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Center for Health Reform & Modernization

Personalized Medicine:
Trends and prospects for the new science of genetic testing and molecular diagnostics

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Table of Contents

Preface . . . 2

Executive Summary . . . 3

Foreword . . . 7

Summary of selected recommendations . . . 8

Chapter 1: Introduction – what are genetic tests and molecular diagnostics? . . . 10

Chapter 2: How widely are genetic tests and molecular diagnostics currently being used? . . . 12

Chapter 3: What do consumers and physicians think about genetic testing? . . . 19

Chapter 4: Ensuring patients benefit from the new science of genetic testing and molecular diagnostics . . . 26

1. Protecting, supporting, and informing patients through data confidentiality, non-discrimination, and decision support . . . 26
2. Benefiting patients by developing the clinical evidence base to determine which tests work . . . 27
3. Stimulating future progress by encouraging the development of tests that are proven to work . . . 28
4. Monitoring care through more transparent coding and reporting . . . 29
5. Protecting patients by ensuring that lab tests are performed safely and accurately . . . 30
6. Making it easier for health professionals to stay up-to-date as genetic science evolves . . . 31

Conclusion . . . 32

Appendices

1. Definitions used in genetic testing and molecular diagnostics . . . 33
2. Types of genetic tests and molecular diagnostics . . . 35
3. Categories of tests, applications in clinical practice, and examples . . . 37
4. Developing the evidence base . . . 38
5. How payers make coverage decisions for genetic testing and molecular diagnostics . . . 39
6. Medicare reimbursement for clinical laboratory services . . . 41
7. U.S. coding practices for genetic testing and molecular diagnostics . . . 42
8. Quality assurance at laboratories performing genetic testing and molecular diagnostics . . . 44
9. Methodology – survey of consumers and physicians and analysis of UnitedHealthcare claims data . . . 46

References . . . 48

Preface

"Without question, man's knowledge of man is undergoing the greatest revolution since Leonardo. In many ways, personalized medicine is already here." [1]

– Dr. Francis Collins
Director of the U.S. National Institutes of Health

The past decade has seen important progress in understanding the genetic causes and best treatment options for health conditions as diverse as age-related macular degeneration (one of the most common causes of blindness), Hepatitis C (which now kills more people in America than HIV/AIDS), and a number of cancers — which it is now clear are genomic diseases.

Yet most clinicians and researchers think this is just the start. In the words of one prominent physician: "The first decade since the human genome sequence was drafted will, in retrospect, be viewed as the long warm-up to making a difference in day-to-day medical practice." [2] In this new working paper we therefore attempt to shed light on several important questions:

- What is the current state of genetic testing and molecular diagnostics?
- What do doctors and patients think about these developments?
- What practical action can be taken to ensure proper safeguards while accelerating progress for patients?

As reported in our new national survey, most physicians think more of their patients could benefit from these new techniques, and most consumers are optimistic about the potential benefits. This working paper is a contribution to the debate about how best to bring this about.

This is the seventh in a series of working papers from the UnitedHealth Center for Health Reform & Modernization. Our published work to date has examined cost containment in Medicare, the future of Medicaid, options for lowering the U.S. budget deficit, new models for diabetes prevention and treatment, modernizing rural health care, and using technology to cut administrative waste. All reports are available at www.unitedhealthgroup.com/reform.

Simon Stevens
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Executive Vice President, UnitedHealth Group

March 2012

Executive Summary

Advances in genetics, genomics and proteomics are leading to progress in identifying and treating disease, developing treatments, and improving health. Use of genetic testing and molecular diagnostics is rapidly expanding in clinical practice, creating a new, personalized approach to medicine. This working paper considers four main questions, and presents new data and analysis to help answer them.

Chapter 1: What are genetic tests and molecular diagnostics?

1. Genetic testing analyzes an individual's or an organism's genetic material, including around 23,000 protein-coding genes and biomarkers. It often uses molecular diagnostic techniques and is available for an estimated 2,500 conditions, both rare and common. Recent estimates suggest that there are 1,000 to 1,300 genetic tests currently available. New tests are regularly emerging at a rate of several per month. Increasingly, information from genetic and molecular screening and testing is helping patients and their doctors:

   - identify a person with a predisposition for a particular disease;
   - detect whether a person has a disease, often at earlier stages of the illness than was previously possible;
   - identify the effectiveness of a particular drug therapy for an individual.

   Some analyses suggest that current genetic tests and molecular diagnostics apply to about 2 percent of the population, but have the potential of benefiting more than 60 percent of the population in the future. Whole genome sequencing — which maps an individual's entire genetic code — is also expected to become widely available in the near future.

Chapter 2: How widely are genetic tests and molecular diagnostics currently being used?

2. Hard data on current patterns of use of genetic testing and molecular diagnostics are difficult to come by. By analyzing proprietary claims and clinical information from UnitedHealthcare, this working paper produces new estimates suggesting that the cost of genetic and molecular diagnostic testing for UnitedHealthcare members was about $500 million in 2010. Of this total, nearly 40 percent was testing for infectious diseases, 16 percent for cancer, and the remainder for other conditions including inherited disorders. The total expenditure was, in part, a function of the customer mix served by UnitedHealthcare. Per person spending was higher for UnitedHealthcare's Medicare and Medicaid members than for UnitedHealthcare's commercially-insured population, by 16 percent and 24 percent per person, respectively. Test procedure usage per person was highest in the UnitedHealthcare Medicaid population, followed by the UnitedHealthcare commercially-insured population, and then the UnitedHealthcare Medicare population. We estimate that spending per member on molecular and genetic tests increased by about 14 percent a year on average between 2008 and 2010.

3. Previous estimates of annual spending in the U.S. on genetic testing and molecular diagnostics vary, as they include different kinds of tests in their definition depending on the market. Estimates using data from 2006 to 2009 suggest $3 billion to $4 billion of spending annually. Extrapolating from the UnitedHealthcare data, combined with additional analysis of Medicare and Medicaid fee-for-service spending, we estimate that national spending for these services reached about $5 billion in 2010, which represents about 8 percent of national spending on clinical laboratory services.

4. This working paper includes three 10-year scenarios to illustrate potential growth trajectories in genetic testing and molecular diagnostics. Based on these scenarios, we estimate that national spending for these tests could reach between $15 billion and $25 billion by 2021.

Chapter 3: What do consumers and physicians think about genetic testing?

5. To understand the latest consumer and physician views on genetic testing, we commissioned two new national surveys in conjunction with Harris Interactive (n=2,760; fieldwork conducted in January and February 2012).

6. Results show that overall, U.S. adults have positive attitudes towards genetic testing. Around three-quarters of consumers surveyed agree that genetic testing helps doctors diagnose preventable conditions and offers more personalized treatment options. U.S. adults' awareness of genetic testing is considerably higher than reported usage: 71 percent of consumers said they were "familiar" with "genetic testing," although only one-in-two felt they were "knowledgeable" about "genetic science." Only 6 percent of consumers reported having had a genetic test themselves and a further 3 percent were unsure. Similarly, 10 percent said a family member has had a test, while a further 10 percent of consumers were unsure. Eighty percent of respondents expect that five years from now the number of genetic tests will have increased and 74 percent expect that the use of testing will have increased.

7. Around three-quarters of doctors surveyed say that genetic testing allows for more personalized medical decisions and more targeted choice of therapy. Around two-thirds (63 percent) say it gives them the ability to diagnose conditions that would otherwise be unknown. On average, physicians report having recommended genetic testing for 4 percent of their patients over the past year. However, about three-quarters of doctors also said that there are patients in their practices who would benefit from a genetic test but have not yet had one. Looking ahead five years, physicians on average said that they expect 14 percent of their patients will have had a genetic test.

8. Seventy-five percent of physicians responding to the survey described themselves as "somewhat knowledgeable" about genetic science, with 7 percent reporting that they are "very knowledgeable" and 16 percent "not knowledgeable." Physicians report that nearly three-quarters of their patients (72 percent) are "somewhat able" to understand the results of genetic tests, with 13 percent "fully able" to do so, and 7 percent "not at all able to understand" them. Nearly three-in-five doctors (59 percent) say that they are very concerned about the cost of genetic tests for their patients; a figure that is three times as large as their concern for their own reimbursement for genetic testing (21 percent). Furthermore, more than half of physicians (56 percent) think that the net effect of new genetic tests will be to increase health care spending, compared with only one-in-five (19 percent) who think such testing will reduce health care costs. A clear majority of doctors say that genetic testing will improve care across a range of health problems in the future.

Chapter 4: Ensuring patients benefit from the new science of genetic testing and molecular diagnostics

9. The working paper explores six domains where action would ensure patients benefit the most from the new science, help advance patient care, and make sure that genetic tests are used effectively and that affordable care is preserved.

10. ***Domain 1: Protecting, supporting, and informing patients through data confidentiality, non-discrimination, and decision support.*** In order for the public and patients to feel confident about making full use of the benefits of genetic testing, it will be essential that strong privacy, data ownership, and non-discrimination measures are in place — and that consumers learn about the strong legal protections that already exist through the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Genetic Information and Non-Discrimination Act of 2008 (GINA), and various other regulations. Consumers also would welcome decision-support tools to enable active participation — in partnership with their health professionals — in identifying potentially useful tests and in making decisions about the use of genetic testing in their care. Outreach programs, such as those in place today for testing for the risk of breast cancer, can identify patients who might benefit from testing, enabling them to access preventive services and, in the case of some medical risks, encouraging them to adopt lifestyle changes to prevent disease onset.

11. ***Domain 2: Benefiting patients by developing the clinical evidence base to determine which tests work.*** Generating and reviewing evidence that a test works and is clinically useful is challenging for this new area. For relatively simple tests that have been used for a long time, such as those for infectious disease or certain screening, there is evidence of clinical utility — that is, the test has a demonstrated ability to improve the process of care and/or outcomes, taking into account the benefits and risks of testing. However, of the roughly 1,000 to 1,300 newer and more complex tests, only a minority have demonstrated clinical utility so far. New research models may provide alternatives to traditional clinical trials (such as randomized controlled trials) that include a less expensive mechanism for evaluating genetic and molecular diagnostic tests. Examples of possible models include those that involve rapid iterative cycles, practice-based interventions, observational studies, prospective and retrospective studies, and comparative effectiveness research (CER).

12. ***Domain 3: Stimulating future progress by encouraging the development of tests that are proven to work.*** Given the pace of change, information gaps, and the evolving evidence base around genetic testing and molecular diagnostics, public and private payers face a challenge in developing coverage policies that provide individuals with access to the most effective treatments. Reimbursement approaches used today, which involve setting an initial rate and subsequent indexing for inflation, may not reflect appropriately the value to the delivery system of a new technology and its continued use. They also may contribute to the rising costs of new and complex tests. New approaches are needed and the working paper discusses some of the options.

13. ***Domain 4: Monitoring care through more transparent coding and reporting.*** Transparency about which tests are being used under what circumstances is a prerequisite both for tracking the appropriateness of care and for responding to the strong concerns expressed by patients and physicians about the affordability of health care. Only a few dozen codes exist to identify tests done for specific diseases, and about one-third of advanced diagnostic spending is estimated to be unidentifiable because of inadequate coding. Action is needed to expedite the development of a coding system that can assign specific codes to individual genetic and molecular diagnostic tests. The implementation of new diagnosis codes (ICD-10 codes) may help connect tests to a broader clinical context.

14. ***Domain 5: Protecting patients by ensuring that lab tests are performed safely and accurately.*** The current regulatory infrastructure for genetic tests and molecular diagnostics — which is primarily housed at the Food and Drug Administration(FDA) and the Centers for Medicare & Medicaid Services (CMS) — has significant gaps. Tests should be assessed based on the risk of harm arising from use of the test's results in a patient's clinical care and oversight should be focused on those where the risk is greatest. This might involve strengthening laboratory accreditation standards for certain higher risk laboratory-developed tests (LDTs), together with higher level FDA review. However, it will also be important not to undermine successful innovation, nor to seek to impose new paternalistic controls on consumers' ability to access and learn about their own genetic information.

15. ***Domain 6: Making it easier for health professionals to stay up-to-date as genetic science evolves.*** Providers will increasingly need the ability to interpret more complex genomic data and make evidence-based recommendations to their patients. Professional medical societies and other independent and research entities should refine existing guidelines to reflect appropriate uses of genetic testing and molecular diagnostics. This could include "triggers" that help care providers identify patients at risk for certain diseases enabling genetic counselors to then help care providers and patients make more informed decisions about treatment options possibly facilitated by educational aids, such as telemedicine and online information.

Conclusion

Continued advances in genetics, genomics and proteomics have the potential to change medicine dramatically over the next several decades. In short, we can do more to realize the full potential of these new scientific discoveries, and improve the health of the population. It is time to do so.

Foreword

As advances in genetics, genomics, and molecular science escalate, so does enthusiasm for the potential that these innovations could have to significantly improve medical care delivery and health outcomes. Those developments, combined with a rich array of new data and analytic tools, communication vehicles for health engagement, and new health benefit designs that are targeted to individual health priorities means that we have reached an era of truly "personalized care." This is an exciting time of energy and innovation directed at preventing disease, promoting health, and tailoring medical engagement to each person. Collectively, new innovations hold great promise for better health and medical care outcomes. However, they also pose significant challenges to a system that is increasingly unaffordable and that uses existing resources sub-optimally. As genetics-based knowledge and products explode into this context, stakeholders across the health care system will need to be innovative in balancing support for molecular science innovation with attentiveness to quality, appropriateness, and cost-effectiveness.

I was privileged to be a member of the Secretary's Advisory Committee on Genetic Testing (SACGT), chartered in 1998 by then Secretary of Health and Human Services (HHS) Donna Shalala, and to chair its successor organization, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), re-chartered by HHS Secretary Tommy Thompson. We expanded the focus of the Committee's work to include the integration of genetic knowledge into health promotion, disease prevention, and clinical management. The Committee focused on developing protections for genetic information and against discrimination based on genetic information, as well as on the need for robust regulatory oversight of genetic tests, mechanisms to close gaps in research, data collection relevant to the clinical utility of existing and emerging genetic and genomic technologies, and challenges in enhancing genetics education for health professionals and the use of genetic counselors.

As the pace of innovation has accelerated, and as genetic medicine has become simply "medicine," there is an urgent need to continue the Committee's work that concluded in 2011. Concerns remain about gaps in the regulatory oversight of genetic tests, evaluation of their performance in clinical practice, and evidence about their contribution to improved health outcomes. We continue to face challenges with integration of genetic testing into care delivery and collecting and analyzing genetic data in a manner that advances appropriate care, while protecting the privacy of patient information.

We hope that this working paper will be relevant to health care system stakeholders in their efforts to harness the fullest benefits of this exciting era of molecular discovery, while also preserving affordable access to health care. It focuses on several key priorities in ensuring patients reap the benefits of new genetic and molecular technologies. They include supporting patient protection of genetic information, closing gaps in regulatory oversight of genetic tests, and generating clinical evidence to support clinical validity and utility. It also discusses how to facilitate a fertile climate for innovation that leads to improved health outcomes, while preserving affordable access to quality care and improving the capabilities of the delivery system, such as through genetic counseling resources. Above all, let us never forget that genetic science is about people, and we should keep those affected by genetic-based diseases at the forefront of our health policy and clinical engagement discussions. In the final analysis, we are all in this together.

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Summary of selected recommendations

Domain	Challenges	Recommendations
Protecting, supporting, and informing patients through data confidentiality, non-discrimination, and decision-support	• The public may not be fully aware of the strong legal protections for privacy and non-discrimination now in force. • Patients and the public may need reassurance about privacy and non-discrimination measures. • Patients may need additional resources and supports to aid in complex decision-making.	• Create materials that provide clearer explanations of statutory patient protections involving the use of genetic testing. • Develop decision-support tools that enable patients to be more active participants in making decisions about their care; incorporate tools into routine patient care and provide access to genetic counselors. • Establish outreach programs to identify patients who might benefit from testing and explore the use of health literacy programs that incorporate genetics and genomics.
Benefiting patients by developing the clinical evidence base to determine which tests work	• Generating and reviewing evidence that a test works and is clinically useful is challenging. • Manufacturers often lack the incentives or resources to conduct the relevant studies. • The pace of change is rapid and the evidence base is still being generated. • Small population sizes may make assessing the effectiveness on a population-wide basis challenging.	• Assess the strength of new research models that may provide alternatives to traditional clinical trials (such as prospective and retrospective studies, and CER). • Develop innovative approaches to help isolate the effects other socio-economic and environmental factors have on disease. • Consider more flexible clinical trial designs based on certain molecular characteristics and surrogate endpoints.
Stimulating future progress by encouraging the development of tests that are proven to work	• Lack of information about existing and emerging tests contributes to a variable reimbursement environment, making it difficult to set rates appropriately. • Fee schedules may not reflect the potential value of any improved outcomes or reduced spending resulting from the test. • Current approaches lock in reimbursement at an initial rate that may not change to reflect future developments. • Innovators need incentives to produce diagnostics for smaller subsets of populations.	• Improve development of payment rates for novel, complex diagnostics. • Foster collaboration between payers and technology developers on what clinical utility data may be required. • Explore approaches to create structured pathways for provisional coverage of certain genetic and molecular tests, while data on clinical utility are collected and refined. • Consider payment reforms now being developed in the broader health care system, including pay for performance linked to quality and efficiency, and more "bundled" payments for care episodes or the management of defined patient populations.
Monitoring care through more transparent coding and reporting	• Few codes exist to describe tests done for a specific disease, leaving it difficult to identify the test conducted, the laboratory performing the test, and the physician ordering the test. • Newer tests are identified primarily by the process used to conduct them.	• Expedite the development of a standardized coding system, created either through the current CPT procedure-based system or through a different third-party entity that can assign specific codes to individual genetic tests and genetic testing services identify the associated laboratories, manufacturers, and ordering providers; incorporate ICD-10 diagnosis codes to give providers broader clinical context.

Domain	Challenges	Recommendations
Protecting patients by ensuring that lab tests are performed safely and accurately	• Weaknesses exist in the current approach to laboratory quality assurance. • The purpose and structure of the current approaches to regulatory oversight are divided, leaving gaps where some tests may not be reviewed to assess their safety and efficacy.	• Tests should be assessed based on the risk of harm arising from use of the test's results in a patient's clinical care, and oversight focused on those where the risk is greatest. • Consider strengthening laboratory accreditation standards for certain higher risk laboratory-developed tests (LDTs), together with higher level FDA review. • Ensure the safety and efficacy of direct-to-consumer tests.
Making it easier for health professionals to stay up-to-date as genetic science evolves	• Only about 400 molecular diagnostic tests (out of the 1,000 to 1,300 tests available) have evidence-based guidelines today. • Rapidly evolving subject matter is complex. • No mechanism to move information from the "bench" to the "point of care" exists. • Need to develop and disseminate materials to providers.	• Refine existing guidelines to reflect appropriate uses of genetic testing; deploy a continuous process for guideline review and updates to reflect rapid developments. • Bolster appropriate use of services by exposing providers earlier to genetics and genomics and increase cross-training with individuals in the related field of bioinformatics. • Encourage greater use of genetic counselors as support for patient decisions on the appropriate course of care; facilitate with telemedicine and online materials. • Deploy evidence-based guidelines related to genetic testing through performance-based incentive programs; also conduct tracking of test use and clinical outcomes. • Develop interoperable health information technology that could provide information to clinicians about diagnostic service use.

Chapter 1: Introduction – what are genetic tests and molecular diagnostics?

The human genome comprises 23 paired chromosomes, with 6 billion bases, which are molecules that form the building blocks of DNA, arranged around a double helix in 400 trillion cells, containing around 23,000 protein-coding genes. Only 0.4 percent of the human genome differs between individuals. Understanding these differences holds the prospect of great advances in disease prevention and treatment. Family history is still one of the most important measurable risk factors for many conditions. But increasingly these insights are being enriched and extended through information derived from genetic and molecular screening and testing, particularly for infectious diseases, cancers, and for certain inherited and acquired disorders. These tests can help:

- Identify a person with a predisposition for a given disease.
- Detect whether a person has a disease, often in earlier stages of illness than was previously possible.
- Identify the effectiveness of a particular drug therapy for an individual with a particular condition (so-called pharmacogenetics/pharmacogenomics).
- Describe the precise nature of a disease, such as condition severity, and the characteristics of an organism.

Genetic tests are diagnostic tests that analyze various facets of an individual's or an organism's genetic material (DNA, RNA, chromosomes and genes). Beyond analyzing genetic material directly, tests also may analyze the molecular products of genes. Those gene byproducts (so-called biomarkers) may include proteins, enzymes, or metabolites, which are molecules involved in metabolism (see Appendix 1 for a glossary of terms).[3] Genetic information is critical in the diagnostic process, including for cancer tumors and viruses.

Genetic testing uses a variety of diagnostic approaches that may include biochemical, cytogenetic, and/or molecular techniques (see Appendix 2). Molecular diagnostics — complex laboratory techniques that focus on molecules and their subunits — represent a significant and often broader category of tests (beyond looking at DNA) for conditions or risks that may be influenced by environmental agents and other factors rather than genetic variation alone.

Genetic and molecular diagnostic testing is a subset of a category of tests that are performed on cell, tissue, and other samples taken from the body. Some are simple tests at the point of care, while others require more sophisticated methods and high-skilled technicians and specialized personnel to interpret results performed in large laboratories. Testing may be guided by physicians, medical geneticists, or genetic counselors, or patients may independently seek testing.

Currently, 1,000 to 1,300 genetic tests are available for an estimated 2,500 conditions, both rare and common.[4] Of the tests available for those conditions, the majority are available for use in clinical settings as opposed to research settings. New tests are regularly emerging at a rate of several per month.[5]

Testing ordered by a physician may occur in different settings: in the hospital, during an office visit, or — as is mostly the case today — in a laboratory.[6] Many lab tests currently use proprietary methods (so-called laboratory-developed tests (LDTs)). The majority of genetic and molecular tests are LDTs.[7] Studies suggest that seven major manufacturers develop tests in this area and about 1,000 labs currently offer the tests with others planning to do them in house.[8, 9]

Some analysts suggest that current genetic tests apply to about 2 percent of the population — but estimates suggest more than 60 percent of the population might benefit from their use in the future.[10] Whole genome sequencing — mapping out, or "sequencing," the entire genetic code for each person — likely will become more widely available in the near future. To support this innovation, there will need to be advances in information technology, security, and management, as well as capacity for analysis, high-throughput data processing, and careful protections for confidential information.[11]

DNA sequencing of the entire genome increasingly will be available due to dramatic reductions in cost and improved ability to interpret the huge amount of data in a human genome. In the short-term, the scope of diseases and conditions that can be understood using genetic analysis and molecular diagnostics likely will expand. Applications may include vaccines to prevent viral disease or virus-initiated tumors (e.g., human papillomavirus (HPV)/cervical cancer) and companion diagnostics — combined diagnostics and drug therapies — especially for cancer.[12, 13] Sequencing of entire tumor genomes is expected to guide combinations of therapies over the next two to five years. Longer-term advances may include new molecular technologies that will open doors for risk identification and treatment options for neurodegenerative conditions like Parkinson's disease and Alzheimer's disease. Carefully targeted combined diagnostic and drug therapy regimens for obesity, rheumatoid arthritis, and cardiovascular disease also are under discussion.[14]

Chapter 2: How widely are genetic tests and molecular diagnostics currently being used?

Hard data on current patterns of genetic and molecular testing use are hard to come by, partly because of the fragmented nature of care delivery and funding, but especially because of weaknesses in information capture by administrative coding systems.

We, therefore, decided to undertake a new analysis using claims data from UnitedHealthcare, the nation's largest and most geographically diverse commercial, Medicare, and Medicaid health plan. Our analysis provides new insights into recent trends in test usage and spending, broken out by funding source, patient group, and clinical category. We then were able to extrapolate from these data to produce estimates for the U.S. health care system. (See Appendix 9 for detail on our methodology.)

UnitedHealthcare's data

Claims data rarely identify specific tests or the number of tests performed; our analysis sheds light on this issue by categorizing test procedures into three general categories — infectious diseases, cancers, and inherited and other conditions (see Appendix 3). Although it may not provide a complete picture of the testing landscape, it nevertheless provides new information using a large national population covered by commercial insurance as well as managed Medicaid and Medicare programs. Our estimates do not include any associated physician or ancillary costs, follow-up service costs, or offsetting savings.

On that basis, we estimate that the cost of genetic and molecular diagnostic testing for UnitedHealthcare members was about $500 million in 2010 (see Table 2.1).

UnitedHealthcare members' use and spending on molecular diagnostics and genetic tests, 2010 [2]

	Category of Molecular Diagnostic and Genetic Test			
	Infectious Disease	Cancer	Inherited Conditions, Other	All Categories
Per Member per Month Cost				
Employer and Individual	$0.48	$0.22	$0.58	$1.28
Medicare Advantage	$0.12	$0.39	$0.98	$1.49
Managed Medicaid	$1.01	$0.08	$0.50	$1.59
All Members	$0.52	$0.22	$0.60	$1.33
Estimated Spending (in millions)				
Employer and Individual	$144	$66	$173	$383
Medicare Advantage	$3	$9	$23	$36
Managed Medicaid	$38	$3	$19	$60
Total	$185	$78	$215	$478

Category of Molecular Diagnostic and Genetic Test				
	Infectious Disease	Cancer	Inherited Conditions, Other	All Categories
Percentage				
Employer and Individual	38%	17%	45%	100%
Medicare Advantage	8%	26%	66%	100%
Managed Medicaid	63%	5%	32%	100%
All Members	39%	16%	45%	100%
Test Procedure Volume (in millions) /1				
Employer and Individual	4.1	0.2	1.7	6.1
Medicare Advantage	0.1	0.03	0.2	0.3
Managed Medicaid	1.0	0.03	0.2	1.3
Total	5.2	0.3	2.1	7.6
Test Procedures per 1,000 Members				
Employer and Individual	166	9	70	245
Medicare Advantage	35	17	100	152
Managed Medicaid	329	10	65	404
All Members	174	10	72	255
Spending per Test Procedure				
Employer and Individual	$35	$286	$99	$63
Medicare Advantage	$43	$271	$118	$118
Managed Medicaid	$37	$93	$93	$47
All Members	$36	$263	$100	$63
Service Units per Procedure /1				
Employer and Individual	1.1	3.3	5.3	2.4
Medicare Advantage	1.7	7.5	3.5	3.6
Managed Medicaid	NA	NA	NA	NA
All Members	1.2	3.8	5.1	2.5

Table 2.1; Source: UnitedHealth Center for Health Reform & Modernization, 2012
Sums may not add to totals because of rounding.

/1 Test procedures represent a count of distinct test procedures conducted. Individual tests may include a single procedure or multiple procedures. Service units per procedure represent the number of times a procedure is performed as part of a test.

/2 Figures exclude members enrolled in Medicare Supplement or Part D stand-alone plans.

NA: Data not available.

As shown in Figure 2.1, of the total cost of genetic and molecular diagnostic testing, 39 percent was for infectious diseases, 16 percent for cancer, and the remaining 45 percent for other conditions including inherited disorders.

Estimated UnitedHealthcare spending by category of test and type of insurance coverage, 2010

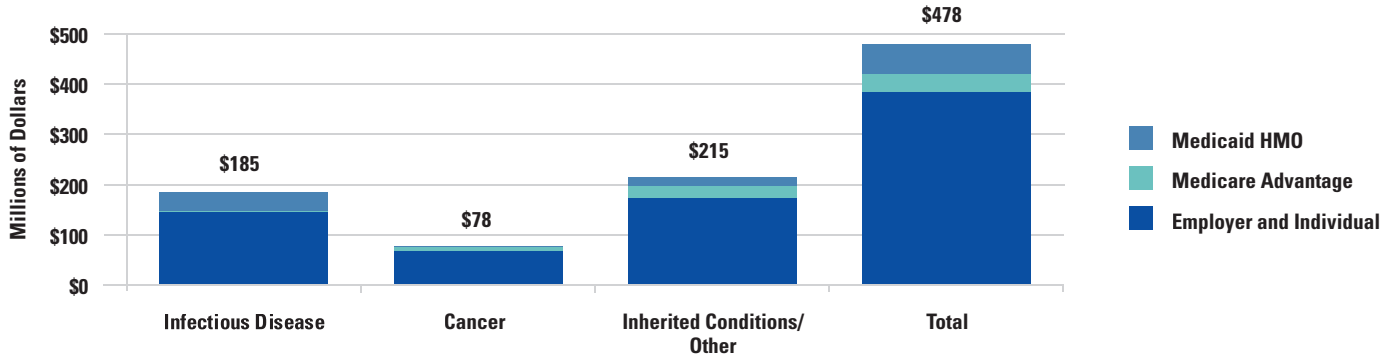


Figure 2.1; Source: UnitedHealth Center for Health Reform & Modernization, 2012

Reflecting the complexity of tests of this nature, the vast majority of spending on testing for people with individual or employer-sponsored coverage (about 80 percent) was for services provided by independent laboratories. Only 13 percent was for tests conducted in physician office settings and the balance was mainly for tests conducted in institutional settings. Cancer-related test procedures appear to have cost about seven times more than infectious disease test procedures, and almost three times the cost of other test procedures, reflecting their greater complexity.

While most (80 percent) of UnitedHealthcare's $478 million of aggregate genetic and molecular test spending was on behalf of people with individual or employer-sponsored coverage, *per person spending* appears to be higher for UnitedHealthcare's Medicare and Medicaid members than for UnitedHealthcare's commercially-insured population, by 16 percent and 24 percent per person respectively (as shown by comparing per member per month totals in Table 2.1).

As for utilization, the overall *per person procedure testing rate* was highest in the UnitedHealthcare Medicaid population, followed by the UnitedHealthcare commercially-insured population, and then the UnitedHealthcare Medicare population (see Figure 2.2). The rate of cancer-related procedure testing was highest in the Medicare population; the infectious disease-related procedure testing rate was highest in the Medicaid population.

Estimated number of test procedures per 1,000 UnitedHealthcare members, 2010

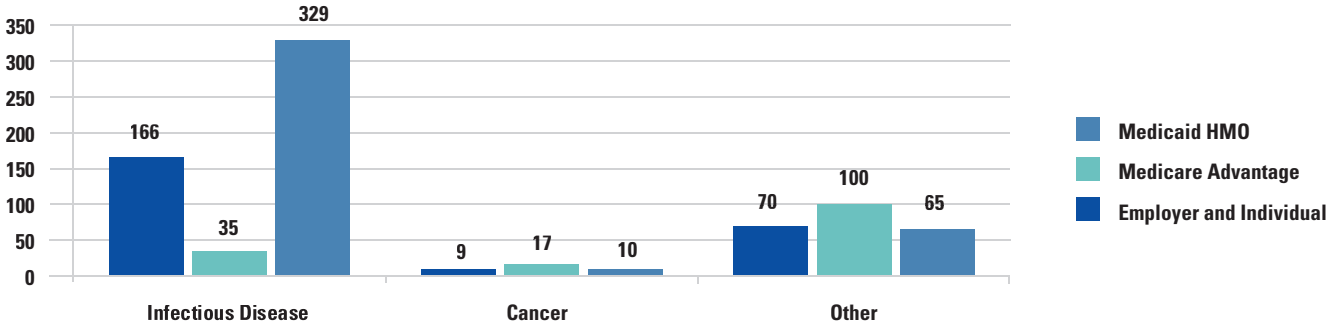


Figure 2.2; Source: UnitedHealth Center for Health Reform & Modernization, 2012

For UnitedHealthcare's employer and individual insurance membership, infectious diseases represented the highest volume of tests, with 4.1 million test procedures out of 6.1 million. Almost two-thirds of spending was concentrated on 10 types of test procedures, including tests for infectious disease (such as HIV), a test for the BRCA gene identifying breast cancer risk, tests aiding in breast cancer management, and several high-intensity genetic test procedures (such as DNA amplification) targeting a range of conditions.

The costs of cancer testing represented a higher proportion (27 percent) of diagnostics spending for UnitedHealthcare's Medicare Advantage population than for the employer and individually-insured population (17 percent), reflecting greater risk of and incidence of cancer in senior populations. As with commercial spending, two-thirds of relevant Medicare Advantage spending was for 10 test procedures.

In contrast to spending on testing for both commercial and Medicare populations, spending on advanced diagnostics for the Medicaid managed care population was primarily for infectious disease and spending was concentrated on a few infectious disease procedures.

Recent spending growth trends at UnitedHealthcare

We estimate that average annual spending per UnitedHealthcare member on molecular and genetic tests increased by about 14 percent between 2008 and 2010 (see Table 2.2). Of that amount, about 70 percent was due to increased utilization of test services; the balance was due to higher prices and intensity or complexity.

Factors underlying growth in UnitedHealthcare spending on molecular diagnostics and genetic testing spending

Average Annual Rate of Growth 2008 – 2010				
	Employer and Individual	**Medicare Advantage**	**Managed Medicaid**	**All Members**
Spending (PMPM)	**13%**	**21%**	**14%**	**14%**
Infectious Disease	10%	8%	14%	11%
Cancer	10%	18%	16%	11%
Inherited Conditions/Other	19%	24%	12%	19%
Test Procedures per 1,000 Members	**8%**	**13%**	**15%**	**10%**
Infectious Disease	9%	9%	17%	10%
Cancer	1%	1%	5%	3%
Inherited Conditions/Other	9%	18%	10%	10%
Cost per Test Procedure	**5%**	**7%**	**-2%**	**4%**
Infectious Disease	1%	-1%	-2%	0%
Cancer	8%	16%	11%	8%
Inherited Conditions/Other	9%	5%	2%	8%

Table 2.2; Source: UnitedHealth Center for Health Reform & Modernization, 2012

For UnitedHealthcare's employer and individual insurance membership, average annual spending growth for advanced diagnostics per person was about 13 percent from 2008 to 2010, with growth for testing for non-cancer inherited conditions at 19 percent. Almost 65 percent of overall growth was due to increased use of test procedures and the balance to rising cost per test procedure. Utilization accounted for most of the growth in testing for infectious diseases, while rising costs per test procedure for non-infectious diseases — about 9 percent a year — contributed to higher spending growth in those areas. Especially in the case of cancer testing, higher price growth per test was in part due to the rising complexity of those tests.

In UnitedHealthcare's Medicare Advantage program, average annual spending growth per person was about 21 percent from 2008 to 2010, with higher rates of growth for non-infectious disease tests than for infectious disease spending (which was about 8 percent on average annually). As in the commercial market, spending growth was utilization-driven, with about 65 percent of growth due to increased use of test procedures. However, the rising cost of cancer test procedures (about 16 percent on an average annual basis) was the main driver of cost growth for that type of testing.

Average annual spending growth per person enrolled in UnitedHealthcare's Medicaid managed care plans was about 14 percent from 2008 to 2010. Spending growth was primarily utilization driven, except in the case of spending per cancer test procedures, which grew at 11 percent on an average annual basis during this period.

Estimating national trends

Genetic testing and molecular diagnostics today account for a relatively small but growing portion of the overall U.S. market for *in vitro* diagnostics, which is estimated to be about a $20 billion market as of 2010.[15] Indeed spending has grown substantially over the last 10 years, with average annual growth of an estimated between 12 percent and 15 percent, rates much higher than for clinical laboratory services as a whole. [16, 17, 18, 19]

Previous estimates of U.S. annual spending on genetic testing and molecular diagnostics vary depending on the kinds of tests used to define the market, but estimates using data from the 2006 to 2009 period suggest $3 billion to $4 billion of spending annually. [20, 21, 22, 23, 24] What can these new UnitedHealthcare data tell us about national usage and spending trends across the United States?

Extrapolation from the UnitedHealthcare data, combined with additional analysis of Medicare and Medicaid fee-for-service (FFS) spending, implies that national spending for these services totaled about $5 billion in 2010 (see Figure 2.3). This represents about 8 percent of national spending on clinical laboratory services and less than half of one percent of national health spending.[25]

About 60 percent of spending nationwide for these novel diagnostics is in the commercially-insured sector. Much of the spending is for health services provided to adult, non-elderly women, in part because of the broad array of tests available today for breast and ovarian cancers.[26]

Estimated U.S. spending by payer on molecular diagnostics and genetic testing, 2010

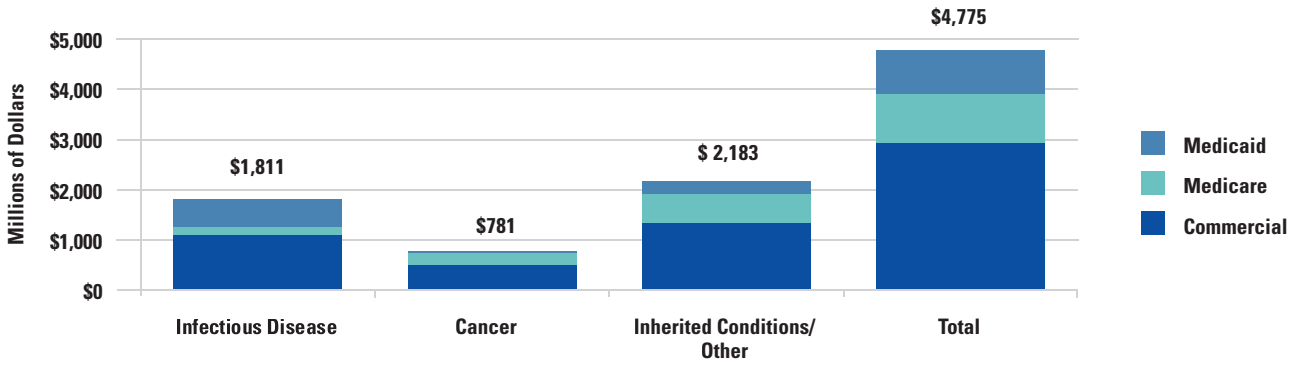


Figure 2.3; Source: UnitedHealth Center for Health Reform & Modernization, 2012.

Spending growth rates over the next decade are expected to be in the double-digits annually, or twice the rate of growth for the overall *in vitro* diagnostics market.[27] One forecast predicts that the market for molecular diagnostics could reach $7 billion by 2015, based on its current rate of growth.[28] Another forecast suggests that the availability of new tests is increasing at 10 percent annually with a 20 percent increase in utilization (compared to a 1 to 3 percent a year projected increase for non-genetic diagnostic tests).[29]

There will likely be a number of contradictory forces at work that will influence spending on such tests over the coming years. On the one hand, the continuing development of new tests, greater physician and patient awareness, lower-cost test settings, and the pairing of tests with new treatments will all contribute to their more widespread clinical uptake.[30] On the other hand, newer molecular diagnostics can cost between $1,000 and $4,000, partly reflecting development costs and partly a lack of competition for patent-protected technologies.[31] Limitations built into the Medicare fee schedule updates for clinical laboratory services may dampen growth rates. Some commentators also have pointed to low adoption of more complex genetic testing services, unproven clinical utility of some tests, reimbursement pressures in Medicare lab services, and questions surrounding the performance and capabilities of some laboratories as other factors that could hold down growth. [32, 33]

Projecting spending growth for these advanced diagnostics is challenging, in large part because of the unpredictable nature of the technologies themselves, their increasing application in medical care, and the rate of adoption by practitioners. Based on our analysis of recent growth rates, we developed three 10-year scenarios to illustrate potential growth trajectories:

- The "low-growth" scenario reflects a low innovation horizon; we assumed that growth in utilization over the last three years is tempered with minimal new adoption and that the cost of new technologies remains low.
- The moderate-growth scenario assumes greater adoption and use of novel testing procedures and that testing complexity and new inventions raise the price per test, starting in the middle of the decade.

- In the final scenario, we assumed that significant changes occur in testing technologies and that there would be a much higher rate of adoption for both cancer and non-cancer tests to both identify diseases and manage treatment courses. All but the last scenario assume that the infectious disease market is relatively mature and do not expect substantial growth over the next 10 years.

Based on these scenarios, we project spending on genetic testing and molecular diagnostics will reach between $15 billion and $25 billion by 2021 as shown in Figure 2.4:

Illustrative growth scenarios for molecular diagnostic and genetic testing spending, 2010 – 2021

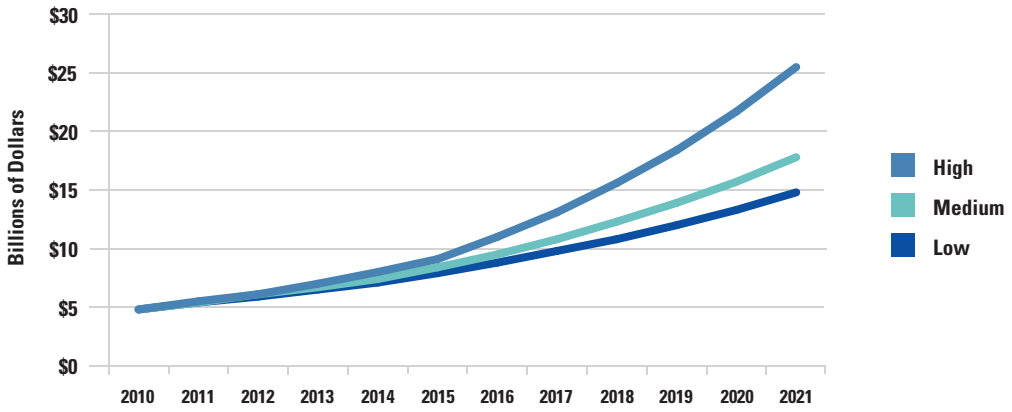


Figure 2.4; Source: UnitedHealth Center for Health Reform & Modernization, 2012

Finally, it is worth noting that although spending on genetic testing and molecular diagnostics is relevant in its own right, the more important question is what broader effects the use of such tests may have on the quality and costs of health care — particularly since, according to one estimate, clinical laboratory tests influence about 70 percent of health care decisions.[34] While history suggests medical advances have often contributed to higher overall spending by making more complex and costly tests and treatments available, they also have the potential to improve health outcomes and the appropriateness of care — for example, by fostering the more targeted use of therapies for those patients who will benefit most from them.[35]

We, therefore, now turn to the question of how consumers and their physicians think about the promise of new genetic science and their views on what the future might hold.

Chapter 3: What do consumers and physicians think about genetic testing?

Francis Collins, director of the National Institutes of Health, has coined the phrase "hope, not hype" to describe a sober but optimistic assessment of the potential benefits that genetic science will offer medicine over the coming years.

To "take the temperature" of physicians and consumers on the topic of genetic testing, the UnitedHealth Center for Health Reform & Modernization and Harris Interactive conducted two national surveys:

1,506 U.S. adults were surveyed by phone between January 11 and February 4, 2012.

1,254 U.S. physicians were surveyed online from January 13 to 31, 2012.

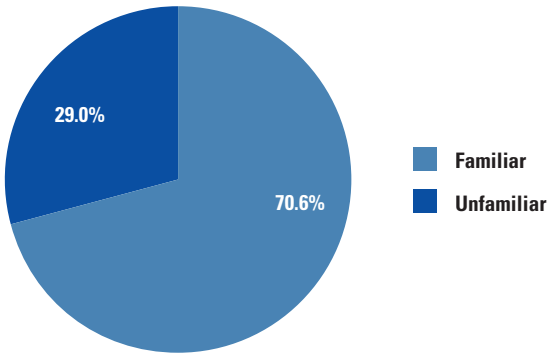
In both surveys, physicians and consumers were provided a basic definition of genetic testing and molecular diagnostics. The definitions reflect those described in this working paper. Data from both surveys were appropriately weighted to provide statistically representative national samples (see Appendix 9).

Consumer views on genetic testing

Consumers' awareness of genetic testing is considerably higher than usage. Figure 3.1 shows that 71 percent of consumers said they were "familiar" with "genetic testing," although only one-in-two felt they were "knowledgeable" about "genetic science."

Consumer familiarity with genetic testing and knowledge of genetic science

How familiar are you with genetic testing?



How knowledgeable are you about genetic science?

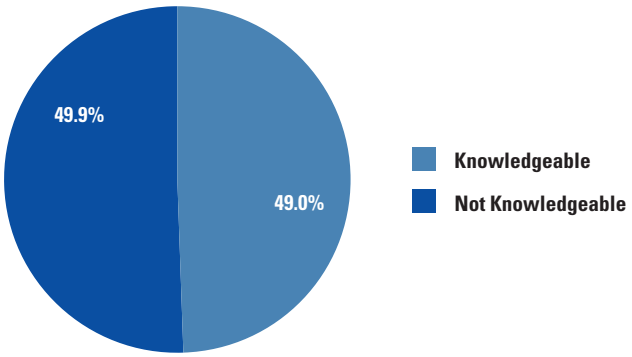


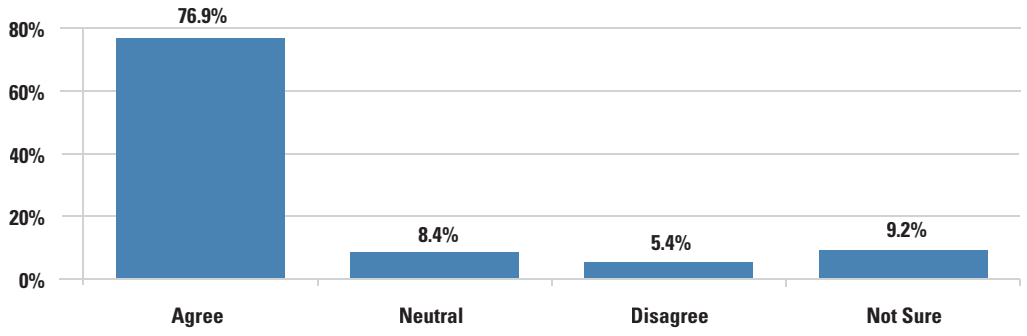
Figure 3.1; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of consumers, January 2012

By contrast, only 6 percent of consumers reported having had a genetic test themselves, and a further 3 percent were unsure. Similarly, 10 percent said a family member has had a test (with a further 10 percent of consumers unsure).

Overall, the survey shows that U.S. adults have positive attitudes towards genetic testing, as shown in Figure 3.2. Around three-quarters of consumers surveyed agree that genetic testing helps doctors diagnose preventable conditions and offer more personalized treatment options.

Consumer attitudes toward genetic testing

Genetic testing allows for more personalized medical decisions.



Genetic testing gives doctors the ability to diagnose conditions that can be prevented.

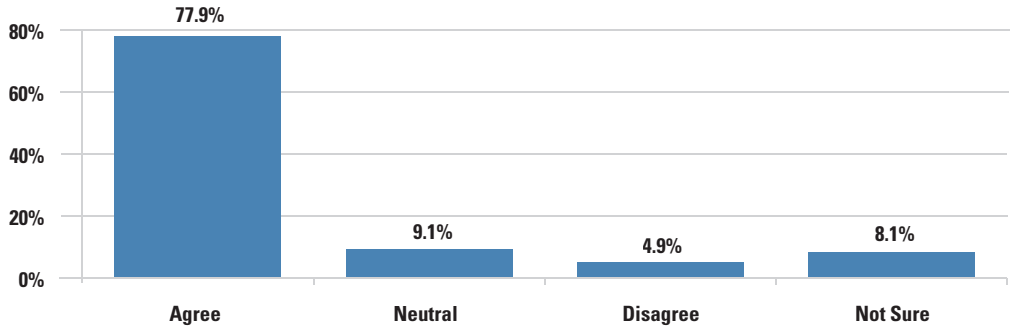


Figure 3.2; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of consumers, January 2012

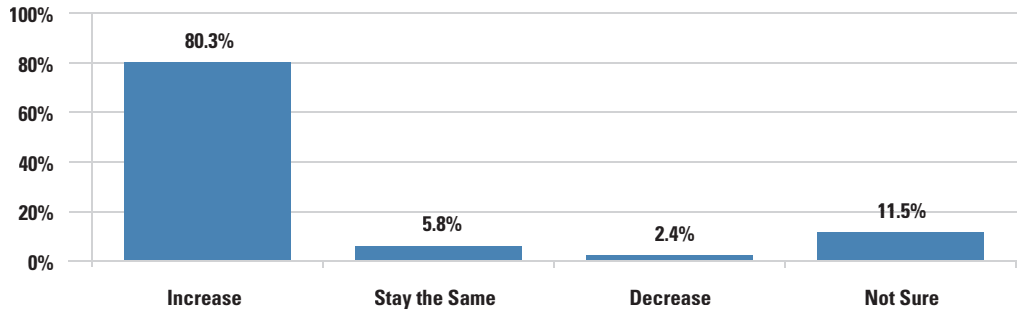
Over half of consumers surveyed are concerned about their physician's ability to interpret genetic testing results, the confidentiality of test results, and possible discrimination. Still, consumers are at least somewhat confident in their primary doctor's ability to know when they might need a genetic test — with 36 percent "very confident."

A majority of consumers reported that a number of resources would be useful when they are making decisions about medical care after a genetic test. Those resources include educational materials that provide information about the risks and benefits of treatment options, literature and information about the condition, consultation with genetic counselors, list of treatment options, and follow-up with a health care provider.

Looking to the future, only 4 percent of respondents expect to get a test in the next five years, while a further 9 percent are unsure. However, 80 percent of respondents expect that five years from now the number of genetic tests will have increased, and 74 percent expect that the use of testing will have increased. A majority of consumers believe that genetic testing will increase health care costs in the future (see Figure 3.3).

Consumer views on genetic testing in the future

Five years from now, do you expect that the number of different kinds of genetic testing available will increase, stay the same, or decrease compared to what is available today?



Five years from now, do you think the use of genetic testing of any kind in the U.S. will increase, stay the same, or decrease, compared to genetic testing usage today?

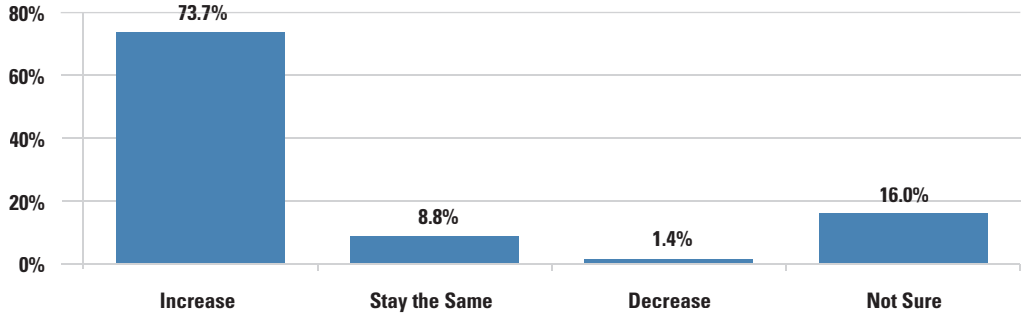


Figure 3.3; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of consumers, January 2012

Physician views on genetic testing

Current usage. Physicians report current usage of genetic tests as being quite low. On average, physicians report having recommended genetic testing for 4 percent of their patients over the past year. Specialists in the fields of hematology, oncology, rheumatology, and neurology were twice as likely to recommend genetic testing for their patients as physicians overall. However, about three-quarters of doctors also said that there are patients in their practices who would benefit from a genetic test, but have not yet had one (see Figure 3.4).

Physician views on the benefits of genetic testing

Do you believe that there are patients in your practice who have not yet had a genetic test but who would benefit from having one?

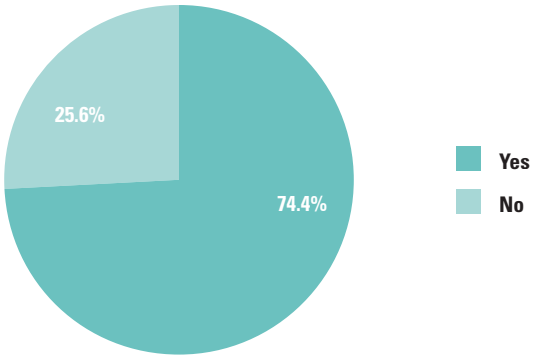


Figure 3.4; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of physicians, January 2012

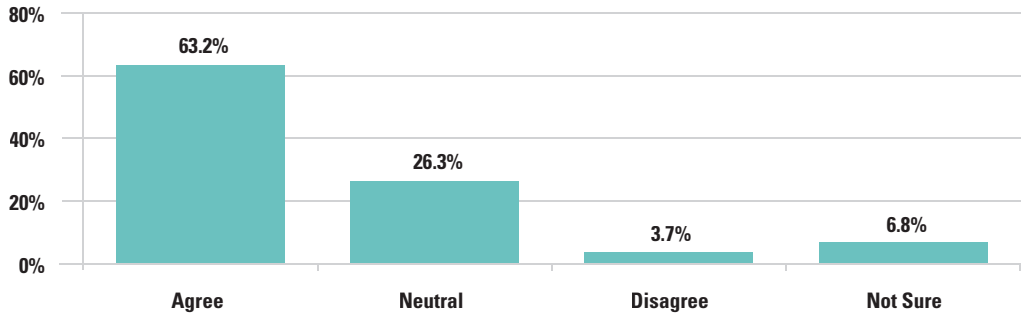
And looking ahead five years, physicians on average feel that 14 percent of their patients will have had a genetic test.

In terms of the types of tests doctors currently recommend, the most frequently mentioned are tests related to cancers (64 percent) and prenatal and newborn baby tests (47 percent). Those tests are most likely to be recommended by primary care physicians than by specialists. Pharmacogenomic tests are less likely to be recommended by primary care physicians than by specialists (23 percent versus 43 percent). In addition, 8 percent of physicians report that tests are performed in the office or facility where they practice.

Perceived clinical benefits. Around three-quarters of doctors say that genetic testing allows for more personalized medical decisions and more targeted choice of therapy; and the majority of physicians feel that therapeutic areas, such as oncology, congenital conditions, neurological disorders, and chronic diseases, would benefit from increased use of testing. As shown in Figure 3.5, around two-thirds (63 percent) of physicians say it gives them the ability to diagnose conditions that would otherwise be unknown. Half (52 percent) say it gives them the ability to diagnose conditions that could be prevented, which is particularly true for primary care physicians compared to specialists — 58 percent of primary care physicians compared to 45 percent of hematology, oncology, rheumatology, and neurology specialists.

Physician belief that genetic testing enables them to diagnose conditions that could be prevented or would otherwise be unknown

Genetic testing gives me the ability to diagnose conditions that would otherwise be unknown.



Genetic testing gives me the ability to diagnose conditions that could be prevented.

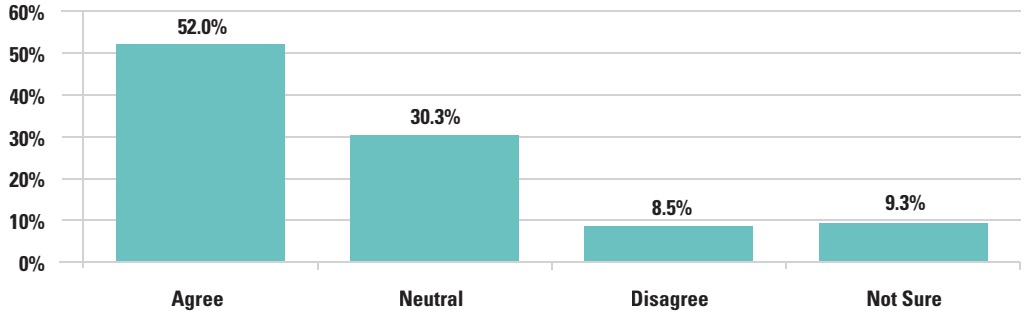


Figure 3.5; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of physicians, January 2012

Physicians' knowledge. Of physicians responding to the survey, 75 percent described themselves as "somewhat knowledgeable" about genetic science, with 7 percent regarding themselves as "very knowledgeable" and 16 percent as "not knowledgeable."

Only 28 percent of physicians surveyed feel comfortable interpreting the results of oncology tests and 25 percent the results of prenatal/newborn tests. There is a greater level of comfort interpreting the results of pharmacogenomic and infectious disease tests (close to half of physicians). However, hematology, oncology, rheumatology, and neurology specialists report having a significantly greater level of comfort interpreting tests results than primary care physicians (49 percent versus 22 percent for oncology tests, 43 percent versus 29 percent for newborn screening tests, and 63 percent versus 35 percent for pharmacogenomic tests).

Patient engagement. Physicians report that nearly three-quarters of their patients (72 percent) are "somewhat able" to understand the results of genetic tests, with 13 percent "fully able" to do so, and 7 percent "not at all able to understand" them. Notably, physicians who have recommended a genetic test for their patients in the past year are more likely than those who have not to believe that their patients are "fully able" to understand the results. Primary care physicians have greater concerns about their patients' ability to understand test results and make decisions than specialists do.

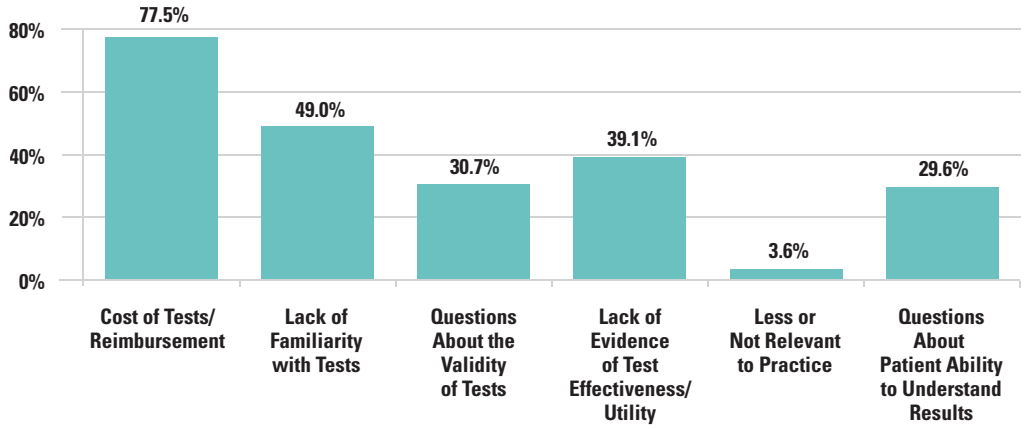
As for conveying the results of these tests to patients and discussing treatment options, at least two-thirds of physicians say they need to refer to additional materials in order to accurately describe in detail the genetic tests they recommend to patients.

Barriers and solutions. About half of physicians surveyed say that lack of familiarity with genetic tests is a barrier to incorporating them in their practices. Nearly 40 percent of physicians also are concerned about the lack of evidence of test effectiveness and utility, a figure which rises to 50 percent when specialists in hematology, oncology, rheumatology, and neurology are queried. Overall, over three-quarters of physicians are either somewhat or very concerned about the lack of evidence supporting the use of genetic testing.

However, the largest barrier (reported by 77 percent of physicians) is the cost and reimbursement for the tests. As shown in Figure 3.6, more specifically, nearly three-in-five doctors (59 percent) say that they are very concerned about the cost of genetic tests for their patients; a figure that is three times as large as their concern for their own reimbursement for genetic testing (21 percent).

Barriers identified by physicians and concern over cost of genetic tests to patients

What are the barriers to incorporating genetic tests in your practice?



How concerned are you about the cost of genetic tests for your patients?

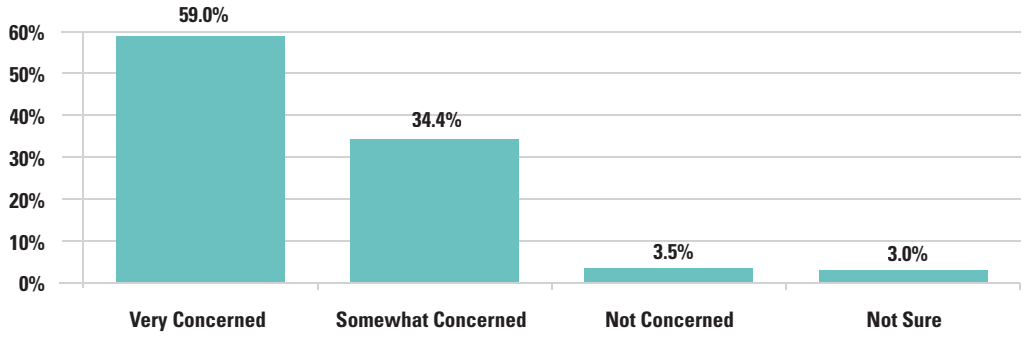


Figure 3.6; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of physicians, January 2012

Furthermore, over half of physicians (56 percent) surveyed think that the net effect of new genetic tests will be to increase health care spending, compared with only one-in-five (19 percent) who think they will lower overall health care costs (see Figure 3.7).

Physicians' expectations about how genetic tests will affect health care costs in the future

On a net basis, how do you believe genetic testing will affect health care costs in the future?

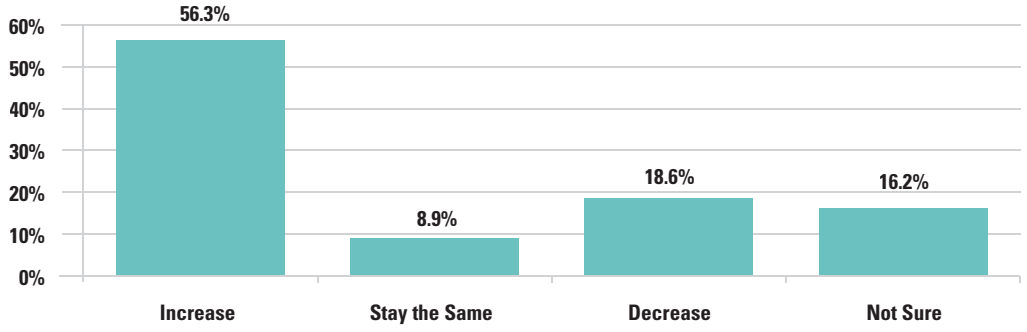


Figure 3.7; Source: UnitedHealth Center for Health Reform & Modernization/Harris Interactive survey of physicians, January 2012

Improved continuing medical education, more affordable tests, use of clinical decision support guides, and better access to clinical evidence are the top four solutions physicians identify that will enable wider use of genetic tests in their own practices. Primary care physicians in particular are more likely to see genetic counselors as helpful than do specialists in hematology, oncology, rheumatology, and neurology (58 percent versus 44 percent).

The future. A clear majority of doctors say that genetic testing will improve care across a range of health problems in the future. As to the timeframe for this progress, 14 percent think most of that progress will occur within the next five years, 25 percent expect to occur over the five-to-10 year time horizon before leveling off, but most doctors (57 percent) expect progress will continue into the foreseeable future.

Chapter 4: Ensuring patients benefit from the new science of genetic testing and molecular diagnostics

How should patients, their health professionals, research scientists, health plans, and regulators best work together to ensure patients are protected from possible harm and are able to benefit from rapidly developing genetic testing and molecular diagnostics?

This chapter considers six concrete domains where action would help advance patient care, recognizing that other areas will be important, too. Nevertheless, progress on these topics will make a major difference in the likelihood that patients will see real benefit over the coming years. They are:

- Protecting, supporting, and informing patients through data confidentiality, non-discrimination, and decision support;
- Benefiting patients by developing the clinical evidence base to determine which tests work;
- Stimulating future progress by encouraging the development of tests that are proven to work;
- Monitoring care through more transparent coding and reporting;
- Protecting patients by ensuring that lab tests are performed safely and accurately; and
- Making it easier for health professionals to stay up-to-date as genetic science evolves.

We now examine each of these areas in more detail.

1. Protecting, supporting, and informing patients through data confidentiality, non-discrimination, and decision support

As full profiles of patient genomes become available in the future, using that information to inform patients' decisions will become even more complex. Results of our UnitedHealth Center for Health Reform & Modernization/Harris Interactive consumer survey (presented in Chapter 3) point to several concerns consumers have about genetic testing.

In order for the public and patients to feel confident about making full use of the benefits that will be offered by genetic testing, it will be essential that strong privacy, data ownership, and non-discrimination measures are in place — and that consumers are made aware of these protections.[36] With respect to health insurance, fortunately, strong legal protections are now in force. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) outlawed genetic discrimination for employer-sponsored insurance. Twelve years later, the Genetic Information Nondiscrimination Act of 2008 (GINA) further strengthened consumers' legal protections regarding genetic information, including family medical history, as it relates to their health insurance and their employers. Among other requirements, GINA also prohibits health plans from requesting or requiring individuals or families to undergo a genetic test.

Patients largely look to their primary care providers for basic information about genetic disorders and referral and treatment options.[37] However, they may need additional resources and support to aid in complex decision-making. These include decision-support tools and shared-decision making guides of the kind currently used to help patients make informed, evidence-based decisions regarding appropriate care in areas such as organ transplants or heart surgery. Because of the complexity and concerns related to these issues, patients are increasingly relying on genetic counselors to coach them in their decision processes.

Recommendations: Results of our Harris Interactive consumer survey, presented in Chapter 3, suggest that the public would welcome clearer explanations of these strong statutory protections, which should provide reassurance that health insurance will not be affected by test results.[38]

Consumers also would welcome decision-support tools that enable them to be more active participants, with their providers, in identifying potentially useful tests and in making decisions about their care. Those tools should be incorporated into routine patient care, such as through materials explaining evidence regarding the use of genetic testing and its potential benefits and harms, or through greater use of genetic counselors.

Outreach programs, such as those in place today for testing for the risk of breast cancer, can identify patients who might benefit from testing, enabling them to get preventive services and, in the case of some medical risks, adopt lifestyle changes to prevent disease onset. Health literacy programs incorporating genetics and genomics could broaden the ability of the population to benefit from the growth in personalized medicine.

2. Benefiting patients by developing the clinical evidence base to determine which tests work

Generating and reviewing evidence that a test works and is clinically useful is challenging for this new area of advanced diagnostics. The evidence base supporting the use of such tests today is mixed, in some cases with significant shortcomings. For relatively simple tests that have been in use for a long time, such as those for infectious disease, there is evidence of clinical utility — that is, the test has a demonstrated ability to improve the process of care and/or outcomes, taking into account the benefits and risks of testing. However, of the roughly 1,000 to 1,300 tests available, only a minority so far have demonstrated clinical utility. Those tests are primarily pharmacogenomic or found in the area of oncology.

Often manufacturers lack the incentives or resources to conduct the relevant studies, and the pace of change is such that, in some cases, the evidence base is still being generated for one product when another emerges to replace it. (Of course, this is not a problem unique to genetic testing, as recent concerns about new hip prostheses have shown.) Various public and private efforts to address this problem are now under way (see Appendix 4).

However, because testing is used for conditions that affect small numbers of people, it raises questions of whether, or under what circumstances, assessing effectiveness can be made valid on a population-wide basis. Increased analytics and studies on the clinical use of molecular diagnostics and similar technologies may be possible as providers implement new health information technology platforms, including electronic health records, and offer data through health information exchanges.[39, 40]

Recommendations: New research models may provide alternatives to traditional clinical trials (such as randomized controlled trials) that include a less expensive mechanism for evaluating genetic tests. Examples of possible models include those that involve rapid iterative cycles, practice-based interventions, observational studies, prospective and retrospective studies, and comparative effectiveness research (CER). Analytic tools, such as computerized bioinformatic systems that analyze variation in genetic sequences, are being developed along with reference genomic information for comparing certain pieces of the genetic code. These tools require population-wide information for their statistical approaches; protection of individual data remains a challenge to these efforts. Innovative approaches will need to help isolate the effects of other socioeconomic and environmental factors on disease. The

Food and Drug Administration (FDA) could allow more flexible clinical trial designs based on molecular characteristics and surrogate endpoints.

3. Stimulating future progress by encouraging the development of tests that are proven to work

Public and private payers face a challenge in developing coverage policies that provide individuals with access to the most effective treatments given the pace of change, information gaps, and an evolving evidence base around genetic testing and molecular diagnostics. For information on how this process currently works, see Appendix 5.

With respect to reimbursement, determining an initial price for new medical technologies may involve looking to the prices of other similar technologies to develop an appropriate rate — known as "cross-walking" — or convening panels of experts and analysts to determine a fair price — known as "gap-filling." Gap-filling is generally used when the technology involved represents a substantial innovation over previous services and attempts to take into account costs and resources used in performing tests.

As an increasing number of novel diagnostics have emerged, the Medicare program has adopted a combination of those cross-walking and gap-filling approaches to supplement its traditional approach for pricing clinical laboratory services. Under that approach, Medicare payment rates are subject to a national ceiling on the median of rates for new diagnostics set in local areas and are adjusted annually by federal law. This process is described further in Appendix 6. Medicare payment rates for certain clinical laboratory services provided in physician offices and in hospitals are determined through the payment systems used for those providers. State Medicaid programs vary in their approaches, but most often follow the Medicare system.

Private payers often establish laboratory rates based upon rates in the Medicare program for the settings where tests are performed. In setting rates, they may also negotiate directly with manufacturers, laboratories, and providers for certain complex diagnostics or open up their contracts for clinical laboratory services to competitive bidding.[41, 42]

Private payers typically contract for laboratory services with national and regional clinical laboratories, as well as specialty laboratories, to provide specific services. Reimbursement to a non-contracted laboratory varies based on payer policies and programs, and can be as much as the amount charged by a non-contracted laboratory.[43] In UnitedHealth Group's experience, for example, non-participating clinical laboratories can charge two to three times the amount that Medicare would pay for an equivalent test.[44]

Reimbursement approaches used today, which involve setting an initial rate and subsequent indexing for inflation, may not reflect appropriately the value to the delivery system of the introduction of a new technology and its continued use. They also may contribute to the rising costs of new and complex tests.

Several challenges for the future are apparent:

- Within the current system, lack of information about existing and emerging genetic tests and molecular diagnostics contributes to a variable reimbursement environment that makes it difficult to set rates appropriately. Setting base rates today through gap-filling approaches can involve burdensome information and time requirements, and may not set rates appropriately for the value of new technology.

- Fee schedules used today to reimburse testing costs may not reflect the potential value of any improved outcomes or reduced spending resulting from a test. Tests that can predict a patient's reaction to a medication, for example, actually incorporate relatively simplistic technologies that may not be costly: currently, reimbursement for such tests is low even though the information they provide can lower the cost and improve the effectiveness of treatment.[45] While obtaining useful information at a low cost is obviously attractive, using cost-based payment rates may not provide sufficient incentives to develop new and informative tests in the future.
- Current approaches to setting rates typically lock in reimbursement at an initial rate that is subsequently adjusted for inflation but may not change to reflect future developments. Post-marketing information, which can provide critical information about the value of a test in improving health outcomes, comes after those initial rates are set. Tests may increase or decrease in value over time as evidence emerges about their application in patient care. More accurate diagnostics may rapidly replace those versions, making them less valuable to the delivery system. Post-marketing systems that can provide feedback to the rate-setting process are not well developed today. Furthermore, payment systems that encourage volume and intensity of testing may contribute to higher, inappropriate spending.
- As greater use is made of personalized care, innovators will need appropriate incentives to produce diagnostics for smaller subsets of populations.

Recommendations: Payers and technology developers have opportunities to collaborate on what clinical utility data may be required in advance of market entry, and what data can be developed through continued study after a new technology has received provisional approval. Additionally, efforts similar to the Medicare program's coverage with evidence development (CED) approach could be explored to create structured pathways for provisional coverage of certain genetic and molecular tests while data on clinical utility are collected and refined. In the near term, efforts could build on the Palmetto's MolDx program that will specifically focus on finding better ways to determine appropriate payment for laboratory services, within the guidelines created by the Centers for Medicare and Medicaid Services (CMS).

Consideration also should be given to alignment with some of the payment reforms now being developed in the broader health care system, including pay for performance linked to quality and efficiency, and more "bundled" payments for care episodes or the management of defined patient populations. Approaches such as the designation of Centers of Excellence for laboratory services could be deployed to ensure quality and reduce costs.

Key to any effort is broader use of analytics that can identify where these diagnostics can reduce downstream medical costs and improve health outcomes. As companion diagnostics continue to evolve, combined reimbursement approaches are already beginning to reflect potential savings from molecular diagnostics — and such adjustments could be incorporated into gain-sharing or risk-sharing arrangements with accountable care organizations or payment bonuses for primary care medical homes.

4. Monitoring care through more transparent coding and reporting

Transparency about which tests are being used under what circumstances is a prerequisite both for tracking the appropriateness of care and for responding to the strong concerns expressed by patients and physicians about the affordability of health care. The main tool for providing this information across the country is the coding system used by health professionals and laboratories to describe the diagnostic services provided to patients. See Appendix 7 for an overview of how this system currently works.

Although there are tests for about 2,500 diseases and conditions currently in use, there are generally not specific procedure codes to reflect the test performed. About one-third of advanced diagnostic spending is estimated to be unidentifiable because of inadequate coding.[46] Genetic and molecular tests that have been in use for a while, such as those for infectious diseases, tend to have specific codes for their use. However, newer tests do not usually have specific procedure codes, with a few exceptions. These tests use procedure codes that identify the process used as part of a test, for example, looking at tissue under a microscope. (One common code used in this area is 83900 — which refers to multiple rounds of DNA amplification.)

Newer molecular oncology and inherited disease tests are the most complex for coding because of the steps involved. Commonly, multiple procedure codes (so-called "stacking codes") are used to represent those combined steps and are used for reimbursement purposes. Some efforts are currently underway to improve the coding landscape. The American Medical Association (AMA) this year introduced about 100 new procedure codes to provide more specificity when billing for certain novel diagnostic tests. In addition, the CMS contractor Palmetto GBA is developing its own improvements in coding and test identification. (See Appendix 7.) An updated coding system for diagnosis (called ICD-10) may help connect tests to a broader clinical context when it is implemented.

Recommendations: A new coding system could be a foundation for better analytics, evidence development and coverage. Such a system would assign specific codes to individual genetic tests and genetic testing services. Considerations include:

- Codes should provide information on the analyte being tested as well as the procedure.
- A mechanism for attributing these tests to their associated laboratories, manufacturers and ordering providers also should be established.
- Codes could be created either through the current CPT coding system, or through a different third-party entity.
- Companion diagnostics to certain therapeutics should have a system for identification.
- Links to ICD-10 diagnosis codes would give providers a broader clinical context.

5. Protecting patients by ensuring that lab tests are performed safely and accurately

Patients and their physicians need to be able to be confident that diagnostic tests are accurate and are both analytically and clinically valid. The current regulatory infrastructure for genetic tests and molecular diagnostics — which is primarily housed at the FDA and CMS — has important gaps. Current approaches focus on the quality of the testing process at laboratories, rather than evaluating the attributes of an individual test, leaving questions about test quality. Approaches also focus on the safety and efficacy of a subset of tests developed by manufacturers; however, there is minimal oversight of tests developed by laboratories (LDTs), leading to questions of the clinical validity of some tests.[47] Furthermore, there are over 1,000 genetic disorders where tests are developed in labs and are not subject to FDA safety and effectiveness review.[48] See Appendix 8 for a more detailed discussion.

Recommendations: Tests should be assessed based on risk of harm arising from use of a test's results in a patient's clinical care, and oversight focused on those where the risk is greatest. This might involve strengthening laboratory accreditation standards for certain higher risk LDTs together with higher level FDA review. Ensuring the safety and efficacy of direct-to-consumer tests is also of importance given the

possible growth in this area as testing costs continue to fall. However, it will also be important not to undermine successful innovation nor to seek to impose new paternalistic controls on consumers' ability to access and learn about their own genetic information.

6. Making it easier for health professionals to stay up-to-date as genetic science evolves

Providers will increasingly need the ability to interpret more complex genomic data and make evidence-based recommendations to their patients. This will require greater time dedicated to interpreting data and assessing what it means for patient health risks and how to convey that information to patients.[49] Also, guidelines are not yet widely available in this area. Some estimates suggest that only about 400 molecular diagnostic tests (out of about 1,000 to 1,300) have any level of evidence-based guidelines today.[50] In any event, physicians are often unfamiliar even with the guidelines that currently exist for these novel diagnostics.[51]

As noted in our survey of physicians in Chapter 3, physicians see many challenges in this area and see opportunity in engaging more genetic counselors or other health professionals with expertise; however, today there are only about 3,000 board-certified genetic counselors and approximately 1,400 board-certified physician geneticists.[52]

Recommendations: New approaches will be needed to move information from the "bench" to the "point of care." Professional societies and other independent and research entities should refine existing guidelines to reflect appropriate uses of genetic testing. This could include "triggers" that help providers identify patients at risk for certain diseases that could be identified or treated more appropriately through genetic testing. A continuous process for guideline review and updates should be deployed to reflect rapid developments. Appropriate use of services could be bolstered by exposing providers earlier to genetics and genomics and cross-training with individuals in related fields of bioinformatics. Other approaches might include:

- Support materials such as content developed by the American College of Medical Genetics.
- Use of shared decision-making guides for facilitating dialogue with patients.

Genetic counselors can help providers and patients make informed decisions on the appropriate course of care, possibly facilitated by educational aids such as telemedicine and online materials. They have specialized training in genetics and the impact of genetics on the course of disease. Some payers contract with genetic counseling providers and encourage their inclusion in the integrated care delivery team. Incentives for use of evidence-based guidelines related to genetic testing could be deployed in performance-based incentive programs, along with tracking of test use and clinical outcomes.

Interoperable health information technology could provide information to clinicians about diagnostic services already performed, particularly if lab results begin to be included in electronic health records. Electronic health record systems could furnish providers with real-time information and alerts that might trigger recommendations for appropriate tests. An example of an active support tool is a digital patient entry system at the Cincinnati Children's Hospital that alerts physicians when a pharmacogenomic test is available that may be used to assess patient response to the use of certain therapies.[53, 54] E-prescribing systems also could serve as platforms to alert providers that genetic tests exist to determine the efficacy of particular treatment options.

Conclusion

Continued advances in genetics, genomics and proteomics have the potential to change medicine dramatically over the next several decades. As this working paper has shown, genetic testing and molecular diagnostics have many new applications in clinical practice, increasingly helping to guide decisions for conditions such as cancer. Both physicians and patients see the potential for genetic testing to improve care, and they expect continued advances in the future. However, this growth also presents new challenges. Hence the need for the sort of approaches this working paper has discussed: to ensure appropriate consumer protections, strengthen the evidence base for interventions that produce real world patient benefits, and help ensure that patients who could in fact benefit are offered the right quality care at the right time with the right support. In short, we can do more to realize the full potential of these new scientific discoveries and improve the health of the population. It is time to do so.

Appendices

Appendix 1: Definitions used in genetic testing and molecular diagnostics

Disease marker: specific molecular signature of disease, physiological measurement, genotype structural or functional characteristic, metabolic changes, or other determinant that may simplify the diagnostic process, make diagnoses more accurate, distinguish different causes of disease, or enable physicians to make diagnoses before symptoms appear and to track disease progression.

DNA (Deoxyribonucleic acid): the polymer that encodes genetic material and therefore the structures of proteins and many animal traits.

Epigenetic: relating to, being, or involving a modification in gene expression that is independent of the DNA sequence of a gene (e.g., epigenetic carcinogenesis, epigenetic inheritance).

Epigenome: the epigenome consists of chemical compounds that modify, or mark, the genome in a way that tells it what to do, where to do it, and when to do it. Different cells have different epigenetic marks. These epigenetic marks, which are not part of the DNA itself, can be passed on from cell to cell as they divide, and from one generation to the next.

Gene-environment interactions: an influence on the expression of a trait that results from the interplay between genes and the environment. Some traits are strongly influenced by genes, while other traits are strongly influenced by the environment. Most traits, however, are influenced by one or more genes interacting in complex ways with the environment.

Gene expression: the process by which the information encoded in a gene is used to direct the assembly of a protein molecule. The cell reads the sequence of the gene in groups of three bases. Each group of three bases (codon) corresponds to one of 20 different amino acids used to build the protein.

Genetic polymorphisms: the recurrence within a population of two or more discontinuous genetic variants of a specific trait in such proportions that they cannot be maintained simply by mutation. Examples include the sickle cell trait, the Rh factor, and the blood groups.

Genome: the full sequence of genetic material encoded in DNA in an organism.

Genome-Wide Association Study (GWAS): a study that identifies markers across genomes to find genetic variation associated with a disease or condition.

Genotype: the genetic sequence of an individual organism, often categorized in terms of known genetic variants. This can either refer to known alleles (or types) of a single gene or to collections of genes. For example, some lung cancers have a mutant EGF receptor genotype while other lung cancers have a wild-type (or normal) EGF receptor genotype.

Molecular biology: a branch of biology dealing with the ultimate physicochemical organization of living matter and especially with the molecular basis of inheritance and protein synthesis; the field of science concerned with the chemical structures and processes of biological phenomena at the molecular level.

Personalized medicine: refers to the tailoring of medical treatment to the individual characteristics of each patient. It reflects the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions then can be concentrated on those who will benefit.

Phenotype: the idiosyncratic traits exhibited by an organism, often categorized in terms of known trait variants. This can either refer to a specific trait or to a collection of traits. For example, blue eyes and brown eyes are phenotypes exhibited in subsets of humans.

Phenotype-genotype association (or correlation): the association between the presence of a certain mutation or mutations (genotype) and the resulting physical trait, abnormality, or pattern of abnormalities (phenotype). With respect to genetic testing, the frequency with which a certain phenotype is observed in the presence of a specific genotype determines the positive predictive value of the test.

Proteome: the entire complement of proteins and associated modifications produced by an organism.

Recombinant DNA: the artificial synthesis of sequences of DNA that may or may not exist in nature using genetic engineering techniques. These techniques are central to much of molecular biology and to the development of modern drugs.

Single Nucleotide Polymorphism (SNP): single genetic variation; DNA sequence variations caused by single base changes at a given position in a genome.

Whole-genome sequencing: determining the sequence of deoxyribonucleotides that compose an entire genome, including all of its chromosomes.

Source: National Academy of Sciences, 2011

Appendix 2: Types of genetic tests and molecular diagnostics

Biochemical tests measure gene products — proteins, enzymes, metabolites, and hormones — and thus can provide insight into genetic factors involved in disease. An example of these types of tests are proteomic studies, which analyze the structure and function of proteins. Testing approaches here are similar to traditional diagnosis of diseases using general chemistry and blood analysis. They have been used in newborn screening for decades and can identify multiple metabolic disorders.[55] Still, these tests continue to evolve and are combined with other areas of science, including immunology. In fact, there is an entire category of tests that utilizes immunohistochemistry to detect proteins and other molecular compounds for identifying conditions. An example of this multidisciplinary testing involving immunochemistry is used to detect the proteins associated with mad cow disease.

Cytogenetic tests analyze changes in chromosomes using stains and fluorescents under a microscope — and have advanced with technical improvements to view and examine chromosomal details. Throughout the 1950s and 1960s, scientists were able to identify chromosomal abnormalities in patients. The introduction of banding techniques, using chemical stains, led to advances in identifying subtle chromosomal changes (such as duplications and deletions) and linkages to various syndromes. These kinds of testing technologies are still used today using high-resolution banding to assess congenital and developmental disorders and tumor analysis.[56]

Molecular tests. Identification and measurement of changes in DNA, RNA, or specific genes is done using tests that analyze organisms at the molecular level. Molecular tests often focus on single genes or mutation, or other products, such as proteins.

- ***Fluorescence and flow cytometry.*** Initial measurement work in the 20th century studied DNA using ultraviolet absorption methods to identify areas of interest. By the 1960s, techniques called *fluorescence* began to be used in combination with *flow cytometry* methods, which suspend particles in a fluid for analysis, though flow cytometry is used primarily to analyze proteins. Next generation applications of this type are being used in cancer diagnosis and risk assessment.[57]
- ***DNA and sequencing tools.*** Some molecular testing techniques discovered in the 1970s are still common tools in genetic testing — these tools manipulate (cut and copy) DNA material itself. One of these techniques allows scientists to "cut" DNA strands at specific places using enzymes and produce fragments they can separate and reproduce. This tool became important in the ability to detect disease-related mutations and in sequencing, or analyzing the nucleotides that create the genetic code in DNA or RNA, so genetic disorders can be identified and further studied.
- ***Comparing DNA, hybridization and FISH.*** An additional common technique uses a process called *hybridization*. It compares complementary sequences of two strands of DNA (or of DNA and RNA), one of which is given a fluorescent "tag." This allows for the detection of mutations, deletions, and other genetic changes on the other comparison strand. Hybridization is combined with more basic analysis of chromosomes to do advanced analysis of chromosomal abnormalities using a modern technique called *fluorescence in situ hybridization (FISH)*, again building off the original labeling and staining approach to studying genetic materials. A related technology to look at chromosomal abnormalities is called comparative genomic hybridization (CGH), and is useful for complex tumor analysis.[58] CGH is the technique of choice for future cytogenetic tests because of its technical performance and its comparable cost relative to older techniques.

- ***Microarray technology, DNA amplification and PCR.*** A key new area of technological advance is analysis of multiple sequences of DNA and RNA and proteins, rather than a more straightforward analysis of single genes or proteins. Testing techniques still rely on comparisons, just on a much larger scale where multiple tests are performed at the same time using an analysis platform of *microarrays*. Microarrays can consist of up to thousands of different DNA sequences (or other molecular level organisms) to be analyzed on entities such as glass slides, silicon chips, nylon membranes, or beads.

  Microarrays of DNA depend on *DNA amplification* — in which strands are replicated by many orders of magnitude, sometimes millions of times, for analysis. The process used for replication is called *polymerase chain reaction* (PCR), in which enzymes are used to copy DNA in a technique that involves repeated heating and cooling. PCR is a powerful tool that can help scientists detect and measure certain DNA sequences or note their absence. It has applications in analysis of the sex chromosomes, infectious disease diagnosis and the diagnosis, prognosis and treatment planning for cancers. Standardized approaches and practices involving amplification have enabled significant advances in disease research, drug development, and use in patient care diagnostic applications.

  The *gene expression microarray* is a type of microarray which can help to analyze the effect of changes in gene expression on protein function and the contribution to disease.[59] These microarrays look at multiple proteins (that are gene byproducts) and can help improve diagnosis and management of disease. A recent development is using this technology for the diagnosis of breast cancer, looking at multiple biomarkers (or proteins), the most well known of which are breast cancer diagnostics Oncotype Dx and MammaPrint.

- Studies of the entire genome have led to even more powerful and complex analytics. Analysis of the diversity of genetic coding across human beings have found correlations between 800 natural and common variations in DNA sequences in the human genome called *single nucleotide polymorphisms* (SNPs) and 150 phenotypes or diseases.[60] Specific analysis of SNPs can help to identify individuals with critical variations, especially those that affect the ability to metabolize certain drugs. The microarray technologies, described above, are used to analyze multiple SNPs.[61] SNPs may eventually be used on a large scale to identify population-level variants that lead to diseases such as heart disease, diabetes, and asthma.

Appendix 3: Categories of tests, applications in clinical practice, and examples

Type of Condition	Application	Test Approach	Examples
Infectious Disease	*Identify Condition*	• Identify indicators of an infectious disease agent (e.g., disease antigens) that cause illness	• Screening tests for sexually-transmitted diseases, both viral and bacterial • HIV tests, including tests that detect proteins associated with the presence of the virus
Cancer	*Identify Condition*	• Identify presence of cancer-related genetic changes (e.g., genetic mutations), precancerous cells and/or tumor markers, or molecular products of cancers	• MLH1 and MLH2 mutation testing for Lynch Syndrome
	Assess Patient Risk of Developing a Condition	• Analyze patient genetic materials (e.g., genetic markers) and other molecules to assess risk for developing certain types of cancer	• BRCA testing, identifies harmful changes in the breast and ovarian cancer susceptibility genes and assesses the potential for mutation and breast cancer development
	Predict Patient Response to Therapy	• Assess likely patient response to targeted oncology drug therapy	• KRAS gene testing is used before starting therapy for both metastatic colorectal cancer and advanced non-small cell lung cancer patients • Human Epidermal growth factor Receptor 2 (HER2), a protein found in aggressive forms of breast cancer, helps guide appropriate therapy
Inherited Conditions, Acquired Chromosome Disorders and Genomic Profile	*Identify Condition*	• Identify the presence of inherited or congenital conditions by analyzing for specific genetic mutations or predispositions for certain non-cancerous conditions	• Genetic prenatal screening to detect extra chromosomes • Genetic test for specific mutations on the gene responsible for cystic fibrosis
	Assess Patient Risk of Developing a Condition	• Analyze genetic materials (e.g., genetic markers) to assess predisposition and risk for developing certain non-cancerous conditions	• Assess genetic mutation that puts an individual at risk for the development of hereditary ataxia, a condition involving lack of muscle coordination
	Predict Patient Response to Therapy	• Analyze specific aspects of an individual's genetic makeup (e.g., genetic markers relating to metabolism) to ascertain likely response to drug therapy • Pharmacogenomics	• Test to assess individual metabolic response to warfarin drug therapy
	Establish Genetic Histocompatibility	• Analyze specific gene sequences, markers, and molecules to create a genetic profile of individual characteristics	• Markers used in determining organ typing for transplants

Appendix 4: Developing the evidence base

Efforts are under way to generate more evidence supporting the use of genetic testing and molecular diagnostics. The Agency for Healthcare Research and Quality (AHRQ) through its Evidence-Based Practice Centers, the United States Preventive Services Task Force (USPSTF), the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), and consensus development panels supported by the National Institutes for Health (NIH) all have programs in this field.[62] The National Cancer Institute (NCI) is pursuing a long-term, large clinical trial for a biomarker for early-stage breast cancer to see if certain women will have better outcomes with or without chemotherapy.[63]

New approaches to facilitate more rapid translation of genetic tests from research into clinical practice are evolving. The Collaboration for Education and Test Translation (CETT) Program, run by the NIH, is one example. The CETT program assesses tests to gauge their level of readiness for use. Although it will not serve as a regulatory body or as an authority for coverage, CETT assessments can be used as a reference by stakeholders to determine the most effective tests.

Payers are also engaged in gathering evidence. Palmetto's MolDx program uses formal evidence review processes that encourage submissions of evidence for review from providers and laboratories, creates a formal technology assessment process, and establishes a system for analyzing use of tests. These mechanisms improve Palmetto's ability to obtain evidence to support review of services for coverage.

A new organization, the Patient-Centered Outcomes Research Institute (PCORI), will expand research.[64] Additionally, the Center for Medical Technology Policy (CMTP), a private, non-profit organization working to improve the process of generating new clinical research for health technologies, has produced effectiveness guidance documents that contain specific recommendations on designing comparative effectiveness studies.

Appendix 5: How payers make coverage decisions for genetic testing and molecular diagnostics

Medicare has formal processes and criteria for establishing coverage of services for the program's beneficiaries. Medicare coverage policy focuses primarily on safety and efficacy of services and it has a process to evaluate whether to cover certain new services not specifically required to be covered by law, such as certain types of colorectal cancer screening. This process is done at both the national and local level, where coverage determinations are left to the discretion of local Medicare Administrative Contractors (MACs). To date, CMS has issued relatively few coverage determinations, either nationally or locally, for genetic and molecular tests, though coverage determinations have been made for certain screening services, such as histocompatability testing for patients preparing for a kidney or bone marrow transplant. Local coverage determinations can impact coverage of certain diagnostic testing services across the country. Tests that are processed in a centralized laboratory, such as some laboratory-developed tests, are subject to that region's MAC coverage policies, even if the sample was sent from another region. In this case, the local coverage determination may serve as a de facto national coverage determination.[65]

In general, local coverage determinations are used as initial steps toward national coverage; therefore, given the mix of evidence supporting use of testing services, combined with the inherent variation as to how different MAC medical directors might interpret evidence, Medicare coverage for testing services varies across regions. CMS and its MACs have various tools to help them evaluate evidence for coverage determinations. Two important tools at their disposal include commissioning AHRQ technology assessments and convening of committees of experts who assess the impact of new technologies.

Private payers also review clinical evidence in order to draw conclusions on whether medical technology works and for which populations it is most appropriately done, and how it compares with other services that treat the same condition. The standards used by private payers to establish coverage for services are similar to Medicare's and include safety and efficacy. Payers also want to see accuracy and standardization, and promote value. In determining whether to cover new technologies and diagnostic tests, payers may consider the following questions:

- What is the strength of the clinical evidence that this technology is safe and effective?
- What group of patients, if any, would benefit most from using a given technology for preventing, diagnosing, or treating a particular condition?
- Under what circumstances and conditions, if any, would the technology be most appropriately used? Does our policy need to specify certain providers or facility types?
- How does the new technology compare to other available treatments for the same condition?

Public and private payers are increasingly focused on direct evidence of clinical utility and the impact of a specific test on patient health outcomes. This demand for clinical utility and outcomes data may drive investment decisions by manufacturers and researchers as to what types of technologies are worth pursuing.

The uncertainties of the evidence base and impact on patient health, as well as a lack of specific codes, make it challenging for payers trying to develop a clinical policy in this area. Where robust clinical data exist, payers are most likely to cover these new diagnostics. As with Medicare, private payers may implement conditions for coverage that are applied to diagnostic tests, such as defining appropriate patient conditions, providers, or settings of care for the services.

Approaches that make the coverage process easier and more transparent are helping to improve coverage policy. The Palmetto Laboratory and Molecular Diagnostic Services (MolDx) program, administered since November 2011 by Palmetto GBA, a CMS MAC, offers a new mechanism to facilitate its coverage determination process in Medicare. The program encourages the submission of coverage requests and supporting evidence for molecular diagnostic services and gives them guidance for evidence submissions. Subject matter experts will review and develop a technology assessment based on information contained in coverage determination requests. Development of standard criteria for evidence that leads to coverage will be an ongoing challenge.

Payers are also beginning to explore coverage approaches that maintain rigorous review, but have flexibility to respond to an evolving evidence base. One emerging approach in the policy environment is using a conditional or phased approach to enable patients to gain access to potentially beneficial technologies while payers can collect the necessary evidence to establish coverage policy. For example, Medicare's CED approach may permit conditional coverage of certain innovations, to allow time for evidence accrual. CED uses observational and randomized research approaches and other studies.

To date, only a handful of genetic tests have been covered under Medicare's CED program. Furthermore, few services that have been covered under CED have subsequently demonstrated the required evidence. Some experts view CED as encouraging inadequate study designs that do not inform future coverage determinations and patient clinical decision-making.[66] CMS is evaluating how to improve the process, for example, by adopting milestones and clear endpoints, greater consistency, and sources of funding for research costs.

Phased approaches have been used by payers in partnership with technology manufacturers, using risk-sharing agreements. Under that kind of arrangement, payers could grant coverage to a diagnostic service and share the risk with manufacturers on its effectiveness in meeting pre-agreed outcomes. Approaches could be designed using phased-in reimbursement that increases with meeting certain evidentiary milestones or that rely on mechanisms to coordinate the efforts of multiple plans. Practical concerns exist in this area, however. Evidence development efforts are costly and small sample sizes may present challenges in developing necessary levels of evidence.

Appendix 6: Medicare reimbursement for clinical laboratory services

The Medicare program is the largest single purchaser of clinical laboratory services. In 2010, Medicare payments for clinical laboratory services totaled $8.1 billion. Medicare is the dominant payer for clinical laboratory services and therefore its approach influences that of other payers.

Medicare includes payment for diagnostic services in its overall hospital reimbursement rates for inpatient care. Clinical laboratory services provided to Medicare outpatients are reimbursed based on a fee schedule or, less often, through an all-inclusive rate paid to physicians. Medicare usually pays for new tests at rates comparable to older tests that use similar laboratory technologies ("cross-walking") rather than by calculating a new rate through the process called "gap-fill" pricing. Medicare, working through its local Medicare administrative contractors, uses 56 separate, geographically-based fee schedules to set payment rates for the more than 1,100 codes used to identify laboratory services. Payment for clinical laboratory services across the 56 clinical laboratory fee schedules varies by geographic area due to variation in local Medicare administrative contractor pricing, which is based on regional laboratory charges. Medicare's payment rates for clinical laboratory services are also subject to an upper limit established by Congress: 74 percent of the median of all 56 fee schedule locality amounts for each service. Most lab services are paid this national cap amount.

Source: MedPAC. Clinical Laboratory Services Payment System: Payment Basics. October 2011.

Appendix 7: U.S. coding practices for genetic testing and molecular diagnostics

Diagnosis codes are a standardized set of codes used to report diseases and patient conditions. Providers and researchers report disease and patient condition information using the International Classification of Diseases, Ninth Revision (ICD-9). Implementation of the ICD, Tenth Revision (ICD-10) coding system is expected several years from now.

Procedure codes identify medical and diagnostic services rendered by providers. Those codes are typically submitted using the Current Procedural Terminology (CPT) coding system, often referred to as Level I Healthcare Common Procedure Coding System (HCPCS) codes. Procedure codes can be expanded upon using code modifiers to denote additional information. Within the HCPCS coding system, there exists an alphanumeric code series, often referred to as Level II HCPCS codes that are used to identify other types of services, such as certain drugs, laboratory services, and many other services that may be provided during the course of care.

Providers and laboratories today commonly use a procedure-based approach to identify genetic tests and molecular diagnostics by the steps involved in the test rather than the nature of the test itself. Commonly, multiple procedure codes (so-called "stacking codes") are used to represent the various steps involved in performing a genetic or molecular tests (e.g., extraction, analysis, interpretation, reporting). Individual procedure codes are given for each type of step to create a "stack" of codes for each test. In some cases, laboratories identify the codes that best represent their own processes for genetic testing services, making variation in code use common. Even when laboratories use the same procedure codes for a test, they may include different services in those procedures, making comparisons — or aggregation of data — across laboratories unfeasible.

For example, the test for the gene that causes Canavan disease, a genetic illness that results in premature death, involves six steps, each of which has its own procedure code.[67] The combination of these six procedure codes indicates the steps involved in processing the test for the disease. The same procedures also are conducted in genetic tests for five other common genetic illnesses, including tests for cystic fibrosis and Tay-Sachs disease, making it difficult to distinguish one test from another.

Health plans often have had to address the lack of coding by developing their own identifying codes for specific genetic and molecular tests, particularly when the tests are commonly used in clinical practice. For example, some payers use alphanumeric codes (S-codes) to identify certain tests for a variety of conditions, such as tests for breast and ovarian cancer genetic mutations, including BRCA1 and BRCA2, and hereditary non-polyposis colorectal cancer and genetic mutation tests, such as the ones used to identify mutations in the MLH1 and MLH2 genes. Manufacturers of some of the most novel and advanced tests in this area are increasingly seeking to use non-identifiable codes.

In addition to the difficulties involved in identifying the tests themselves through codes, identifying the therapeutic area (e.g., oncology) in which genetic and molecular tests are being used is also a challenge. Claims submitted for laboratory services may use a diagnosis code that reflects the immediate issue facing the patient rather than the result of a genetic test or subsequent diagnosis. Diagnosis codes — or a combination of diagnosis and procedure codes — therefore, cannot be relied on as a source for information on the use of a genetic or molecular test or a test result.

The AMA introduced a new set of codes for molecular diagnostics and genetic testing that will be analyte-specific and not focused as exclusively on the steps involved in a given advanced molecular diagnostic service.[68] Those codes primarily will be for very specific types of analysis or frequently performed tests such as breast cancer or cystic fibrosis tests, and will use test-specific codes.

The Medicare program is leading other improvements in coding and test identification through the Palmetto MolDx program. The program will assign unique billing codes for individual tests in order to collect information on utilization, apply coverage determinations, and facilitate reimbursement. As of March 1, 2012, Palmetto will only consider advanced diagnostic claims for adjudication that contain specific codes developed by McKesson (Z-Codes).[69, 70] Progress with coding has been made in the area of newborn screening, which has its own universe of codes and analytics. The National Library of Medicine (NLM) has assigned certain codes to all of the newborn screened conditions.

The updated coding system for diagnosis (ICD-10) will eventually allow for combinations of codes, and is structured to capture additional detail about diagnoses and related procedures. For genetic testing and molecular diagnostics, the increased detail, such as genetic susceptibility to disease, will enable providers to better understand how tests relate to their patients' conditions.

Efforts are also underway to improve access to data about the landscape of tests and increase transparency. One concept promoted by some stakeholders is a public registry for genetic tests, including biomarkers tested, their use in clinical practice, and names of laboratories or manufacturers.[71] An example of such a registry is the voluntary NIH Genetic Testing Registry (GTR). The database will provide information about tests for inherited and somatic genetic variations, including arrays, multiplex panels and pharmacogenetics, and will incorporate information from the National Center for Biotechnology Information's (NCBI) databases on diseases.

Registries have potential to aid in understanding what tests work and for whom, but they have limitations. Building repositories of information and data is an alternative approach that has been used and made available to laboratories, providers, and patients. For example, a system called "GeneTests" contains a directory of labs and clinics, peer-reviewed disease descriptions, and other educational materials. This system is hosted and funded by the NIH and sponsored and updated in partnership with the University of Washington.

Appendix 8: Quality assurance at laboratories performing genetic testing and molecular diagnostics

CMS has authorization under the 1988 Clinical Laboratory Improvement Amendments (CLIA) to certify clinical laboratories for the accuracy, reliability and timeliness of certain diagnostic test results.[72, 73] Most genetic and molecular testing is considered "high-complexity testing." Laboratories conducting such tests are required to get CLIA high-complexity certificates. However, CLIA oversight of tests is limited to a focus on the quality of testing processes rather than evaluating the attributes of an individual test.[74] Recent federal legislation has led to an increased focus on quality assurance for laboratories involved in screening newborns and children.[75]

State agencies regulate clinical laboratories using CLIA standards, though some states have stricter standards, such as New York and Washington.[76] All laboratories that submit or receive specimens to or from a state, such as New York, are subject to that state's requirements. Since major reference laboratories submit or receive specimens from New York, it is estimated that 75 percent of all genetic and cytogenetic specimens in the United States are subject to New York clinical laboratory requirements.[77]

A different body of regulations governs the safety and efficacy of diagnostic tests considered medical devices. The FDA has regulatory authority over all tests considered to be medical devices, including those tests made by manufacturers and sold to laboratories.[78] These devices cannot be marketed in the U.S. without FDA clearance, which follows one of two tracks depending on how novel a technology is and the degree of risk that the test may involve for patients. The standards used in each of these two regulatory approval tracks differs, with the most stringent standard involving determinations of which tests are safe and effective.[79] Because diagnostic devices are often sold to laboratories and physician offices in the form of "test kits," FDA approval serves as an important variable in the ability of providers and patients to access these technologies.

In some instances, tests may accurately detect genes or mutations — and thus have analytic validity — but lack significant evidentiary strength to be clinically valid. Tests may detect genetic mutations but these mutations may not be linked by evidence to a specific clinical condition. For other conditions (e.g., Apo-E Alzheimer's disease), the presence of the gene indicates that the patient has an increased risk for the disease but that patient may or may not actually develop it for a long time. This creates particular problems for predictive tests that are done before patients show any symptoms of disease. Post-market data is critical to establish clinical validity but it is challenging to collect for rare diseases.

In other cases, such as newborn screening and selected areas of genetic risk identification, there may be strong evidence to support the clinical validity of certain tests. Some genetically determined conditions (e.g., cystic fibrosis or Tay-Sachs disease) are almost certain to occur if a particular gene is detected. Tests of the genetic make-up of certain cancer cells (e.g., Oncotype DX) also have been shown to have a high prognostic value in determining whether a cancer may recur.[80]

Despite the fact that laboratories are required to assess the performance of tests, reviews may vary in terms of rigor and independence.[81] Furthermore, CMS does not evaluate tests themselves for either analytic or clinical validity, and cannot do post-market review or adverse event reporting.[82] In some cases, gaps in proficiency testing have been identified in CLIA regulated labs.[83] Likewise, although the FDA reviews some diagnostic testing services, the agency does not currently review the safety and efficacy of LDTs, tests that are developed, manufactured, and distributed by the same laboratory.[84, 85] There are over

1,000 genetic disorders where tests are developed in labs and are not subject to FDA safety and effectiveness review.[86] The FDA also narrowly regulates components used in genetic tests sold to labs called "analyte-specific reagents," or ASRs.[87] The FDA has signaled increased interest in LDT oversight by announcing plans to implement a risk-based approach toward oversight of certain more complex LDTs (such as in vitro diagnostic multivariate index assays, or IVDMIAs).[88] The FDA also intends to review companion diagnostics. A therapeutic product may be approved even if a companion diagnostic does not receive approval through its own regulatory review. For cases where a therapeutic product is approved without a companion diagnostic, the FDA may consider additional protections to ensure patient safety.[89]

Furthermore, while some genetic tests sold directly to consumers have proven analytic validity, others may not be clinically valid. Some published studies have found limited analytic validity in some direct-to-consumer (DTC) genetic tests.[90] The FDA is currently working directly with DTC companies on how to best evaluate the safety and efficacy of these tests.[91]

Appendix 9: Methodology – survey of consumers and physicians and analysis of UnitedHealthcare claims data

Survey of consumers and physicians

In January 2012, the UnitedHealth Center for Health Reform & Modernization commissioned Harris Interactive to create a nationally representative survey of primary care and specialty physicians and health care consumers. Physicians and consumers were asked a broad range of questions on their existing knowledge, awareness, and experience in the use of genetic testing, as well as their perceptions on existing barriers to current use and opportunities for use in the future. Surveyed physicians and consumers were given a definition of genetic testing to capture pharmacogenomic tests and tests for certain molecular biomarkers. The survey consisted of 1,254 U.S.-based primary care physicians (PCPs) and specialists, and 1,506 adult U.S. health care consumers. Physicians from each specialty and geographical region were weighted to accurately reflect their respective populations using targets from the 2010 AMA database of physicians. For analysis purposes, the sample of physician data includes 250 specialists who may be more likely to be using genetic testing in their practice, including hematologists, oncologists, rheumatologists, and neurologists. Consumers were selected to generate a representative random sampling of adults across all geographic regions. Measures for statistical differences in the physician and consumer surveys were conducted at the 95 percent confidence level.

Analysis of UnitedHealthcare claims data

Using UnitedHealthcare monthly claims data for the 2008 to 2010 period for molecular diagnostic codes, we categorized spending and utilization data into three areas — infectious disease, cancer, and other genetic tests (including inherited and certain acquired conditions) based on an analytic claims tool. We applied this approach separately to a majority of claims for our Employer & Individual, Medicare Advantage, and Medicaid managed care plans, and identified allowed spending, counts of procedures, and service units for each category of test. Procedure count data reflect the count of individual procedures captured in the claims data, while service units reflect the number of times a given procedure was reported on a claim.

We extrapolated those data to our total membership in each segment (based on enrollment), and then derived per member per month spending and annual growth for each UnitedHealthcare segment, as well as procedure counts per 1,000 members. Because current coding practices underlying claims data generally do not identify the number of individual tests, we measured utilization using counts of procedures as a proxy. Some tests include only one procedure, but others, particularly newer molecular diagnostic tests, include multiple procedures. The number of service units per procedure provides information on the complexity and intensity of given tests; additional service units per procedure typically raises the cost of that procedure (and the test).

Estimates of the total U.S. market by payer and test category were based in part on UnitedHealthcare's claims experience, and in part on analysis of data from government sources. First, we adjusted UnitedHealthcare's commercial market data to national totals — both employer and individual — using data on employer-sponsored and non-group coverage from the U.S. Census Current Population Survey. We then calibrated UnitedHealthcare's Medicare Advantage data to a national Medicare Advantage total based on enrollment estimates from the Congressional Budget Office. We estimated Medicare fee-for-service spending for those categories of molecular diagnostics by applying an analytic tool to molecular

diagnostic codes from a 5 percent sample of claims from Medicare fee-for-service beneficiaries for 2008 to 2010. Additionally, we derived Medicaid totals by extrapolating UnitedHealthcare Medicaid managed care spending and utilization to the Medicaid market overall, based on managed care enrollment data and estimates of non-dual eligible Medicaid enrollees in fee-for service Medicaid using administrative data from CMS. This approach effectively assumes that patterns of spending and utilization for molecular diagnostics experienced in UnitedHealthcare's different segments are similar to national patterns (except for Medicare fee-for-service, where we had claims data).

Our illustrative scenarios of spending growth over the next decade show a range of possible trajectories for growth in molecular diagnostics and genetic testing, taking into account possible rates of adoption, the number of new innovations, and the cost of new tests. We based near-term projections of spending in part using UnitedHealthcare's recent historical experience in the growth of the number of procedures per 1,000 members and spending per procedure for each of the three categories of tests and type of insurance. To project spending per procedure over the next decade under our three scenarios, we developed different sets of assumptions of excess growth over inflation to account for the higher prices of new diagnostics emerging in the market. We estimated growth in utilization, or procedures per 1,000, using two metrics — the growth in available tests and the rate of adoption in the population. Because the market for infectious disease testing is relatively mature, we assumed lower growth in adoption and procedure costs than for newer genetic tests. We developed three different levels of possible growth using those metrics and estimated average annual rates of growth could range from 11 to 16 percent over the decade. UnitedHealthcare's recent historical experience showed annual rates of growth totaling about 14 percent, which would fall in the middle of our projected range.

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- Reducing health disparities, particularly in underserved communities
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- Payment reform strategies that better support physicians, hospitals and other providers in delivering high quality patient-centered care
- Modernizing Medicare, including chronic disease management
- Practical cost containment strategies to slow the growth of U.S. health care costs

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