Context

While numerous evaluation frameworks for the assessment or adoption of genetic tests exist, there is no single, standardized process. A lack of consensus on the appropriate evidentiary requirements is believed to be the main reason why a standardized approach to the evaluation of genetic tests is not currently in place. However, the use of different frameworks may lead to inconsistent findings even when evaluating the same test. The purpose of this report is to identify the main evaluation frameworks that are used internationally and outline some of the most commonly used criteria.

Genetic test evaluation frameworks have been developed by Canadian and international government and academic organizations. Each of these evaluative frameworks is underpinned by principles of evidence-based decision-making and technology assessment. The evaluation frameworks involve the assessment of numerous parameters; most of which have commonalities, although they may be labelled in different ways. The primary test performance measures include analytic and clinical validity, as well as clinical utility. Some of these evaluation frameworks also consider ethical, legal, and societal implications. Several evaluation frameworks provide general conceptual guidance, while others provide key questions that address issues such as relevant populations, interventions, comparators, outcomes, time points, and settings.

The development of evaluation frameworks for genetic tests is challenging for a variety of reasons. Some of the most often cited reasons relate to study quality, small populations, and the application of different evaluative requirements. There is a lack of high-quality studies (largely because regulatory and reimbursement policies do not require these studies), and those that do exist often do not necessarily fit in well with recognized benchmarks of systematic reviews of evidence. For most rare single gene disorders, there is often insufficient data on analytic and clinical validity because of inadequate numbers of patients with rare diseases and a shortage of interventions that demonstrate efficacy. While genetic tests can be evaluated in a similar way to other clinical tests, there are certain distinctions in how some criteria are applied and the extent of the relevance of these criteria for specific categories of genetic tests. For example, pharmacogenetic tests may have different evaluative requirements than predictive genetic tests or screening tests.

Objectives

The objective of this report is to identify existing genetic test evaluation frameworks and commonly used criteria.

Findings

It is not intended that the findings of this Environmental Scan provide a comprehensive review of the topic. Results are based on a limited literature search. This report is based on information gathered as of February 2012.

Frameworks

North America

Canada

McMaster University Evaluation Framework

Background: McMaster University developed an evaluation framework in 2001 to guide an Ontario advisory committee on coverage decisions for new predictive genetic tests.

Scope: The evaluation framework was developed specifically for new predictive genetic tests.
Method and Process: The framework consists of three main domains. The first domain relates to evaluative criteria; this includes the intended purpose, effectiveness, additional effects, unit price, demand for, and the cost-effectiveness of a predictive genetic test. The second domain relates to the development of acceptable cut-offs. The third domain relates to coverage decisions under conditions of uncertainty. Each of these domains centers on addressing gray areas of policy-making, in particular: questionable objectives, unclear cut-offs, missing information, changing parameters, and conditional coverage.\(^5\)

Additional information: In 1986 McMaster University, in collaboration with Guyatt, created a framework for the clinical evaluation of diagnostic technologies. The framework emphasized the importance of a systematic assessment of technological accuracy, impact on health care providers, therapeutic impact, patient outcomes, and cost-effectiveness. The framework iterates that the randomized controlled trial is the preferred study design to determine therapeutic impact and patient outcomes.\(^6\)

Blancquaert Evaluation Framework

Background: In 2006, Blancquaert developed a health technology assessment framework for the Agence d'évaluation des technologies et des modes d'intervention en santé that has been used to evaluate genetic tests.

Scope: This model considers all technologies.

Method and Process: This evaluation framework consists of a critical analysis of the evidence, based on the analytical and clinical validity of a test, an assessment of a test’s utility, acceptability, and the feasibility of the diagnostic and screening strategies, as well as an organizational analysis of how the technology interfaces with health care delivery and services. Ethical, legal, and societal implications are expected to be present and addressed at each stage of the analysis. An economic analysis is also expected to be carried out either at each stage of the framework or for the framework as a whole.\(^7\)

United States

Fryback-Thornbury Evaluation Framework

Background: The 1991 Fryback-Thornbury evaluation model provides general conceptual guidance for the evaluation of diagnostic test efficacy. It is believed to be the most widely used and well-known evaluation model.\(^2\)

Scope: The proposed use of this framework is to evaluate the efficacy of all diagnostic tests.

Method and Process: The evaluation model consists of six hierarchical tiers of diagnostic efficacy. The tiers include technical, diagnostic, diagnostic thinking, therapeutic, patient outcome, and societal. A diagnostic test is considered technically effective if its result is accurate and precise. The model indirectly considers costs and the cost-effectiveness of a technology in the context of societal efficacy. The framework advocates randomized controlled trials for tests that have a higher risk of harm, are more expensive, and/or have wide utilization.

ACCE Evaluation Framework

Background: The US Centers for Disease Control and Prevention established and supported the ACCE evaluation model between 2000 and 2004. The ACCE model was discontinued in 2004, when it was superseded by another US Centers for Disease Control and Prevention initiative, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP).\(^8\) In addition to providing a benchmark for EGAPP, the ACCE evaluation model has also been adopted and built on by the Genetic Testing Network in the United Kingdom.\(^9\)

Scope: The framework was developed for the evaluation of all emerging genetic tests.\(^8\)

Method and Process: The framework consists of four core principles that are used to assess genetic tests: analytical validity; clinical validity; clinical utility; and the ethical, legal, and societal implications of genetic testing.

A set of 44 key questions are used to frame each of the components. Questions also address the nature of the disorder, the clinical setting, and the type of testing. Economic considerations are a component of the
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evaluation of clinical utility. The framework is a process that includes collecting, evaluating, interpreting, and reporting data on genetic tests in a format that allows policymakers to have access to up-to-date and reliable information for decision-making. The elements of the process and their relationship to each other are depicted in the ACCE wheel (Figure 1). A rapid ACCE model has been developed that employs the same 44 key questions used in the original ACCE framework.

Figure 1: ACCE Wheel


EGAPP Evaluation Model

Background: In 2004 the EGAPP initiative was established by the US Centers for Disease Control and Prevention to analyze the potential benefits and harms of genetic tests. EGAPP provides unbiased, transparent, and evidence-based assessments. The central components of EGAPP’s methodology are based on the criteria from ACCE and the US Preventive Services Task Force, as well as some of the components of the Fryback-Thornbury model. EGAPP established a working group (EWG) to develop a systematic process for the evidence-based assessment of genetic tests. The EWG consists of a panel of approximately 16 multidisciplinary experts. EGAPP also develops recommendations to inform decision-making on genetic testing.

Scope: EGAPP mostly prioritizes pharmacogenomic tests and genetic tests that are involved with common diseases, although it also focuses on other genetic tests that have a wide population application (e.g., higher disorder prevalence, higher frequency of test use) and those with the potential to impact clinical and public health practices. Tests could include those used in a specific clinical scenario to guide intervention (e.g., diagnostic workup, treatment, or prevention) or tests used for risk prediction or population screening. EGAPP does not routinely assess tests for rare single gene disorders, newborn or prenatal screening, or tests for reproductive decision-making.

Method and Process: EGAPP’s analytic framework builds on the core components of the ACCE framework: analytical validity; clinical validity; clinical utility; and the ethical, legal, and societal implications of genetic tests. This framework focuses on clinical factors and health-related outcomes, key questions, and methodological models that the EWG may recommend. As well, the EWG may request information pertaining to other familial, ethical, and societal characteristics of a genetic test, and information on a test’s impact on issues such as management decisions by physicians and patients, and on the cost-effectiveness and feasibility of the use of the test. EGAPP has also developed frameworks for the production of rapid reviews.

The United States Preventive Services Task Force (USPSTF) Evaluation Model

Background: The USPSTF is an independent panel of non-Federal experts that conducts rigorous, impartial assessments of scientific evidence and develops recommendations for primary care physicians and health systems. USPSTF was established in 1984 by the US Public Health Service. Since 1998, the Agency for Healthcare Research and Quality has sponsored USPSTF.

Scope: USPSTF conducts scientific evidence reviews on a wide range of preventive services including screening, counselling, and preventive medications, and develops
recommendations for primary care physicians. As part of its role in conducting reviews and providing recommendations, USPSTF also conducts clinical reviews of selected gene-based tests.

**Method and Process:** USPSTF uses the same analytic framework for evaluating genetic tests as it uses for making evidence-based recommendations on all preventive services. The foundation of this framework is built on systematic review methodology. An independent process that is based on the randomized controlled trial design guides the evaluation of evidence. Indirect evidence is considered if it addresses key questions within the analytic framework. Evidence that directly links to health benefits and harms is the primary focus. The framework also considers ethical, legal, and societal issues. Economic costs are considered but not as a first priority. Explicit criteria are used to find evidence of net benefit. The framework grades evidence as “high,” “moderate,” or “low” in certainty.

**Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)**

**Background:** In 2003, the ACHDNC was established by the US Secretary of Health and Human Services to evaluate genomic tests for use in newborn screening panels and make national recommendations concerning candidate disorders for newborn screening panels. The recently revised framework builds on various methodologies that include the ACCE and EGAPP models.

**Scope:** The framework focuses on screening newborns and children for rare conditions.

**Method and Process:** The new analytic framework consists of six key questions. These questions relate to: the need for direct evidence of improved health outcomes, the application of a case definition, the sufficiency of analytic validity, the adequacy of clinical validity, determinants of clinical utility, and the cost-effectiveness of the technology. When making recommendations, ACHDNC considers three main elements: the extent of the net benefit, the overall adequacy of evidence, and the certainty of the net benefit.

**International**

**The GETT Evaluation Tool**

**Background:** The International Federation of Clinical Chemistry and Laboratory Medicine’s Scientific Committee on Molecular Diagnostics, a largely Canadian affiliated group, developed the GETT Evaluation Tool in 2009.

**Scope:** This tool is applicable to any molecular genetic test.

**Method and Process:** This is an operational tool that is intended to build on existing frameworks. It consists of a checklist of 72 questions and their definitions that should be considered when evaluating genetic tests. The checklist is categorized into 10 major themes: overview of the disease, diagnostic tool, quality improvement programs, clinical validity, diagnostic and screening strategies, impacts on health care system, psychological and societal impacts, ethical and legal impacts, synthesis of information—including missing data—and identification of research priorities. This approach aims to systematically identify and organize published peer-reviewed knowledge necessary for assessing the health care benefits of genetic tests. The framework also identifies research gaps that will require further investigation. The tool incorporates areas that are typically absent from most models, such as the availability of quality improvement/proficiency programs and the availability and accessibility of professional services, health care and follow-up, and expertise and training.

**Eurogentest Evaluation Model**

**Background:** Eurogentest is a network that was established for the development of genetic tests, the harmonization of practices, and the validation and standardization of genetic test services in Europe. Eurogentest created a standardized framework for the validation and verification of clinical molecular genetic tests.
**Scope:** The framework is applicable to all genetic tests.

**Method and Process:** The main component of this evaluation model draws on the ACCE framework. However, this framework also asserts that analytical validity, clinical validity, and clinical utility are often dependent on contextual circumstances that may differ from one country to another. The evaluation of clinical utility is influenced by ethical, legal, and societal issues. Eurogentest created the “Clinical Utility Gene Cards” as a tool to evaluate new genetic tests.

**The United Kingdom Genetic Testing Network (UKGTN)**

**Background:** The UKGTN was established in 2002 as a collaborative network of National Health Service molecular genetic laboratories. The UKGTN developed a “Gene Dossier” process to evaluate new genetic tests based on the ACCE program.

**Scope:** This framework was designed for the evaluation of genetic tests for rare single gene disorders.

**Method and Process:** The UKGTN has developed criteria that are used by an evaluation panel to assess new genetic tests. The criteria consists of nine key components: the seriousness of the condition; the prevalence of the condition; the purpose of the test — diagnosis, treatment, prognosis and management, presymptomatic testing, and risk assessment; the complexity of the test; the context in which the test is to be used — population groups; the characteristics of the test — its clinical sensitivity, specificity, and predictive value; the utility of the test — how it adds to the treatment of the patient and the availability of alternative diagnostic procedures; ethical, legal, and societal considerations; and the cost of the test. Since the final decision regarding the recommendation of a test is a matter of professional judgment, the evaluation framework ensures that this judgment is made in the context of an open, explicit, and transparent process.

**German Society of Human Genetics**

**Background:** The German Society of Human Genetics (GfH) was founded in 1987. It is the primary professional membership organization for human geneticists in Germany, consisting of more than 1,000 members. Its main purpose with regard to evaluating genetic tests is to promote the use of guidelines rather than develop an evaluation framework.

**Scope:** The guideline is applicable to all genetic tests.

**Method and Process:** GfH has developed a set of indication criteria that are meant as a guide for clinical practice. The criteria relates to clinical validity and utility, and includes disorder and test characteristics.

**Andalusian Public Health System Assessment Framework**

**Background:** The Andalusian Public Health System has proposed the main component and criteria of an evaluation framework for new genetic tests that is based on the ACCE model. However, further information is not currently available.

**Key Characteristics of Selected Evaluation Frameworks**

While several frameworks and models exist for the assessment of genetic tests, there is a lack of consensus on the evidentiary requirements for a standardized approach. Some of the most commonly used criteria are presented in Table 1.
### Table 1: Common Characteristics of Evidentiary Requirements for Reviewing Genetic Tests

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Overview of Disease and Underlying Genetics</strong></td>
<td>Information on the disease prevalence, treatment, costs, and outcomes of the disease. Description of the genetic underpinning, such as pattern of inheritance; mutational spectrum, including details on the prevalence and penetrance of the mutation; other diagnostic/screening methods and whether any are “gold standards.”</td>
</tr>
<tr>
<td><strong>Target Population and Intended Use</strong></td>
<td>Prevalence for target population, including factors such as age, ethnic group, the eligibility criteria for the test. Intended use of the test: indicate whether the genetic test can be used for diagnosis, treatment, prognosis and management, presymptomatic testing, carrier testing, and/or prenatal testing.</td>
</tr>
<tr>
<td><strong>Laboratory Information</strong></td>
<td>Description of how the test has been validated; if the test is already in use/markedeted, and if so, the number and rate of positive and negative mutations; the other similar tests that are available; current activity (including index cases and family members with genetic mutation); the turnaround time for results; the number of tests that could be supplied if funding was approved (including index cases and family members with genetic mutation), whether there are other laboratories that could offer the test; the infrastructure requirements; and an interpretation guide for any jargon or statements used to interpret the results if they are not clear to a lay person. Describe quality improvement programs (internal and external) that will help control the standards, accuracy, etc. of the testing. This could include processes like blinding procedures and exchanging samples between laboratories, or external quality control.</td>
</tr>
<tr>
<td><strong>Analytic Validity</strong></td>
<td>Measures such as precision, reliability, accuracy, sensitivity, specificity of the genetic test, and how these measures compare with other relevant/used screening and diagnostic methods.</td>
</tr>
<tr>
<td><strong>Clinical Validity</strong></td>
<td>Measures such as diagnostic specificity and sensitivity, positive predictive value, negative predictive value, likelihood ratios, and how they compare with any other screening and diagnostic methods.</td>
</tr>
<tr>
<td><strong>Economic Considerations</strong></td>
<td>Cost estimates for the test and associated equipment, personnel, and consumables. Costs of disease with and without treatment (e.g., how the genetic test will affect these costs). Costs of the genetic test and associated costs and costs saved (include current and downstream costs) as compared with current clinical pathway per case and per annum based on patient population and uptake estimates of test. Expected current and future utilization of the test (e.g., would the target population expand over time?)</td>
</tr>
<tr>
<td><strong>Clinical Utility</strong></td>
<td>Anticipated benefits and risks of using this test, how it will add to the treatment of the patient, how it will change the patient’s health outcome, and whether the results will affect the patient and family members. Can a diagnosis be made through another clinical pathway; if so, describe the alternative diagnostic methods including burden to the patient.</td>
</tr>
<tr>
<td><strong>Ethical, Legal, and Social</strong></td>
<td>Details on ethical, legal, and societal issues, such as patient access to the test in Canada, and patient access to the proper interpretation of the results (e.g., can the family physician offer this or would a genetic counsellor be required), as well as support and follow-up.</td>
</tr>
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</table>
Conclusion

Twelve evaluation frameworks for genetic tests were identified in this Environmental Scan. Most of these models expand on the ACCE framework of analytic and clinical validity; clinical utility; and ethical, legal, and societal issues. Several of these frameworks provide general conceptual guidance, while others provide key questions in the form of an analytic framework or a checklist. Many of the existing evaluation frameworks apply to specific classifications of genetic tests, while others provide a standardized approach that can apply to all genetic tests.

The evaluation of genetic tests is often methodologically challenging, due, in part, to a lack of high-quality studies and to small patient populations.

References

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