Clinical Test Evaluation Process (CTEP) M00096

Version 5.0

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SECTION 1: BACKGROUND

1. Background
1.1. Objective

The MolDX Clinical Test Evaluation Process (CTEP) describes the method Palmetto GBA uses in its technical assessment process to evaluate newly developed tests or for established tests that have not been validated for clinical utility (CU) and analytical and clinical validity (AVCV). In order to determine if a test meets the Medicare reasonable and necessary criteria, a test must demonstrate CU and AVCV. Although CU and AVCV are separately addressed in this document, the MolDX Team will evaluate the two components at the same time. This document further defines the evaluation process and does NOT represent a change to the TA process as stated in the active Molecular Diagnostic Testing (MDT) LCD.

1.2. CMS Instructions

The Centers for Medicare and Medicaid Services (CMS) emphasized the need to follow the ACCE criteria developed by the Centers for Disease Control and Prevention (CDC).

“The methodology will use an evidence framework that is consistent with the ACCE criteria developed by the CDC for the evaluation of genetic tests as articulated from 2009 onward in the application of the ACCE criteria to Medicare coverage in its national coverage determinations (NCDs) pertaining to molecular diagnostic tests.”

In addition to these criteria, the MolDX process strives to utilize proven and accepted industry standards currently in place. This document details these additional standards to enhance understanding.

Centers for Disease Control (CDC) ACCE Criteria Overview
SECTION 2: CLINICAL UTILITY (CU) TEST TRACKS
(See Section 10 Figure 1)

Once the MolDX team determines a submitted dossier is complete, the test is categorized into one of the following three tracks for CU:

1. **Expedited CU for FDA Companion Diagnostics (FDA CU):** Applies when a clinical test has been submitted as part of a successful new drug application (NDA) and is the exact test specified in the FDA-approved package insert (PI) of the associated drug, or is appropriate based on the FDA-approved labeling for the companion diagnostic.

2. **Expedited CU for Partner Specialty Societies or Group Approved Test (PSS CU):** Applies when a test has already been formally reviewed by a MolDX-designated specialty society or other group, which has recommended the test as a “standard of care.”

3. **Traditional CU (CU):** Modeled after the FDA New Drug Application (NDA) process; approval is based on published, peer-reviewed trial information.
SECTION 3: ANALYTICAL AND CLINICAL VALIDITY (AVCV)
TEST TRACKS
(See Section 10 Figure 4)

To demonstrate the AVCV, the test is categorized into one of the following two tracks:

1. **Expedited AVCV for FDA Companion Diagnostics (FDA AVCV):** Applies only when a test has been approved by the FDA as a companion diagnostic and adheres to the intended use (IU) and indication(s) for use (IFU) approved by the FDA.

2. **Traditional AVCV:** All tests must demonstrate AVCV as evaluated by both subject matter experts (SME) and the MolDX executive committee. This track includes the review of evidence as outlined in MolDX CTEP: Analytical and Clinical Validation Guidelines.
SECTION 4: EXPEDITED FDA CU AND AVCV FOR FDA COMPANION DIAGNOSTICS
(See Section 10 Figure 1)

When the FDA has already performed a systematic review of the proposed clinical intervention and associated companion diagnostic and has identified the appropriate indicated use (IU) and indications for use (IFU) for the test and treatment, evaluation by MolDX of the same information is unnecessary. Therefore, the MolDX Team will confirm FDA approval for CU and AVCV. As for all Medicare services, the drug and the test must meet the Medicare reasonable and necessary criteria prior to final approval.

From the FDA’s website:

“A companion diagnostic device can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.”

Because the nuances of testing (including, but not limited to, differences in analytical and clinical sensitivity and specificity, reproducibility, etc.) can impact results or their interpretation, the final coverage decision may be based on specific FDA approved labeling. When the FDA does NOT specify the platform for the companion diagnostic, the test must follow the Traditional CU and AVCV tracks.
SECTION 5: EXPEDITED CU FOR PARTNER PROFESSIONAL SOCIETIES OR GROUPS (PSS CU)
(See Section 10 Figure 2)

Many professional societies and academic groups consistently promote cost-effective, evidenced-based healthcare and publish guidance documents to educate and standardize treatment protocols. Whenever possible, Palmetto GBA will collaborate with specialty groups and societies to advance appropriate molecular testing. When possible, existing guidelines may be applied to the review and approval process. (Figures 1 and 2)
SECTION 6: TRADITIONAL CLINICAL UTILITY (CU)
(See Section 10 Figure 3)

6.1. MolDX Clinical Trial Designations (mCTD)

The MolDX Team will review each clinical utility trial included in the dossier and assign a MolDX Clinical Trial Designation (mCTD). These designations are as follows:

**mCTD 3A** - Randomized, Prospectively Controlled Trials (PCT) directly demonstrate that therapeutic intervention based on test results leads to statistically and clinically significant improvement in patient outcomes compared to a currently accepted standard of care. End points of the trial must be widely considered to be clinically appropriate by the medical community (e.g., overall survival). The trial must be adequately powered to address the outcome of the intervention based on the test.

**mCTD 3B** - Prospective-Retrospective Trials (PRT) use archived samples from a previously reported prospective controlled trial to demonstrate that treatment based on a molecular test result in a specified patient population is associated with improved outcomes in a statistically and clinically significant manner versus a currently accepted standard of care. The chosen samples and study design must be sufficiently characterized and powered to permit definition of the indications for use and the intended use population for the test.

**mCTD 2A** - Prospective Observational Studies (POS) involve prospectively enrolling patients in a registry, treating according to a defined pathway using the molecular test as an integral part of the care plan, and demonstrating statistically and clinically significant improvement in healthcare outcomes versus a currently accepted standard of care as shown by contemporary, although historical controls.

**mCTD 2B** – Retrospective Data Modeling (RDM) involves complex data modeling using large data sets to demonstrate statistically and clinically significant improvement in healthcare outcomes when a given molecular test is used to guide treatment versus a standard of care approach.

**mCTD 1** - Retrospective Observational Studies (ROS) do not stipulate treatment pathways or follow-up based on results from the molecular test.

**mCTD 0** - Preclinical Studies (PS) involve only preclinical data (e.g., animal or in vitro experiments), or related studies or trials.

6.2. Preliminary MolDX Level of Evidence Determination

A preliminary MolDX level of evidence (mLOE) will be calculated based solely on the mCTD of the submitted trials according to Table 1. If the preliminary mLOE is below IIB, then the application will be rejected with an explanation of the findings. If the mLOE is IIB or greater, the test will undergo a full clinical review (Figure 3).

Table 1: MolDX Level of Evidence

<table>
<thead>
<tr>
<th>mLOE</th>
<th>Strongest CU Trial mCTD</th>
<th>Other CU Trial(s) mCTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>3A</td>
<td>3A or 3B</td>
</tr>
<tr>
<td>IB</td>
<td>3A</td>
<td>2A or 2B</td>
</tr>
<tr>
<td>IB</td>
<td>3B</td>
<td>3B</td>
</tr>
<tr>
<td>IIA</td>
<td>3B</td>
<td>2A or 2B</td>
</tr>
<tr>
<td>IIB</td>
<td>2A or 2B</td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>2B</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2A or 2B</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
6.3. Establishing the Final MolDX Level of Evidence (mLOE)

During the full clinical review process, subject matter experts (SME) review the submitted clinical trials and assign a final mLOE based on the trial type and its clinical relevance. Upon completion of their analysis, the assigned SME will supply a written report to the MolDX Executive Committee for final review.
SECTION 7: MOLDX FINAL REVIEW

7.1. MoIDX Executive Committee (EC) Review

Once the CU and AVCV analyses have been completed, the EC will review all information and apply Medicare reasonable and necessary criteria to make a final coverage decision and rationale for the findings. Final decisions may include noncovered, covered, limited coverage, or coverage with data development (CDD).

Although Palmetto GBA considers the work performed by the FDA, the PPS and such groups, in addition to findings from the SME, the final coverage determination resides with the EC in compliance with current regulation. Every effort will be made to achieve consensus prior to the finalization of coverage decisions.
**SECTION 8: MOLDX REVIEW STEPS**

The MolDX Team and MolDX consultants perform the following steps during a technical assessment to demonstrate CU:

1. Review dossier to determine if all required documents are included and identified with MolDX ID, which creates a valid TA submission
2. Categorize test by appropriate track for CU and AVCV assessment
3. MolDX Team reviews submitted clinical trials and assigns a MolDX Clinical Trial Designation (mCTD).
4. If the mLOE is greater than IIB, redacted test information assigned to at least two SME for CU evaluation and clinical recommendation
5. MolDX Team assigns and sends redacted test information to up to two SME for AVCV evaluation and recommendation using the elements outlined in the MolDX CTEP: Analytical and Clinical Validation Guidelines
6. SME recommendations reviewed by EC
7. EC makes final determination regarding the CU and AVCV
8. EC review tests that demonstrate CU and AVCV for Medicare reasonable and necessary criteria.
9. EC determines one of the following for test: covered, limited coverage, CDD, noncoverage
10. Tests determined as covered, limited coverage, or CDD, progress for pricing determination
SECTION 9: MOLDX FINAL REVIEW APPEAL

At the developer’s request, the EC will meet with the developer to discuss the completed review and initial coverage decision. The developer will have 60 days after issuance of the initial decision to ask for redetermination of the initial coverage decision. A final written response from MolDX will be provided within 60 days of receipt of the developer’s request for redetermination.
SECTION 10: FIGURES

Figure 1: MolDX Clinical Utility Algorithm for a New Clinical Test
Figure 2: PSS Expedited Clinical Utility Review Process
Figure 3: Traditional Clinical Utility Review Process
Figure 4: Analytical and Clinical Validity (AVCV) Review Process

New Clinical Test

FDA approved companion diagnostic (FDA AVCV)

Yes → Coverage

No

Subject Matter Expert (SME) Review

MolDX Executive Committee (CE) Review

Satisfies AVCV Requirements

Yes → AVCV Accepted*

No → Non-coverage

Company Request For Redetermination

MolDX Executive Committee (CE) Final Review

Final AVCV Decision*

* CU still required for coverage
SECTION 11: SELECTED REFERENCES


