

“The Advent of Personalized Medicine”

by Peter Miller and Keith Batchelder, MD with Margaret Johns

Reader,

This is the fifteenth edition of BlueLake Partners' Newsletter – **The Perspective from BlueLake**. The Newsletter is published periodically and focuses on and analyzes trends in the growth-oriented industries. And few industries have higher growth rates than healthcare.

We hope you find it informative and thought provoking, and we welcome any suggestions or thoughts you might have on the content. Please feel free to pass it along to others that you think might find it interesting.

Sincerely,

BlueLake Partners, LLC

This is a paper about Personalized Medicine (“PM”) and why PM is of interest to a variety of people and organizations for growth, profits, and liquidity.

Why should you care about PM? Because if you don't pay attention, you're going to miss the Next Big Thing.

Why now?

Why now? Because there's a disruptive change in the healthcare market that's well underway. There's a lot of press about Personalized Medicine, and all the noise makes it very confusing. Each story seems to focus on a single therapy or diagnostic.

What's happening is quite different. Personalized Medicine isn't just one invention or one new thing, like the transistor or the light bulb or the CD or microwave popcorn. PM is here because of a concatenation of events. These events include:

- Scientific discoveries are happening really fast, faster than the traditional health care system can keep up with
- Smart people are realizing that diagnostics will drive everything. The era of the expensive \$1 billion blockbuster drug prescribed for everyone is over. Diagnostics will target which expensive drugs will be given to which patients – the patients for whom they'll work.
- Because therapies (drugs) will be better targeted, health care costs will go down. Here's where real savings will come from, not from delegating taking your blood pressure to a physician's assistant.

- The internet is an extraordinary source of information about therapies, diagnostics, and all other aspects of health; advocacy groups and blogs flourish.
- There are 70 million baby boomers who are fretting about aging. They have disposable income, they're internet-literate, they worry about their health, and they vote¹.



What is Personalized Medicine?

What do these factors mean when you think about Personalized Medicine? And what is Personalized Medicine?

There are a variety of definitions of PM. One popular definition is something like “the right dose of the right medication for the right patient at the right time.” Another definition is as simple as “genomically informed health care.”

At Genomic Healthcare Strategies we believe that Personalized Medicine is a bunch of things all coming together now and working together in new ways to cause disruptive changes in health care. We suggest that Personalized Medicine includes all of the following:

- Genomically informed medicine – certainly this definition is a big part of Personalized Medicine – analyzing an individual’s genome to specify the right treatment for a disease
- Biomarker-guided dosing – determining the rate at which someone will metabolize a medicine in order to prescribe the right dosage, both for effectiveness and also to avoid bad side effects and bad outcomes. Drug metabolism has both a pharmacokinetic and pharmacodynamic component. Pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug. PD and PK can be studied by biomarkers beyond just genomic ones. Adverse drug reactions, which can be very expensive to deal with and more importantly, are sometimes fatal, are often related to slower drug metabolism. Poor efficacy may result from overly fast drug metabolism.
- Personalized Health – not treating medical problems, but anticipating them. Providing pre-symptomatic indications, genomically or using other biomarkers, that a predilection toward a disease exists in an individual.
- Active consumers – controlling their own health care, buying their own tests directly, making life style choices based on those tests, taking test results to their physicians and demanding appropriate responses.
- Entry of new players into the health care space – non-traditional firms will enter the PM space with new offerings, especially at the wellness end of the spectrum.
- Individual control of computerized medical records – individuals will increasingly control their own medical records, determining who may have access to what information under what conditions.

¹ See Batchelder and Miller, *A Change in the Market – Investing in Diagnostics*, Nature Biotechnology, August 2006, pp 992

- New legislation and regulation – changing regulatory requirements, changing reimbursement speed and levels based on clinical utility, forbidding genetic discrimination, guarding patient privacy.
- Decentralization of diagnosis and treatment – in-home diagnostic equipment, connected to your primary care physician via the internet, with capacity both to take standard readings – pulse, temperature, blood pressure – and accept multiple test kits (purchased at your local pharmacy or on line). You don't believe this? It's already happening

These are some of the things which Personalized Medicine will be. There are also some things that Personalized Medicine won't be, at least in the immediate future:

- PM won't be what the medical traditionalists think of and assume/hope they'll control.
- PM will work in oncology, but in an odd way. The sensitivity and specificity (fraction of false positives and false negatives) of diagnostics isn't good enough and cancer is a life-threatening disease. No physician will tell a patient who is facing death that a diagnostic test indicates there's an 80% chance that a new medication won't work, after all other options have been tried, and that therefore she won't prescribe it. If your only chance is a 20% chance, you'll still want it. So the order of which therapies you receive may be assisted by PM, but no treatments will be denied to those who push for them.
- PM isn't about reimbursement – consumers will pay and legislation, government agencies, and insurance companies will follow.

Our belief is that PM is too important and too big to fit within the constraints of the existing doctor-, hospital-, and insurance-focused health care system.

Diagnostics will drive everything

Diagnostics will be a key enabler of Personalized Medicine.

For years, *in vitro* diagnostics (those done on a sample, as opposed to *in vivo* tests, which look at your body from the outside, usually using expensive pieces of capital equipment like CT scan machines) have gotten very low cost reimbursement.

According to S.G. Cowen & Co., *in vitro* diagnostics (IVD) was a \$26 billion industry in 2004. Within this industry, the molecular diagnostics, or PM market segment is expected to show the most robust growth, increasing from \$1.8 billion in 2004 to \$3.6 billion in 2009, representing an annual growth rate of 15%. We believe that this is a low estimate; it focuses on traditional markets and doesn't include the broad non-traditional growth we foresee.

IVD have traditionally told you things like: no, there's no sugar in your urine; yes, you have strep causing your sore throat. They've told you some things, in an aggregate way, about the state of your disease. Because of their history of being



manual tests and not being “economically validated” as saving healthcare dollars, their reimbursement has been mostly for the time and effort a lab technician spends to perform the test. If you have an MD reading an x-ray or looking at a slide, the professional component of the reimbursement was higher, but still not substantial. This situation is changing.



The new diagnostics will answer questions which are much more important:

- Before you have symptoms, do you have a predilection toward a particular disease?
- Do you carry a genetic marker which says that you're at high risk of developing a particular disease?
- Which therapy will work with your particular disease; which ones won't?
- What dosage is best for you, to treat the disease without bad outcomes?

Diagnostics will be important. They are essential to companies entering the PM space. Think about it. If you're a new entrant (or an existing company pursuing a new direction) you want a market with these key characteristics:

- Little regulation compared to mainline health care
- Some sort of razor and razor blade model to cause a customer to buy from you for years
- Some differentiator which builds brand loyalty

Diagnostic tests will create the most revenue when they're used to test for and monitor chronic conditions. Currently in test is RFID/blood glucose monitor implants, where the patient wears the readout.

However, what's the most common and least regulated chronic condition? Wellness. That is, if you're healthy, and you want to stay healthy, you'll pay for lots of tests and use a lot of pills, powders, juices, salves, creams, supplements, and foods if tests tell you (a) that you need to take these things, and that (b) they're succeeding in fending off the bad things. And you'll buy the all the preventatives from the same folks who sell you the diagnostic.

New Personalized Medicine Business Models for Diagnostics Companies

Thanks to PM, there are new business models for diagnostics (Dx) companies. We'll give you an overview and then go into some examples.

The summary is that (some) diagnostic companies are going to be worth considerably more than traditional diagnostic companies, because they'll present themselves as PM companies and deliver on that promise. They'll be sought after as partners, both by pharma and biotech companies and by new entrants into the health care market. These companies will attract significantly increased investment and m/a activity.

Some Dx companies will pursue a PM strategy from the outset. Others exist today which have disappointed their investors but which have the potential, if properly focused, to change their image and approach to PM, rescue themselves from obscurity, and become financial successes.

How does all this work? Let's get into some detail and give some examples.

Example 1 – High Clinical Utility Plus Branding

PM diagnostics companies which can show clinical utility will be in demand. For example, look at Genomic Health (NASD: GHDX). Genomic Health's annual revenues were \$5.2 million in 2005, and are currently at a \$32 million run rate. The Company was founded in 2000, with funding from Kleiner Perkins, Caufield & Byers, Versant Ventures, Texas Pacific Group, Panorama Capital (J.P. Morgan Partners) and Credit Suisse First Boston. The Company went public in September, 2005 with a market capitalization of \$292 million, which is now about \$350 million.

Genomic Health has a breast cancer predictive diagnostic: "Oncotype DX is a clinically validated laboratory test, ordered by physicians, that predicts the likelihood of breast cancer recurrence in women with newly diagnosed, early stage invasive breast cancer. Oncotype DX also assesses the benefit from certain types of chemotherapy." Moreover, Genomic Health has given this test a name; built a brand around its test.

Genomic Health has realized how to take advantage of their differentiation. If they had been a traditional diagnostic company developing a traditional diagnostic, they would have spent their time in the lab, working on the test and attempting to get it into use by the large labs (LabCorp, Quest, etc.) No one would know the name of the test or who produced it.

Instead Genomic Health has created a product which is known worldwide. The company has a first-class professional web site. Their Oncotype DX brand is prominent – the URL www.genomichealth.com/oncotype/ and the URL www.oncotypeDX.com both lead to the same page. Moreover, they've fought hard to obtain insurance reimbursement for their test at a level close to the \$3500 price they charge individuals.

Example 2 – Razor and Razor Blade

Interleukin Genetics (AMEX: ILI) was started as Medical Science Systems to commercialize a genetic test to show predilection toward inflammatory gum disease. ILI is 57 % owned by Alticor subsidiary Pyxis Innovation. The Company went public in 1997 at \$9 per share, at a valuation of \$64 million, but encountered difficulty in the dental market. Traditional practice is hard to change unless profound clinical utility is demonstrated. Since dentists encourage patients to pursue practices (flossing, brushing) which avoid gum disease, and since dentists check for gum disease at every visit, the utility of the test was in question.

In October of 2002, ILI's share price was \$.52. As of this writing, it's around \$6.66 per share. Although revenues in the first quarter of 2006 were only \$232K, and \$1.6 million (TTM) their market capitalization is \$161 million. What has



caused the change in valuation? There were two key steps – one was to change clinical focus; the other was to form a crucial marketing alliance.

First, the company's focus was changed from gum disease to using their intellectual property to look at an individual's predilection to inflammatory cardiovascular disease with the Gensona Heart Health Genetic Test. This area has much more to recommend it in terms of clinical utility. An individual who knows that he's at risk can pursue life style changes which can help to reduce the risk. Unfortunately, prevention is not reimbursed by insurance and managed care companies – because prevention usually takes longer than two years to show a positive ROI; and by then over 60% of patients have moved to competing health plans and so individuals must pay for both the test and preventive measures out of their own pockets.

Then Interleukin faced the problem of reaching the market. A small diagnostics company can't build a large national sales force to try to make a bunch of small one-time sales to individuals. The second key step, in 2003, after redirecting the company's scientific focus was to form an alliance with a multi-billion private firm called Alticor, which now owns 57 percent of ILI and is also the parent of Amway. Amway is a multi-billion dollar, multi-level marketing company with a strong channel direct to the consumer. For Alticor, Interleukin's test is the "razor" and their own line of anti-oxidants is the "razor blade."

A press release at the time said: "Alticor has made a commitment, in equity, research funding and credit facilities, of approximately \$16,000,000 (and if the noted milestone is achieved, \$18,000,000) to Interleukin's future," commented Philip Reilly. "We are delighted to have entered into this broad alliance with Alticor," added Philip Reilly, the CEO of Interleukin Genetics. "Our research in genomics has opened up new possibilities for using genetic information to choose products that promote wellness. With Alticor, we believe that we will have the ability to develop and market such products through a proven distribution channel."

In September, ILI announced that it has acquired the assets and business of Alan James Group, LLC, a privately held, healthcare-focused consumer products company, in a cash and stock transaction. In connection with the transaction, Alticor, Inc. which owns a majority interest in Interleukin, will provide \$30 million in financing in the form of a \$15.6 million private placement with Alticor, Inc., and a new \$14.4 million credit facility. The combination is expected to allow the company to accelerate its development of a predictive and preventive product portfolio, expand its presence in the personalized health and wellness marketplace, and broaden its revenue base to include consumer, commercial, and professional healthcare channels.

Example 3 – Companion Diagnostic



Pharma and biotech companies, which produce therapeutic drugs, increasingly need companion diagnostics to target the use of the therapy. Genentech (NASDAQ: GENE) developed a breast cancer treatment called Herceptin. The drug can be effective in treating a particular type of breast cancer, that which is characterized by the overexpression of a protein, Her2/neu. Herceptin also has the potential for toxicity in some patients: “HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure. Left ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN.”

Thus Herceptin treatment makes sense for the 20-25% of women who have the kind of breast cancer in which the Her2 protein is overexpressed, but not for the other 75-80% of breast cancers in which this is not the case.

A Danish firm, DAKO A/S, developed the first test to be approved by the FDA. DAKO's HercepTest® is an immunohistochemistry (IHC) test which measures the level of expression of the HER2 protein. DAKO was founded in 1966 and in 2005 had sales of \$278m and a profit of \$7.9m. DAKO is privately held, though it discloses financial information. Dako's shareholders include the Harboe family, which controls 61% of the shares, and Novo Nordisk A/S, which owns 27% of the shares. The remaining 12% of the shares are mainly owned by employees and the previous owners of Cytomation Inc. merged with Dako in 2002.

The Herceptin web site says: “Because of Herceptin's significant clinical benefits in extending survival for HER2-positive metastatic breast cancer patients, it is important to accurately determine the HER2 status of all patients with metastatic breast cancer.”

Note well – what this says is that 100% of women with breast cancer should be tested for Her2 overexpression, but only 20-25% will potentially be given Herceptin. So 4-5 times as many tests will be sold as are courses of the companion therapeutic. Moreover, since the test involves interpretation by a pathologist, a significant amount of retesting is done for borderline cases.

The point here is that we're looking at a terrible disease for which a diagnostic will be much more prevalently used than the treatment with which it is associated.

DAKO's test has been promoted by Genentech's marketing. For Genentech, Herceptin sales have grown from \$30.5 million in 1998, its year of introduction, to \$764 million in 2005.

In September, Dako moved its focus further away from traditional diagnostics by selling its microbiology business to Oxoid (a Fisher Scientific company) for an undisclosed amount.

Example 4 - Instruments and Cosmeceuticals



A recent announcement by Nu Skin (NYSE: NUS) reads: “The Nu Skin® ProDerm™ Skin Analyzer takes a measurable approach to skin care, revealing what your mirror and best friend can't. Developed by combining the worlds of pattern recognition science, optical imaging, and dermatology, this portable tool provides a scientific assessment of skin and skin care.”

And then, of course, Nu Skin adds: “ProDerm™ Certified Products—guaranteed to improve your appearance and your score—may then be recommended.”

Nu Skin, based in Provo, UT, is a billion dollar revenue, \$1.22 billion market capitalization company which is 54% controlled by the Raney family.

Also in the field is a UK firm, Astron Clinica, a small venture backed company. They have an instrument in their Beau Visage line, which is described as follows: “Beau Visage includes Beauty Timeline which is generated by images of blood, melanin and sun damage taken before every treatment session. These images are automatically compared as time goes on, and can show a percentage change in the skin before the customer can see change with the naked eye.”

And: “Beau Visage also includes Dr Leslie Baumann's new Skin Type Solution, which helps the client choose the right products for their skin type. Dr Baumann is one of the leading dermatologists in the USA, based at the University of Miami.”

Here are several examples of firms providing both the assessment, via optical instruments, and the solution to the problems found. They're using science to keep a firm grip on the customer.

Example 5 – Not Yet Announced

GHS is aware of additional initiatives, which cannot be fully disclosed at this time because of confidentiality agreements.

In broad outline, these initiatives involve:

- Non-pharma, non-biotech companies in fields related to mainstream health care looking at the use of rich data bases and creation of diagnostic intellectual property to guide cost savings and enter markets with higher margins than their core businesses
- Companies with significantly superior imaging technology will be able to produce measurements not possible today; they will create new molecular diagnostics which will provide new targeting information for therapeutics
- Large providers of nutraceuticals, cosmeceuticals, functional foods, and supplements will expand their reach to the consumer and look for diagnostics to serve as the “razor” as mentioned above. They will use the coupling of diagnostics and prevention at the wellness end of the spectrum to build customer loyalty and unit sales.

Economic implications



There are some opportunities in the PM diagnostics space for those who can reach out and grasp them.

Opportunity #1 – for the investor in the stock market

Take a good look at Dx IPOs and at companies which have a sound strategy around combining metabolic or genomic diagnostics with good marketing and branding. Look for these companies to form strong alliances with pharma and biotech, with new players yet to be identified, and with direct-to-consumer firms. The value of these companies will increase as regulations and reimbursement rules change for the better.

Opportunity #2 – for the major investor in pre-public Dx companies

With help from those who have the vision and the connections in the PM field, reorient your companies toward a PM focus. Change your boards of directors and your scientific advisory boards. Develop a PM strategy and plan. Don't spend all your funding in the lab; spend some on marketing, alliances, and branding.

Opportunity # 3 – for the major investor in pre-public Dx companies

If you've been through one or two mid-course corrections and have turned from seemingly unprofitable directions, get some help and look at the intellectual property you have sitting on the shelf. There may be more value there than in the rest of the beat-up company you're trying to salvage. Don't expect to sell the IP off for big bucks; it won't happen. But you may be able to find skilled people to take an option on your orphan IP and either build a company around it (in which you'll participate) or perfect it and license it out (again, you'll participate.) Since the only thing happening now is that the asset is decaying, what do you have to lose?

Opportunity # 4 – for the CEO of a Dx company

If you're someone who sees the future in this space, with some outside help and an investment banker, you may be able to put together a roll-up around a particular set of symptoms or a particular chronic disease. With the right strategy and the right help, and with a good plan and good communications, you can build sizeable value in your company and increase the chances of a great liquidity event.

Opportunity #5 – for the CEO of a public non-traditional health care firm

Like diagnostics entrepreneurs, you may see the Personalized Medicine opportunity. You're likely to have more resources and reach to do a targeted roll-up in molecular or metabolic diagnostics. You can even take on a few carefully selected "science projects" to perfect diagnostic assets. Moreover, as a public company, you're likely to have more clout with university technology licensing



offices. With strategic and investment banking help, you can very efficiently find and form relations with a set of companies which will increase margins and enhance your stockholder value.

Summary

Diagnostics may not provide the same “bubble” run-ups that we saw in the late 1990’s, but they’re also unlikely to have their bubble burst in the same way. These companies will have real and enduring value. They’ll be part of a massive and disruptive change in the health care system. And there are going to be many opportunities in this space because most people don’t fully understand the potential yet, and can’t evaluate the science, understand the strategy, select and perform the transactions and partnerships.

This is the right time.

About the Authors

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Genomic Healthcare Strategies is a consulting firm focused on the changes that are coming as a result of the umbrella phrase “personalized medicine.”

Peter Miller, Chief Operating Officer is an entrepreneur and manager. He was a founding member of Abt Associates, Inc., now a \$200 million firm in fields such as health care research and policy, clinical trials, and survey research; former Board Chairman of the International MIT Enterprise Forum and currently services as Co-Director of the MIT Venture Mentoring Service.

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