Evidence and Transparency Recommendations to Support Coverage and Reimbursement Decisions for Medical Testing

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Introduction

Medical tests are an important yet often under appreciated service in health care. They are mainly comprised of laboratory tests (in vitro diagnostics) and medical imaging tests and are undertaken to identify the presence or absence of a disease or medical condition. While laboratory tests comprise only about 1.6% of all Medicare costs, their findings influence as much as 60-70% of health care decision-making[1]. By enabling accurate detection of health risks and disease at earlier stages and improving treatment and disease management, while diminishing subsequent health problems and their associated costs, laboratory testing and medical imaging serve a key role in the health value chain. It is expected that the number of tests developed and marketed will continue to increase over the next few years, as the research community continues to mine the emerging and new knowledge about human health generated by our robust medical research infrastructure.

The Current Environment for Test Evaluation and Reimbursement

Laboratory test kit devices and components that are manufactured for commercial distribution by in vitro diagnostics device manufacturers and medical imaging products are generally subject to Food and Drug Administration (FDA) premarket clearance or approval. The FDA generally has chosen not to exercise its regulatory authority over in-house testing. Tests developed in-house by the clinical laboratories that perform them ("Laboratory Developed Tests" or "LDTs") are overseen by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"). While greater evidence of clinical utility is currently required for FDA clearance or approval of test kits and imaging products than for LDTs, in none of the cases are randomized, controlled trials, technology assessments or cost-effectiveness evaluations routinely undertaken. Furthermore, there are no uniformly applied evidence-based methods to inform coverage and reimbursement decisions for medical tests, and decisions often seem to be ambiguous.

As the volume of tests increase, some health care payers are beginning to require substantially more clinical data and information on the value of technology from device manufacturers and laboratories (often rising to the level of cost-effectiveness modeling). CMS is also pursuing new policies such as "coverage with evidence determination", in which coverage of some tests or procedures may be contingent upon the reporting of data from prospective, practical clinical trials. It is expected that such requirements will increase in number and stringency.

Coverage and reimbursement decisions for medical tests will likely continue to move towards an evidence- and value-based approach, using tools similar to those that have largely been adopted for drugs by international government decision making organizations and many U.S. health plan pharmacy and therapeutics committees.

Today's environment for the coverage and reimbursement of medical tests is

very much like the conditions that prevailed years ago with prescription drugs, prior to the evolution of organized technology assessment and formulary management tools, whether undertaken internally by a carrier, or through a PBM. These existing pharmaceutical models will likely guide the evolving process of decision making for coverage and reimbursement of medical tests, as payers increasingly request information regarding the clinical uses, evidence of accuracy and benefit, and cost-effectiveness for a given test.

Generating and Supply Clinical and Economic Evidence

In light of this changing environment, we describe a process designed to improve the availability, timeliness, quality and presentation of the evidence available at the point that a coverage and reimbursement decision is considered; a process that will also increase the transparency and uniformity of the information that payers request from laboratories or device manufacturers in consideration for coverage. This process requires that producers of medical tests develop and submit packets of clinical and economic evidence (dossiers) in response to a specific request from a payer or health system. Producers of medical tests will have the opportunity to present a full and scientific portfolio of clinical and economic evidence to support coverage and reimbursement decisions.

The process calls for the parties to engage in substantive discussions so that requests are clearly understood and replies are specific to the needs of the payer. Given the amount and variety of medical tests available, many tests will not warrant the creation of an evidence dossier. It is expected that the payer will identify medical tests whereby information of the type described below would be beneficial to include in the reimbursement and coverage decision process. However, in areas where there is debate about the utility and pricing of certain medical tests—especially for newer tests, this process will be a valuable tool in the coverage and reimbursement process.

This document outlines a structured list of evidentiary elements that would comprise a complete dossier for a new medical test. It is expected that payers would request and use this information as part of a fully transparent and evidence-based coverage and reimbursement process.

EVIDENCE AND TRANSPARENCY RECOMMENDATIONS

The following guidelines are comprehensive by design. It is understood that in many cases all of the recommended information will not be available.

Section 1. PRODUCT INFORMATION
This section comprises information about the medical test itself.

Product Description:
Producers of medical tests are asked to provide detailed information about their product. The product description consists of information that traditionally has been incorporated into an evidence report and includes the following:

a) Proprietary name of test and name of manufacturer or clinical laboratory
b) Intended use: Diagnosis, prognosis and management, risk assessment, treatment, pre-symptomatic testing
c) FDA cleared or approved and other studied indication(s), if applicable: A detailed discussion of the cleared or approved Food and Drug Administration (FDA) indications and the date approval was granted (or is expected to be granted) must be included. FDA clearance or approval is not required for Laboratory Developed Tests (LDTs), and therefore is not applicable to those tests.
d) Test type: technical i.e. immunohistochemical, flourescent in situ hybridization (FISH), gene expression profile, magnetic resonance imageing (MRI), other specify
e) Target: Please describe the test target (i.e. biomarker, microarray pattern, imaging target, other specify)
    a. If genetic test, please indicate:
        i. Gene(s)
        ii. Mutational spectrum
f) Please indicate if it is a stand alone test or multiple tests
    - If multiple, indicate whether parallel or series
g) Indication and target population(s)
h) Prevalence of disease/condition in target population
i) Prevalence of biomarker (if applicable).
    - If genetic test, report the estimated gene frequency (carrier frequency and allele frequency)
j) Analytic Validity: Measure of how well a test identifies the target or marker it is intended to identify.
    - Sensitivity: how often is the test positive when the marker is present?
    - Specificity: how often is the test negative when the marker is not present?
    - Accuracy: how often is the test correct?
    - Precision: reproducibility of the test (i.e. average replicate error)
    - Area under the receiver operating characteristic curve

- Confirmatory test(s) for positive results
- Reference standard test for positive and negative results
- Proportion of patients where the test is expected to give an indeterminate result

k) Clinical Validity (for each target population): Measure of how well a test identifies the disease or medical condition of interest.
    - Sensitivity: how often is the test positive when the disorder is present?
    - Specificity: how often is the test negative when the disorder is not present?
    - Positive predictive value (PPV)
    - Negative predictive value (NPV)
    - If genetic test,
        - What is the genotype/phenotype relationship?
        - What are the genetic, environmental or other modifiers?
    - In which populations has the test been validated?
    - Reference standard test for positive and negative results
l) Clinical Utility in target populations
    - Interventions based on test results (positive and negative)
    - Efficacy/effectiveness of interventions (impact on disease progression, morbidity, quality of life, and survival)
m) Copy of product label (if available).
n) CPT coding

Section 2: PLACE OF MEDICAL TEST IN CLINICAL PRACTICE

DISEASE DESCRIPTION (LIMIT TO 2 PAGES PER DISEASE) The disease description should include the disease and characteristics of the patients in the target population.

Disease specific descriptive information should include, but not be limited to:

- Epidemiology and relevant risk factors
- Pathophysiology
- Clinical presentation
- Societal and/or economic impact

APPROACHES TO DIAGNOSIS AND PROGNOSIS (Limit to 2 pages per major indication or use)

Present a brief summary of information from the literature for each topic:

a. Approaches to diagnosis - principal options / practice patterns
b. A description of alternative diagnostic options
c. The anticipated uses of the **test** in patient management (e.g. first line)
d. Relevant treatment guidelines from national or international bodies
e. The expected intermediate health outcomes
f. The expected net health outcomes of treatment and
g. Other key assumptions and their rationale.

The generalizability of these findings to the payer population should be addressed. Discuss the implications of any differences that exist between the literature and typical practice patterns and patient populations.

SECTION 3: SUPPORTING CLINICAL INFORMATION

KEY CLINICAL STUDIES: [3 page maximum per study; please complete evidence tables in the format presented in appendix A]

Submit summaries of the key clinical studies that have been conducted, **whether published or not**, in each of the following categories:

1. Analytical and clinical validation and utility studies [No more than 3 pages per study + evidence table]
2. Prospective effectiveness trials; randomized, before-and-after, etc. [No more than 3 pages per study + evidence table]
3. Case series [No more than 3 pages per study + evidence tables]
4. Retrospective studies [No more than 3 pages per study + evidence table]
5. Systematic reviews and meta-analyses. [No more than 3 pages per study + evidence table] Place particular emphasis on the inclusion and exclusion criteria and main outcome measure(s) for studies analyzed.

Where there are National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs), such documentation should be included. Some NCDs will now be issued under the new Coverage with Evidence Determination (CED) policy, under which coverage will be granted contingent upon the submission of data from prospective, practical clinical trials; if applicable, information relevant to the CED should be submitted.

Studies reported in this section should be summarized in a clear, concise format **and include all relevant positive and negative findings.** The payer is particularly interested in head-to-head comparison clinical studies between the proposed product and the principal comparators. Summaries of trial results of key comparator products are desirable but not required. Discuss important study findings and comment on their implications for the patient populations represented by the payer. Systematic reviews or meta-analyses may be discussed. In the appendix, include a reprint or unpublished manuscript of each study discussed or referenced.

All of the following items that apply should be included in the study summaries:

a) Name of the clinical study, location and study date;
b) Setting and location of study
c) Study design, Research question(s)
d) Inclusion and exclusion criteria;
e) Patient characteristics (demographics, number studied, disease severity, co-morbidities);
f) Intervention and control groups

g) Patient follow-up procedures (e.g., if an intention-to-treat design is used, were drop-outs followed and for what time period?);
h) Treatment/follow up period
i) Clinical outcome(s) measures;
   - Outcomes evaluated
   - Delineate primary vs. secondary study endpoints and their corresponding results
j) Other results/outcomes reported (e.g., quality of life, assay performance);
k) Principal findings
l) Statistical significance of outcomes and power calculations;
m) Validation of outcomes instrument (if applicable);
n) Compliance behavior;
o) Generalizability of the population treated;
   - Relevance to enrolled populations.
p) Publication citation(s)/references used.
q) Medical test producers should state whether trials or other studies for the product are registered in a public trials registry, and if so, provide access information (e.g. www.clinicaltrials.gov).

EVIDENCE TABLE SPREADSHEETS (NOTED ABOVE) OF ALL PUBLISHED AND UNPUBLISHED STUDIES:

Information from all known studies on the test should be summarized in evidence tables (spreadsheet format) noting which studies were presented previously (items 1 - 5). **Include negative or null findings as well as positive findings.**

- Citation, if published
- Setting and location
- Sample size
- Primary Endpoints
- Secondary Endpoints
- Treatments
- Design and research question(s)
- Inclusion/exclusion criteria
- Statistical significance
- Results
- Study dates

SAFETY DATA

Please provide summaries of the key safety issues including all relevant studies. These could include estimates of the direct risks of tests and the risk and patient-related consequences of false positive and false negative results. If a risk management program is available for the medical test, a complete description of the program and payer, prescriber, producer and patient processes should be provided.

Section 4: Outcomes studies and Economic Evaluation Supporting Data [3-4 pages maximum per study]

Provide summaries addressing items a-q (see Section 3 above) for all studies in each of the categories listed below. Studies reported in this section should be summarized in a clear, concise format **and include all relevant positive and negative findings.** The payer is particularly interested in head-to-head comparison studies between the proposed product and the principal comparators. Analyses that focus on actual outcomes rather than intermediate endpoints are preferred. Summaries of principal trial results of key comparator products when these data are referenced or used in economic models are extremely helpful, but not required. Discuss important study findings and comment on their implications for the patient populations of the payer. In the appendix, include a reprint of each study discussed or referenced.

1. Economic modeling studies [No more than 3-4 pages per study + evidence table]
2. Cross-sectional or retrospective costing studies and treatment pattern studies
3. Systematic review articles
4. Quality of life studies
5. Patient reported outcomes (PRO) studies, including quality of life studies
6. Other relevant economic studies (cost-utility, cost-benefit, cost-consequence)
7. Prospective, trial-based cost-effectiveness studies [No more than 3-4 pages per study + evidence table]

Evidence table spreadsheets (noted above) of all published and unpublished outcomes studies.

Information from all relevant outcomes studies on the product should be summarized in evidence tables (spreadsheet format) as indicated in Section 3, noting which studies were presented previously (items 1 – 7 above). **Include negative or null findings as well as positive findings.**

Section 5. ECONOMIC AND BUDGET IMPACT M O D E L I N G R E P O R T [maximum 20 pages]

This section contains a detailed report of any studies undertaken to estimate the economic value or financial impact of the medical test to the payer. Many researchers have expressed concern over the quality of some published economic evaluations.[2] [3] Since the focus of this portion of the dossier is a comprehensive assessment of available evidence, the number of studies considered will not be restricted by imposing methodological standards. However, the payer and its medical and economic consultants will judge the merit of individual studies based on published standards for conducting and reporting these analyses.[4] [5] [6] [7] [8] [9] [10]

MODEL OVERVIEW

When comparing two or more interventions, properly constructed model-based evaluations can combine evidence on health consequences and costs from many different sources, including data from clinical trials, observational studies, claims databases, case registries, public health statistics and preference surveys, and a measure of uncertainty in any estimates. The goal is to evaluate the value of the product and project the health and economic consequences to the payer of potential coverage and reimbursement changes.

Laboratories and device manufacturers are strongly urged to provide cost-effectiveness models or analyses supporting the value of their test from a payer perspective (vs. societal or other perspective). This approach is the best means to accomplish this goal because they establish the value of a new technology relative to the most clinically appropriate comparator(s). Ideally, these models/analyses are disease-based and take into account the impact of the new technology on the clinical outcomes for the target population, and include evidence on the incidence of the disease or condition in the target population, the medical care required to diagnose and treat the disease, the relative and absolute risk reductions offered by the technology, survival and quality of life impacts, and the costs of the interventions.

Models developed in this manner can:

- Aid decisions regarding the addition of a new test to the fee schedule,
- Help define a test's specific role, and
- Assist in creating benchmarks against which the test's future performance can be measured.

In contrast, 'product cost' or budget impact models, by strict definition, are not used to establish the overall value of new technologies because they do not include the impact of the technology on clinical outcomes, medical resource use and adverse effects. These models provide an estimate only of the financial impact of a new technology on the laboratory/testing budget because they typically only include direct costs, network or other discounts, rebates, and other benefit design impacts. Although these models may be provided as part of the laboratory's or device manufacturer's submission, they are not central to the

evidence- and value-based decision making process. These limitations should be noted and the budget impact model presented separately from the cost-effectiveness model.

Cost-effectiveness analyses should depict the following:

a) Disease or condition, patient population, natural history, clinical course and outcomes.
b) Primary diagnostic/treatment options and the treatment process for each option. Each process of treatment utilizing a specific product or other intervention follows a clinical pathway. If the [---] employs a treatment guideline for this condition, this framework should be followed. Alternative clinical pathways presented by the laboratory or device manufacturer may also be considered.
c) Patient population eligible for treatment.
d) Product and other medical resources used when following clinical pathway (include treatments for complications related to treatment).
e) Costs of product and other medical resources consumed within each clinical pathway.
f) Outcomes of diagnosis/therapy for each clinical pathway, including expected proportion of treatment failures and mean or median time to failure, if known. These outcomes can be broadly and uniquely defined by the laboratory or device manufacturer and can be modeled from other data sources. The laboratory or device manufacturer should address the relevance of the selected outcomes measure and generate both baseline and projected outcome impact assessments.
g) Incremental cost and outcomes analysis presented in either cost/consequences tables or as cost-effectiveness ratios.
h) Time horizon for expected costs and outcomes. Suggested time horizons include 1-year, 5-year and over the course of the disease. The exact time horizon used will depend on the natural course of the disease. In some cases, multiple time horizons might be appropriate.

In addition, the medical test producer is requested to:

i) Separate the volume of resources utilized and the unit costs for each resource.
j) Perform sensitivity analyses on pivotal estimates and assumptions [in presentation section]
k) Consult with the payer staff in the early stages of model development to ensure the incorporation of appropriate comparator products and endpoints.
l) Present the following information in tabular form: data and sources, assumptions, total resource utilization, total costs, total effectiveness, incremental costs, and incremental effectiveness. Measures of total and incremental effectiveness should incorporate natural units (e.g. clinically important events avoided) as well as quality-adjusted survival when possible.

The analysis should be based on scientifically appropriate clinical trial, epidemiological and economic data and should be capable of being modified by the payer to better reflect practice patterns in their enrolled population. For the analysis and model to be realistic, it may be necessary to include data from the payer, e.g. demographic data. Data derived from expert panels are not generally acceptable, especially for key clinical and treatment pattern variables. However, this approach may be reasonable for other variables where estimates are not available through literature, databases, trials or other normal sources.

The model framework should consider recommendations published by the *Panel on Cost-Effectiveness in Health and Medicine* convened by the U.S. Public Health Service.[11] **Although no standard model approach is proposed, we recommend that producers and users of modeling studies subscribe to the sound guidance provided by the ISPOR Good Practice Modeling Principles**.[12]

We have found that models have certain desirable qualities. These are listed in Appendix B and are not meant to prescribe model development or impede good scientific design. Rather, this list is to provide some guidance to the laboratory or device manufacturer as to those elements of an economic model that are desirable to the payer.

PARAMETER ESTIMATES FOR MODELS

In general, the best quantitative estimates of clinical effectiveness are required, with uncertainty in the estimate(s) handled analytically via sensitivity analysis.

PERSPECTIVE, TIME HORIZON AND DISCOUNTING

The payer perspective is recommended for the primary analysis. We welcome a societal perspective analysis as a secondary evaluation. The analytic model should consider a time horizon that is appropriate to the diagnostic strategy being studied and reflect the decision-making and financial and budget constraints of the payer. When appropriate, adjustment for the time preference should be incorporated and should follow US PHS Panel recommendations.[11]

ANALYSES

Analyses should follow accepted approaches for economic models. Transparency and clarity of presentation are a necessity. Therefore, we recommend that all data and calculations be contained in the model spreadsheet and visible to the user. This will help ensure transparency and allow the user to verify that the data used in the model is appropriate. The need for and value of transparency is widely recognized and can provide some protection against the negative effects of bias and error. The users of models need to be able to understand all steps in the modeling process to improve their understanding of the key factors and variables in the model and its limitations.[13] Therefore, researchers are encouraged to focus efforts on the clarity and transparency of results.

All assumptions must be presented and justification should be provided. Also, detailed notes that show the flow of data through the model are recommended. All calculations should be explained in a simple straightforward manner to allow a non-health economist to comprehend the analysis. This information may be accessible both in a manual form as well as shown directly in the model, to maximize the ease of review.

Comprehensive (all variables) one-way sensitivity analysis is highly recommended. Other evaluations of uncertainty such as confidence interval determination, best/worse case scenario analyses, net-benefit and acceptability curve estimation are also useful.

When a test is to be used in the management of more than one disease, its impact should be modeled for each approved indication, unless a reasonable case can be made for a single model. Because of the complexity involved in constructing a model that simultaneously addresses several indications, we recommend using a separate model for each condition.

PRESENTATION OF MODEL RESULTS

At a minimum, laboratories and device manufacturers should present models and model results as follows:

1. Provide a figure displaying the structure of the model (e.g., a decision tree or Markov model). A simplified schematic diagram may be used for ease of presentation, but a detailed figure should also be included.
2. Provide a table listing **all** of the model inputs, including probabilities, costs, and utility estimates if appropriate, including references to sources for inputs used.
    a. Provide a range of values upon which sensitivity analyses are based for each input.
    b. Include references in the table for all inputs, including ranges.
    c. Note in the table estimates that lack supporting evidence.
3. Provide an explicit list of model assumptions, including assumptions about comparator interventions, clinical events, patient management, and costs.
4. Present the disaggregated results in a table (e.g., cost-consequence style, with costs presented separately from health outcomes).
    a. Further disaggregate costs into total medical and pharmacy costs and then various resource components including drug costs, as appropriate.
    b. Include the total cost of implementing the therapy and the resulting cost offsets.
    c. Finally, present incremental cost-effectiveness ratios, if appropriate.
5. Present one-way sensitivity analyses on all model inputs in a figure (e.g., tornado diagram) or a table. Ideally, the sensitivity diagram should be dynamic and allow the health system to pick specific variables to evaluate and to determine the upper and lower limit for each.
    a. Clearly present the model inputs or assumptions that drive the difference in costs, effects, and incremental cost-effectiveness.

b. When appropriate, present multiple sensitivity analyses (e.g., 2-way, best/worst case scenario, probabilistic)

Media: In addition to the written report, the medical test manufacturer should provide a transparent, unlocked copy of the model without the graphical interface. It should be presented on a CD ROM as an Excel workbook, ASCII tab-delimited file or an alternative format that is agreed upon by the payer or its consultants and the medical test producer. The model should be transparent, i.e., designed to allow staff or consultants to investigate the assumptions and calculations, and to perform independent sensitivity analyses by varying individual parameters. The payer **will retain this model for internal analyses and *will not release it to any other party*.** Manuscripts that support the development and reporting of the model are to be attached as appendices.

SECTION 6: PRODUCT VALUE AND OVERALL COST [2 PAGE MAXIMUM]

This section of the submission recommendations represents the principal opportunity for the medical test producer to communicate the overall clinical and economic value of its test to the payer. The medical test producer should briefly summarize all clinical and economic information presented previously and state the expected per unit test cost. Based on this information, the producer should articulate a value argument to justify these expected expenditures for this test in the context of its anticipated effects on the clinical and other outcomes and the economic consequences for the payer. Through this process, test value is redefined as both parties move beyond cost containment to focus on optimizing test utilization in an environment of limited resources.

SECTION 7: SUPPORTING INFORMATION

REFERENCES CONTAINED IN DOSSIERS

Submissions should list and provide copies of all relevant clinical and economic references.

Appendix A: Reporting Format for Clinical Evidence

[Note: This is a generic table format. You can change column headings, subdivisions, etc. as necessary to fit the data you are reporting. A general overview of these data including the key "take home" points should be given in the main report. Detailed comments about a particular study, such as weaknesses in data or study design, can be put in the right hand column of this table.]

Ref.	Test /Intervention	n	Setting, location, and study dates	Patient demographics	Study Design	End points	Results/ Comments
1.							
2.							
3.							
4.							
5.							

Appendix B: Desirable Qualities of Economic Models for Inclusion in Submissions

Model Structure

- To the extent feasible, the model, its logic and its calculations should be clear and self-documenting using best practices for formatting, comments and explanatory guides such as text boxes. [39]
- A transparent disease progression model with an appropriate time horizon for a health system.
- Diagnostic and treatment pathways that are relevant to the coverage and reimbursement decision and correspond to nationally recognized or treatment guidelines. To help illuminate the proposed treatment pathways, the laboratory or device manufacturer is encouraged to provide decision trees.
- Usual clinical practice, including relevant comparators, is included in the model.
- Mathematics and calculations included in the model are accurate and available for inspection.
- Allowance for analysis of relevant sub-populations (age, gender, co-morbidities) where applicable.
- An interactive model that allows the health system to incorporate its own data (membership size, prevalence rates, cost estimates, etc.) or, if requested, use default data, such as national norms.

Data

- Sources of data are clearly defined and from the most recent studies.
- Data have been interpreted and accurately incorporated into the model.
- Uncertainty is defined, especially for key variables.
- Linkages between intermediate and longer-term endpoints are valid and based on reasonable scientific evidence.
- Assumptions that drive the model are clearly identified.

Results/Output

- Outcomes need to be relevant to coverage and reimbursement decision.
- Incremental analyses of both health effects and costs.
- Results are verifiable and traceable back to the inputs.
- Uncertainty in model and data tested in a reasonable fashion and reported.
- Results presented in such a fashion that facilitates incorporation into subsequent reviews and monographs.

References:

[1] The Lewin Group. The Value of Diagnostics Innovation, Adoption and Diffusion into Health Care. Available at http://www.advamed.org/publicdocs/thevalueofdiagnostics.pdf. Accessed August 2005.

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[11] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York, NY, Oxford University Press, 1996.

[12] Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice fordecision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices – modeling studies. *Value Health*. 2003; 6: 9-17.

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