

Diagnostic Quality Assurance Pilot



Summary of Themes – March 22, 2021

Addressing lessons from the Diagnostic Quality Assurance Pilot

Introduction

In 2013, the Sustainable Predictive Oncology Therapeutics and Diagnostics (SPOT/Dx) working group committed to developing a new approach to assess laboratory test validation and performance. Consequently, the Diagnostic Quality Assurance Pilot was launched in 2016 with the aim of ensuring that oncologists could confidently select appropriate targeted therapies for treatment, regardless of which molecular diagnostic test was used to inform their recommendation.¹ A multistakeholder steering committee—which included representatives from the American Society of Clinical Oncology, the College of American Pathologists, Friends of Cancer Research, public and private payers (including Palmetto GBA, Blue Cross Blue Shield Association, and others), industry representatives from Amgen and Illumina, and observers from the National Cancer Institute, US Food and Drug Administration (FDA), and Centers for Medicare and Medicaid Services—helped inform the pilot's efforts. The Scientific and Technical Working Group, overseen by the College of American Pathologists and comprising leading molecular pathology experts, supported the pilot's technical design and execution. Steering committee and working group leadership convened in December 2020 with alumni from the original SPOT/Dx working group and other stakeholders for a summit to discuss the pilot's results and implications.

Over the course of implementation, the pilot provided clinical laboratories with engineered wet-lab reference samples, in-silico sequence data file samples, and digital images of tissue section slides, and it developed an evaluation methodology to assess the analytical performance of validated laboratory-developed tests (LDTs) relative to an FDA-approved companion diagnostic (CDx) for a targeted cancer therapy. During the summit, pilot leadership and others contended that well-defined reference samples and in-silico files could offer an enhanced quality assurance (QA) approach that could complement existing processes such as proficiency testing.² Many participants agreed there is value in understanding how performance compares across laboratories. Some stakeholders, however, emphasized the complexities and limitations of the pilot's approach. That said, even the pilot's skeptics recognized its value as a starting point to improve understanding about laboratory test validation and QA as large-scale, complex next-generation sequencing (NGS) panels become more prevalent.

This *Summary of Themes* provides further synthesis of the December virtual summit. *Please see the Diagnostic Quality Assurance Pilot website for additional background and details on the pilot. For a list of summit participants, please see the appendix on page 12.*



Stakeholders have diverse interpretations of the pilot's outcomes

The summit aimed to understand whether the community agreed on the pilot's findings, recognizing that the pilot itself was small scale. Participants debated the pilot's design and conclusions throughout the three-day summit. The pilot data have not yet been published but were presented to participants to inform the basis of summit discussions. Summit conversations demonstrated that the community has diverse perspectives on interpretation of the pilot's data, though some noted the pilot's approach could lay the groundwork for future pragmatic approaches to QA.

The pilot was designed to determine whether the reference samples and in-silico files outlined by the Scientific and Technical Working Group could provide a diverse group of laboratories with an opportunity to demonstrate the performance of their tests relative to a CDx. The candidate CDx used for comparison was a two-gene, multiple-variant NGS panel—the Praxis Extended RAS Panel—voluntarily proposed by biopharmaceutical developer Amgen and Amgen's CDx partner, Illumina. Praxis helps identify patients with colorectal cancer who are eligible for treatment with Vectibix (panitumumab), which, at the time of the pilot's launch, was undergoing FDA review for a new indication.³ Pilot leadership aimed to develop the samples prior to FDA approval of Praxis and Vectibix so that they could be available for postmarket utilization by laboratories, should the pilot's approach be expanded.

Proof-of-concept data verified that the reference samples and in-silico files worked as planned. Pilot leadership distributed the first round of wet-lab samples in December 2018 and received results from laboratories in March 2019. Pilot data indicated that the reference samples and in-silico files worked as intended. As an incidental finding, most participating laboratories' performance met that of the CDx, although the pilot observed variability by some laboratories. The latter point prompted robust discussion among participants.

Across conversations about the pilot, some members of the pathology community dismissed the variability the pilot demonstrated, expressing concerns that the pilot was too difficult and, in short, *"intended to force labs to failure."* Leadership of the pilot vigorously countered this point, emphasizing that such an outcome was not the intention of the group and that concerns about the pilot's level of difficulty did not arise until after the pilot's data was revealed. Others emphasized that most laboratories demonstrated strong performance, which suggests the bar for the pilot was not set too high. One laboratory expert said, *"To insist [the project intended to force labs to failure] is to ignore the labs that did well."* Another, underscoring that the pilot occurred at a specific point in time in a technology landscape that is constantly changing, said, *"It's almost too easy to criticize the pilot's design in hindsight, and that would just be unfair."*

The following specific areas of disagreement featured prominently in summit discussions.



Clinical implications of the variability observed in the pilot on the patient population

Participants engaged in debate over whether the variability around laboratories' lower limit of detection (LOD) that the pilot identified was clinically meaningful. The pilot assessed, among other factors, performance around laboratories' LOD as defined by the CDx, which was set at 5% variant allele frequency (VAF) or "the percentage of sequence reads observed matching a specific DNA variant divided by the overall coverage at that locus."⁴ Some participants agreed with the observation of one pathologist who said that the variants involved in the pilot "were unusual variants seen at very low variant allele fractions." Therefore, some concluded that the impact on the patient population would be limited.

Others disagreed, highlighting that, rare or not, the variants included in the pilot were clinically meaningful because of their inclusion in the CDx kit. "These variants were selected based on the companion. These were not somehow picked to exploit weaknesses in bioinformatic pipelines or anything like that. They were picked because that's what was actually on the Praxis panel and were related to the selection of Vectibix," one participant said. Others noted that, on the whole, patients with variants at low VAFs may not be exceptionally rare, with one participant citing that "studies show that between 10% and 15% of clinical samples for many actionable targets may be in the 5%–10% VAF range," depending on whether the patient has primary or recurrent disease.

"If these variants are placed on a specific CDx but there has only been five or fewer of such variants ever detected in clinic, how relevant is it to clinical practice?"

—Payer

"There is a premise to these questions that I think is concerning, which is basically to suggest that just because these variants are rare or because we tested at the limit of detection of 5%—which, again, was because it was pegged to the companion—that somehow miscalling these is okay."

—Subject matter expert

Preanalytical and operational issues involved in targeting low VAFs

Some participants from the pathology community noted other issues related to the inclusion of low VAFs in the pilot. Many laboratories, some noted, do not report on specimens with low VAFs as a general policy. Pilot leadership underscored that only laboratories that incorrectly reported variants that were present above their stated LODs were cited as having made an error.

Additionally, some pathologists expressed concern about the inclusion of variants at laboratories' stated LODs because of preanalytical complexities. VAF is, several stakeholders emphasized, inextricably linked with tumor cellularity, or the amount of tumor cells in the specimen and their arrangement into clusters.⁵ Assessments of cellularity can vary extensively in clinical practice and require pathologists' analysis of several factors upon examining a specimen, as summit participants reported. Therefore, some emphasized that because claims about a test's ability to detect certain VAFs cannot be isolated from a specific specimen's cellularity, the failure of laboratories to appropriately detect or report low VAFs near their LOD in engineered reference

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“We do put allelic frequencies out there very, very low. We go down to 5%, 2.5%, and we’ve even put out 0.1% allelic frequency. And again, it comes back to giving the labs the opportunity to interrogate their data to see whether or not their assay would pick it up, regardless of whether or not they would report it clinically.”

—European quality assurance laboratory expert

samples should not be afforded much weight.⁶ A pathologist said, *“Clinical significance of VAF is entirely dependent on the variant and the percentage of tumor cellularity. By itself, VAF has little meaning.”* Others acknowledged this complexity, highlighting that metrics that seamlessly integrate tumor cellularity and VAF remain elusive, but they urged that the community not *“make the perfect the enemy of the good.”*

One stakeholder noted that *“many laboratories claim 5%”* VAF, and thus it is important to assess how those claims compare with practice, at least to the extent that practice can be mimicked through use of reference samples. Furthermore, others emphasized that visual assessments of tumor content and reporting on VAFs are already included in existing QA

methods, and some European stakeholders noted that their QA assessments routinely test low VAFs for certain types of assays, including NGS.

The role of the CDx as the gold standard

The pilot aimed to assess LDT performance characteristics based on the specification of the FDA-approved Praxis Extended RAS CDx. Some participants emphasized challenges with doing so. One questioned the value of using the CDx as a performance standard given the rapid pace of innovation: *“In light of thinking of what we want, which is the right information for proper patient management, a CDx may or may not align with that. The CDx goal may be, as stated by a pharmaceutical company, to know whether that specific drug may be useful for that patient—but that might not be a broad enough diagnostic test to give the physician all of the information that they need, particularly in light of the technologies that we have at our disposal.”*

Others disagreed, emphasizing the pragmatism of comparing laboratory performance to the CDx. An industry representative underscored, *“I certainly don’t believe that the in vitro diagnostic is the gold standard, but it is the standard. Right or wrong, it’s what was used to determine the clinical validation for that analyte paired with that drug. Is that perfect? As I just stated, absolutely not, but it’s what’s available.”*

Finally, some stakeholders from the laboratory community did not question the value of using the CDx as the standard but instead called for enhanced dissemination of CDx performance characteristics for laboratories to more readily duplicate. Other stakeholders contested this point, indicating that information on performance characteristics is available—*“performance characteristics of FDA-approved companion diagnostics are always available on the FDA website, including the test’s package insert,”* one said—which signals a need for greater clarity on the resources and appropriate level of detail available to laboratories.



Participants proposed several high-level concepts for improving similar studies and QA efforts

The pilot's implementation did not occur in a vacuum: the technology landscape for diagnostics has evolved rapidly in recent years, especially in oncology. Data collected by the American Society of Clinical Oncology in 2017 indicated that 75% of oncologists used NGS test results to inform patient-care decisions.⁷ Against this backdrop and despite an absence of consensus about the pilot's outcomes, participants discussed how the pilot, as an initial effort, could help inform or shape the future of molecular diagnostic QA.

Future research studies or pilots in this space should focus on clinical reporting and LOD complexities

Participants debated how the community could gather more or better data to help understand potential QA vulnerabilities. Future studies like the pilot should,

some urged, focus on laboratory reporting practices, given that laboratory reports may communicate important claims, complexities, and/or test limitations. External QA programs in Europe have evaluated and scored the content of clinical reports for many years as an accompaniment to the technical performance demonstration.⁸ Mock clinical reports were omitted from the pilot study, which pilot leadership and others acknowledged as a limitation. Some stakeholders cautioned that assessing clinical reports lies at the *"border of technical issues and practice of medicine"*; however, several continued to advocate for closer understanding of laboratory reports. A

regulatory representative emphasized their importance: *"We look very carefully at the reports, what they say, what the limitations are. And now FDA has very clear recommendations for what can be in a 510(k) report for an assay. What do you report? If there are certain variants or amplicons, depending on how the assay is set up, that you repeatedly in your validation cannot detect, then that just needs to be communicated in the report."* Similarly, for some stakeholders, future studies that assess how laboratories address LODs in their reports is of particular interest and may help inform future good practices. *"I would definitely push for a way to capture whether a response was below a lab's LOD—did they see it and just did not report it? So, I think that clearly needs to be added in some capacity."* The pilot provided this information in part through laboratories' responses in the pilot's data collection form, but some participants believe this issue warrants more detailed clarification and evaluation in the future.

"There are so many variables that we have to consider. And that professional practice piece of it—that is just as critical as the technical aspect. That's where having that clinical report, knowing how that pathologist, that molecular diagnostics expert can communicate, is super critical."

—Pathologist

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The pilot's in-silico process could have merit for QA in the short term

The in-silico process was prioritized by several stakeholders as a valuable component of the pilot. It could be employed to inform QA efforts today or to educate laboratories about potential bioinformatics vulnerabilities. The promise of the pilot's in-silico process could be further realized, some emphasized, if operational bottlenecks for laboratories, especially the importation of in-silico mutagenized sequence files into vendor-supplied bioinformatics pipelines as is discussed below, were resolved.

The pilot took a novel approach to assessing laboratories' bioinformatics pipelines. One pilot leader explained, *"We have not seen studies until this one that have paired samples of wet-lab and in-silico data files that are on the same variants and assay, tested by the labs at the same time."* Pilot leadership underscored the value of the customized in-silico processes implemented as part of the pilot. Customized in-silico files, when compared with engineered wet-lab samples, are lower cost, flexible, and able to test a wide variety of variants. Furthermore, the in-silico process proved valuable in helping to isolate the root cause of some laboratories' difficulties.

Pilot leadership and other stakeholders also discussed several caveats to in-silico performance assessments. First, they would optimally be offered in parallel to a wet lab/reference sample-based challenge. Second, laboratories encountered several operational challenges for which they were *"really not prepared."* In particular, laboratories faced logistical challenges in introducing external files into vendor-supplied bioinformatics pipelines that were not linked to a corresponding clinical sample that had been assessed internally. One subject matter expert said, *"There is a bottleneck in laboratories understanding how to insert these files, especially laboratories that may not be in an academic or tertiary-care medical center. There are a lot of laboratories that don't necessarily have that expertise, and anything that we could do to help them use these files would go a long way in positioning labs to develop highly validated tests for higher quality."*

Finally, some participants recommended that platform manufacturers should play a role in identifying and sharing work-around procedures to facilitate a more seamless process for laboratory staff. One expert cautioned that *"there's always going to be a challenge by introducing an electronic signature of a variant into a data file, versus having those variants in the samples";* the expert noted, however, that *"it's not insurmountable"* and suggested further conversations to advance this concept.

"One of the best use cases for these data is to use it to arm the consumers—in this case, laboratories who are shopping for assays, for kits, for bioinformatic pipelines to understand that the thing that they're purchasing can detect the variants that it seeks or states that it can detect. It would be good for providers to have the pipelines tested in advance of them purchasing them to understand the limitations of what these tests can and cannot do. So that's one way that this could be used moving forward."

—Payer

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Reference samples have value, but how to incentivize and sustain their utilization remains an open question

Despite divergent viewpoints in the pilot's outcomes, most stakeholders agreed that engineered reference samples have a role to play in enhancing test validation and/or ongoing QA. However, some emphasized that more salient questions lie in understanding how to use reference samples

"Having standardized reference materials is absolutely the right way to go."

—Pathologist

in a way that is timely, meaningful, and cost effective for the community. Judging from the tenor of summit discussions, answering these questions in a consensus-based fashion may take time. One stakeholder said, *"To me, the single biggest challenge here is not, Can you use reference samples? Rather, it's, How do you do it in a way that generates sustainability and timeliness?"* Participants addressed several issues to

resolve for development and implementation of reference samples and in-silico data files to enhance QA on a large-scale basis.

Both engineered reference samples and patient specimens have a role to play, but the community lacks consensus on the optimal use cases for each

Broadly, many participants recognized that relying solely on patient specimens is not a scalable or sustainable solution. Some, however, emphasized that specific types of reference samples should be used for specific types of QA activities. A laboratory representative said, *"One thing that would be good to differentiate is the goals of providing either digital or wet-lab specimens and whether these would be intended for use primarily for proficiency testing or for test validation and development, because the kind of specimens and the variant frequencies that we would require for those two different scenarios could be very different."*

"We had a lot of discussion [in our breakout group] about NTRK [neurotrophic tyrosine receptor kinase fusions]. And there are going to be those variants that are even less frequent, and it's just very difficult for labs to get samples to validate their tests."

—Industry representative

Some pathologists specifically highlighted the preference for patient specimens, especially for initial test validation. If test validation is primarily conducted on engineered samples, laboratory systems can develop biases for detecting variants in reference samples that they may miss in real clinical specimens, some participants argued. Others disagreed, underscoring that reference samples can be helpful during validation to understand a test's performance with less common variants. One payer noted, *"When you're getting samples to validate a test, SNVs [single nucleotide variants] are everywhere—so it's no surprise that labs have no difficulty in finding them, whereas indels are more difficult to find and, especially if you don't do a thorough validation, you may not even be sampling them as a part of your validation."*

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It remains unclear what institutions should define gold standards and develop reference materials

Some stakeholders underscored that the value of the pilot's approach lay in introducing an external standard that can allow laboratories to assess how their assays compare with one another. However, who sets that external standard and who pays for reference samples and in-silico file development remains a topic of debate. Participants offered several considerations:

- **Institutions with appropriate expertise should lead.** Some stakeholders continued to reiterate the need for third-party institutions with a core business relating to standards development to focus on crafting “*universally accepted*” QA standards and materials.
- **Regulators could help define and develop reference samples.** Some recommended an enhanced role for regulatory bodies in defining standards and even directly developing reference samples to compare performance across assays. Some participants pointed to the FDA's development of a well-characterized reference panel during the COVID-19 crisis, which enabled laboratories to compare the analytical performance of their COVID-19 assays, as a precedent that could be expanded.⁹
- **Pharmaceutical manufacturers may not support reference-sample development.** Summit participants discussed the role of pharmaceutical manufacturers in future enhanced QA approaches. In the pilot's methodology, a pharmaceutical manufacturer underwrote the cost of reference-sample development as part of a premarket development process. Industry representatives indicated that in the future, doing so would be challenging. Pathways for developing highly regulated products are already complex, and reference-sample development remains outside of the industry's core business. An industry representative said, “*I don't know that we, as individual companies, are in the best position to do it successfully.*” That said, industry players echoed support for ongoing involvement in similar efforts and noted that an industry role would be best suited as part of a broader multistakeholder consortium.

“In-silico samples are a useful means of identifying or being able to test a platform's ability to detect certain kinds of variants, particularly more difficult to come by variants.”

—Payer

The community could consider incentives for investing in enhanced QA

Recognizing that there is always value in improving quality, participants at the summit discussed methods for incentivizing QA strategies, including those that involve reference samples. Specifically, for some participants, one of the principal challenges is how to encourage the use of reference samples on a sustainable basis. Other participants noted that efforts to incentivize quality must be carefully balanced with the need to increase access to biomarker testing, which is currently underutilized, to prevent any negative impact for patients in need of testing.

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Some acknowledged that laboratories may not have the resources to invest accordingly in reference samples unless validation and ongoing QA processes are more systematically required and standardized by relevant stakeholders. The significant cost of these samples is a factor the community needs to consider. One subject matter expert said, *“Horizon, SeraCare, and other groups, they could make beautiful controls. A problem comes in an LDT laboratory space where people are going to think about money—and well-manufactured GMP [Good Manufacturing Practice] control material is expensive. And so people are still going to err on the side of using their own favorite. I think the pressure needs to be on the payers to demand that some sort of validation is given such that assays are testing the relevant genes.”*

As noted in the comment above, some stakeholders considered whether payers have a more prominent role to play in encouraging test validation and assurance processes. For some payers, a laboratory *“is considered as a manufacturer of a service or test and still has to abide by all the same rules to demonstrate that the service that’s being performed is a quality service and results are accurate.”* One described his institution’s specific experience: *“Upon reviewing validations, we’re refusing to reimburse 50% of these tests because we don’t think that the lab performance characteristics are good enough.”* Some acknowledged the role of Palmetto GBA’s MoIDx Program as a leader in laboratory-related coverage policies, given that MoIDx requires detailed validation data from laboratories for tests to receive coverage. However, participants acknowledged that some payers may not be sufficiently educated in laboratory related topics to be able to assess for quality and others emphasized the laboratory community should lead on QA-related issues.

More broadly, lack of consistency and standardization in testing can create undue burden on patients and inefficiencies across the healthcare system. Specifically, a payer noted that some cancer institutions require re-testing of patients within their own laboratories once a patient enters the system.

Additional lessons from the pilot can support enhanced QA for the technology landscape of tomorrow

In addition to conversations that considered short- and mid-term application of the pilot’s outcomes, summit participants discussed the pilot’s long-term relevance to an ever-changing molecular diagnostics landscape. More gene sequencing test panels are available to survey hundreds of genes and inform oncology treatment, including FDA-approved companion diagnostics, such as Foundation Medicine’s FoundationOne CDx.¹⁰ During the summit, participants discussed the importance of the pilot’s QA approach for a two-gene panel, considering the advancement of larger panels since the pilot’s launch. One payer described the present moment as a period of transition from *“an analyte-specific view of the world, where we have to look at specific analytes—one gene, one mutation for one drug—”* to a stage where *“we can look at literally everything all at once.”*

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The discussion among participants moved to acknowledge that as therapies increasingly target rare biomarkers and as the size of panels increases, the advancement of laboratory competency in detecting a range of mutations—including complex and rare ones—is of utmost importance. Thus, most emphasized the need for pragmatic approaches. Specifically, several participants called for a QA paradigm that focuses on assessing performance for classes of variants such as “*single nucleotide variants, indels, structural variants, copy number variations, etc.*” Participants noted that such an approach underscores that the community cannot test for every single possible variant; rather, it would be a starting point that, over time, could be augmented by real-world evidence generated by laboratories that could contribute to the growing body of data linking variants to therapeutic approaches.

Conclusion

Individual pathologists and pathology professional organizations have diverse interpretations of the pilot’s outcomes and their generalizability. However, many stakeholders that participated in the summit agree that reference samples that enable enhanced test performance analysis and comparison are valuable. Several also agreed that bioinformatics pipelines and their potential vulnerabilities need greater attention. Some want to learn more from stakeholders outside the United States who frequently implement external QA approaches that are not dissimilar to the pilot’s approach.

Despite the divergent viewpoints, all stakeholders acknowledged that science is changing rapidly and performance of tests for detecting rare, complex mutations will become increasingly important. As the science advances, some noted that quality assurance processes will continue to evolve in parallel. As this evolution occurs, participants agreed on the ongoing importance of patient-centricity in diagnostics and testing. One industry participant said, “*If we think in terms of patients, what really gets us to the bottom line is, Can we produce high-quality tests despite the evolution of the technologies?*”

Pilot leadership will consider comments from all stakeholders participating in the summit as it revises a technical manuscript detailing the pilot’s methodology and data and a white paper discussing lessons learned and remaining questions for the community to consider.

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About this document

This *Summary of Themes* reflects the use of a modified version of the Chatham House Rule whereby comments are not attributed to individuals, corporations, or institutions. Italicized quotations reflect comments made by participants before and during the meeting.

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Appendix: Participants

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 - Megan Doyle, Global Regulatory and R&D Policy Lead, Diagnostics, Digital Health, and Combination Products
 - Greg Friberg, VP & Therapeutic Area Head, Global Development
 - Molly Martell, Global Lead, Diagnostic Payer Strategy
 - Dave Stanforth, Director, Clinical Biomarkers and Diagnostics, Head of Diagnostics Strategy and Development, Amgen
- **American Society of Clinical Oncology:** Tom Oliver, Director, Clinical Practice Guidelines Division
- **Association for Molecular Pathology:**
 - Mary Williams, Executive Director
 - Robyn Temple-Smolkin, Director, Clinical & Scientific Affairs
- **Blue Cross and Blue Shield Association:** Naomi Aronson, Executive Director, Clinical Evaluation, Innovation and Policy
- **Centers for Disease Control and Prevention:** Lisa Kalman, Health Scientist
- **Centers for Medicare and Medicaid Services:**
 - Joseph Chin, Deputy Director, Coverage and Analysis Group
 - Sarah Harding, Policy Analyst, Director Division of Ambulatory Services, Center for Medicare
 - Penny Keller, Division of Laboratory Services, Center for Clinical Standards and Quality, CLIA
 - Faye Valcarel, Center of Clinical Standards and Quality, Survey & Certification Group, Division of Laboratory Services, CLIA
 - Amy Zale, CLIA Policy Branch B, Branch Manager
- **College of American Pathologists:**
 - Dara Aisner, Associate Professor, Pathology, University of Colorado School of Medicine, CAP Genomic Medicine Resource Committee

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- Neal Lindeman, Vice Chair for Molecular Pathology at the Brigham and Women's Hospital, Associate Professor of Pathology, Harvard Medical School, Vice Chair, CAP Molecular Oncology Committee
- Christina Lockwood, Associate Professor and Director of the Genetics and Solid Tumor Diagnostics Laboratory at the University of Washington, Medical Director of the Brotman Baty Precision Medicine Institute, and Clinical Director of the Northwest Genomics Center, CAP Molecular Oncology Committee
- Eric Konnick, Pathologist, Seattle Cancer Care Alliance and University of Washington Medical Center, Assistant Professor of Laboratory Medicine (UW), Vice Chair, CAP Genomic Medicine Resource Committee
- Patty Vasalos, Technical Director, Scientific Resources, CAP
- **Emory University School of Medicine:** Barbara Zehnbauer, Adjunct Professor of Pathology
- **European Medicines Agency:** Markus Paulmichl, Vice Chair, EMA Pharmacogenomics Working Party
- **eviCore:** Lon Castle, CMO, Laboratory and Specialty Drug Services
- **Food and Drug Administration:**
 - Steven Lemery, Acting Division Director, Division of Oncology 3, CDER
 - Michael Pacanowski, Associate Director, Genomics and Targeted Therapy, Office of Clinical Pharmacology, Office of Translational Sciences, CDER
 - Wendy Rubenstein, Director, Personalized Medicine
 - Julie A. Schneider, Regulatory Scientist, Office of Hematology and Oncology Products, CDER
 - Zivana Tezak, Associate Director for Science and Technology, Office of In Vitro Diagnostics and Radiological Health, CDRH
- **Frederick National Laboratory for Cancer Research/FNIH:** Mickey Williams, Director, Molecular Characterization Laboratory
- **Freenome:** Girish Putcha, Chief Medical Officer
- **Friends of Cancer Research:** Jeff Allen, President and CEO
- **Genentech-Roche:**
 - Katia Basset, Principal CDx Project Leader
 - Danelle Miller, VP, Global Regulatory Policy & Intelligence, Roche Diagnostics

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- Eric Peters, Director and Head, CDx
- **Genomics Quality Assessment:** Sandi Deans, Consultant Clinical Scientists and Director; also NHS England, National Laboratory & Scientific Lead (Genomics)
- **Gilead:**
 - Terrell Baptiste, Senior Manager, Sr. Manager Regulatory Policy and Intelligence
 - Neville Mehenti, Senior Director, Global Commercial Product Strategy
 - Scott Patterson, VP, Biomarker Sciences
- **Horizon Discovery:**
 - Keith Cannon, Director, Commercial Product Management, Diagnostics
 - Jennifer Keynton, Manager R&D Diagnostics
- **Humana:** Bryan Loy, Physician Lead, Oncology, Laboratory, and Personalized Medicine
- **Illumina:**
 - Phil Febbo, SVP and CMO
 - Karen Gutekunst, Vice President of Diagnostic Development
- **LabCorp:** Anjen Chenn, Discipline Director, Molecular Oncology
- **Len Lichtenfeld,** former Deputy Chief Medical Officer, the American Cancer Society
- **LUNGevity Foundation:** Andrea Ferris, President and CEO
- **Massachusetts General Hospital:** Keith Flaherty, Director of the Henri and Belinda Termeer Center for Targeted Therapy
- **National Cancer Institute:**
 - Tracy Lively, Chief, Diagnostics Evaluation Branch, and Deputy Associate Director, Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis
 - Lisa Meier McShane, Associate Director, Division of Cancer Treatment & Diagnosis, and Chief, Biometric Research Program
- **National Institute of Standards and Technology:** Justin Zook, Human Genomics Team Leader
- **NorthShore University Health System:** Karen Kaul, Chair of Pathology and Laboratory Medicine
- **New York State Department of Health:** Erasmus Schneider, Associate Director for Research and Technology, Wadsworth Center

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- **Pacific Business Group on Health:** Emma Hoo, Director, Pay for Value
- **Palmetto GBA:** Gabriel Bien-Willner, Medical Director and CMO, MoIDx
- **Thermo Fisher:**
 - Garret Hampton, President, Clinical Sequencing and Oncology
 - Kelli Tanzella, Senior Director, Global Regulatory Affairs, Clinical, & Compliance
- **UnitedHealthcare:** Jennifer Malin, Senior Medical Director, Oncology & Genetics
- **University of Chicago Medicine:** Blase Polite, Associate Professor of Medicine, Deputy Section Chief for Clinical Operations, and Executive Medical Director for Cancer Accountable Care
- **University of Michigan Comprehensive Cancer Center:** Daniel F. Hayes, Stuart B. Padnos Professor of Breast Cancer Research
- **Washington University School of Medicine:** John Pfeifer, Vice Chair for Clinical Affairs, Pathology and Immunology and former Quality Pilot Scientific Technical Working Group Chair

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Endnotes

¹ For additional details on the pilot, please see [“Diagnostic Quality Assurance pilot,”](#) Tapestry Networks, accessed January 28, 2021.

² For a definition of proficiency testing and more information on its processes, please see Centers for Medicare and Medicaid Services, [Proficiency Testing and PT Referral Dos and Don'ts](#) (CMS: September 2017), 2.

³ Vectibix and Praxis were approved by the FDA in 2017. [“FDA Approves Vectibix® \(Panitumumab\) for Use in Wild-Type RAS Metastatic Colorectal Cancer,”](#) Amgen, news release, June 29, 2017.

⁴ Samuel P. Strom, [“Current Practices and Guidelines for Clinical Next-Generation Sequencing Oncology Testing,”](#) *Cancer Biology & Medicine* 13, no. 1 (March 2016), 5. Note that in the clinical trial for the Extended RAS panel and Vectibix, clinical response was seen in patients with as low as 2.6% VAF.

⁵ Irina Heid, et al., [“Co-clinical Assessment of Tumor Cellularity in Pancreatic Cancer,”](#) *Clinical Cancer Research* 23, no. 6 (2017), 1462.

⁶ Some stakeholders noted following the meeting that another critical challenge is that the manner in which laboratories determine their LODs can vary and is not transparent to external stakeholders. A participant said, *“Labs need to provide greater clarity about what their LOD VAF truly means. Is 5% VAF detected by mixing 5% variant DNA with 95% normal DNA? Or is 5% VAF detected from a starting sample of 50% or greater tumor-cell content? 30% tumor? 10% tumor?”*

⁷ Andrew N. Freeman, et al., [“Use of Next-Generation Sequencing Tests to Guide Cancer Treatment: Results From a Nationally Representative Survey of Oncologists in the United States,”](#) *JCO Precision Oncology* (November 13, 2018), 1.

⁸ Lien Tembuysen, et al., [“Higher Quality of Molecular Testing, an Unfulfilled Priority: Results from External Quality Assessment for KRAS Mutation Testing in Colorectal Cancer,”](#) *Journal of Molecular Diagnostics* 16, no. 3 (2014), 371-377; Susan D. Richman, et al., [“RAS screening in colorectal cancer: a comprehensive analysis of the results from the UK NEQAS colorectal cancer external quality assurance schemes \(2009–2016\),”](#) *Virchows Arch.* 471, no. 6 (2017), 721–729; Ellen Bellon, et al., [“External quality assessment for KRAS testing is needed: setup of a European program and report of the first joined regional quality assessment rounds,”](#) *The Oncologist* 16, no. 4 (2011), 467-478.

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