Review Companion Diagnostics Forum, Dec 6-7 2017, New Jersey Hospital Association Conference and Event Center, Princeton, NJ

1. High-level Messages and Key Points

On December 6 - 7, 2017, a group of experienced and knowledgeable leaders in companion diagnostics convened in Princeton, NJ, to present talks and discuss recent and emerging advances. Speakers were invited to address how companion diagnostics coupled with precision medicine have been demonstrating value in clinical trials and in the market. In some cases, the markers were already in the List of Cleared or Approved Companion Diagnostic Devices, others were in trials but had already shown value for other marketed indications.

A clear set of messages was reinforced throughout the Forum: the first point, ***companion diagnostics are well into the first generation of operational use and a new generation is already entering the market***. Issues yet to be determined are the market value of reimbursement and the designation of diagnostic devices with a particular therapeutic use (e.g., complementary vs companion). In short, the question is the competitive value of having a diagnostic device "... stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product." (FDA List of Cleared or Approved Companion Diagnostic Devices, paper on Current Status of Companion and Complementary Diagnostics: Strategic Considerations for Development and Launch).

A second point was that the ***next generation of precision*** * ***diagnostics is more likely to be based on panels of analytes***. In fact, the timing of the event coincided with a recent spate of announcements about approvals for Foundation One CDx, Oncomine Dx, MSK-Impact panel, and the first FDA-approved, biomarker-defined tumor indication (Pembrolizumab for MSI-high cancer).

* Precision diagnostics as used here includes companion diagnostics, complementary diagnostics, and laboratory-developed tests, as well as other tests that can lead to specifying a medical intervention. FDA's definition of companion diagnostics retains its distinction as "***essential*** for the safe and effective use of a corresponding drug or biological product.

Third, the ***supporting bioinformatics will become more sophisticated*** as more panel assays are released to market. Not only will bioinformatics become more powerful (draw on larger data sets, faster processing) but the user interfaces will become more intuitive, allowing for easier adoption by researchers and healthcare providers. Along these lines, Katarina Wikstrom (Almac Group) mentioned a development project to use IBM Watson for its potential to analyze gene assay results for actionable alterations, therapies with clinical trials, and existing FDA-approved drugs. Tools like Watson will need to become more accessible to users in parallel with increasing power to structure and mine data.

A fourth point, also emphasized already by many in the field, is the critical need for ***collaboration and coordination*** in the development of new precision diagnostics including, e.g., finding the best partners, agreeing on goals, roles, responsibilities, timelines, and deliverables. Kim Folander, Michele Cleary, Flora Berisha, and Chris Major related their perspectives in their talks based on their experiences. A point stressed by all speakers ist that all stakeholders (internal and external) must be aligned for a project to succeed.

In the background of all this activity, business models are also being developed to determine the optimal paths for different assay types, applications, and positioning both the diagnostic and therapeutic in new growth areas. Critical to the models will be the value of inclusion on the label, reimbursement, and uptake by practicing physicians. We will keep an eye on these developments as the field continues to mature.

2. Lessons Learned

Participants agreed generally on the consensus that **companion diagnostics are already influencing biopharma practices** - e.g., coordination with partners, timing of projects, bridging studies from clinical trials to market. - and will inform the upcoming generations.
Also, the fact that multi-panel assays are now more likely to emerge than the current paradigm of "single-analyte diagnostic for one specific therapeutic indication."

BioInformatics will need to be made more accessible to all users, especially as panel-based assays become more prevalent. Conveying complex data to physicians, payers, and other stakeholders will require transparent analytical capabilities, explanatory graphic displays, clear treatment options, and user-friendly interfaces.

Strategies for identifying companion diagnostics are becoming more refined and precise and will require biology-based criteria for biomarker selection. Both Nicholas Dracopoli and Kenneth Emancipator stressed that a deep understanding of the underlying biology is critical to finding and confirming a companion diagnostic in oncology. Several speakers chimed in with the point that good science and medicine need to go hand-in-hand to develop an effective device and a safe and efficacious drug.

Applications of precision diagnostics has grown to include areas beyond oncology. In general, cancer testing was the first field to apply next-generation sequencing (NGS) in diagnostics. NGS is becoming routine in other fields as well. Oscar Puig addressed the use of cascade NGS to expand the offerings for early and accurate diagnosis of genetic causes for sudden arrhythmic death syndromes (SADS). He discussed how cascade screening (identifying relatives at risk for a genetic condition after molecular diagnosis in an index case) could result in more affordable diagnostics for patients in rare, hard-to-predict conditions. Puig also noted that precision medicine could also expand to include *preventive* precision medicine (e.g., implantable cardiac defibrillators before an episode for those at risk for SADS). As a consequence of expanded applications, the cost for NGS would be driven lower to the benefit of all therapeutic areas.

3. Overview of Selected Talks

1. The Evolution of Oncology Companion Diagnostics from Signal Transduction to Immuno-oncology
    - Nic Dracopoli, Vice President and Head of Oncology Diagnostics, Janssen Pharmaceuticals

The majority of novel oncology drugs are still approved without a companion diagnostic even though the probability of regulatory approval is much higher for drugs developed with a diagnostic biomarker (for Phase 1 to Approval, 25.9% with a predictive biomarker, 8.4% without

a predictive biomarker[1]). HIs presentation reviewed the development of companion diagnostics for novel immuno-oncology drugs and described strategies to release a prior, but suppressed, immune response to a tumor, or to prime a new response in patients with no prior immune response.

Dracopoli discussed a characteristic profile for drugs with a strong biomarker hypothesis. To increase likelihood of success, programs need to establish a large effect size to select a predictive biomarker for testing in very early development trials, e.g., Phase I extension or Phase II. At this stage, single-analyte tests using an established diagnostics technology may be used for screening (PCR–Sequencing, immunohistochemistry (IHC), and/or fluorescent in situ hybridization (FISH)). If successful in identifying a biomarker with an established diagnostics technology, partners will be better able to make the platform globally available in all markets where the therapy will be sold.

Dracopoli described a decision-tree strategy to determine if a patient should receive standard of care or be eligible for specific treatments, in this case, checkpoint inhibitors or inducing an immune response. He emphasized the point that DNA testing for driver mutations is insufficient and the molecular, cellular and protein assays to monitor immune response need to be used.

Dracopoli concluded his presentation summarizing his points:

1. Immuno-oncology drugs will require more complex biomarker tests
    a. Measure the interaction of the immune system and the tumor to evaluate system biology and identify biomarkers
    b. Perform vitro cell and protein assays to simulate system biology
    c. Test hypotheses with NGS and/or PCR for driver mutations
2. Complex molecular profiles are required to predict immune response
    a. Single analyte diagnostics may prove insufficient to assay complex biological interactions
    b. Clinical strategies need to change to allow for development and testing of more complex biomarker hypotheses
3. Biomarker assay development needs to be started earlier to allow for routing co-development of drugs with companion diagnostics

2. Next-Generation Immuno-Oncology Biomarkers: Insights for Developing Companion Diagnostics for the Future of Immuno-Oncology

- Andrew Aijian, Senior Project Leader, DeciBio Consulting

Driven by the complexity of tumor-immune interactions and the potential for a wide variety of combination treatments, cancer immunotherapies have spurred an explosion of research into novel biomarkers using a broad range of analytical technologies. Aijian undertook a review of available databases (e.g., clinicaltrials.gov, biomarker literature, etc.) to conduct an analysis of biomarkers from >1,000 immuno-oncology clinical trials; he also interviewed and surveyed oncologists, pathologists, and other oncology experts. His analysis led to several observations, starting with the point that immunotherapies will drive the adoption of new companion diagnostic technologies, strategies, and business models. Major trends

include increasing utilization of blood-based markers and assays both for therapy selection and monitoring purposes, emphasis on biomarker-driven (i.e., site-of-origin independent) drug strategies, and a shift towards multiplex “signature” biomarkers.

Tissue analysis by IHC accounts for the largest share of biomarker mentions (~42%); flow cytometry (19%) is commonly used for monitoring assays; while sequencing is relatively small (12%), its use is growing rapidly. PD-L1 remains the most commonly explored biomarker, the combined top 15 Immuno-Oncology (I/O) biomarkers comprise ~65% of all biomarker mentions. Clinical trial analysis reveals that there is more to I/O biomarkers than PD-L1. In fact,I/O is entering the phase of “next-generation” biomarkers. For example, stakeholders have identified tumor mutation burden (TMB) and tumor-infiltrating immune cells as the I/O markers likely to have the highest near-term clinical impact.

Tumor-mutation burden and gene-expression signatures will become more common companion diagnostics for cancer immunotherapies. Only a small share of labs will be equipped to conduct these assays. DeciBio’s analysis confirms that stakeholders are open to outsourcing next-generation companion diagnostic testing. Consequently, multiple different biomarkers and modalities may ultimately be centralized and integrated.

There are over 440 primary and secondary sponsors associated with the trials analyzed to-date; while the NCI is the top overall sponsor, industry players comprise the primary sponsors of I/O biomarker-driven trials. Immune monitoring has yet to been taken up for routine clinical care, however most stakeholders expect immune monitoring assays to become commonplace in clinical care in the next 5–7 years. A high-level market analysis indicates that immune monitoring testing could represent an annual Dx market opportunity of ~$65 M in 2022, with an upside of up to ~$110 M based on adoption rates and technology utilization.

In his summary, Aijian described an approach to mine the use of diagnostics in clinical trials that would stimulate hypothesis generation based on DeciBio’s primary and secondary research. He concluded with questions in key areas to consider when planning for future immuno-oncology diagnostics:

1. How do established cancer diagnostic technology companies (e.g., IHC, PCR-oriented) adapt to the increasing complexity and technological shifts for future I/O companion diagnostics?
2. How do Dx kit/instrument makers that rely on a distributed cancer Dx model fit into a landscape that may become increasingly service-oriented?
3. How can Dx companies position themselves to capitalize on the immune monitoring market opportunity?
4. How do “next-gen” biomarker technology companies differentiate and establish themselves as optimal CDx partners?

5. How do Dx companies prepare for the increasing integration of different classes of biomarkers (e.g., genomics, proteomics, cellomics) as well as other clinical and diagnostic information (e.g., radiology, clinical history, etc.)

3. First Biomarker-Defined Tumor Indication: FDA Approval of Pembrolizumab For MSI-high cancer

- Ken Emancipator, Executive Medical Director and Head of Companion Diagnostics, Merck & Co.

Dr Emancipator presented an overview of the tumor immunogenicity-inflammation pathway. In his talk, he showed how important is to have a solid scientific knowledge combined with clinical data, which in this case led to accelerated FDA approval of a treatment for patients whose cancers present the Microsatellite Instability (MSI) biomarker. This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the body tissue where the tumor originated. Emancipator's talk emphasized that the circumstances around this project led to a somewhat unprecedented – and unorthodox – path to FDA approval of pembrolizumab. Emancipator closed by placing MSI and mismatch repair deficiency (MMRd) in the broader context of biomarkers in immuno-oncology.

Origins of MSI as a predictive biomarker for response to anti-PD-1 came from an observation that only one of 16 patients with colorectal cancer responded to anti-PD-1 therapy in a Phase 1 trial. Routine histologic section of the tumor which responded showed the medullary pattern with abundant lymphocyte infiltration, characteristic of MSI-high DNA. Microsatellite instability was well-established as disease entity (at least in colorectal cancer).

MSI and MMRd had well-established tests, with accepted consensus standards for colorectal cancer. Neither MSI nor MMRd, however, were so well-established for other types of cancer, and an FDA-approved test was completely lacking. FDA was not necessarily convinced that assays for microsatellite instability (PCR-based) and mismatch repair deficiency (IHC-based) are interchangeable (and definitely not yet for non-CRC cancers).

Given the circumstances at the time, why did FDA approve pembrolizumab for MSI-high cancer? Dr Emancipator proposed several factors were driving decisions at the time: first, this work addressed a pressing, unmet medical need; second, FDA recognized the power of the underlying science; third, metadata analysis of multiple cohorts showed a consistency of efficacy across indications In addition, MSI was probably at the top of the list for enforcement and well-defined tests for microsatellite instability have been widely available in accredited clinical laboratories for some time. FDA was planning to regulate laboratory-developed tests (LDTs), however, the marketing strategy had to be changed to a post-market commitment when the LDT Draft Guidance was withdrawn.

Emancipator concluded with thoughts about what the oncology community desires in a biomarker (e.g., high negative predictive value, objective read-out, etc). He also shared his historical perspective, noting in hindsight that co-development might arguably have been easier than the post-market commitment that arose from the singular circumstances of the MSI/MMRd biomarker development.

4. Factors that Impact the Commercial Utilization of Companion Diagnostics
    - Steve Anderson, Chief Scientific Officer and Senior Vice President, Covance

Many factors have a significant impact on the commercial introduction and clinical utilization of specific companion diagnostics, for example: meeting a clinical need; inclusion in clinical practice guidelines; ease of use; fit with standard-of-care patient management; broad or general access to the technology and/or specific application; specimen type and requirements; and reimbursement policies. Dr Anderson's teams have evaluated data on the utilization and performance for a variety of companion diagnostics and he reported on the most important factors for each of the testing modalities and applications.

Anderson discussed factors for uptake by healthcare providers. Many view a diagnostic of use only if it changes clinical practice. Such a barrier requires that any diagnostics have a well-defined intended use clearly stated on the label, preferably as being essential for the safe and effective use of a corresponding drug or biological product. To get to this point, the clinical utility of the diagnostics and therapy would have had to have been clearly demonstrated.

He also covered factors that a clinical laboratory considered before adopting a test, starting first with ensuring that the format is compatible with lab workflow and intended use (including specimen type and requirements). Compatibility with laboratory workflow leads to a timely turnaround for a medical decision. He also touched on the the global nature of healthcare, noting that before a laboratory should consider offering a test, two conditions must apply: 1) an approved therapy is available to a patient (e.g., approved in the country) and 2) the cost for therapy and test are both in line with a patient's benefit.

Anderson cited practical operational points of launching a therapy-associated diagnostic. By nature, CDx launches are complex requiring coordination among many partners to ensure that the test is available on or close to approval dates. Such timing requires that both internal and external parties (stakeholders, laboratory and manufacturing resources, et al) be aligned to accommodate potentially shortened test launch timelines. Collaboration and coordination among these parties will ensure a more successful CDx launch to support access to impactful therapeutic innovations.

Finally, he touched on a couple of topics for future consideration: adoption of precision diagnostics and precision therapies. Adoption brings in new and multifaceted partners as part of a launch strategy. He noted that labeling of the therapy and the CDx is not enough to drive adoption and that practical matters such as size and distribution of the target populations, fit to patient management flow, and pricing and reimbursement, have a significant impact on adoption success. He ended by pointing out that whereas coding, pricing and access were once a given, the coordinate strategy to make a CDx tests and therapy accessible will have to become more sophisticated.

5. Planning and Execution of a Companion Diagnostic Bridging Study: Migration from a Central Clinical Trial Assay to an investigational-use-only (IUO) Companion Diagnostic in a Phase 2 Clinical Trial

- Christopher Major, Director of Oncology Diagnostics, Janssen Pharmaceuticals

Dr Major started off by describing two trials using different therapies and biomarkers as the basis for the presented case study on planning and executing companion diagnostics work at Janssen. In parallel with the ongoing trials, a companion diagnostic was developed with an IVD partner. Samples originally screened by a central laboratory using a Clinical Trial Assay (CTA) were retained for a bridging study between the CTA and IUO companion diagnostic assay.

He focused the case study on lessons learned to support FDA filing and registration during the bridging projects with partners, including practical points of logistics. Echoing fellow speakers, Major noted the need for clearly define respective roles and responsibilities for pharma, CRO, and IVD partners, especially with countries running a trial.

He pointed out that a bridging study is particularly important to show equivalency between the CTA and a market-ready CDx assay (see FDA Document for more information). Agreements with partners need to be in place to share samples among all parties, including for samples collected and acquired during the trial. Samples need to be retained for sharing with partners and for later companion diagnostics testing and validation. Consent forms should be drafted accordingly so that enrollees are informed about the intended use, both for the indication as well as developing a diagnostic. Retained samples can be tested with the final market-ready assay (MRA). He also brought up the importance of assessing the potential risk that an IVD adds to a trial and to communicate that risk to all partners and (especially) FDA.

Dr Majors stressed the preparation of all teams for the biostatistics protocol, including informing all parties about the analysis to be used and the protocol to transfer data. These steps are critical to ensure quality and continuity in data integrity, analysis rigor, and efficient processing in a timely manner.

What has been learned from bridging studies? Bridging studies are an inevitable reality of clinical timelines and have to be scheduled in the timeline accordingly. Historically, having validated IUO assays available for “first patient in” studies is *not* common. Planning for the timeline should include the purchase of commercially-available good quality samples - lots of them and early. And one has to be prepared to screen them and arrange to bank them for potential future use and to allot sufficient space for sample banking in context of the clinical trial (allowing for extra sample collection), then be proactive in sample management with real-time inventory updates. This will avoid logistic nightmares should critical samples be “lost”, unaccounted for, or simply unavailable for assay development.

On a final note, Dr Major recommend the use of the FDA Pre-Submission Program, thereby signalling intent to submit an application with FDA, opening channels for information exchange, and soliciting constructive feedback to prepare a submission.

6. The Diagnostics Milieu: What Makes a Good Partner in a Challenging Environment

- Kim Folander, Executive Director, Enabling Technologies, MRL Business Development & Licensing, Merck & Co.

As the focus on personalized medicine continues to mature, it has become one of the most active areas in biopharma dealmaking for oncology. While all partnerships come with challenges, there are special considerations in this space to align the drug developers, diagnostics companies, payers and regulators. Partnerships must have a strong foundation to face hurdles as the process moves from development to submission and, finally, to commercialization.

Due diligence is a critical component to forming partnerships. Each party must share need-to-know information with others in the partnership. For example, each partner parties need to have a clear understanding of all partners' approach to quality, compliance, and relevant technology data. Considerations of potential strengths or weaknesses when performing due diligence to select partners include:

- assay protocol and technology platforms
- clinical development capabilities
- regulatory and clinical development capabilities
- regulatory submission capabilities
- data transfer and management among partners
- quality systems and compliance record
- sales and marketing (global reach)
- rigorous vetting of financial stability (long-term viability; potential to be acquired by a competitor?)

Folander articulated a vision for success in precision immuno-oncology focused on the benefits for all parties - partners, healthcare providers, and patients. This vision anticipates that the number of immunotherapy regimens will expand, and patients and physicians will need a rational way to choose among available options. Consequently, diagnostics must identify the treatment option that most likely benefit the individual patient. Current single diagnostics that tend to give a single response to indicate a single treatment option will have limited utility. Instead, future diagnostics could provide graded treatment options based on a multi-analyte assay response combined with patient history, standard clinical laboratory assays, and healthcare provider's observations.

7. The Role of Philanthropy in Accelerating Cancer Precision Medicine
    - Michele Cleary, Chief Executive Officer, The Mark Foundation for Cancer Research

Dr Cleary discussed critical barriers for delivering on the promise of precision medicine to cancer patients, citing particularly the di scovery and development of optimal biomarkers for early detection, predicting response to therapeutics, forecasting resistance to treatment, and diagnosing recurrence. To that end, Dr Cleary outlined how the Mark Foundation will support programs that fill knowledge gaps in cancer biology that may not be funded by government or industry organizations (that is, work that may not have immediate commercial return). She noted a few criteria for funding programs that would boost the creation of technologies that address big challenges and achieve better outcomes for patients and their families.

To achieve its mission, the Mark Foundation aims to be a premier partner to cancer researchers by:

- First, identifying and overcoming barriers in cancer research;
- Finding and funding highly innovative solutions to cancer's biggest challenges, and;
- Developing sustainable resources
    - Create a network of passionate collaborators
    - Sustain the best science currently in practice
    - Invest in the next generation of revolutionary science.

Above all, the Mark Foundation is driven by a mission to inspire, and be inspired by, scientists and their science. Please also see video link with Dr Cleary on Companion Diagnostics Forum website or on YouTube for more detail.

https://www.youtube.com/watch?v=c6zu34tIrcs

4. Panel discussions

Three panel discussions were held over the two-day event: Participants in two panels discussed current issues and future directions for companion diagnostics (e.g., biomarkers, applications, etc); a third panel of regulatory experts considered challenges posed by these assays and applications. Attendees raised questions in the course of the panelists' discussions, leading to a lively dialogue.

Panel 1: Regulatory Considerations for US FDA Submissions for Companion Diagnostic Tests

- Jeffrey Allard, Lakeside Life Science (Moderator); Debra Rasmussen, Janssen Pharmaceuticals; Aaron Schetter, CDRH; Julie Engel, Celgene; William Pignato, WJ Pignato & Associates

Dr Allard presented a talk to introduce the topics to be discussed by the panel, after which he chaired a discussion that explored regulatory submissions to the US Food and Drug Administration (FDA) for Companion Diagnostic. The talk and panel highlighted the regulatory requirements and nuances of the pathways for CDx.

Communicating with FDA

Allard and the panelists started with a discussion on philosophical approaches to address what FDA wants for CDx submission. Allard started off by noting that, first and foremost, FDA wants to see good science and good medicine; regulatory compliance, while critical, will not make up for a submission that lacks compelling data. He further made the point that groups can ask FDA for guidance by stating their cases and asking for comment and agreement.

A detailed discussion was held on pros and cons of developing an in vitro companion diagnostic (IVCDx) or LDT, especially about Class II De Novo vs Class III PMA classification. They also discussed cases that might be considered for an investigational device exemption (IDE). All panelists agreed that communication about Class and IDE status with FDA throughout filing is paramount: be prepared to assess the risk of the IVD in the trial, be open to feedback, and avoid surprises. In this regard, analytical validation is critical and could facilitate future approval for IDE designation.

Panel discussions then moved on to recent breakthrough CDx approvals and the different device classifications for each (see Table 1). An important point is that FDA is handling companion diagnostics and LDTs by its standard device classification categories. Panelists noted the breakthrough nature of approving panels of markers, and designating a marker for an oncology therapy (pembrolizumab) instead of the tumor origination location. Consensus was reached among panelists that complementary diagnostics will be reviewed, regulated, and classified with the same rigor.

As the panel wrapped up, questions were raised about reimbursement and paths to broader uptake of companion diagnostics by the healthcare industry. Of particular note, discussions on LDTs, complementary, and companion diagnostics focused on how each can be positioned in the regulatory space, and the potential of each for reimbursement. All agreed that these topics should be taken up in a subsequent meeting with appropriate industry and regulatory participants.

Table 1. List of recently approved biomarker panels as Companion Diagnostics

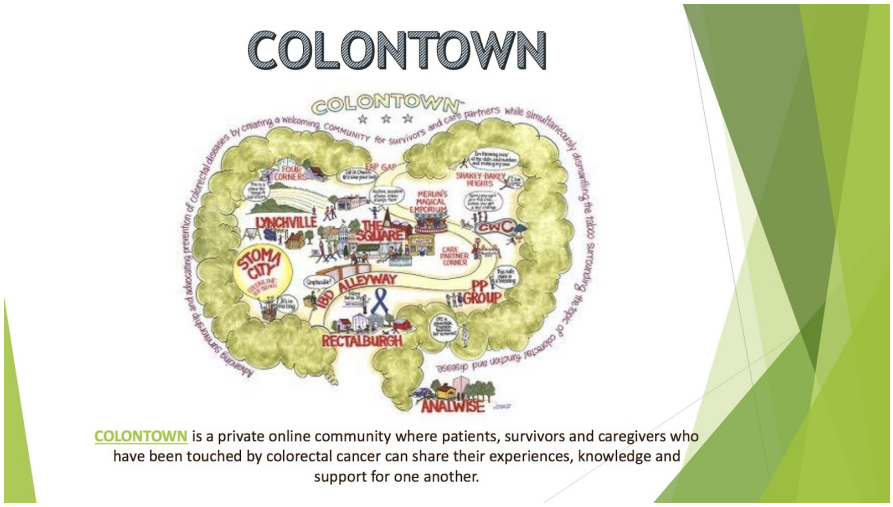
Assay Platform	Affiliated organization	Device classification
Oncomine DX[A]	ThermoFisher	Class III PMA
MSK-IMPACT[B]	Memorial Sloan Kettering	Class II De Novo
F1CDx[C]	Foundation Medicine	Class III PMA
MSI-H (or dMMR)	Dako	Class III PMA

A. Oncomine Dx: FDA Approves First Companion Diagnostic Test to Simultaneously Screen for Multiple Non-Small Cell Lung Cancer Therapies
B. MSK-IMPACT™ Is the First Tumor-Profiling Multiplex Panel Authorized by the FDA, Setting a New Pathway to Market for Future Oncopanels
C. F1CDx: FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers
D. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR): First-ever agency approved cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

Panel 2: Navigating the Challenges in Companion Diagnostics

- Kamala Maddali (Panel Moderator), Vice President, Biopharma Collaborations, Market Development and Companion Diagnostics, Cancer Genetics, Inc; Katrina Wikstrom, Almac Group; Flora Berisha, Daiishi Sankyo; Andrew Aijian, DeciBio; Christopher Major, Janssen Pharmaceuticals

Kamali Maddali started the panel discussion with introductory comments on the need for a community effort to realize the long-term benefits of companion diagnostics. She used one example including representatives from biopharma, diagnostics, clinical, and commercial working with advocates in grass-roots communities. Specifically, Dr Maddali cited Colontown for its inclusion of patients, survivors, and caregivers in the colorectal disease community.



Panelists discussed the perceived value of diagnostics in companion with therapeutics. Andrew Aijian addressed a question about what his research revealed regarding preference of FDA-approved IVCDx vs LDTs. He said that, in the US, CDx have higher perceived value, a combination of FDA approval, brand identity, global support. Further, he noted that many smaller clinical laboratories were either not equipped to develop an LDT or simply chose not to do so. Aijian mentioned that launching a CDx requires significant effort but that, once launched, they are readily handled by IVCDx protocols in clinical laboratories.

Chris Major noted that the current Janssen approach is focused on the CDx path. He did not discount LDTs, but noted that Janssen had already invested in the global infrastructure to support pharmaceuticals and IVCDx. In addition, Janssen prefers the FDA-approval for the additional confidence in markets beyond the US borders. Janssen recognizes that laboratories in the US and Europe will continue to develop LDTs, and Janssen will keep track of the field.

The panel noted that diagnostics in general face technical and financial risks during development but also can create risks in a trial - e.g., burden of a tissue biopsy. In the course of the discussion, Dr Wikstrom said that diagnostics company must learn to manage both IVCDxs and LDTs, and figure out which projects would benefit for a given type.

All agreed that panels of markers will now become more accepted but it was not clear if this would be the case world-wide. Acceptance in the US received tacit momentum due to FDA approvals and current review by CMS to consider reimbursement for these tests.

Panel 3: Round Table Discussion: Are we reaching too quickly for the low hanging fruit? Will multi-omic biomarker panels be better CDx candidates than strictly genomic ones?

- Don Very, Naviter Bioanalytics (Moderator); Karen Keating, Almac; Jeff Allard, Lakeside Life Science; Chris Major, Janssen Pharmaceuticals; John Mudgett, JsM Bioscience

Don Very opened the panel with a brief overview and then posed two questions to the panelists: how might the future unfold for multi- vs single-marker assays? Or for multi-omic assay panels?

Jeff Allard started the discussion by citing the recently announced multi-gene panels: MSK-Impact, F1CDx, and Oncomine panels. He noted that choices for panel types will be driven by quality and value - in this instance, F1CDx and Oncomine have assays on board that are directed to specific pathways and drugs; MSK-Impact is a collection of important genes, but the link to a therapy is unclear (for time being anyway).

Chris Major added that biomarker panels, in general, have the potential to develop new signatures. He pointed out that results from panels may not be immediately translatable to a drug; instead, the goal could be to generate and test hypotheses for future actionable decisions. Since many algorithms already exist to analyze multi-analyte assays for tumors, these analytical tools could be developed and validated for specific indications.

Karen Keating noted that single-analyte assays targeting mutations are effective markers for specific indications, but somewhat limited relative to covering the underlying biology. She contrasted these applications with immuno-oncology therapies that target downstream pathways; these therapies may well drive the need for more complex assays.

The panel closed with a discussion about educating the public, payers, insurers, and regulators about where the field is heading[2]. Panelists agreed that education is needed 1) for uptake of the technology and 2) to justify reimbursement. In the meantime, companies will continue to build the case for the value of identifying responders and demonstrating that precision medicines yield better overall outcomes (measured in QALYs or another appropriate metric).

Jeff Allard had the last word and reinforced the message that developing and communicating the science of precision diagnostics and therapies will continue to be key to getting the right drug to the patient and convincing payers about the value of the approach.

5. Possible Topics for the Next Forum

- Uptake of Precision Diagnostics by groups internal to pharma, CDx, and CRO and partners (collaborations, suppliers, etc)
- Education and training of healthcare providers regarding uptake of precision diagnostics and therapeutics - Are drugs prescribed whether the physician requests an associated diagnostics or not?
- What are physicians perspectives on treatment efficacy, side effects to patients who receive therapies based on companion diagnostics?
- Reimbursement of diagnostic and therapeutic (https://www.cms.gov/Medicare/Coverage/DeterminationProcess/)
- Value of diagnostic on the drug label - potential marketing differentiation?
- Use in clinical trials to prepare the way for validation and commercialization
- Input from patients and advocacy groups (esp for more rare conditions that could be targeted with precision diagnostics)

- Expand beyond oncology to other therapeutic areas

6. Summary

The Forum was well-timed for covering recent news about new releases but also was an opportune time to review and reinforce points that needed updating. Given the yet-somewhat early stage, it was worth being reminded of the critical role that basic biology will continue to be core to the success of this approach. Researchers and developers have now learned to translate the science to the marketplace, which will now become the basis for the next generation of precision diagnostics as they make their way onto the market. Below is an abbreviated summary of the highlights.

- A deep understanding of the underlying biology is critical to finding and confirming a companion diagnostic and related therapies or interventions.
- Strategies for identifying companion diagnostics are becoming more refined and precise and will require biology-based criteria for biomarker selection.
- The first generation of companion diagnostics are well into operational use.
- A next generation of precision diagnostics is more likely to be based on multi-analyte panel assays than the current paradigm of "single-analyte diagnostic, single-therapeutic indication."
- BioInformatics will continue to grow in importance and become more sophisticated. As more complex biology is explored, more powerful software will be needed to make results accessible and understable to users.
- Collaboration and coordination among partners are critical skill sets in the development of new precision diagnostics including, e.g., finding the best partners and agreeing on goals, roles, responsibilities, timelines, and deliverables.
- Applications of these precision modalities diagnostics has grown to include areas beyond oncology, and will continue to expand to other therapeutic areas.

The Forum ended with a discussion what still needs to be done to facilitate the uptake precision diagnostics. The discussion centered on two areas: educating healthcare providers and decisions on reimbursement. To that end, a 3rd Companion Diagnostics Forum will include these topics in the agenda. Please visit the website for more detail: www.companiondiagnosticsforum.com.

1. Clinical Development Success Rates 2006-2015 in BIO Industry Analysis, DW Thomas et al, 2016, pp 1-26.

2. Public Knowledge of and Attitudes Toward Genetics and Genetic Testing, Susanne B. Haga, William T. Barry, Rachel Mills, Geoffrey S. Ginsburg, Laura Svetkey, Jennifer Sullivan, and Huntington F. Willard, Genet Test Mol Biomarkers. 2013 Apr; 17(4): 327–335

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Informational background (not to be included)

IDE Regulation with significant risk (SR) and nonsignificant risk (NSR) device studies.
Investigations covered under the IDE regulation are subject to differing levels of regulatory control depending on the level of risk. The IDE regulation distinguishes between significant risk

(SR) and nonsignificant risk (NSR) device studies. Submit the device information and investigational plan to the IRB for concurrence with the sponsor's SR/NSR determination.

Device Advice: Investigational Device Exemption (IDE)
An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.