Methods Guide for Medical Test reviews

Paper 3

Considering the Range of Decision-Relevant Effects

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Effectiveness and Comparative Effectiveness Reviews, systematic reviews of existing research on the effectiveness, comparative effectiveness, and comparative harms of different medical tests, are intended to provide relevant evidence to inform real-world health care decisions for patients, providers, and policymakers. In an effort to improve the transparency, consistency, and scientific rigor of the work of the Effective Health Care (EHC) Program, through a collaborative effort within the Evidence-based Practice Center Program, have developed a Methods Guide for Medical Test Reviews. We intend that these documents will serve as a resource for our EPCs as well as for other investigators interested in conducting systematic reviews on medical tests.

This Medical Test Methods guide is intended to be a practical guide for those who prepare and use systematic reviews on medical tests. This document complements the EPC Methods Guide on Comparative Effectiveness Reviews (http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318), which focuses on methods to assess the effectiveness of treatments and interventions. The guidance here applies the same principles for assessing treatments to the issues and challenges in assessing medical tests and highlights particular areas where the inherently different qualities of medical tests necessitate a different or variation of the approach to systematic review compared to a review on treatments. We provide guidance in stepwise fashion for those conducting a systematic review.

The *Medical Test Methods Guide* is a living document, and will be updated as further empirical evidence develops and our understanding of better methods improves. Comments and suggestions on the *Medical Test Methods Guide* and the Effective Health Care Program can be made at www.effectivehealthcare.ahrq.gov.

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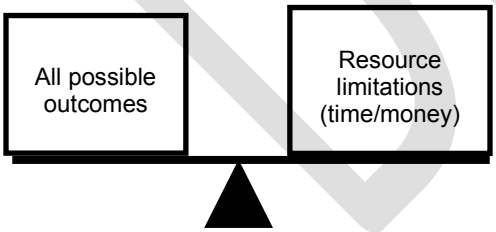
Paper 3. Considering the Range of Decision-Relevant Effects

In this paper, we describe the range of decision-relevant effects, or outcomes, that medical tests have and how these outcomes may be incorporated into a systematic review. "Decision-relevant" refers to those outcomes that result from the testing encounter and have an impact on decisions downstream. The outcomes to be discussed are those that are relevant to screening tests, diagnostic tests, and prognostic tests, although prognostic tests are discussed separately in Paper 12 in this *Medical Test Methods Guide*. We also briefly address unique issues that might arise if the test in question is a genetic test; this topic is explored in greater detail in Paper 11. Other topics considered here include the challenges involved in encompassing a range of outcomes in a systematic review, a framework for generating potential outcomes for inclusion, the role of stakeholders in choosing outcomes for evaluation, and a way to prioritize the outcomes that should be considered. Finally, we give examples of systematic reviews that either included a range of outcomes in the review or might have done so.

Common Challenges

Investigators working in Evidence-base Practice Centers (EPCs) are tasked with choosing the outcomes to consider in a systematic review of a medical test. Resource limitations require judicious selection from among all possible outcomes, which necessitates setting priorities for the outcomes to include. If EPCs do not explore the full range of outcomes at the outset of the project, the likelihood of excluding important outcomes is high, and the systematic review may miss outcomes relevant to stakeholders. However, if the initially broad range of outcomes is not carefully reduced, the quality of the review will be threatened by resource limitations (Figure 3-1).

Figure 3-1. Balancing outcomes against resources



If EPCs do not adopt a methodical approach to considering the range of outcomes that might be covered in a review, they may inadvertently exclude important outcomes. On the other hand, if EPCs attempt to cover all outcomes without carefully setting priorities, they may end up with an overly ambitious review. A misstep of either type can result in a suboptimal review—the first type of review may be incomplete, and the second may be too broad to provide meaningful insights.

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Principles for Addressing the Challenges

We recommend a two-step approach, applying two principles in sequence, for selecting the outcomes to be included in a review of a medical test. The first step is to catalog potential outcomes methodically, and the second is to solicit input from stakeholders. Below is a description of a conceptual approach to identifying outcomes to ensure that relevant outcomes are not overlooked.

Principle 1: Catalog Outcomes Methodically

Paper 2 describes frameworks for designing systematic reviews of medical tests that include consideration of PICOTs (Patient population, Intervention, Comparator, Outcomes, Timing, Setting). Here we present another framework specifically for thinking about the outcomes attributable to using a test in a clinical setting. Outcomes may be broadly separated into those attributable to the testing process and those attributable to knowledge of the test results. In general, outcomes attributable to the testing process are direct effects of the test (harms and benefits from the test procedure). Outcomes attributable to the test results are more plentiful and include the patient's response to the test results and outcomes deriving from how the patient and clinician act upon the results.

Bossuyt and McCaffery recently described a useful framework for thinking about patient outcomes attributable to medical testing.[1] They classified outcomes into three groups—outcomes that result from (1) clinical management based on the test results, (2) the direct health effects of testing, and (3) the patients' emotional, cognitive, and behavioral responses to testing. We extend this model by including two additional elements to arrive at five types of outcomes: (4) the legal and ethical effects of testing, which may or may not be appropriate depending on the test under consideration, and (5) the costs of the test. These five categories of outcomes can be associated with the testing process or the test result, or with both. For example, a medical test for HIV may have behavioral responses associated with the testing process: the act of getting an HIV test is associated with getting other tests, such as for hepatitis C. However, behavioral responses to the test result are also conceivable, including high-risk sexual behavior if the test is negative.

Reviewers should also consider an additional axis; namely, who experiences the outcome. The individual being tested is not the only one who can experience outcomes from the testing process. Outcomes may be experienced by family members (e.g., in the case of testing an index person for heritable conditions). Outcomes may be experienced by the population *away* from which resources are diverted by a screening activity (e.g., widespread newborn screening that diverts resources away from population-based smoking cessation activities). Society as a whole may experience some outcomes, as when a test of an individual leads to a public health intervention (e.g., prophylactic antibiotics or quarantine after exposure to an infectious individual) or diversion of resources in order to pay for testing of other individuals. Payers are affected if they need to pay for a treatment of a newly diagnosed condition. Figure 3-2 illustrates these additional considerations.

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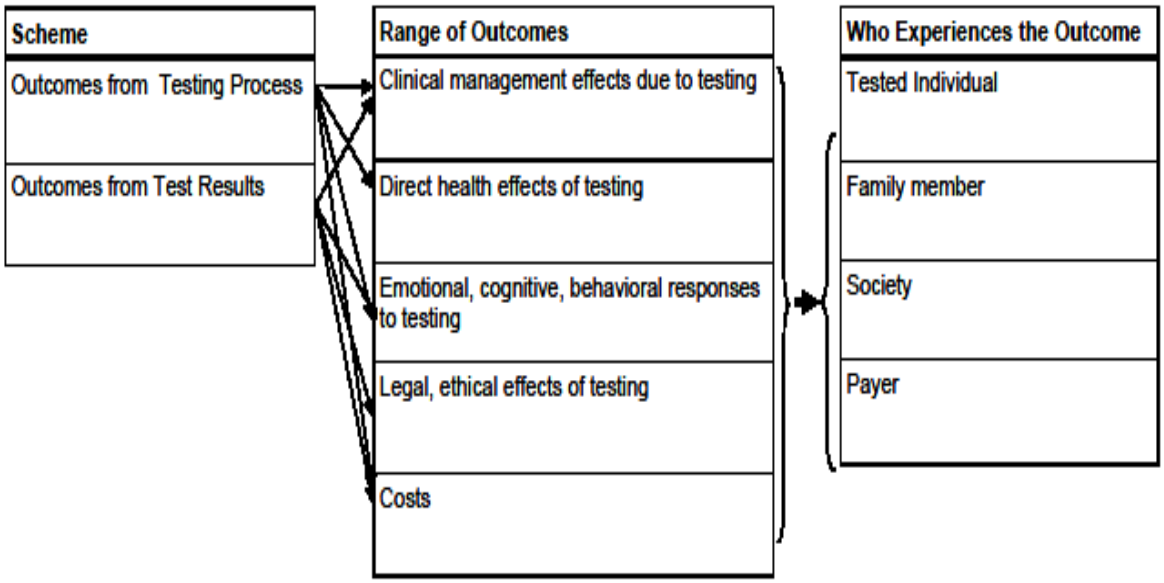
Figure 3-2. Mapping outcomes to the testing process and to testing results



In summary, the range of outcomes that might be included in a systematic review of a medical test is wide. We encourage EPCs to think systematically through this range of outcomes and consider the testing process, the test results, the range of associated outcomes, and the parties that may experience the outcome. These considerations may differ depending on the type of test under evaluation, as discussed below.

Principle 2: Solicit Input From Stakeholders

As described above, the range of outcomes that EPCs might include in a systematic review of a medical test is broad, and expecting such reviews to include all possible outcomes is unrealistic due to time and resource limitations. The Agency for Healthcare Research and Quality's (AHRQ's) *General Methods Guide* recommends that stakeholders be involved at several steps in the systematic review process.[2] We describe additional considerations regarding the role of stakeholders in reviews of medical tests, as their input is particularly relevant to the choice of outcomes for inclusion.

Little to no empiric evidence exists regarding what outcomes are most essential for inclusion in a systematic review. We suggest that the choice of outcomes depends largely on the needs of stakeholders and how they intend to use the review. The stakeholders (or sponsors) who submit requests for evidence reports from the EPCs represent many different interests. Therefore, the outcomes they consider essential will also vary.

For example, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group of the Centers for Disease Control and Prevention (CDC) has sponsored several EPC reports.[3-5] EGAPP uses these reports to generate guidelines that the CDC issues about genetic testing. EGAPP's interests are broad; it aims to maximize the effectiveness of genetic testing at a

societal level. The outcomes EGAPP considers to be relevant are correspondingly broad and range from the analytic validity of the test to the impact of the testing process on family members. When the possible outcomes for inclusion are many, the EPC has a responsibility to work with stakeholders to refine the questions carefully so that the task can be accomplished.

Other stakeholders (e.g., professional societies such as the American College of Physicians) may be most interested in systematic reviews that can be used to generate recommendations or guidelines for practicing clinicians. Therefore, as stakeholders, they may be more focused on how clinical outcomes vary as a result of medical testing, and they may be less interested in outcomes that are more relevant to payers, such as cost-shifting to accommodate costs of testing and downstream costs.

Not infrequently, the primary users of an EPC report are Federal agencies such as the Center for Medicare and Medicaid Services (CMS). CMS is responsible for decisions regarding coverage of their beneficiaries' medical care, including medical tests. Therefore, CMS may specify that the outcome most relevant to their coverage decision is the analytic validity of the test because it would not want to cover a test that inadequately identifies the condition of interest.

EPCs have a role in helping stakeholders understand the breadth of outcomes that could be considered and to think through the clinical questions. Conversely, EPCs also have the responsibility of focusing their key questions so that the selected outcomes can be addressed in accordance with the resources allocated. These choices will depend on the context within which the evidence review is being done. Investigators should assist stakeholders with mapping the range of outcomes depicted in Figure 3-2. This will allow the stakeholders to review the breadth of outcomes and characterize the outcomes as being more or less vital depending on the intended use of the review.

Illustrations

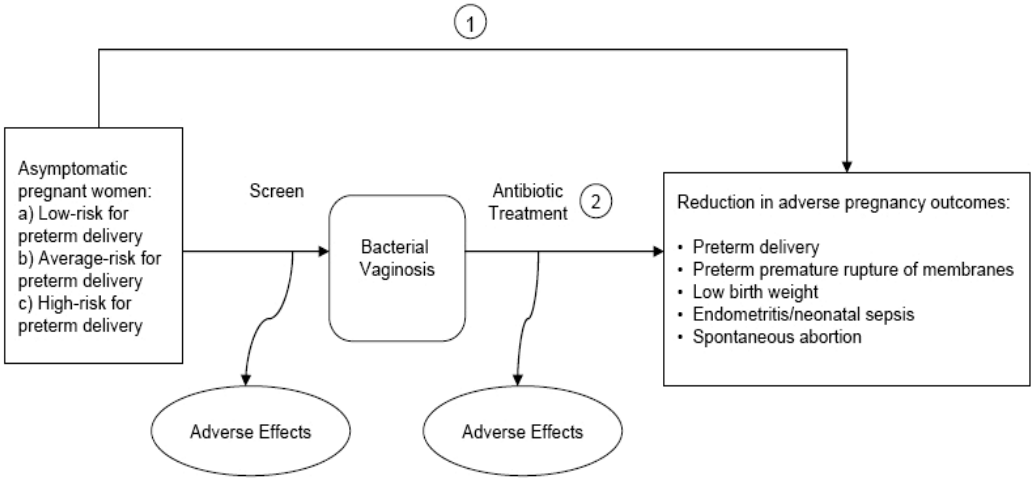
To explain these points in greater detail, we describe three examples: one each of a screening test, a diagnostic test, and a prognostic test. We assume that after EPC investigators have done the mapping proposed above (Figure 3-2), they will discuss the range of outcomes that might be included in a systematic review with stakeholders. In discussing these examples, we consider outcomes that result from the process of testing, outcomes associated with the results of testing, and outcomes that affect the tested individual and others. We conclude with a discussion of additional considerations for evaluating a genetic test. In these illustrations, we are not suggesting that the reviewers should necessarily include any or all of the potential outcomes in their evaluation; we are simply demonstrating how one might go through the exercise of considering each class of potentially relevant outcomes.

Example of a screening test. Screening tests are used to detect disease in individuals who are asymptomatic or who have unrecognized symptoms.[6] In essence, screening tests should be able to separate individuals with the disease of interest from those without the disease and should be used when there is a treatment available and where early treatment is known to improve outcomes.

The United States Preventive Services Task Force (USPSTF) is an independent panel of experts that systematically reviews the evidence and develops recommendations for use of clinical preventive services in the United States. The USPSTF makes recommendations about the use of screening tests such as colonoscopy or mammography. An EPC is sometimes tasked with preparing the supporting systematic review of the evidence.[7-8] Other stakeholders obviously have an interest in screening tests as well, including professional organizations involved in guideline preparation for their practitioners; cases in point are recommendations made by the American College of Obstetrics and Gynecology regarding cervical cancer screening[9] and the American Cancer Society's recommendations for early cancer detection.[10]

To illustrate outcomes in a systematic review of a screening test, we present the example of a systematic review about screening for bacterial vaginosis in pregnant women.[11] This review was first done for the USPSTF in 2001 and was later updated. Figure 3-3 depicts the analytic framework developed by the authors.

Figure 3-3. Screening example: bacterial vaginosis



Critical Key Questions:

1. Does screening for bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
   a. low-risk for preterm delivery?
   b. average-risk for preterm delivery?
   c. high-risk for preterm delivery?
2. Does treatment of bacterial vaginosis during pregnancy in asymptomatic women reduce adverse pregnancy outcomes for those at:
   a. low-risk for preterm delivery
   b. average-risk for preterm delivery
   c. high-risk for preterm delivery

Clinical management effects. The authors of this review addressed whether screening for bacterial vaginosis during pregnancy in asymptomatic women reduces adverse pregnancy outcomes. They included a review of the clinical management effects that would result from antibiotic treatment based on screening results. These include adverse effects of therapies and the beneficial effects of reduction in adverse pregnancy outcomes, such as preterm delivery. The authors might also have explicitly included an outcome that examines whether screening leads to receipt of antibiotic treatment; that is, whether screening leads to a change in clinical

management. This would be a relevant intermediate outcome on the path between screening and the outcomes attributable to therapy.

Direct test effects. Appropriately, the authors of this review did not include outcomes that are a direct result of the testing process because direct effects are unlikely in this example. The screening test (a vaginal swab) should not result in any injury; neither does the test confer any direct benefit because the testing procedure does not treat the infection. The process of screening may, however, include added contact with health care providers, which may confer some direct benefit. Thus, the authors might have included this as a decision-relevant effect.

Emotional, cognitive, and behavioral effects. The authors might also have looked at emotional, cognitive, and behavioral effects from the screening process or from the screening test results. It may have been appropriate to consider outcomes that are associated with screening but are not the result of antibiotic therapy. In thinking about these effects, consideration may be given to the emotional or cognitive effects of the testing process (likely to be few in this example) and the effects stemming from testing positive for bacterial vaginosis, such as emotional responses to a diagnosis of infection leading to either healthier or riskier prenatal activities, or maternal worry as an outcome itself. As with any measure, the EPC may require that the instrument used to measure emotional response be a validated and appropriate instrument.

Legal and ethical effects. Although specifying ethical issues in screening for bacterial vaginosis (which is not a sexually transmitted infection) may seem unnecessary, bacterial vaginosis testing may be done as part of an infectious disease screening for reportable diseases such as syphilis or HIV. Therefore, a review of the effects of testing should consider whether the test being reviewed might be administered with concurrent screening tests that could themselves raise ethical issues.

Costs. The authors of this review did not consider the costs of the test to the patient as an outcome, probably because such costs are unlikely to be very important in this example.

Parties experiencing the effects. The authors of this review on screening for bacterial considered the effects of screening for bacterial vaginosis on the mother and on the fetus or infant. However, they might have also considered other relevant parties; these might include the mother's partner and society since antibiotic resistance is a conceivable outcome from widespread testing and treatment of bacterial vaginosis.

Example of a diagnostic test. We differentiate diagnostic tests from screening tests largely by the population being tested. Whereas screening tests are used in asymptomatic or presymptomatic people, diagnostic tests are applied to confirm or refute disease in symptomatic individuals. The USPSTF mostly makes recommendations about screening tests that may be used in the general population; other organizations are more concerned with ensuring safe use of diagnostic tests in patient populations. Payers are also interested in optimizing the use of diagnostic tests because many are costly. EPCs have been involved in many systematic reviews of diagnostic tests.

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We discuss the example of a systematic review from outside the EPCs that addressed the diagnostic value of 64-slice computed tomography (CT) in comparison to conventional coronary angiography.[12] Stating that their review concerned the "accuracy" of CT, the authors aimed to assess whether 64-slice CT angiography might replace some coronary angiography for diagnosis and assessment of coronary artery disease. This was a very narrowly focused review since an assessment of accuracy alone cannot address the question of whether or when CT angiography should replace conventional angiography. If an EPC were to assess the effectiveness of CT angiography, the investigators should consider the full range of outcomes.

Clinical management effects. Numerous clinical management effects might follow testing for coronary artery disease with CT. The authors of the review focused exclusively on detection of occluded coronary arteries and not on any downstream outcomes from identification of occluded coronary arteries. Individuals diagnosed with coronary artery disease are subjected to many clinical management changes; these include medications, recommendations for interventions such as angioplasty or bypass surgery, and recommendations for lifestyle changes—each of which has associated benefits and harms. All of these may be appropriate outcomes to include in evaluating a diagnostic test. If one test under consideration reports more or fewer occluded coronary arteries (correctly or not) than another, this will be reflected in more or fewer clinical management interventions and their resulting outcomes.

Other conceivable clinical management effects relate to the impact of testing on other health maintenance activities. For example, a patient might defer other necessary testing (e.g., bone densitometry or colonoscopy) to proceed with the CT. We would expect, however, that this would also be the case in the comparison arm. Family members may be affected as well by testing; for instance, they may be called upon to assist the diagnosed patient with future appointments, which may necessitate time away from work and cause emotional stress.

Direct test effects. The test under consideration is a radiographic test. It confers no direct benefit itself (unlike the comparison procedure in which an intervention can be performed at the time of conventional diagnostic angiography). The testing process poses potential harms, including allergic reaction to the intravenous contrast material, renal failure from the contrast material, and radiation exposure. These are all outcomes that could be considered for inclusion. In this example, the comparison test carries comparable or greater risks.

Emotional, cognitive, and behavioral effects. The testing process itself is unlikely to have significant emotional consequences since it is not an invasive test and is generally comfortable for the tested individual (unlike other radiographic procedures such as magnetic resonance imaging). The results of testing could indeed have emotional or behavioral consequences. An individual diagnosed with coronary disease might alter his or her lifestyle to reduce disease progression. On the other hand, an individual might become depressed by the results and engage in less self-care or in riskier behavior. These behavioral effects are likely to affect the family members of the tested individuals as well. However, in this example, the emotional or behavioral effects are expected to be similar for both CT and conventional angiography and therefore may not be relevant for this particular review. In contrast, they would be relevant outcomes if CT angiography were being compared with no testing.

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Legal and ethical effects. Testing could have legal consequences if the tested individual is in a profession that requires disclosure of health threats for the safety of the public; this might arise if, for example, the tested person were an airline pilot. However, this outcome is not expected to differ between CT and conventional angiography.

Costs. The relative costs of the two tests to the insurer and the patient, and the costs of diverting equipment away from other uses, could also be of interest to some stakeholders.

Example of a prognostic test. Prognostic tests are tests used in individuals with known disease to predict outcomes. The procedure itself may be identical to a procedure that is used as a screening test or a diagnostic test, but the results are applied with a different purpose. Given that this is the case, additional considerations for outcomes should be included in reviews of prognostic tests. For example, consider the use of spirometry for predicting prognosis in individuals with chronic obstructive pulmonary disease (COPD). The test is commonly used for making the diagnosis of COPD and monitoring response to treatment, but the question has been raised as to whether it might also predict survival. In 2005, the Minnesota EPC did a systematic review of this topic on behalf of the American Thoracic Society, American College of Physicians, American Academy of Family Physicians, and American Academy of Pediatrics.[13] The discussion below focuses on one of their key questions, which was whether prediction of prognosis with spirometry, with or without clinical indicators, is more accurate than prediction based on clinical indicators alone. Investigators were interested in predicting survival free of premature death and disability.

Clinical management effects. The results from prognostic testing will have effects on clinical management. Although the prognoses for some diseases are minimally modifiable with current treatments (e.g., some malignancies, some dementing illnesses), most prognostic information can be used to alter the course of treatment. In the present example, spirometry may suggest a high likelihood of progressing to respiratory failure and prompt initiation of processes to avert this possibility (e.g., pulmonary rehabilitation efforts, changes in medication, avoidance of some exposures). Conversely, the prognostic information may be used to make decisions regarding other interventions. If the likelihood of dying of respiratory failure is high, patients and their physicians may choose not to proceed with a colonoscopy and other screening procedures from which the patient is unlikely to benefit. Similarly, treatments of other conditions may be of less interest if life expectancy is short.

Direct test effects. Spirometry has few direct test effects, although patients can have adverse reactions to testing, particularly if they are challenged with methacholine as part of the test. In general, it is unlikely that tests used for prognosis are more or less likely to have direct test effects than tests used for other purposes.

Emotional, cognitive, and behavioral effects. We doubt that many emotional or cognitive effects would arise in response to the testing process; spirometry is a noninvasive test that most patients tolerate well. Emotional effects to the results of testing, however, are likely; they may be even more pronounced for prognostic tests than for screening or medical tests because the test may yield more specific information about mortality risk than is usual from a diagnostic test. This could have a range of effects on behavior, including efforts to alter prognosis (e.g., smoking

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cessation). Test results with prognostic information would be expected to affect family members as well.

Legal and ethical effects. Results of tests that provide prognostic information could have legal outcomes too, especially if the tested individual acts in ways that belie the information he has received (e.g., entering into a contract or relationship that he is unlikely to fulfill). In the example being considered here, it is unlikely that the prognostic information from spirometry would actually raise legal issues, but in other cases, such as a test that demonstrates widely metastatic cancer, legal or ethical issues might arise. These legal and ethical effects of testing may reach beyond the tested individual and affect society if many individuals have substantial concealed information that influences their actions.

Costs. The costs of the test to the insurer and the patient, relative to the costs of collecting information from a history and physical examination, could be of interest to stakeholders.

Additional considerations involved in evaluating genetic tests. Paper 11 describes in detail unique issues regarding evaluation of genetic tests. With respect to relevant outcomes, we note only a few considerations here. Most prominent is the effect of genetic testing on family members. Genetic information about the tested individual has direct bearing on family members who share genes. Emotional and behavioral outcomes need to be considered, as well as ethical outcomes if family members feel pressured to proceed with testing to provide better information for the rest of the family. A second issue is the possible impact of testing on health insurance eligibility. Recent legislation in the United States prohibits the use of genetic test results to exclude an individual from health insurance coverage, making this less a relevant outcome than in the past. This policy varies worldwide, however, and may be a relevant consideration in some countries.

Summary

In specifying and setting priorities for outcomes to address in systematic reviews of medical tests, EPCs should remember these key points:

- Consider both outcomes relevant to the testing process and outcomes relevant to the test results.
- Consider inclusion of outcomes in all five domains: clinical management effects; direct test effects; emotional, cognitive, and behavioral effects; legal and ethical effects; and costs.
- As part of the process of choosing the outcomes for inclusion, consider to whom the outcomes are most relevant.
- Given resource limitations, prioritize which outcomes to include. This decision depends on the needs of the stakeholders, who should be assisted in prioritizing the outcomes for inclusion.

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