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Unlocking the Promise of Molecular Diagnostics

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Executive Summary

Breakthroughs in medical therapies, devices and diagnostics have enabled us to live longer, better lives. Vaccines have eradicated what were once deadly and paralyzing diseases. Antibiotics have made the threat of many serious illnesses no more worrisome than the threat of the common cold. Thanks to specialty pharmaceuticals, even AIDS and many cancers can now often be managed as chronic conditions. All of these advances and countless others have had a profound impact on our lives and have led us one step closer to what's possible next.

At this moment, we stand at the threshold of another exciting step in healthcare. The development of molecular diagnostics (MDx) is beginning to change the way healthcare works in fundamental and compelling ways. By uncovering expression patterns of the human genome, physicians can more accurately pinpoint potential disease states and recommend therapies that are tailored to a person's unique genetic makeup or "molecular signature." In some cases, MDx do more than help physicians diagnose illnesses; they indicate a course of treatment. These tests will help physicians avoid inappropriate therapies and adverse affects, and improve care with more precision than ever before.

However, we face serious barriers to the effective use of MDx today. Criteria for accepting them into standard medical care have not been established. Few participants in healthcare feel entirely comfortable dealing with a deluge of MDx questions, uses and reimbursement issues. Meanwhile, the number of new diagnostics continues to grow at an unprecedented rate. The creation of an organized registry that differentiates among tests and includes clinical, performance and use information presented in a convenient and user-friendly way to doctors, patients, labs and payers can speed the adoption and benefits of MDx integrated into clinical practice.

The good news is that many organizations have strong proposals and approaches to address the many challenges we face. These efforts will eventually help us realize the full potential of MDx by making them easy to recognize, understand and use.

This paper details the barriers we face to the effective use of MDx, what's being done to solve those issues, and our view of what more is needed to realize the full promise of MDx.

Introduction

Molecular diagnostics (MDx) are creating an exciting transformation in the way healthcare is practiced today. These breakthrough diagnostics are:

- Providing precise information on disease states
- Improving accuracy of therapies
- Saving doctors from prescribing expensive drugs to patients who wouldn't respond to them
- Enabling physicians to help their patients avoid adverse events
- Helping to manage healthcare costs
- Lending themselves to quantified results

There's real enthusiasm among patients, physicians, investors and the press for MDx. Looking forward, these tests may provide physicians and payers with a prospective, proactive way to coordinate care. MDx could also eventually explode the number of patients coming to labs as we transition from reactionary to more prospective healthcare. The tests' producers are beginning to make claims as they seek regulatory approval. Research results around biomarkers and diagnostics are constantly announced online and in the press, informing patients and physicians. There are numerous MDx start-ups — many venture-funded — promising great results.

In addition, there are commercial companies reaching out directly to consumers to offer simple and even complicated genomic tests. This is both good and bad. On one hand, it may help consumers take a more proactive role in caring for their health. However, without appropriate guidance, people could be misled about treatments based on inaccurate, incomplete or misunderstood results. That's probably why payers are skeptical about direct-to-consumer genomic tests.

Meanwhile, the number of new diagnostics entering the market is unprecedented. National costs for MDx reached \$6.2 billion in 2010, and are growing 15 to 20% a year. Based on the abundance of new science chronicled in peer-reviewed publications and the enthusiasm for funding MDx start-ups, the flood won't diminish any time soon.

The Reality of MDx Use Today

Regulatory rules and processes exist for traditional diagnostics. For the most part, these diagnostics fit within existing CPT codes and have low reimbursement rates compared to drugs.

MDx are different. They enable physicians to analyze how genes and proteins interact within a cell. By uncovering expression patterns of the human genome, physicians can more accurately pinpoint disease states and recommend therapies that are tailored to a person's unique genetic makeup or "molecular signature." So in some cases, MDx do more than help physicians diagnose illnesses; they indicate a course of treatment. That's why it requires extensive research and development to bring new MDx to the market. As a result, they command much higher prices than traditional diagnostics.

Despite the benefits of MDx, criteria for accepting them into standard medical care have not been established. Opinions about their effective use vary. Some think multiple double-blind prospective trials should be required before any MDx test is used. Others feel the rigor of the approval process should be proportional to the importance and seriousness of the consequences related to the test's outcomes. Still others believe findings that are consistent across multiple peer-reviewed articles provide enough information to permit use.

The following table outlines some of the issues facing various healthcare entities regarding the effective use of MDx.

MDx Challenges by Healthcare Stakeholder	
Stakeholder	Challenges
Primary Care Physicians	<ul style="list-style-type: none"> • Having patients, with or without family histories of potentially deadly disease, demanding tests such as hypercholesterolemia or BRCA1 and BRCA2 • Staying updated on new tests: Which are appropriate? Which have strong evidence of accuracy?
Payers/Managed Care Organizations	<ul style="list-style-type: none"> • Keeping diagnostic “formularies” up-to-date in the face of constantly changing information on MDx • Determining how to code and value tests • Knowing which tests should be covered, and understanding if certain tests can potentially reduce overall cost for patients — and do so over a time frame that makes sense for payers • Dealing with the growing number of labs seeking — or worse, not seeking — network participation • Dealing with having MDx ordered by physicians who don’t know whether the tests will be covered
Reference Labs	<ul style="list-style-type: none"> • Performing tests ordered by physicians that labs assume will be covered, but are denied by payers due to confusion in coding. For example, there are three Hereceptin® receptivity tests on the market, and some payers don’t cover all of them
Pharmacy Benefit Managers	<ul style="list-style-type: none"> • Lacking up-to-date information to use in encouraging the prescribing of appropriate medications for their members

There’s a great deal of work to do.

Some worthy solutions have been developed by private industry, including decision-support tools from McKesson Health Solutions discussed later in this paper.

Genomic Healthcare Strategies has been talking about the importance of MDx since 2006. However, those who deal with basic issues such as usefulness and reimbursement of MDx have been slow to respond to the need for improving the categorization of these new diagnostics.

“The CPT codes being used today neither accurately reflect what tests are actually being done, nor do they link to specific types of results,” writes Emad Rizk, M.D., president of McKesson Health Solutions, in his April 2009 article in *Managed Care*. “I equate it to going to a furniture store to buy a table. If, instead of having an order for a table, you got an itemized bill for eight pieces of wood, 12

screws, and three hours of labor, that wouldn't tell you very much about what you just purchased. Confusing as this sounds, it is how many MDx tests are billed and reported."

Dr. Rizk points out a fundamental problem that had to be addressed before any useful system could be created. Describing something by its components says very little about the potential benefits of its creation and use.

Where Do We Begin?

Can the needs of patients, physicians, labs and payers be met instantly? No, not any more than would have been possible to buy books on Amazon.com in the first days of the Internet.

For patients, physicians, labs and payers to realize the full benefit of MDx, the healthcare industry needs a responsible, organized and current knowledge base of information about these tests.

This system must:

- Uniquely identify and classify the clinical and utilization information for each test
- Objectively explain key attributes of each test and differentiate among tests that seem similar
- Be readily accessible and usable by patients, physicians, labs and payers

The American Medical Association CPT Editorial Panel and the Centers for Medicare and Medicaid Services (CMS) HCPCS Panel are responsible for evaluating and assigning HIPAA-compliant codes for laboratory services. Thus, many people assumed that the AMA would be more active in this area than has been the case. In December 2009, the AMA Molecular Pathology Coding Workgroup was established and charged with creating a new section of the CPT Pathology and Laboratory for MDx. To date, the workgroup has proposed codes for more than 90% of the molecular diagnostics it deems "medically useful," and the group is working to publish these new codes by 2013.

However, the term "medically useful" is controversial and encompasses only a small number of MDx tests — perhaps 50 out of some 2,000 available unique assays. This is because to develop a new CPT code, a proposed service must have established clinical evidence. As mentioned earlier, the vast majority of MDx are still in their infancy; the clinical evidence of benefit or "clinical utility" is incomplete. So while the AMA effort continues, it is unlikely to fully address the many issues around classification and use we are facing today.

Fortunately, other projects are also under way. McKesson recognized the need for a comprehensive, industry-wide master catalog and began assigning unique IDs and gathering information for MDx. McKesson "Z-codes" identify the test, laboratory, ordering physician, reason for ordering and results — similar to the health plan-defined HCPCS S-codes. Utilizing a 5-character coding algorithm starting with 'z' (1.4 million potential identifiers), the McKesson system assigns and maintains the codes in an automated registry. Since there's no embedded classification system, the Z-code model can accommodate changes on the fly.

McKesson Z-codes have been discussed with the National Institutes of Health, which is also working on a classification system for MDx with a focus on medical research and technology development. As two exclusive initiatives, the efforts of McKesson and of the NIH are surprisingly well aligned. The two organizations share the goals of using codes immediately to track research and evidence on the tests, rather than waiting for these facts to be established in peer-reviewed journals before assigning identifier codes.

However, creating and maintaining an up-to-date database of MDx isn't as easy as it might seem. Challenges include maintaining potential changes about each test's:

- Description
- Regulatory status
- Effectiveness based on clinical evidence
- Insurance coverage and policy rules

In addition, information on any superseded or reinforced research supporting the existence of specific biomarkers/diagnostics must be included as well. Finally, double-blinded, controlled trials that are the gold standard for evaluating therapeutic trials don't make sense for diagnostic testing; other mechanisms for evaluating the 'clinical utility' and value of these tests must become generally accepted.

CMS tackled a similar classification problem more than 30 years ago by establishing National Drug Codes (NDC) to improve the safety of outpatient pharmaceuticals. Back then, mislabeled drug packages had led to safety issues, including some patient deaths. Now, a universal 11-digit alphanumeric code identifies:

- The drug name
- Whether it has a generic or brand-name status
- Its strength and packaging information

However complex, capturing and maintaining a repository of information about MDx is the cornerstone of a functioning system for its effective use. What's needed next? If MDx are going to be used effectively, clinical content must be made available through database design and system development.

- Physicians need information on when their use is appropriate. The fire hose flow of information about MDx tests is too intense for PCPs (and even some specialists) to keep up with it.
- Physicians must be able to double-check their knowledge of certain tests, look up the range of tests available under the same general headings, understand the circumstances under which each test is appropriate and find which facilities are best to perform them.
- Financial transactions must be clear and understandable: Physicians and labs must know beforehand whether tests will be reimbursed by their patients' insurance.
- The managed care organization or physician practice needs to know which lab can perform the test.
- If the test is being reimbursed, the participants (especially the lab performing the test) must know whom to bill and if they will get paid.
- If tests aren't covered, physicians need to explain why to patients — is it due to the patient's situation or some concern about the viability of the test itself?

The authors have both been senior executives in entrepreneurial companies that produced software. We understand how challenging it is to take these first steps — to capture the data, turn content into a functioning database, develop a wholly new system and maintain and grow that system.

The information must be current. It must be available in an easy-to-use form. It should be available at the point of care. Physicians, labs and payers must receive information that is consistent. The MDx registry must be amenable to being accessed in a variety of ways for different users.

Equally important is to design and implement a solid, transparent system for keeping the data current, including:

- A robust and flexible coding system to allow changes in classification of a diagnostic test as scientific and regulatory results are published
- A precise data management system for vetting, formatting and allowing information to be entered into the system and displayed, and doing this in a cost-effective and rapid way
- An organizational unit that focuses on capturing all of the necessary information from reference labs, payers, health plans, diagnostic companies, scientific journals and others involved in the creation and use of MDx

The registry and the system are the cornerstones required for using MDx effectively.

The Future of MDx in Healthcare

McKesson's Clear Coverage™ and Clear Orders™ solutions have been created to perform the tasks bulleted above. These systems run on the Web — they only require a PC with high-speed Internet access to run. With powerful real-time decision-support engines, these solutions operate at the point of care. McKesson has been steadily moving forward, now establishing a functioning system that allows physicians, payers and reference labs to provide useful information for themselves and their patients. McKesson's solutions also provide a quality management tool for healthcare organizations and reimbursement information for labs.

As Matthew Zubiller, vice president, Advanced Diagnostics Management at McKesson says, "What gets measured, gets managed." For each test, he cites specific:

- Codes
- Guidelines
- Costs
- Coverage

Measurement systems provide a significant step forward. They offer the clarity that is needed for MDx, and more important, allow organizations to deal with MDx in a rational, procedural way. Below are two scenarios depicting some typical difficulties in the use of MDx today, along with how those scenarios play out in the future (McKesson) model.

Scenario 1: Factor V Leiden Genotype

A busy orthopedic surgeon sees a new female patient, the wife of an attorney, for hip replacement surgery. While the surgeon is affiliated with a teaching hospital, its academic medical center hub is 250 miles away. He performs most surgeries in the local community hospital. The surgeon is well acquainted with and uses anticoagulant therapy as prophylaxis to avoid DVTs that can present as life-threatening pulmonary embolism following joint replacement surgery.

In this case, there is a family history of DVT in the patient's mother, and the surgeon is concerned about the recent spate of litigation over standard of care, "preventable" DVTs, and upcoming changes in reimbursement making post-op DVTs a "non-payment" hospital event. He considers whether a Factor V Leiden genetic test might be in order.

The following chart provides a comparative view of how this scenario would unfold when using a traditional model and a future model.

Scenario 1: Factor V Leiden Genotype

Current Model	Future (McKesson) Model
1. The surgeon researches scientific literature online and re-acquaints himself with venous thrombosis facts: Known genetic causes explain about 50% of venous thrombosis cases, and 40% of patients with inherited coagulation disorders have Factor V mutations.	1. The surgeon's office assistant inputs information about the patient's health status and history into a decision-support tool at the point of care to see if a Factor V Leiden genetic test is appropriate.
2. He decides to request a Factor V genetic test.	2. The tool indicates that in joint replacement patients with adequately managed anticoagulant prophylaxis, those with Factor V fail to show any statistically significant increase in DVTs over normal patients.
3. His staff calls the local hospital about information on Factor V testing and is told the local hospital lab does not perform Factor V.	3. The surgeon decides the test would be unnecessary, and continues with plans to use anticoagulant therapy as prophylaxis to avoid DVT in his patient.
4. The staff leaves a message with a community pathologist to see if he knows where the testing is performed.	4. He discusses his plans with the patient, citing the evidence to back his determination. She agrees that the test would be inappropriate, and thanks the doctor for his thorough research.
5. The local community pathologist calls the surgeon back and informs him that both a regional lab and the academic medical center lab perform Factor V tests, but that the tests are different because one uses CPT codes 83891 Isolation, 83898 Amplification, 83896 Nucleic acid probes and 83912 Interpretation and report while the other uses CPT codes 83890, 83894, 83898(x2) and 83912.	5. The surgeon and patient are fully satisfied with their plan, given her family history and unique health status.
6. The surgeon decides to request a Factor V test from the academic lab because he knows the pathologist there.	
7. The academic lab pathologist calls the surgeon with the results: The patient does have a Factor V mutation, but the pathologist has read several peer reviewed articles showing that in joint replacement patients with adequately managed anticoagulant prophylaxis, those with Factor V failed to show any statistically significant increase in DVTs over normal patients.	
8. The academic lab submits its CPT codes to the patient's insurance company, without knowing beforehand whether those codes will be accepted or if there are other codes that might be accepted.	
9. The patient's insurer receives the stacked CPT code bill, but does not have a way to associate the CPT codes with Factor V testing for joint replacement, or tracking of DVTs. The claim is referred to the medical director for review and denied.	
10. Three months later, the patient finds out that she is liable for the full cost of the lab.	
11. The surgeon feels the test was unnecessary, since his standard anticoagulant protocol seemed to be sufficient.	
12. The patient wonders why there was a co-pay to determine her susceptibility to DVTs in all settings, something that seemed obvious given her family history.	

Scenario 2: Plavix®

Plavix (clopidogrel) is an oral, antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. In 2009, Bristol-Myers derived almost one-third of its total sales, or \$6.1 billion, from this blood-clot inhibitor, co-marketed with French drug maker Sanofi-Aventis. However, in March 2010, Plavix received a black box warning from the FDA, indicating that mutations in the CYP2C19 gene render certain patients unable to respond to the drug, placing them at increased risk for heart attack and stroke.

Meanwhile, a patient with a history of coronary artery disease, angioplasty and stent placement has been taking clopidogrel for three years to reduce the chance of recurrent ischemic events. The patient has changed his lifestyle and is now a competitive long-distance runner and listens to The Wall Street Journal podcast daily. The patient has heard about the black box warning and that up to one-third of patients don't respond well to clopidogrel. He also heard there is controversy over the value of genetic testing for long-term use of clopidogrel. The patient schedules a visit with his cardiologist to discuss the issue.

The following chart provides a comparative view of how this scenario would unfold when using a traditional model and a future model.

Scenario 2: Plavix	
Current Model	Future (McKesson) Model
1. The cardiologist and the patient decide having the test results may be useful.	1. The cardiologist's assistant inputs information about the patient's health status into a decision-support tool at the point of care to determine if the test results may be useful.
2. The cardiologist chooses to order the test from the local lab because it has offered a Roche Amplichip test for years, which includes CYP2C19 and other liver metabolizing enzymes. (The cardiologist does not know that an in-network lab with national reach, has been offering a PCR-based CYP2C19 test with result reporting tailored to Plavix at \$200 since October 2009.)	2. The tool indicates that based on evidence, Plavix-specific genetic testing is appropriate in this case, and that the test can be obtained from Quest Labs.
3. The test results indicate the patient doesn't metabolize clopidogril well to the active form.	3. The test results indicate the patient doesn't metabolize clopidogril well to the active form.
4. Taking into account the patient's improved exercise regime and lack of benefit of clopidogrel (which costs \$5 per pill), the cardiologist suggests a switch to generic aspirin as an anticoagulant.	4. Taking into account the patient's improved exercise regime and lack of benefit of clopidogrel (which costs \$5 per pill), the cardiologist suggests a switch to generic aspirin as an anticoagulant.
5. The health plan receives a bill for the Amplichip test and denies reimbursement because they only authorize payment at \$200 for Plavix-specific genetic testing, but not other liver-metabolizing enzymes.	5. The health plan receives the bill for Plavix-specific genetic testing and pays it in full. While the patient wonders why he wasn't switched to aspirin sooner, he is satisfied with the outcome and that his health plan covers the cost of the test.
6. The patient and cardiologist wonder why the health plan won't pay for a test that clearly saves money. The patient wonders why he wasn't switched to aspirin sooner.	

Conclusion

In the past, the elements of developing advances in medicine stood alone. Pharmaceutical companies could develop a drug, move it through regulation and price it. What remained was selling it to doctors, and more recently, encouraging patients to ask about it. Those days are gone. New therapies, devices and diagnostic tests will no longer be introduced and priced without being examined in the larger context of outcomes and costs. The future of healthcare will require both clinical and economic validation of all its components.

With diagnostics informing decisions that impact 70% of the healthcare dollar, the measurement, tracking, regulation and utilization of MDx must be a priority. These tests more closely tie diagnosis to therapy than ever before. Yet the most current systems and processes don't allow capturing useful metrics about them from either a clinical or economic perspective.

Fortunately, there are many smart and innovative approaches being developed to overcome this barrier. These approaches will promote best practices, inform patients, facilitate caregivers, streamline reimbursement and measure outcomes for MDx. Healthcare organizations that adopt and embrace these approaches will be the most successful. For the future of MDx — *of medicine* — lies in the interconnections, data, and measures that support and make their thrilling promise real.

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This publication was written by Genomic Healthcare Strategies for McKesson Corporation. The opinions presented are solely those of Genomic Healthcare Strategies.

Genomic Healthcare Strategies provides strategy and implementation services for companies looking to enter or grow in the new markets emerging as a result of predictive diagnostics and preventive medicine.

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