DEX® Molecular Syndromic Panels for Infectious Disease FAQs

1. What molecular syndromic panels for infectious disease pathogen identification require DEX Z-Codes®?

Molecular (DNA/RNA) syndromic panels ('panel' as defined a test that detects >1 pathogen) for infectious disease pathogen identification testing are tests that simultaneously detect multiple different pathogens associated with similar and overlapping clinical symptomatology.

If a molecular test detects multiple types or strains of one common pathogen – i.e., the test detects only influenza (even if it detects both influenza A and B), only herpes simplex virus (even if it detects both HSV-1 and HSV-2), or only human immunodeficiency virus (even if it detects both HIV-1 and HIV-2) - then the test does not require a Z-Code, as it is not a ***syndromic*** panel.

NOTE: A syndromic test panel is a single test with multiple components and is characterized by a single unit of service. A syndromic panel cannot be unbundled and billed as individual components regardless of the fact that the test reports multiple individual pathogens and/or targets.

2. If my test is a Laboratory Developed Test (LDT) syndromic panel for infectious disease pathogen identification, do I have to register for a DEX Z-Code and submit for a Technical Assessment (TA)?

Services that do **not** have Food and Drug Administration (FDA)-approved/cleared indicated uses, as well as FDA-approved/cleared tests performed in ways not consistent with their intended-use labeling directions (i.e., the test has been modified in any way), will require a Z-Code and a TA.

By definition, syndromic panels that are CLIA waived should be unmodified FDA-approved/cleared tests and registration of these tests would not be required.

For CLIA waived tests that remain under Emergency Use Authorization (EUA) status, the **manufacturer** may submit the test to DEX for a Z-Code and we will contact them if additional documentation is required.

3. Do I need to register for a DEX Z-Code and submit a Technical Assessment (TA) if >1 FDA-approved/cleared molecular infectious disease pathogen identification test is performed on a given patient on the same date of service (DOS)?

If you perform multiple (>1) FDA-cleared/approved molecular infectious disease pathogen identification tests on the same date of service (DOS), for the same intended use on the same patient sample, it is considered one distinct service and requires a Z-Code.

Additional information:

As long as the FDA-approved/cleared test is being used within its intended use labeling, there is no need to perform additional validation work (only verification, and Palmetto GBA® does not need to review this). A validation is still necessary if the test is being used in some way outside of its intended use labeling instructions.

The unique situation presented is if the FDA-approved/cleared test is being used within its intended use, in addition to other services, as part of a multi-assay service, which is still within the tests' intended use. In this case, the service must still be evaluated in a TA for the payer to understand the clinical validity and clinical utility of the test for its new intended use. However, in the circumstance that the intended use STILL aligns with the FDA-intended use, then the analytical validity (AV) will not need to be reviewed, only clinical validity (CV) and clinical utility (CU).

Examples:

- A lab may be performing an FDA-approved respiratory panel according to its intended use labeling instructions. In that case, the lab must only have verified the performance characteristics of the test – but Palmetto GBA does not need to review the test.
- If the above FDA-approved respiratory panel test is routinely offered in combination with another FDA-approved panel test (also performed within that test's intended use), Palmetto GBA will need to review the CV/CU *of the entire service*. A review of AV is not necessary. If, however, any of the FDA-approved test components of the service are being performed *according to different intended use labeling instructions (including off-label sample types, etc.)*, we would have to review AV (for those specific test components) as well as CV and CU for the entire service.
- If the FDA-approved respiratory panel test (performed according to its intended use) is routinely offered in combination with a lab-developed test (LDT), then AV would have to be reviewed for the LDT portion of the service, while CV/CU would be reviewed for the entire service.

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4. If my panel is not described by a CPT® or a PLA code, do I have to register for a DEX Z-Code and submit for a Technical Assessment (TA)?

Yes. Panels that do not have an appropriate specific CPT® or PLA code would require the use of CPT® code 87999 and thus require a Z-Code and TA, even if it is FDA approved/cleared.

NOTE: A syndromic test panel is a single test with multiple components and is characterized by a single unit of service. A syndromic panel cannot be unbundled and billed as individual components regardless of the fact that the test reports multiple individual pathogens and/or targets.

5. What is needed for a complete Technical Assessment (TA) submission?

Submit ALL of the following:

- DEX Z-Code(s)
- The most current version of required forms for review and completion
    - *Technical Assessment Checklist* (GEN-CQD-003)
      NOTE: The Executive Summary must always include the test's intended use. For component panels (of larger panels) that can be separately orderable, please include an intended use statement for EACH component panel, as well as the larger comprehensive panel.
    - *Analytical Validity and Clinical Validation Summary Worksheet, Syndromic Infectious Disease Panels* (MID-PF-019)

      NOTE: Complete all tabs in entirety.
- Laboratory Validation Report – this is the document that describes how the test was validated in the lab. This includes what samples were used, how the validation was performed, signed off and attested to by a medical director. If you are offering this test clinically and performing it on patients, you should already have this document readily available containing a statement from your medical director indicating that the test has been approved for use in patient care.
- A PDF copy of peer-reviewed publications that demonstrate clinical validity and clinical utility **for the intended use of this (or similar) tests in the intended-use population.**
    - Not every lab has to publish its own data regarding clinical validity (CV) and clinical utility (CU). However, the policy requires that laboratories provide peer-reviewed publications that adequately demonstrate clinical validity (CV) and clinical utility (CU) for the relevant test/service in the intended-use population.

- Note that CV and CU are not limited to whether a test can identify pathogens more rapidly. There must also be clear evidence of clinical significance as well as an impact on patient management/outcomes.

- **Additional Items Specific to Urinary Tract Infection (UTI) Panels:**
  - Please see Insufficient Literature for UTI Panels (PDF) for publications that have been reviewed and have **NOT** adequately met the clinical validity and clinical utility criteria.

6. What constitutes a unique clinical sample?

Clinical patient samples are **unmodified** (i.e., not spiked/contrived) samples from intended-use patients. While spiked clinical samples may also be tested as part of the laboratory's validation, such samples alone are not adequate to fulfill the requirements of a **clinical validation**.

Clinical validation samples must be tested according to the entirety of the testing process (i.e., including DNA isolation/extraction) for a reasonable majority of organisms and targets. However, we understand that in exceptional cases some organisms and targets will be difficult to obtain from clinical specimens. In such cases, contrived samples using the correct sample matrix (i.e., spiked samples; DNA from clinical samples obtained from a biorepository) may be used. These should be clearly identified as contrived samples in the TA documentation submitted, along with the rationale for why unmodified clinical samples could not be obtained for the particular organisms or targets.

Additionally, aliquots of a sample are not considered a unique sample.

We recommend that before laboratories submit their test for a TA, they first refer to the relevant CLSI guidance documents as well as to the following resource, which describe the appropriate ways to perform a clinical validation with the appropriate number and types of clinical samples:

> Burd EM. Validation of laboratory-developed molecular assays for infectious diseases. *Clin Microbiol.* Rev. 2010 Jul;23(3):550-76. doi: 10.1128/CMR.00074-09. PMID: 20610823; PMCID: PMC2901657.

7. If I have a panel test with components that can also be ordered separately, how do I submit for a DEX Z-Code and Technical Assessments (TA)?

DEX Z-Codes are assigned to **component test panels (i.e., 'sub-panels' with at least 2 different pathogens)** that may be individually orderable. The lab test requisition form may serve as a guide for what constitutes an orderable **component panel** test. **Though separate Z-Codes may be assigned to these, the number of TAs submitted for a given service is ONE.**

Therefore, when multiple Z-Codes are received for sub panels of a larger service, only submit one TA as defined in #5 above and include all applicable Z-Codes on the *TA Submissions Checklist* (GEN-CQD-003) and *Analytical Validity and Clinical Validation Summary Worksheet, Syndromic Infectious Disease Panels* (MID-PF-019) forms. In the Executive Summary, you must also outline the intended use of each separately orderable component panel as well as that of the comprehensive service.

If pathogens are always or often interrogated together for a clinical indication, they should be included as part of a panel. If pathogens are not interrogated together frequently for the same clinical indication, they should not be included as part of a panel. Services should be provided based on clinical need, not because pathogens exist on an *a la carte* testing menu. If a panel service requires a specific pathogen for patient management, that pathogen must be present on the panel. Of note, an assay and a test are not necessarily the same thing. The 'test' can be thought of as the service rendered for a given patient indication. An assay can make up multiple tests/services (i.e., a large panel subdivided into smaller targeted panels), or multiple assays can make up one test/service. **In either case, the resultant service panel must stand alone for its intended use and have its own Z-Code.** However, for the sake of a TA, a single comprehensive assay can be submitted with all its subordinate subpanels together as part of a single review. We expect the provider to explain in an executive summary the subpanels and their components so we can understand the intended use of each subpanel test.

For example, a vaginitis panel should always include a combination of at least 2 of the following: *Gardnerella vaginalis*, other BV-associated bacteria (BVAB) (such as *Fannyhessea [Atopobium] vaginae* and/or *Megasphaera* sp.), *Trichomonas vaginalis*, and *Candida* species. There is no clinical value in creating a vaginitis panel that does not include the necessary relevant organisms nor is it of any clinical value to create a panel with pathogens not related to vaginitis. Though the individual assays may be performed on separate platforms, all components of the service should be submitted together as part of a comprehensive TA.

In cases where there is overlapping symptomatology requiring a broader panel to be created, this is acceptable. However, it may also be acceptable that two separate panels for narrower, but different symptomologies and intended uses are created and used together when the patient presents with two clinical indications. For example, in a patient with vaginal discharge as well as a genital lesion, it may be clinically warranted to have only a panel for "discharge" indicative of vaginitis or cervicitis and a test for a genital lesion, when the patient has both clinical symptoms. However, in the same scenario it may be equally appropriate to have a single panel for a clinical presentation that includes both discharge plus a genital lesion.

Due to limitations in claims processing systems, it is generally preferred that, when appropriate, the most comprehensive and clinically relevant panels are utilized to prevent unnecessary denials. Specific to this example, that would be a panel for "vaginitis/discharge and genital lesion." In this case, the TA submitted would be inclusive of the entire service, comprised of the tests for vaginal discharge and for genital lesions, with explanation of the defined subpanels in the Executive Summary. This comprehensive service would have one discrete Z-Code. **However, given that discharge and genital lesions are not expected to**

frequently co-occur in most patients, the following approaches are also acceptable – (a) billing for 2 separate panels, 1 for discharge/vaginitis and 1 for genital lesions, using 87999 for any panel that is not otherwise defined by a unique CPT® code (note that in this case, the panels could be submitted as 2 separate TA submissions and they would each have distinct Z-Codes) or (b) billing for a discharge/vaginitis panel and a separate single-pathogen test (i.e., for HSV) (note that in this case, only 1 TA submission would be required for the discharge/vaginitis panel, since the HSV test is a separate single-pathogen test and therefore not subject to a TA).

There can be various approaches for submitting syndromic test panels for consideration. *If additional organisms are not included in a panel, testing for those organisms separately for the same indication may be acceptable in limited circumstances.* As such, the following is allowed when necessary: (a) use of a second panel **for a distinct clinical indication**, (b) use of modifiers (such as modifier 59), or (c) use of a single-pathogen CPT® code.

8. My test/service includes antibiotic resistance genes on the patient report. Do I need to submit complete validation data for the components of the antibiotic resistance testing as part of the TA?

Although antibiotic resistance testing as a standalone test on its own is not a molecular syndromic panel for infectious disease, if it is performed concurrently with organism identification or offered as a reflex test and added to a panel, then validation data for the antibiotic resistance components must be submitted.

NOTE: A syndromic panel that includes reflex antibiotic resistance testing should be submitted as a single lab test in the DEX Diagnostics Exchange Registry. When reflex antibiotic resistance testing is offered, it is not considered a separate component from the syndromic panel and will not be assigned a separate DEX Z-Code.

9. How do I use the single-pathogen CPT® codes?

Single-pathogen CPT® codes should not be used for a panel (i.e., unbundled). If >2 are billed for the same intended use, this would constitute a molecular syndromic panel for infectious disease and would require a Z-Code.

NOTE: The same intended use refers to use of the same (or highly similar) ICD-10 code on a given day of service (DOS).