MolDX® Technical Assessment FAQs

General Technical Assessment (TA) Inquiries

1. What can I do to facilitate the Technical Assessment (TA) review?

Download the most current version of required forms for review and completion.

It is recommended that the following documentation be submitted in addition to the required forms:

- Validation report
- Sample-level data
- Formulas used for calculations
- Detailed information on orthogonal method(s) used
- Clear description of intended use

NOTE: *It is recommended that someone familiar with the validation complete the required documentation.*

2. What is the definition of a "clinical specimen"?

A clinical specimen is a sample from a patient affected with a disorder or disease that aligns with the test's intended use. Purchased reference material or contrived samples can be used to establish analytical validation, however, they are not considered to be clinical specimens.

3. Do we need to submit a Technical Assessment (TA) for each single gene assay or sub-panel that is done as part of a larger hotspot panel, but with masking of the other genes?

The TA must show that the test for which a claim is being submitted was validated. If the test was validated as part of the validation of a larger panel or platform validation, that is acceptable. If you wish to offer tests to patients consisting of single genes or small groups of genes from a large panel and submit claims for these tests, we ask that you register each gene or group of genes (i.e., each test) with a unique DEX Z-Code® identifier and provide us with an executive summary in your TA request noting what tests (identified by Z-Code) corresponds to which validation documents submitted.

4. For the Analytical and Clinical Validation documents to be submitted for the Technical Assessment (TA) of NGS tests, should raw data be provided?

No, the raw data are not required. For CGP tests and "targeted panels", please provide a copy of the approved validation summary for the assay.

5. **Are non-molecular based methods acceptable as orthogonal methods (i.e., IHC, FISH, and culture)?**

Yes, however, discordance in variant detection between the differing methodologies will need to be included in the validation documentation and explained/resolved.

6. **Will my "Pan Cancer Panel" be approved for all malignancies?**

The performance characteristics must be demonstrated in the cancer types for which it is intended to be used.

7. **What is the appropriate number of samples in each variant type (SNV, Indels, CNVs, Fusions, TMB, etc.) to be included in this assessment?**

Regarding the number of samples for the clinical validation, per CAP/AMP guidelines you should use at least 59 samples. Ensure these are representative of the kinds of tumors being tested and that there is enough of each variant class tested to show with some confidence that the test operates as expected in a clinical setting.

Technical Assessment (TA) Forms

1. **Please clarify the difference between analytical and clinical validation? Are both necessary for all components, or is clinical sample testing sufficient?**

It is important to do an analytical validation to demonstrate the boundary conditions for the operations of the test. The different variant classes should be handled as distinct, and the contrived samples (like cell lines) should have enough of each variant class to accurately determine the capabilities of the test and set appropriate thresholds for the limit of detection (LOD). Clinical validation tests these parameters in clinical samples, wherein the test will be typically limited to clinically relevant variants. Because these are relatively few in number, using only the latter will not result in a clear understanding of the working parameters of the test.

2. **What are Critical Loci?**
   Critical Loci are defined as variants clinically acknowledged (e.g., included in guidelines) as having diagnostic, predictive or prognostic implications.

3. **Is it necessary to have specimen confirmation of every specific variant listed on forms SOM-PF-004 (AV_CV Summary worksheet, Solid Tumors) and/or SOM-PF-005 (AV_CV Summary worksheet, Myeloid Malignancies) if the position is covered by the assay?**

No. It would not be reasonable to know a priori that all variants are found in your validation set. Furthermore, it would not be feasible to ensure every variant, particularly rare ones, are tested. However, there are some common variants we would ensure are covered in your test, such as those commonly seen in *EGFR* and *BRAF*. Test coverage for the intended use of the test is required.

4. **How should we account for a single unique specimen that has multiple mutations in the same gene (e.g., *APC* or *TP53*)? Is that considered two unique specimens?**

For forms SOM-PF-004 (AV_CV Summary worksheet, Solid Tumors) and/or SOM-PF-005 (AV_CV Summary worksheet, Myeloid Malignancies), it would be considered one specimen. We want to ensure you are validating the platform on an acceptable number of clinical samples.

5. **What about genes or variants that our assay covers, but are not listed on the form SOM-PF-004 (AV_CV Summary worksheet, Solid Tumors) or SOM-PF-005 (AV_CV Summary worksheet, Myeloid Malignancies)?**

It is not required that you enter this information here. You should provide aggregated information in Table 2 on the AV & CV Summary tab for the performance of the test as a whole..

6. **In the somatic documents SOM-PF-004 (AV_CV Summary worksheet, Solid Tumors) or SOM-PF-005 (AV_CV Summary worksheet, Myeloid Malignancies), what is the intent of Samples with Specified Variant Expected versus Samples with Specified Variant Detected in Table 4 of AV & CV Summary tab?**

Samples with Specified Variant Expected requires existing data from established orthogonal method and Samples with Specified Variant Detected is experimental data collected from the validation of the test's intended use.

7. **My "targeted tumor NGS panel" includes hotspot fusions and CNAs but does not fit the description for "comprehensive genomic profiling." What should I select on GEN-CQM-003?**

While commercial NGS panels are marketed as "targeted," we abide by the definition of "targeted" as tests that identify somatic alterations known to occur in certain regions (i.e.,

'hotspots') within specific genes of interest for cancer management (i.e., diagnosis, selection of molecularly targeted therapies, prognosis in a context where prognostic classification is essential for treatment selection). Generally, these NGS panels can detect single nucleotide variants (SNVs) and small insertions or deletions (INDELs) within these regions.

8. **When is form GEN-PF-001 (Technical Assessment (TA) Summary Form) required? Is it required if we are performing an NGS cancer test that outputs genomic alterations but includes proprietary components in the process of determining those alterations?**

No. Form GEN-PF-001 (TA Summary Form) is required when the test result is novel or a proprietary result that requires independent clinical validity and utility assessments. If your test measures genomic alterations (such as mutations), wherein the utility and validity of such measurements are already established (like predictive biomarkers in cancer), the validity of performing such tests is established. Utility will be determined by ensuring the required test conditions for biomarker coverage are met. GEN-PF-001 (TA Summary Form) is reserved for new technologies or wherein validity of utility of a test is not established on the literature or cannot be established because there cannot be comparators to determine validity.