Concept Note
SPOT/Dx Working Group

SUSTAINABLE PREDICTIVE ONCOLOGY THERAPEUTICS AND DIAGNOSTICS

MAY 2016

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Committed stakeholders chart a course for future molecular diagnostic quality assurance

> **"Getting the right diagnosis is a key aspect of health care: It provides an explanation of a patient's health problem and informs subsequent health care decisions … improving the diagnostic process is not only possible, but also represents a moral, professional, and public health imperative."[1]**

Note: The following concept note was finalized at the end of 2015 based on inputs from the SPOT/Dx *Working Group (details below). Tapestry is pleased to share the concept note publically as a historical document reflecting the initial design of a diagnostic quality assurance pilot that was subsequently launched by a subset of SPOT/Dx stakeholders in March 2016. The final design of the pilot has evolved since this original concept note. Further details on the pilot's scope, execution, and progress will be published throughout 2016.*

The development of new molecular techniques and the identification of new biomarkers are dramatically increasing the scope and value of molecular diagnostics. With this acceleration comes a need for greater system-wide assurance that the correct patients are selected for targeted cancer therapies regardless of the particular lab or diagnostic test employed in their care. This need has become more acute with the interest and expansion of personalized medicine as demonstrated by the President's Precision Medicine Initiative. In service to this, the U.S. Food and Drug Administration (FDA) has noted the need to consider novel ways to optimize regulations of Next Generation Sequencing (NGS) tests for human genomes with the end goal of developing a "flexible, adaptive regulatory approach that ensures that patients receive accurate and meaningful results, while accommodating innovation in test development."[2] There is cross-stakeholder agreement that identifying and implementing consensus reference standards and quality assurance measures to address this issue in a sustainable manner would offer significant benefit to the field of molecular pathology and the healthcare system as a whole.

The Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) Working Group[3] recently announced the development of a Quality Assurance Pilot for Companion Diagnostics.[4] The multistakeholder-initiated effort will test a process to improve molecular companion diagnostic quality and consistency. To do this, the SPOT/Dx Working Group has designed an approach focusing on the creation and adoption of platform-agnostic (commutable) consensus performance standards set by the specifications of a companion diagnostic (CDx) and targeted drug in phase 3 of development (pre-market process). The goal is to equip labs with traceable quality standards materials and specifications (including preanalytic and analytic

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[1] Improving Diagnosis in HealthCare – Report in Brief, *Institute of Medicine*, September 2015, https://iom.nationalacademies.org/~/media/Files/Report%20Files/2015/Improving-Diagnosis/DiagnosticError_ReportBrief.pdf.

[2] FDA Public Workshop - Standards Based Approach to Analytical Performance Evaluation of Next Generation Sequencing In Vitro Diagnostic Tests, November 12, 2015, http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf.

[3] Established in 2012, SPOT/Dx brings together premier groups of healthcare leaders from across the United States who are committed to improving patient outcomes by equipping healthcare leaders with tools to advance clinical decision making, the diagnosis and treatment of cancer, and the regulatory/reimbursement infrastructure that underlies the field of precision medicine. SPOT/Dx was assembled and independently led by Tapestry Networks. For further information regarding the SPOT/Dx Working Group, please visit http://www.tapestrynetworks.com/initiatives/healthcare/oncology-therapeutics-and-diagnostics-working-group.cfm.

[4] For a complete list of contributors to the pilot design, see the Annex of this document.

components) in the pre-market phase that will subsequently enable them to demonstrate equivalent levels of molecular diagnostic performance. Labs will be able to demonstrate their ability to accurately discriminate at the clinical decision point for a given product regardless of whether they are using an FDA-approved in vitro companion diagnostic (IVD) or a laboratory-developed test (LDT). Simply put, the intention is to ensure that regardless of the CDx used, that diagnostic would identify the appropriate patient population for the associated targeted therapy.

Appreciating the oncology community's commitment to using molecular diagnostics while also concerned about the widespread variability in the accuracy of results gleaned from their use, SPOT/Dx participants asked, *"What can we do to ensure that different measurement procedures for new biomarkers will give comparable and appropriate results?"* The solution? A proposed process to support the *"search for diagnostic truth."* As a molecular pathologist noted, *"We want to focus on getting to a diagnostic truth for any particular molecular diagnostic given to any particular patient. If we can develop a set of quality standards materials that are platform agnostic, make them available to all of the laboratories out there, and ask 'are you getting diagnostic truth?' then we have achieved our goal."*

The pilot will include participation of key stakeholders impacted by molecular diagnostics quality including patient advocates, clinicians (pathologists and oncologists), payers, regulators, drug and diagnostic developers, and labs. The proof of concept pilot is initially oncology-focused with a potential candidate CDx that will be a two gene (multiple variant) NGS panel proposed by Amgen and Illumina. The intention is to start deliberately with a small scale in this pilot. The pilot will involve a limited number of laboratories on a voluntary basis to test and evaluate this approach.

Principles underlying the pilot

Quality assurance questions are present across several dimensions of healthcare delivery in the United States. The Working Group proposed a collaborative approach that recognized existing organizations' mandates, expertise, and processes. The Working Group agreed on several core principles to inform the pilot design including:

- The pilot **should leverage the existing infrastructure and mandates** of the various actors in the oncology, pathology, and lab accreditation domain rather than build new models or organizations from scratch.
- The **management and secretariat role for the pilot should be assumed by an unbiased party** that is readily accepted as a trusted intermediary for the broader group.
- The pilot process must include **provisions to avoid conflict of interest**, whether real or perceived.
- The pilot should **address the perceived opacity regarding lab performance** on a given diagnostic.
- At first, the **pilot should focus on demonstrating a proof of concept**, but its design should take into account questions that may impact its scalability and sustainability.

- **Outcomes from the pilot are non-binding**, but will be shared with the public to facilitate continuous learning.

With these principles in mind, the group will leverage the framework and infrastructure of organizations well versed in the areas of harmonization, performance standards, and molecular pathology. Early candidates to support the pilot include institutions like the College of American Pathologists (CAP), the International Consortium for Harmonization of Clinical Laboratory Results, Association for Molecular Pathology (AMP), U.S. Centers for Disease Control (CDC), and the National Institute of Standards and Technology (NIST), among others.

An independent multistakeholder advisory group will assume responsibility for supporting the process and will include representatives from public and private payers and CAP, along with the regulators such as the FDA and Centers for Medicare and Medicaid Services' (CMS) Clinical Laboratory Improvement Amendments (CLIA) as observers. A secretariat may be required to manage the coordination of key advisors and pilot implementing organizations including a subset of the above organizations, as well as developer and diagnostic partners, reference material manufacturers, labs, and additional subject matter experts.

Pilot approach: Six step process

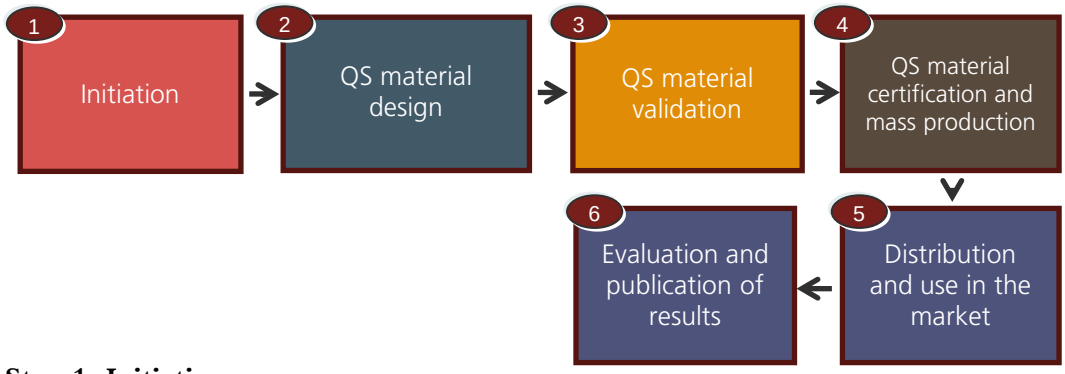
Having identified the challenges that could emerge in a world with wide-ranging validation standards for multiple molecular diagnostics, some leaders in this space have proposed improvements to the current system for quality assurance.

The situation could be significantly improved if the development of quality standards around defined performance metrics were made in parallel with the development of the measurement procedure for a new biomarker/CDx. To minimize any conflict of interest and to allow for broader access and utilization, officially recognized quality standards (QS) materials[5] could be made available to all manufacturers very early on through an impartial third-party organization. Such organizations could also facilitate cooperation and collaboration among all relevant constituencies (diagnostics, pharmaceuticals, laboratories, regulatory agencies, payers), thus strengthening acceptance by the scientific community in the end.[6]

To that end, the Working Group designed a process for the pre-market creation of QS materials that (1) are linked to clinical trial findings, (2) can evolve over time as diagnostic platforms change, and (3) will minimize confusion when multiple drugs are developed that rely on the same biomarker (e.g., PD-1 or PDL-1). As one payer noted, *"This pilot proposes the creation of quality standards materials that will allow one to test whether labs are getting the right analytical result, but also whether they are correctly interpreting their analytical results."* In brief, the pilot approach consists of the following 6 steps:

[5] The proposed quality standards materials would also include technical specifications. Further, the quality standards materials proposed for this pilot should not be confused with quality control materials, which are currently utilized for operational controls; rather, quality standards materials in the pilot will be utilized for evaluating equivalence to the CDx.

[6] Greg Miller et al., "Harmonization of Test Results: What Are the Challenges; How Can We Make It Better?" *Clinical Chemistry* 60, no. 7 (2014), 926.



Step 1: Initiation.

A pharmaceutical company approaches a multistakeholder committee or established advisory body, if available, 18 months prior to the launch of a therapy and its CDx and articulates the need for a harmonization effort. The advisory body decides to move forward and the pharmaceutical company assembles a technical Working Group to execute the process. Select members of the advisory body will serve as an independent steering committee to the pilot consisting of representatives from key stakeholders engaged in development and use of diagnostics in clinical practice.[7] The technical Working Group will comprise a smaller subset of these organizations and include the drug developer and their diagnostic partner – essentially the organizations with the necessary technical expertise required for execution of the next steps.

Step 2: QS material design

Design consists of two phases: 1) agreement about a consensus performance standard and 2) collaboration with a commercial vendor to create QS materials to measure that performance standard and for use in interlab comparison studies. The QS materials must include assessment of the preanalytics process.

Step 3: QS material validation

Validation will involve an interlaboratory round-robin sample exchange. The commutability of new materials for external assessment purposes will be pretested early in a validation step with a small group of three or four labs prior to rolling the materials out to a broader group of 15 labs of varied size, throughput, geography, and platform. Several Working Group participants suggested that CAP, working with the developer, could select the appropriate mix of labs.[8]

Step 4: Reference material certification and production

Once the commutability and analytical validity of the QS materials have been established, the technical Working Group will certify that the materials may be used for the task of determining the proficiency of a lab's CDx testing. The technical Working Group will subsequently endorse production of the QS materials for the broader pool of approximately 15 labs.

[7] Proposed participants include CAP, American Society of Clinical Oncology (ASCO), Palmetto GBA, Blue Cross Blue Shield Association (BCBSA), Friends of Cancer Research, and regulatory representatives from CMS CLIA and FDA as observers of the pilot.
[8] Additionally, NIST has noted their interest in being a validation lab as their contribution to the pilot process. A third-party subject matter expert could coordinate and analyze the statistical data from these early interlab comparisons.

Step 5: Distribution and use in the market

The technical Working Group will leverage CAP's external quality assurance infrastructure for the distribution of materials. Once certified and produced in sufficient quantity, the QS materials will be distributed to the 15 labs participating in the pilot.

Step 6: Evaluation and publication of results

A representative from the advisory group or an independent, unbiased entity will grade the labs' QS performance.[9] The grade will be based on consensus performance criteria (traceable to the candidate IVD) developed at the outset by the advisory body. The results will be shared with relevant parties including laboratories, drug developers, regulatory agencies, payers, etc. Lessons learned about the pilot's approach and process will also be disseminated broadly to healthcare stakeholders with a vested interest in oncology and molecular pathology.

Next steps

Amgen has agreed to pilot this proposed model with a candidate asset. Amgen is currently collaborating with Working Group participants and their organizations to finalize the pilot protocol and carry this proof of concept pilot forward from design to implementation later this year. The group is dedicated to sharing the outcomes from the pilot to support broader learning within the precision medicine community to ensure equivalence and high performance standards to the satisfaction of all stakeholders.

[9] The CDC, Palmetto GBA, and the BCBSA technology center have been nominated as possible institutions that could serve in this capacity.

Annex: SPOT/Dx quality pilot contributors

Patient/policy advocates

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- Calaneet Balas, Chief Executive Officer, Ovarian Cancer National Alliance
- Andrea Ferris, President and Chairman, LUNGevity Foundation
- Marina Kozak, Science Policy Analyst, Friends of Cancer Research
- Nancy Roach, Founder and Chairman, Fight Colorectal Cancer

Payers

- Naomi Aronson, Executive Director, Clinical Evaluation, Innovation and Policy, Blue Cross and Blue Shield Association
- Mike Barlow, Vice President, Operations, Palmetto GBA
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