G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Walgreens Takes Leading Role in Experimental Delivery Models

As health care delivery models are transforming, laboratories are watching a number of emerging trends, including the establishment of accountable care organizations (ACOs) and the growing interest in the retailization of health care, as they try to figure out their role in this evolving landscape.

Laboratories can gain some beneficial insight in transformation of traditional roles from pharmacy giant Walgreens (Deerfield, Ill.), which has announced participation in several dynamic partnerships. Most talked about in the laboratory industry is the pharmacy's fall 2013 announcement of its partnership with Theranos (Palo Alto, Calif.) to bring convenient, affordable laboratory testing to Walgreens stores nationwide. Walgreens also became the first pharmacy to form ACOs with three large physicians groups in Texas, Florida, and New Jersey. Through these ACOs, pharmacists will play an integral role in coordinating care with clinical teams by monitoring medication adherence, primary prevention and screening, and minor episodic care through in-store clinics.

As laboratories explore the value they can bring to stakeholders along the care continuum and address the need to deliver patient-centric care, Walgreens can serve as an example for expansion of traditional delivery roles. For more information on Walgreens' partnership with Theranos, please see *Inside the Diagnostics Industry* on page 5. For more information on how laboratories can address consumerism, see the *Special Focus* section on page 8.

M&A Expected to Pick Up in 2014; Private Investment to Be a Challenge

By nearly all calculations there was nothing exceptional regarding the number of transactions or the value of merger and acquisition (M&A) deals in the diagnostics space in 2013. Companies and investors played it safe while trying to forecast the financial impact of the industry's two most pressing challenges—the uncertainties surrounding the Affordable Care Act (ACA) and reimbursement. For 2014, though, most industry watchers are buoyed by slight optimism, believing that as more late-stage diagnostics companies reach commercialization, buyers may be enticed by efficiency gains from newer platforms and the high growth potential of emerging clinical technologies, including molecular diagnostic-related products.

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▲ **M&A Expected to Pick Up in 2014,** *from page 1*

A 2013 Recap

The headline-grabbing announcement of Thermo Fisher Scientific's pending $13.6 billion purchase of Life Technologies sent excitement through the industry last spring but failed to trigger a hoped for series of follow-on acquisitions. According to research from Ernst & Young and Dealogic, insecurity regarding the impact of the ACA kept the broad category of health care-related deals slightly below 2012 numbers, but by some measures deal value was up slightly for life science transactions.

"Global life sciences M&A deal values hit $131.8 billion in 2013 in 203 transactions with disclosed deal values greater than or equal to $20 million. That compares to $108 billion in total deal values for 211 transactions in 2012," writes Marie Daghlian, in a Jan. 6 entry of the *Burrill Report*. "Although 2013 total deal values were 21.3 percent higher than in 2012, the number of deals was down by 3.8 percent."

Completed Diagnostics IPOs in 2013

Company	IPO Date	Amount Raised
Oxford Immunotec Global	11/2013	$64 million
Veracyte	10/2013	$65 million
Foundation Medicine	9/2013	$106 million
NanoString Technologies	6/2013	$54 million
Cancer Genetics	4/2013	$6 million
LipoScience	1/2013	$45 million

Source: Burrill & Co.

Rather than bold expansions into new business lines, the M&A activity in the laboratory and diagnostics segments reflected the "substantial" pressure the industries are under to reduce cost and drive greater operational efficiencies. Reimbursement challenges, increasing provider consolidation, shrinking preferred networks, and consumer price sensitivity, are hitting reference lab margins and leading to laboratory consolidation and pricing pressure that in turn puts pressure on in vitro diagnostics manufacturer margins and drives consolidation there, as well. The result is that some players will leave the space by spinning-off or divesting noncore assets, underperforming units, or more commoditized lines so that they can focus resources on higher-margin, more core segments.

A prime example of this is Quest Diagnostics (Madison, N.J.), which undertook a five-point strategy to refocus on its core diagnostic information services business, drive operational excellence, restore growth, simplify the organization, and deliver disciplined capital deployment. As a result, the company divested its OralDNA dental diagnostics business, HemoCue diagnostic products business, Ibrutinib royalty rights, and its Enterix colorectal cancer screening test business, which generated combined gross proceeds of approximately $800 million.

"Big service providers and large life sciences companies (pharmaceutical and medtech) alike will divest and spin off business lines that are non-core or low-margin in order to be more nimble," write Ernst & Young Capital Advisors in a forecast of 2014 deal activity. "All participants in the continuum of health care are streamlining the business to prepare for the changes happening now and the expectations of continued shifting regulatory landscapes."

On the acquirer side, Soren Peterson, Ph.D., a senior analyst with the consulting firm Health Advances, says acquisitions were targeted to products of demonstrated value that in many cases improve workflow efficiency. Peterson cites Roche's (Switzerland) $220 million purchase of Constitution Medical Investors as an example. Constitution, which developed the Bloodhound complete blood count testing instrument, received a high valuation, Peterson says, even before regulatory approval or commercial validation, because of the system's potential cost savings for laboratories through a reduced need for technicians with the automated system.

With a slow pace of acquisitions of venture-backed biotech companies, companies turned to the public markets to access capital and provide some return to investors. Initial public offerings (IPOs) were unusually active for biotech, with 52 U.S. life science IPOs in 2013 versus 16 in 2012, according to the *Burrill Report*. Experts don't expect this pace to continue in 2014, so eyes will once again turn to see if M&A activity will pick up, or if softer alternatives to outright acquisitions, such as licensing agreements and partnerships, will be more attractive this year.

Looking Ahead: M&A

"Multi-billion dollar trades have occurred because innovation is and will continue to be the lifeblood of this industry," said Ben Perkins, U.S. Life Sciences Sector leader for Ernst & Young Capital Advisors, in a statement about industry mergers and acquisitions. "Research and development groups will return to the era of going where the science takes them and allowing internal programs to cross over into other disease areas. High quality assets are difficult to find, and we will continue to see high-priced acquisitions and robust valuations for unique assets."

However, experts caution that those products and companies able to attract high valuations will be very select. Broadly, products and services that are immediately accretive financially or add substantial technical advances will be favored, while those without commercial validation will be of less interest to buyers.

"Payers and providers will no longer accept a slightly better product; innovation under the Affordable Care Act will mean producing products with demonstrable improvements in quality of life and life expectancy, which could drive M&A activity," write Ernst & Young Capital Advisors. "Specifically, medtech and pharma subsectors will see a tectonic shift in how drugs and devices are being reimbursed and each product will be more closely scrutinized to understand the price to value benefit."

Peterson, with Health Advances, tells *DTET* that technologies that drive down costs by increasing lab efficiency and increase retention of provider contracts will continue to be in demand as labs continue to face an increasingly difficult landscape. Assets, such as those in health IT, that assist labs in demonstrating their value to providers, are expected to be in demand in the coming years. Peterson also says that, driven by labs' scramble to improve margins, higher value and more efficient molecular diagnostics such as multiplexed and automated molecular diagnostics have played an outsized role in M&A deal volume.

In 2013 the buyers of diagnostics companies tended to be more traditional players, reversing a trend towards nontraditional buyer activity seen in the previous few years. In the several years before 2013, nontraditional buyers, such as life science tool companies, industrial onglomerates, and non-health care companies,

2014 Acquisitions Start Quickly

Deals in 2014 got off to a quick start with several large deals announced in early January.

- **GE Healthcare** (United Kingdom) agreed to buy three business units from **Thermo Fisher Scientific** (Waltham, Mass.) for roughly $1.06 billion. The deal, announced Jan. 6, includes a gene modulation business for drug discovery, magnetic beads business for protein analysis and diagnostics, and the HyClone cell culture business. The divestiture will allow Thermo Fisher to overcome antitrust concerns in the European Union regarding its pending acquisition of sequencing firm Life Technologies. For GE this acquisition represents further expansion of its life science businesses, which John Dineen, chief executive of GE Healthcare, says is the company's fastest-growing business area. Together the three units, Thermo Fisher said, had estimated combined revenue of $250 million in 2013.
- **Johnson & Johnson** (New Brunswick, N.J.) announced the sale of its Ortho Clinical Diagnostics unit to private equity firm **Carlyle Group** (Washington, D.C.) for $4.15 billion on Jan. 16. The divestiture allows J&J to reallocate resources from a slow-growing, non-market leader business segment to more lucrative products. According to a report by Reuters, Carlyle believes that Ortho Clinical Diagnostics, which includes equipment for laboratory diagnostics and blood transfusion screening, has growth potential in emerging markets.

accounted for a substantial share of molecular diagnostics deals. However, given integration troubles, uncertainty surrounding diagnostic reimbursement, and a decreasing number of nontraditional buyers, who themselves have been acquired, Peterson expects the appetite for nontraditional buyers to enter the diagnostics space will be "tempered" in the coming years. Pharmaceutical companies, for example, have preferred lower-risk partnerships for the development of companion diagnostic products. While some buyers such as tools companies like Illumina will likely continue to penetrate the clinical diagnostics market through acquisitions, core diagnostics players will likely continue to be key players in deal activity as they seek to increase scale and breadth of product lines and private equity firms look to leverage debt financing to acquire companies with strong cash flow. With a longer time to exit than other life science companies, emerging diagnostics companies will need to continue looking for additional private investment to get them to the late-stages of development associated with more lower-risk and attractive acquisition targets.

Looking Ahead: Private Investment

"Private financings of U.S.-based companies grew 4.5 percent to $8.9 billion, [but] early-stage financings continued to be constrained for many start-ups, which turned to non-traditional sources including angel investors, philanthropic groups, disease advocacy organizations, and corporate venture," writes Steve Burrill, CEO of the life sciences financial services group Burrill & Co. "At the same time, Big Pharma and Big Biotech increased their venture activities in early-stage financing through centers of innovation and partnerships with venture capitalists, incubators, and research institutes to launch companies. Expect corporate venture to take a more active role in 2014, especially in early-stage deals. Early-stage capital will remain tight with a handful of companies raising large initial rounds."

Despite the challenging fundraising environment, Burrill sees a brighter year for the diagnostics industry.

"Diagnostics will grow in value in 2014 as increased pressure from payers to pay only for those drugs that work will demand defining the patient population most likely to benefit from their use," writes Burrill. "At the same time, diagnostics companies will have to demonstrate to payers their tests' effectiveness in reducing overall costs and/or improving outcomes in order to get them reimbursed. . . . Expect to see insurers embrace value-based pricing in the United States, much as it has been embraced in European countries and elsewhere."

Takeaway: Signs point to a rebound in M&A in the laboratory and diagnostics segments in 2014. With tremendous pressure to reduce costs, technologies that drive greater operational efficiencies will be acquisition targets for traditional buyers. G2

Domain Associates' Fund Invests in Diagnostics

Among the venture capital funds committed to investing in diagnostics companies is Domain Associates (Princeton, N.J.). In 2009 the firm raised DOMAIN VIII, a $500 million fund. The fund's most recent diagnostic placements include:

Xagenic (Toronto; December 2013). Domain led a $20 million series B round for point-of-care developer Xagenic. The company is developing lab-free molecular diagnostics platform with 20 minutes time-to-result based on patented nanostructured microelectrodes that allow for direct nucleic acid detection from clinical specimens without the need for extraction.

BioNano Genomics (San Diego; follow-on October 2013). BioNano Genomics completed a $10 million follow-on round of funding that will allow for further development and commercialization of its automated, benchtop IRYS system that can identify genomic structural variation.

Applied Proteomics (San Diego; August 2013). Applied Proteomics will use its $28 million series C round to begin commercializing protein-based diagnostic tools. The company is building a CLIA-lab that will use an MRM mass-spectrometry-based platform for its first blood test that detects precursors to colorectal cancer.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Theranos Aims to Transform the Medical Diagnostic Industry

Elizabeth Holmes, Founder and CEO, Theranos

After years of speculation, Theranos (Palo Alto, Calif.) last fall unveiled its revolutionary plan to reshape the future of laboratory testing. With a laser-sharp focus on lowering testing costs (always 50 percent or below Medicare reimbursement rates) and standardizing quality, the company's plans potentially hold benefits for stakeholders across the health care industry.

Patients benefit from the convenience of Theranos draw centers in Walgreens pharmacies and from the company's proprietary and patented infrastructure for processing microsamples (one-one thousandth the size of a typical blood draw). The company believes its quick return of precise results will provide enhanced efficiency and informative, longitudinal value for physicians and pathologists. Theranos also poses a disruptive threat to the laboratory industry through a transformative emphasis on transparency reflected in the company's commitment to both price transparency (all test prices are on the company's Web site) and publication of margin of error variation for aiding interpretation of test results.

The company's goal of deploying a national network of accessible testing centers is becoming a reality with the expansion of its Walgreens-based Wellness Centers to the Phoenix area in mid-November 2013, following the opening of the first center in Palo Alto in September 2013. Elizabeth Holmes, Theranos's founder and CEO, recently spoke to *DTET* about the unique infrastructure powering the company's pioneering vision.

Please tell us about how Theranos's proprietary infrastructure helps the company achieve its vision.

Our focus has been to build a high-complexity CLIA-certified lab so as to provide the level of oversight and quality that we think is really imperative to be able to provide data back to physicians for clinical decisionmaking. We focused on two things: to reduce the volume of blood that's required to run tests and to reduce the variance and the associated coefficient of variation. As you well know, so much of the error in laboratory testing comes from the preanalytic process where manual protocols or exposure of the sample to temperature or the amount of time before processing it can create variability—anything from the degradation of the analyte and its associated concentration to differences in the ultimate results that can be generated across lab locations. What we wanted to do was introduce a level of automation to that process that could help to minimize that variance and associated error and make it possible to do this testing on a microsample, while in a CLIA-certified framework. We have an infrastructure that can create very consistent data such that we can ultimately provide pathologists and physicians with more robust longitudinal data by helping to minimize variance and associated errors.

How did you decide on your initial test menu?

We had the opportunity as we built the company over the years to do a lot of work with pharmaceutical companies, having served as the infrastructure for their clini-

cal trials. In that context we had the opportunity to develop some really sophisticated assays for markers that were used to characterize the efficacy or safety of a drug. If one were to provide those tests in the clinical care setting, I think there are a lot of questions about how they would or should be interpreted clinically. What we tried to do with this menu was to focus on tests that physicians know how to use so that we could provide the most value in the context of clinical care. What we did when we started to develop our lab was to focus on tests that are most commonly ordered by physicians and could provide the most clinical utility.

As molecular testing becomes more commonplace, even in primary care, will Theranos expand its menu to include these tests?

We have the opportunity to do that given the laboratory framework we have in place. The goal and hope in the industry is that [physicians' molecular] knowledge will be there in the future, and our goal as the laboratory is to provide those tests that can create the most utility for physicians when providing care to patients.

A focus on consumerism is infiltrating all aspects of health care including laboratory testing. With its Walgreens partnership, Theranos seems ideally positioned to address these changing expectations.

My motivation for starting this company and our mission is around being able to provide access to actionable information at the time it matters. There is an inherent goal there to be able to help ultimately facilitate early detection in any way we can.

When you think about access to actionable information, the first step is getting tested in the first place. As you know in the laboratory world today there is a huge percentage of patients, even when they are given a requisition to do a test, who don't do it. When you break down the research on why, there is a very big fear of needles that is right up there with heights and spiders and other very high-ranking human fears. People don't enjoy having a big needle stuck into them. Children, elderly persons, oncology and chronically ill patients, and others who are difficult to draw through traditional venipuncture not only go through tremendous pain in the collection process but also experience physical limitations around being able to get enough blood for the tests needed.

> ***"My motivation for starting this company and our mission is around being able to provide access to actionable information at the time it matters."***
>
> ***—Elizabeth Holmes***

There are also issues of convenience with having to leave work to go to a location, not being able to do testing on weekends or at night, and long drives to get to wherever they are supposed to go to get tested. We established our partnership with Walgreens to allow people to do testing in a location that is most convenient for them and for the first time to be able to do testing during hours that fit their schedules. We designed a whole new environment in our centers, from check-in to microsample collection, with the aim of making the lab testing experience a wonderful one and getting people in and on their way in minutes.

Another aspect of access is the speed and turnaround time of results, to be able to get that information back to the physician such that it can be used at the time it matters most. Patients can now get a test in the morning and see their physician that afternoon and on the same day have that data. So in that one visit when the patient and physician are seeing each other, the information is there as opposed to having to go do a test, come back, do another test because it was out of range. We have created a framework that allows us to process these different tests from a single microsample draw, instead of multiple sets of different venipuncture tubes, and the physician can order comprehensive panels ahead of time with instructions that if a given analyte is out of range, then a set of specified follow-on tests should be run, all from the same microsample. Our mission is all about access to actionable information at the time it matters, starting with access to be able to get tested, and in doing so create a framework that provides the physician as early as possible with the most comprehensive biochemical information so they can make the best possible decision about how to take care of that patient.

"The transparency around cost is about access. We believe very strongly that people should know up-front, ahead of time, how much they will owe if they decide to buy a testing service."
—Elizabeth Holmes

You also believe price transparency improves access to testing. Please explain.
There are also issues around affordability of being able to pay for the test patients need to get. The transparency around cost is about access. We believe very strongly that people should know up-front, ahead of time, how much they will owe if they decide to buy a testing service. The work we've done makes it possible to not only know up-front how much the test will cost, but how much a copay or deductible is going to be. This is about access. We can make sure they are able to afford the test by making pricing available that it is the same no matter who you are or what type of insurance you have. We want to make sure that prices are low enough so that people can afford to do the tests they need.

Price transparency is a new concept for the health care industry. What has the reaction been?
I think it is very powerful. Today no matter what kind of insurance you have or don't have, you are going to have to pay out of pocket because you are going to have some type of deductible. How much you have to pay matters to a lot of people. Current practice is that you don't know when you go in how much you are going to have to pay and often you don't find that out until quite some time after the test. That can be really difficult. We have seen in the early days of our operation people who are coming to us who haven't gotten tested for a long time, but they are coming now because they know they can afford it. That is really important to us, getting back to the access point.

We also know that financially for Medicare and Medicaid that is very powerful because there is a great need to save money. We will help to realize savings that can be significant over time. That is an important thing in the context of being

able to provide a footprint that can serve patients, while providing the lowest-cost testing.

The way we are billing, we are generally the lowest-cost provider around period, irrespective of network. Having a network with the lowest-cost provider seems to make us important to the insurance community. As we grow, that is an important part of our framework and our partnerships. But irrespective of which patient comes, we are billing the same and that rate is lower, as far as we have seen, than any other rate on the market. These prices are the same for both the payer and for the individual who has to pay out of pocket.

Your focus on transparency is not limited to prices but extends to margin of error. Please explain.

The margin of error variation is another element relevant for access to actionable information. The actionable information, in our minds, comes back to understanding the variance in testing. If a physician knows exactly what the variance is, if you are on the border of being in or out of range, that can help the physician or pathologist in the way in which they are interpreting that information. As we start to think about being able to minimize variance associated with preanalytical processing and by having a more standardized framework, we can confidently look at how laboratory data changes over time. The physician with this type of information and the margin of error variance has the opportunity to begin understanding change over time in a way that provides much more insight into the clinical significance of these values than they have when looking at in range or out of range with a single snapshot.

By-the-Numbers

Year Founded: 2003

Sample Volume: 1/1000th of a traditional draw

Test Pricing: Always lower than 50 percent of Medicare reimbursement

Walgreens Locations: approximately 8,200

How will testing evolve in the coming years?

We think there is a huge opportunity, going back to the actionable information point, to begin to leverage what I call the movie instead of the snapshot in the way laboratory data is used. In the analogy I use, if I were to watch a movie I'd never seen before and you took one frame and said, 'OK, Elizabeth, tell me the story.' I would look at that single frame and have a really tough time telling you the story. But if you gave me a series of frames, I could begin to put that story together.

When you think about minimizing variance, minimizing preanalytic error, you have the opportunity to get very high-integrity information. If that infrastructure is standardized in such a way that that high-integrity information can be the same across locations, then longitudinally this data begins to be very powerful for the physician. During a visit physicians don't have to just look at whether the patient is in range or out of range but can start to look at what rate the patient is changing across visits. We think that information is going to be very powerful for pathologists and physicians to begin looking towards earlier detection and intervention. The goal is that if you can engage people in the testing process, so that they get the test when they need it, and you have this rich ability to look at that rate of change over time, you can use laboratory data in more actionable way.

Labs Must Address Convenience, Price, Value In Patient-Centric Delivery Models

Strong consumer trends are reshaping how patients access and purchase health care. The coming year is expected to be a pivotal one as health care companies transform their business strategies to address the growing importance of the end user. Experts say that in order to survive this transition, laboratories must act now to address this cultural shift by considering such issues as convenience and price transparency.

"As patients become more sophisticated purchasers of health care, they will push competition in health care delivery to look increasingly like that in consumer-goods industries," write Robert S. Huckman, Ph.D., and Mark A. Kelley, M.D., in a perspective piece published Oct. 16 in the *New England Journal of Medicine*. "This competition could lead to product offerings that appeal to consumers with different needs. While some patients may seek greater odds of survival, others may seek a faster return to work or lower out-of-pocket costs. These options are at the core of 'patient-centered' care."

> ***"Consumers are starting to demand better pricing or at least transparency in pricing and 'what am I getting for my money?'"***
> ***—Ceci Connolly***

Early manifestations of these trends can be witnessed in shifting delivery models and laboratories' adoption of information technology systems capable of integrating multiple systems to provide additional informational value from laboratory results and unified, real-time financial data for both the patient and the laboratory. These emerging models all coalesce around the unifying themes of convenience, transparency, and access.

The Convenience Factor

With an emphasis on moving care to lowest-cost, decentralized settings, comes a focus on convenience and patient satisfaction.

"As 'patients' behave more like 'consumers,' health care companies need to deliver a higher level of personalized service, satisfaction and overall experience—or risk losing business to the competition," conclude the authors of Pricewaterhouse Coopers's (PwC's) 2012 Experience Radar survey, which measured the experiences and attitudes of 6,000 U.S. consumers across 11 industries.

The survey found that while health care is beginning to look more similar to other consumer industries, it is still unique in some ways. Price was the top influencer in selecting a provider for all other industries, except health care (8 percent in health care versus 55 percent in retail and 69 percent in leisure airline purchases). In health care, personal experience was ranked first by 42 percent of respondents. For factors of convenience, though, health care expectations show a similar pattern to other retail options. Individuals value convenience in a physical health care setting, with nearly 70 percent of survey respondents wanting multiple services in one location and nearly 65 percent valuing online and mobile information exchange. More specifically, half of consumers value extended clinic hours (Monday to Saturday, 8 a.m. to 10 p.m.) and nearly half of consumers said they want insurer information in paper and online formats.

"The consumers just by virtue of the fact that they are spending more of their own money are beginning to take a much harder look at what they get for their health care dollars," Ceci Connolly, managing director of PwC's Health Research

Institute, says in a *Health Leaders* interview. "So they are saying, if I can do my banking in my pajamas at midnight on my couch why can't I make my doctor's appointment then or why can't I get my lab results on my smartphone? Consumers are starting to demand better pricing or at least transparency in pricing and 'what am I getting for my money?'"

The earliest indicator of this focus on convenience in health care delivery has been in the development of retail health clinics. The Convenient Care Association, the national trade association for retail-based health care locations, says that since these clinics' inception in 2000, the industry has grown to between 1,500 and 1,600 clinics in 40 states and Washington, D.C. But, a recent study from the Center for Health Care System Change suggests that penetration, while growing, remains rather low, with 3 percent of U.S. families having used a retail clinic in the previous year. The industry, though, has plans for significant expansion. Walgreens (Deerfield, Ill.), which has also begun to integrate laboratory testing into stores through a national partnership with Theranos (Palo Alto, Calif.), has integrated 400 retail health clinics into its 8,100 existing stores across the country, and according to *USA Today*, the company plans double-digit percentage growth in the number of these clinics during 2014.

While experts believe other laboratories will attempt to partner with retail clinics, the competitive advantage offered by the Walgreens-Theranos partnership is significant and not just limited to the added convenience factor for the patients.

"With new customer paradigms, laboratories need to evaluate where they will fit in."
—Robert Boorstein, M.D., Ph.D.

"It is a national footprint with a robust information management system," says Robert Boorstein, M.D., Ph.D., director of the laboratory consulting firm ClasGroup (New York). "Doctors are already used to ordering prescriptions online and patients are used to going there to pick up their prescriptions … Spreading out demand will affect labor costs and be much more efficient than standalone draw stations."

Boorstein predicts much like Amazon is changing the retail model through use of technology and new distribution methods, laboratories need to think outside of the box for wholly new models.

"With new customer paradigms, laboratories need to evaluate where they will fit in," says Boorstein. "It is hard to envision the logic of freestanding draw centers at some point. Why would you need separate facilities if draws can be done at drug stores up to 24 hours a day?"

Boorstein says that if laboratories think of extensions of customer-driven models and the fact that most pricing models underestimate the value of time and that consumers are willing to pay for convenience, home or office draws may be appropriate in some markets where people may be willing to pay. And while much of the convenience discussion revolves around the ease of specimen collection for the patients, laboratories must consider ease of results for physicians as well. Returning all results at one time, when possible, in one format adds value for time-constrained physicians.

Actionable Data

Many clinical laboratories today are developing data repositories to logically link all transactional and other information about a patient, says Michelle Del Guercio, vice president of marketing for health care technology company Atlas Medical

(Calabasas, Calif.). When data is coalesced in a patient-centric way, physicians can see all relevant clinical information, identify longitudinal trends, and provide better care, enabling labs to provide greater value to their physician customers, as well as other system stakeholders, including increasingly accountable care organizations.

"In strictly an accession-based model there is no way historically to track if a patient has already had the test from a different physician," explains Del Guercio. "Laboratories need to adopt a patient-centric approach to survive. With duplicate or unnecessary testing they won't get reimbursed and will be losing money."

A key component of these laboratory data repositories is financial data including test pricing, real-time information on copays and deductibles, as well as any past due or collections data. With patients footing a larger portion of their own medical bills as a result of higher-deductible plans, for the first time laboratories are having to deal with consumers' increased price sensitivity.

Price Transparency

Average deductibles are increasing for both in-network and out-of-network services. Additionally, the number of high-deductible plans is increasing. According to PwC the number of employers only offering high-deductible health plans jumped from 13 percent in 2012 to 17 percent in 2013. For 2014 and 2015, more than 44 percent of employers are considering offering high-deductible health plans as the only option.

"One of the problems of high-deductible plans is that the high deductible is not really backed by financial resources," says Boorstein. "If you have a high-deductible auto policy and don't pay your bill at the body shop, you won't get your car back. In health care we don't have those levers and patients can run up significant bills."

As consumers make more cost-conscious choices, laboratories will face an increasing number of "walk-outs" of patients who arrive at a laboratory to get a test, discover the price is too high, and walk away without being tested.

"This is retail terminology, but laboratories need to have a strategy and scripts to handle walk-outs," says Boorstein.

The challenge for laboratories is not just posting the prices of tests but also being able to keep up in real time with patients' deductible status as well as past-due amounts owed directly to them. To do so, laboratories are increasingly turning to information systems capable of integrating disparate systems in order to achieve a patient-centric view so that when a patient shows up for a new draw, past-due balances will be evident so the laboratory can attempt to collect in person, which has been shown to have a higher success rate. Similarly, a patient-centric view allows for combined statements from three different encounters that will both reduce mailing costs and enhance clarity in patients' ability to understand that receiving three bills was not a mistake.

Takeaway: In order to survive the transition to new patient-centered delivery models, laboratories must immediately focus on adding value for end users in terms of convenience and price (both transparency and sensitivity).

PwC's Advice to the Health Care Industry

In order to adapt their businesses and address patients as consumers, PwC suggests that the health care industry:

- Invest in understanding customer preferences;
- Focus on transparency and convenience;
- Allow for different preferred means of communication;
- Allow for multiple access points and seamlessly moving between channels to engage consumers;
- Invest in customer service training for all patient-facing staff; and
- Be committed to enhancing the customer experience.

Source: PwC's 2012 Experience Radar survey

Alliance to Standardize Biomarker Discovery, Validation Process

The success rate in identifying and incorporating clinically meaningful biomarkers into practice is "dismal," says the newly formed National Biomarker Development Alliance (NBDA). The alliance was announced in January with the goal of establishing an agreed upon comprehensive, evidence-based biomarker development process. These standards are urgently needed, the group says, to identify the high-quality biomarkers required to support personalized medicine.

The group, established with assistance from the Research Collaboratory of Arizona State University, will be "disease agnostic" and will focus on developing standards including best practices, guidelines, and standard operating procedures; a national biomarker biorepository; a network to reproduce selected biomarker results; and a common biomarker database. The input of stakeholders nationally representing industry, academia, patient groups, and government is being sought.

"Creating the standards and systems for successful biomarker development is complex but achievable through a new generation of networks of stakeholders that integrate knowledge to solve critical problems of this scale," said Anna Barker, director and co-founder of the NBDA. "The NBDA was developed not just to relegate the flawed and fragmented approaches to biomarker development processes to history but also to serve as a working example of what purposeful convergence of scientific knowledge and multisector collaboration can accomplish."

Despite a "tsunami of biomarker discovery" seen through the publication of more than 150,000 published papers, the translation of biomarker discovery through development and validation has been severely lacking, organizers say. Fewer than 1.5 protein markers are approved each year by the U.S. Food and Drug Administration and fewer than 100 biomarkers are used in routine clinical practice today. The founders say the standardization they seek will economically boost the diagnostics industry, which has been stymied by an undervaluation of biomarkers in investment and reimbursement, in part because of the "explosion of genomics-based assays and other nonregulated laboratory-developed tests" that have not necessarily undergone technically "robust" processes or independent reproduction.

Dearth of Validated Markers Seen in Multiple Sclerosis

"Validation and clinical application of biomarkers is still an unmet need in multiple sclerosis (MS)," write Manuel Comabella, M.D., and Xavier Montalban, M.D., both from Hospital Universitari Vall d´Hebron in Spain, in a review published in January in *Lancet Neurology*. The authors argue that given the high degree of heterogeneity in clinical presentation of MS, reliable biomarkers would be particularly useful in better diagnosing and predicting the disease progression. Among the desired properties of molecular biomarkers are diagnostic markers with strong performance characteristics, disease activity biomarkers that are process-specific (neurodegeneration or repair), and treatment-response biomarkers.

The authors cite publication of more than 63 exploratory biomarkers but note that there are only five validated biomarkers with a strong evidence base (GWAS genes, human neurofilament heavy chain (NFH), human neurofilament light chain (NEFL), 25-hydroxyvitamin D, and CD56bright natural killer cells) and an additional five clinically useful biomarkers with strong evidence (IgG OB, IgG index, anti-aquaporin 4 antibody (Anti-AQP4), antibodies against JC virus, and anti-varicella zoster virus antibodies).

NBDA says setting up demonstration projects is already under way for the development of standards for four classes of biomarkers, including genomics, proteomics, imaging, and complex biomarkers such as biosignatures. Additionally the group is assembling a database of all guidelines, standard operation procedures, and standards for the collection, stewardship, and management of biospecimens. These efforts will culminate in a consensus conference.

Takeaway: Standards that address the entire process, from biomarker identification through validation, may improve the utilization of new biomarkers in clinical practice, ultimately benefiting the diagnostics industry. 

AMP Open to Expanded Regulation of LDTs Under CLIA Umbrella

The Clinical Laboratory Improvement Amendments (CLIA) program remains the appropriate source for oversight for the vast majority of diagnostic laboratory-developed tests (LDTs), but the Association for Molecular Pathology (AMP) is open to some additional oversight under the CLIA umbrella, according to a position statement published in the January issue of the *Journal of Molecular Diagnostics*.

CLIA oversight, the organization says, preserves flexibility and innovation that might be lost if the U.S. Food and Drug Administration regulated LDTs as traditional medical devices and CLIA also appropriately recognizes the professional services component that AMP says provides critical value to LDTs.

In recognition of the continuous supervision that trained professionals have over the development, validation, and interpretation of complex LDTs, AMP proposes the term laboratory-developed procedure (LDP) to distinguish LDTs from traditional medical devices. They define an LDP as a "professional service that encompasses and integrates the design, development, validation, verification, and quality systems used in laboratory testing, and interpretative reporting in the context of clinical care."

"Molecular testing continues to rapidly increase in complexity, generating ever-increasing amounts of potentially useful data. In turn, this enhances the complexity and value of the interpretive component," writes the AMP's Professional Relations Committee, which authored the paper. "This professional service yields the final information that can be applied by direct caregivers to establish a patient's diagnosis, estimate his/her prognosis, and identify optimal, appropriate, and/or potential treatment options, and more. . . . LDTs require a regulatory pathway that acknowledges these differences from medical devices and preserves the role of the laboratory professional."

As such, AMP reaffirmed "that the CLIA program, in combination with laboratory accreditation programs and professional certification, provides a rigorous and flexible framework for ensuring high quality laboratory testing in the United States," said Elaine Lyon, Ph.D., AMP president, in a statement.

"The current regulatory oversight system enables pathologists and other laboratory professionals to rapidly incorporate new findings into practice, and to modify existing laboratory tests and their usage in accordance with advances in clinical knowledge. This has allowed timely and appropriate introduction of innovative testing into practice, and it has also helped foster patient access to the most up-to-date treatment options."

However, AMP recognizes that there are three areas where expanded regulation under the CLIA umbrella may be appropriate. These include:

- Verification of LDP's clinical validity, such that a clinical consultant reviews the appropriateness of testing ordered and interpretation of test results.
- Increased transparency by making public the CLIA registry of laboratories and their test offerings, including making public information about adverse events and other significant problems that have occurred within a laboratory.
- Requring preintroduction review by a third-party reviewer for exceptionally high-risk LDPs, including those for which methods or determinants of results (black box algorithms or proprietary software) lack transparency, or assays for which a skilled laboratory professional cannot independently interpret or assess the validation of the test or its results.

Takeaway: The CLIA umbrella remains the preferred means of enhancing regulation of LDTs, says AMP, which also believes that the professional service component LDTs needs to be more formally recognized as a differentiator between LDTs and traditional medical devices.

Emerging Biopsy Tools Could Change Pathological Analysis

Recognizing the genetic heterogeneity of tumors, researchers are developing new biopsy tools that aim to expand the spatial diversity of sample collection, while simultaneously lessening the invasiveness of the biopsy procedure.

These new techniques, if adopted into surgical practice, have the potential to alter laboratory workflow and pathological analysis not only in terms of the quantity of samples retrieved and sent for analysis but also in terms of the progressively more complex nature of interpreting the increasingly sensitive molecular findings in a clinically applicable manner.

Keri Donaldson, M.D., medical director of molecular diagnostics at Penn State Milton S. Hershey Medical Center (Hershey, Pa.) explains to *DTET* that these technologies are designed to decrease sample selection error, increase the area of an organ surveyed, and increase the sensitivity of the biopsy procedure, but may pose a challenge for clinicians to apply the increasingly complex, mutifocal data to influence treatment decisions.

Among the emerging technologies that rely upon an increased number of microsamples are microgrippers developed by researchers at Johns Hopkins University. The microgrippers are submillimeter, untethered tools that retrieve tissue samples, initially from the gastrointestinal tract. The researchers say that they represent a statistically more efficient means to screen large-area organs' tissue, with samples that are suitable for either conventional cytologic analysis or genetic analysis.

"Historically speaking, scientists are more optimistic than warranted, but there is clearly room for cutting-edge engineering in medicine," says Florin Selaru, an assistant professor of gastroenterology and hepatology at Johns Hopkins School of Medicine. "There is a move towards miniaturization of tools that are minimally invasive but with a higher sensitivity of diagnosis. These techniques can redefine

disease as we know it by finding more variety in diseases that we currently bulk together and oversimplify."

Sealru says the microgrippers could represent a clinical improvement in colonoscopies, which typically utilize a much larger forceps to remove 30 to 40 pieces of tissue. But despite the physician's best intentions, the limited number of specimens may miss diseased or precancerous lesions.

"What's the likelihood of finding the needle in the haystack?" said Selaru. "Based on a small sample, you can't always draw accurate inferences. We need to be able to do a larger statistical sampling of the tissue. . . . We could deploy hundreds or even thousands of these grippers to get more samples and a better idea of what kind of or whether a disease is present."

In addition to colonoscopies, particularly in ulcerative colitis or other higher-risk patients, the microgrippers may have applications in esophageal cancers and potentially outside of oncology in other disorders where diagnosis is based on spotty lesions that are difficult to see endoscopically, Selaru says.

The researchers are working on improving the delivery of the microgrippers, but prior to a biopsy, the grippers are kept cold, so that the fingers remain in this extended position. Within five minutes of insertion, body heat leads to a softening of the polymer coating resulting in the inward curling of fingers, which then grasp some tissue. A magnetic tool is then inserted to retrieve them. Future iterations may include a color-coding of the grippers to improve location-based identification of samples.

The higher volume of samples, Donaldson says, does not concern him, but he would be concerned about the potential increase in cost for analysis of additional samples and the translation of this additional molecular information (i.e., an increase in the percentage of subclones detected) into clinically meaningful data that clinicians can apply to treatment decisions. Down the road, this increased sensitivity to detect molecular alterations could transform diagnostics from a binary—positive or negative—molecular outcome (is it EGFR-positive or -negative?) to a percent expression score, but he cautions translation of these new reporting methods into practice is likely years off.

Takeaway: New biopsy technologies aimed at increasing the diversity of sample selection will alter laboratory workflow and pathological analysis, potentially increasingly the complexity of interpreting molecular findings. G2

Other Emerging Biopsy Technologies

Other emerging biopsy tools focus on improving surgical margins and noninvasive sampling, both of which are biopsy trends that could impact pathological practice, experts say.

Blaze Bioscience (Seattle)uses tumor paint to improve real-time intraoperative visualization of cancer cells. The paint uses a targeting peptide, which binds to the cancer cells, and a fluorescent dye, which emits light in the near-infrared range. The company is initiating its first phase 1 clinical study of the tumor paint product candidate, BLZ-100, at two sites in Australia, melanoma to evaluate the safety, tolerability, and pharmacokinetics of BLZ-100 after injection during surgery. Blaze closed a second round of financing of $9 million, primarily from existing angel funders, to finance the trials. By the end of 2014, the company anticipates initiating a U.S. clinical program for additional solid tumor types.

DermTech (San Diego) analyzes noninvasively collected samples of suspected melanoma (on specialized tape) for specific RNA signatures on a high-throughput quantitative polymerase chain reaction platform, rather than relying on histopathological analysis of surgically removed skin biopsies. The company initiated commercial validation testing of its proprietary pigmented lesion assay in its CLIA-certified laboratory at the end of September 2013. Funds raised from a $5.6 million series B round (closed in August 2013) are financing these efforts.

Lowering WBC Threshold Cuts Rate of Negative Appendectomies in Kids . . . Lowering the threshold of white blood cells (WBC) to the range of 8,000 per μL to 9,000 per μL as a diagnostic criterion for appendicitis can reduce the rates of negative appendectomies (NA) in children to less than 1 percent, according to a study published in the January issue of *Pediatrics*.

While maximum sensitivity has always been emphasized in diagnosis of appendicitis, given the significant negative consequences associated with a missed case of true appendicitis, the national rate of NA remains over 3 percent in the United States. Given the commonness of appendicitis, this NA rate indicates a large number of unnecessary surgeries, which do carry some risks to children.

In an effort to further decrease the false-positive rate associated with appendectomies, researchers retrospectively reviewed all appendectomies performed for suspected appendicitis at a tertiary children's hospital over a 42-month period with regard to preoperative clinical, laboratory, and radiographic data.

Over the study period, 847 appendectomies were performed with 2.6 percent (n=22) having a pathologically normal appendix, or NA. WBC count and neutrophil count were found to be normal in more than three-quarters of the NAs (89 percent and 79 percent, respectively). Applying WBC cutoffs of 9,000 per μL and 8,000 per μL achieved sensitivities of 92 percent and 95 percent, respectively, and reduced the NA rates by 77 percent and 36 percent, respectively.

These anticipated sensitivities and specificities were confirmed looking at 204 cases in the subsequent 12 months. During this period there were two NAs (0.98 percent). In these patients, WBC counts on admission were 6,400 per μL and 8,200 per μL, yielding a false-positive rate of 0 percent using the 9,000 per μL cutoff and 0.5 percent for the 8,000 per μL cutoff. There were 18 patients over the same period with true appendectomies with WBC counts less than 9,000 per μL, with six of these patients having WBC counts less than 8,000 per μL. For WBC cutoffs of 9,000 per μL and 8,000 per μL, the observed sensitivities were 91 percent and 97 percent, respectively, which was not statistically different from the expected values.

"Using the WBC count as a continuous variable, rather than as a true/false measure of leukocytosis, may help us reduce our NA below 1 percent without significantly affecting the sensitivity of our diagnosis," conclude the authors, led by Maria Bates, M.D., from the Alpert Medical School of Brown University (Providence, R.I.). "WBC count cannot reasonably be used as the sole determinant of acute appendicitis at the exclusion of all others. . . . However, a WBC count <8,000 to 9,000 per μL in a child who has had symptoms for <24 hours merits a period of observation, provided there are no signs of advanced disease."

Company References

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