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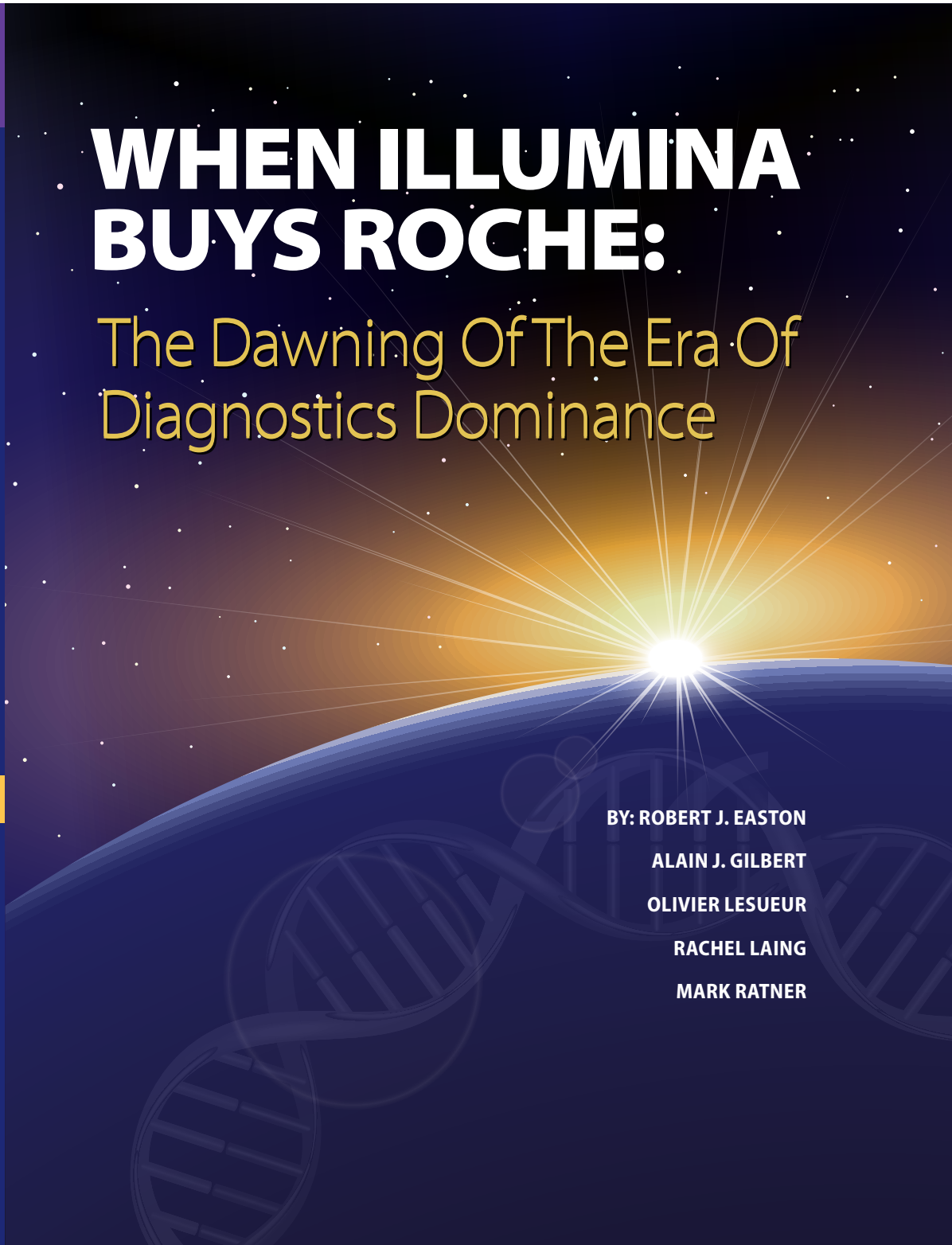

WHEN ILLUMINA BUYS ROCHE:

The Dawning Of The Era Of Diagnostics Dominance

BY: ROBERT J. EASTON
ALAIN J. GILBERT
OLIVIER LESUEUR
RACHEL LAING
MARK RATNER

WHEN ILLUMINA BUYS ROCHE:

The Dawning Of The Era Of Diagnostics Dominance

A great opportunity is at hand to turn data acquisition and analysis into medical knowledge. But few if any pharma or diagnostics companies appear poised to take advantage.

BY ROBERT J. EASTON, ALAIN J. GILBERT, OLIVIER LESUEUR, RACHEL LAING, AND MARK RATNER

- With current technology and resources, a well-funded IVD company can create and pursue a strategy of information gathering and informatics application to create medical knowledge, enabling it to assume the risk and manage certain segments of patients.
- Such a champion would establish dominion over and earn higher valuation that less-aggressive players who only supply compartmentalized drug and device solutions.
- We see the first step in the process as the emergence of new specialty therapy companies coming from an IVD legacy, most likely focused in cancer, infection, or critical care.
- Roche's acquisition of pathology specialist Ventana Medical Systems and its attempted takeover of Illumina may reflect the first glimmer of progressive thinking along these lines.
- But if the entrenched mind-set of current health care players persists, Illumina – or a relative newcomer to health care – could wind up buying Roche, instead of the other way around.

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When **Illumina Inc.** acquired the regulatory consulting firm Myraqa, a specialist in in vitro diagnostics, in July, the press release announcement characterized the deal as one that would bolster Illumina's in-house capabilities for clinical readiness and help prepare for its next growth phase in regulated markets. That's not surprising given the US Food and Drug Administration's approval a year and a half ago of its *MiSeq* next-generation sequencer for clinical use. But the deal could also suggest Illumina is beginning to move along the path toward taking on clinical risk – that is, eventually advising physicians and patients, which would mean facing regulators directly.

Such a move – by Illumina, another life sciences tools firm, or an information specialist from the high-tech universe – is inevitable given the emerging power of diagnostics and traditional health care players' reluctance to themselves take on such risk. Alternatively, we believe that a well-funded diagnostics company could establish this position. Either way, such a champion would establish dominion over and earn higher valuation than less-aggressive players who only supply compartmentalized drug and device solutions.

A BREAK WITH HISTORY

Diagnostics companies have long been dogged by a fundamental issue: they are viewed and valued more along the lines of a commodity business than as firms that deliver a unique product or service – as ubiquitous as electricity, and also as non-differentiated as a utility.

The industry may have always felt like a poor stepchild to drug companies. Its intellectual property protections are much less than for pharmaceuticals, and margins are small. But the bigger reason it hasn't stepped up and demanded to be paid commensurate

with its contribution to health care is that to do so, diagnostics companies would have to take on harder problems – in essence, they would have to take on some of the risk of managing patients. And while loath to attempt this in the past, diagnostics companies are in position to do just that today because they are now advantaged by having access to more data points. In short, if they were to cobble together the right capabilities, diagnostics companies would have the ability to turn information into true medical knowledge.

"Diagnostics became sort of a generic business because the power was in the customer: too many players selling the same thing," says Jack Schuler, former president and COO of **Abbott Laboratories Inc.** and chairman of **Ventana Medical Systems Inc.** until its acquisition by **Roche**. But now, "we are going into a realm where a diagnostics company can ask the question of what value they offer compared with a therapeutic," he says. "I think it's going to be a brand-new ballgame."

The key is that diagnostics can now offer unique information and potentially unique tools to capture that information. "Information is valuable and if you can maneuver yourself so that you are the only one who can provide that information, you then should try to maneuver in such a way that you get fair value for what you are providing," Schuler says.

There are some signs of this happening already, and precedent. As the techniques underlying diagnostic tests have increased in their biological complexity and the knowledge base of their developers about specific disease areas has deepened, the value proposition for diagnostics has become more biotech-like, echoing if not emulating biotech's origins as partners to pharma prior to the emergence of some as competitors to major drug companies. (*See "Is Diagnostics the New Biotech...and Will Pharma Embrace It?"* — IN VIVO, *September 2011*.)

Diagnostics acquisition trends over the last five years – largely by nontraditional buyers including companies with only tangential prior contact with diagnostics and, in some cases, limited reach into health care generally – further evidence this trend. These acquirers have been snapping up molecular diagnostics assets with increasing frequency. (*See "Matchmaking And Integration In The New World Of Diagnostics M&A"* — IN VIVO, *April 2013*.)

The advent of sequencing is often cited as the cornerstone of a looming revolution in diagnostics. Yet what we propose is more than just the logical consequence of the growing use of genomics tools – which are already becoming embedded in cancer treatment. It will be the use of the wider array of data points that will enable a broad change. To gain more power in the health care industry, IVD must move up the value chain, from providing tools that generate information for application and understanding by others to creating understanding from the data it generates, and then to supplying that knowledge to users who will value and act on that knowledge.

It's already happening in cancer, where complex genomic tests, as much as physical examination, may be the first meaningful touch point for physicians' classification of disease – and increasingly the first economically significant interaction with payors: even if lab tests are more expensive, it is a cheaper means for deciding what to do first for a patient than the trial and error of prescribing medication without that information.

And that information is gaining in value as the amount of treatment data available on genomically characterizable subpopulations increases – the kind of clinical decision support providers increasingly have access to, in some cases directly from academic labs that have constructed their own panels of genomic diagnostic markers.

SEEKING DOMINANCE

Examples of niche domination in medicine over the years exist, many from the IVD industry: Abbott's development of hepatitis understanding as captured in its hepatitis test portfolio and Roche's development of CEA as a cancer marker are perhaps the most prominent, along with **PerkinElmer Inc.**'s competitive position in newborn screening and the **Johnson & Johnson** unit **Ortho Diagnostic Systems Inc.**'s in blood bank testing. But in those cases, the dominance was in holding a set of customers away from competitors, not in a company seeking control over the patient, and in so doing gaining control over the access other suppliers of products and services have to that patient.

Diagnostics companies now are working with drug companies on companion diagnostics. As medical knowledge grows and understanding a disease becomes the predicate for treating it, we foresee companies grounded in an IVD heritage de facto becoming specialty pharma companies: in essence, their knowledge of how to use drugs will allow them to seize control over prescribing. They can do this through the leverage of being able to apply a proprietary diagnostics platform – and importantly, the data it generates – to gain a foothold in the drug business. Then they can backward integrate and source molecules.

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For now, however, most diagnostics companies appear to be content with the utility model, largely out of concern for competing with their customers (a fear shared by clinical labs, whose lifeblood is contracts with payors). But were they to take a broader view of the proteomic and genomic information they are amassing with a panoply of markers – instead of the atomistic one-drug, one-marker mentality that still pervades – they could envision building a better model for drug discovery, eventually adding on other information such as ion measurements and blood glucose, and getting to the point of being able to advise a patient. And it is the ability to perform that advisory function that will add tremendous value above what any test provides.

Some will use other people's tools (e.g., **Foundation Medicine Inc.** with its next-generation sequencing-based tumor profiling service), whereas others will use their proprietary platforms (e.g., **Integrated Diagnostics Inc.** and **Biodesix Inc.** with mass spectrometry). Both approaches yield significant information on how to segment patients.

CHANGING THE FACE OF IVD

The Old View – IVD As A Utility: An IVD company supplies a product used by a lab to generate information the lab then provides to a medical practitioner who adds understanding to make a decision about a medical therapy.

The New View – IVD As A Value Add: The IVD company creates a product that generates information to which the IVDCo adds informatics technology to generate knowledge that it then provides to a payor or provider in the form of a recommendation of the medical therapy to be employed.

HOW IT WILL WORK

The past two decades have witnessed a remarkable explosion in the ability to generate medical knowledge, fueled most visibly by advances in diagnostic technology that continue to reduce the cost of generating genomic information at a pace that far outstrips Moore's Law.

Indeed, the notion in diagnostics used to be to say whether or not a patient had a disease. "Now it is changing," says Jean-Luc Belingard, chairman of **bioMérieux SA**. "We have enriched the notion of the yes," he says, by characterizing the disease. And the next step will be to characterize the host response to the disease, then to predict individual reaction to the disease and to monitor the evolution of that disease.

Unlike in the past, "You have important players today who have nothing to do with health care, but with technologies [to enable] this evolution," says Belingard: experts in Big Data, sequencing, and mass spectrometry to name a few. "We are working with all kinds of players who may not have biology as part of their background," he says. "And we compete very efficiently because we have the biology culture."

A top executive at one Big Pharma told Belingard recently that his firm was getting ready to move toward more content in the Big Data space. "I said be careful," Belingard says, "because the Big Data guys have already moved toward health care."

The enormous progress in informatics capabilities and data storage, if less visible than diagnostic tests themselves, is the real point of leverage for creating knowledge from the avalanche of data spewing out of genomic instruments, managed care EMR systems, home glucose devices, ICU monitors, and literally hundreds of other sources and devices. The ability to understand disease processes and mechanisms, the key to finding useful interventions, is growing exponentially.

So the tools exist for unravelling disease processes, and numerous players are quite visibly in or are getting into the business of providing medical knowledge and clinical decision support in pursuit of a huge payout for those who actually solve important disease mysteries. They include managed care organizations, major medical institutions, large pharma organizations and commercial labs, and also diagnostics specialists like **Genomic Health Inc.** and Foundation Medicine.

But among the major IVD companies, those that to date have created the tools that generate most medical information, the only one with a substantial and visible commitment to knowledge generation is Roche, which in 2007 acquired Ventana and 454 Life Sciences (which it ultimately cannibalized), and five years later aggressively pursued Illumina with an unfriendly approach that was successfully staved off. The other usual suspects – like Abbott, the **Beckman Coulter Inc.** division of **Danaher Corp.**, and **Siemens AG**'s **Siemens Healthcare Diagnostics Inc.** – are surprisingly absent from the current scene.

Even Roche has not lived up to its vision with Ventana: it has failed to deliver on the promise of boosting Roche's pipeline, which was a significant factor in the high price Roche paid. The combined company was to be "uniquely positioned to further expand Ventana's business globally and together develop more cost-efficient, differentiated, and targeted medicines," Roche's then-CEO, Franz Humer, commented in announcing the acquisition. (*See "Roche Finally Gets Nod With Sweetened $3.4 Billion Bid For Ventana"* — "The Gray Sheet," *January 28, 2008*.) If Ventana remains solidly profitable, its impact in advancing Roche's long-standing personalized medicine goals has not been felt. (*See "Does Roche Have It Right?"* — IN VIVO, *July 2007*.)

Similarly, **Novartis AG**'s Novartis Molecular Diagnostics was set up as a separate commercial molecular diagnostics division to be both profitable in its own right and also an adjunct to internal R&D. (*See "Novartis Follows Its Own Business Development Model into Molecular Diagnostics "* — IN VIVO, *May 2010*.) But after just a few years, it was folded into the parent's oncology business – an upstream R&D move counter to any direct patient-oriented business.

Abbott, for its part, has shown reinvigorated interest in companion diagnostics, the logical entry point for an integrated risk-assuming patient management strategy. bioMérieux has a powerful franchise in infectious disease diagnostics, with a drug/vaccine legacy, and an ownership/management team that leads for the longer term. Indeed, it could be advantaged in pursuing a patient management strategy focused on infectious disease. Sample prep specialist **Qiagen NV** has KRAS and EGFR tests and has recently moved into the development of autoimmune disease diagnostics.

Then there are newcomers to consider. Illumina has moved closer to the patient with its acquisitions of **Verinata Health Inc.** and **BlueGnome Ltd.** and deeper into knowledge generation through a companion diagnostics deal with **Amgen Inc.** for the latter's *Vectibix* (panitumumab), as well as an assortment of academic collaborations and a recent cardiovascular "omics" collaboration with **Global Genomics Group**.

Google, moving farther outside the traditional health care realm, is also gaining in influence. It has extended its reach – and eventual dominance, perhaps – in genomics and mobile sensors that gather and relay health information. In what could be a sign of potential disruption akin to the *iPhone*'s usurpation of laptop computing, it is expanding into a variety of device applications – the most recent being a collaboration with the Novartis division **Alcon Inc.**, announced this July, to commercialize sensor-embedded soft contact lens technology, a step it acknowledges doing with an eye to potentially transforming disease treatment and management.

As *IN VIVO*'s sister publication, *START-UP*, reported in 2013, backing for companies like oncology software and data analysis start-up **Flatiron Health Inc.**, which is supported by Google Ventures, is the harbinger

that data-driven solutions to health care problems aren't going to be incremental improvements generated from within existing pillars of the industry. (*See "With Google Backing, Flatiron Aims Broadly At Cancer Analytics"* — START-UP, *February 2013*.) (More recently, Google Ventures led Flatiron's $138 million Series B round.)

Perhaps the most interesting strategic move to date has come from Biodesix, a small IVD firm**,** which begin life as a technology start-up developing a better mousetrap for detecting proteins using mass spec. It exploited the technology to discover protein patterns that relate to lung cancer (marketed as *VeriStrat* and coupled with a CLIA lab commercial model). In April 2014, Biodesix formed an alliance with **Aveo Pharmaceuticals Inc.**, mostly funded by Biodesix, to develop a new cancer therapy for which the clinical trial will be guided by VeriStrat testing. (*See sidebar, "Biodesix/Aveo: A Harbinger Of Deals To Come."*) A diagnostics firm pursued a similar strategy with **Eli Lilly & Co.**'s *Xigris* (drotecogin alpha activated), but the controversial sepsis drug was withdrawn from the market nonetheless in 2011. (*See "The Long Goodbye: Lilly Finally Kicks Troubled Sepsis Drug Xigris To The Curb"* — "The Pink Sheet" DAILY, *October 25, 2011*.)

Aggressive IVD innovators like Biodesix will take on ever-larger roles in selecting drugs for clinical trials and in selecting patients for those trials. The most ambitious will eschew the fee-for-service model common to companion diagnostics, invest alongside the drug originator, and share in the success of the drug through royalties and joint venture arrangements, which could include a shared sales/marketing role.

These model IVD companies will learn much about clinical trial design and management, and also the secrets of the drug discovery process, which will have been accelerated by incorporation of their genomic/proteomic tools early in the process. As newly key players in drug discovery and validation, they will begin to invest for their own account in molecule sourcing and drug discovery. Then, as pipelines progress, they will begin to develop pharma sales and marketing capability. IVD sales forces are typically more sophisticated than their drug company counterparts anyway, so the first drug commercialization step will be to expand and redirect the IVD sales force, possibly as the successor step to a joint sales/marketing effort on partnered drugs.

BIODESIX/AVEO: A HARBINGER OF DEALS TO COME

In April 2014, **Aveo Pharmaceuticals Inc.** and **Biodesix Inc.** entered into a worldwide agreement to develop and commercialize Aveo's ficlatuzumab, an antibody that inhibits hepatocyte growth factor, using Biodesix's serum-based companion diagnostic *VeriStrat*, which guides treatment decisions for patients with advanced non-small cell lung cancer (NSCLC).

The deal came about after Aveo's Phase II trial of the drug in first-line NSCLC failed to show statistical significance in the intent-to-treat population. Biodesix decided to use VeriStrat to look back and analyze the trial data to try to ascertain which patients would benefit from ficlatuzumab. Blinded to the actual results, it predicted which ones benefited with remarkable accuracy, showing that a differential treatment benefit existed for the subgroup using the combination of ficlatuzumab plus the tyrosine kinase inhibitor *Tarceva* (erlotinib) over Tarceva alone. The predictive effect was observed in both progression-free survival and overall survival endpoints, and encouraged the companies to conduct a proof-of-concept study of ficlatuzumab in combination with Tarceva in advanced NSCLC patients selected using the VeriStrat test. Biodesix will fund up to $15 million of the cost of the study after which the two will share costs equally. Importantly, they will also share profits and losses equally on eventual drug sales.

WILL PHARMA PLAY – AND PAY?

Collaborations such as Foundation Medicine's role in a Lung Cancer Master Protocol, in which five biopharma companies are testing their experimental compounds in a clinical trial, and Illumina's 2013 arrangement with Global Genomics Group to conduct a prospective multi-center study to characterize novel disease networks and biomarkers for coronary artery disease, are the first toe-in-the-water manifestations of our scheme. In Illumina's case, it is seizing territory in metabolic diseases as multiple firms are doing in cancer and others potentially can do elsewhere (e.g., bioMérieux in infectious diseases and Qiagen's aim in autoimmune diseases).

Big Pharma, on the other hand, is not likely to participate until it shows a willingness to embrace partnerships on drugs beyond a failed compound or for life cycle management. This would mean a shift in how drug companies view portfolio management. And pharma is not likely to get excited over a diagnostics firm's ability to help rescue a drug. Meanwhile, a diagnostics or health IT firm could help manage a patient by using data to tell a payor which drugs to use on which patients – and presumably, many of those drugs will be generic. Such a data aggregator would in essence be taking on risk and advising a physician directly.

The second phase of IVD evolution will be far more challenging to pharma, when the most accomplished companies begin to assemble and integrate much broader data sets, thereby gaining knowledge sufficient to actually manage patients and dictate therapy, including drug selection.

As the therapeutic landscape grows ever more complex, and unit costs continue to mount, payors will look farther and wider for solutions. Progressive product companies will respond with risk-sharing approaches that exploit their own technology and their superior knowledge about patients.

Ideally, the patient manager has all available patient information at his disposal. Such is typically the domain of the physician, who considers and integrates all that can be known about the patient to make medical decisions: appearance and palpation; history; genetics and genomics; non-genetic lab tests; images; and vital signs – blood pressure, temperature, respiration, etc.

But no individual physician has or will have access to all of this information on thousands of patients, combined with the informatics to tease out from trillions of data points the optimal personalized medical approach for

the patient in front of him. Much of the relevant information is not IVD-generated, but much is, and the multi-discipline IVD major is advantaged over any other technology player to maximize patient data acquisition.

We foresee major IVD companies moving into assumed-risk patient management, exploiting their informatics and data base advantages to manage the risk and extract premium returns on their technologies. The first entrants will likely be IVD-oriented players that have previously developed risk management tools in oncology or critical care, perhaps through acquisition of one or more specialists.

Diagnostics companies might also consider getting directly into pharmaceutical development. Partnerships on companion diagnostics are already giving them a window into drug discovery. Using their tools earlier for their own accounts, to source and test existing drug-like molecules, would be a more efficient mode for drug development without some of the upstream costs of discovery and target validation. For some less innovative drugs or drug classes – older drugs, fast followers, and generics in particular – it may even be possible to amass sufficient information via the literature, without running new clinical trials.

IVD DOMINATES RX: THE DRUG AS COMMODITY

The value creation we foresee will happen for several reasons: of necessity because of the drive to streamline and make health care delivery more efficient; because the time is now ripe; and because there already are forward-thinking participants who will make it happen.

In some ways, the new paradigm is akin to the knowledge base-oriented strategy some genomics firms adopted a decade ago, such as the 2004 deal between Gene Logic and Millennium Pharmaceuticals Ltd. (now **Millennium: The Takeda Oncology Co.** division of **Takeda Pharmaceutical Co. Ltd.**) under which Gene Logic acquired certain assets and technologies that it believed would enable it to set up a drug development service that identifies new therapeutic indications for already marketed drugs or failed drug candidates.

Gene Logic did not have anywhere near the breadth of technology to do what it had proposed, and its offer was pure service: part of the deal was to allow Millennium to buy back a drug it rescued in this manner. In 2014, however, there is an abundance of diagnostic information gathered in clinical practice that can be tapped alongside genomics tools. That's where diagnostics can seize the initiative in a new way. (Admittedly, issues of informed consent under HIPAA might have to be addressed up front.)

Of course, pharma has not and may not ever buy into the rationale, falling back on the argument that no matter how much insight a company can offer it, all the genomic and proteomic data in the world have not dropped the cost of developing drugs nearly enough for pharma to be giving up the economics up front. And it may well watch and wait, then pounce, herd-like, as it did with acquisitions of pharmacy benefits managers.

When the IVD-origin knowledge integrator amasses enough data and understanding to guide therapy decisions in large categories, particularly drug choices, it will become more valuable than any of the drug suppliers.

In this new framework, with so many drugs of various classes available, drugs become the commodities, in a sense, and take on a secondary importance to the diagnostic regime. Thus, the risk assumer who controls the patient will also control those who sell products and services for the patient. In a sense, this power of diagnostics in harnessing and wielding information would be the health care equivalent of the Yelp-like crowdsourcing to which restaurants (in this analogy, the drug companies) must now pay attention, as Yelp takes on more of the relationship with the customer.

The risk assumer might also backward integrate to control its costs by buying suppliers of high-ticket elements. If its legacy is products, it will be comfortable buying important product suppliers, or may dominate them to such an extent that it captures most of the value added. Remember in the 1990s when McKesson dominated US drug distribution? It considered backward integration into generic drugs via acquisition, or even via green field start-up before deciding instead to use its economic leverage to extract much better prices from its generics suppliers, rather than invest the capital to buy them.

When the IVD-origin knowledge integrator amasses enough data and understanding to guide therapy decisions in large categories, particularly drug choices, it will become more valuable than any of the drug suppliers. It might also be able to control the drug bill, to the detriment of drug developers, by finding algorithms that generate equal-to-innovative-drug outcomes using generics for most of the patients, thereby limiting the margins of drug suppliers and the upsides for new drug discovery/development.

At that point the IVD industry will truly influence a wide array of medical decisions, and the industry leader will be far more valuable than any "pure" drug company. Illumina will buy Roche, unless it finds **Pfizer Inc.** even more attractive.

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Robert J. Easton (reaston@bionest.com) *and Alain J. Gilbert* (alain@bionest.com) *are co-chairmen of Bionest Partners, based in New York and Paris, respectively; Olivier Lesueur* (olesueur@bionest.com) *is a managing director with Bionest in New York and Paris and Rachel Laing* (rlaing@bionest.com) *is a senior consultant with Bionest in New York. Mark Ratner* (mlratner@verizon.net) *is a freelance writer.*

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