Deloitte.

# Bench to bedside
# Formulating winning strategies in molecular diagnostics

# Contents

Each day brings new headlines of scientific discovery. The first report on microarray technology appeared in *Science* just over a decade ago. But until recently, microarray technology had been burdened with issues of reproducibility and standardization, preventing its use in clinical applications. Belying this is the promise of molecular therapeutics – the "holy grail" of cancer research, translation and therapy – which could target the underlying defects leading to disease. Many have put their hope into novel genomic technologies which are rapidly driving the development of molecular diagnostics to optimize drug therapy and companion diagnostics as a method to better define a patient's need or predict clinical outcome from a specific drug.

Now, DNA microarray technology has matured to the point where some applications are deemed reliable enough for use in patient care. In 2004 Roche's AmpliChip CYP450® assay became the first to receive approval in the US. The FDA recently approved a HER-2 test from Invitrogen called SPoT-Light® that can be used to identify breast cancer patients who are candidates for treatment with Herceptin®. Microarray technology has also recently received a vote of confidence and approval from the US Food and Drug Administration, laying the groundwork for its broader clinical application.

This presents an opportunity to not only bring novel scientific innovation to patients, but also an opportunity for companies which have historically focused on the scientific research market to bring their products directly to the healthcare market. The payoff for successful molecular diagnostic products can be significant; Kalorama Information predicts that this market currently exceeds $3.2B worldwide and will reach $5.4B in four years, both by increases in the number of commercially available tests and the increase in adoption of use in a clinical setting.

Taking the bench to the bedside is the crucial goal in today's biomedical environment. Around the world, several companies have taken on this quest to accelerate the promise of these new discoveries by linking research more directly to patient clinical care. Roche, Affymetrix and Illumina have created array-based products that enable high-speed analysis of DNA, RNA, and proteins as tools for disease research, drug development, and molecular tests. However, as seen with micro-array technology, moving from the bench to medical practice is more easily talked about then done. Companies hoping to capture a piece of this market need to not only have the technological superiority, but must also develop products that are safe and reliable (there is a requirement that the consistency of the performance of the test system can be guaranteed in different people's hands) and must have the commercial capabilities to infiltrate the complexity of the healthcare marketplace.

This article is a Deloitte Point of View on the opportunities and key requirements for commercial success in the emerging markets of molecular diagnostics. This point of view is specifically relevant to analytical instrument companies, research tools companies, and others focused on making products for the academic and commercial R&D labs, seeking to transition into molecular diagnostics markets. In addition to retaining technological superiority, such companies will also need to significantly enhance their core commercial capabilities in order to capitalize on the growth in the Molecular Diagnostics markets.

# Effectively leveraging commercial capabilities for growth in the molecular diagnostics market

In vitro diagnostics are playing an increasingly important role in the provision of healthcare. Approximately 80% of the information that physicians use to make medical decisions is produced by clinical laboratories and diagnostics are now seen as critical inputs into overall quality of patient care.[1] Whereas clinical assay output a generation ago consisted of basic blood chemistry and infection tests, the modern clinical laboratory has grown to offer a large array of diagnostics for immunological, cardiovascular, cancer, chromosomal/gene, and pharmacogenomic markers. Many of these tests are still based on classic techniques such as cell culture, staining, and microscopy, but advancements in molecular biology technologies over the past several decades have driven the rapid growth of molecular diagnostics.

Analytical instruments, already a mainstay in the pharmaceutical and biotechnology industry, are becoming equally important in molecular diagnostics as part of the evolution of medicine toward targeted therapy – and recognizing the revenue and profits available in these new markets. Although the molecular diagnostics market is mostly driven by technologies adapted from the analytical instruments market, capitalizing on the growth opportunity requires significant modifications to existing commercialization structures and capabilities that are often more suited to serving academic laboratory and commercial R&D customers. Whether analytical instrument companies are considering entry into the molecular diagnostics market or have been collaborating there for years, bridging the gaps in their commercial operations must be central to any growth strategy.

Most analytical instrument companies have not previously needed to develop the level of commercial capabilities required in the molecular diagnostics market. The biggest challenge for analytical instrument companies will be to understand and manage the complexities of a different customer base. Analytical instrument companies have typically sold to lab-based users who make the purchase decision based on quality, features, and funding. In contrast, the customer base for molecular diagnostics products is comprised of physicians, clinical laboratory staff, hospital administrators, payers, regulatory agencies, and individual consumers, each with unique needs and each influencing the purchase decision. In order to be successful in diagnostics, analytical instrument companies need to expand their core capabilities in commercial operations, as well as develop and grow new capabilities as key differentiators for meeting the needs of molecular diagnostics customers.

Most critical to this transition, we believe, are increased maturity and sophistication around reimbursement, regulatory/compliance, business development/alliances, and sales & marketing/medical affairs.

- Reimbursement capabilities, which typically are not needed in the tools and analytical instrument markets, may be the primary barriers to successful market entry of a molecular diagnostics product.

- Most analytical instrument companies have not historically needed to be involved in regulatory affairs, but regulations for molecular diagnostics are complicated and changing rapidly. Proactive regulatory and compliance strategies should help companies avoid potentially damaging scrutiny from regulators and payors in the future.

- Analytical instrument companies should focus on forming strong alliances with other molecular diagnostics, life sciences, and medical device companies, particularly given the expected increase in drug-diagnostic combinations.

- Sales & marketing functions will need to develop relationship-oriented sales models which are sensitive to the unique needs of a broad customer base. A medical affairs function that targets the specific needs of physicians should augment operational capabilities.

Transitioning into, and growing within, the molecular diagnostics market will require an actionable strategy. Companies may attain the necessary commercial capabilities through a variety of business models, which will be shaped by both external constraints such as market conditions and customer needs and internal constraints such as existing commercial operations and presence in the diagnostics field. The transition strategy must account for a company's current non-diagnostic business as well—analytical instruments companies risk alienating existing customers if changes are made to commercial operations in support of the new market without maintaining operations in their primary market. As companies plan to bridge the gaps in commercial capabilities, efforts must be coordinated across functions to make sure the resulting commercial operations model can serve current and future customer needs.

# Changing landscape and trends for analytical instruments companies

## Molecular diagnostics: A growing market

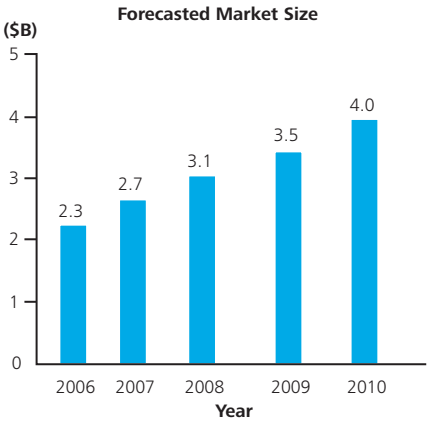
Many laboratory tools and analytical instrument companies have set their sights on the bounty of the adjacent molecular diagnostics market, which is estimated at $2.3B in the US and is to grow at 15% CAGR over the next several years.[2]

The growth of this market is being driven by the development of targeted therapies and companion diagnostics fueled by the same genomic and proteomic technologies that these companies already have on the market or under development.

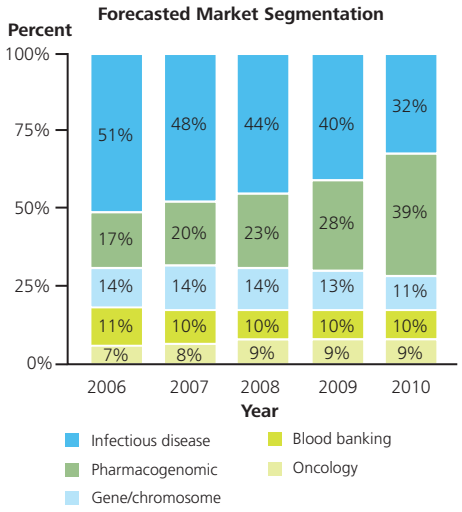
Molecular diagnostic products typically take a specialized research technology for which some therapeutic relevance has been established and apply it to a mainstream activity of the clinical laboratory. In the years to come pharmacogenetic testing will displace infectious disease as the dominant segment, based on the use of genetic information to design and develop drugs correlating gene sequences with disease states to identify therapeutic targets. The next fastest growing segment considers testing to assess cancer susceptibility as well as cancer diagnosis and management. Other major application segments include gene and chromosome testing and blood banking.

Molecular diagnostics offer hope for understanding the molecular mechanisms of disease and eventually for improved understanding of disease prediction, diagnosis and progression. The most dramatic impact has been in the areas of early detection, targeted treatment, theranostics and evidence-based medicine. Both FDA and the pharmaceutical industry share a mutual interest in pairing therapeutic pharmaceutical drugs with an accompanying diagnostic to identify candidates for clinical trials. Better qualification of patients can help improve the effectiveness and efficiency of clinical trials with a higher probability of clinical success. Additionally, these tests can later be used by physicians to determine which patients will benefit more from a specific therapy.

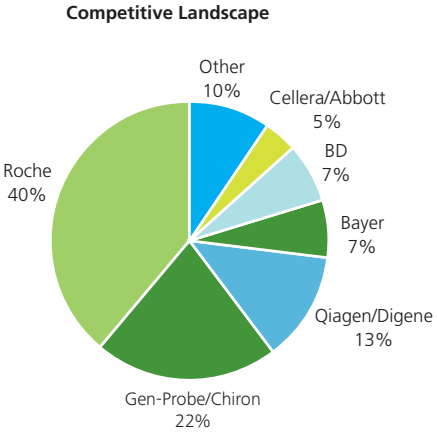
**Figure 1. Market growth, segmentation, and shares of the molecular diagnostics market**




Source: Pacific Growth Equities

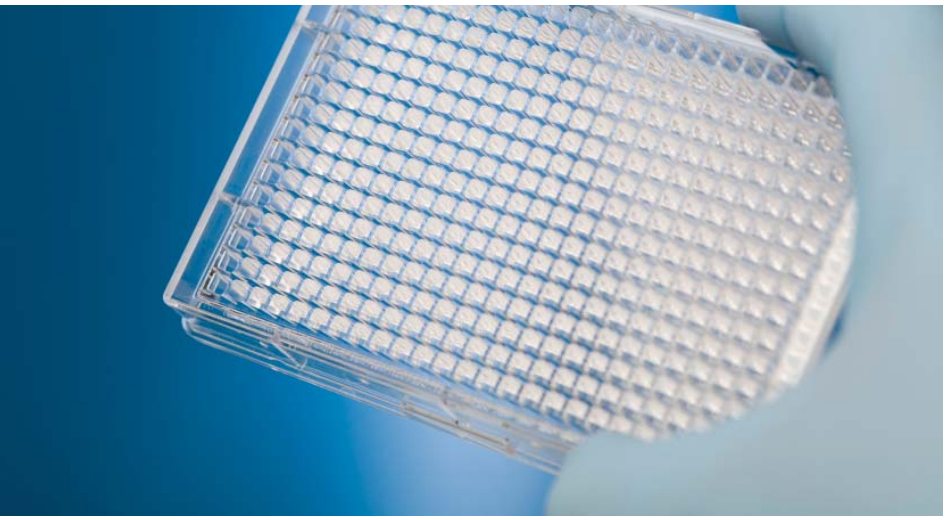



Source: Kalorama Information




Source: Pacific Growth Equities

The majority of molecular diagnostics tests today are "home-brew" methods or "for-research-only" products offered by university, medical center and commercial laboratories that are currently run on analytical instruments rather than purchased as a kit or reagent that carries specific diagnostic claims. Most of these tests are performed without the benefit of FDA review or approval. Currently over 1,000 labs offer molecular tests in the US with more laboratories and smaller hospitals planning to perform molecular testing in-house.[3] The FDA is expected to continue increasing its surveillance of these "home-brew" assays and several entities have suggested that the agency take a more active role in requiring premarket approval for tests that have components that might be considered medical devices.[4]



### Analytical instruments: Transitioning into molecular diagnostics

Analytical instruments encompass a diverse industry with technologies designed for both measurement and control and that have laboratory and field applications. The industry is developing technologies and tools that are expanding the genomic and proteomic knowledge base at an accelerating pace by making gene and protein analysis faster and easier to conduct. These tools are increasingly important in molecular diagnostics applications, and analytical instrument companies are adapting them to molecular diagnostics products. Indeed, the molecular diagnostics market represents an increasingly attractive revenue-generating opportunity for instrument providers to leverage existing technologies into adjacent markets.

Key analytic technologies that have enabled molecular diagnostics include gene and signal amplification technologies, blotting technologies, probe technologies, electrophoretic technologies, microarray technologies, polymorphism analysis, RNA inhibition analysis, and biophotonics. The $8.6B analytical instrument market in the United States is expected to continue growing, albeit more slowly than the molecular diagnostics market, at 5.7% CAGR over the next several years.[5]

# Transition of analytical instrument companies

For analytical instrument companies, the molecular diagnostics market presents an opportunity for significant growth. Analytical instrument companies, whose core capabilities lay in the development and distribution of analytical technologies (e.g. instruments and systems), now see an opportunity to leverage their deep scientific knowledge in an adjacent market. Other companies, like BioRad, have been able to use their products as a basis to move further downstream into the development of diagnostic kits and assays.

A quick scan of the market demonstrates that many scientific instrument companies, with a traditional R&D focus, have not only recognized the growing opportunity

**Table 1. Selected analytical instrument companies, key products, and alliance activities**

| | Luminex | Gen-Probe | Illumina |
|---|---|---|---|
| **Products** | • 3 Platforms<br>• 5 R&D Assays<br>• 6 MD Assays | • 2 Platforms<br>• 9 Clinical Assays<br>• 3 Blood Assays | • 1 Platform<br>• 3 Genotyping Assays<br>• 1 Protein Assay |
| **Revenue trend** | ↑ ↑ | ↑ ↑ | ↑ ↑ |
| **5-Yr CAGR (Revenue)** | 42.1% | 22.9% | 107.3% |
| **Op margin trend** | ↑ ↑ | ↑ | ↑ ↑ |
| **2007 Op margin** | -1.1% | 24% | 20% |
| **Shareholder equity (3-Yr Growth)** | 11.9% | 2.3% | 70.1% |
| **Acquisitions & alliances** | • Acquisitions: TM Bioscience<br>• Alliances: 36<br>• Top 6 alliances account for 61% of revenue<br>• Alliances are primarily distribution channel | • Acquisitions: N/A<br>• Alliances: 18<br>• 16 Molecular Diagnostics alliances<br>• Novartis accounts for 47% of revenue (distributes and markets blood screening products) | • Acquisitions: Solexa, Cylvera<br>• Alliances: 8<br>• Research alliances only<br>• Direct sales through company |
| **Representative products & uses** | xTAG™ Respiratory Viral Panel, approved in Jan 08, is a device that can simultaneously detect and identify nucleic acids of multiple respiratory viruses. The device is used by clinicians to identify potential causative viruses responsible for a respiratory infection. | The APTIMA system is Gen-Probe's core nucleic acid testing system used for detection of STDs in blood samples. Gen-Probe offers diagnostic systems for STDs, virals, bacterial infections, strep, and other bacterial and fungal pathogens. | BeadXpress™ is Illumina's first product in the molecular diagnostics market. The product launched in March 2007 may be used in the areas of biomarker research and validation, pharmaceutical development, industrial testing, agriculture, clinical research, and the development of molecular diagnostic assays. |

presented by the (molecular) diagnostic market but have been using alliances and acquisitions (previously used to increase core R&D technologies) to quickly move into this space. These companies have demonstrated that by capitalizing on their strengths in traditional R&D markets to transition focus to the molecular diagnostics market, they have been able to accelerate revenue growth and improve margins…and quickly.

So far, most analytical instrument companies have entered the molecular diagnostics market through alliances and acquisitions. On one end of the spectrum, Applied Biosystems (now part of Life Technologies) and its former sister company Celera have largely built their core molecular diagnostics capabilities internally through subsidiaries, or by licensing rights to genetic markers or other technologies to develop tests internally. Specifically,

| BioRad | Applied Biosystems* | Affymetrics | Agilent | Roche |
|---|---|---|---|---|
| • 4 Instrument System Categories<br>• Multiple Assays/Reagents | • 25 major product/service categories | • 9 Instruments<br>• Multiple array reagents | • 5 Instrument Systems<br>• Other reagents, consumables and software | • 2 Platforms<br>• 50+ systems, lines, reagents and assays<br>• ~100 therapeutics |
| ↑ | ↑ | ↑ | ↑ | ↑ |
| 10.2% | 5.6% | 5.2% | 14.0% | 9.5% |
| — | ↑ | ↑ | ↑↑ | ↑ |
| 12% | 11% | 7% | 19% | 31% |
| 12.1% | 5.6% | -31.4% | -3.5% | +6.4% |
| • Acquisitions: Diamed, Pasteur Sanofi Diagnostics Provalis<br>• Alliances:<br>• R&D collaborations and co-marketing agreements<br>• Direct sales through company and subsidiaries | • Acquisitions: Agencourt Ambion (genomics)<br>• Alliances:<br>• Multiple R&D collaborations<br>• Direct sales/research | • Acquisitions: USB Corp, ParAllele Biosciences<br>• Alliances:<br>• Roche, Perelegen Biosciences & Sysmex<br>• Alliances are major distribution channel; moving into direct sales | • Acquisitions: Silicon Genetics (genomics), Stratagene, Velocity 11<br>• Alliances:<br>• Direct sales through the company | • Acquisitions: Ventana, Nicholas, Syntex Corp Corange Igen, GlycArt, BioVeris<br>• Alliances: 10<br>• Clinical testing, R&D, and marketing |
| Bio-Rad 's specialty diagnostic products are recognized as the gold standard for diabetes monitoring and broad-spectrum screening. | HER-2 test called SpoTLight®, approved in July 2008, is a diagnostic assay made by Invitrogen (AB and Invitrogen merged in 2008) that can be used to identify breast cancer patients who are candidates for treatment with the drug Herceptin®. | GeneChip® System 3000Dx was the first federally approved DNA microarray instrumentation system for in vitro diagnostic use. | Agilent introduced in April 2007 the first commercially available microarray based assay for microRNA (miRNA) and can be used to aid in drug discovery research programs. | Roche's AmpliChip CYP450 assay, approved in 2004, may be used by physicians to consider unique genetic information in selecting medications and doses wide variety of common conditions such as pain medication, cardiac disease, cancer and depression. |

*Applied Biosystems is now part of Life Technologies

companies such as Luminex and Affymetrix have invested in multiple alliances with diagnostics companies, clinical labs, as well as BioPharma for testing, validation, development and distribution of diagnostics as well as sales and marketing efforts. Others, such as Siemens AG, capitalized on their presence in allied markets (imaging) to expand into molecular diagnostics primarily through acquisition.

These companies owe their historic success to the strong customer relationships they have been able to forge with (often-times) a few large-account research and development organizations, either academic or commercial. However, as analytical instrument companies enter into growing markets outside of R&D, including molecular diagnostics, they must think critically about the modifications that are required to their current operational structure and capabilities to realize these emerging opportunities.

**Successful transition: Luminex**

**Luminex's** growth strategy has focused on placing xMAP® technology (a technology that can be applied to molecular diagnostics and immunoassays) within third party equipment and systems in five markets, three of which are clinical diagnostics markets. Luminex provides microsphere beads and consumables for assay development and also receives ongoing royalty payments. Starting in 2000, Luminex signed multiple agreements with other companies for the development and commercialization of diagnostic tests (One Lambda, Zeus Instrumentation, Tm Bioscience, Bayer, Celera Diagnostics, Abbott Molecular). From 2001 to 2006, Luminex saw revenue growth of 42% and its stock price increased 12%. In 2007, Luminex acquired Tm Biosciences, which allowed Luminex to secure FDA approval for its diagnostic tests.[6] And subsequent to the approval of its latest xTAG™ Respiratory Viral Panel molecular diagnostic assay in early 2008 (obtained through the acquisition of Tm Biosciences), Luminex posted total revenues of $29 million, a 49% increase over 2007.[7] Luminex currently holds 43 FDA-cleared assays utilizing the xMAP® technology.

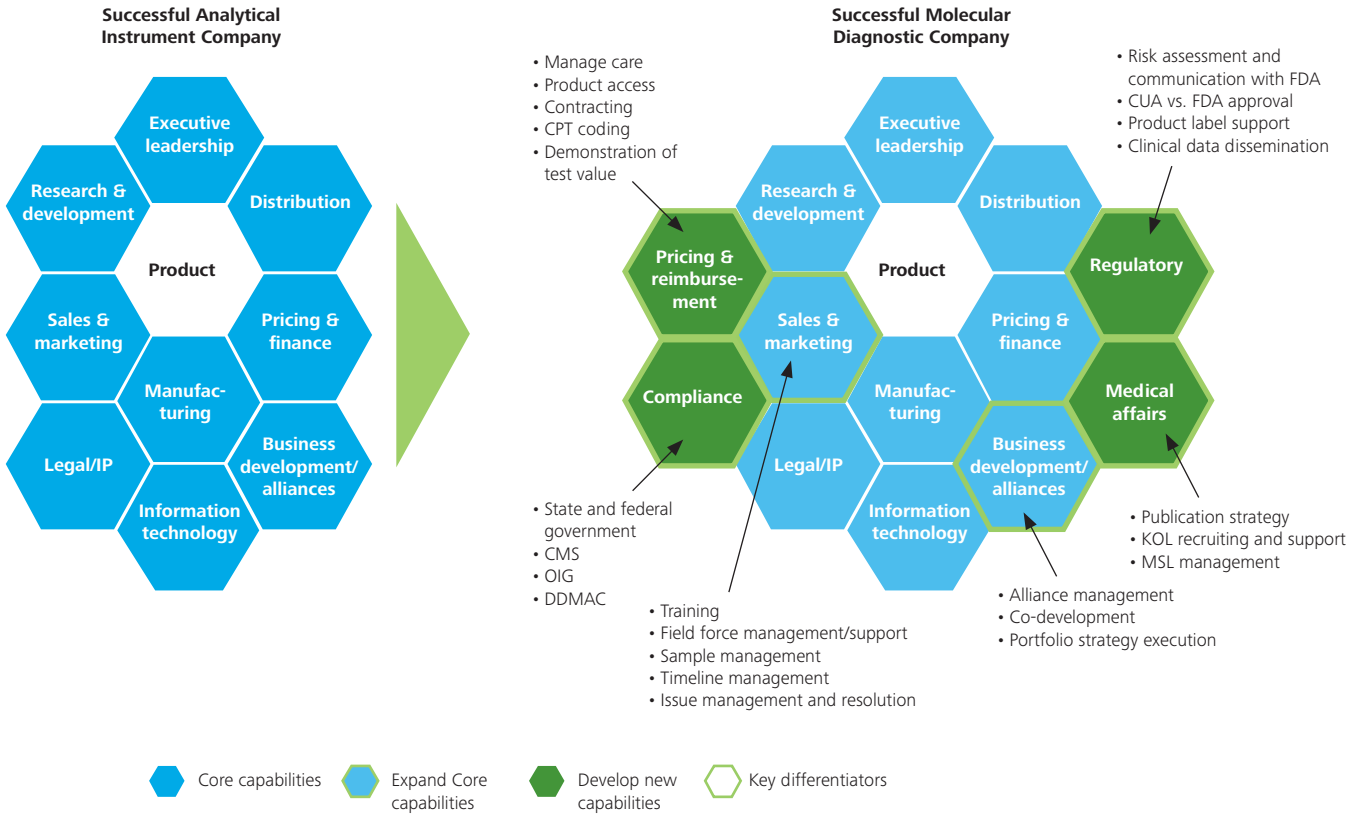
# Differentiating aspects of commercial operations in molecular diagnostics

One of the most critical aspects of this transition hinges on the ability to adapt to the needs of a larger, more diverse customer base (e.g., healthcare providers). Commercial models that were developed around large university, medical center, R&D, and commercial laboratories will not be sufficient to fit the greater complexity and size of the molecular diagnostics customer base. Those analytical instrument companies which choose to take advantage of the growing demand for molecular diagnostics can look to the commercial capabilities that therapeutic companies have built to identify and address the needs of a similar population. Furthermore, companies transitioning into the diagnostics space will need to expand their core capabilities and develop new commercial capabilities (Figure 2) to meet the needs of the new market.

While most functions have some aspect that has a customer-facing impact (e.g. supply chain and product packaging), there are six that can be commercial differentiators in the molecular diagnostics market: compliance, pricing & reimbursement, sales & marketing, business development/alliances, regulatory and medical affairs (highlighted in Figure 2). Strong capabilities in these six functions are essential for success in molecular diagnostics. Building and expanding these differentiating commercial capabilities is the core of a successful molecular diagnostics growth strategy.

As analytical instrument companies enter the molecular diagnostics market, the basic science will remain similar to their traditional market. However, the customer and

**Figure 2. Commercial functions of successful analytical instrument and molecular diagnostics companies**



channel to the customer will change dramatically and with it the use and implications of their product. Where before analytical instruments companies could sell into a few dozen academic and pharmaceutical R&D labs, the customer base for molecular diagnostics is now comprised of patients, physicians, payors and clinical lab personnel, all with different needs and requirements. Development or expansion of commercial operations capabilities unique to the healthcare market are required to target and support this diverse set of stakeholders. Reimbursement, compliance, regulatory affairs, and medical affairs capabilities are crucial for success in molecular diagnostics but negligible or nonexistent in most analytical instrument companies. Existing commercial capabilities such as sales & marketing and business development may already be strong but need modification to support growth in a new market. A company transitioning into this space must establish these capabilities as a means of understanding and meeting the needs of the various players in the molecular diagnostics market.

As patients and providers become increasingly cost-sensitive, a diagnostic's reimbursement status largely determines its success in the market. A company must have a broad understanding of the reimbursement criteria for molecular diagnostics, and it is imperative to understand whether to use existing CPT codes or apply for new CPT codes that reflect the test's value in use.

Most analytical instrument companies have not needed to be involved in regulatory affairs, but regulations for molecular diagnostics are complicated and changing rapidly. Proactive regulatory and compliance strategies should help companies avoid potentially damaging scrutiny from regulators and payors in the future. By working with regulatory bodies in a transparent and collaborative way, these companies should be able to reduce development and review times for their products, particularly in areas that are also new to the agencies. In addition, companies that establish relationships with the FDA early on in a developing market are often asked to become advisors on key regulatory issues and may therefore be in an advantageous position to influence policy decisions or bring their products to the market. It is likely that regulations more formalized than the current Clinical Laboratory Improvement Amendments (CLIA) requirements for "home-brew" tests will result before this technology matures.

Analytical instrument companies would need to expand their business development capability to encompass alliances formed with diagnostics companies and pharmaceuticals. New alliances, specifically with pharmaceutical companies, may help the co-development of drug-diagnostic (Rx-Dx) combinations and establish the clinical parameters for tests. Such alliances may also facilitate sales and marketing and lower development costs for molecular diagnostics. To date, the most notable advance in Rx-Dx combination has been the development of the *Herceptest*® assay in support of Genentech's *Herceptin*® therapy for breast cancer.

Entry into the molecular diagnostics market also requires expanded sales and marketing capabilities and a medical affairs function to develop relationships with the medical community. Sales and marketing capabilities must support connecting with a more complex customer base that includes both physicians and patients, who have an entirely different user perspective than the traditional instrument customer. Moving away from the simple direct channel model will require new sales channels, improved training and a different type of sales force to better serve the molecular diagnostics market.

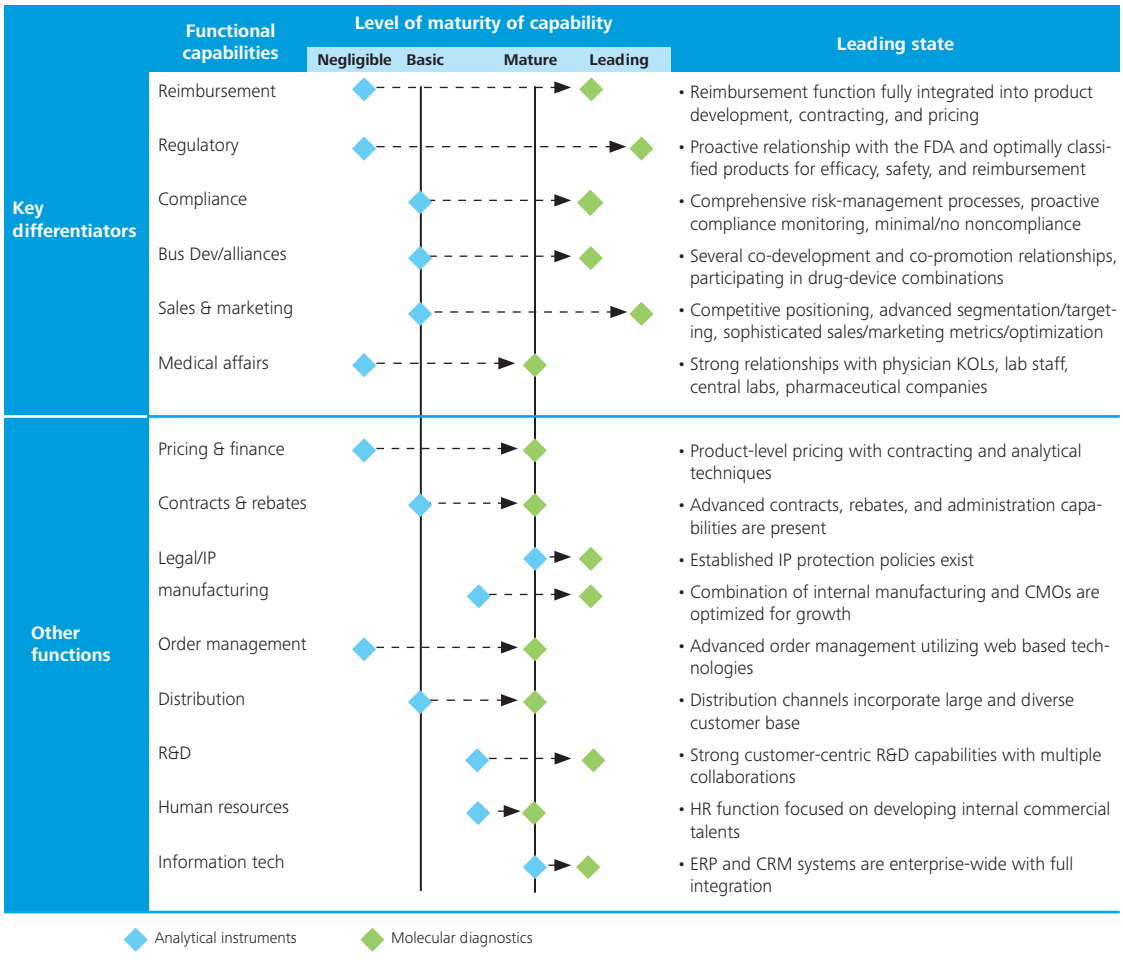
Investing in these areas will better position a company to respond to evolving market pressures and to drive product use and profitability. In addition to building and expanding the differentiators, greater cross-functional sharing and integration must be built into the product development and commercialization processes. All of the functions of the company will be affected by the shift to a different type of and a larger customer base. To realize and accelerate growth in the molecular diagnostics space, improvements to the key capabilities must be coordinated to work with the supporting functions.

# Significantly improving capabilities to succeed in the molecular diagnostics market

Successful expansion into the molecular diagnostics market requires more than just augmenting a few key capabilities – all commercial capabilities are impacted. Because commercializing a molecular diagnostic is more complex than an analytical instrument, it follows suit that those functional capabilities need to be significantly more robust. To build strong commercial operations that accelerate path-to-market timelines and achieve high product sales growth, enhancements must also be tightly coordinated so that new or improved capabilities are adequately supported cross-functionally.

While all commercial capabilities will be impacted, some will require substantial investment to bridge the gaps. We have used Deloitte's Capability Maturity Model (Figure 3) to compare the analytical instrument industry's average levels for key and supporting commercial capabilities with the levels required to support molecular diagnostics. In some cases, the changes require significant investment to move from negligible to appropriate positions. It is important to bear in mind, however, that not **all** capabilities must be "market-leading;" instead, companies must identify those which represent their basis of competition/differentiation and focus on bringing those capabilities to leading state.

**Figure 3. Capability maturity levels for analytical instrument and molecular diagnostics companies (illustrative)**



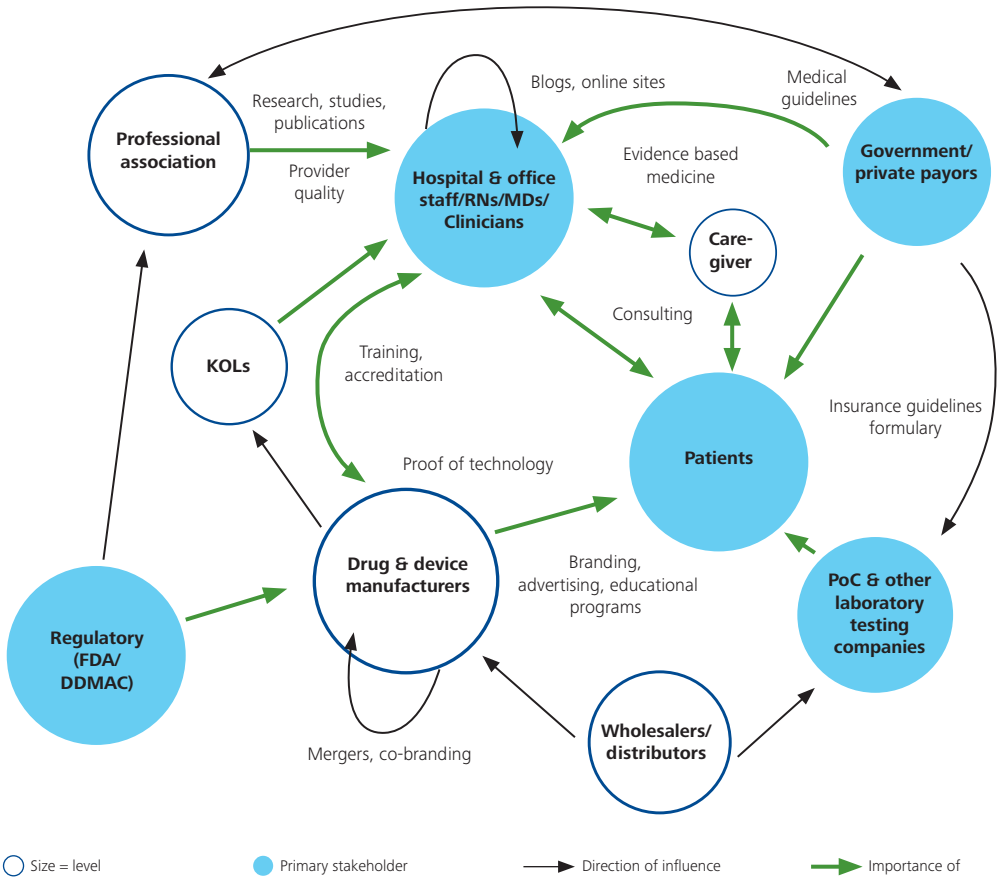
### Sales & marketing and medical affairs

Sales, marketing, and medical affairs capabilities underscore a true understanding of customers and their needs and contribute to the ability to identify and seize opportunities in market offerings. Specific sales & marketing capabilities that are called for encompass marketing and sales strategy, voice of customer insights and segmentation, brand/product management, campaign management and effectiveness, customer service & support, CRM, and distribution channel management.

Transitioning from a narrowly defined base of research-based customers to a broader base of customers including clinicians demands new capabilities in these areas. In the molecular diagnostics and theranostics market, there are many customers and influencers--clinicians, hospital administrators, payors, patients, lab personnel, testing companies, office staff, regulators--each with unique sales and marketing needs.

With intensifying pressure to control healthcare costs, power is shifting to those who pay for and use drugs and diagnostics, yet the proliferation of channels makes the patient and physician populations difficult to reach effectively. Diagnostic products, which are currently high-volume and minimally-differentiated, require different support than low-volume, highly-differentiated analytical instruments. In addition, commercialization of diagnostics

**Figure 4. Primary influencers of purchasing decisions**



requires coordination of several integration points to create a product that is economically viable for all parties (manufacturer, physician, payor and, the patient), is compliant with medical guidelines, and can enhance the user experience through convenience, accuracy or ease of use. Molecular diagnostic companies will find, as pharmaceutical companies have already learned, that despite all of the product virtues, they may require expensive campaigns with longer lead times to educate the various constituents of the healthcare system, through disease management, medical education or patient/caregiver awareness programs, who ultimately influence the purchasing decision.

Many companies have explored and developed sophisticated sales & marketing capabilities that help them reach their current customer base of academic and commercial laboratories and investigators. However these traditional approaches will not prepare them for the customer diversity and the complexity of the selling process in a regulated environment. The sheer number of influencing factors precludes a "black box" model that can seemingly magically provide an answer under any condition of uncertainty. Factors including therapeutic area, product portfolio, practice size, geography, practice economics, physician education, and relationships with managed care organizations, among others, will call for coordinated, multi-touch point marketing campaigns and relationship-oriented selling models.

With pharmaceutical sales reps currently visiting, on average, 10 physicians per day, new entrants in this field must be willing to invest significant resources to compete with an already high level of volume in the marketplace to achieve penetration. In addition, the nature of the sales force may change, as scientific/medical liaisons take over responsibilities from traditional sales representatives and resources are redeployed to focus on key influencers and decision-makers as well as multiple direct-to-customer channels. Different vendors and communication strategies may need to be employed for different customer and influencer segments.

**Purchase process**

In recent years, several studies have looked at provider decision-making processes used during the purchase of medical products, and how those processes impact patient safety. An often-cited study found the following purchase process characteristics at several leading hospitals:

- A general perception among providers that patient safety was important and played a role in the decision
- The inclusion of a wide range of stakeholders in the decision-making process
- The use of device user feedback as a component of the device evaluation process
- Safer devices may have been overlooked, as very few alternative devices were considered
- Two important stakeholders, device users and patients, did not participate directly in the purchasing decision
- The device selected for purchase often was determined before the evaluation process had been completed
- No explicit, formal usability testing was conducted for the purpose of assessing device safety

Source: "The Role of Patient Safety in the Device Purchasing Process": Johnson, Todd R. et al, May 2005

In this new world, companies will need to establish a relationship with a different type of professional and develop a true understanding of customer needs. In additional to the traditional sales & marketing, medical affairs capabilities will be required to help build long-term relationships with key opinion leaders and physicians in the medical community based on sponsorships/grants, medical education programs, collaborative research projects and deep understanding of the scientific and medical topics of interest.

Succeeding in the molecular diagnostics market will require a customer-focused sales & marketing approach combined with streamlined processes and technology to manage stakeholder interactions. Changes will include realignment of the sales organization and channels and new go to market models. Key elements of the end-to-end service processes must be improved through technology enablers and data-driven insights. Enhanced CRM capabilities and analytics, integrated between professional and consumer programs, should allow business needs and customer experience and insights to impact strategies. Expansion beyond the US introduces further complications in sales and marketing strategy, as divergent regulatory environments in Europe and Asia allow for a wide variety of legitimate and appropriate sales & marketing approaches.

### Reimbursement

Customers of in vitro diagnostic products are generally reimbursed for the cost of the tests by Medicare, Medicaid, or private insurance. As with medical devices, manufacturer reimbursement planning is typically done in parallel with product development and informs clinical trial design so that study endpoints support future coverage decisions. Reimbursement is a complex and constantly changing area subject to government action and private insurance policies.

**Reimbursement codes**

Diagnostics based on the analysis of nucleic acids use CPT codes 83890–83914, a long list of molecular biology techniques. Examples:

- **83900:** "amplification of patient nucleic acid, multiplex, first two nucleic acid sequences"
- **83907:** "lysis of cells prior to nucleic acid extraction (e.g., stool specimens, paraffin embedded tissue)"
- **83909:** "separation and identification by high resolution technique (e.g., capillary electrophoresis)"
- **83914:** "mutation identification by enzymatic ligation or primer extension, single segment, each segment (e.g., oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE))"

Each of the codes specifies a specific dollar amount, and a single experiment usually involves billing multiple codes.

Source: American Society for Clinical Laboratory Science

Reimbursement is an important determinant of commercial success in the molecular diagnostics market. Without sufficient reimbursement, physicians generally will not adopt a diagnostic regardless of its clinical validity. Adequate reimbursement depends on whether or not payors choose to cover the diagnostic and the level of reimbursement that they offer. As a general principle, a payor's determination of coverage is based on the demonstrated clinical validity and medical-economic value of a particular test, but in practice many other factors influence coverage decisions.

In the U.S., all in vitro diagnostics must be assigned a CPT (Current Procedural Terminology) code in order to be reimbursed. Unfortunately CPT codes have not kept up with developments in molecular diagnostic technology. If a new diagnostic is "shoehorned" into an existing CPT code, it may be reimbursed at a lower rate that does not reflect its cost of development, clinical benefit, or medical-economic value. Applying for a new CPT code can take 10–20 years and is a resource-intensive process.

Positioning a diagnostic for reimbursement by Centers for Medicare and Medicaid Services (CMS) for Medicare, Medicaid, and Veteran patients is the most important reimbursement function. CMS is the largest insurer in the country, and many payors follow its lead with regard to reimbursement decisions. CMS reimbursement of diagnostics has historically been inflexible and inconsistent (e.g., Medicare currently covers "diagnosis tests" but not "screening tests"), but (yet to be passed) legislation was recently proposed (Medicare Advanced Laboratory Diagnostics Act of 2007) to improve the reimbursement process for molecular diagnostics.[8]

Reimbursement outside the US is driven primarily by single-payor systems. European countries, which, although operating under a more or less common regulatory regime, vary significantly in their reimbursement processes and criteria for molecular diagnostics. Successful firms in these markets have sought either local alliances or advisors with deep understanding of the idiosyncrasies unique to each geography.

The differing experiences of Immunicon and Genomic Health highlight how critical the reimbursement issue is to the eventual commercial success of a product.

**Immunicon** developed a molecular diagnostic based on circulating tumor cells (CTCs) to help physicians monitor patients with metastatic breast cancer. However, the company failed to show a definitive link between the composition of CTCs and patients' tumors. Despite partnering with Veridex (a Johnson & Johnson company) for marketing, many physicians and most payors have not adopted the test.[9]

**Genomic Health** developed a multiplex biomarker diagnostic, Oncotype Dx®, to identify patients who are likely to benefit from chemotherapy. The company spent three years and an estimated $100M on its development, including laboratory testing and two large clinical trials to demonstrate validity and relevance. Several health plans, including United Healthcare, Cigna, Aetna and Kaiser, agreed to cover the test (costing ~$3500). The final decision by these providers and Medicare to provide coverage was most influenced by the oncology community that lobbied them with the belief that the test was both necessary and relevant for patients.[10] Share prices rose 504% after the test was introduced in 2006.[11]

## Regulatory and compliance

Molecular diagnostics are subject to the same regulations as medical devices. The level of potential harm to users drives FDA's pre-marketing approval requirements.[12] The regulatory environment is already complex and the FDA is growing increasingly cautious as diagnostics are becoming more relied on for critical medical decisions.

The FDA is attempting to increase regulation of home-brew tests, which currently fall under the CMS Clinical Laboratory Improvement Act (CLIA). FDA regulates the components of home-brew tests but not the tests themselves.[13] Analyte Specific Reagents (ASRs) are subject to regulation as medical devices when they are purchased by clinical laboratories for use in home brews or certain diagnostics. Most ASRs are currently classified as Class I.[14]

As diagnostics drive more treatment decisions, the FDA is increasing its role in enforcing the safety of assays available on the market. The FDA is increasingly declaring complex diagnostics as Class II and III devices. In September 2006, the FDA introduced a new class of diagnostics, In Vitro Diagnostic Multivariate Index Assays (IVDMIAs), tests that use biomarkers for diagnosis of genetic diseases. The agency has proposed applying standards to home brew assays that fall under IVDMIA classification. Products already on the market may also be required to go through FDA's IVDMIA pre-marketing approval process.

Successful molecular diagnostics companies will closely engage with FDA and will invest in regulatory operations and the supporting research and risk management functions. Typical regulatory operations include submission of new product applications, promotion and labeling, FDA communications, and adverse events monitoring. Analytical instrument companies will need to adopt standardized, repeatable, adaptable, and auditable processes and technology. Rigorous and expensive clinical trials may be required to demonstrate safety. Planning for a changing regulatory environment and engaging with the FDA may prevent potentially damaging scrutiny following the commercialization of a diagnostic test.

**FDA classification**

FDA approval and surveillance requirements of a molecular diagnostic are highly dependant on the diagnostic's medical device class:

- Class I – General Controls: simple in design and presents minimal potential for harm. Usually requires establishment registration, product listing, and labeling compliance
- Class II – Special Controls: more assurances of safety and effectiveness. Usually requires Class I plus premarket notification [510(k)], manufacturing standards (GMPs), performance standards, and postmarket surveillance
- Class III – Premarket Approval: usually supports human life, prevents impairment of health, or presents a risk of illness or injury. Requires Class II plus a premarket approval application (PMA)

Most devices are classified according to the "medical specialty panels," a list of device types published by FDA.

Source: FDA

In additional to regulatory involvement in product development and patient safety, when it comes to the healthcare marketplace, a number of regulatory bodies monitor activities across the value chain. Industry groups (e.g., PhRMA, AdvaMed, BIO, MDMA) as well as government regulatory bodies, closely monitor a host of sales and marketing activities including: Off-Label Discussions, Sales Promotional Expenses / Kick-backs, Scientific Research Grants, Opinion Leader / Speaker programs, Promotional Messaging, Samples Distribution, Pricing and Contracting.

Finally, the molecular diagnostics data is being increasingly scrutinized for Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliance, designed to protect patient and healthcare professional data. Molecular diagnostic products must support clinical laboratory standards for the use, disclosure, and control of individual patient health information.

### Business development/alliances

Molecular diagnostics companies require more advanced business development/alliance capabilities than analytical instrument companies. This is increasingly being driven by the opportunity for alliances with pharmaceutical and biotechnology companies to co-develop and co-commercialize new drug-diagnostic combinations. Relationships with pharmaceutical and biotechnology companies are expected to support sustained revenue streams for molecular diagnostics companies.

The growth in targeted therapeutics is driving opportunities for drug-diagnostic combinations for both routine and more complex tests. In a 2006 survey of pharmaceutical, biotech, and CRO organizations, 30% of respondents reported having at least two paired drug-diagnostics in development and 19% expected to have four or more in development by 2010.[15] A variety of drugs in late preclinical trials and early clinical development hope to follow Genentech's lead with Herceptin®, targeting disease-specific gene and protein defects. These therapies will require corresponding diagnostics to gain approval. Taking it a step further, it isn't far-fetched to believe that many therapeutic companies will look for opportunities to acquire the corresponding diagnostic technologies.

Drug-diagnostic (Rx-Dx) and diagnostic-diagnostic (Dx-Dx) alliances have been particularly prevalent in cancer therapy. Examples of Rx-Dx alliances in this space include Amgen and GenData (now LineaGen) for biomarkers as well as Merck and ParAllele / Affymetrix for SNP markers. Other types of alliances include research collaboration and technology convergence as evidenced by Bio-Rad Laboratories' and Affymetrix's alliances with Caliper Life Sciences for its microfluidics systems. Additionally, technology licensing activities include Gen-Probe's and Cepheid's licensing of Roche Diagnostics' HPV molecular IP and PCR, respectively.[16]

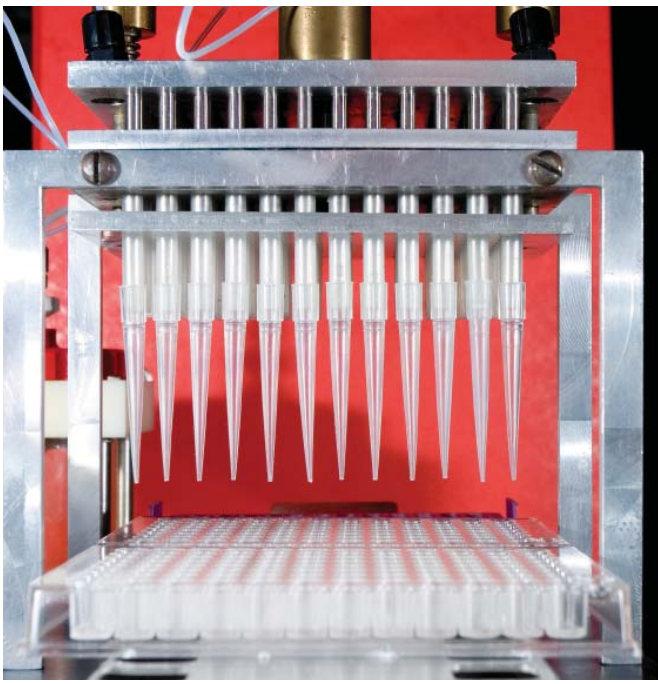
**Alliances and deals**

Analytical instrument companies can form alliances to strengthen molecular diagnostics development and commercialization capabilities. Typical alliances include:

- Established molecular diagnostics companies
- Pharmaceutical companies
- Biotechnology companies
- Diagnostic services providers
- Large hospitals and hospital systems
- University and government institutions

Typical deal types include:

- Technology licensing
- Co-development
- Co-marketing/sales
- Research collaborations
- Technology convergence
- Diagnostic services
- M&A/carve-outs
- Joint ventures



# The path forward

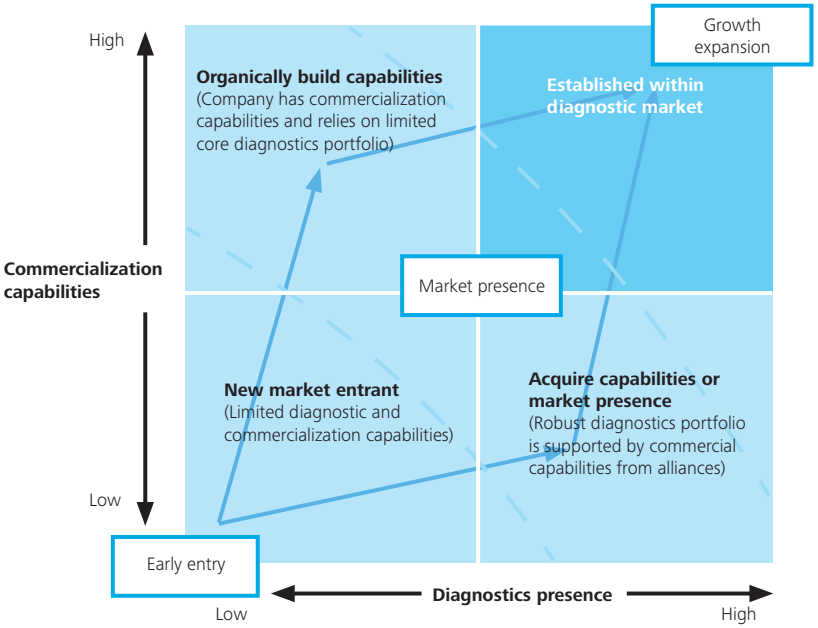
### Transitioning from strategy to execution

Of the analytical instrument companies we were able to observe during this study, that are in the midst of their transformation into molecular diagnostics, each fell into one of three stages: Early Entry, Market Presence, Established – Seeking Growth . This transformation can occur via two paths: 1) Organically build capabilities, or 2) Alliance/Acquisition (see Figure 4). The targeted diagnostic market position will guide the company's strategy and tactics and will determine the investment required as well as the complexity of implementing a growth strategy. At the most extreme, a company may choose to build a highly-integrated company (upper right) with a broad diagnostics product portfolio and co-development, co-commercialization and co-promotion alliances. On the other hand, a company might focus on developing an expansive diagnostic product portfolio supported through acquisitions and collaborations for commercialization capabilities (lower-right). Alternately, it might focus on building diagnostics commercialization capabilities (upper left) for a limited portfolio. These positions may be intermediate or final goals for the company's diagnostics business.

While simplistic enough in concept, the path taken will be determined by a host of factors including financial position, strength of the diagnostics portfolio and the maturity of the company's commercialization capabilities.

A company makes strategic decisions and develops tactical initiatives based on its choice to transition from one stage to the other via a move from one quadrant to another. The most appropriate option for a specific company depends on a unique combination of external factors (market drivers, customer needs, competitor space etc) and internal organizational constraints (commercialization capability sophistication, product portfolio, organizational buy-in). For example, an instrument company that has just entered the molecular diagnostics market probably already has a strong R&D product portfolio and may have been gradually expanding its commercial capabilities to support that portfolio. That company may transition to the next stage, establishing market presence, by focusing on evolving its commercial capabilities to meet the needs of the molecular diagnostics market because it has strong internal and allied capabilities. If it has always relied on the strength of product and has relatively weak commercial capabilities, the company might choose to focus on building its diagnostics portfolio.

**Figure 5. Evolution of strategic position in the molecular diagnostics market**



When choosing a transition strategy, companies will want to make a critical assessment of their current business and capabilities and how these will fit with the company's envisioned molecular diagnostics business. A successful transition strategy will also consider and plan for the impact of these changes on current operations, and on perceptions in the marketplace. For example, in evolving to serve this new market and a set of new customers, the company may risk alienating current customers who fear their needs will be de-prioritized. Existing customers will notice immediately if their customer experience changes as a result of a company's decision to transition into new markets.

Similarly, an evolving company may see a parallel effect internally—developing one capability may have an impact on other functions and capabilities, including those supporting other lines of business. As focus and importance of different functions shift within the organization, so will information flow, decision rights, and ultimately perceptions of political power. Careful planning and coordination is required to make certain that the transition is effective for the new market, but also seamless for the existing market and organization. Figure 5 provides a roadmap for developing commercialization capabilities based on a company's current and desired position.

**Figure 6. Roadmap for developing commercialization capabilities over time**

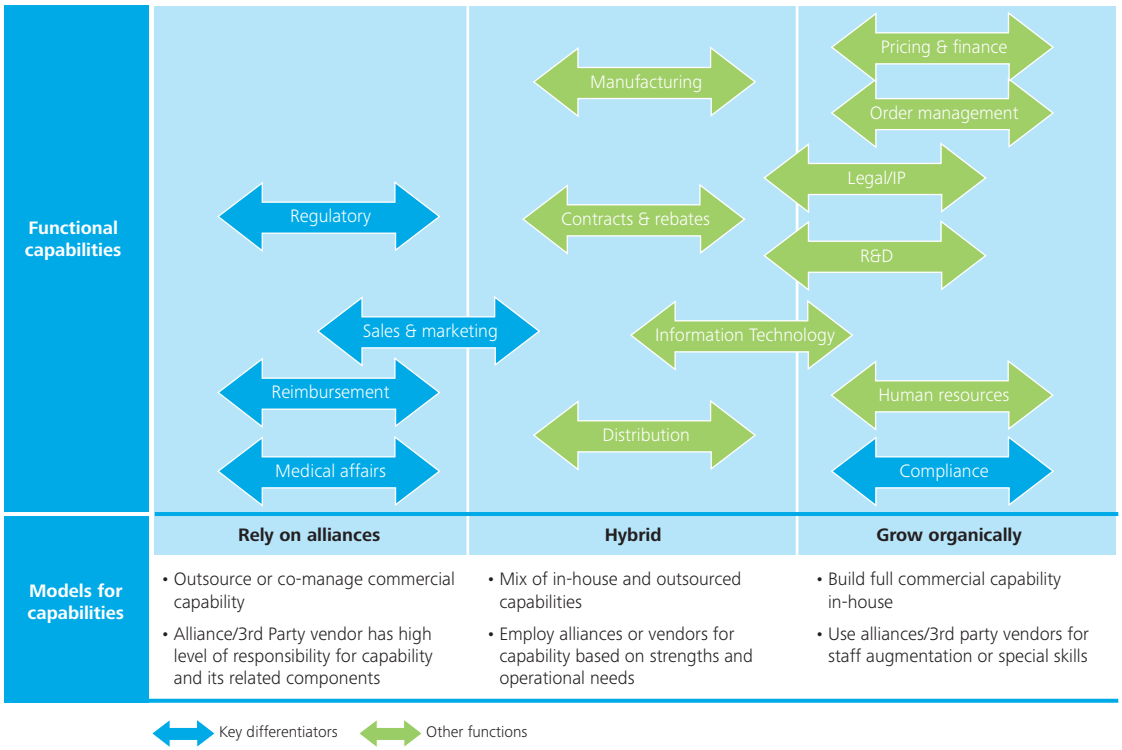
| | Early entry | Establishing market presence | Growth and expansion |
|---|---|---|---|
| **Reimbursement** | • Ensure initial reimbursement support including development of cost and revenue sharing models<br>• Invest in rigorous testing to demonstrate clinical relevance<br>• Develop education and knowledge of reimbursement policies | • Establish reimbursement department<br>• Establish pricing & reimbursement strategy based on a regulatory change model<br>• Establish customer service support and call center solutions | • Conduct education campaigns to demonstrate product value-add<br>• Conduct pharmacoeconomic studies to demonstrate product's impact on medical decisions and outcomes<br>• Develop advanced metrics for performance optimization |
| **Regulatory and compliance** | • Collaborate with regulatory bodies (FDA, CMS) to facilitate initial support<br>• Initiate development of capabilities and understanding of the regulations<br>• Assess brand security and secure supply chain/distribution channels | • Establish regulatory support function with risk assessment and management capabilities<br>• Initiate risk management strategy based on overall product portfolio<br>• Develop clinical trial management, CRO, and clinical data expertise | • Expand effort placed on clinical trial safety, rigor, and FDA collaboration<br>• Develop risk management strategies that align with corporate strategy<br>• Develop standardized and auditable processes and technology with R&D, clinical trials, and marketing |
| **Business development/ Alliances** | • Explore alliances with current molecular diagnostics companies<br>• Explore co-development and research opportunities<br>• Consider potential co-development opportunities with biopharma | • Diversify and expand alliances with diagnostics companies<br>• Optimize alliance management (contracts, information sharing, and program mgmt)<br>• Identify drugs in preclinical trials for co-development opportunities | • Expand drug-device alliances<br>• Develop optimized cost and revenue sharing models for value demonstration<br>• Develop joint campaigns to improve drug-diagnostic importance and adoption |
| **Sales & marketing and medical affairs** | • Identify market needs, commercialization potential, and market entry strategies<br>• Build/enhance sales and marketing channels (physician-payor relationships, medical liaisons, DTC channels)<br>• Develop and implement a product launch plan driven by market trends with integration across cross-functional plans | • Develop customer experience plans<br>• Refine product launch management based on market evaluation and alliances<br>• Develop holistic brand management strategy<br>• Invest in customer education campaigns | • Optimize strategies based on market needs and VOC insights<br>• Optimize service effectiveness<br>• Adopt advanced analytics, CRM capabilities, and professional and consumer programs<br>• Enhance medical affairs to increase competitiveness and customer satisfaction |

# Build versus buy options for acquiring commercial capabilities

For life science tools or analytical instrument companies pursuing growth in the molecular diagnostics market, a variety of business models, including internal development and external alliances, can be effective in order to address gaps in current commercial capabilities. However, there is no "one size fits all" answer. The model a company chooses for developing a specific capability depends on a unique combination of market needs and the company's growth strategy and objectives, organizational capabilities, and constraints.

The solution set of potential operating models falls along a continuum from building the capability in-house to outsourcing the capability entirely to third parties (Figure 6). Building capabilities in-house provides a company greater control but also requires financial investment and time – which the market may not have patience for as competitors roll out suites of products. However, second to market may also have advantages if the first mover has been able to establish reimbursement coding, etc. Relying on alliances has the advantage of allowing flexibility in matching capabilities to their current needs and benefiting from the experience and market leading capabilities of alliances. Because alliances make commercial success more dependent on other entities, alliances should be chosen and managed carefully, and having mature alliance capabilities becomes more important.

**Figure 7. Typical "Build vs. Buy" options for commercial capabilities**



Analytical instrument companies expanding into molecular diagnostics have typically relied on alliances for distribution, sales, and marketing. For example, Luminex's 23-plus commercial alliances act as their primary distribution channel. For Gen-Probe, Novartis is responsible for marketing all blood screening products which account for 47% of Gen-Probe's revenue.[17] Most analytical instrument companies also rely on alliances for medical affairs, reimbursement support, and regulatory affairs. Other capabilities, including R&D, legal/IP, and pricing and reimbursement, are more likely to be developed internally because they are extensions of capabilities that many instrument companies already have.

Reliance on external alliances for commercialization brings its own challenges around coordination costs, control, and limited contact with end users. If not addressed, these challenges may ultimately constrain the company's ability to grow profitably and be competitive in the molecular diagnostics market. Developing strong internal commercial structures and capabilities must be part of a company's overall growth and operational strategies.

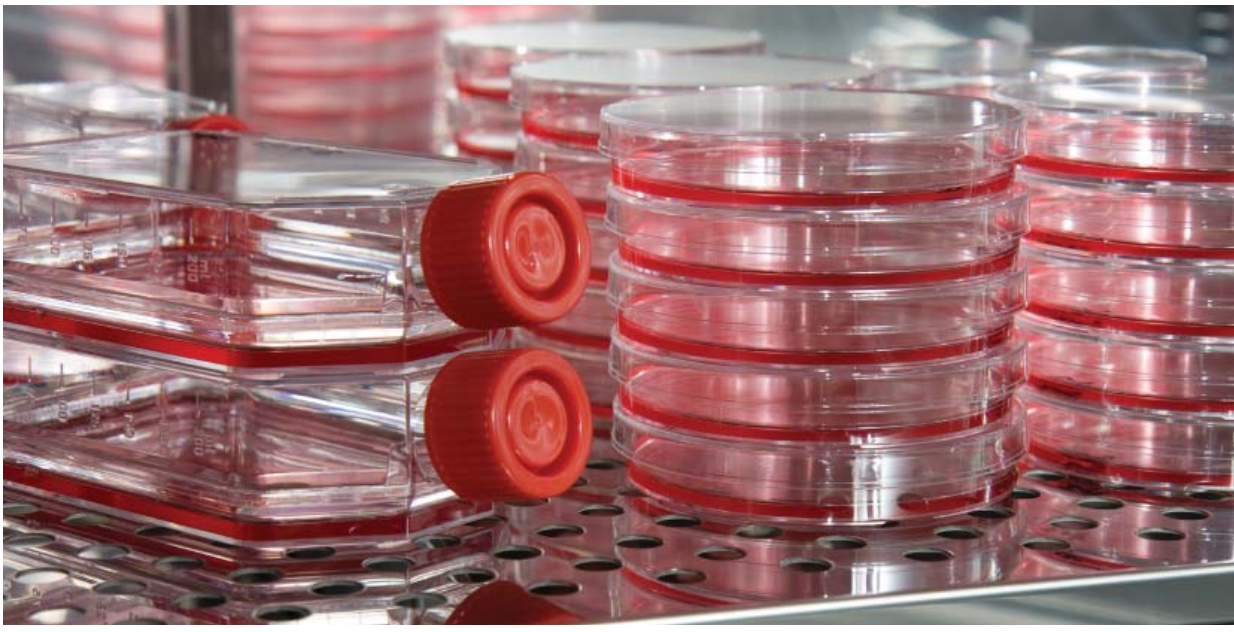
# Conclusion

Rapid growth of genomics knowledge and technology is expected to continue, and with it more life-saving applications in medical science. While analytical instrument companies will remain at the forefront of developing new technologies for scientific applications, commercializing the technologies for clinical diagnostics applications will require an increasingly complex commercial infrastructure. The key differentiator commercial areas will be reimbursement, regulatory/ compliance, business development/alliances, and sales & marketing/medical affairs. There are several paths available for bridging the capabilities gap, with both "go it alone" and "build vs. buy" considerations. By developing an effective strategy, analytical instruments companies will be much better positioned to successfully bring their cutting-edge innovations to profitable medical markets while helping patients with improved screening, diagnosis, monitoring, and treatment of different disease conditions.

### Making sense of It all – Choosing the right path for you

Some fear the dream of molecular diagnostics may seem to rest on a far off horizon. However, for those who have set their sights on seizing the opportunity in molecular diagnostics, start by asking yourself a couple of simple questions:

- Does your current portfolio provide a natural entry point to the MDx market?
- What test type and market segment should you enter first (e.g., detection, planning, companion Rx-Dx)?
- What is the viable time horizon to enter the market with sustainable advantage?
- How can you establish a basis for competition in MDx?
- Do you currently have the capabilities required? If not, what are the major gaps?
- What is the best path forward to fill the gaps?



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