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NAM: Report on Evidence Framework for Genetic Testing

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Committee On The Evidence Base For Genetic Testing

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Committee On The Evidence Base For Genetic Testing

Expertise represented

- Basic science
- Molecular genetics
- Clinical genetics
- Pediatrics
- Medicine
- Family medicine
- Medical oncology
- Clinical epidemiology
- Bioethics
- Health economics

Statement of Task

- Examine the relevant medical and scientific literature to determine the evidence base for different types of genetic tests (e.g., predictive, diagnostic, and prognostic) for patient management
- Provide recommendations to advance the development of an adequate evidence base for genetic tests to improve patient care and treatment
- Recommend a framework to DOD for decision making regarding the use of genetic tests in clinical care.

Committee Approach

- Agreed on definitions of key terms and discussing the similarities and differences between genetic and genomic tests and tests used in other medical contexts.
- Focused on the clinical applications and clinical utility of genetic tests as directed by the statement of task.
- Examined how evidence is generated, evaluated, and summarized.
- Reviewed approaches to and frameworks for decision making in the context of genetic tests.

Definition of Genetic Testing*

"Analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes. Such purposes include predicting risk of disease, identifying carriers and establishing prenatal and clinical diagnosis or prognosis."

Includes:

- Prenatal, newborn and carrier screening
- Testing in high risk families

Excludes:

- Tests for metabolites unless they predict with high certainty heritable mutations in single genes
- Tests conducted purely for research
- Tests for somatic mutations
- Testing for forensic purposes

* NHGRI Task Force on Genetic Testing, 1997

Purposes of Genetic Testing

- ***Diagnostic***: to identify, rule out or confirm a diagnosis suspected on the basis of physical signs and symptoms and family history. The results can influence clinical management choices made by patients and physicians.

- ***Predictive***: to identify gene variants associated with increased risk of developing heritable disorders before signs or symptoms appear. This includes population screening, such as newborn screening; and pharmacogenetic testing to identify patients who are at increased risk for adverse effects or who are not likely to respond.

- ***Reproductive***: offers the opportunity to identify people who are at increased risk for having a child with a genetic disease or to identify an affected embryo or fetus. Includes carrier or heterozygote testing, prenatal genetic testing, and preimplantation testing.

Evidence

- Considered the current state of the evidence base for genetic tests. The main challenges to the field are:
  - Lack of direct evidence
  - Rare variants and rare diseases
  - Genomic sequencing and the large number of variants

- Organized report around 3 domains for evaluating genetic tests:
  - Analytic validity
  - Clinical validity
  - Clinical utility

Evidence

- ***Analytic validity*:** ability to accurately and reliably identify genetic variants of interest in the clinical laboratory specimens from the population of interest. Includes analytic sensitivity, analytic specificity, within- and between-laboratory precision, and assay robustness.
- ***Clinical validity*:** ability to identify or predict accurately and reliably the clinically defined disorder or phenotype of interest. Clinical validity encompasses clinical sensitivity and specificity and predictive values of positive and negative tests that take into account the prevalence of the disorder, also expressed as a measure of association
- ***Clinical utility*:** ability of a test to improve clinical outcomes measurably and add value for patient management decision making compared with current management without genetic testing.

Evidence - Analytic Validity

- The ability to assess evidence on analytic validity is challenged by
  - Lack of appropriately qualified samples and gold-standard reference methods and the constantly emerging and evolving genetic techniques
  - Availability of unbiased, detailed data on the analytic validity of existing tests
  - Technical issues
- Evidence on analytic validity comes from
  - FDA summaries
  - Validation studies
  - Proficiency testing schemes
  - Inter-laboratory comparison programs

Evidence - Clinical Validity

- Relies on the ability to conclude that there is a causal relationship between a genetic variant and a disease or phenotype
- Challenges include
  - Identifying genes responsible for disease
  - Identifying causative variants among the large number of variants detected by genomic sequencing
  - Variants in multiple genes causing a similar phenotype (locus heterogeneity)
  - Limited understanding of characteristics of Mendelian disease including penetrance, variable expressivity, and pathogenic mechanisms
- Evidence regarding clinical validity is often organized in databases and generated by observational studies

Evidence - Clinical Utility

- Often based on the utility of the intervention guided by the test, rather than the test itself
- Sometimes determined by a “chain of indirect evidence” showing the effect of alteration of patient management on outcomes because direct evidence is not available
- Evidence on clinical utility includes clinical trials, with randomized controlled trials (RCTs) most desired but least available
- Because evidence on clinical utility is often lacking, other approaches - such as decision modeling - aid in decision making.
- Outcomes that may be desired by the patient but are not yet clinically measurable (e.g. end of diagnostic odyssey) are recognized as “personal utility”

Research Recommendations: Generating Evidence

The committee recommends that DoD advance the evidence base on genetic testing through independent and collaborative research (5 specifics follow)

The DoD should look for reasonable and practical opportunities to engage in evidence generation by making evidence requirements risk-based and dependent on the test and clinical scenario; and setting priorities based on feasibility and the likelihood that evidence generated will improve clinical practice and patient outcomes.

Research Recommendations: Generating Evidence

Supporting high-quality studies of clinical validity and clinical utility (including patient-centered outcomes) of promising tests.

Including:

- Prospective studies such as RCTs, when numbers allow
- Outcomes that reflect the clinical utility of genetic testing, including ones that extend beyond clinical outcomes such as well-being, quality of life, and impacts on family members (personal utility)
- Discovery efforts related to the evidence base for causation between observed variants and phenotypes

Research Recommendations: Generating Evidence

Implementing processes for data collection and analysis of the DODs' own experience with genetic testing.

Establishing an infrastructure for data collection will facilitate tracking and monitoring of diagnostic outcomes and provide an opportunity to refine established policies for testing on a continuing basis. This could include:

- Evaluating test use through claims or clinical databases
- Assessing test findings through collaboration with laboratories and providers
- Identifying clinical-practice changes related to use of test results
- Tracking effects of test-informed treatment changes on patient outcomes

Research Recommendations: Generating Evidence

Supporting evidence-based systematic reviews of genetic tests.

Identifying opportunities and gaps in evidence for specific tests applied to certain clinical scenarios will require conduct of systematic reviews.

Research Recommendations: Generating Evidence

Contribute genetic variants and associated clinical data to public evidence repositories.

To generate evidence of clinical validity of genetic tests, DoD should participate fully in evidence repositories (such as ClinVar) and work with partners to improve the clinical relevance and usefulness of genetic tests

Research Recommendations: Generating Evidence

Partnering with other organizations to facilitate these recommendations.

Many initiatives under way are complementary to those seeking to provide evidence for clinical utility at the National Human Genome Research Institute, the Agency for Healthcare Research and Quality, and the Patient Centered Outcome Research Institute.

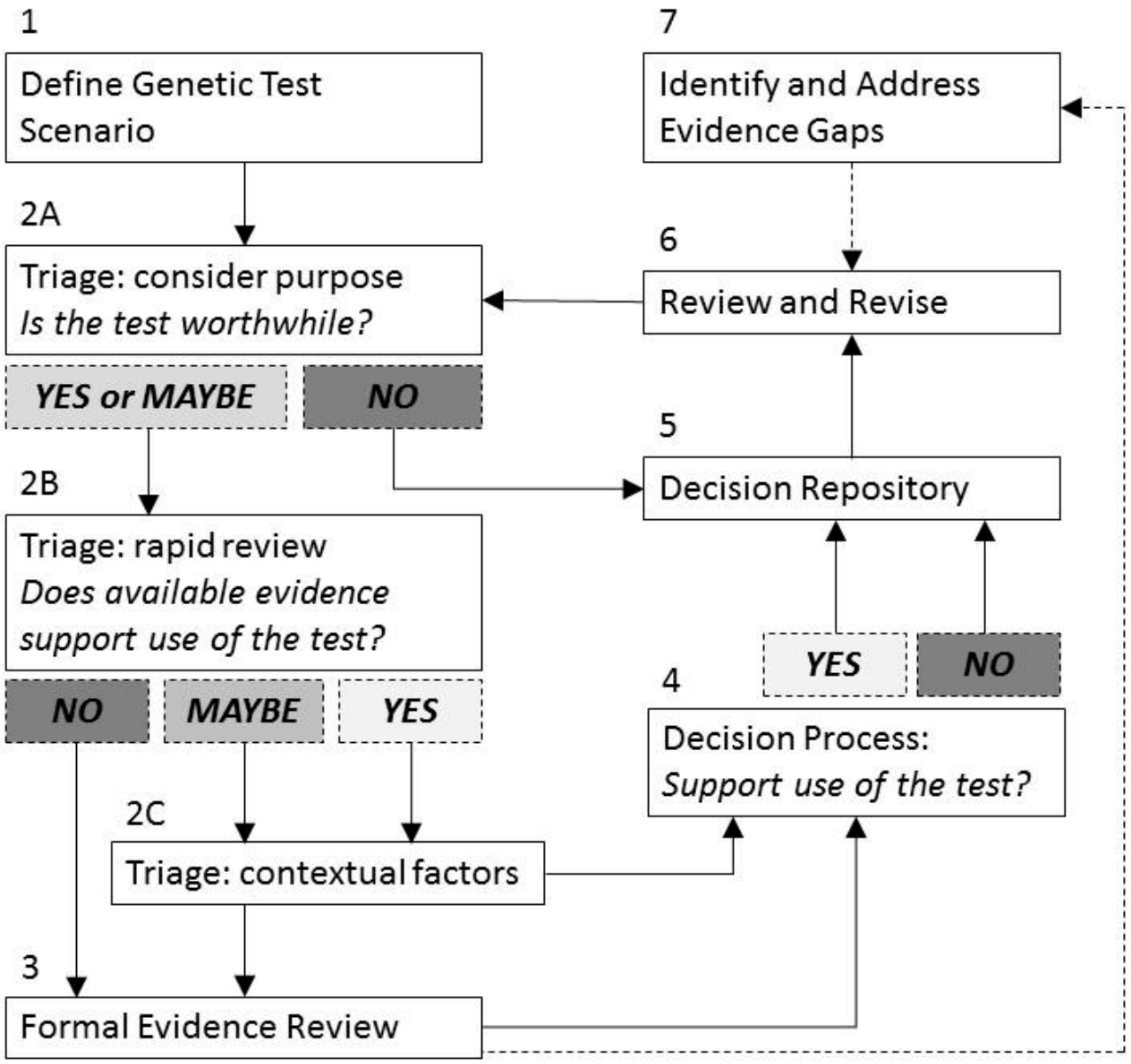
Genetic Test Evaluation Methods

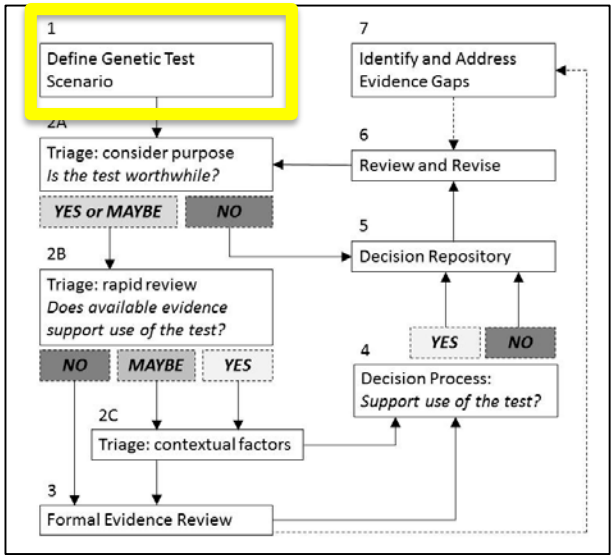
- The committee identified and reviewed seven methods that have been published for the evaluation of genetic tests (or healthcare technology in general)
  - USPSTF
  - Fryback-Thornbury
  - ACCE
  - EGAPP
  - GETT
  - McMaster University
  - Frueh and Quinn

Recommendations

The committee recommends the following decision framework for the use of genetic tests in clinical care.

1. Define genetic test scenarios.
2. Conduct an initial assessment to determine whether the test should be covered, denied, or subject to additional evaluation.
3. Conduct or support evidence-based systematic reviews for genetic test scenarios that require additional evaluation.
4. Conduct or support a process to produce clinical guidance.
5. Publicly share resulting decisions and justification, retain decisions in a repository.
6. Implement timely review and revision of decisions.
7. Identify evidence gaps to be addressed by research.


1
Define Genetic Test Scenario
2A
Triage: consider purpose
Is the test worthwhile?
YES or MAYBE
NO
2B
Triage: rapid review
Does available evidence support use of the test?
NO
MAYBE
YES
2C
Triage: contextual factors
3
Formal Evidence Review
4
Decision Process:
Support use of the test?
YES
NO
5
Decision Repository
6
Review and Revise
7
Identify and Address Evidence Gaps

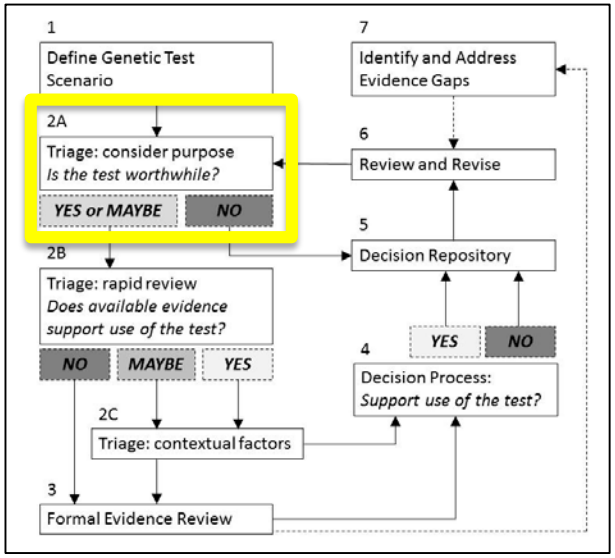


Component 1: Define the genetic test scenario

Define genetic test scenarios on the basis of the clinical setting, the purpose of the test, the population, the outcomes of interest, and comparable alternative methods.

The scenario should include:

- The test being performed,
- The population in which testing is considered appropriate,
- The purpose of the test in that population (clinical scenario),
- The outcomes of interest, and
- Comparable alternative methods to accomplish those tasks.

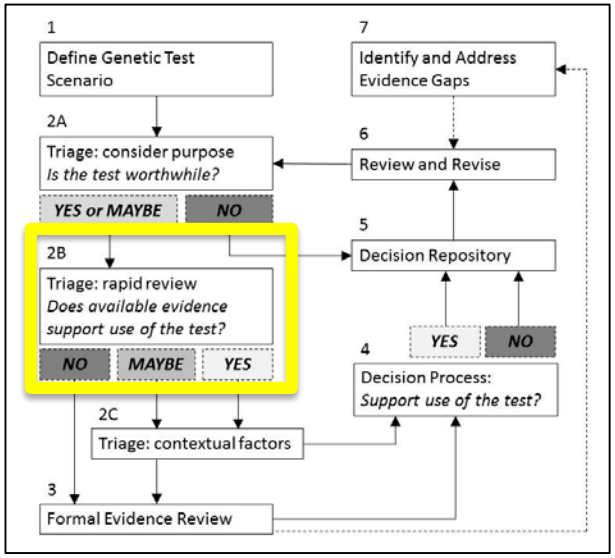


Component 2: Prioritize and Triage

For each genetic test scenario, conduct an initial structured assessment to determine whether the test should be covered, denied, or subject to additional evaluation.

Component 2A: Is the test for a given clinical scenario worthwhile?

- If no, then no further evidence evaluation is required, but the judgment should be transparent.



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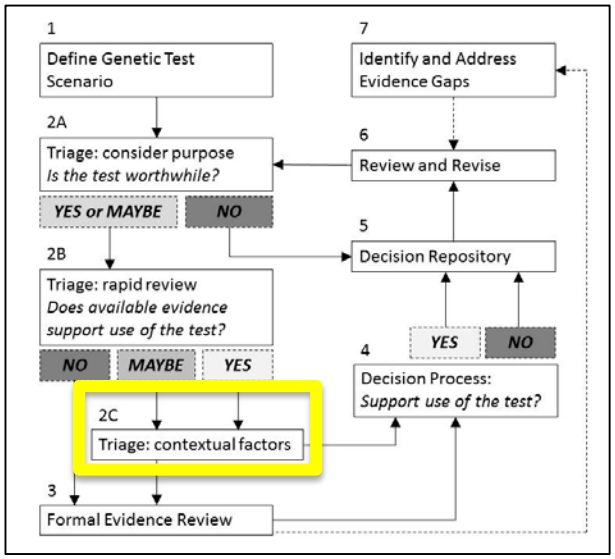
Component 2B: Is there evidence that supports use of the test (according to practice guidelines tools such as ACCE or GETT)?



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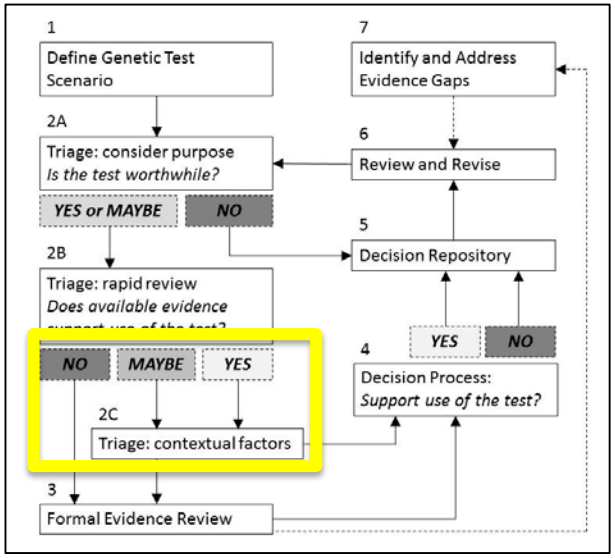
Component 2B: Is there evidence that supports use of the test (according to practice guidelines tools such as ACCE or GETT)?

Component 2C: Consider contextual features such as the aggregate costs and the consequences of not covering the test.

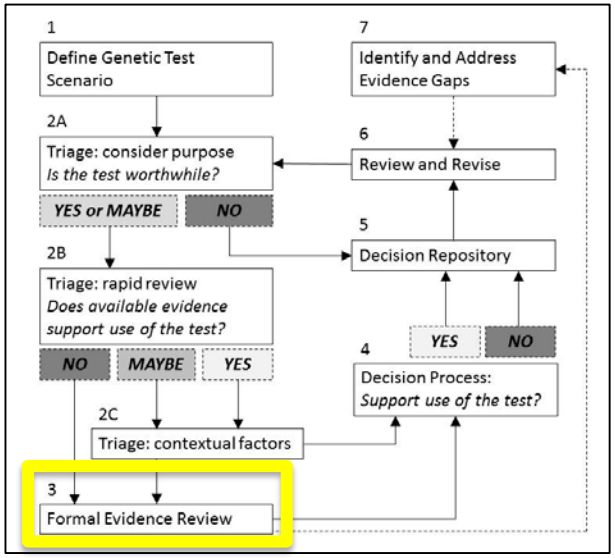


Component 2: Prioritize and Triage

If the rapid review (2b) indicates adequate evidence, cover the test unless negative contextual factors (2c) outweigh the evidence.

If insufficient evidence is available after rapid review:

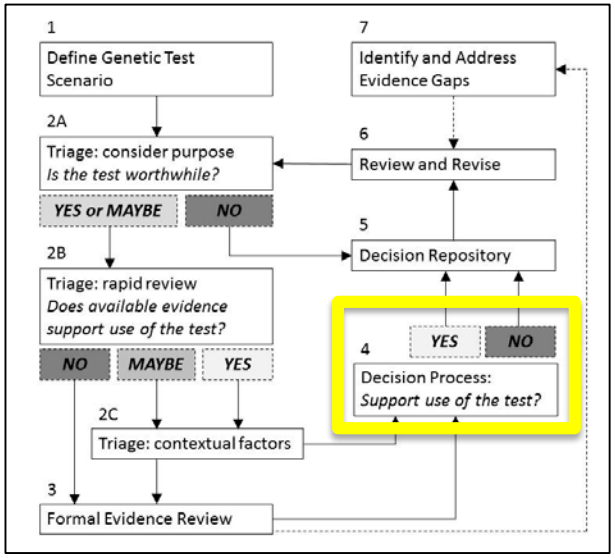
- If the test is worthwhile but specific evidence gaps need to be clarified before a decision can be made, a systematic review (Component 3) may be required.
- If the consequences of not covering the test are significant, and aggregate costs are generally acceptable based on the volume of test requests and the unit costs, provisional coverage of the test with systematic evidence collection may be considered.



Component 3: Formal Evidence Review

Conduct or support evidence-based systematic reviews for genetic test scenarios that require additional evaluation.

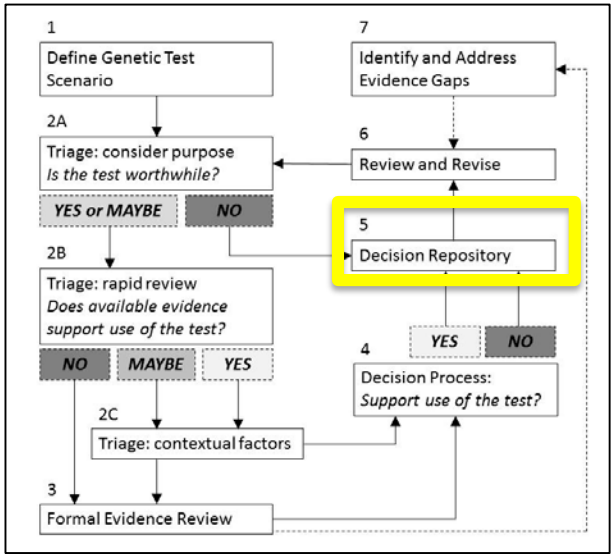
- Identify the purpose, important outcomes of testing, and any relevant comparators
- Use systematic review methodology (eg. EGAPP) with key questions appropriate for the purpose of the test and the outcomes of interest.



Component 4: Decision Process

Conduct or support a structured process to produce clinical guidance for a genetic test scenario.

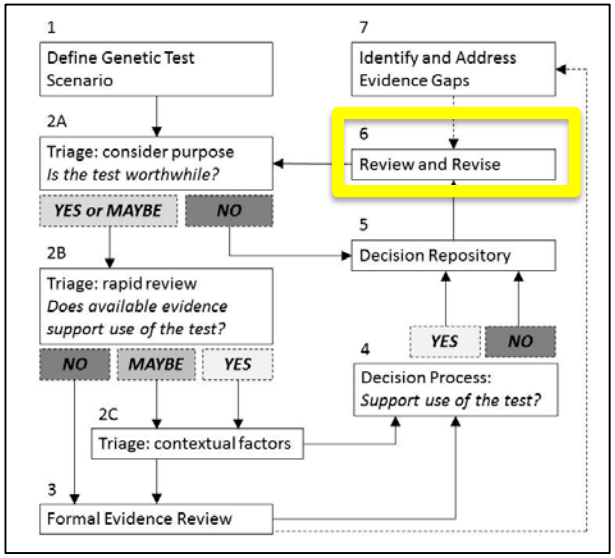
- Incorporate the preceding evidence review and contextual factors such as social issues, potential harms, or benefit/cost considerations and result a "YES" or "NO" decision
- Set standards for "sufficient" evidence in a clear and consistent way to reflect its values and needs



Component 5: Decision Repository

Publicly share resulting decisions and justification about evaluated genetic test scenarios, and retain decisions in a repository.

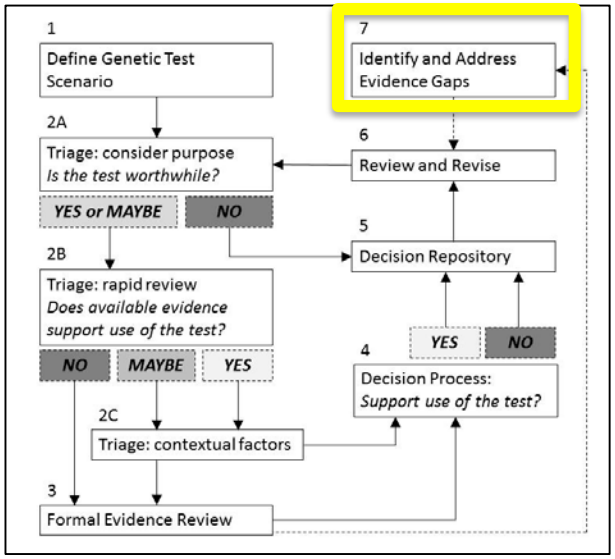
- Structure the repository to allow reviewers to evaluate new scenarios rapidly in light of previous decisions that have been made for similar tests, populations, purposes, and outcomes of interest and for comparable methods
- Use the decision repository as a record of the value judgments made about whether particular genetic-test scenarios are deemed worthwhile so that stakeholders can understand the decisions and DOD can ensure consistency among decisions



Component 6: Periodic review and revision

Implement timely review and revision of decisions on the basis of new data.

- Facilitate a systematic process, such as time stamps and automated prompts in the decision repository, for regular re-review of decisions
- Provide a process for stakeholders to request revised decisions



Component 7: Periodic review and revision

Identify evidence gaps to be addressed by research.

- Note any evidence gaps identified by evidence review processes in steps 2b or 3
- Conduct gap analysis on a regular basis as part of a process of continual quality improvement that uses a clinical implementation science process
- Use evidence gaps to inform research priorities and areas for evidence generation

Recommendations

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