Personalized Medicine

Part 3: Challenges Facing Health Care Plans in Implementing Coverage Policies for Pharmacogenomic and Genetic Testing

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This is the third article in a three-part series on the future of personalized medicine. Part 3 focuses on trends in health plan insurance policies and coverage for genetic tests.

Key words: personalized medicine, pharmacogenomics, manufacturer pipeline, drug pipeline, medical device pipeline, diagnostic pipeline, medication coverage and underwriting

INTRODUCTION

Most health care payers recognize that personalized medicine (PM) and genetic testing will create important changes in clinical practice in the future. Insurers will need to determine which medical expenses to cover in their policies; which tests have clinical utility; which ones actually change the treatment choices for physicians; and which ones are more interesting to consumers but do not affect the clinical setting.

Many questions are cropping up in the payer community, some coming from the media and some arising from people in the field of PM. Per Lofberg, Executive Vice President of CVS Caremark and President of Caremark Pharmacy Services, and his team spoke to many in the insurance industry as they traveled around the country.[1] Almost without exception, these payers were poorly equipped to answer questions that Lofberg's group asked. For example, for Medco Health Solutions, Inc., and other pharmacy benefit managers (PBMs), the natural evolution is to incorporate genetic testing, when shown to be valuable, into the prescription drug choices that physicians are making. PBMs are in the interesting position of being able to capture prescription data at an early stage; they have an opportunity to make suggestions to patients and physicians. In the future, the Lofberg team suggests, certain genetic tests will need to be performed before drug selection is finalized.[2] It thus makes sense for PBMs to be in the forefront of this change in terms of pharmacogenomic testing in relation to drugs that they manage.

A few years ago, Medco became the pioneer in this area, and in 2009 CVS Caremark chose to participate in a strategic partnership with Generation Health.[3] These types of partnerships will be one of the ways in which the PBMs can add value to their relationships with health plans and employers.

So far, most organizations do not have a comprehensive gene-testing program, but various initiatives are getting under way. Several insurance plans have implemented rules for covering certain genetic tests, such as the BRAC*Analysis* (Myriad Genetics) for breast cancer testing. Some plans have eligibility requirements or prior authorization protocols for the BRACA gene test, one that has the widest set of gene-testing programs in the industry. Another test for women with breast cancer, Onco*type* DX (Genomic Health), an assay that is used to predict whether chemotherapy is likely be beneficial and whether the cancer is likely to recur. If the test result indicates that there is a good chance that the disease will return, the patient's physician will need to prescribe drug treatment.

These examples are isolated instances, and they are usually decided only once, when establishing policy. Using vendors, PBMs try to develop a comprehensive approach that covers all genetic tests. The new model will provide the framework for health plans to decide which tests they should cover, to ensure that the tests found to be valid are made available to patients, and to eliminate coverage for tests that are found to be less useful.

Cancer represents an area in which genetic testing is going to be adopted quite rapidly over the next few years; several tests in development will be able to detect the risk of cancer and to indicate which drug regimens have a good chance of benefiting individual patients—and there will be increased opportunities for physicians and health plans to take advantage of these discoveries. In addition to testing for cancer, genetic testing may also become applicable for HIV infection and cardiovascular disease. In the coming years, there are likely to be more ways to predict genetic risk and select the appropriate pharmacotherapy.

QUESTIONS FACING HEALTH PLANS

How Useful and Cost-Effective Is Genetic Testing?

The primary questions raised by health plans focus on the clinical utility and cost effectiveness of PM and genetic testing. Basically, the idea is to assemble available scientific and outcomes research to help build models around each test to allow payers to project the financial risks and benefits of introducing coverage programs to patients. It will be necessary to show the prevalence of a disease or a specific drug treatment and to calculate the resulting diagnostic expense.

Ideally, this strategy will offset changes in treatments costs and outcomes and will bring about improved results and/or reduced side effects. Using vendors, PBMs try to create a value-based proposition for each test and then present it to payers so that they can make an informed choice as to what makes the most sense within the parameters of their health plan.

Currently, payers are solicited by various laboratories that have tests to sell and need to seek reimbursement for them.

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These are basically sales pitches, and there is no objective way to evaluate the usefulness of the tests or to make recommendations for their network physicians.

The first phase of a PM strategy offers a menu of various testing opportunities that payers can evaluate and then select for the program. Medco and Generation Health had planned to conduct pilot tests in 2010 that would be heavily subsidized by Medco to give payers a chance to experiment with this approach and to gather data that would allow them to measure the cost benefits of these services for their organization. Ultimately, this will be a per-member per-month administrative service. Medco as a PBM will negotiate the testing costs with the laboratories, and the terms that the PBM negotiates will be passed along to customers. The PBM hopes to be able to charge the full retail price. Compared with most other aspects of health care, this area consists of little selective contracting. PBMs hope to introduce cost savings for payers by building a laboratory network with contracted commercial terms for the participating laboratories.

Do Comparative-Effectiveness Research and Pharmacogenomics Work Together?

Comparative-effectiveness research (CER) and personalized medicine (PM) go hand in hand, in the sense that a valid biomarker and the companion diagnostic can be used to improve patient selection, according to Lofberg.[1] Of course, the odds are that patients who have been tested are more likely to respond to a drug and are less likely to experience complications. If we compare a drug that has a known biomarker and a companion diagnostic with a drug that does not have it, chances are good that the former modality will be more cost effective. For certain drugs or comparisons, biomarkers might make a substantial difference in CER and patient outcomes.

A genetic test cannot be performed unless the patient gives consent. In the early stages of these programs, most health plans will be introducing these concepts and will inform physicians and patients that genetic testing may be useful in evaluating whether a drug regimen will be successful. If the evidence is compelling, the health plan could want to make the requirements for insurance coverage more stringent and would probably state something like the following to physicians: "Because the genetic test for this particular drug is quite conclusive as to whether patients will benefit from this agent, you are required to conduct this test before we can authorize the drug's use."

This second phase (requiring the test as a condition for dispensing and paying for the right drug) involves a stricter requirement, but some plans will want to adopt it to ensure compliance with protocols. This type of requirement is likely to be implemented in the foreseeable future, and some plans may have already introduced it. An example is trastuzumab (Herceptin, Genentech). The FDA label requires the HER-2 test; therefore, it is already well established as the standard of care for a certain type of breast cancer. Another example beginning to gain traction is the selective prescribing of cetuximab (Erbitux, Bristol-Myers Squibb/ImClone). The United Kingdom's National Institute for Health and Clinical Excellence (NICE) has decided that a handful of cancer drugs will be covered if a genetic test has been performed beforehand.

When Will Medical Genetics Evolve Into a Consumer Business?

Medical genetics is unlikely to become a consumer business in 2011. Nonetheless, thanks to the confluence of two transformational technologies—the Internet and the sequencing of the human genome—what appears to be a seismic shift actually fits nicely into a continuation of macro-trends that have been under way for some time.

Patients' dissatisfaction with the health care system in the U.S. has been growing exponentially for more than two decades. It is well known that WalMart, CVS/Caremark, and Walgreens have been aggressively introducing consumer clinics in their stores. Other retailers are evaluating the same opportunity. According to Scientia Advisors,[4] so-called rapid-care clinics can be licensed to provide basic health care services for common illnesses (e.g., strep throat) at a low cost in or near a convenient retail outlet with convenient hours of operation.

There are many valid reasons for selling genetic tests or genome scans directly to patients. Companies specializing in ancestry testing can offer consumers a tool with which to pursue their hobby of learning about their family tree. Some thought leaders argue that genomic medicine is coming quickly, whether we like it or not, and patients who are armed with genetic information will be speeding up the process even more quickly. Others argue that patients can benefit from knowing their own genetic information, in that they have greater motivation to adhere to preventive and health-promoting strategies, even if their doctors do not use the information in treatment. The ability to make purchases securely online became the catalyst that made consumer genetics take off.[5] These services are not inexpensive; prices range from hundreds to thousands of dollars for a single test.

Although mainstream medical genetic testing will continue to expand in its own right, much of this genomic work and associated business revenue will stay within traditional clinical laboratory testing services. Still, the Internet has allowed an innovative mini-distribution of genetic testing that can empower patients as consumers.[6]

COVERAGE AND REIMBURSEMENT FROM HEALTH PLAN SPONSORS

The advent of personalized medicine (PM), which targets tailored treatment and care based on genetic variations, is creating a booming market. In reality, however, PM is a disruptive innovation that creates both opportunities and challenges for traditional health care and participants in an emerging market. The promise of PM has been predicated upon advances in genomics and proteomics, completion of the human genome map, and development of targeted diagnostics and therapeutics. Genomic testing enables physicians to:

- identify a patient's susceptibility to disease
- predict how a given patient will respond to a particular drug
- eliminate unnecessary treatments
- reduce the incidence of adverse drug reactions
- increase the efficacy of treatment
- improve health outcomes

FUTURE STRATEGIES AND TRENDS[7,8]

A Projected Pipeline for New Biologics

Although pharmaceutical, biotech, diagnostic, and medical device pipelines will have an effect on medical practice in the near term, the speed of change, along with the overlap in the use of technologies, is escalating the financial impact to payers and providers alike. As a consequence of rapid advances in the development of clinical applications, oncology has been a leading area in the trend toward commercialization of PM. As an example, physicians have caught up to thought leaders and have learned how to best apply the HER-2 test for trastuzumab (Herceptin).[8] As a result of experience in areas like oncology, drug manufacturers are increasingly looking to create products for specialized populations. PM, therefore, will continue to play a larger role in drug development in the near future.

Within the specialty drug pipeline, three general trends are emerging in the marketplace:

1. New products to treat conditions that have no therapeutic alternatives and new biologic or unique patented formulations. Examples include:
   a. injectable collagenase *Clostridium histolyticum* (Xiaflex, Auxilium) for Dupuytren's contracture
   b. pirfenidone (Esbriet, InterMune; Pirfenex in India, Cipla) for idiopathic pulmonary fibrosis
   c. belimumab (Benlysta, Human Genome Sciences/GlaxoSmithKline), under review for lupus
2. New products with new formulations. Injectables today will become oral-dose forms very soon, as in therapies for cancer, multiple sclerosis, and osteoporosis.
3. Additional indications for products already being marketed ("a pipeline within the pipeline"). As a result of the underlying pathway that new biologic and genomic therapies are targeting, an immunomodulatory drug can affect any condition with an immune component (e.g., rheumatoid arthritis, psoriasis, hepatitis C).[8]

Diagnostic firms are testing products at a rapid rate for marketing to drug research firms and laboratories as well as for use in clinical trials. Some examples include:

- Febit: messenger RNA (mRNA) biomarker profiling expression patterns, serving as biomarker signatures to detect and classify diseases like cancer.
- Almac: pharmacodynamic biomarkers in discovery and development.
- Metanomics Health: metabolomics for metabolite profiling in drug screening and development.
- Thermo Scientific: protein biomarker identification with tandem mass tags to reduce proteome complexity and dynamic range during identification and quantitation.
- Caprion Proteomics: secretome-plus-depletion columns to identify biomarkers in low-abundance disease (i.e., affecting fewer than one million lives, such as Crohn's disease) and drug-related proteins in the circulation.

The pipelines are diverse and sometimes sound exotic, but all of them are focused on improving patient safety and outcomes. These advances, however, come at an increased cost within sectors of care; this will require examining how health care is managed as well as how insurance coverage is underwritten.

Five- to 10-Year View: The Future From a Health Plan Sponsor's Perspective

Integrating Personalized Medicine Into Health Plan Coverage

The speed at which basic research is moving through rapid application and commercialization into clinical products is perhaps best illustrated by the field of oncology research, for instance, with trastuzumab. Another example is the use of novel diagnostics to define the metastatic process. In breast cancer, which has a metastasis-related death rate, the detection of circulating tumor cells can be a valuable prognostic factor that can accurately predict prognosis and treatment efficacy in patients with advanced disease.

Two major trends are emerging in genetic testing:

1. *Tumor typing:* More treatments will be decided according to where the mutation occurs, such as the KRAS mutation that may be in the skin, lung, and colon. Oncologists now understand the need for typing tumors earlier instead of waiting.
2. *Blood-level monitoring:* The cytochrome P450 (CYP 450) system, which affects drug metabolism, will be monitored more closely.

Many drugs travel in various pathways within the CYP 450 system, with the result that patients may metabolize certain medications more slowly or quickly than others. There is a good chance that clinicians are not checking blood levels, because many drugs going through the CYP 450 system lack titration information on their product labels. However, physicians will begin to titrate immunosuppressant drugs in transplant recipients very closely; this trend has been emerging in oncology practice recently.[8]

Trends in Drug Coverage and Underwriting Practices

Health insurance underwriting is the process used by health plans and insurance companies to weigh potential health risks in their pool of insured people against potential costs of providing coverage. To conduct medical underwriting, the insurer asks those applying for individual or family coverage about pre-existing medical conditions. Prior to passage of the 2010 health reform bill, known as the Patient Protection and Affordable Care Act (PPACA), insurance companies in most states were allowed to ask about an applicant's medical history; the company would then use the information to offer or deny coverage and to add or modify charges if it so desired.

Although most discussions about medical underwriting in health insurance focus on medical expenses, similar considerations apply in other forms of individually purchased health products, such as disability income insurance and long-term care insurance. The focus of coverage and management of disease has shifted from cardiovascular disease alone to include a variety of chronic conditions such as attention-deficit/hyperactivity disorder (ADHD), diabetes, and cancer. As a result of the anticipated expansion in coverage resulting from health

reform, the overall market size will likely increase, thereby increasing underwriting pools.

Proposed price negotiations in health care reform may reduce both comparative bargaining power with drug manufacturers and comparative margins on branded and generic medications by third parties, such as health plans and PBMs. However, the good news is that the higher number of insured people will increase the number of covered lives. This expansion will necessitate a deeper emphasis on education and support for this population. The challenge will be to improve efficiency and cost competitiveness, including developing communications for both health care providers and patients.[8]

On November 2, 2009, a health industry trade association—the DMAA–Care Continuum Alliance—wrote to the heads of three government agencies (the Health and Human Services, the Treasury, and Labor). The DMAA (Disease Management Association of America), representing more than 200 corporations and individual members, requested an immediate moratorium on implementing and enforcing the Genetics Information Nondiscrimination Act (GINA) until an inter-agency investigation could determine how the law's restriction on the use of genetic information for "underwriting" purposes would affect wellness and chronic disease-management programs under health plans.[9]

On the same day, the DMAA also asked members of the U.S. Senate to clarify the definition of underwriting, as included in the original GINA statute. The coalition claims that the law's definition of underwriting overreaches Congress' intent and that it would have "dramatic and unintended consequences" for programs designed to support at-risk and chronically ill patients.[9]

DMAA takes issue only with the broad underwriting restriction within the law, fearing that it will restrict the ability of employers and insurers to offer incentives for completing health risk assessments (HRAs), according to DMAA Chief Executive Officer Tracey Moorhead. The Personalized Medicine Coalition, for one, has taken a position against a moratorium on GINA.[9]

How National Health Care Reform Might Affect Insurance Coverage

The PPACA, which was signed on March 23, 2010, and the Reconciliation Bill to the PPACA, signed in April 2010, will no doubt slowly change the landscape for health insurance as well as health care delivery in the U.S. Most of the focus in PPACA was on expanding coverage for uninsured populations with subsequent cost reductions in payment for services to hospitals, clinicians, home care, and other benefit reforms throughout this decade.

Advances in health care technologies, including PM, will continue to put cost pressure on the payment systems during the same decade of change. Already, adverse selection and unintended effects of the economic recession have resulted in problematic medical loss ratios for insurers. For the first time in decades, 2009 saw a slight decline in the number of new prescriptions filled in pharmacies.

Most changes in primary areas of coverage will begin in earnest in 2011 and 2012, then again in 2014 and 2018. Transformation will occur throughout the decade as a result of the way in which different channels of care are integrated for payment, coverage, and the use of technology in areas like PM. Although advances in technology may result in minimal increases in the total cost of care, antiquated reimbursement rules and legislation may create barriers to success.

More troubling are the planned cuts in diagnostic and related therapeutic service areas both inside and outside of hospitals, thereby limiting opportunities for innovation in delivery of care. PM benefits will be directed primarily to older patients, the same group that will face the most complex changes in coverage along with relative reductions in benefits. For the U.S. economy, limiting such application of medical innovation could result in a boomerang financial impact, requiring more spending on outmoded diagnostic and treatment modalities and thereby curtailing opportunities for savings that could be achieved with a more rational use of newer technologies in appropriate patient populations.

PERSONALIZED MEDICINE IN THE CONTEXT OF HEALTH CARE REFORM AND INCREASED CONSUMER-DRIVEN CARE

As complicated as health care has been in the U.S. in the past, the perfect storm of consumer focus, health insurance reform, and PM is just now starting to converge, bringing with it increased complexity as well as scrutiny from all quarters. Health plans and plan sponsors today are increasingly struggling to redefine "adequate coverage," in an effort to meet the conflicting expectations of the various stakeholders.

Unlike PM, conventional drug therapy has historically regarded patient populations as a relatively homogeneous group, using a "one-drug-fits-all" approach. Only recently have genetically based differences, in response to a single-drug or multiple-drug treatment, begun to be considered. The 20th century brought about a broad arsenal of therapies against the major illnesses of the time: infections, cardiovascular disease, cancer, and mental disorders. However, although drug therapy can cure disease, it can also cause unintended adverse effects. Moreover, the use of drugs throughout the world in the 21st century has revealed many inter-individual differences in therapeutic response. A drug can be beneficial in some individuals but ineffective in others, and some patients experience side effects, whereas others are unaffected.

Diagnostic and drug research today seeks to target specific cells, tissues, and organs at the genomic and molecular levels. Often distinct submolecular mechanisms that underlie intended therapeutic and unintended adverse effects may hold the potential to improve or even revolutionize medical therapeutics. PM also offers an opportunity to enhance the value of approved drugs that currently have a limited market share because of significant toxicity or limited efficacy—by enabling prescribers to identify patients for whom these agent can be both effective and safe. The recognition of differences in drug response among individuals is an essential step toward using the best therapy. The marriage of drug-related diagnostics and old and new drugs often provides fertile ground for new uses of drug products and may improve the safety and efficacy profiles of older, chemically based medications.[10]

Over the previous decades, it has become clear that much of the variability in drug response is genetically determined,

with age, nutrition, health status, environmental exposure, and concurrent therapy playing important contributory roles. To achieve effective drug therapy with a reasonably predictable outcome for a specific patient, one must further account for different patterns of drug response among geographically and ethnically distinct populations.[10]

The observations of highly variable drug response, which began in the early 1950s, led to the birth of a new scientific discipline arising from the confluence of genetics, biochemistry, and pharmacology known as pharmacogenomics. Commercialization of this research application has become known as PM. Whether and to what extent an individual, genetics-based approach to medicine results in improved, economically feasible therapy remain to be seen.[10]

Tailoring drug therapy to the individual raises issues with enormous practical consequences. The dynamic complexity of the human genome, multigenic disease origins, and the involvement of numerous genes in drug response impede effective routine clinical application.

In addition to these daunting scientific challenges, ethical matters need to be resolved. Having access to information about an individual's genetic makeup raises privacy questions and ethical dilemmas about disease susceptibility, prognosis, and treatments. These legal and regulatory issues, as well as significant economic matters, are not likely to be resolved quickly.[10]

Regardless of how these new genomic technologies find their way into everyday clinical use during the next few years, they will undoubtedly prove valuable tools in improving outcomes in drug therapy, thereby affecting the larger landscape of medical care. The 21st century vision of PM is leading us to a more individualized approach to prescribing medications and closer to curing diseases while revealing 20th century limitations inherent in the management of disease in the population at large.[8]

CONCLUSION

As PM becomes more widely used, it will enable manufacturers to develop drugs that are specifically intended for subpopulations of responders to medications that might have otherwise failed to work within the confines of traditional health systems. At the same time, the introduction of PM will require changes in practice patterns and management for physicians and other health care professionals and for manufacturers in terms of product reimbursement, regulatory compliance, and knowledge sharing with other stakeholders.

New product value assessments call for new organizational strategies. Health plans and their sponsors may initially believe that PM represents yet another challenge in difficult times. Just as drug manufacturers will need to adapt, health insurance plans and plan sponsors will need to offer transparency in benefit under- writing and management. Society must also provide clarity in terms of regulatory and legal requirements as new health insurance regulations emerge.

It is hoped that PM will impel all stakeholders toward faster, more efficient decision-making; systems of care and payment structures will have to be redesigned at a more rapid pace than is now the case. Many of the identified elements in the health care system (hospitals, insurers, licensed clinicians) that are changing or that are likely to change have been visible and active during the previous 60 years. In these early decades of the 21st century, health care will be reframed for years to come.

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ADDITIONAL RESOURCES

For a complete description of selected references on personalized medicine, please see the October 2010 issue of *P&T* on pages 567 and 576 and www.ptcommunity.com. Here is an abbreviated list of Web sites:

1. www.labresultsforlife.org.
2. www. pharmacogenomicsociety.org.
3. www.fda.gov/NewsEvents/Newsroom/Press Announcements/2006/ucm108619.htm.
4. www.fda.gov/downloads/Medical Devices/Device RegulationandGuidance/GuidanceDocuments/ucm071075.pdf.
5. www.hhs.gov/healthit/HITFinalReport.pdf.
6. www.egappreviews.org.
7. www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083374.htm.
8. http://oba. od.nih.gov/SACGHS/sacghs_ home.html.
9. www.nigms.nih.gov/Initiatives/PGRN.
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11. http://scienceinsociety.northwestern.edu/content/articles/2008/what-is-personalizedmedicine?gclid=clatmksg_aecfufm 5qodbhzifg.
12. www.cgm.northwestern.edu/cgm/Academics/Graduate-Program-in-Genetic-Counseling.
13. www.healthleaders media.com/content/led-250352/The-Impact-of-Personalized-Medicine-Today-60k. ■