SPOT/Dx Working Group first meeting: launching a collaboration

"Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it is the only thing that ever has."

– Margaret Mead, an American cultural anthropologist

Reliable and effective diagnostics are critical to the future of cancer treatment. While important lessons have been learned through the development of single-analyte, single-treatment companion diagnostics, healthcare experts believe that precision medicine in oncology has reached an inflection point and that diagnostic development in particular is not able to match the pace of biomarker discovery.[1] Taking the next meaningful step forward in precision medicine will require stakeholders across the healthcare system to rethink their current models of business and employ new approaches. To address existing challenges and consider multistakeholder approaches to advancing precision medicine in oncology, Tapestry Networks, in partnership with public- and private-sector agencies, has convened the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) Working Group.

As reflected in its name, SPOT/Dx focuses on predictive diagnostics that are used to help determine whether to administer a therapeutic (as opposed to prognostic or susceptibility tests which serve a different function). SPOT/Dx brings together key thought leaders and decision makers from the public and private sectors, including clinical and policy experts, regulators, third-party payers, patient advocates, and industry leaders. By working together through 2014, the group aims to improve patient outcomes by equipping healthcare leaders with the tools to advance the diagnosis and treatment of cancer, clinical decision making, and the regulatory/reimbursement infrastructure that can support a shift to precision medicine. An additional aim is to identify specific opportunity areas in support of this broader mission, determine what is needed to carry recommendations in these areas forward, and develop pilot plans to test/validate these recommendations.

On December 2–3, 2013, the SPOT/Dx Working Group convened in Washington, DC, for its first meeting. Please see the Appendix for a list of meeting participants. The meeting opened with an ambitious conversation on collaboration and a reminder that a dedicated group of individuals and institutions can indeed change the world. Centered on the theme of collaboration, the launch meeting confirmed aspirations for the group, acknowledged and validated the systemic challenges facing molecular diagnostics and precision medicine in oncology, and identified and prioritized opportunity areas for multistakeholder action through plenary discussion, case study analysis, and small-group breakouts. This document presents a summary of themes from the meeting.

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[1] See, for example, Daniel Hayes et al., "Tumor-Biomarker Diagnostics: Breaking a Vicious Cycle," *Science Translational Medicine* 5, no. 196 (July 2013).

Tapestry Networks

Aspirations for the working group and reflections on the day

The meeting achieved results on a number of different levels. At the most basic, many participants appreciated the opportunity to learn from other stakeholders in the group. A regulator described the need for better communication and likened the current state of affairs in molecular diagnostics to the Indian fable of the blind men and the elephant. Just as the blind men in the story had distinct descriptions after touching different parts of the elephant, the distinct stakeholder groups in SPOT/Dx are, as the regulator put it, *"looking at things from their own perspective. I really appreciate learning what happens outside of the regulatory agency and the perspectives of everyone, from the payers to the test-makers and drug developers. I found this very useful."*

Participants were also very open to working together. For example, a payer said that he was looking for *"novel suggestions as to how private payers can contribute to development."* An oncologist aspired to determine *"how we can better equip oncologists to understand and use diagnostic tests in delivering high-quality, high-value care to their patients."* A diagnostic developer stated his goal as to instill *"a better understanding across the system of how to bring quality diagnostic products to patients and the market in a sustainable way."* And as a patient advocate summed up the day, *"This has been like watching a really big Rubik's Cube. Rather than just sitting and looking at a scrambled cube, I think we're all committed to changing the configuration and figuring out where to go from there."*

Finally, SPOT/Dx participants committed themselves to innovating in the molecular diagnostic space, whether through a technical, process, or policy innovation. For example, a drug developer remarked, *"My primary passion is to enhance the access to new technologies for patients."* SPOT/Dx participants were largely in support, but also supplied clarification. In the words of a payer, innovation for this group *"is not an end in itself; it is a means to bringing greater benefit to patients."* In pursuit of these aspirations, much of the rest of the meeting focused on developing concrete areas of action for the working group.

The promise and challenges of precision medicine in oncology

SPOT/Dx participants largely felt that the potential therapeutic and economic benefits of precision medicine in oncology were well understood. The great promise of precision medicine in oncology arises from the ability to characterize the molecular signature of a patient's tumor and subsequently make treatment decisions based upon an understanding of cancer-related molecular pathways. In the participants' collective vision of the future, powerful diagnostic tools and targeted therapies combine to produce more effective treatment responses (in the form of extended remissions and cures) for dollars spent.

However, as summarized by one clinician, *"The sheer biological complexity of cancer is both the source of the promise for precision medicine and the greatest challenge to achieving it."* Participants described two major types of challenges that are slowing the advancement of precision medicine in oncology: challenges owing to complexity in science, technology, and institutional processes, and challenges related to the diminishing financial incentive to bring molecular diagnostics to market. The following paragraphs briefly describe these two types of challenges in turn.

Participants discussed the complexity that distinguishes precision medicine in oncology from other areas in medicine: tumor heterogeneity; primary versus metastatic disease; variability of functional impact of biomarkers; treatment resistance; synchronization of drug and diagnostic development; the need for validation processes; informatics requirements; complexity of biological signaling pathways; and rapidity of science/technology evolution. In particular, the group explored process complexity – how the multiple distinct regulatory pathways for bringing a test to market and the inability of payers to know exactly which test was performed combine to raise concerns about quality, equivalency, and efficiency. SPOT/Dx participants felt that the nexus of these issues created a ripe opportunity for multistakeholder action.

The group also discussed how regulatory and reimbursement frameworks are acting as a choke on the innovation engine for molecular diagnostics. In contrast to drugs, where strong intellectual property rights and value-based pricing allow developers to recoup R&D expenses, the current system fails to provide appropriate incentives to develop evidence of clinical utility for molecular diagnostics. Payers stated that they are willing to pay for molecular diagnostics, but that *"the evidence in terms of outcomes and benefit [to support such reimbursement levels] is currently missing."* In response, diagnostic developers explained that the current level of cost-based reimbursement and the lack of market exclusivity for their tests prohibit the necessary investment to generate the costly evidence on outcomes. One subject matter expert concurred: *"On top of the low reimbursement, anybody can run a LDT [laboratory-developed test] around a mutation once it is known. There is a real danger that if we don't support them, these powerful diagnostic tools will fall by the wayside."*

The lung cancer case study: highlighting the limitations of the current system of oncology care and suggesting new approaches

The group explored the limitations of the current single-analyte, single-treatment paradigm by studying a case history of a woman (nonsmoker) who presented with metastatic lung cancer. In accordance with current guidelines, diagnostic testing was performed for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) abnormalities. The test was positive for the ALK fusion, and the patient was put on crizotinib. The patient had an initial response, but the disease progressed after three months (an early failure relative to crizotinib's median time to progression). The patient was then placed on chemotherapy.

The case study suggested the need for new approaches to development, regulation, and data collection in order to optimize the system's ability to consistently generate meaningful patient outcomes. The case focused participants' attention on the need for the healthcare system to generate convincing evidence that targeted therapies provide a real clinical benefit. From the payer perspective, the question is, *"What is the evidence that we are really improving the outcome by adding the expense?"*

SPOT/Dx participants acknowledged that systemic barriers have to date prevented precision medicine from delivering on the promise of "cures" or long-term "remissions" with respect to solid organ tumors. However, rather than second-guessing the viability of the precision medicine approach, the group chose to view these barriers as opportunities. As a clinical expert explained, *"I think it's fairly clear from the available evidence that this is the way forward. In virtually every case so far where a targeted agent has been*

compared to a previous standard of care/chemotherapy in a selected patient population, the targeted therapy has won. So there's plenty of evidence already that this can be a better approach. The challenge, as illustrated in this case study, is that the responses are not universal and are often short-lived, so that gets us back to the issue of needing a better understanding of the biology that underlies all this."

The lung cancer case study triggered a broader discussion about how to improve the outcomes of patients receiving targeted therapy. SPOT/Dx participants considered possible reasons for why a patient's therapy may fail earlier than expected. Among others, they include the possibility that the diagnostic test may be inaccurate and the fact that the tumor biology is complex and evolving. A clinician explained that *"the natural history of this disorder may be such that the drivers change over time and a single targeted agent isn't going to take care of that evolution."*

The group discussed the following opportunities to improve patient outcomes and maximize the benefits of precision medicine in oncology:

- **Raising diagnostic test quality and equivalence across tests through enhanced proficiency testing**

  Participants considered increasing the rigor of proficiency testing programs as a way of dealing with accuracy concerns and variance across labs and platforms. One subject matter expert remarked, *"Part of what this group has to figure out is how to come to some common platform of regulatory standards that achieve the goal of improving the quality without setting the bar so high that it drives everyone out of the business."* In other words, how can we preserve the innovation that comes through LDTs but increase the assurance that those tests are measuring the analytes they claim to be measuring and using the correct cut-off value or clinical decision point?

- **Commercializing a common panel of cancer mutations**

  As described above, tumor heterogeneity and evolution introduce great treatment complexity. All participants agreed that simultaneously determining the status of numerous actionable biomarkers early in the patient's care pathway would provide beneficial information and preserve precious treatment time. A common predictive panel would assist with the challenge of limited tissue and could also be used to accelerate the development of combination therapy. However, one developer worried, *"It's very unclear how that panel could be paid for, because many of those markers wouldn't be medically necessary at the point in time. This seems to be one of the biggest challenges."* One payer explained how they have assigned a code that covers all the markers with demonstrated clinical utility for each disease indication; for example, the code for non-small-cell lung cancer would cover and reimburse for different markers than the code for pancreatic cancer.

- **Developing precision medicine by capturing off-label use data**

   Patients are taking an active role in their care by obtaining next-generation sequencing (NGS) data, often outside of the relationship with their oncologist.[2] One oncologist described how a recent patient *"with non-small-cell lung cancer walked in with a NGS report that found nine different abnormalities in her tumor and listed some drugs that supposedly would work. In actuality, there is no knowledge that they would work, so what do we do with that? We don't know."* Another factor in the development of precision medicine is that the clinical utility of a tumor biomarker often depends on the anatomical origin of the tumor. For example, a second oncologist said that *"EGFR testing in breast cancer has been completely without value. There is no sensitivity or benefit to treating or targeting it, period … So one has to remain cognizant that precision medicine is going to be context specific, which may not be what everybody wants to be true."*

   A diagnostic developer suggested that this type of physician uncertainty demonstrates the need for additional protocols, studies, and patient registries. SPOT/Dx participants discussed how capturing data from off-label use would benefit the entire range of stakeholders. For example, payers could see which treatments are most effective in practice, and developers and regulators could detect meaningful signals that might lead to smaller clinical trials for FDA approval. While all stakeholders saw the potential value of such data, a key question remains on who should pay for its collection.

- **Enhancing the delivery of precision care through adherence to treatment guidelines**

   Separate from data accumulation is the need to measure to what extent oncologists are following professional guidelines. One clinician suggested that *"individually, oncologists should be looking at how they're treating disease and then comparing that to benchmarks such as the NCCN [National Comprehensive Cancer Network] guidelines."* SPOT/Dx participants applauded the efforts of the American Society of Clinical Oncology (ASCO) in this area, especially its Quality Oncology Practice Initiative (QOPI). QOPI is an oncologist-led, practice-based quality assessment and improvement program that employs measurement, feedback, and improvement tools for hematology-oncology practices.[3] Participants were also very enthusiastic about ASCO's CancerLinQ database program, which has the potential to deliver decision-support information to doctors while also measuring treatment decisions in real time against standards.

Opportunity areas for SPOT/Dx

To commit itself to the best use of its time and resources, the group discussed various priorities before narrowing its focus from the field of opportunities identified above. Participants selected two immediate priority areas: 1) improvement of the overall quality of diagnostic testing through some form of increased standardization and 2) consideration of the broader challenge of evidence collection in the real-world setting.

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[2] Next-generation sequencing (NGS) is a relatively new approach to DNA sequencing that increases the volume, speed, and accuracy of sequencing by performing millions of sequencing operations, known as reads, in parallel. Labs are able to use NGS to selectively sequence areas of the genome that may harbor cancer-related mutations. Panels of these areas may be viewed as an extremely data-rich version of multianalyte testing.

[3] For more information, see the QOPI website.

Improving diagnostic quality through more robust proficiency testing

Participants agreed that a set of quality standards, if systemically adopted, would allow patients and doctors to make more accurate treatment decisions and do so with greater confidence. By focusing on quality standards that are biomarker specific, participants want to ensure that the choice among available test platforms does not change the clinical prescription for a given patient.

A subject matter expert made the analogy to how physicians are assured that all drugs sold in the United States comport with the standards laid out in the United States Pharmacopeia and the National Formulary (USP-NF). The United States Pharmacopeial Convention is the nonprofit organization that not only publishes the written standards in the USP-NF but also provides highly characterized physical specimens that are used as reference standards by the pharmaceutical industry to help ensure the identity, strength, quality, and purity of medicines.[4] A similar set of documentary and reference standards for diagnostic tests would increase confidence in patients receiving oncology treatment based on currently available knowledge.

In addition, the group discussed how quality standards will be important as precision medicine moves toward narrower and narrower subtypes of cancer. Without standardization and collaborative databases, a regulator explained, *"We are not going to have enough patients with the necessary data points to make any sense of it."*

The participants who focused on this approach emphasized their desire to use existing pathways rather than reinvent the wheel. One clinician suggested, *"Let's put more rigor around the processes that already exist, and let's involve our pathologist colleagues. As we deal with more and more molecular testing, they are the gatekeepers and are partnering with the oncologist to help drive therapy decisions."*

The group emphasized the need to clearly define the incentives for labs to adopt any particular set of standards. Oncologists can play an important role by demanding that the labs that are testing their patients meet these standards. Most SPOT/Dx participants found it difficult to imagine that the FDA would itself administer proficiency testing of lab tests through a regulatory enforcement mechanism. Instead, most participants believed that payers should provide a financial incentive through differential pricing for laboratories to demonstrate compliance with a set of standards set by a professional society, such as the College of American Pathologists (CAP) or the Association for Molecular Pathology (AMP).

Participants discussed approaches to and considerations involved in widely implementing biomarker-specific quality standards. All agreed that the results of the proficiency testing should be transparent. One participant explained that a McKesson-type database of the variety used in Palmetto GBA's MolDx Program could be expanded to include a field showing that the particular test has satisfied the new accreditation standards.[5] Whether working with laboratories to build up a proficiency panel ahead of market authorization for a new cancer drug would be prohibited as pre-promotion of the drug is an open question, and this issue could be a barrier to implementation. Finally, a developer noted that proficiency testing for multianalyte diagnostics

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[4] For more information on USP-NF and reference standards, see the U.S. Pharmacopeial Convention.

[5] For more information, see Palmetto's MolDx website.

could have a heavy informatics burden and urged SPOT/Dx to consider additional informatics expertise if the group decides to address multiple-marker panels or NGS.

SPOT/Dx participants were excited at the prospect of continuing to work this problem. One industry participant remarked, *"It's not a dogmatic question about whether you're left or right, up or down. It's a process question, and the great thing about process questions is that they're solvable."*

Definition of outcomes and utilization of observational data

To truly realize a precision medicine paradigm, the healthcare system must be able to incorporate new scientific understanding into drug and diagnostic labels (potential for "adaptive labeling") as well track and evaluate broader outcomes from use of these treatments (diagnostics and drugs together). Participants acknowledged the value of the current randomized, controlled trial (RCT) system for establishing an evidence base, but also noted the current underutilization of the vast amounts of data available beyond the RCT.

One subject matter expert challenged the group to think expansively regarding data: *"When a new product is introduced into the marketplace, be it a test or a drug, it's introduced based on a very limited amount of evidence that typically is derived from relatively small studies and relatively homogeneous groups of individuals. All of the real information about the performance of that product comes in after the market introduction, and yet, that highly valuable information is never captured in any meaningful and useful way. So the real challenge is how to capture that post-market information in a way that helps inform the decisions that regulators, payers, doctors, and patients have to make every day."* This broader data set could be used for multiple purposes, including capturing off-label use data (as described earlier), adaptive labeling, and in the creation of a continuously learning system to develop more effective treatment courses based on real-world outcomes. Participants discussed how data from sources such as CancerLinQ, the MolDx database, registries, and other such data networks could be used to build a broader base of evidence for decision making.

One key challenge to using these broader data sources is the lack of agreement on what outcomes are of value to the health system and hence worth monitoring. At the meeting it became clear that different stakeholders valued different outcomes and lacked a common language for discussion. One industry participant found that, to his surprise, *"Many of the baseline definitions are missing."*

On the matter of defining endpoints, the group acknowledged that the preferred endpoints for the FDA are very different than those for the Centers for Medicare and Medicaid Services (CMS) and private payers. A diagnostic developer remarked, *"From our point of view, the demands for data by FDA and those for clinical utility by their sister agency CMS for coverage decisions and reimbursement decisions are not well coordinated."* The group noted the existence of a parallel review process for the FDA's Center for Devices and Radiologic Health and CMS and hoped to investigate whether there might be opportunities to expand this approach and create the basis for common understanding of outcomes. A payer expressed openness to *"convergence on the evidence side … as there are many positive benefits to harmonization between the regulatory and the reimbursement system,"* but warned that complete harmonization is unlikely because of

different institutional mandates. *"The regulatory system permits treatments on to the market. Payers are responsible for designing a benefits scheme that will in some affordable fashion permit them to deliver the care that is promised to a particular population. So payers must consider affordability, design, and other attributes."*

As the FDA and industry move more rapidly to recognize innovative "breakthrough medicines" and as precision medicine encourages stratified and hence smaller randomized, controlled trials than previously, there is increasing urgency to understand how to use the broader data networks to enable or refine better treatment decisions and outcomes, however defined. An oncologist, in considering observational databases, put it this way: *"I hear the great promise of this. On the other hand, I hear the tremendous angst about whether it is going to work or not. So I think my message is that we've got to get into the water and try it. It may not work, but we've got to have a plan here to get an observational database up and running in the oncology field."*

Next steps and conclusion

Tapestry Networks, together with the Working Group participants, will clarify and refine these priority areas, define principles and approaches to guide recommendations, and, in parallel, work to understand existing pilots and programs that can be built upon to address opportunities as they arise.

The Working Group participants were unanimous in committing to improving patient outcomes and moving the oncology field forward. As a drug developer said, *"I'm optimistic of the potential for this group to bring forth something that's truly actionable, to use the word of the day."*

About this document

Appendix: SPOT/Dx Working Group participants

Patient/policy advocates

- Jeff Allen, Executive Director, Friends of Cancer Research
- Andrea Ferris, President and Chairman, LUNGevity Foundation
- Nancy Roach★, Founder and Chairman, Fight Colorectal Cancer

Payers

- Naomi Aronson, Executive Director, Clinical Effectiveness and Policy, Blue Cross and Blue Shield Association
- Elaine Jeter★, Pathologist and Medical Director, Palmetto GBA
- Michael Kolodziej, National Medical Director, Oncology Solutions, Aetna
- Lee Newcomer★, Senior Vice President, Oncology, Genetics and Women's Health, UnitedHealthcare
- Ed Pezalla★, Vice President, National Medical Director, Pharmacy Policy and Strategy, Aetna
- Jeff Roche★ (Liaison to the Working Group), Lead Medical Officer, Coverage and Analysis Group, Center for Clinical Standards and Quality, Centers for Medicare and Medicaid Services

Regulators (Liaisons to the Working Group)

- Pamela Bradley, Personalized Medicine Staff, Office of In Vitro Diagnostics and Radiological Health, FDA – CDRH
- Jonathan Jarow, Acting Deputy Office Director, Office of Hematology and Oncology Products, FDA – CDER
- David Litwack, Personalized Medicine Staff, Office of In Vitro Diagnostics and Radiological Health, FDA – CDRH
- Michael Pacanowski, Associate Director, Genomics and Targeted Therapy, Office of Clinical Pharmacology, Office of Translational Sciences, FDA – CDER

Subject matter experts/technology specialists

- Steven Anderson, Global Head, Clinical Trials; Chief Scientific Officer, Oncology and Genetics, LabCorp Clinical Trials
- Frank Cockerill, Chair, Department of Laboratory Medicine and Pathology; President and Chief Executive Officer, Mayo Medical Laboratories, Mayo Clinic
- Stephen Grubbs, Principal Investigator, Delaware Christiana Care CCOP, Medical Oncology Hematology Consultants, PA
- Cliff Hudis, Chief, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center
- Kris Joshi★, Global Vice President – Healthcare, Oracle Health Sciences (former)
- Bob Lechleider, Chief Scientific Officer, United States Diagnostic Standards
- Doug Moeller, Medical Director, McKesson Health Solutions
- Richard Schilsky, Chief Medical Officer, American Society of Clinical Oncology
- Matt Zubiller★, Vice President, Strategy and Corporate Development, McKesson

Continued overleaf

Industry representatives

- Paul Billings, Chief Medical Officer, Life Technologies
- Peter Collins★, Vice President, Diagnostics, GlaxoSmithKline
- Nic Dracopoli★, Vice President, Head of Oncology Biomarkers, Chief Scientific Officer, Next Generation CTC Technology, Janssen R&D, Pharmaceutical Companies of Johnson & Johnson
- Rob Dumanois, Manager, Reimbursement Strategy, Life Technologies
- Chris Jowett, Global Commercial Head, Companion Diagnostics, Abbott Molecular
- Ron Mazumder, Global Head, Research and Product Development, Janssen Diagnostics
- Jonathan Pan, Director, Oncology Companion Diagnostic and Disease Strategy, GlaxoSmithKline
- Scott Patterson, Executive Director, Medical Sciences, Amgen
- Patrik Ringblom, Global Commercial Strategy Leader, Oncology, Janssen Global Services
- Ryan Saadi, Global Market Access Head, Health Economics and Reimbursement, Oncology, Johnson & Johnson
- Peter Sandor, Vice President, Therapeutic Area Head, Oncology Global Marketing, Amgen

Dinner guest speaker

- Bill Novelli, Distinguished Professor, McDonough School of Business, Georgetown University

★Participant was unable to attend December 2–3, 2013 meeting.