



## EDITORIAL

### Diagnostic Quality Assurance Pilot



# *A Model to Demonstrate Comparative Laboratory Test Performance with an Oncology Companion Diagnostic Assay*

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Formal evaluation of interlaboratory equivalence of clinical molecular laboratory testing has been hampered by the relative absence of suitable reference materials. Furthermore, the validation of laboratory tests in individual laboratories may not itself result in equivalent diagnostic test results. Development of technically sound strategies for demonstrating test equivalence is urgently needed, particularly for rapidly changing and complex technologies, such as next-generation sequencing. One challenge for diagnostic laboratories is demonstration of laboratory-developed testing (LDT) methods as equivalent to Food and Drug Administration (FDA)—cleared or approved assays, especially for companion diagnostic testing for oncology therapies.

The current model to achieve this goal for oncology diagnostics and therapeutics focuses on the design and evaluation of appropriate and sustainable reference materials to test comparable performance of LDTs to a companion diagnostic (CDx) assay approved for targeted cancer therapy. LDTs or procedures that meet the same performance specifications as defined in the FDA approval of the companion diagnostic may be demonstrated with appropriate reference materials to produce both laboratory test harmonization and higher levels of confidence from health care providers, patients, and payers in LDT results. The intended outcome of using the reference samples is to ensure use of equivalent LDTs and CDx as effective diagnostic tools to best identify patients who will most likely benefit from the associated targeted therapy and avoid administration of therapy to patients with tumors that will not respond. Demonstration of substantial equivalence will increase the likelihood that the use of targeted therapies is offered to all patient groups according to the same criteria.

Laboratory test harmonization will enhance the fulfillment of the President's Precision Medicine Initiative in a manner that multiple stakeholders can trust. Patients, providers, payers, manufacturers, regulatory agencies, and laboratories all seek not only consistent and accurate laboratory testing but also transparent and comparable results with quality measures implemented across test platforms and laboratories. The FDA has noted the need to consider novel ways to optimize regulatory oversight of next-generation sequencing tests for human genomes to provide a "flexible, adaptive regulatory approach that ensures that patients receive accurate and meaningful results, while accommodating innovation in test development" (FDA, <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf>, last accessed November 17, 2016).

Standardization is the achievement of equivalent results by different clinical laboratory tests conducted by different laboratories using reference samples that can be measured and traced to a reference measurement procedure (American

Accepted for publication October 31, 2016.

Disclosures: B.Z. has received consulting fees from Amgen, Inc. C.L.-D. is an employee of Amgen, Inc., and owns Amgen stock. J.P. is a cofounder, PierianDx and cofounder, P&V Licensing LLC. P&V Licensing LLC is a vendor for *in silico* data sets used by the College of American Pathologists in this work. E.S. and L.G. are employees of Tapestry Networks assigned to the Sustainable Predictive Oncology Therapeutics and Diagnostics initiative, which has received sponsorship fees from Amgen, Inc.

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Association for Clinical Chemistry, [https://www.aacc.org/~/media/files/harmonization\\_white\\_paper\\_july2015.pdf?la=en](https://www.aacc.org/~/media/files/harmonization_white_paper_july2015.pdf?la=en), last accessed June 6, 2016). The key element is to use reference samples of defined composition and characterized measurements that closely resemble clinical sample material as much as possible. Because the use of actual patient tumor samples is difficult to sustain and meet scalability needs, human cell lines were selected by stakeholders involved (details below) as the reference sample type that would be the focus of this pilot. These could be grown, harvested, fixed, and embedded into paraffin blocks, and then divided into sections to approximate the human tissue samples commonly tested in clinical laboratories. Commutability of results from analysis of the reference samples in the diagnostic test to the results obtained from analysis of actual clinical specimens is also desirable but is beyond the immediate goals of this quality pilot.

To address these needs for reference materials to achieve test standardization, a multi-stakeholder initiative, the Diagnostic Quality Assurance Pilot, has been launched to design, develop, test, and evaluate traceable reference sample materials (referred to in the pilot as reference samples) to provide molecular pathology laboratories with the means to demonstrate equivalent performance of LDTs comparable to a selected CDx for targeted cancer therapy (Tapestry Networks Inc., <http://www.tapestrynetworks.com/initiatives/healthcare/oncology-therapeutics-and-diagnostics/upload/Diagnostic-Quality-Assurance-Pilot-FAQs-August-2016-final.pdf>, last accessed October 19, 2016). This Quality Pilot emerged from the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group, launched in 2013 by Tapestry Networks (Waltham, MA) and composed of diverse stakeholders for the purposes of designing a quality pilot to advance the above goals. Stakeholders who were represented included patient/policy advocates, payers, regulatory agencies, subject matter experts, biotechnology and biopharmaceutical specialists, health care providers, professional laboratory and oncology organizations, and diagnostics industry sponsors.

Participants in the SPOT/Dx working group proposed an initiative to design, identify, test, and implement consensus reference samples for ensuring laboratory performance in identifying patient populations for targeted therapies that

would offer significant benefit to the field of molecular pathology and, given the importance of this testing in precision medicine initiatives, to the health care system as a whole. Members proposed a quality assurance pilot to establish that molecular diagnostic quality may be delivered via a sustainable, multi-stakeholder approach that offers transparency about the performance of high-complexity diagnostics among different test types and among different laboratories. The pilot outcomes will serve to ensure that specific diagnostic tests provide clinicians with consistent and correct answers, regardless of which laboratory uses the test and which diagnostic platform the laboratory uses. The pilot's technical components will be implemented by the College of American Pathologists (Northfield, IL) and guided by a scientific technical working group of leading experts in the field of molecular pathology and next-generation sequencing. Amgen, Inc. (Thousand Oaks, CA), a biopharmaceutical developer, is underwriting the cost of the development of reference samples, project management, and laboratory resources needed to implement this pilot. In partnership with Illumina (San Diego, CA), a CDx manufacturer, Amgen will also contribute relevant technical specifications about the candidate CDx' performance specifications as guidance for the reference samples' design requirements and development criteria.

An independent, multi-stakeholder Steering Committee (SC) will provide governance for the Quality Pilot, advise the scientific technical working group, gather feedback from the represented health care sectors, and inform constituent organizations about the pilot. The SC is composed of representatives from the patient advocacy community, payers, laboratory professionals, clinical oncologists, and diagnostics industry. Liaisons from the FDA and the NIH National Cancer Institute will also participate on the SC as observers. The SC will share outcomes and lessons learned from the pilot's implementation process and results to foster collaborative learning and consensus definitions for design and development of other reference samples. Tapestry Networks will advise and support the SC and its chair to promote continuity with the original SPOT/Dx working group goals and with the broader health care community (Tapestry Networks Inc., <http://www.tapestrynetworks.com/initiatives/healthcare/oncology-therapeutics-and-diagnostics/index.cfm>, last accessed June 6, 2016).

**Table 1** Phases of Technical Implementation

Group	Phase		
	1	2	3
STWG	Develop specifications for reference samples	Engineer reference samples Test with validating laboratories	Distribute to pilot laboratories Analyze and share results
SC	Advise STWG on laboratory selection criteria and results capture	Advise STWG on process Share lessons learned to date	Analyze and share results with broader community Address scalability/sustainability

SC, Steering Committee; STWG, Scientific Technical Working Group.

The technical implementation of the pilot will be conducted in three distinct phases (Table 1).

Throughout the course of the pilot's execution, the SC and scientific technical working group will collaborate on assessing lessons learned, deciding implications for the broader precision medicine community, and sharing results with critical stakeholders. The pilot's completion is projected to be mid-2017.

The Genetic Testing Reference Materials Coordination Program, led by the Centers for Disease Control and Prevention, has been a successful model for characterization of reference materials for inherited disorders and illustrated cooperation of clinical testing laboratories to work within a multi-stakeholder study design (Center for Disease Control and Prevention, <http://wwwn.cdc.gov/clia/>

[Resources/GetRM/default.aspx](#), last accessed June 6, 2016). The hallmark of the Genetic Testing Reference Materials Coordination Program is the publication of all findings and the subsequent availability of reference materials for use by all interested laboratories. These steps are also planned for the SPOT/Dx Quality Pilot results. In addition, the outcomes of the pilot will inform a diverse range of stakeholders in health care practice—beyond clinical laboratories—about clinical laboratory test design, efficient uptake of assay technology, and interlaboratory agreement. The transparency of the laboratory quality pilot performance findings should also facilitate greater insights, communication, and understanding of molecular pathology laboratory test quality measures and standardization for all stakeholders.