capability to address potential barriers to using it

7. **Equity:** The test's conformity to the principle of just and fair distribution of health

8. **Economic impact:** Assessment of the cost and economic benefits of genetic testing

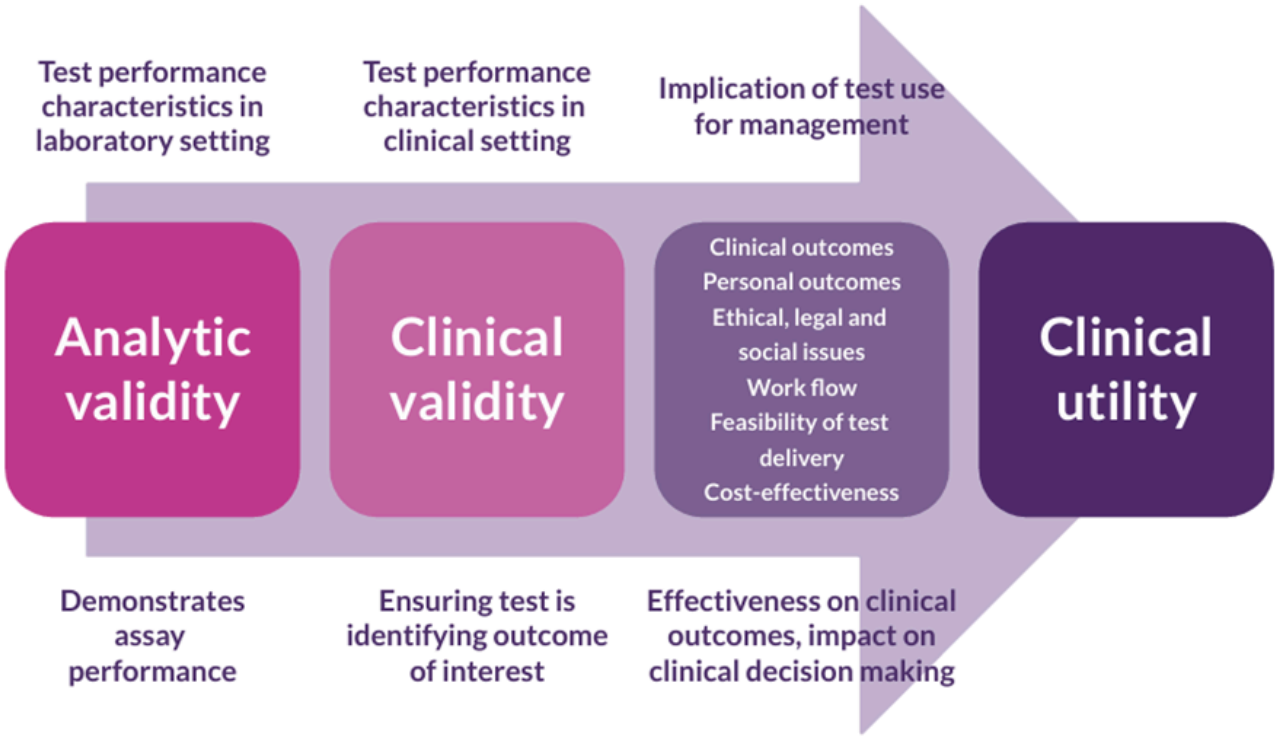
9. **Legitimacy:** The conformity of a test to social preferences expressed in ethical, principles, values, norms, mores, laws, and regulations

10. **Context:** Description of the test use, including the genetic variability, target condition, availability of treatment options, and recommendations.

How is clinical utility established?

To determine whether a genetic or omic test is truly useful in healthcare, it must undergo a stepwise evaluation process. This begins with **analytic validity** (the ability of a test to correctly detect an analyte), followed by **clinical validity** (test performance in a clinical setting). Finally, clinical utility is assessed by considering test performance characteristics, practical implications on care pathways, and also safety, effectiveness, and efficacy of a test.

The figure below outlines this pathway from technical performance to real-world impact:



Overview of the processes that can ultimately lead to demonstration of clinical utility (courtesy from PHGF)

Evidence for clinical utility can take multiple forms depending on the context and purpose of the test. While randomized controlled trials (RCTs) are often seen as the gold standard, they are not always feasible, especially for rare conditions or long-term outcomes. Instead, a range of evidence types may be considered, including observational studies, diagnostic accuracy studies, modelling analyses, and expert consensus. Smaller studies or expert case reports may also be valuable where trials are impractical. Ultimately, clinical utility is a holistic judgement, drawing on both quantitative and qualitative evidence to assess whether a test leads to better outcomes, informs clinical decisions, and is feasible and acceptable within healthcare settings.

Illustrating clinical utility of genetics : the case of BRCA testing for breast cancer prevention

A well-known example of a personalized prevention pathway that integrates genetic testing with preventive interventions is breast cancer risk assessment and management through *BRCA1/2* testing. Breast cancer risk is influenced by a combination of factors, including reproductive history (e.g., age at menarche and menopause, parity, age at first childbirth), lifestyle factors (e.g., alcohol consumption, physical activity, body mass index), hormonal exposures, and genetic predisposition. Among genetic factors, pathogenic variants in the *BRCA1* and *BRCA2* genes are associated with a significantly increased lifetime risk of developing breast and ovarian cancer.

In many countries, *BRCA* testing is currently offered to women with additional risk factors such as a strong family history of breast or ovarian cancer, early-onset disease, or bilateral tumors. Women identified as *BRCA* mutation carriers are then offered intensified surveillance programs (e.g., annual MRI and mammography), risk-reducing mastectomy, and/or chemoprevention with selective estrogen receptor modulators (e.g., tamoxifen). These interventions are guided by national and international guidelines.

According to the framework outlined by Pezzullo et al., below is a dimension-by-dimension illustration of how *BRCA* testing meets or challenges these criteria:

1. **Analytic validity**
   Does the test accurately detect BRCA1/2 mutations?
   Yes – Next-generation sequencing (NGS) technologies used for *BRCA* testing have >99% sensitivity and specificity.

2. **Clinical validity**
   Is the presence of a BRCA mutation predictive of disease?
   Yes – *BRCA1/2* mutations are strongly associated with increased lifetime breast cancer risk (up to 72% for *BRCA1*, 69% for *BRCA2*).

3. **Clinical efficacy**
   Does the test lead to effective interventions?
   Yes –
   - Risk-reducing mastectomy reduces breast cancer incidence by approximately 90%
   - Chemoprevention with tamoxifen reduces cancer risk in high-risk women
   - Surveillance with MRI/mammography improves early detection and survival

4. **Personal value**
   Does the information have personal or emotional value for the individual?
   Yes – Many women report reduced anxiety after testing and feel empowered by understanding their risk and available options.

5. **Acceptability**
   Is the test aligned with patient preferences and values?
   Generally yes – While some may choose not to know or to avoid invasive interventions, studies report high acceptability when proper genetic counseling is provided.

6. **Feasibility**
   Can the test and follow-up interventions be implemented in practice?
   Yes – *BRCA* testing is integrated into preventive care pathways in many health systems. However, logistical and resource challenges remain in some settings.

7. **Equity**
   Does the test reduce or exacerbate health disparities?
   Mixed – Testing is available in many countries, but disparities persist in access for ethnic minorities and low-income populations.

8 **Economic Impact**

Is the test cost-effective?

Yes – Economic modelling demonstrates cost-effectiveness and even cost-savings of *BRCA* testing in high-risk groups and, under some scenarios, in population screening.

9 **Legitimacy**

Is the test consistent with ethical and legal standards?

Yes – *BRCA* testing is regulated by national laws and European frameworks, including the In Vitro Diagnostic Regulation (IVDR). Informed consent and confidentiality procedures are well established.

10 **Context**

Is the test embedded in a clear clinical pathway?

Yes – *BRCA* testing is part of structured care pathways with clearly defined follow-up options including surveillance, surgery, and chemoprevention.

Why is clinical utility important in policy and practice?

- Health Professionals need clear, evidence-based guidance to determine whether to use genetic tests in prevention, diagnosis, and treatment. The aim is to focus on tests that improve patient outcomes and are feasible and acceptable in clinical settings.
- Policymakers rely on robust evaluations of clinical utility to guide responsible decisions on implementation, funding, and regulation.

Yet, evidence for direct health benefits of genomic testing in prevention remains limited, nonetheless it's crucial. Clear definitions and agreed frameworks are essential to avoid inconsistent assessments and to support transparent, accountable decision-making in both clinical and policy contexts.

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