Personalized Medicine

The path forward

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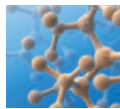
Foreword

Entering the age of personalized medicine?

The potential for personalized medicine to transform clinical practice has been the subject of much discussion and hype over the last decade. But aside from a few success stories like Herceptin and Xalkori, personalized therapeutics have had only a limited impact thus far. We believe, however, that the industry is now poised for rapid growth because of recent advances in the field, including more sophisticated diagnostic technologies and a greater understanding of disease heterogeneity.

Pharmaceutical and biotech companies have adopted different strategies to capture the promise of personalized medicine. Some have incorporated these therapeutics into their corporate mission by embedding them into all functions, while others have adopted a "wait-and-watch" strategy with selective investments. Diagnostics companies have also pursued various approaches to personalized medicine because uncertainty abounds about many important topics, such as the extent to which clinicians will adopt next-generation sequencing and other novel technologies. In addition, diagnostics companies are still attempting to identify ways to effectively capture value for their innovation in the current regulatory and reimbursement landscape.

In this compendium, we highlight the critical issues facing pharma, biotech, and diagnostics companies in personalized medicine, providing our perspectives on winning strategies for all players. We begin by describing the overall outlook for personalized medicine, while highlighting the key uncertainties and issues facing the industry. We then dive into topics of particular interest to pharma and biotech companies, including the best approaches for managing biomarker R&D efforts and launching companion diagnostic tests. Finally, we discuss how diagnostics companies can overcome the obstacles that have largely prevented them from capturing meaningful value from personalized medicine.

We hope that these articles stimulate debate and discussion, and look forward to continuing the dialogue as you help your company, or the industry as a whole, navigate the complex personalized medicine landscape.

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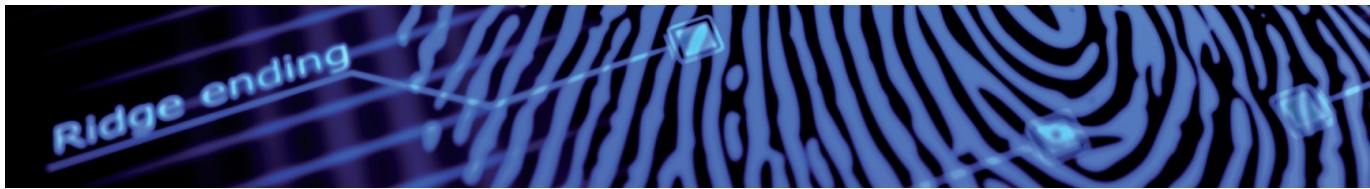
The outlook for personalized medicine

Samarth Kulkarni, Philip Ma, Laura Furstenthal and Matthias Evers

Is personalized medicine going to be a reality outside oncology? Will next generation sequencing (NGS) become commonplace in clinical diagnostics? Where is the value going to accrue in personalized medicine? These are just some of the questions we hear regarding the uncertainties facing personalized medicine and its evolution.

Over the last two years, we discussed the future of personalized medicine with many top executives from the leading pharmaceutical and diagnostics companies. During these discussions a handful of themes consistently emerged related to their efforts to develop their personalized medicine strategies.

Personalized medicine leaders interviewed

Mara Aspinall is President and CEO of Ventana Medical Systems and Global Head of Roche Tissue Diagnostics.

Roy Herbst is Professor of Pharmacology, and Professor and Chief of Medical Oncology at Yale Cancer Center.

Raju Kucherlapati is Professor of Medicine and the Paul C. Cabot Professor of Genetics at Harvard Medical School.

Larry Lesko is Professor and Director of the Center for Pharmacometrics/Systems Pharmacology at the University of Florida.

Stephen Little is Vice President of Personalized Healthcare for Qiagen.

Gordon Mills is Professor at the University of Texas M.D. Anderson Cancer Center.

Mike Pellini is President and CEO of Foundation Medicine.

Peter Maag is CEO of XDx and previously, President of Novartis Dx division.

In this article, we offer our perspectives on these critical themes and questions based on McKinsey research, client experience and interviews with eight recognized leaders in the field. These perspectives are meant to be discussion starters rather than definitive answers about how the field may evolve. Our hope is that these perspectives spark transformative ideas about your business.

We interviewed eight recognized leaders in the field of personalized medicine across both academia and industry to obtain insights and a range of viewpoints into critical issues related to personalized medicine. Excerpts from those interviews follow (please note some of the quotes have been edited for clarity). These expert opinions are combined with McKinsey research insights and our observations from client work within the sector.

In interviewing these experts we focused on five questions:

1. How do you see personalized medicine growing over the next five years? What do you believe the key growth drivers to be and where is the value likely to accrue?

2. How can personalized medicine evolve beyond oncology?

3. How rapidly do you see multi-gene approaches and next generation sequencing being adopted in clinical testing?

4. How is heterogeneity of disease going to impact the field of personalized medicine? How do you see it being operationalized?

5. How is the regulatory and reimbursement environment likely to evolve with respect to drugs and diagnostics?
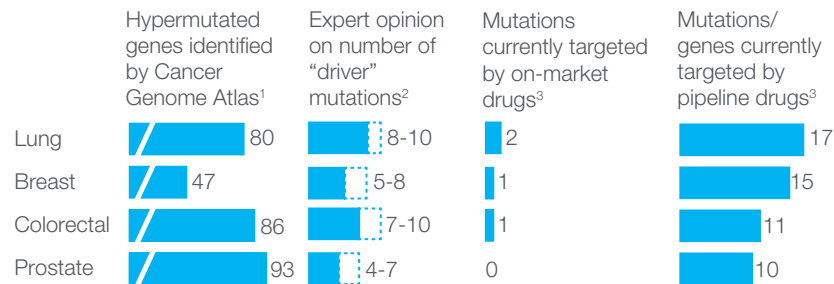
1. Growth of personalized medicine

There are many dimensions to the growth of personalized medicine. We have broadly categorized the growth along two dimensions—the number of drugs with companion/ associated diagnostics, and the use of advanced diagnostic techniques for screening and risk identification. The first dimension can be further sub-divided by markers for sensitivity/ efficacy, safety and resistance, for both new and on-market drugs.

The majority of the experts believe that although the number of new drugs with associated diagnostics will follow linear growth patterns, the use of advanced diagnostics for therapy selection will have exponential growth. On the drug side, despite several drugs with associated biomarkers being in the pipeline, if we apply the typical attrition factors in drug development we are likely to see a 2 to 3x increase in the number of drugs with companion Dx over the next five years, rather than an explosion (Figure 1). Beyond that horizon, however, growth is likely to accelerate as nearly half of the pre-clinical and Phase 1 assets in the pharma pipeline have associated diagnostics, especially in oncology, immunology and CNS. The identification of markers for safety, sensitivity and resistance for on-market drugs will drive growth to a larger extent in the near term. The identification of markers for on-market drugs will be driven not only by pharma, but also by academic medical centers and health systems.

FIGURE 1

Potential for additional personalized therapeutics in Oncology

	Hypermutated genes identified by Cancer Genome Atlas[1]	Expert opinion on number of "driver" mutations[2]	Mutations currently targeted by on-market drugs[3]	Mutations/genes currently targeted by pipeline drugs[3]
Lung	80	8-10	2	17
Breast	47	5-8	1	15
Colorectal	86	7-10	1	11
Prostate	93	4-7	0	10

1 Based on q-value analysis using MutSig software from the Broad Institute
2 Based on expert interviews
3 Based on Evaluate Pharmaceuticals database; for pipeline, includes Phase 1 and above only

A significant number of hyper-mutated genes have been identified in the four major tumor types, although only a limited set have been shown to be true "driver" mutations

However, pharma companies are developing drugs against a number of other gene targets, and applying typical attrition factors show that there is likely to be a significant increase in number of relevant markers in each of the tumors

While there are many factors that will spur the growth of personalized diagnostics in therapy selection, the most significant are payors mandating Dx to ensure proper use of therapeutics, advances in our understanding of the heterogeneity of disease and safety signals, improvements in the underlying technology and quality of Dx testing, and physicians' need for more information. Additionally, the increasingly informed and active consumer and the advances in digital and information technology will drive growth.

Advanced tests for screening and risk-identification will also have significant growth over the next few years as screening tests become less invasive, and establish greater clinical relevance. Some payors have called into question the benefit of some screening assays such as PSA, which have limited clinical actionability. In the near term, however, the ability of physicians to obtain all the information possible on the disease profile, and the desire from patients to have this information will drive adoption of screening and risk-identification. In the long run, advances in the understanding of linkages between genotypic markers, proteomic markers and disease will make these tests clinically relevant and actionable, increasing their use and overall impact on healthcare outcomes.

Aspinall: We will know that this transformation is mature when we all refer to "personalized medicine" as just "medicine" like in AIDS diagnosis and treatment today.

Little: Growth will depend upon the segment within personalized medicine. In the companion diagnostic space, growth will be more linear rather than exponential, gated by the pace of approval of drugs. Screening through genetics is likely to grow much faster.

Herbst: There are close to 200 markers in lung cancer, but only 5 to 10 of them are driver mutations. We have probably found most of the driver mutations as we can find in this disease.

Mills: Two factors that will drive growth are 1) identifying people at risk—physicians will want this information at hand, and 2) toxicity/safety testing—pharmacos will drive for legal protection to eliminate the one in a million AE that knocks approved drugs off market.

Maag: Digital health and proactive patients taking control of their own health will drive exponential growth. The portion of disposable income spent on healthcare will increase considerably over the coming years.

Personalized medicine will create significant value for the healthcare system but there is quite a bit of debate over where the value will accrue. From a payor perspective, the number of non-responders in some therapeutic areas such as rheumatoid arthritis is greater than 50 percent, and significant value can be generated by applying markers which predict response and reduce wastage of drugs on non-responders. From a pharma perspective, there will be winners and losers—some high-value drugs will see their market share decline as markers for sensitivity and safety are identified, whereas other drugs will capture disproportionate value through higher price and duration of treatment for a defined population. Diagnostics will also capture value, however, new business models within diagnostics may be required (see article on Capturing Value for Dx in this compendium). Unless the model for reimbursement of diagnostic tests changes drastically, diagnostics companies will only capture a fraction of the value created through advanced personalized diagnostics. A new class of data/IT players will also emerge and capture meaningful value by developing solutions for diagnostic data interpretation, clinical decision support and analytics for R&D.

2. How to move personalized medicine beyond oncology

While oncology has been at the forefront of the personalized medicine revolution, the big question facing the industry is: where next? In our 2010 article on personalized medicine[1] we highlighted that immunology and anti-infectives had emerged as the areas with the greatest activity in applying personalized medicine. Experts interviewed for this article were asked for the top three therapeutic areas beyond oncology which would be significantly impacted by personalized medicine. The four key factors cited by experts in evaluating potential impact by disease area were understanding of the basis of disease heterogeneity, the clinical relevance of markers of disease heterogeneity, the technical feasibility and tractability of measuring markers, and the relative economics of the personalized Dx (Figure 2).

Oncology will continue to be the leading "playground" for personalized medicine with new understanding of disease and new Dx technologies

In the near term (3 to 5 years), the next frontier of personalized medicine is likely to be in immune-related, pediatrics/pre-natal, and infectious diseases

In the long-run, CNS and cardiovascular have tremendous potential for personalized medicine, but still in early stages of development

FIGURE 2

Potential for personalized medicine across disease areas
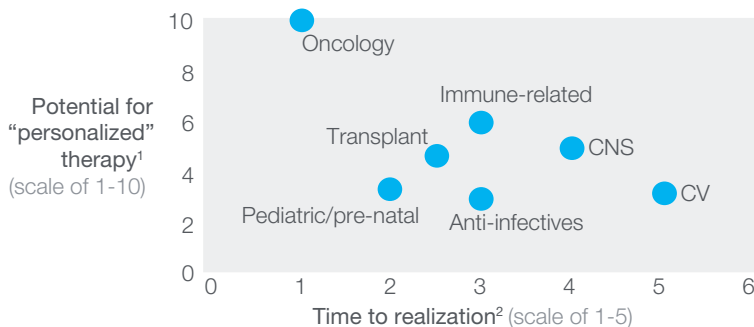
1 Potential based on understanding of disease heterogeneity, clinical relevance of personalized Dx and economic attractiveness

2 Years to realization based on disease understanding, technical feasibility and development timeline for therapeutics

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1   *The Microeconomics of personalized medicine: today's challenges and tomorrow's promise,* accessed at http://www.nature.com/nrd/journal/v8/n4/full/nrd2825.html

Based upon these factors we believe that within 10 years immunology/transplant, CNS, pediatrics, pre-natal, infectious diseases and cardiovascular will hold the greatest potential. Each of these disease areas is likely to have a different flavor of the type of advanced diagnostic testing. In immunology, given the complex nature of interactions between different interleukins and other factors, panel-based testing with a complex scoring system is likely. In contrast, much of the value related to CNS is likely to be in early genetic detection of late-onset diseases such as Alzheimer's.

Kucherlapati: Outside oncology, pediatrics, pre-natal and CV are promising areas... Psychiatry could be an opportunity but (companies will) need to overcome MD reluctance. Auto-immune is further off since we don't understand the genetic basis yet.

Aspinall: PM started in infectious disease and will dominate disease diagnosis and monitoring when genetic or epigenetic variations are dynamic: pathogens evolve and are highly diverse within one patient's disease. The next areas for transformation are virology, transplant and cardiovascular.

Lesko: I see a lot of potential in safety...especially in diseases such as cardiovascular.

Little: I see the greatest potential in early diagnosis of late-onset diseases such as Alzheimer's. AE prediction has significant potential too.

3. Next generation sequencing and multi-gene approaches

The adoption of next generation sequencing in clinical diagnostics is one of the most hotly debated topics in the field and, not surprisingly, elicited divergent opinions from the experts. The cost of sequencing a genome has decreased exponentially, replicating in lifesciences Moore's law in semiconductors. The leading NGS platform players—Illumina and Life Technologies—have both made claims that whole genomes can eventually be sequenced for less than $1,000 on their platforms. Our own analysis, based on interviews with several experts, shows that costs for whole exome sequencing could cost less than $500 in a few years. There are a number of factors which determine the extent of NGS usage in clinical diagnostics: clinical relevance and actionability of sequencing information in the disease, usability of NGS (cost, quality of sequencing and ease of use) and lastly, the regulatory environment.

From a clinical relevance perspective, not every indication is going to benefit from the increased information made possible by NGS because there are limited therapeutic interventions which physicians can choose from. Additionally, sequencing data using NGS does not provide a holistic clinical perspective, and other modalities of testing such as proteomic testing will continue to be relevant. Even within oncology, NGS has greater relevance in some tumor types such as lung cancer, where there are a greater number of therapeutic options available on-market or in the pharma pipeline. From a cost perspective, the costs of NGS have sufficiently declined where it is close to reaching a tipping point, where it as cost-effective as alternate testing modalities. In oncology, the costs of NGS may already have reached that tipping point relative to the sum total of costs of testing a set of individual markers. In other disease areas such

as infectious diseases, the costs need to come down even further to reach the tipping point. Lastly, there is a question of whether NGS platforms and tests will need FDA approval for use in Dx—most experts believe this is unlikely in the near term. In the current environment, CLIA-waived labs can conduct Dx using NGS as a lab developed test (LDT).
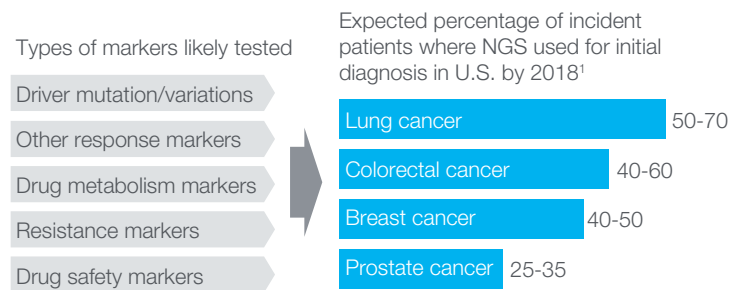
We estimate that a large fraction of presenting adjuvant and metastatic patients are likely to be sequenced using next generation sequencing (NGS) in five years, based on expert interviews and industry analogs

Different types of markers (efficacy, safety, resistance) are likely to have association with various therapeutic interventions, and are expected to be tested using NGS

Penetration outside the U.S. likely to be lower overall, except for some markets such as France, assuming current regulatory/ reimbursement paradigm continues

FIGURE 3

Relative penetration of next generation sequencing in Oncology in the future

Types of markers likely tested

- Driver mutation/variations
- Other response markers
- Drug metabolism markers
- Resistance markers
- Drug safety markers

Expected percentage of incident patients where NGS used for initial diagnosis in U.S. by 2018[1]

Lung cancer	50-70
Colorectal cancer	40-60
Breast cancer	40-50
Prostate cancer	25-35

1 Based on expert interviews and McKinsey analysis; both adjuvant and metastatic patients

Opinions among the experts interviewed were mixed on all these factors. Some experts believe that a majority of all oncology patients would receive NGS Dx in 4 to 5 years. On the other end of the spectrum others asserted that NGS adoption will be slower than anticipated due to concerns around quality of testing, and that targeted panels for genetic testing will see greater adoption because of the limited number of genes with clinical relevance. In any case, we are likely to see dramatic progress compared to the single gene testing regime in place today. Our forecasts on the adoption of NGS in oncology show that penetration can range from 25 to 70 percent of newly diagnosed patients depending on tumor type, which alone puts the market size at greater than $2 billion in 2018 (Figure 3).

Pellini: Nearly 50 percent of the newly diagnosed cancers in the U.S. would benefit from the targeted deep sequencing approach. In 3 or 4 years, we believe a majority of these would be done using next gen sequencing.

Little: Panels of testing and arrays will likely become more commonplace in near term before next gen sequencing… testing-controlled sets of 7 to 8 genes in particular disease areas in a regulated fashion may address the needs of companion testing and next gen may be used as a reflex.

Aspinall: Many believe that diagnostics will migrate to NGS. My view is that current technologies will be synergistic with sequencing. In cancer, we will always need to look at the tumor micro-environment.

Kucherlapati: I see costs coming down rapidly in the next couple of years and once costs are down to a manageable level, there will be increased adoption. In some centers today, if you do separate tests for *EGFR, KRAS, BRAF* and *ALK,* test costs add up to $3,000 …you could do it all together using next gen for less than $2,000.

Maag: It is not inconceivable in the near future that governments in smaller countries like Singapore choose to sequence entire populations using next gen sequencing.

The ability of companies to capture the value of NGS, and identify winners and losers, may reflect the evolution and adoption behaviors seen in personal technology. The use of NGS could evolve like the semiconductor space, where Intel and AMD retained leadership for a long time in a duopoly. In the next generation sequencing platform market, current leaders Illumina and Life Technologies hold a similar position. Given the disruptive nature of the market, however, we believe that smaller companies could change the game quickly in NGS such as what happened in the PC and tablet markets. Further, with significant changes on the platform side, we believe much of the value capture in NGS will occur on the diagnostic services side, with data and bioinformatics becoming a key competitive advantage.

4. Heterogeneity of disease

The heterogeneous basis of different diseases, especially oncology, has been well-recognized over the last 10 to 15 years. During the last two years, there have been several advances in defining the heterogeneity of disease and the topic has gained attention outside scientific circles. Our understanding of heterogeneity is relatively advanced in oncology compared to other disease areas, where the heterogeneity of a disease is known but still relatively less-understood. Within oncology, while inter-tumor heterogeneity is a well-recognized concept, the biology and reasons behind intra-tumor heterogeneity are still in early stages of understanding. Recently, the Genome Atlas has been published for various types of cancer including breast, colorectal and squamous cell carcinoma.[2, 3, 4] While there are more than 50 different types of mutations within the same type of cancer, experts believe that only a handful of them are truly "driver" mutations, while recognizing that there is much more to learn about these diseases. There is debate as to the role of the "passenger mutations," in particular, their role in how the tumor usually responds to treatment. A major challenge facing pharmaceutical companies going forward is to clearly identify these driver mutations from the passenger mutations and develop therapeutic approaches against each of the driver mutations.

From the perspective of the diagnostics players, heterogeneity presents an interesting opportunity given the increased number of targets to test and the increased complexity of testing. From a drug perspective, however, the number of actionable mutations remains limited, and the additional diagnostic information is unlikely to meaningfully change treatment of patients except in those with certain types of tumors.

Similarly, intra-tumor heterogeneity represents an opportunity for diagnostic companies to gain additional information about the tumor and how genes evolve in the tumor over time. However, the set of actionable drugs remains limited to the driver mutations. Nonetheless, there is an opportunity and solid argument to further explore mutations that cause the cancers to recur, such as the *T-790M*[5] mutation on the *EGFR* gene in lung cancer. Such mutations that occur during a course of treatment or after preliminary treatment represent

2   *Comprehensive molecular portraits of human breast tumours* accessed at http://www.nature.com/nature/journal/v490/n7418/full/nature11412.html

3   *Comprehensive molecular characterization of human colon and rectal cancer* accessed at http://www.nature.com/nature/journal/v487/n7407/full/nature11252.html

4   *Comprehensive genomic characterization of squamous cell lung cancers* accessed at http://www.nature.com/nature/journal/v489/n7417/full/nature11404.html

5   *The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP* accessed at http://www.pnas.org/content/105/6/2070.abstract

Little: Heterogeneity presents an opportunity for Dx companies. Biopsies are an issue, and therefore there is a need for testing through blood at low concentrations. Additionally, beyond the heterogeneity at initial diagnosis is the change in genetic profile as disease progresses. This is an opportunity for the blood-based tests as well.

Mills: Intra-tumor heterogeneity has always been known but the number of therapeutics available ultimately limits what you can do with that information.

Lesko: Intra-tumor heterogeneity has been known for decades. For example, prostate biopsies are sometimes done with 12 punches to account for the heterogeneity. It is a solvable problem to measure genetic heterogeneity; not sure if it will matter though, as ultimately it is the phenotype of the disease that matters.

Pellini: How are community oncologists expected to keep up with every marker, every therapeutic, and every clinical trial for each different cancer type? It is too much to ask of anyone. We need a different approach to sort through the information overload.

opportunities for drug companies to develop new second- or third-line treatments. They also underscore the potential for diagnostic companies to develop better biopsy tools and less-invasive testing modalities such as those based on circulating tumor cells.

Outside of oncology, heterogeneity of some of the rare diseases, such as mucopolysaccharidosis, has been found to be clinically relevant and actionable. However, the real breakthrough in the field will likely occur when the basis for disease heterogeneity is well understood in diseases such as CNS and cardiovascular.

5. Regulatory and reimbursement environment

The regulatory environment for drugs and diagnostics is likely to have a significant impact on the evolution of personalized medicine. A majority of the experts believe that the regulatory environment has not kept pace with the rapid advances in the field of personalized medicine. For example, on the therapeutics side, the US FDA last published guidance for approving drug—diagnostic combinations which relies on prospective trials in 2005. However, the world of "one drug–one diagnostic" in personalized medicine may already be passé. The challenge for pharma has been that given the number of emerging biomarkers in the field and the various correlations, it is complex and expensive for the industry to conduct prospective trials in all these settings without knowing the parameters of regulatory compliance.

On the diagnostics side, while there is a set process for obtaining approval via the PMA (pre-market authorization) or the 510(k) approval process in the U.S., there is also significant use of laboratory developed tests (LDTs) which do not require FDA approval but are governed under oversight mechanisms such as CLIA (clinical laboratory improvement amendments). Knowing where the line is poses a challenge for diagnostics companies to capture value, since they could spend millions on clinically validating a diagnostic that can be easily replicated as an LDT by a competing service provider. If however, the FDA mandates that newer technologies such as next generation sequencing need FDA approval for use in clinical diagnostics, it could severely hinder the pace of innovation and adoption of advanced testing.

Overall, the majority of the experts see regulations changing slowly, with some seeing meaningful change in four or five years. While there is general agreement that the system needs to change, there is significant debate about the right path forward. On the diagnostics side, one school of thought is to create an easier path for regulations for newer technologies, and then stricter enforcement of the approved diagnostics. The opposing camp believes that such a model will stifle innovation and put the U.S. at a disadvantage vis-à-vis the EU, where the regulatory stance is lighter.

Lesko: We may need a whole new process for regulations within personalized medicine…it may require creating a new center such as the CDER and Congress may need to act.

Little: In diagnostics, the EU is very lightly-regulated, whereas the U.S. is stringently regulated…the best system may reside somewhere in between.
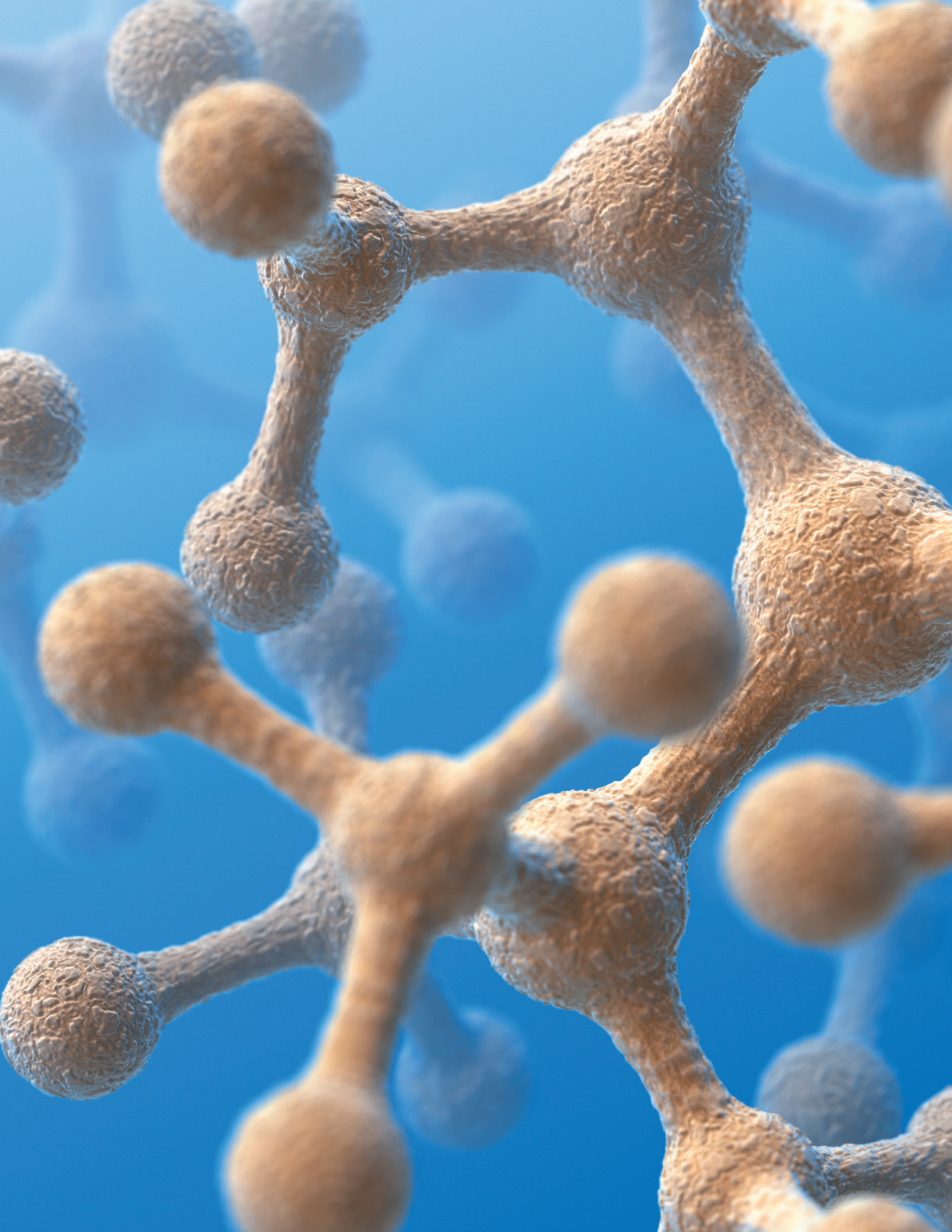
Aspinall: The FDA's recent concurrent drug-diagnostic approvals demonstrate their acknowledgment that PM has taken hold for multiple stakeholders.

Kucherlapati: The FDA knows that PM is a wave they will have to deal with; on diagnostics, they will need to declare a clear standard…right now there is no such standard.

Maag: Given the regulatory environment today, CLIA labs have become the hotbed of innovation.

The reimbursement landscape for advanced diagnostics is quite different by region today and has significantly influenced the adoption of personalized medicine. In Europe, the penetration of molecular diagnostics tests is highly influenced by the existing reimbursement regime. For instance, the penetration is relatively high in France, where there is broad reimbursement coverage, compared to Italy or the UK, where the coverage is much more restricted. The majority of the experts agree that the reimbursement model will need change to keep up with the pace of change of personalized medicine, and the existing "cost-plus" mindset for reimbursement of diagnostics will severely hinder innovation. Unlike pharma companies in the U.S., who have a much greater ability to set the price of a new drug, diagnostics companies have to rely on a complex process known as "code-stacking" to obtain any premium for innovation. This system creates challenges for all stakeholders involved—lack of coverage for patients who deserve these high complexity tests, limited visibility into testing usage and patterns for payors, and unclear path to reimbursement for the diagnostics companies. Reimbursement reform will be critical to encourage innovation in personalized medicine and accelerate its adoption.

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The next three to five years will be critical in the development and adoption of personalized medicine. While personalized medicine is attractive for investment, it is a volatile and dynamic environment. Leaders within stakeholder groups such as pharmaceuticals, diagnostics, payors, providers and regulators face critical choices that will shape the environment, determine the relative value capture among stakeholders and differentiate the winners from the losers.

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Managing for success in biomarker R&D: Challenges and opportunities

Matthias Evers, Samarth Kulkarni, Philip Ma, Martin Moller and Ivan Ostojic

Over the last decade companion diagnostics and biomarkers have become increasing relevant in the practice of medicine, leading to improved diagnosis, treatment and monitoring across a number of disease areas. There are now over 85 CDx on-market and more than 500 clinically relevant biomarkers.[1] The promise of personalized medicine is having a tremendous impact on how R&D is conducted within pharma companies, particularly in the use of biomarkers and genomic information. Just five years ago pharma companies were hesitant about personalized medicine given the threat of potentially narrowing commercial value of a drug, but today a majority of companies embrace personalized medicine as part of their R&D strategy. The successful launch of drugs for narrow populations based upon a companion diagnostic, such as Xalkori from Pfizer, show the commercial viability of serving even small addressable populations. Generally, personalized drugs are appropriate for increased duration and can command a price premium, making them an attractive commercial proposition.

Currently nearly a third of the drugs in clinical development are associated with some form of a genomic or proteomic marker, a 50 percent increase over the last two years. Disease areas such as oncology are early adopters, with nearly 35 percent of oncology trials using defined biomarkers in the trials. Furthermore, pharmacodynamic biomarkers are starting to play a fundamental role in the discovery and validation of targets and screening of drug candidates.

While some pharma/biotech companies have built successful biomarker programs and incorporate them into the larger R&D strategy, most pharma companies are just now beginning to establish a meaningful biomarker program in R&D.

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1   *FDA Table of Pharmacogenomic Biomarkers in Drug Labels* accessed at http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Within the top 15 pharma companies, we found a wide range of investments in biomarker research based on discussions with R&D leaders. The front-runners allocate 3 to 4 percent of total R&D spend to biomarkers, while the bottom quartile of companies spend less than 0.5 percent — an eightfold difference.

What does it take to reach excellence in biomarkers from an R&D perspective? Interviews with biomarker and translational medicine leaders from the top 15 pharma and biotech companies reveal challenges on several fronts: a lack of strategic alignment, sub-optimal organization structure and mindset, and operational challenges among them. This article describes these critical challenges as well as others, and the key success factors to overcome them.

Strategic choices and alignment

A number of pharma companies today are grappling with the issue of investments and return on investment (ROI) in biomarkers. While the positive ROI for personalized medicine has been proven in oncology with drugs such as Zelboraf and Xalkori, the relative economics are still unclear in therapeutic areas such as diabetes or cardiovascular. Consequently, a key issue facing R&D leaders is finding the appropriate level of investment in biomarker research for therapeutic areas outside of oncology. While a systematic review comparing the track-records of "personalized" versus "all-comer" drugs has not been conducted, we illustrate how the ROI for the two can be compared in oncology (see Figure 1).

While a comprehensive historical analysis of pharma pipeline attrition has not been performed, estimates indicate that personalized drugs have higher probability of success and ability to price higher, with lower drug development costs, resulting in comparable or higher ROI than broad-based drugs

FIGURE 1

Case can be made for superior ROI of personalized therapeutics in Oncology

	Assumptions to compare broad pan-tumor programs to niche personalized ones				Relative ROI of pan-tumor vs. targeted therapies
	Patients[2] 000s	Peak share[3] %	PTS[4] $	Variable dev cost[5] $M	IRR of R&D investment[6] %
Broad Tx, incremental	300	15%	7%	500	12
Broad Tx, transformative	300	25%	5%	500	15
Personalized niche Tx	30	40%	15%	250	10
Niche Tx, fast approval[1]	30	40%	15%	200	17

1 "Fast" assumes approval after Ph2, Ph3 still required
2 Broad Tx equivalent of Her2- mBC, mCRC, and mNSCLC; Niche equivalent of GBM or EGFR+ mNSCLC
3 Niche drug based on driver mutation attains high share, pan-tumor shares lower and vary by efficacy
4 Probability of Therapeutic Success (PTS) from pre-clinical through approval. Low PTS for Broad Tx with lower probability it will be transformative
5 Variable development costs, pre-clinical through launch; assume pan-tumors need broad development program; not fully loaded costs and do not include post-launch development costs
6 Includes preclinical development but not research, assumes drug costs $60K/patient
SOURCE: McKinsey analysis

We believe that R&D heads can apply a tiered investment approach to disease areas and use criteria such as potential clinical relevance of biomarkers, feasibility of discovering biomarkers and commercial potential to "right size" investments. Using these criteria therapeutic areas such as immunology, CNS, transplant and cardiovascular are emerging as the next set of therapeutic areas (after oncology) which justify greater investment in biomarker R&D. For companies focusing on these disease areas, there is a risk of losing leadership position and competitive advantage tomorrow by not investing in biomarker research today.

Investments can be made in creative ways to allow companies to both be prudent with resources and maintain a competitive edge in R&D. Internally, investments can be carefully prioritized for select modalities, platforms and markers in a hypothesis-driven fashion. Some examples of creative external investments include multi-company partnerships, venture investments and academic grants. For the other disease areas which are relatively lower potential such as diabetes, obesity, and urology, investments can be scaled to keep a "foot in the door" and made on a case-by-case basis.

We are moving beyond the "one-drug one-diagnostic" paradigm. Medicine is shifting towards multi-marker and multi-modality diagnostics for each patient, necessitating investments from pharmacos across different types of markers and modalities.

Another strategic choice facing both the front-runners and followers in biomarkers is the level of investment in different modalities. Heads of R&D are confronted with data and choices on different types of markers including predictive and prognostic efficacy markers, safety markers, and pharmacodynamics markers. Additionally, there are a number of diagnostic techniques across imaging and in-vitro diagnostics, including genetic, proteomic, and other phenotypic information. We believe that the days of the "one drug– one diagnostic" paradigm are coming to a close, and medicine is shifting to multi-factorial diagnostics informed by different Dx modalities. That said, the need for investments across different modalities has to be carefully balanced against what biomarker leaders call "biomarker phishing." Biomarker leaders at pharma companies have described the classic case of "too many small bets" across modalities, a non-focused approach that can lead to poor ROI on biomarker investments. In one instance, a biotech company made bets on seven different modalities for biomarkers including imaging, expression, mutations and single-cell analysis techniques, leading to inefficient spend and limited market impact. A disciplined portfolio prioritization approach like that used for drug/molecule portfolio planning needs to be instituted with a customized set of criteria for ROI.

Lastly, a critical issue facing pharmacos is how to build capability, specifically the choice between in-house development versus partnering for capabilities. There are several emerging companies which provide outsourcing services for biomarker characterization, sample collection, sample analysis and data interpretation. All the top contract research organizations (CROs) view biomarker research services as a growth area, and now offer these services to pharmacos. Additionally, specialty service laboratories such as Clarient

(GE) and Caris have entered the sector, offering services ranging from assay development to patient diagnostic registries. Adding to this complexity are the academic medical centers (AMCs) which have established advanced offerings such as next generation sequencing for clinical trials and provide the services through independent business units. We believe the optimal mix of in-house versus outsourced depends on a number of factors including the size of the R&D organization, therapeutic area focus, financial strength, and level of organizational commitment to personalized medicine. Most often, a hybrid model is the right solution. Activities which do not deliver a core competitive advantage such as assay development are out-sourced, and more distinctive capabilities such as data analysis and biomarker characterization are kept in-house.

Organizational effectiveness

With the exception of 3 to 4 companies, the biomarker organizations within most pharmacos have been built in an ad-hoc manner, typically resulting in patch-work organizations with several organizational challenges. Based on our discussions with senior R&D leaders, the most significant and common challenges include: a) gaining strategic alignment for the biomarker program, b) designing a productive and efficient organization structure, c) staffing the right people and talent, and d) instilling a common mindset and behavior. For companies that are just beginning to institutionalize a biomarker program the challenges are much more basic. Although these challenges are quite complex, there are potential ways to overcome them.
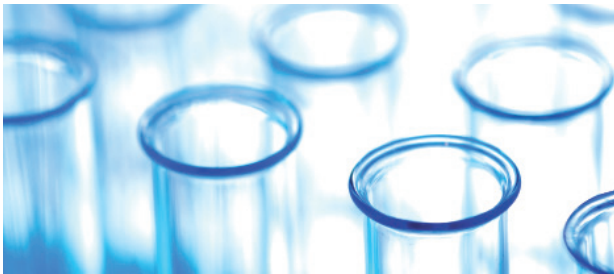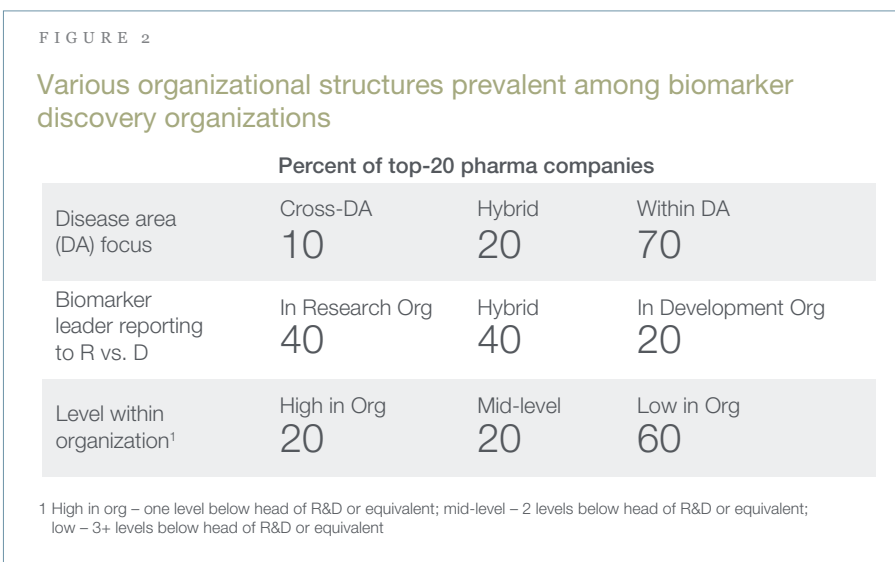
Gaining strategic alignment around biomarkers: Biomarker and translational medicine leaders within pharma companies often cite examples where decisions and investments in biomarkers were not made early enough, or where the biomarker strategy was reactive rather than proactive. Often times, we see a disconnect that exists among the overall R&D strategy, portfolio planning, and biomarker strategy. While there could be several reasons for this lack of alignment, the most typical ones are the biomarker group lacks a strategic leader, or the biomarker representatives do not have a "seat at the table" for decision-making and investment decisions are made at a molecule-level, instead of the portfolio level.

The impact can be on many levels: broader portfolio-level questions on biomarkers, such as those related to panel testing across multiple drug candidates or new modalities such as molecular-based imaging are not addressed since the biomarker decision-makers are several levels below the leaders controlling resourcing. A localized-level of decision-making often leads to tension in aligning incentives across the organization; for example, clinical operations focus on cost and speed while the biomarker TM group wants to test biomarker hypothesis. There is frequently uncertainty about how to organize new capabilities such as TM, Dx alliance management Dx marketing personnel.

Companies have successfully overcome these alignment challenges by selecting a senior level leader to spearhead biomarker strategy, integrating a biomarker governance process with overall R&D governance, and creating groups to address portfolio-level questions. In some organizations, the senior biomarker leader is also involved in commercial strategy, given the potential impact of biomarkers on the success of on-market drugs.

Refining a sub-optimal organizational structure: To date, a wide range of organizational structures have been employed by pharma companies for the biomarker group (Figure 2).

FIGURE 2

Various organizational structures prevalent among biomarker discovery organizations

Percent of top-20 pharma companies

Disease area (DA) focus	Cross-DA 10	Hybrid 20	Within DA 70
Biomarker leader reporting to R vs. D	In Research Org 40	Hybrid 40	In Development Org 20
Level within organization[1]	High in Org 20	Mid-level 20	Low in Org 60

1 High in org – one level below head of R&D or equivalent; mid-level – 2 levels below head of R&D or equivalent; low – 3+ levels below head of R&D or equivalent

While a range of organizational structures have been adopted for biomarker organizations, a majority of them are within individual DAs, do not span research and development, and are not elevated in the organization

To build a successful biomarker organization, it is critical to establish coordination across research and development groups and select a senior executive to lead the group

While the optimal structure for the biomarker organization will be highly dependent upon the overall R&D structure and operating philosophy of the company, there are some tenets of organizational design which are important to consider. First, we advise companies to invest in a senior leader. It is critical to find an experienced leader who is familiar with the pharma R&D process, drug commercialization and the diagnostic/translational side of the coin. Second, it is not necessary to build everything in-house. Several functions such as next generation sequencing, assay development, etc., can be outsourced. Key capabilities to build in-house are data analytics and informatics, especially as they relate to safety markers. Finally, the decision to organize around cross-TA versus TA-specific biomarkers groups is highly dependent on the rest of the organizational structure. However, centralizing some elements which can make organization more efficient and allow for transformative thinking across TAs.

Finding the right people and talent: There are two issues related to people and talent within biomarkers: 1) it is difficult to find people with a skillset that spans both pharma R&D, clinic and diagnostics, and 2) the lack of clear career path within biomarker research to other parts of the organization is seen as limiting by high potential candidates. What we have heard from leaders in biomarkers is that often the "Dx-minded" people in the biomarker organization do not have a full understanding of the drug development process, resulting in lack of alignment between the biomarker and development teams. Similarly, there is a shortage of translational medicine capabilities, for example people with MD/PhD backgrounds who understand bench science as well as clinical applicability. These issues can

be addressed by elevating the biomarker role, ensuring a "seat at the table" for a biomarker team on the clinical development leadership group and providing the right resourcing level. These actions will attract top talent to the biomarker group. Additionally, it is important to have a mix of experience from clinical development, bench science and diagnostic backgrounds within the team to bring the best knowledge to bear.

Instilling a common "pro-biomarker" mindset: Another topic of concern is the need to establish a biomarker mindset within the organization. Promoting the biomarker concept and clarifying commitment to personalized medicine are critical to embedding "biomarker thinking" across the R&D and commercial organization. Companies such as Novartis and Roche have made public commitments to the personalized medicine concept and are attempting to infuse the biomarker mindset across the entire organization. The keys to embedding this biomarker mindset are ensuring top level leadership buy-in, role modeling in decision meetings and other forums and ultimately, the appropriate resourcing of initiatives to further biomarker discovery within the company.

A "biomarker" mindset which permeates the pharma organization is critical in realizing the potential of personalized medicine. Biomarker organizations with the belief that biomarkers must have a causal link to disease mechanism will have a biomarker strategy that is much more closely linked to the drug discovery strategy. Companies which have used a "phishing" approach to biomarkers have typically been unsuccessful.

Operational challenges and opportunities

Companies are facing both first-order and second-order operational challenges based on the stage of development of the biomarker organization. The typical operational challenges include: a) lack of clarity of process for including biomarkers in the company's development program, b) unclear clinical trial strategy and regulatory pathway for biomarkers, c) limited knowledge of appropriate platforms and know-how, d) difficulty of sample collection and storage strategy, and e) the complexity of data management and informatics.

Clarifying the process for biomarker development: Currently most companies have an ad hoc, unstructured process for incorporating biomarker R&D into the broader R&D process. For example, the target product profiles (TPPs) used in prioritization decisions in a majority of companies do not include biomarker criteria or the criteria is not clearly defined. The sample collection and storage policy may be ill-defined as well. There are a number of cases where the biomarker development process lagged the rest of development, resulting in exclusion of the biomarker in pivotal trials or delay of these trials. We have seen companies struggle with the stage-gate process because biomarker development is sufficiently different from drug development, and the traditional stage-gate models do not apply. Establishing

clear stage-gates for biomarkers, integrating biomarker development within broader development timeline and including prioritization criteria are the three most important process elements necessary for biomarker excellence.

Additionally, the regulatory processes for biomarker development are quite different from traditional drug development, and the regulatory and quality teams need to master a whole new set of regulations and regulatory process.

Establishing an effective trial strategy and regulatory approach: There are several strategic options for inclusion of biomarkers in trial design and regulatory approval. The critical choices within trial design typically are:

1. Whether to include the biomarker in pivotal/registrational versus supporting trials,

2. Identifying the type of end-point based on biomarker,

3. Establishing appropriate cut-offs in defining target population, and

4. Selecting the appropriate format of biomarker read-out.

Making the right decisions early in trial design can impact the success of the biomarker. For example, innovative formats for biomarker inclusion such as adaptive trials (I-SPY in breast cancer) can be considered in trial design.[2] Inclusion in registrational trials is key; biomarkers such as Tarceva were not included which resulted in the biomarker not being on the initial label. This severely handicaps the salesforce, who are unable to promote the biomarker-drug combination benefits, resulting in poor uptake. The level of testing of *EGFR* mutation in lung cancer is still less than 60 percent in the U.S., for example.

Similarly, determining the cut-off for biomarkers which do not have a clear positive/ negative signal ("dirty" biomarkers), such as IgE or *KRAS* expression are critical in commercial success of the drug. The cut-off has to be carefully determined by balancing the breadth of target population, level of efficacy and physician confidence in biomarker rationale. Lastly, selecting the appropriate platform or assay format for biomarker read-out is critical. While the choice is clear for mutation or translocation-based markers, there are several options for expression-based markers including mRNA levels or protein levels. Additionally, for blood-based protein markers, selecting the appropriate isoforms of the protein and the appropriate domain to detect are critical.

While trial design should be based on specific circumstances of the molecule and indication in consideration, establishing the design choices early in the development program and including commercial input into the design selection are important for success.

Expanding knowledge of appropriate platforms: For biomarkers launched as companion diagnostics, the choice of platform has a significant impact on the adoption of the drug-diagnostic combination. Two recently launched "personalized" drugs, Zelboraf and Xalkori, selected different platforms for their companion diagnostic. Zelboraf was launched with a large instrument-based CDx on the Cobas™ platform, while Xalkori was

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2   Barker et al., *Clinical Pharmacology & Therapeutics* 86, 97-100 (July 2009).

launched with a FISH-based assay kit. Based on recent customer interviews, it appears that there is a greater level of laboratory-developed tests (LDTs) being used in the case of *BRAF* testing for Zelboraf relative to the *EML4-ALK* testing for Xalkori. The use of less-validated LDTs can be problematic as it limits the quality of testing and use of companion drug. In addition, the timeline and investments required in developing these tests across different platforms vary significantly, impacting choice of platform. Lastly, several companies have chosen to use multiple competitor platforms versus a single company's platform. In consolidated markets such as immunohistochemistry, launching on the Roche and Leica platforms covers the majority of the market. However, if launching on molecular (MDx) or immunoassay (IA) based platforms, coverage across multiple manufacturers is needed to ensure access to the test for physicians and patients.
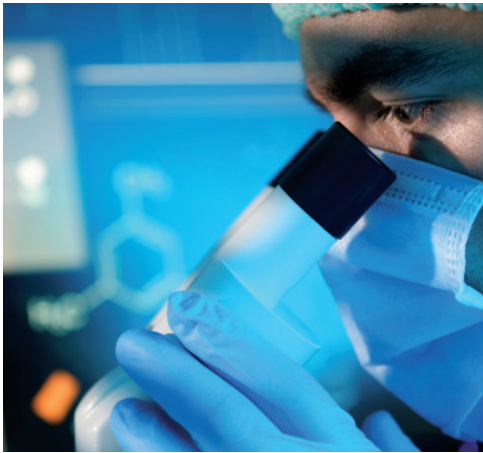
Ensuring adequate sample collection and data analysis: Most companies underestimate the challenges of sample collection and analysis, especially in tumor samples. Key challenges include a lack of sufficient samples, especially in indications such as lung cancer; low-quality control in sample collection and storage; and lack of usability of the data from samples. Several trials have rendered genomic data useless; in one instance a sample was stored in different buffers by different physician groups while in another the patient authorization for sample analysis was improperly collected.

In addition, most clinical research organizations (CROs) are in early stages of developing capabilities to collect and store samples, so monitoring CRO sample collection and analysis is critical. Biobanks are moving into the space to establish a level of standardization of sample storage, but still early in development. Two companies have now established dedicated "sample integrity" groups within clinical development to ensure high-quality sample collection and analysis.

"Pharma companies need to realize that information is more valuable when shared. It's Metcalfe's Law—information technology companies recognized this 20 years ago. If pharma companies open source their data from clinical trials and discovery efforts, it will be a significant boost to innovation." – *Randy Scott, CEO, InVitae and Founder, Genomic Health*

Data collection and informatics are also cited as substantial challenges within clinical development. There has been an explosion of data being collected for each patient, including genomic data as a result of next generation sequencing. This poses some problems in adequate data management and analytics because historically data groups within clinical development focused on biostatistics of patient outcomes and safety. There is now a need for sophisticated correlative analysis of biomarker and genomic data to the efficacy and safety of drugs.

Consequently, some pharma companies are working with "Big Data" companies to better understand advanced analytics and implications for the biomarker discovery group because deep informatics capability will be critical to biomarker success.

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Success in biomarkers will be critical to pharmacos as personalized medicine becomes more the rule than the exception. While the promise of personalized medicine can be over-played, the importance of having an effective biomarker group within R&D cannot be overstated. We believe that establishing biomarker excellence can be a source of distinctiveness and competitive advantage, and is important enough to be on the CEO-agenda. We hope our ideas on managing biomarker R&D for success can help your biomarker research group and trigger transformational ideas.

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Well begun is half done: Success factors for companion diagnostic launch

Leeland Ekstrom, Edd Fleming, Daina Graybosch, Hyung-do Kim, Samarth Kulkarni, Pawel Poda and Devin Scannell

Pharmaceutical companies recognize the importance of a successful drug launch, and have spent many years perfecting the launch process. With some of the new "personalized" drugs, the launch success of the companion diagnostic (CDx) is just as critical in determining the ultimate success of the drug. For instance, the launch of the companion diagnostic for Xalkori for *ALK* testing was a critical driver in ensuring usage and penetration of the drug to treat lung cancer. Today, there are 85 Rx/CDx on-label combinations and R&D pipelines show that number is growing rapidly; 13 of the top 20 pharmacos we analyzed revealed nearly 150 Phase 3 trials with a CDx listed and almost twice that number in Phase 2. Given these trends, it is clear that Rx/CDx launches will become much more common and that perfecting them a key competitive advantage.

Despite the importance of successful CDx launches, each of the major companion diagnostics tests launched to date faced significant challenges in adoption. For instance, the *EGFR* diagnostic test for Tarceva and Iressa reached penetration levels of less than 50 percent among lung cancer patients in 2011. Of the factors contributing to this low level of adoption, the most important is that the Dx test was not launched with FDA approval, preventing pharma companies from promoting the diagnostic. Other products ran into different hurdles: the companion diagnostics for Her-2 testing faces significant accuracy challenges, with nearly 20 percent of tests being diagnosed inaccurately. Meanwhile, the scoring system for the *KRAS* diagnostic associated with Erbitux had to be redefined after questions arose regarding test interpretations with the initial version.

Given this uneven record and the importance of getting companion launches right, this article discusses both the challenges inherent in the launch of companion diagnostics and the keys to success. In summary, launching a companion diagnostic successfully requires companies to "get it right" across the entire value chain, starting with drug/Dx development and continuing through to an effective promotion strategy.[1] There are a handful of specific success factors that CDx launch teams need to attend to:

- **Coordinating Rx–CDx development:** Lack of coordination can lead to launch of drug without the diagnostics on label, or delay in Phase 3 study.

- **Navigating regulatory:** Choosing a PMA vs. 510(k) versus LDT strategy for the associated diagnostic undercuts both access to and quality of the diagnostic test.

- **Partnering successfully:** Several different archetypes of partnerships between pharma and Dx companies are used today but only few are fully optimized for success.

- **Ensuring market access:** Mainly an EU challenge, with tailored strategies required by country. In the U.S., getting "value" for the diagnostic is the challenge.

- **Maximizing adoption:** This requires addressing three primary barriers—test availability and access, physician awareness and buy-in and finally, testing quality and accuracy.

Coordinating Rx-CDx co-development

Given the distinct development timelines and risks of drugs and diagnostics, careful coordination is needed to ensure that the companion diagnostic can be brought to market successfully with the drug. The requirements for a diagnostic from a clinical and regulatory perspective are different based on the type of diagnostic being developed, for example whether it is an on-label requirement, on-label recommended or on-label information only. In terms of clinical development, we believe that it is critical to generate the CDx hypothesis early, position the CDx optimally, enable the CDx development by collecting the appropriate samples and begin the CDx assay development early. The last two activities are particularly important.

Begin assay development early and position appropriately: Nearly 50 percent of companies do not begin commercial assay development until completion of the preliminary Phase 2.[2] Additionally, the specifications of CDx to be developed are not

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1   While some define companion diagnostics narrowly as only on-label diagnostics mandated by the FDA for a particular drug, we define them more broadly to include diagnostics required or recommended in association with a particular drug.
2   Cutting Edge Information Report.

finalized until completion of Phase 2 trials, sometimes leading to delays in the start of Phase 3. Early on in CDx development, it is critical to establish the hypothesis and modality for assay development—whether kit, platform-based or service-based, and whether immunohistochemistry (IHC), molecular or other modality. Also important is identifying the appropriate cut-offs and segment definition early in development. In one instance, input from commercial leaders was not provided until commercial assay development was commissioned, with the result that the assay developed had a cut-off that had to be changed and required a new set of development steps. For "dirty" markers choosing a cut-off in Phase 2 trials is especially important. For instance, Xolair (for severe asthma) is prescribed with a recommended companion diagnostic that measures IgE levels. Yet, because a clear cut-off was not established early in product launch, several different standards are used by labs and physicians in determining whether to prescribe the companion therapeutic, thereby limiting its adoption. Additionally, the shift from "one-drug one-diagnostic" to a multi-marker testing paradigm brings a new set of challenges for pharma companies. Developing a multi-analyte panel requires a different approach on regulatory and commercialization.

Enable commercial assay development through the clinical trials: A lack of samples for biomarker validation can be a major development bottleneck, especially in oncology. In general, there is little motivation among clinicians and patients to provide samples, consequently requiring biopsies as a condition for trial enrollment is one way to ensure future supply, especially if any tissue analysis findings can be shared back. Another approach is to look beyond clinicians for tissue sources. Publicly-maintained tissue banks are often mandated to share samples while academic banks are also usually of high quality and can often be accessed through strategic collaborations or partnerships.

Navigating regulatory requirements

A majority of the experts believe that the regulatory environment has not kept pace with the rapid advances in the field of personalized medicine. The initial FDA draft guidance on the approval process for companion diagnostics was released in 2005, and was not clear about the different regulatory paths and potential impact of each path on drug approval. Additionally, most service labs are regulated by the Centers for Medicare and Medicaid Services for laboratory developed tests (LDT) regulation under clinical laboratory improvement amendments (CLIA) rules. The different regulatory paths available and the lack of clarity in the requirements make it challenging for CDx development and launch.

Pharma companies can choose to take different paths to regulatory approval, of course, seeking co-approval of the drug/Dx combination together or separate approvals if the drug is already on market. Additionally, within this framework, different approval paths can be selected for the diagnostic itself. Roche adopted the pre-market authorization (PMA) path for approval of the *BRAF* test as a companion diagnostic to Zelboraf, while Pfizer adopted a

510(k) approval strategy with the *ALK* test as a CDx for Xalkori. Previously Pfizer pursued a regulatory strategy for the Tropism test, which relied on CLIA approval. For drugs that are not first-in-class, companies have adopted a "home brew" approach, which relies on lab-developed tests for CDx.

The key trade-off in selecting a regulatory strategy is the time required to develop the CDx versus control over the quality of the testing. The PMA strategy used for Roche's *BRAF* test can be time-consuming and burdensome, yet it is also true that the closed-box Dx test ensures high testing accuracy. At the same time, the platform-based tests which rely on PMA typically limit the number of labs that can perform the test. The 510(k) approval route with the development of a CDx kit has been the preferred route for most companies, reducing reliance on the platform and allowing flexibility for change in the test in the future.

Regardless of the regulatory strategy adopted, it is safe to assume that a large percentage of the tests will be performed in-market as LDTs, especially with the increase in the number of tests being performed using next generation sequencing (see Figure 1). We estimate that nearly 45 percent of *BRAF* testing is performed via LDT methods (CE sequencing, PCR or next generation sequencing) even with the approved Cobas test being available.

Significant variance in usage and adoption of molecular tests in different regions largely driven by reimbursement and regulatory differences. Greatest adoption in markets such as France, driven by government funding of molecular diagnostics

Relatively high usage of lab developed tests (LDTs) in several geographies driven by regulatory environment, mainly within academic medical centers

FIGURE 1

Relative penetration of molecular-based companion diagnostics and level of usage of lab-developed tests

	Relative penetration of molecular-Dx[1]	Relative rate of usage of LDTs in molecular-Dx[2]
France	70	90
US	40	70
UK	30	70
Germany	30	60
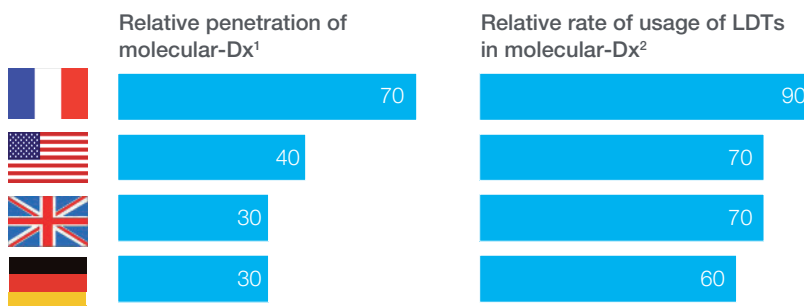
1 Based on customer interviews/survey; penetration defined aspercent of biopsies tested across 3 different companion diagnostics

2 Based on customer interviews; LDTs in U.S. defined as non-FDA approved but CLIA waived, in EU and APAC defined as tests without clinical validation
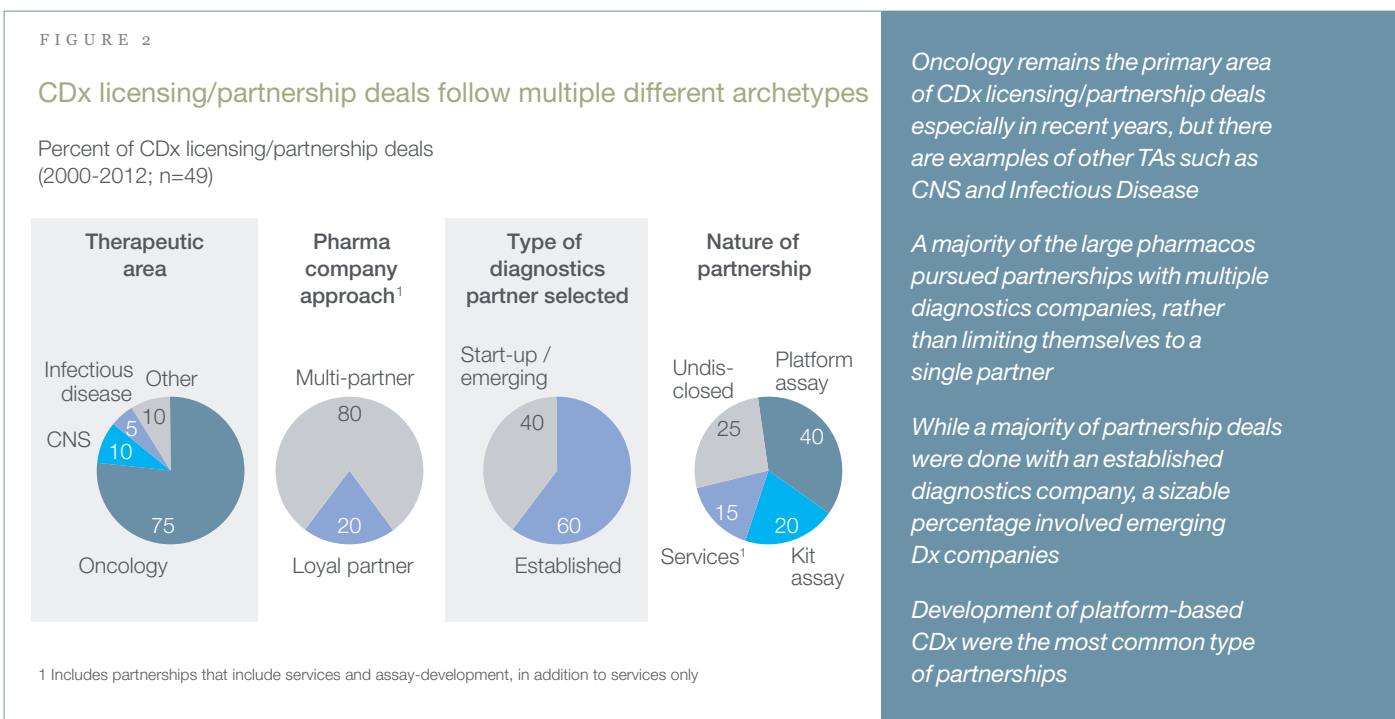
Given these complexities, pharma companies need to perform a systematic analysis of development timelines, potential LDT exposure, and level of access to the test under different regulatory strategies to determine the optimal regulatory path.

Partnering effectively

Only three of the top 15 pharma companies we analyzed have meaningful capabilities and presence in commercial diagnostics—Roche, Novartis and Abbott. For most of the other top

pharma companies, development of commercial diagnostics is not a core competency and they need to rely on diagnostics or life science companies to successfully launch companion diagnostics. In fact, over the last five years, we have seen more than 50 major deals between the top 15 pharma companies and diagnostic players.

Pharmacos have adopted different approaches to such partnerships, showing that there is not yet one clear model for success. Pfizer placed bets across multiple CDx platforms/ partners, while Merck pursued a more limited set of deals. Still others have focused on deals with established Dx players such as Roche or Siemens, while others have targeted start-ups and emerging players (e.g., Lilly is teaming with PrimeraDx). Our analysis indicates that over the last 10 years, 75 percent of the deals were related to oncology, while the remaining 25 percent was spread across CNS, metabolic, cardiovascular and infectious diseases. Additionally, within oncology, 45 percent of the deals were for a single molecule only, whereas the balance was for multiple molecules (see Figure 2).

FIGURE 2

CDx licensing/partnership deals follow multiple different archetypes

Percent of CDx licensing/partnership deals
(2000-2012; n=49)

Therapeutic area
- Other 10
- Infectious disease 5
- CNS 10
- Oncology 75

Pharma company approach[1]
- Multi-partner 80
- Loyal partner 20

Type of diagnostics partner selected
- Start-up / emerging 40
- Established 60

Nature of partnership
- Undisclosed 25
- Platform assay 40
- Kit assay 20
- Services[1] 15

1 Includes partnerships that include services and assay-development, in addition to services only

Oncology remains the primary area of CDx licensing/partnership deals especially in recent years, but there are examples of other TAs such as CNS and Infectious Disease

A majority of the large pharmacos pursued partnerships with multiple diagnostics companies, rather than limiting themselves to a single partner

While a majority of partnership deals were done with an established diagnostics company, a sizable percentage involved emerging Dx companies

Development of platform-based CDx were the most common type of partnerships

Although there is not yet a clear winning model, there are critical questions to consider such as: Who is the best partner? Should single or multiple partnerships be pursued? What is the optimal financial structure for the arrangement?

In selecting the optimal partner, an important consideration is whether the Dx partner is a product-based or services-based company. Some partnerships are grounded on the diagnostic platform (e.g., Bayer's alliance with Ventana) while other deals center on services (Eisai's work with Foundation medicine is one example). A majority of the partnerships have been with more established diagnostic players such as Roche diagnostics or Abbott diagnostics, but there are examples of partnerships with specialized diagnostic companies such as the partnership between Eli Lilly and PrimeraDx.

Most of the partnerships have been exclusive, at least for an agreed-upon period. This provides upside to the diagnostic company by being first-to-market and justifies its investment in co-development. However, for less specialized tests which use well-established platforms pharma companies should consider partnerships with multiple Dx companies. For example, a companion diagnostic that is blood- or saliva-based (e.g., CYP2C9 for Celebrex) is a routine diagnostic test, and partnering with only one platform severely limits access in central labs since no one player holds more than 30 percent market share.

Various financial structures have been used for these partnerships as well. The most prevalent is a co-development deal where both the pharma and diagnostic company co-invest in the development costs of the diagnostic. For more platform-based deals, unique deal structures with specific milestone-based payments have been struck. Regardless of the financial structure used, the critical factors in ensuring successful partnership are to make sure there is a liaison on both sides from an operational perspective and an established, clear governance model to keep the partnership productive and to resolve conflicts. Additionally, going forward, new deal types involving payors and other stakeholders are likely, which will require a different approach than current deals.

Ensuring market access

Unfortunately, the reimbursement landscape has not kept pace with the increasing complexity of the companion diagnostics landscape as evidenced by the wide range of reimbursement for companion diagnostics today in the U.S. Some academic labs using a lab-developed test for *BRAF* testing were reimbursed at $900 per test, whereas the same test done in a small hospital using Roche's Cobas platform resulted in reimbursement of $400. Additionally, different types of CDx see varying reimbursement levels depending upon whether the test is platform versus kit-based. Broadly speaking, however, companion diagnostics have been well-covered by Medicare and private insurance companies in the U.S., although at a relatively limited reimbursement level. Furthermore, there are ongoing discussions about disrupting the current model where the drug and diagnostic are reimbursed separately in favor of an approach where the drug/Dx combination receives joint reimbursement.

In contrast, market access in the EU and Asia has been more challenging. Even today, companies have to subsidize costs of established testing such as HER2 in the UK. France has a system of grants for advanced molecular testing across the top laboratories in the nation, and access is relatively easier there than in the other EU countries. In China, a large part of the population has to pay out-of-pocket for some of the companion diagnostic tests. These disparities underscore the need for companies to make a careful market-by-market analysis as part of the pre-launch effort for companion diagnostics. Given the differing reimbursement procedures and standards companies will need to develop targeted strategies to ensure market access.
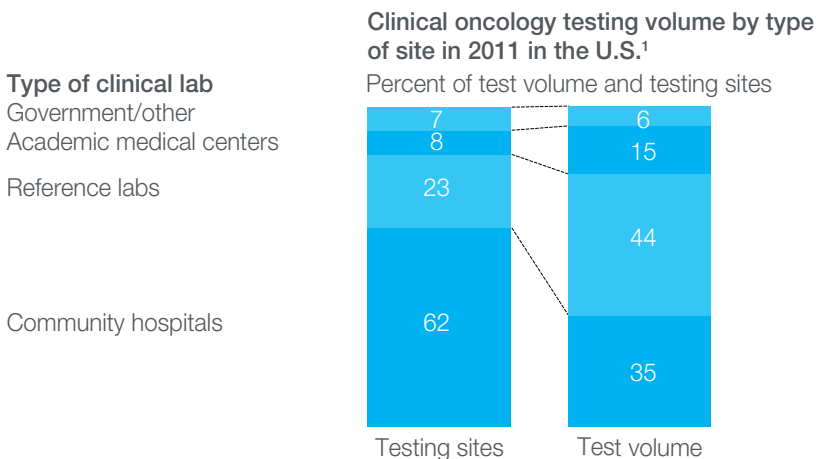
Maximizing adoption and reducing leakage

Once the Rx/CDx combination is ready to be launched, there are three keys to commercial success of the CDx: ensuring adequate access to the test, maximizing physician awareness and demand, and ensuring high quality of testing.

Ensuring adequate access to the test. A key decision to be made early in the launch cycle is whether the test should be launched broadly or in a restricted base of clinical labs. The typical trade-off is ensuring the broadest possible access to the test versus maintaining maximum control over the quality of testing. For more complex tests, the tests are restricted to fewer sites which ensures greater quality control in general. In contrast, open channel distribution of assay kits (e.g., *KRAS*) allows widespread lab testing but reduces control over pricing and consistency, which can negatively impact adoption. Closed channel distribution (such as that employed by the test for Trofile) allows higher pricing and better test consistency, but has lower adoption because test is not promoted by hospital pathologists, is not fast turnaround and usually higher cost. Additionally, the type of platform selected can have important implications for the base of testing. Large molecular platform-based assays (e.g., the *BRAF* Cobas assay from Roche) are usually performed in a smaller number of clinical labs than kit-based tests (e.g., *KRAS* test kit from Qiagen).

The size and distribution of the testing base selected has implications for the sales and marketing resources needed to drive adoption of the tests. Some companies deploy field forces dedicated to CDx adoption and quality of testing. These field forces need to be carefully designed based on the distribution of the testing base. Specialized tests such as Selzentry used a single lab for testing, whereas broad blood-based tests such as cytochrome p450 tests are conducted across more than 5,000 labs in the U.S. Understanding and controlling this base of diagnostic testing sites is very important in launching the CDx (Figure 3).

Clinical lab testing base for companion diagnostics

Clinical oncology testing volume by type of site in 2011 in the U.S.[1]

Type of clinical lab — Percent of test volume and testing sites

Type of clinical lab	Testing sites	Test volume
Government/other	7	6
Academic medical centers	8	15
Reference labs	23	44
Community hospitals	62	35

1 Based on customer surveys, interviews and public reports

Beyond the major reference labs and academic medical centers, the testing lab landscape is relatively fragmented in oncology

Some of the other disease areas that rely on clinical chemistry have an even more fragmented testing landscape

If pharma companies are developing lab-related programs, such as a field force for lab education, careful planning to select the top sites of testing will be important

Increasing physician awareness and demand. Market development to educate oncologists (or other specialists as relevant) and pathologists about a novel CDx is critical to increasing adoption. Approaches include pathologist-directed activities, such as setting up training groups and preparing lab-specific educational materials, and diagnostics partner-directed activities, such as deploying a dedicated sales force to targeted clinical labs or an "education" force targeting prescribing physicians. Tests such as *EGFR* and *KRAS* had limited penetration for the first 2 to 3 years after launch even though there were clinical studies which showed benefit of testing for these mutations. Our estimates indicate that sub-optimal levels of testing (and awareness and demand-generation) of *EGFR* and *KRAS* translated into a loss of over $50 million in sales of each of those drugs in the U.S. alone.

Additionally, there is significant variance in the level of testing of these markers across markets in EU and APAC. As new treatments come on board for heterogeneous diseases such as lung cancer, the hierarchy of testing becomes critical. Given the limited amount of biopsy samples to test from, selecting a particular test first could eliminate certain markers from being tested. While these dynamics of drug/Dx marketing have generally not been top-of-mind for pharma companies, they are becoming increasingly important factors in the success of the drug.

> Pharma companies are developing various programs to educate lab directors and pathologists to ensure quality of testing, including training programs, specialized diagnostic medical science liasons and certification courses.
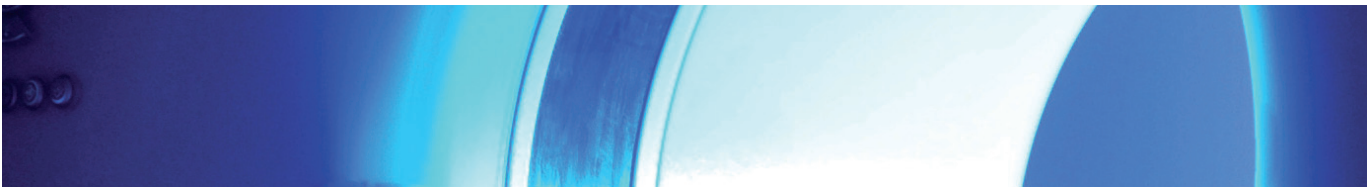
Improving quality and accuracy of testing. There are several sources of inaccuracies and misdiagnoses in companion diagnostics testing, among them are poor sample extraction and testing, inconsistent or incomplete test reporting and re-testing. Consequently, it is critical to educate lab pathologists on how best to minimize inaccuracies in testing. Anticipating and launching providing pre-test education can yield significant benefits for both the pharma and diagnostic companies.

Within oncology our analysis showed that the quality of sample extraction was an issue with most of the markers tested today, resulting in false negatives. Improved tissue handling and compliance education of not only the lab directors, but the surgeons performing the biopsies are important in mitigating these errors. A second cause of inaccurate testing relates to the heterogeneity of samples, particularly in oncology. A significant portion of the cases have positive indicators in one area and negative in another. Ensuring multiple points of testing and reflex testing if there is a doubt is another lever to consider. Additionally, quality can vary among the test kits offered by different manufacturers depending upon the platform used. Several smaller companies offer home-brews which have low-quality buffers and reagents which can lead to inaccurate results. Ensuring reflex testing with platforms such as FISH to augment routine IHC testing can reduce inaccuracies. Lastly, poor interpretation of results is also a source of inaccuracies, particularly with markers which do not have a binary output but rather a scoring system. With coagulation factors in particular there have been several reports of inaccuracies with the calibrators, resulting in sub-optimal dosing of the patient with the drug.

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In summary, the launch of a Rx/CDx combination does present unique challenges but does not require a completely different approach to that used in a standard drug launch. The functions and players involved are the same, namely R&D, regulatory, reimbursement/market access and ultimately commercial. The challenges faced, however, add significant complexity to launch planning and require the development of new capabilities within pharma and diagnostic companies to ensure success. For several types of drugs, successful launch of the companion diagnostic plays a pivotal role in the ultimate success of the drug, and will become increasingly important. While the ultimate launch manual for a companion diagnostic has not been developed yet, we hope that our perspectives generate further discussion among leaders and increase their ability to navigate a successful CDx launch.

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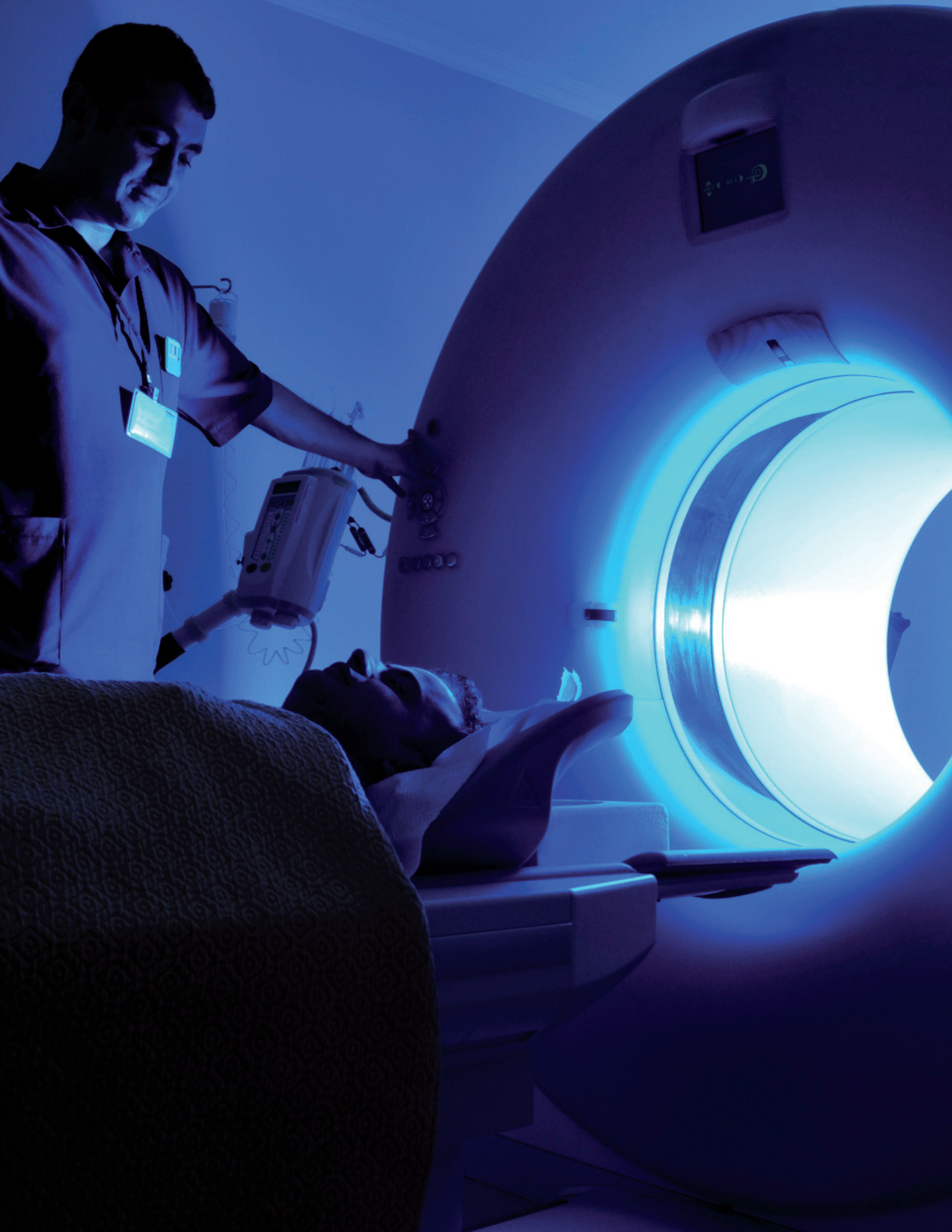
Capturing value for Dx in personalized medicine – is there a path?

Leeland Ekstrom, Denise Flaherty, Jake Henry, Samarth Kulkarni, Kanaka Pattabiraman and Thomas Rudolph

The diagnostics industry has traditionally failed to capture its fair share of value in the healthcare system. Diagnostics tests are estimated to influence 70 percent of the decisions made by U.S. physicians, yet only 2 percent of the $2 trillion spent annually on healthcare flows to diagnostics providers.[1] Much of this discrepancy arises because physicians and payors have long applied a "cost plus" mindset to diagnostics that leads to valuing even patented tests at a fraction of what similarly specialized pharmaceutical treatments—where price is much more closely linked to value generated.

Many have hailed personalized medicine as ushering in the next wave of growth for diagnostics companies, and in fact the capital markets have rewarded diagnostics companies pursuing personalized medicine: the Burrill Personalized Medicine Index has increased 50 percent from 2005 to 2012 (versus only a 19 percent increase for the S&P 500). While there have been isolated cases of success such as Genomic Health, most diagnostic companies have not been successful in capturing meaningful value from the advances in personalized medicine. *KRAS* testing in colorectal cancer is a good example. Payors typically save nearly $50,000 per patient by preventing treatment for non-responders while pharma companies also benefited from having a clear population to target and increased coverage for their drugs as a result of the diagnostic. Yet, the diagnostic test for *KRAS* developed by DxS was commercialized at a relatively low cost of $300 per patient, and in many cases the value captured by Dx players was even lower due to low-cost lab developed tests (LDTs) adopted for some *KRAS* testing. Thus, even when the value of the Dx is clear and its use pivotal to effective care, the vast majority of the value it creates migrates to other players.

While personalized medicine may indeed represent the next "big thing" for diagnostic companies, we also believe a disruptive change in the model will be necessary for Dx players to capture value commensurate with their contribution to treatment efficacy and cost

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1   *Diagnosis or drug?* accessed at http://www.nature.com/embor/journal/v8/n10/full/7401080.html

efficiency. In this article we describe potential ways to disrupt the system and business models needed to win in personalized medicine.

Personalized medicine presents a very attractive opportunity for Dx companies

The market for high-value diagnostics in oncology alone is expected to reach $3 billion by the end of 2018. Together with the other therapeutic areas, the diagnostics products and services global market related to personalized medicine could surpass $6 billion. The key drivers of growth will be payors mandating Dx to ensure proper use of therapeutics, better understanding of the heterogeneity of disease and drug safety, improvements in the underlying technology and quality of Dx testing, and physicians' need for the information generated by diagnostics in order to provide optimal treatment. Additionally, the increasingly informed and active consumer and advances in digital and information technology will drive growth.

A number of factors driving greater use of high-value diagnostics

Therapies are becoming increasingly expensive, and payors will mandate Dx: Prices of specialty pharmaceuticals have increased significantly, yet a large fraction of the patient population in several indications does not respond to these high-priced drugs (e.g., 25 percent for diabetes and 40 percent for rheumatoid arthritis are non-responders).[2]

Disease understanding is improving rapidly and more drugs with associated diagnostics: We estimate that 30 to 40 percent of novel drugs in the pharma pipeline are being developed in conjunction with a biomarker, making Dx much more relevant in treatment decisions.

Capturing value of diagnostics remains challenging

In spite of these tailwinds, Dx companies have struggled to capture value in personalized medicine. Several structural barriers impede retention of value:

Diagnostics reimbursement not value-based: Many payors approach diagnostics with a "cost-plus" mindset that covers only cost and activity, rather than reflecting the actual value

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2 *Pharmacogenomics in clinical practice and drug development* accessed at http://www.nature.com/nbt/journal/v30/n11/full/nbt.2424.html#t1

provided by a diagnostic. In Europe, several models exist that can boost reimbursement rates, from DRG-based to fee-for-service, however none of them are primarily value-based for innovative diagnostics.

Establishing clinical validation shifts burden of proof: Even when payors are willing to consider value-based pricing, Dx companies have to bear the upfront cost of demonstrating clinical utility (e.g., Genomic Health's Oncotype Dx) without any guarantee of value-based reimbursement.

Reduced intellectual property (IP) protection limits returns: Dx companies with approved tests cannot protect their IP under the current regulatory system and CLIA governance. Lab services companies can provide substitutes to the FDA-approved Dx tests without fear of patent challenges, undercutting the value captured by Dx companies themselves.

Path forward: Disruptive models are necessary to capture value for Dx
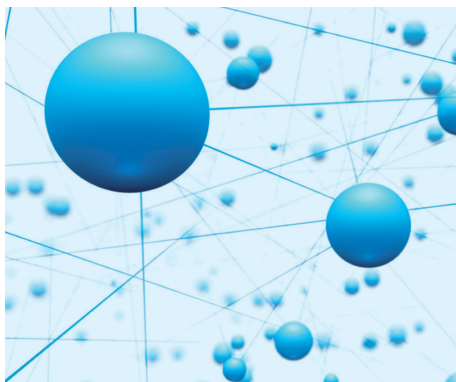
Novel commercial strategies and models will be necessary for Dx players to disrupt the current playing field and capture their fair share of value. Dx players can either pursue strategies to capture greater value from payors and pharma companies, or aim to capture greater value directly from consumers.

Reconfigure partnerships with payors and pharma to capture value: While it is widely recognized that Dx companies are integral to delivering innovation in personalized medicine, they lack leverage vis-à-vis payors and pharma because of their inability to protect IP. Fundamentally, Dx companies will need to adopt a model which builds greater leverage in the value chain—either by protecting IP through captive services, or using data as a barrier against competitors.

With better-protected IP, Dx players can pursue unique partnerships with payors and drug companies to either extract higher prices, generate stronger uptake or share risk of clinical validation. For instance, the price of the diagnostic can be hard-wired into the drug and the drug reimbursement can be linked to usage of the "approved" diagnostic. Another model would have payors share the clinical validation costs and only pay for the drug/Dx if there is real-world evidence of clinical benefit. Other mechanisms such as direct partnerships with payors or pharmacy benefit managers (PBMs) to combine Dx data with patient records to develop treatment algorithms can also be considered.

Use strong branding as a competitive advantage to target consumers: Dx companies can use consumer-targeted branding and product offerings to capture greater

portion of consumer disposable spend. The $9+ billion blood glucose monitoring market offers a clear example of the power of consumer branding in diagnostics. The four leading providers have largely preserved their combined 90+ percent share despite relatively commoditized products and the presence of low-cost competition. Targeting patients directly by identifying applications in which they are willing to pay for new or additional levels of service could also help Dx companies capture more value. 3-D pre-natal sonography provides an example where expectant parents are willing to pay hundreds of dollars (out-of-pocket) above the cost of a standard ultrasound. Several personalized medicine diagnostics players such as 23andMe have already started to tap the self-pay markets demonstrating that branding is a viable strategy in personalized medicine. Ultimately, if a critical mass of patients recognize the value of these advanced tests and begin to demand it, it will force the hand of the payors.

How to win as a Dx player in the current landscape

Even in the absence of real disruption of the diagnostics business model, however, there are several actions Dx companies can take in the near-term to compete effectively:

1. Identify the most attractive value pools,

2. Experiment with and choose the optimal business model, and

3. Build differentiated capabilities to compete effectively.

Find the attractive value pools: Previous McKinsey research on the factors that drive growth concluded that 80 percent of growth was due to "where" companies decide to compete (i.e., capturing underlying growth in existing markets and moving to new markets via M&A) and only 20 percent was due to "how" they compete (i.e., share gain).[3]

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3 *The granularity of growth* accessed at
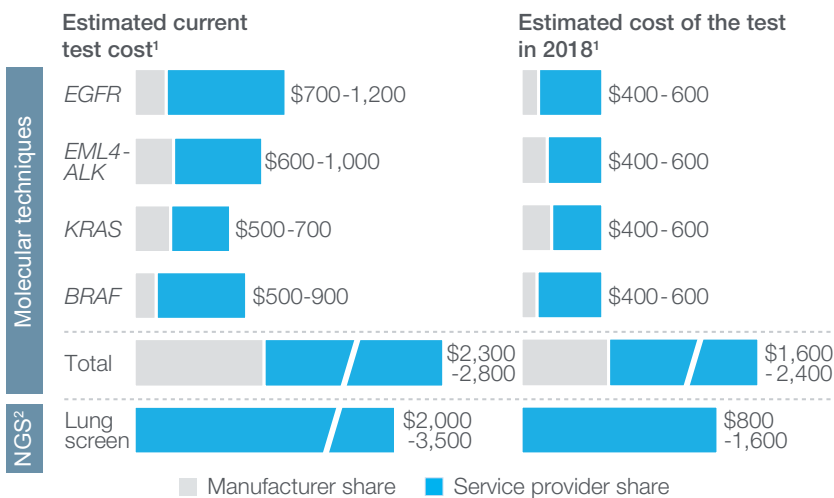   http://www.mckinseyquarterly.com/The_granularity_of_growth_1993

Dx companies face critical decisions in choosing which therapeutic areas they will compete in, which geographies to focus on, and what types of technology platforms will be most useful. These choices make for a complex gameboard of options. While oncology has been the hot-bed of innovation in Dx, it has also been highly competitive—hence, uncharted therapeutic areas such as immunology and CNS could be more attractive. For service offerings, picking the appropriate markets to focus on is quite important. Given the nationalized healthcare systems in Europe, markets there are generally not conducive for outsourced lab services offerings. Emerging markets such as Brazil or Turkey can be more attractive for esoteric testing within the private-pay market. Finally, the type of product offering to pursue can be critical. For example, our analysis indicates that multi-gene approaches (panels or NGS) in oncology are likely to capture more value than traditional "one drug–one Dx" approach (Figure 1).

FIGURE 1

Potential opportunity for panel testing—lung cancer example

Estimated current test cost[1]

Molecular techniques		
EGFR		$700-1,200
EML4-ALK		$600-1,000
KRAS		$500-700
BRAF		$500-900
Total		$2,300 -2,800

NGS[2]		
Lung screen		$2,000 -3,500

Estimated cost of the test in 2018[1]

$400-600
$400-600
$400-600
$400-600
$1,600 - 2,400
$800 -1,600

■ Manufacturer share   ■ Service provider share

1 Cost to payors for the particular test or assay, USD
2 Cost of whole exome sequencing
SOURCE: Expert inverviews; McKinsey analysis

Under the current paradigm of single marker testing, manufacturers capture a limited portion of the value reimbursed by payors

The costs of testing with NGS may have already reached a tipping point where it is less expensive than the sum of individual tests

In the near-term, there is an opportunity for manufacturers to create validated multiplex panels at a total cost below the cost of NGS

Over a 5-year horizon, NGS costs will continue to decline and majority of the testing will likely migrate to NGS

Choose the right business model: A myriad of business models have been pursued in diagnostics. Examples include differentiated platform technologies (e.g., Gen-Probe/Hologic), proprietary assay content (e.g., Qiagen), services model (e.g., Clarient, Caris) or other combinations of platform, content and services.

Over the last few years companies that offer services (either content together with services or services alone) have captured a disproportionate share of the value captured in complex diagnostics, and have grown faster than traditional in vitro diagnostic manufacturers in the U.S. Going forward, services players will have greater agility to keep up with the rapid advances in science and technology, and continue to capture greater value (Figure 2).

FIGURE 2

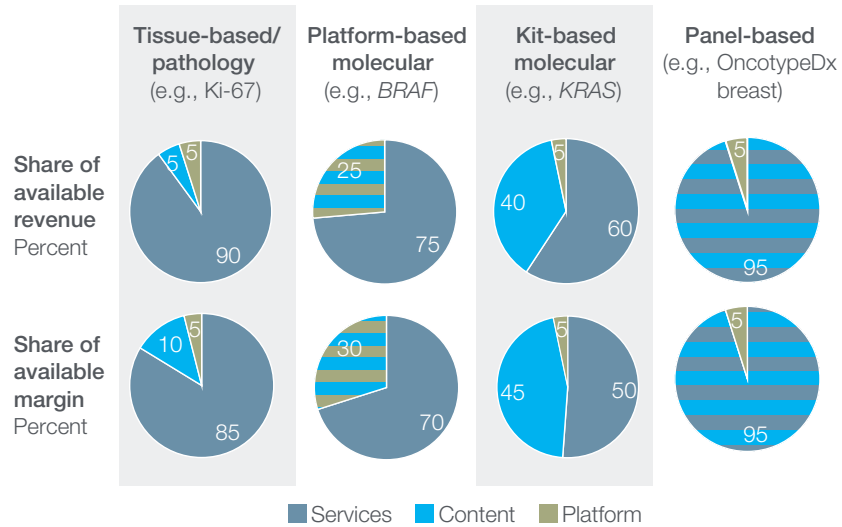**Available value pools and share–oncology example**

Across a range of personalized medicine diagnostics, the service provider that performs and interprets the assay captures the majority of the available value

There are, however, several examples of commercial model innovation (e.g., Genomic Health's Oncotype assays), where the diagnostics company has managed to significantly expand their share of value captured by offering a proprietary panel run in their own laboratory

	Tissue-based/ pathology (e.g., Ki-67)	Platform-based molecular (e.g., *BRAF*)	Kit-based molecular (e.g., *KRAS*)	Panel-based (e.g., OncotypeDx breast)
Share of available revenue Percent	5, 5, 90	25, 75	5, 40, 60	5, 95
Share of available margin Percent	10, 5, 85	30, 70	5, 45, 50	5, 95

■ Services ■ Content ■ Platform

SOURCE: Expert inverviews; McKinsey analysis

A second critical choice facing Dx players is whether they will compete as a first mover and invest in clinical validation or be a fast follower. Recent examples show that in the "one drug–one Dx" paradigm, first mover advantage is limited. Roche Dx and Abbott are both facing significant competition from LDTs and fast-followers for their *BRAF* and *ALK* assay, respectively. Being a first mover is a distinct advantage where IP can be protected—either through captive service offerings or proprietary panel tests.

Build differentiated, critical capabilities: As personalized medicine evolves several capabilities are critical for Dx companies to develop to compete effectively. These include partnership and alliance building, data analytics and informatics, and multi-stakeholder selling.

Partnering within Dx companies to date has been focused on pharma companies and academia to source content. In the future, partnerships with many different types of stakeholders will be necessary to disrupt the model. For example partnering with payors directly to better capture the value created from improved outcomes or share risk of clinical validation would seem especially critical. The importance of pharmacy benefit managers (PBM)s and academic centers in personalized medicine is increasing as evidenced from deal activity (e.g., Medco-FDA, Medco-Mayo Clinic, UPMC-BGI). Additionally, deals with pharma companies are moving beyond traditional product development to include co-promotion and pathologist education. We believe that the greatest disruptive action and the highest value for diagnostics companies will derive from multi-stakeholder deals such as academic centers coming together with pharma and Dx companies to generate a robust decision support database containing genomic data, clinical trial data and real-world patient outcome data (Figure 3).

Financial structures in different business models

	Platform providers	Proprietary content & services	Service providers
Examples	• Cepheid • Gen-Probe • Life Technologies • Roche Diagnostics	• Genomic Health • Myriad	• Clarient (GE) • Caris • Genoptix
COGS	30-50%	10-20%	40-45%
R&D	20-25%	5-20%	0-5%
Operating margin	0-20%	5-40%	15-35%
Price to revenue	~3-6x	~4-8x	~2-3x
Scalability	High	Medium	Low

Note: Representative financial information collected from publicly available examples in each category

Platform development is expensive, given high R&D and materials costs, but the market does recognize some growth potential largely due to its scalability

Some companies have chosen to pursue largely internal development, creating proprietary IP-protected content, with a hybrid service model; IP-protected assays can lead to higher valuation, but are more difficult to develop

Service labs which offer esoteric testing typically have minimal internal R&D, and rely on externally developed tests. These labs have seen high growth over the last few years and have been attractive acquisition targets

Data and analytic capabilities will be key differentiators in personalized medicine given the sheer volume of data generated and its complexity. Several start-ups have launched offerings based on "Big Data" capabilities that promise to generate meaningful clinical insights. For the incumbent Dx companies, investing in data through innovative partnerships with healthcare-focused and non-healthcare focused data companies is critical.

Call-point ownership and multi-stakeholder selling are additional critical capabilities for Dx companies. Historically, Dx companies have used a sales force-centric model that targets lab directors and pathologists, but that model is changing. The roles of physicians and payors are becoming increasingly important in the diagnostic decision-making. At the same time, pharmacos have realized the importance of the pathologist in the choice of therapy. Consequently, given the expanding number of influencers and their varied communication preferences, multi-stakeholder and multi-channel sales capabilities will be necessary for Dx companies to compete effectively.

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Personalized medicine remains an area of immense opportunity and promise for diagnostics companies, but capturing real value will require a disruption of the current reimbursement and delivery model. Carefully selecting where to play, how to play and building the relevant capabilities that are truly differentiating will help Dx players capture value and compete effectively in this evolving landscape.

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