

History: NYSDOH Wadsworth Center's Clinical Laboratory Evaluation Program (CLEP) and its Clinical Laboratory Reference System's (CLRS) scientific staff adopted a three-tiered model for the review and approval of laboratory-developed tests (LDT) beginning November 14, 2016.

Update: Effective June 3, 2019, CLEP and CLRS recognizes two new classifications to this tiered system. They are Clinical Trial and Lifestyle. Please see below for a description of these new classifications. Other updates are also included to provide further clarification of some provisions of this policy. This revised policy applies to all laboratories applying for or holding a New York State clinical laboratory permit and all assays that require submission as required on the Test Approval webpage, which can be found at <http://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval>.

Laboratory-developed tests that were conditionally approved prior to the date of implementation of this revised policy will continue to hold such approval.

Laboratory-developed tests proposed by laboratories that do **not** currently hold a NYS clinical laboratory permit or the appropriate permit category for the testing proposed will continue to require review and approval before testing on NYS specimens may commence. Conditional approval is not available for such assays. Approval can only be granted when the laboratory has met all requirements and is issued a permit (initial) or permit amendment (new categories). Please refer to the Clinical Laboratory Evaluation Program Guide to Requirements and Services available on our website at <http://www.wadsworth.org/regulatory/clep/clinical-labs>.

Features of the tiered evaluation process

1. All LDTs must be submitted to CLEP following the appropriate test submission guidelines and include all the required materials. This includes a **Risk Attestation Form** containing a succinct summary of the assay and responses to the questions listed on the Form; a description of each question is provided at the end of this policy document. The summary and responses to the questions will inform the assignment of the LDT to a risk classification by CLRS staff.
2. A classification assignment (**high, moderate, low, clinical trial, or lifestyle**) will be made by CLRS staff as part of the existing CLEP LDT validation review and approval process described on the CLEP Test Approval webpage. Laboratories will be notified of the risk assignment within three weeks of the submission of a complete package. Incomplete, vague, or unclear responses on the Risk Attestation Form may result in delayed review.
3. Questions about completing the Risk Attestation form can be submitted to CLEPVAL@health.ny.gov. However, the department is unable to perform pre-submission risk determinations.

Classifications

- **High risk:** LDTs assessed as **High risk** will **NOT** receive Conditional Approval and testing cannot be offered on specimens from NYS until the CLRS review has been completed and full approval has been granted. Review of LDTs assessed as **High risk** will be prioritized. Laboratories will be required to respond to CLRS reviews within 60 business days to avoid inactivation of the application but can apply for a one-time 60 day extension. Requests for extension should be made to CLEPVAL@health.ny.gov. **High risk will apply to all packages submitted by laboratories that are pending a permit or the appropriate permit category, unless the package qualifies for either a Clinical Trial or Lifestyle classification.**
- **Moderate risk:** LDTs assessed as **Moderate risk** will receive Conditional Approval if the laboratory holds a permit in the appropriate category of testing. Laboratories may offer the test once notified by CLEP of the moderate risk classification and conditional approval. However, the department reserves the right to withhold or withdraw conditional approval at its discretion. LDTs assessed as **Moderate risk** may not be reviewed further if they are well-established and are not a key determinant or have low impact. However, only those that are reviewed may receive full approval. Laboratories will be required to respond to CLRS reviews within 60 business days to avoid the rescinding of conditional approval. A one-time 60 day extension may be granted upon request. Requests must be made to CLEPVAL@health.ny.gov.
- **Low risk:** LDTs assessed as **Low risk** will receive full approval and will not be subject to review by CLRS staff, provided the laboratory holds a permit in the appropriate category of testing. Laboratories will be able to offer the test once notified by CLEP of the low risk classification and approval. However, the department reserves the right to withhold approval and/or require CLRS review of the test at its discretion.
- **Clinical Trial:** LDTs assessed as being performed **solely** for **Clinical Trial** purposes will receive notification from CLEP recognizing that the proposed test is part of a clinical trial and may be offered to clients. The trial for which the LDTs are performed must be approved by the National Institutes of Health (NIH) or another relevant independent Institutional Review Board. For additional information, please visit: <https://clinicaltrials.gov/ct2/manage-recs/fdaaa> . **If the assay is used for both diagnostic and clinical trial purposes, then this classification does not apply. If the assay qualifies for this Clinical Trial classification initially but is then proposed for diagnostic use in the future, a new method validation package must be submitted.**
- **Lifestyle:** LDTs assessed as **Lifestyle** will receive notification from CLEP that the test may be offered to clients with the disclaimer that it has not been evaluated by the New York State Department of Health. This classification will only be assigned when the laboratory presents documentation from the Centers for Medicare and Medicaid Services (CMS) that the testing is not clinical. If the proposed assay includes a panel of tests or markers where a portion of the tests or markers are deemed clinical by CMS, the validation package is not eligible for the Lifestyle classification. Tests assessed as lifestyle tests will not be reviewed by CLEP/CLRS. However, the department reserves the right to withhold approval and/or require CLRS review of the test at its discretion.

Category	Submission required	Initial Approval	Review required	Review Priority
High	Yes	None	Yes	High ¹
Moderate	Yes	Conditional ^{2,3}	Yes	Medium
Low	Yes	Full ^{2,3}	No ⁴	--
Clinical Trial	Yes	N/A ^{2,4}	No ⁴	--
Lifestyle	Yes	N/A ⁴	N/A ⁴	--

¹Submissions for laboratories pending a permit or permit category are automatically assigned High Risk, unless the package meets the conditions for Clinical Trial or Lifestyle.

²Provided the laboratory holds the appropriate permit category.

³The department reserves the right to withhold approval at its discretion.

⁴The department reserves the right to review all applications at its discretion.

Definitions of terms used in classifications

Well-established: The laboratory has demonstrated the ability to consistently submit complete and organized applications that adequately prove competence for development of LDTs with the same or similar technology and where an appropriate validation protocol is followed on a consistent basis over time; **AND** the methodology:

- a. has been previously approved by FDA or NYS; or
- b. has without significant modifications resulted in a meaningful clinical impact as has been described in multiple peer-reviewed publications.

Key determinant: the test result provides critical or essential information to

1. diagnose, **and/or**
2. indicate a greater likelihood of developing a disease or condition, **and/or**
3. indicate eligibility for a specific treatment, **and/or**
4. provide prognostic information that influences patient management or treatment decisions, **and/or**
5. provides information on treatment adherence and/or drug use.

Impact: the likelihood that an inaccurate test result will negatively impact a patient's condition or lead to patient morbidity/mortality. An LDT will have a high impact if an analytically or clinically inaccurate result leads to erroneous diagnosis and/or prediction of an inappropriate treatment, thereby increasing the risk of significant harm or death.

LDT Classifications (see flow diagram below)

- **High risk:**

- An LDT that uses a methodology that is not well-established in the submitting lab and provides critical or essential information (key determinant) about a serious or life-threatening disease, disorder or condition, whether or not the reported result, if inaccurate, could be used to support an incorrect diagnosis and/or an inappropriate clinical treatment that is likely to increase the risk of significant harm or death (high impact), or
- An LDT that uses a methodology that is not well-established in the submitting lab, does not provide critical or essential information (key determinant) about a serious or life-threatening disease, disorder or condition, but the reported result, if inaccurate, could be used to support an incorrect diagnosis and/or an inappropriate clinical treatment that is likely to increase the risk of significant harm or death (high impact).

- **Moderate risk:**

- An LDT that uses a well-established methodology and provides critical or essential information (key determinant) about a serious or life-threatening disease, disorder or condition, whether or not the reported result, if inaccurate, could be used to support an incorrect diagnosis and/or an inappropriate clinical treatment that is likely to increase the risk of significant harm or death (high impact), or
- An LDT that uses a well-established methodology, does not provide critical or essential information (key determinant) about a serious or life-threatening disease, disorder or condition, but the reported result, if inaccurate, could be used to support an incorrect diagnosis and/or an inappropriate clinical treatment that is likely to increase the risk of significant harm or death (high impact), or
- An LDT that uses a methodology that is not well-established in the submitting lab, but is not considered a key determinant, and an inaccurate reported result is not likely to support an incorrect diagnosis and/or an inappropriate clinical treatment (low impact).

- **Low risk:**

- An LDT that uses a well-established methodology, does not provide critical or essential information (key determinant) about a serious or life-threatening disease, disorder or condition, and an inaccurate reported result is not likely to support an incorrect diagnosis and/or an inappropriate clinical treatment (low impact). Packages that are submitted under an approved exemption may also be classified as Low Risk. Laboratories may apply for an exemption from full method validation submission by following the instructions available at <https://www.wadsworth.org/regulatory/clep/clinical-labs/obtain-permit/test-approval>.

- **Clinical Trial:**

- An LDT that is being performed as part of clinical trial approved by NIH or another relevant independent Institutional Review Board (IRB), on specimens for participant enrollment or management where the results are reported and are used for clinical decision making. Examples of testing performed for participant management include those that influence enrollment (exclusion or inclusion), safety, toxicity, or dosing.

- **Lifestyle:**

- **Lifestyle** tests are not clinical tests. If CMS determines that a test is clinical, then CLEP will consider the test to be clinical as well. Generally, an LDT is considered a lifestyle test when the intended use relates to the maintenance or adoption of a general state of health or healthy activity; or an intended use that relates to the widely-accepted role of a healthy lifestyle in the management of certain chronic diseases or conditions. A claim that the healthy lifestyle choice(s) may play an important role in health outcomes should be generally accepted; such associations are described in peer-reviewed scientific publications or official statements made by healthcare professional organizations. A **Lifestyle** test would include, but is not limited to, a test to detect the

best diet for your genotype, your risk for wrinkles and/or freckles, the best fitness plan, your aptitude for learning languages, your snacking profile, your food metabolism traits, etc. The following intended uses are examples of tests that would **not** be considered **Lifestyle** tests: genetic markers for risk of chronic disease, identification of carrier status of variants for diseases known to be caused by genetic mutation, identification of variants suspected to be associated with disease states or risk of developing a disease. If the proposed assay includes a panel of biomarkers or tests where a portion of the biomarkers or tests are deemed clinical by CMS, the validation package is not eligible for the Lifestyle classification.

Submission Requirements:

All packages **must** be accompanied by a completed **Risk Attestation** Form. The form requires the following:

- **A summary of the assay**, not to exceed 400 words, specifically including the following:
 - Methodology and technology (e.g., sequencing by next generation sequencing, LC-MS/MS, etc.)
 - Intended use to include target population if applicable
 - Specimen type(s)
- An indication of whether the test is considered a **Clinical Trial** or **Lifestyle** test. A justification is required.
- An indication of whether the submission is a **modification** of an FDA-cleared, approved, or exempted IVD or of an existing LDT with full CLEP approval; and a description of the modification and its impact on test performance is required.
- Disclosure of LDTs that have been approved by CLEP that utilize the same methodology or a statement and justification for determining that the methodology is **well-established** in your laboratory and generally accepted by the field.
 - If the laboratory has no LDTs previously approved by CLEP utilizing the same methodology, provide supporting information to demonstrate that the laboratory has consistently submitted complete and organized applications that adequately prove competence for development of LDTs with the same or similar technology and where an appropriate validation protocol has been established; and
 - Provide supporting evidence by citing at least 2 and no more than 3 relevant references (with PubMed ID or complete reference citation) or identify an available test that has FDA approval/clearance/exemption for the same methodology.
- **The basis for the clinical use claim of the LDT.** Provide a listing of three key publications (with PubMed IDs or complete reference citations). Relevant additional supporting publications and/or clinical or laboratory data must be included in the submission package. Indicate whether the publication is from the submitting laboratory.
- **Explanation of how this LDT does, or does not, provide critical or essential information to**
 - 1) diagnose and/or
 - 2) indicate a greater likelihood of developing a disease or condition, and/or
 - 3) indicate eligibility for a specific treatment, and/or
 - 4) provide prognostic information that influences patient management/treatment decisions.
 - 5) provide information on treatment adherence and/or drug abuse.
- **Briefly describe the potential impact of an inaccurate test result and whether it is likely to increase or decrease the risk of significant morbidity or mortality.**

Additional Documents Required:

For modifications to fully approved or conditionally approved LDTs or modifications to FDA-approved/cleared/exempted assays:

- Completed **Assay Modification Form**
- Description of the modification
- Narrative summary of the validation

For assays to be used solely in Clinical Trials:

- Narrative summary
- Sample reports for all possible outcomes
- At least one of the following:
 - IRB approval letter including a statement that the assay does not pose a significant risk to the trial participants;
 - clinicaltrials.gov identifier for the study protocol of the clinical trial; or
 - FDA letter indicating that the assay poses no significant risk.

For assays that are determined to be non-clinical (Lifestyle or wellness tests):

- a written determination from CMS that the test is not clinical

For assays included under an approved exemption from full validation package submission:

- Completed **Add Test Under Exemption Form**
- Narrative summary
- Sample reports of all possible outcomes
- Informed consent materials for Genetic Testing – Molecular and Cytogenetics assays (except cytogenetics testing for cancer)

For all other assays requiring method validation submission:

- Appropriate **submission checklist** for the category of testing and all required supporting materials

NYSDOH Policy for Tiered Evaluation of Laboratory Developed Tests (LDT)

