Combating complexity: partnerships in personalized medicine

We are entering an era of unprecedented complexity in personalized medicine. Therapeutic targets, biomarker detection technologies, regulatory and reimbursement pathways, and commercialization strategies have all reached new levels of intricacy. These complexities are occurring in the context of the current economic environment, in which outsourcing offers a way for innovators to decrease large internal investment. These factors combine to create a perfect setting for a partnership explosion. Now, and as we move into the future, it will be critical for innovators to access outside expertise with a diverse set of partners in order to bring novel personalized medicine products to the market successfully and economically. Only companies that truly embrace this trend and adopt a collaborative approach will emerge successful.

When companies require new capabilities in emerging fields, they face the critical decision of whether to build internally or access external help. A number of criteria are weighed, including competency, cost, feasibility, long-term value and resource availability. As companies look to preserve cash in times of economic turmoil, the pendulum swings toward outsourcing [1, 2].

The current economic environment serves as an overarching driver of outsourcing and partnering across the healthcare industry. However, within personalized medicine, an additional trend is driving significant partnership expansion. That trend is an unprecedented growth in complexity, which makes it absolutely essential to look outside of one’s own walls to avoid millions of dollars of internal infrastructure spending to develop capabilities that are constantly changing and difficult to maintain. In the past, the pharma industry turned to outside contract manufacturing organizations for help controlling manufacturing costs and for know-how in manufacturing their drugs, and to clinical research organizations to better manage and streamline clinical trials. Similarly, companies across personalized medicine are now turning to each other proactively and intentionally to share the burden of developing the best products for patients. Figure 1 illustrates these driving forces behind the partnership expansion.

Granted, ‘personalized medicine’ – the blanket term that encompasses the goal of delivering the right treatment to the right patient at the right time – is by its very nature complex. However, that level of complexity is expanding far more rapidly today than ever before. Each step in the development of a personalized medicine product, from initial target development to final diagnostic commercialization, is accelerating in its intricacy. Across the continuum, that complexity is manifested through the integration of new cutting-edge technologies, with highly specialized expertise. Innovators must rely on partnerships among scientific, clinical, logistical, political and business stakeholders, who each bring different and necessary strengths to development.

Over the past decade, one set of stakeholders, namely the therapeutics and diagnostics companies, essentially controlled the destiny of a new personalized therapeutic or diagnostic. Based on the trends we will discuss in this article, we believe that all stakeholders will play an important role moving forward, and control must be shared among stakeholders in order to streamline costs and develop the strongest personalized medicine products. This evolving paradigm of stakeholder interconnectivity is illustrated in Figure 2.

We are beginning to see evidence of stakeholder interconnectivity across all three major segments of the personalized medicine product continuum. In discovery, development and commercialization, new partnerships are emerging, with a broader set of stakeholders, as illustrated in Figure 3. Given the current economic environment and rapid growth in complexity, we anticipate these partnerships accelerating in the near future across all three segments.
Much of the complexity growth driving partnership expansion in the discovery segment of personalized medicine stems from the paradigm shift we see in targeted therapy. Led by oncology, targeted therapy—drugs aimed at molecular targets specific to a patient’s disease state—is quickly sweeping the industry. (Given the complexity and rapid evolution of cancer treatment, this article provides many oncology-focused case examples; personalized medicine in other indications is also evolving and will be addressed in other publications.) Over the past decade, treatment has moved from nontargeted chemotherapeutic-based approaches to molecularly targeted therapy. A stark difference exists between the majority of launched drugs and those currently in clinical development. As illustrated in Figure 4, today, only approximately 15% of launched oncology drugs are considered targeted; that percentage rises to nearly half of compounds in development earlier in the pipeline.

At the same time, the number of targets is expanding rapidly as researchers discover new drivers of disease and segment tumor types into smaller subsegments. This trend is illustrated in Figure 5 through the evolution of lung adenocarcinoma genetic subtyping. Analyzing the growth in characterization from 1980 to 2012 shows how researchers continue to elucidate novel paths forward in drug development for this disease through new biomarker discovery.

However, the complexity does not stop there. The targets themselves are becoming more and more complex. In the past, translational medicine needs across pharma were more straightforward. Pharmacodynamics and dosing of traditional cytotoxic agents were less complex and centered on maximum tolerated dose. Even early targeted therapies such as Herceptin® were associated with relatively obvious and easily assessed predictive markers such as HER2. Today, novel cancer agents are attacking complex signaling pathways on multiple levels. This includes novel complex signaling targets, such as PI3K/Akt and mTOR for multiple cancers, and synergistic combinations of targeted therapies, such as the BRAF, MEK and PI3K combination in melanoma, the EGFR and c-Met combination in lung cancer, and the HER1, 2 and 3 combination in breast cancer. They also include targeted immunotherapy such as PD-1/PD-L1 for melanoma and targeting protein complexes, and dimerization such as P53/MDM2, HSP90 chaperone complexes, and FLT3 for multiple cancers.

From multikinase inhibitors and targeted immunotherapies to inhibitors of protein complexes and dimerization, pharmacodynamic markers are more complex. Predictive markers are elusive and multifactorial, and maximum tolerated dose is no longer the optimal biological dose. These research streams require specialized expertise and pharma can look to partners without having to build broad and deep knowledge in biomarker and diagnostics development.

And there is plenty of help to be had. Companies such as Biodesix (CO, USA), Almac...
(Craigavon, UK) and Biomarker Strategies (MD, USA) help pharma to decipher the complex signaling relationships, and guide predictive marker development as described above. For example, the diagnostics company Biodesix has signed over 14 pharmaceutical and biotech deals over the past few years, including ones with Kadmon (NY, USA) and GlaxoSmithKline (London, UK). These deals focus on leveraging their MALDI mass spectrometry platform and diagnostic expertise in serum protein biomarker elucidation to discover biomarker signatures that support novel targeted therapy discovery and development [103]. Importantly, these deals are not one-sided. They play a critical role for early biomarker companies looking for access to valuable clinical samples and validation of their platforms, which can be provided by their pharma partner.

Another key source of expertise in this area is academic research institutions. Partnerships between industry and academia have grown significantly, and these partnerships could not come at a better time because government funding continues to dry up. In recent years, academia has seen NIH and federal funding move from 66% of its total funding in 2004 to 60% in 2009, while industry funding has grown at a 10% annual rate over that same period [104,105]. In turn, academic institutions provide the industry an economical, highly skilled discovery vehicle with access to rich patient sample populations.

For example, Exosome Diagnostics (NY, USA), a company harnessing exosomes in multiple body fluids to develop innovative diagnostics for cancer and neurodegenerative diseases, has partnered with Columbia University Medical Center (NY,
USA) to develop the largest urine-based prostate cancer sample bank in the world. Its management team underscores the importance of their partnership with Columbia in accessing those samples to develop its highly accurate prostate cancer test (the first of multiple tests in its portfolio) – and in doing so more economically [McCullough J, Pers. Comm.].

Specific pairing of a pharmaceutical to a diagnostic is only a part of personalized medicine. The vast majority of diagnostics are not being developed to guide a specific branded therapy. More often, biomarkers that become diagnostics inform treatment, but do not directly link to a specific branded therapy. These ‘complementary’ diagnostics also play a critical role in personalized medicine as prognostic gene signatures such as Agendia’s (Amsterdam, The Netherlands) MammaPrint® test [13] for breast cancer recurrence, predictive markers of toxicity such as UGT1A1*28 mutation analysis for irinotecan [14] and molecular monitoring such as BCR–ABL testing to monitor chronic myeloid leukemia progression [15]. Classically, diagnostic companies have developed these diagnostics and launched them into the market, but these companies increasingly need to look to partnerships to better disseminate their tools to those that will use them. For example, Life Technologies (CA, USA), a global life sciences company, has inked two partnerships with Bristol-Myers Squibb (NY, USA) to support the development of diagnostic products, with initial focus on oncology, with expansion into other therapeutic areas. Bristol-Myers Squibb provides the robust pipeline, while Life Technologies provides the specific tools and expertise in life sciences and diagnostics discovery and development. Life Technologies can leverage a number of platforms to more quickly assist Bristol-Myers Squibb in their companion and complementary diagnostic program pursuits [106].

**Development**

As personalized medicine moves from discovery to development, the regulatory and reimbursement environments take center stage. The experience needed to successfully navigate the ever-changing regulatory environment from a diagnostic perspective is lacking within pharma and is best accessed through a partnership with a diagnostics company. That way, pharma can avoid building out a large diagnostics regulatory infrastructure internally and having to learn the evolving landscape too quickly. While the US FDA draft guidance on companion diagnostics started the conversation, the brief was not prescriptive enough and has not become formal guidance; the brief leaves us in a still-nebulous environment [107,108]. Topics still under debate include clinical trial patient populations, inclusion of biomarker-negative patients, and applicability of prognostic, predictive and selective claims [109]. Therefore, companies are turning to each other to navigate the developmental, regulatory and reimbursement landscapes, driving a rapid increase in companion diagnostic alliances. The growth of these alliances is illustrated in Figure 6 [110].

![Figure 5. Evolution of lung adenocarcinoma molecular characterization](image)

Lung adenocarcinoma genetic subtyping is rapidly expanding the number of viable targets in this disease. Analyzing the growth in characterization from 1980 to 2012 shows how researchers continue to elucidate novel ways forward in drug development for this disease via new biomarker discovery.

Data taken from [3,102].
on various areas in their development. Another well-publicized example was Abbott and Pfizer, who partnered to walk through the regulatory process together with the targeted drug Xalkori® and the companion diagnostic to Xalkori, the ALK FISH test. In early studies, Xalkori exhibited strong efficacy, but only in the approximately 4% of non-small-cell lung carcinoma patients that harbor an EML4–ALK translocation. With this activity limited to such a small patient subsegment, Pfizer needed a companion diagnostic to gain FDA approval in these highly-responsive patients. Given the dramatic level of response and revenue potential, Pfizer had plans to submit its new drug application in a compressed timeline. This made it critical to find a reliable partner that could quickly develop a valid diagnostic with minimal risk. Abbott was able to meet that need. Although Pfizer and Abbott emerged victorious with this plan, experts close to the matter claimed that the road was not easy and both parties learned multiple logistic lessons, which they are taking into consideration while forming new partnerships [LONG K. PER. COMM.]. These logistical issues highlight pharma’s need to expand its understanding of the diagnostics space in order to better initiate and manage partnerships with diagnostic companies, and to clearly define roles and conflict resolution strategies amidst different business models and incentives.

While the traditional diagnostic companies are seeing an increase in deals, we are also witnessing a rise in partnerships with companies with highly specialized companion offerings. One such example is the deal between PrimeraDX (MA, USA) and Lilly (IN, USA) in June 2012 [111]. PrimeraDX is using its ICEPlex platform, which combines end-labeled PCR and capillary electrophoresis to produce tests for Lilly that can simultaneously detect mRNA, miRNA, DNA and SNPs. This type of offering will become more important as Lilly advances more combinations of multi-factorial therapeutics through the pipeline. Partnerships such as these will continue to be crucial to launching these companion products into the market quickly, safely and economically.

Partnerships that provide outside scientific, clinical and logistic knowledge to bring forward personalized medicine products in an accelerated timeframe are in full swing. However, the influx of targeted therapies and companion diagnostics will create another unique issue in some clinical indications in the not-too-distant future. Figure 7 highlights this phenomenon by examining the breast cancer treatment paradigm [112]. Today, the targeted landscape is relatively limited and physicians are able to select treatment for their patients without too much difficulty, with a choice among Herceptin, Tykerb® or Perjeta®. In the future, however, the pipeline is rich with a variety of targeted therapeutics and resulting companion diagnostics likely to launch.

The variety of targeted therapy options in the future will create a clinical quandary for physicians and pathologists who will not have enough tissue to send out tens of separate companion or complementary diagnostic tests for one patient. They will need to look to laboratories and/or vendors who can provide consolidated tumor profiles. Examples of companies that can provide those options today include companies such as Response Genetics (CA, USA) with its ResponseDx® comprehensive panels for lung, gastric, melanoma and colon cancers [113], Caris Life Sciences (TX, USA), Foundation Medicine (MA, USA) and MolecularHealth (Heidelberg, Germany) are other companies that offer compelling tumor profiling panels. These panels are the future of personalized medicine, as they continue to pinpoint the treatment options that best suit individual patients with more and more granularity. In addition, they represent important emerging partners as therapeutic companies recognize that these panels may supplant their individual companion diagnostics in the future.

Figure 6. Companion diagnostic alliance growth. A host of different targeted agents across various mechanisms of action will hit the market, driving an unprecedented need for biomarker development and personalized medicine solutions. Therefore, companies are turning to each other to navigate the development, regulatory and reimbursement landscapes, driving a rapid increase in companion diagnostic alliances among those groups. Data taken from [110].
Beyond the diagnostics described above, there are other complementary diagnostics that will play a critical role. These include prognostic gene signatures, predictive markers of toxicity and molecular monitoring assays. Companies developing these products all impact the personalized medicine ecosystem and represent important players in the partnership web. However, they will have to satisfy the needs of an increasingly skeptical stakeholder in that web: the payer.

The reimbursement landscape for personalized medicine diagnostics is currently in a state of flux. The system is fraught with limitations around coding, coverage and pricing, all of which make it more difficult than ever for developers to achieve broad coverage and value-based reimbursement in a timely fashion [114,115]. To overcome these challenges, diagnostic developers are increasingly partnering with a seemingly unlikely partner: the US payer community itself. These partnerships are typically aimed at generating real-world health economic and clinical utility data, and can be an effective way for the developers to generate the critical data that many payers are increasingly requiring for broad coverage [16].

One particularly high-profile ‘coverage with evidence development’ agreement occurred in 2007 between Genomic Health (CA, USA) and United Healthcare (MN, USA). United Healthcare agreed to reimburse Genomic Health’s Oncotype DX® for breast cancer recurrence at its list price for 18 months while tracking clinical effectiveness, after which point it would seek a lower price if certain expectations were not met [116]. Ultimately, the project had a positive outcome. After the first round of reviews, only 16% of physicians were using the test incorrectly, and that number has continued to fall [117]. United Healthcare has therefore not had to re-open the contract and re-price the test. This agreement allowed Genomic Health to gain access to a large customer base and required that the test developer stand behind its product’s performance in the real world. This was a progressive risk-sharing agreement in the diagnostics area and one that may be replicated as more novel diagnostics seek value-based pricing.

The other component of reimbursement and value-based pricing is system economic justification. Increasingly, diagnostic developers seeking premium pricing are wisely dedicating resources to system economic studies. These studies typically begin in silico with economic models typically satisfying the baseline needs of the payer community. However, leading companies are partnering with payers to bring these health economic studies to a much higher level. One successful example again involves Genomic Health, this time with Humana (KY, USA). A 2011 study analyzed the real-world outcomes and costs of 925 Humana patients managed with Oncotype DX, demonstrating significant cost savings after accounting for the cost of the test [17].

Figure 7. Need for decision support tools. Within a few years, targeted treatment options for metastatic breast cancer will increase dramatically, necessitating new partnerships for the development of decision support tools. Data taken from [101].
Procedural Terminology (CPT) code stacking for molecular diagnostics, system economic justification will be critical moving forward [118]. Leveraging the expertise of reimbursement experts and collaborating with payers will be a growing trend in personalized medicine moving forward.

**Commercialization**

The final component of the personalized medicine continuum undergoing a paradigm shift to more partnering is commercialization. Diagnostic developers are beginning to look to a broader set of players as commercialization partners for a variety of reasons. In many cases, it is not economically viable for a smaller single-product diagnostic company to develop a large internal sales force. Traditionally, we have seen some companies partner with large national reference laboratories to help sell their products — with varied success. EXACT Sciences (WI, USA) partnered with LabCorp (NC, USA) in 2001 to sell its colorectal cancer detection test. More recently, Vermillion (TX, USA) partnered with Quest Diagnostics (NJ, USA) in 2012 to sell its test for ovarian cancer. While those large reference laboratories have a broad sales reach, they did not classically bring the same clinical expertise and effort to the sale as another partner might. However, in recent years, large reference laboratories such as Quest and LabCorp have acquired specialty reference laboratories and companies, such as Genzyme Genetics (MA, USA), Monogram Biosciences (CA, USA), Athena Diagnostics (MA, USA) and Esoterix (TX, USA), and invested internally as well to provide an offering that serves this new customer base.

Companies are also seeking regional, specialty laboratories to help reach specific populations more economically. In the urology space, there has been a move to partner with regional uro-pathology laboratories. Mitomics (ON, Canada), a company developing a novel prostate cancer diagnostic, partnered with both Bostwick Laboratories (VA, USA) and QDx (NJ, USA) in 2011 based on the laboratories’ strong relationships with urologists, and the ability of their representatives to make a highly clinical sell. Therapeutic companies are also gaining interest as attractive partners. In 2012, Veracyte (CA, USA) partnered with Genzyme Genetics to sell its thyroid cancer diagnostic test [119]. Rather than build out a large endocrinologist-focused sales team, Veracyte brought its Afirma® test to Genzyme, which markets Thyrogen®, a thyroid cancer therapeutic that had been on the market since 1998 and had seen decreasing interest from endocrinologists. Veracyte leveraged Genzyme’s existing sales force to access endocrinologists and Genzyme gained a critical new angle to improve physician relationships and interest in its offerings.

Attention to global issues is also of importance as applications of personalized medicine spread into Europe and even further into the Middle East, China and Brazil. Partnerships that bring sophisticated personalized medicine diagnostics while leveraging local presence provide the best combination for success. For example, Genomic Health partnered with Unilabs (Geneva, Switzerland), a pan-European reference laboratory, in October 2012, to offer Oncotype DX in the UK [120]. This was a win–win situation: Genomic Health gained access to a difficult European market through a well-connected internal reference lab, while Unilabs further differentiated itself by offering a highly desired proprietary personalized medicine diagnostic.

A final example of burgeoning partnerships in the commercial space is the pairing of companies with those that can offer superior health information technology. With all of the complexity inherent in personalized medicine, the decision support tools and sheer analytic capabilities health systems will need in the future is immense. Thankfully, we are seeing the formation of interesting partnerships that will meet those needs. For example, MolecularHealth is a clinical molecular informatics company whose goal is to advance personalized medicine by translating patient-specific molecular and genomic data, clinical history, and published scientific and medical evidence into safer, more effective drug choices for patients through informatics-based prediction and decision-support tools. It is powered by a partnership with SAP AG (Waldorf, Germany), utilizing its SAP HANA platform to manage the roughly 2 terabytes of genomic data per patient and create a cloud-based offering for physicians that promises to dramatically accelerate the decision-making process [121]. The company is currently collaborating with the University of Texas MD Anderson Cancer Center (TX, USA) and the FDA. Although the collaboration is in early stages, it is difficult to quantify the economic advantages that both the University of Texas (TX, USA) and MolecularHealth are enjoying because these collaborations are so new. However, accessing the necessary specialized IT expertise that MD Anderson did not have in order to develop this new decision-making process more quickly is likely to create a win–win outcome for both parties.

**Return on investment**

Partnerships in personalized medicine may be formed for scientific, clinical or logistic reasons...
in order to leverage specialized expertise outside one’s walls without having to take on the expense and burden of building internally. However, with all of these partnerships, both parties must consider the economic incentives and disincentives to partnering. As mentioned previously, the broad trend and comfort with outsourcing for pharma companies allows those teams to take on diagnostic partners as vendors, working with a company to develop and commercialize a single companion diagnostic or multiple companion diagnostics for a fixed fee or series of milestones. Other partnerships focus less on a vendor relationship and more on a pure partner-to-partner relationship—trading platform use for sample access, for example, or with the diagnostic company taking on greater risk, but also garnering a greater upside than a typical vendor relationship. Finally, a new breed of partnerships, more common with payers, focuses on true risk-sharing arrangements in order to trial a new diagnostic in their populations without having to take on all of the expense upfront. With each partnership, it is essential that management teams determine their comfort and structure upfront, vet options with the potential partners and carefully calculate their return on investment for several paths and partners before making a final decision on the partnership. With adequate partner-to-partner transparency and an understanding and agreement of roles and incentives by each partner, this step leads to the most fruitful partnerships.

Conclusion & future perspective
Increasing complexity and innovation paired with increasing cost constraints point to a need for partnerships at every step of the continuum in personalized medicine. In order to develop the most successful partnerships, companies need to prepare for this environment by:

- Understanding their internal and external needs all the way through the personalized medicine continuum, and when partnership makes sense;
- Arming the company with a business development team who can scout the best partners across the continuum and craft terms amenable to all parties;
- Outlining expectations and milestones upfront and keeping to those milestones;
- Agreeing with and embracing each partner’s role in the partnership, and fully understanding each partner’s value and return on investment upfront;
- Frequently reviewing partnering options, being mindful of new technologies, approaches and deal structures.

The partnership expansion in personalized medicine will have a significant impact on the industry – so much so that business development will likely become as important (if not more important) than any other function within a company developing a companion therapeutic, a companion diagnostic or a standalone personalized medicine diagnostic. The most successful companies in the next 5 years will be those that embrace this trend and prioritize the above steps in order to capitalize on this new paradigm.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.
Influential example of how system economic

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