Conference Scene

Diagnostics and personalized medicine: observations from the World Companion Diagnostics Summit

World Companion Diagnostics Summit Boston, MA, USA, 1–2 December 2010

On 1–2 December 2010 worldwide leaders in the field of co-diagnostics gathered in Boston, MA, USA, to discuss the state of predictive medicine and the complexities of biomarker implementation and partnering. Flanking the primary conference were three workshops where participants could increase their understanding of companion diagnostic commercialization, best practices from well-known case studies and regulatory guidance and practice. The primary conference reviewed here consisted of 18 lectures and one round table discussion. Topics for the summit included biomarker discovery and validation, partnering between pharmaceutical development and diagnostics companies, commercialization models and evolving regulatory perspectives and guidance. While it is clear that there are many difficulties remaining in making personalized medicine a broad-based reality for all therapeutic areas, it is equally clear that much progress has already been made and that the conference participants are optimistic and dedicated to fulfilling the personalized medicine promise of bringing the right drug to the right patient at the right time.

Conference details

This article provides an overview of the companion diagnostic (co-Dx) discussion sessions held at the World Companion Diagnostics Summit organized by Biorbis. The meeting was held at the Boston Park Plaza in Boston (MA, USA) on 1–2 December 2010. The meeting was attended by an estimated 125 individuals and focused on the complexities of personalized medicine and the commercialization of meaningful co-Dx biomarkers.

World Companion Diagnostics Summit: Day 1

Day 1 of the Summit was chaired by Dr William Campbell of Millennium (Takeda Oncology Company, MA, USA). Dr Campbell set the stage for ten presentations and a concluding round table by noting the important roles that biomarkers play in development, how incorporating predictive biomarkers into medical decision-making would evolve current treatment paradigms and benefit patients by optimizing the use of healthcare spend, and how predictive markers will provide for better overall treatment outcomes.

Dr Joachim Reischl (Bayer Schering Pharmaceuticals, Berlin, Germany) provided a keynote presentation on co-Dx and added value in development. Several important points were discussed which set the foundation for the upcoming presentations. Dr Reischl stressed that the primary consideration in predictive biomarker work

was to identify and implement tests which would add therapeutic value to the patient. Markers of this type should reduce trial-and-error in therapeutic selection and drive more informed decision-making. He then discussed success factors for predictive markers, including biomarker availability, robust technical assay validation, the importance of demonstrating clinical utility and the ability to bring an investment positive commercial value proposition. Examples of predictive biomarkers for breast and colorectal cancers, organ transplant, long QT syndrome and rheumatoid arthritis were utilized to demonstrate impact across multiple therapeutic areas. Dr Reischl concluded his presentation with a discussion of potential clinical trial designs to validate co-Dx markers and summarized value drivers, including health economic and pricing qualifications along with the potential of co-Dx programs to drive the development of new agents.

The morning lectures consisted of several detailed presentations by William Campbell, Wei Zhou (Pfizer, CT, USA) and Mark Curran (Centocor, PA, USA). Dr Campbell discussed the development of MLN0264, a monoclonal antibody targeting guanylate cyclase C, and the consideration of imaging and immunohistochemistry markers in colorectal cancer. He described issues surrounding what types of studies to perform in Phases I and II for this project, and concluded with the considerations needed to develop a Dx

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test based on target expression. Dr Zhou then presented thoughts on the challenges facing the gathering of sufficient data to identify and confirm potential biomarkers. This presentation approached questions regarding the accuracy and suitability of published datasets and asked if standard epidemiology approaches might allow for complex datasets to be better utilized in the future. Additional discussion on the emerging role of large collaborations and partnerships with patient registries concluded this presentation. Dr Curran took the opportunity to discuss issues regarding the co-development of Dx in the context of full development programs and commented that logistics and planning need to be paramount in designing biomarker programs attached to high-value pharmaceutical development programs. He also commented that although co-Dx were unlikely to rescue drugs lacking efficacy or having serious safety concerns, it had tremendous potential to 'make good drugs great'. The main focus of this presentation was the use of economic models to predict the value of pursuing co-Dx tests. Dr Curran demonstrated modeling results utilizing economic tools and presented one case study which demonstrated the financial and operational upside to conducting co-Dx development concurrent with late-stage pivotal studies. He also commented that not all co-Dx projects have a high return on investment and therefore understanding the value of co-Dx and the probability of success on a case-by-case basis was necessary to inform investment decisions. This theme was elaborated further by Dr Mark Trusheim (MIT, MA, USA) on day 2 of the summit.

The afternoon of day 1 continued with a scientific presentation by Dr Suso Platero describing biomarker development for oncology programs and the difficulties of translating initial biomarker discoveries into clinical practice. Dr Platero used the brivanib alaninate (a VEGFR2/FGFR1 inhibitor) development history to illustrate both scientific and clinical partnering concerns in co-Dx development and how to overcome them. From the scientific viewpoint, one needs to start early to look for biomarkers. From the clinical viewpoint, one needs to have clinical 'buy-in' for biomarker studies. The collaboration with clinical and biostatistic departments

is essential to properly design the clinical trials to include the biomarker analysis. Two examples of using pharmacodynamics assays and one predictive biomarker in a Phase I study for brivanib were used to illustrate both points.

Day 1 concluded with several excellent presentations and a round table discussion group focusing on partnerships and establishing commercial relationships between different companies; particularly pharmaceutical organizations and Dx companies and how to craft win-win relationships. The afternoon presentations were delivered by Dr Miu Chau (Genentech, CA, USA), Dr Stephen Little (Qiagen, Manchester, UK), Dr Paul Zavodny and Dr Cecilia Schott (AstraZeneca, MA, USA). Dr Chau's lecture was well received and focused on the development of the Her-2-neu test for Herceptin® in the setting of gastric cancer. She noted the importance of planning for validation studies and debate around the use of prospective versus retrospective samples. Another key theme was partnering for final assay development and placement. The discussion centered on the need to understand early on in co-Dx development how the assay would be developed, validated and delivered. Once delivered there needs to be sufficient assay capacity to satisfy demand. In addition, it was noted that different tumor types require separate validation studies. Finally Dr Chau noted that internal alignment amongst stakeholders in drug development and Dx development was paramount to success in bringing a co-Dx product to the market. At present, there are few success stories and as such, individuals with skills that cross these barriers are somewhat rare. Dr Little followed with an informative presentation from the Dx company perspective. He elaborated that Dx companies add value by providing expertise, tools and instrumentation to facilitate Dx development. Dr Little elaborated, and the audience agreed, that at present few pharmaceutical companies have depth of experience in the Dx arena and can benefit from strategic partnerships. These partnerships can address experimental design, assay discovery, assay validation, marketing and commercialization.

Dr Little offered a financial perspective suggesting that many Dx opportunities are between US\$10–100 million opportunities and that he sees a fee-for-service model as viable. Further considerations include timing and cost. A Dx program may take 0.5–1.5 years for assay development with another 0.5–1.5 years for finalization and regulatory approval. Consequently, he also stressed the need to start early. Although costs will vary, assay considerations alone will be approximately US\$10–20 million with potential to exceed this depending on circumstances. It was noted in further discussion that cost of running prospective clinical studies to validate novel biomarkers was a significant investment depending on size and duration required to test specific end points. Dr Cecilia Schott continued the big pharma collaborating with Dx company theme by outlining her perspective of the perfect development partner who would offer robust science and technology, global regulatory experience in Dx, manufacturing and distribution expertise, a global commercial footprint, financial flexibility and the potential to make different types of deals based on the drug, the market and the impact of the co-Dx. Dr Schott noted that AstraZeneca had learned from past experience that Dx programs and partnerships all need to start early, consider multiple technologies and platform access issues and geographical distinctions. While enumerating these concerns, Dr Schott noted that it is often very hard to form partnerships early on in development because the value of the drug, the Dx and the combination are difficult to predict. As such, both partners will need to have some level of trust and risk in crafting a successful partnership. This theme was explored in additional depth by the discussion panel with several attendees noting that some partnerships could not be formed simply because there was no satisfactory model to determine upfront how the Dx company would be reimbursed if the program was successful. Dr Paul Zavodny had the daunting task of following the trio of talks as he provided an insight into Merck's (NJ, USA) perspective on the partnering issue. Zavodny suggested that his organization

echoed the AstraZeneca perspective, was casting a wide net in considering Dx partners and placed value on fee-for-service arrangements with options based on successful outcomes. He also noted the value of consortia and in forming large databases that single organizations cannot complete on their own. This sentiment was echoed by numerous conference attendees who recognize that Dx development will often require multiple organizations to collaborate in innovative ways, which may cause stress within formally structured pharmaceutical development organizations.

Day 1 closed with a round table to validate the day's discussion. Primary considerations shared by the group were: the need for clarity in regulatory guidance and expectations, openness between pharmaceutical and Dx companies to consider new partnership models, collaboration models and types of exclusivity around intellectual property, and the need for Dx to be highly predictive with analytics appropriately validated both technically and scientifically.

World Companion Diagnostics Summit: Day 2

Day 2 of the conference focused on a few primary themes: the evolution of regulatory guidelines, lessons from the pharmaceutical perspective and systematic market evaluation utilizing economic models. The session was ably chaired by Dr Mark Trusheim whose expertise in regulatory and commercial aspects of Dx development is well recognized.

The task of representing the regulatory perspective fell to Dr Alberto Gutierrez (US FDA, MD, USA) who did a thorough job of providing the agency perspective on co-Dx. Dr Gutierrez noted that several expected guidance documents were in progress at different regulatory organizations worldwide and that they will be delivered in the near future. The expectation is that the guidance documents will inform best practices and provide clarity and consistency in assay development and marketing approval. It is recognized that guidance documents cannot account for all possibilities and sponsor discussions with regulators will remain key components of development. Dr Gutierrez noted

four key components to a Dx: reliability, accuracy, clinical significance and known value limitations. In addition, it was discussed that when possible, there should be strong support for the key parameters applied to evaluate a test: sensitivity, specificity, positive-predictive value and negative-predictive value. During the question period an audience member commented that the perfect study design may, in some situations, be impossible to perform as it would require asking patients with severe disease to accept placebo treatments. This possibility would be untenable to many sponsors and practically speaking would result in a trial design that could not be enrolled. As with all complex problems, this is an area that we will continue to wrestle with and to define innovative solutions for. Dr Gutierrez emphasized the need for pharmaceutical and Dx companies to reach out early in the process to the US FDA to gain recommendations on how to proceed to have both the Dx and the drug approved.

Carol Berry (Asuragen, TX, USA) shifted the discussion from regulatory to commercial considerations when developing co-Dx. She mentioned the need for the five A's: access, affordability, awareness and advocacy, all leading to adoption. Dr Geert Kolvenbag (AstraZeneca, DE, USA) continued the morning session with a discussion on value creation and pragmatic issues in co-Dx discovery and development. Dr Kolvenbag painted an interesting picture of the probability of success, suggesting that if probability of successfully developing and marketing a drug was 10% and probability of a successful co-Dx project was 10%, then the overall potential for success was not a particularly compelling investment. Dr Kolvenbag noted the need to maintain 'real-world' perspectives on the timing scenarios for Dx development and the expectations for impact of the emerging Dx tests. Perhaps a staged model can be crafted into drug development programs; first, proof of mechanism is developed, then proof of principle and finally proof of concept leading to a Dx product. The advantage of this approach is containing expenses while allowing sponsors to determine the feasibility of identifying a valuable Dx test while also pursuing a novel

drug. Dr Kolvenbag's pragmatic view of drug and Dx development was clearly appreciated by the attendees.

The pragmatic Dx development paradigm was further discussed by Dr James Gallarda (Novartis, Basel, Switzerland). Dr Gallarda emphasized the theme that the test and drug must work together. Furthermore, the perfect development path was unlikely to exist so there must be some flexibility in developmental and regulatory approval. He noted the importance of quality systems regulation and the potential to improve laboratory-developed tests, which can be bridged to fully validated *in vitro* Dx. He provided advice to those working in this space to give early consideration to developing Dx and drug pathways which converge. Building upon the regulatory discussion, Dr Gallarda noted the value of the FDA preinvestigatory new drug meeting for discussing co-Dx projects. Similar to Dr Kolvenbag's presentation, Dr Gallarda commented on the staged approach to co-Dx development coupled with drug discovery: define a biomarker concept and test feasibility early in Phase I and II clinical trials, design and develop the co-Dx in Phase II and III, prepare for launch readiness in Phase III, and then launch and consider lifecycle and commercial management in Phase IV. This paradigm resonated with many of the attendees from pharma who are utilizing a similar approach, modified of course for specific program conditions.

Dr Tracey Colpitts (Abbott Molecular, IA, USA) continued the morning's theme and made several points regarding the Dx development path. She noted that an approved co-Dx is a single test, meaning a single marker (or a panel) with one cutoff for one sample type in one specific disease. The test should be supported by proper prospective and bridging studies with clinical samples and population statistics to support test claims. If performed well, the regulatory path for approval is understood and a single international trial to validate the Dx should be sufficient. Dr Colpitts further noted that the analytical and regulatory concerns are a portion of the development problem with reimbursement being another hurdle. At present there is no single path for reimbursement and organizations should consider this factor as early as possible in development.

Dr Mark Trusheim completed the morning session with an outstanding discussion on how to define the value of a co-Dx program. He noted that it is often held as truth that all markets will stratify and that a co-Dx will return value. He argued persuasively that this is not always the case and that developers need to consider market forces and variability when deciding upon investment in a program. More to this point is the effect of personalized medicine on specific individuals. Drug development often evaluates mean responses but co-Dx is directed at individual outcomes. The variance in this equation needs to be as well understood as possible when considering a co-Dx development. Dr Trusheim's discussion around market and economic models and the different ways to determine these structures is beyond the scope of this article, so readers are directed towards his prior publications [1] and new review which is expected to be published early in 2011.

The final session of the conference was held following lunch. This session focused on case examples and new technologies. Dr Vijay Modur (Novartis) discussed work in chronic myeloid leukemia and imatinib. He noted the importance of good pharmacodynamics, target engagement and mechanism of action markers during the development of chronic myeloid leukemia drugs. Modur concluded his discussion by engaging the technology side of the Dx equation. While many teams focus on biopsies or blood samples, his team has taken an interesting look at protein phosphorylation and expression in hair follicles. Dr Modur's presentation illustrated a critical path concern for test developers: the consideration of final platforms which provide easy access to patients and physicians who run and interpret new Dx tests.

The summit was closed with two scientific presentations by Arlene Hughes (GSK, NC, USA) and Joseph Krueger (Flagship Biosciences, AZ, USA). Dr Hughes concentrated on adverse event biomarkers, specifically on common genetic variants that impart adverse drug reactions leading to liver toxicity. She elegantly illustrated the point by using, as an example, abacavir (a HIV drug used to treat infection) and the *HLA-B*5701*

variant. This program is a well-known success in personalized medicine with over 10 years of research and publications supporting it. Hughes presentation was well received and provided insights that while the problems of bringing co-Dx tests to market are significant, they are not insurmountable and the rewards are high. Dr Joseph Krueger then ended the conference by describing a new technology for quantitative immunohistochemistry using an automated process for image acquisition and quantification. He highlighted that inaccuracies in pathologists' scores and the presence of tumor heterogeneity lead to different results even within the same tumor. Perhaps this 'new' method of reading pathological slides could lead to a more accurate diagnosis using the same 'old' way of producing slides for pathology.

Conclusion

The World Companion Diagnostics Summit gathered experts in various fields, all of whom are active in the pursuit of Dx tests that can make personalized medicine a reality. The presence at the conference of participants from pharmaceutical, Dx and regulatory agencies gave the conference a very dynamic feel, leading to substantive discussions between experts from all three fields. The presentations spanned a large scope, including basic science, technology, regulatory considerations, development, commercialization, valuation and market access. Judging by the large amount of highly interactive discussion between attendees, the conference provided both intellectual stimulation and high value. It was clear that many of the less commercial and marketing-oriented participants came away with a new knowledge base and additional elements to consider as they seek to implement personalized medicine in their programs. While we have sought to provide a flavor of the conference in this article, perhaps the primary take-home message is that almost anything worth doing is hard. In the case of the co-development of Dx and drugs, sponsors are combining two very hard objectives: a successful development program yielding a therapeutically efficacious drug along with a highly accurate and analytically validated biomarker Dx, which is a predictor of outcomes. As with

most difficult and complex problems, the take-home message from these discussions is that there are no black and white solutions, but rather multiple shades of gray which must be navigated.

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Reference

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