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Commercialization Considerations for Individualized Diagnostic and Drug Therapies Resulting from Pharmacogenomics

Jeffrey L. Moe*

Imagine I go onto the Internet, order a home test for the most common gene variations, or “alleles,” associated with commonly prescribed prescription drugs. I swab the inside of my mouth and send it back to the lab. Weeks later, I receive what looks like a credit card. This card is actually a CD-ROM, holding information about approximately 50–100 drugs that I may metabolize in an idiosyncratic manner, therefore requiring, for my unique response, different product information (“PI”) about dosing and risks associated with that drug. The CD-ROM will also give me information about many over-the-counter preparations and how my body may process them differently. Perhaps, it may also require different dosing and safety information than what has been approved and printed on the product.

This scenario reflects the fact that we now have the pharmacogenomic technology to identify individual gene variation associated with drug receptors, drug transport mechanisms, and drug-metabolizing enzymes which affect individual drug response.¹ The potential of individualized drug therapy raises a number of questions for manufacturers (“How do we provide individualized drug response information?”), for care providers (“How do I interpret individualized versus population-based information? Do I need this new genome-based information or do I have other available clinical information to gauge individual differences in drug response?”), for patients (“Do I want individualized information? How much will I pay for this information? What benefits will I gain and can I understand this information? Are there risks to me if others discover this

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1. See generally *Essentials of Genomics and Bioinformatics* (C. Sensen ed., Wiley 2002); Michael J. Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 Hous. J. Health L. & Pol’y 31 (2003); Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients’ Genetic Profiles*, 43 *Jurimetrics J.* 1 (2002).

information about me as an individual?”), for regulators (“Should we require this information be provided by manufacturers and make it available to patients and care providers? Should we require some diagnostic tests be administered before a drug is administered to improve patient safety?”), and for reimbursers (“Should our benefits design include coverage for pharmacogenomic-based diagnostics and individualized drug therapies?”). As these five stakeholders respond to these and other questions we will see the potential of pharmacogenomics shaped by the market realities of commercialization. We can look to historical examples of market responses to innovation to gain some insight into the future for pharmacogenomics. Of course this innovative new technology will not simply replicate the history of earlier innovations. It will have its own course which we cannot perfectly predict.

For each gene, there is a pair of copies, known as alleles.² Over many generations, variant alleles have emerged.³ When these occur in the general population at a rate greater than one percent, they are deemed single nucleotide polymorphisms (“SNPs”).⁴ When we find these variants in the individual, we are able to look at transport mechanisms, metabolism, absorption, toxicity, generally how individuals differ in drug response. In the clinical trial context for developing new drugs, patient sub-populations can be created where they share certain genetic profiles which can show drug responses that are safer or more efficacious. We speak of these genetic differences regarding drugs in two general ways—pharmacogenomics⁵ and pharmacokinetics.⁶

2. See Genome Glossary, http://www.ornl.gov/sci/techresources/Human_Genome/glossary/glossary.shtml (last visited Nov. 2, 2005).

3. For basic information about the human genome, visit the Internet site of the National Human Genome Research Institute (NHGRI), <http://www.nhgri.nih.gov>.

4. See SNP Fact Sheet, http://www.ornl.gov/sci/techresources/Human_Genome/faq/snps.shtml (last visited Nov. 2, 2005); SNPs: Variations on a Theme, <http://www.ncbi.nlm.nih.gov/About/primer/snps.html> (last visited Nov. 2, 2005).

5. See Virna Ignacio Alumete, *Drug Therapy and Pharmacogenomics* (2000), <http://www.medscape.com/viewarticle/419158>; National Center for Biotechnology Information, *Pharmacogenomics Factsheet, One Size Does Not Fit All: The Promise of Pharmacogenomics*, <http://www.ncbi.nlm.nih.gov/About/primer/pharm.html> (last visited Nov. 2, 2005).

6. For general information about pharmacokinetics and pharmacogenomics, see Food and Drug Administration, <http://www.fda.gov> (last visited Nov. 2, 2005); ALS Therapy Development Foundation glossary, <http://www.als.net/resources/glossary.asp> (last visited Nov. 2, 2005); and Environmental Health Center glossary, <http://www.nsc.org/ehc/glossar1.htm> (last visited Nov. 2, 2005).

The first involves screening candidates based upon the presence of a genotype marker,⁷ while the second centers on metabolizing activities.⁸

Two pharmacokinetic applications that come to mind include individualized patient differences in response to Warfarin, a drug used to stop blot clots from forming and growing larger, and mercaptopurine (6MP), a drug used in the treatment of acute lymphoblastic leukemia—a childhood leukemia. One study on Warfarin was conducted with about 185 patients who had two variant alleles.⁹ The study compared the two variant allele sub-populations and asked, “Do they, in fact, have differing anticoagulation conditions? Do they differ in their response to drug treatment and does following the recommended dosing lead to safety concerns? Do they have serious or even life-threatening bleeding when their unique drug response, in effect, causes them to be under-medicated and therefore at greater risk of uncontrolled bleeding?”

Of these patients, there were two that had a life-threatening occurrence resulting from their genetic variation and resulting drug response.¹⁰ This was a statistically significant finding which triggered questions such as, “Should all patients be tested to determine their individualized drug response?” and “How much risk, measured in cost and adjustments to life years, does this unique response create and how much additional cost is the diagnostic for the benefit of adverse drug response costs compared with those that could be avoided?” The opportunity to use innovative gene-based diagnostics is available to us. But as payers, patients, and providers we are quickly led to questions like these about the cost-effectiveness of these new therapies. And we have very little experience, and therefore very little data, upon which to make these calculations and these judgments. The history of the uptake of innovation in medicine tells us that the lack of cost-effectiveness studies or severely limited data will not necessarily impede adoption. If the past is prologue, that history also tells us that there will likely be predictable requirements for gene-based diagnostics and therapies to become widely used. Ultimately, cost-effectiveness will have to be established if there is to be sustained, long-term use of these new therapies. But in the

7. See sources cited *supra* note 5.

8. See sources cited *supra* note 6.

9. See generally Mitchell K. Higashi et al., *Association Between CYP2C9 Genetic Variants and Anticoagulation-Related Outcomes During Warfarin Therapy*, 287 J. Am. Med. Ass'n. 1613, 1690–98 (2002).

10. *Id.* at 1695.

short run, when we're establishing a market and commercializing, it's almost certain that we won't know if individualized therapy really avoids, or improves, total costs and improves patient outcomes in a measurable way. Markets and commercialization in medicine frequently occur in the absence of a real understanding of cost information. The U.S. market, in particular, has a built in pro-innovation bias to allow new technologies to gain market access first.

Let us take, for example, mercaptopurine (6MP) where one could argue the right constellation of forces were aligned to suggest wide-spread adoption of a gene-based diagnostic test to individualize 6MP therapy. Those factors were: 1) a life-threatening outcome and high overall costs of treatment, 2) treatment by a small sub-specialty of care providers, 3) good association of the gene variation with clinical differences, and 4) a reliable and "affordable"—as considered in the context of the overall costs of treatment and patient outcomes from the disease—diagnostic.¹¹ It suggested to many that mandatory diagnostic testing before the commencement of mercaptopurine therapy made sense and was something the FDA was considering. However, as discussed in Dr. Woodcock's presentation, physicians were, unexpectedly, opposed to mandatory diagnostic testing.¹² They argued that other clinical markers were typically monitored and, therefore, they should not be required to use the diagnostic. This suggests a fifth factor which may influence commercialization: the prevalence of other clinical markers to monitor individualized differences in drug response. The care provider may not need to know the actual gene variation responsible for differences in drug response to adequately protect the patient and avoid creating significant, unnecessary treatment costs.

There are other barriers or concerns for practitioners in the application of pharmacogenomics in clinical practice. While an advantage of pharmacogenomics is to potentially reduce the number of patients required in clinical trials while improving their responses to the new therapy, these advantages also have a downside. Limiting the number of patients in trials exacerbates the limited knowledge clinicians have as a new therapy is launched. Moreover, if we consider the additional concern that has been

11. With some cancer pharmaceutical therapies having ex-factory prices in the \$10,000's per year, a diagnostic costing less than \$1000, which holds out the promise of making the therapy more effective, is likely to be viewed by many patients as "affordable" even if that cost is not insurance reimbursable.

12. Janet Woodcock, *FDA Policy on Pharmacogenomic Data in Drug Development*, 66 La. L. Rev. (Special Issue) 91, 93, 95, 101 (2006).

raised—that women and minorities have been under-represented in clinical trials—we find that the promise of this new technology also will allow, under the current clinical trials and approval regime, a drug to be launched into the market with an even lower number of patients than we have today.¹³ We should note that the FDA introduced a patent extension incentive for manufacturers who conduct trials for pediatric indications.¹⁴ Having narrower, more focused, and targeted populations, while an advantage in reducing variation in response and reducing populations, exacerbates the problem of sparse information at launch and of specific sub-populations.

Interestingly, we are discovering, with the advent of molecular level diagnostics and therapies, that minority populations are frequently the patients who would benefit most from individualized drug therapies.¹⁵ There have been a number of studies sponsored by the National Pharmaceutical Council suggesting that, due to these individualized differences in response, minorities need much broader access to medicines than might be assumed. Using restrictive formularies and high co-pays to favor one drug over another in the same therapeutic class rests on the assumption of therapeutic substitution without any increase in patient safety risk. The genomics revolution raises important challenges to the assumption of fungibility among same-class drugs. If the foundation of “managed care pharmacy” and price negotiation with manufacturers is challenged by pharmacogenomics, this too could be a barrier to adoption and wide-spread commercialization. How do the incentives for health plans, insurers, pharmaceutical benefit managers (“PBM’s”), and employers to manage pharmacy benefit costs reconcile with the desirability and costs of individualized care?

At the clinical level, let’s consider the package insert for Strattera, a stimulant used to treat, among other conditions, attention deficit hyperactivity disorder (“ADHD”) in children.¹⁶

13. See, e.g., Andrew Pollack, *DNA Chip May Help Usher in a New Era of Product Testing*, N.Y. Times, Nov. 28, 2000, at F2; Valentine J. Burroughs et al., *Cultural and Genetic Diversity in America: The Need for Individualized Pharmaceutical Treatment*, Nov. 2002, <http://www.npcnow.org/resources/PDFs/CulturalFINAL.pdf>.

14. See generally Food and Drug Administration, *The Pediatric Exclusivity Provision: Status Report to Congress (2001)*, available at <http://www.fda.gov/cder/pediatric/reportcong01.pdf>.

15. Burroughs et al., *supra* note 13, at 13–14.

16. See Press Release, Eli Lilly and Company, *Lilly Announces Important Strattera® Label Update (Sept. 29, 2005)*, available at <http://www.prnewswire.com/micro/lly>; Strattera.com, *About Strattera*, http://www.strattera.com/1_1_about_strattera/1_1_about.jsp (last visited Nov. 2, 2005).

The label gives the provider information about metabolism and the enzymatic pathway. Clinicians have expressed concern about the inadequacy of guidance in using these new data.¹⁷ There are typically very small population studies or non-existent clinical information regarding dosage changes appropriate to guide clinicians who would individualize therapy based on this additional labeling. If clinicians cannot easily use the information, how will its inclusion increase the value to clinicians and patients or the reimbursers who share the payments for these medications? If individualized therapy “fails” at the one-on-one interaction level between doctor and patient, it is hard to see a market develop for widespread use under the current circumstances. More clinical guidance information will be needed. There are approximately twenty prescription products on the market now with this kind of labeling information included.¹⁸

So we find that there are barriers to the adoption of gene-based diagnostics and therapies due to inadequate clinical information and our current approaches to pharmacy management invite physician skepticism about their relevance and necessity. Yet, if we look at a historical example of a novel diagnostic we find that, in spite of barriers, adoption increased and a market was established.

The example I have in mind is the prostate specific antigen (“PSA”) testing phenomenon, where testing for elevated PSA was used to identify heightened susceptibility to, and diagnose, prostate cancer.¹⁹ Early on, there were many Type 2 errors with the diagnostic; cost effectiveness studies were not available to suggest that PSA diagnosis increased early identification, improved outcomes and avoided disease-related costs.²⁰ But because of

17. Strattera product label information (the package insert) is available at http://www.fda.gov/cder/foi/label/2002/21411_strattera_lbl.pdf.

18. See Center for Drug Evaluation & Research Report to the Nation, *Improving Public Health Through Human Drugs* 17 (2002), available at <http://www.fda.gov/cder/reports/rtn/2002/Rtn2002.PDF>.

19. See American Cancer Society, *Can Prostate Cancer Be Found Early?*, http://www.cancer.org/docroot/CRI/content/CRI_2_4_3X_Can_prostate_cancer_be_found_early_36.asp (last visited Nov. 2, 2005); About.com, *The Prostate-Specific Antigen (PSA) Test Controversy*, http://prostatecancer.about.com/od/thepsacontroversy/i/issue_p.htm (last visited Nov. 2, 2005); Yale-New Haven Hospital, *Diagnosing Prostate Cancer*, <http://www.ynhh.org/cancer/diagnosis/prostate/diagnosis.html> (last visited Nov. 2, 2005).

20.

Type 2 is refusing approval of a drug that is capable of saving many lives or relieving great distress and that has no untoward side effects. If you make a type 2 error, few will know it, as the people whose lives might have been saved will not be around to protest, and their families

wide-spread awareness of the existence of the test and poor alternatives, the tests became more prevalent.²¹ It suggests that if there is sufficient concern by patients and physicians, if the diagnostic or treatment fills in an existing void, if its specificity and sensitivity may be somewhat flawed, then new innovations, like individualized therapies, may take hold. The “proof” of cost-effectiveness and the impact on overall quality of care will trail behind as use increases.

The classic cost effectiveness measure is the cost of the new strategy, minus the cost of the current method, divided by the effect of the new strategy and effect of the current method.²² This calculation is very sensitive to fatalities. The Warfarin and 6MP examples are not typical; fatality is not a common outcome associated with a drug-response related to variant alleles. Adverse drug events from individual differences in drug response may create costs but our current understanding suggests they rarely result in death. Most of the work on pharmacogenomics and cost-effectiveness has been done in the in-patient setting.²³ We have very little data and very little experience in understanding the fully loaded costs of outpatient treatment failure. So making the case for the cost-effectiveness of individualizing therapies will be just that much more difficult in the out-patient setting, which is relevant to many of the most widely used medicines and over-the-counter (OTC) preparations. So again, it seems unlikely that for the most widely used prescription medicines, a business case can easily be made that individualizing therapy is going to reduce health care costs. It suggests that the “value story” for pharmacogenomics will be targeted to specific therapeutic areas, sometimes for improved patient safety and in other cases for improved patient outcomes and efficacy. In either case this may be particularly challenging.

will have no way of knowing that their loved ones lost their lives because of the caution of an unknown FDA official.

John Grohol, *Food and Drug Administration*, http://www.psychcentral.com/psych/Food_and_Drug_Administration (last visited Nov. 2, 2005).

21. Robert G. Evans, *Going for the Gold: The Redistributive Agenda Behind Market-Based Health Care Reform*, 22 *J. Health Pol. Pol’y & L.* 427, 461 & n.18 (1997).

22. M.F. Drummond et al., *Users’ Guides to the Medical Literature. XIII. How to Use an Article on Economic Analysis of Clinical Practice. A. Are the Results of the Study Valid? Evidence-Based Medicine Working Group*, 277 *J. Am. Med. Ass’n.* 1552–57.

23. David L. Veenstra et al., *Assessing the Cost-Effectiveness of Pharmacogenomics*, *AAPS Journal*, Sept. 14, 2000, available at <http://www.aapspharmsci.org/view.asp?art=ps020329>.

Having noted these difficulties, there are cost-related advantages to a widely-available diagnostic, such as one available on the Internet as I described at the outset. These advantages can be described in terms of cost avoidance and cost minimization. For example, let us say that I have a variant allele that causes the statin therapy I have been put on to be non-beneficial because I am a “fast-metabolizer.” My doctor and I may work on a regimen of diet and exercise while increasing the dosage in the hopes of better cholesterol numbers. Imagine that the genetic diagnostic allows my doctor and me to quickly eliminate ineffective dosages and whole therapy approaches. Those are costs avoided. These advantages could also be extended to other therapeutic areas beyond cholesterol testing if, let’s say for example, I needed an anti-depressant as well. There too, it is possible that my physician and I could more quickly get my condition under control as a result of the findings of a single diagnostic test. The possibility of taking a test once at a single cost and being advantaged over the rest of my lifetime, assuming the alleles at issue are not highly susceptible to change from environmental exposures, is appealing and may, over time, support a “cost avoidance” story to patients who pay out-of-pocket or to reimbursers considering covering all or part of the costs for the test.

One can also anticipate a treatment expansion effect, where more patients might seek treatment because they are more confident medicines will work for them. Similarly, practitioners may more readily prescribe treatments because of increased confidence in individualized therapy. While, at the surface, treatment expansion would seem to be advantageous, for some payers this is not necessarily in their self-interest. We have experience with insurance coverage for smoking cessation, and examples where specialized programs to identify and more aggressively treat patients with statins were not continued or reimbursed.²⁴ Why? Because near-term costs increased and avoidance of greater costs in the future were not likely to accrue to the benefit of the current payer. Based on their experience, patients were likely to opt-out of their health plan or employment by the time the cost savings of greater investments in health today would be realized tomorrow. Pharmacogenomics could face a similar reaction where near-term increases in costs toward future

24. Statins are the class of cholesterol-lowering drugs, which stop the enzymes they bind with from producing more cholesterol. Some nationalized health care systems and commentators have questioned overuse. See Nick Freemantle et al., *The Use of Statins: A Case of Misleading Priorities?*, 315 *British Med. J.* 826 (1997).

cost avoidance might be resisted for fear that some other payer will realize the benefits, rather than the current third party payer.

It is very compelling, as a patient safety concern, that a significant number of hospital admissions are due to adverse drug events.²⁵ On the face of it, it makes you want to reach for the promise of pharmacogenomics. But it is difficult to envision the broad-scale implementation of pharmacogenomics for improving patient safety. To illustrate this point, consider Propulsid (cisapride), which was used to treat severe heartburn.²⁶ Propulsid had a number of cardiovascular side effects.²⁷ The FDA became concerned enough to require 800,000 letters to go out to physicians that relayed, "You need to know this. This needs to be handled very carefully." However, those letters had little or no effect on physician prescriptions. And what reason did the physicians give for not responding to the letters and the rest of the precautions? They said they already were overwhelmed with information, too much so to focus on more data about one drug. So physician non-responsiveness to pharmaceutical-specific risk information, even at a population level, strikes me as a difficult challenge when considered at the individual, personalized level.

Physician resistance or reluctance may prove to be a significant barrier to adoption. To illustrate my point, consider an example both Dr. Woodcock and I used earlier: testing for TPMT, an enzyme that metabolizes 6MP, which is a drug used in childhood cancer therapy. In response to this testing, physicians said, "I already have other clinical markers that are easier and cheaper to see." While this reaction caused the FDA to back away from a requirement that the diagnostic be used before the onset of 6MP therapy, it did not keep reimbursers from making this requirement. It is my understanding that many insurers make their reimbursement for 6MP contingent upon the diagnostic results.²⁸ This may be an example where a market mechanism such as reimbursement is more efficient than a regulatory requirement to gain compliance and improve patient safety.

25. Estimates vary regarding the incidence of adverse drug reactions in different U.S. patient populations; there is some debate within the literature regarding appropriate estimation techniques. See David Classen, *Medication Safety: Moving from Illusion to Reality*, 289 J. Am. Med. Ass'n 1154 (2003).

26. Walter Smalley et al., *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*, 284 J. Am. Med. Ass'n 3036 (2000).

27. Janssen Pharmaceutica Research Foundation, Dear Dr. Letter (June 26, 1998), <http://www.fda.gov/medwatch/safety/1998/propul.htm>.

28. Malorye Branca, *The New, New Pharmacogenomics*, BioIT, Sept. 9, 2002, <http://www.bio-itworld.com/archive/090902/pharma.html>.

TPMT/6MP also raises the question of increased complexity relating to gene-based therapies. If there are less complex alternatives, as physicians claimed for 6MP adverse reactions, and not a significant increase in patient risk, physicians may prefer more familiar and less complex alternatives. The uptake of pharmacogenomics will likely increase where these new data are the only option to gain a significant increase in efficacy or patient safety. Continuing along this line of complexity, there is the phenomenon where, although you have a gene aberration, it does not express itself phenotypically—a type of false positive. As a practical matter, one can also question whether a particular assay can be done quickly and relatively inexpensively. Also relevant is whether the variant allele frequency is relatively high. In the wake of an explosion of activity, we are finding many alleles that represent small variances and appear with low frequency. Throughout the field of genomics there is some concern that, if you have too many discriminators, then the marker will not work in commercial application. For commercialization and broad adoption we must find the middle ground between too few and too many genetic markers to create sub-populations that are adequately sized.

Patient demand can push uptake. One of the factors that increases demand is a significant recent change in the patient's or a family member's health status. In other words, if I have just received a diagnosis that moves me from "healthy," as self-identified, to much less healthy, I am more risk-seeking and willing to experiment with newer, less certain therapies. We can also make the generalization that patients prefer relative certainty to uncertainty. If patients were to seek out novel new treatment options, they would be attracted to those that hold some promise of improving their health status or improving their odds against serious side effects. The more those "promises" are equivocal or heavily weighted with uncertainty, the more they lose attractiveness. We can extrapolate from these insights that a unified "bundle" of strong association between the phenotype with the variant allele, a reliable diagnostic, and an effective treatment could create greater demand by patients for these newer therapies.

Price sensitivity also must be considered. Price sensitivity is a function of health benefit, design, disposable income, and risk-seeking disposition. It is interesting to me that for TPMT, \$100–\$300 out-of-pocket was identified as a barrier given the severity of

the consequences.²⁹ Of course these are direct expenses to the patient, out-of-pocket, but nonetheless across a distribution of patients from a distribution of disposable income levels this still seems relatively low. The general principle we're seeing here is that as gene-based therapies are available for targeted, smaller populations, the cost of therapy must generally be higher because the populations are smaller. For example, Herceptin, a treatment for a very aggressive breast cancer associated with over-expression of HER-2, is fifteen times the cost of the standard course of therapy.³⁰ We can expect that as you get smaller markets and smaller numbers of patients, the therapy, and especially the combination of the tailored therapy with associated diagnostic prices, will be higher. Whether that creates any sensitivity depends, in part, on whether the costs for diagnosis and treatment are reimbursed and what the actual co-pays for patients are.

We should note that John Rowe, chairman and CEO of Aetna, has publicly stated the advantages and importance of pharmacogenomics, offering that Aetna encourages patients to seek these diagnostics and treatments.³¹ It would be interesting to look carefully at the individual benefit designs of his company's insurance products and those they administer for large employers. Are they reimbursing for gene-based diagnostics and treatments and the move toward individualized care? What is their experience with patient costs and outcomes when they have access to these new technologies? I strongly suspect that manufacturers who are pursuing the commercialization of these products are working closely with insurers to make these determinations and provide support through benefit designs.

An additional concern, and potential barrier to commercialization, that patients have expressed is confidentiality. Information that one is more "difficult to treat," a conclusion that could be drawn for some patients whose individual response to some treatments is highly idiosyncratic, could prove to be a liability to the patient. Patients may fear they will be labeled as a

29. Eliot Marshall, *Preventing Toxicity with a Gene Test*, 302 *Science Magazine* 588, 590 (2003), available at <http://www.sciencemag.org/cgi/reprint/302/5645/588.pdf>.

30. Information about Herceptin is available at <http://www.herceptin.com>. Herceptin generally is administered in combination with Taxol, and the total cost of this cocktail is approximately £12,000 per patient for a six-month course (£6,000 per drug). See Bezy Marsh, *The Miracle Cocktail*, *Daily Mail*, May 16, 2001, available at 2001 WLNR 2653507.

31. Associated Press, *Genetic Testing Gets Backing from Aetna: Insurer Asks Rivals to Back Anti-Bias Bill*, *Boston Globe*, June 19, 2002, at C6 (quoting Aetna Chief Executive Dr. John W. Rowe).

result of test results regarding their individual drug response. In partial response to this confidentiality concern, and to take the burden off their own internal staff to provide complex customer service, direct to consumer pharmacogenomic diagnostics results go straight to the patient. Patients are encouraged to take their disc to their doctor and confer with them. Can the doctor, under certain circumstances, be required or unwittingly reveal that personalized information about the patient to an insurer or employer? If patients believe such a breach of confidentiality is possible, it could create an additional barrier to their seeking more individualized information. In addition, many doctors have suggested to me they would be very concerned about that consultation. They simply don't have the training and the paucity of well-controlled and available data would make an interpretation of these results very difficult.

Liability could be another barrier to broad adoption. Already, there are issues associated with the commercial application of pharmacogenomics that are the subject of litigation. For example, a young boy, nine years old, suffered a Prozac-related death, and variant alleles were subsequently identified as an explanation for his adverse event.³² The case settled out of court.³³ There was also litigation against the former SmithKline regarding its Lyme disease vaccine in which plaintiffs alleged that the manufacturer should have a warning on its label about an arthritis side-effect associated with patients with specific variant alleles.³⁴ Another company was sued because it preconditioned use of its drug on screening for an allele associated with a granular cytositis side effect.³⁵ The basis for the suit was that the company was inappropriately tying the diagnostic with the drug and thereby artificially inflating the price of the therapy, so the company moved away from linking distribution and sales of the drug with the test.³⁶ These cases illustrate that companies, which probably have the best information about the clinical utility of coupling pharmacogenomic diagnostics and drugs, may face not only criticism but legal challenges and allegations of illegal tying arrangements.

32. Stan Bernard, *The 5 Myths of Pharmacogenomics*, Pharmaceutical Executive, Oct. 2003, at 7, available at <http://www.pharmexec.com/pharmexec/article/articleDetail.jsp?id=72796>.

33. *Id.*

34. Press Release, Mealey Publications, SmithKline Sued Over Lyme Vaccine, available at <http://www.whale.to/vaccines/lyme2.html> (last visited Nov. 2, 2005).

35. Bernard, *supra* note 32, at 74.

36. Noah, *supra* note 1, at 21.

From the test supplier perspective, remember that there are about a thousand commercial and home brew diagnostic tests. The markets for each of these tests tend to be small, which has discouraged some of the early innovators. With such small markets, the unit price is likely to be higher, and that may create greater price sensitivity depending on insurance coverage. For the example I've used earlier, direct to consumer testing, the volume is low. Orchid pharmaceuticals never came to market with its predictive tests, even though people had invested a lot. Even so, there is some competition in the field. Pay attention to Roche Diagnostics and its partnership with Affymetrix for a p-450 chip product to become commercially available. Many of the barriers I've discussed will be confronted if this product comes to market and we should learn a great deal from their marketing strategies. It will be interesting to see if this draws new players into the market and those that have delayed or withdrawn from the market.

Finally, from the perspective of the drug companies, there are differing scenarios for the impact of pharmacogenomics on their existing business models. Many drug executives have argued that personalized medicine simply creates smaller markets and they, therefore, are somewhat ambivalent about the impact of these new therapies.³⁷ Yet, many of these same executives are simultaneously making significant investments in alliances, acquisitions, and research in their own pharmacogenomics labs.³⁸ The opportunity of the new sciences is leading somewhere, but it's still too early to tell where. But a major company does not want to be unaware of the application of the evolving science. One attractive model is a market expansion model, often applied to cancer therapies. Imagine that cancer therapy begins to look like HIV treatment. Understanding the cancer(s) at the genetic level allows the physician and patient to track it as it mutates. With initial diagnosis, a patient receives a cocktail of drugs to attack the current presentation of the disease. As that therapy becomes less effective, a second diagnostic shows how the disease has mutated and a new cocktail is prescribed. This model moves toward a more chronic care model.

With all these commercialization challenges in mind, my own judgment is that pharmacogenomics will most likely exacerbate the current challenges we face in health care rather than solve them. We are struggling, and many times failing, to practice the current standard of care based on population-level understanding, much less attempting to take the standard of care to a higher level of

37. Branca, *supra* note 28.

38. *But cf. id.*

individualization. There are IOM studies, and others like the RAND study published this past year in the *New England Journal of Medicine*, that suggest we are having significant problems with implementing appropriate use of basic medications in the context of accepted clinical practice guidelines for widely recognized and common conditions.³⁹ If we can't meet expectations at the population level, how can we expect to raise the standard even higher toward individualized therapy? That, of course, is not to say that individual doctors and their patients achieve a high level of compliance to the best standards of care. Certainly there are provider institutions that have made significant commitments and have data to substantiate the significant progress they have made at raising the quality of care. But my own data and interaction with providers suggests it has been, and will continue to be, a significant commitment of time and resources to achieve high-level quality at the population level. It would be a significant challenge for our best providers, as individuals and institutions, to raise the level of care to that of so-called "personalized medicine."

39. Elizabeth A. McGlynn et al., *The Quality of Health Care Delivered to Adults in the United States*, 348 *New Eng. J. Med.* 2635 (2003).