



The ROI for
Targeted Therapies:
A Strategic Perspective
Assessing the Barriers and
Incentives for Adopting
Personalized Medicine

Foreword

Personalized medicine is not a promise of the future; it is fast emerging as the current state in diagnostics and therapeutics. Innovations based on genetic and molecular designs offer patients better care at lower cost because conditions are predicted sooner, diagnosed more accurately and treated more effectively.

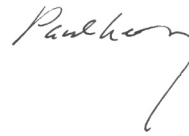
The U.S. health care system is the world's leader in personalized medicine. It is the epicenter for personalized medicine research and development that benefits citizens and governments of the world. Like every endeavor that's innovative and capital-intensive, it faces challenges: how to expedite development to get its solutions to market faster, how to access capital to stimulate increased R&D, how to rationalize the financial risks borne by inventors and scientists in their development, and how to justify coverage by health plans often pressured for short-term savings although longer-term cost increases result.

In this analysis, we offer a strategic perspective on the potential that personalized medicine holds within the context of cost-effectiveness. This analysis is not about finding rights and wrongs. All stakeholders in the system recognize the value of personalized medicine. All seek to develop, deliver and cover the right care in the most cost-effective ways.

The U.S. health care system can embrace and expand its efforts in personalized medicine. Personalized medicine facilitates better care and lower costs, its pursuit is the right thing to do, and doing so can benefit every major stakeholder in the U.S. system – most importantly, its patients.

We are grateful to the Personalized Medicine Coalition members for their interest in and support of this goal. And we are optimistic that the movement toward personalized medicine will grow in influence and support in coming years as it reaches its potential to improve care while reducing costs.

Respectfully,

A handwritten signature in black ink, appearing to read "Paul H. Keckley". The signature is fluid and cursive, with a long, sweeping tail that curves back towards the end of the line.

Paul H. Keckley, PhD
Executive Director
Deloitte Center for Health Solutions

Introduction

Personalized medicine has the power to transform health care within the foreseeable future, from a population-based model to a subpopulation and individual model. Scientific advances in biotechnology, health information technology (HIT), genomics, proteomics, therapeutic delivery, and computational biology have made possible a new approach to the diagnosis, treatment, and management of disease and disease risk. Personalized medicine is the application of these advances to the population at large, with distinction possible on an individual molecular level. As such, personalized medicine is a disruptive technology: It increases the functionality of disease detection, diagnosis and treatment beyond the current knowledge of most health care consumers and many providers, and fundamentally changes the business model for key health care business stakeholders.¹

Because genetic analyses enable the design of therapies targeted to specific individuals who are most likely to benefit from the treatments, there is downstream benefit not only for those individuals, but for those paying for and prescribing the more efficacious treatment. Standard practices in discovering, approving, and administering drug therapies are based on entire disease populations, rather than on subgroups within those populations. This fundamental difference between current and potential practice presents challenges to the current health care business model, and varying economic and clinical benefits and barriers for stakeholders. It is a topic of national importance, as evidenced by a recent report, *Priorities for Personalized Medicine*, prepared by the President's Council of Advisors on Science and Technology. The Council

emphasizes the potential of personalized medicine to not only improve disease prevention and patient care, but also to affect two economic trends: the decreasing rate of medical product development and increasing health care costs.² To better understand some of the economic factors of personalized medicine, this project explored the following questions:

1. Does personalized medicine have a quantifiable return on investment (ROI)?
 - a. Are clinical case study data available that could be used to develop a framework for determining ROI?
 - b. If a positive ROI is demonstrated, to whom do the benefits accrue and in what timeframe?
2. Can an economic framework be derived from case studies that will demonstrate differences in ROI across industry stakeholders?
 - a. If so, can these ROI differences clarify the incentives/barriers for stakeholders to invest in or adopt personalized medicine?
 - b. If there are significant gaps in value experienced among stakeholders, are there strategies that might bridge these gaps and accelerate adoption?

This paper focuses on personalized medicine's economic value proposition and the importance of ROI for multiple stakeholders in advancing adoption of personalized medicine.

¹ Disruptive technology is not to be confused with disruptive innovation. "Disruptive innovations convert expensive products and services into simpler, more affordable ones. In industries other than health care, cost-reducing technologies have been linked with innovative business models. Such linkage has resulted in increasingly affordable and accessible products and services." p. 1329. A business model consists of four components: the value proposition, profit formula, processes, and resources. Hwang, J and C M Christensen, "Disruptive innovation in health care delivery: A framework for business-model innovation," *Health Affairs*, 27:5 (2008) pp.1329-1348. Personalized medicine will likely add complexity and costs to clinical practice, making it a disruptive technology versus a disruptive innovation that results in more simple and cost-saving products and services.

² President's Council of Advisors on Science and Technology. Report: *Priorities for Personalized Medicine*. September 2008. Executive Office of the President of the United States, Office of Science and Technology Policy.

Methodology

The Deloitte Center for Health Solutions, part of Deloitte LLP, initiated this study to better understand the ROI of personalized medicine – specifically what is the ROI, to whom the benefits accrue, and in what timeframe. A literature review of the cost/benefits of personalized medicine was conducted. More than 300 articles were reviewed from both the scientific and the grey literature. This review provided the basis for generating two fundamental scenarios for how personalized medicine might affect current care processes, and the associated costs and benefits of current therapies (Figure 1, next page). In Scenario 1, a personalized medicine diagnostic test alters the standard course of therapy; in Scenario 2, a personalized diagnostic test results in the introduction of a companion targeted therapy.

During the review, it became clear that a meta analysis would not be possible due to variation in the level of evidence reported in the literature. The review method was refined to examine the literature for case studies that might be used to develop a personalized medicine ROI framework.

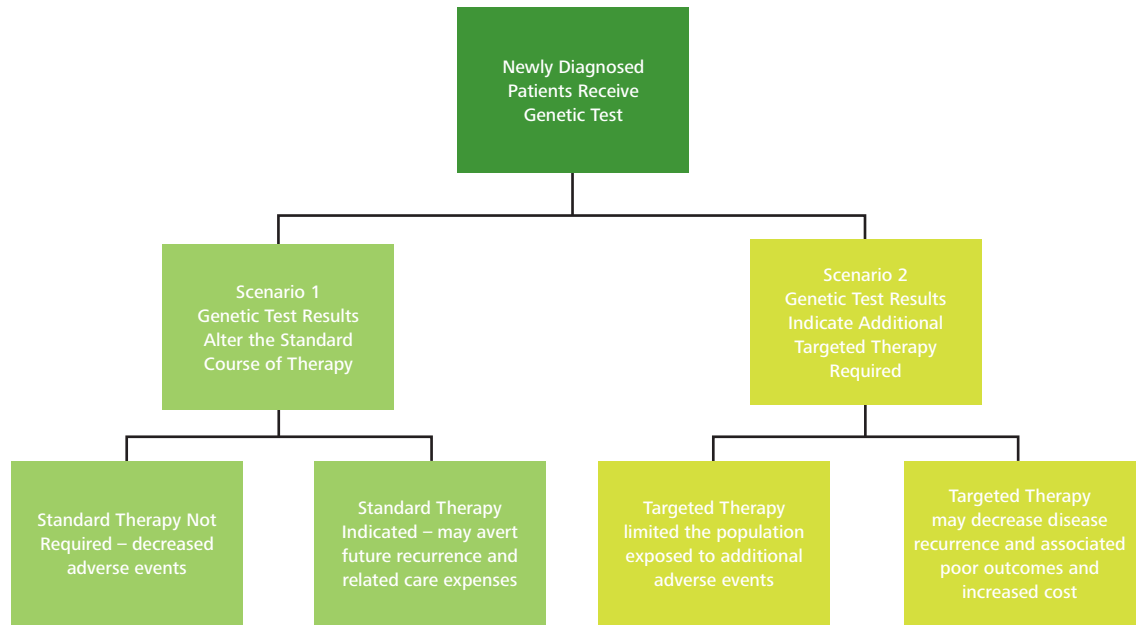
Inclusion Criteria

From the 300 articles reviewed, the Deloitte team identified ~75 articles with relevant information that could be used to develop an ROI framework. Empirical studies with control groups and sufficient outcomes data were included. These articles reported various aspects of the ROI for personalized medicine for a number of clinical conditions. In order to develop a coherent ROI approach, case studies were selected which addressed the fundamental characteristics of the two scenarios: altering the current course of therapy or introducing a companion therapy. Selections of case studies and clinical conditions were made based on the studies containing sufficient data to substantiate an ROI.

Key Terms

- **Personalized Medicine** – the use of molecular analysis of genes, gene expression, proteins, and metabolites to achieve optimum health outcomes in a person’s disease or disease predisposition.
- **Targeted Therapies** – therapies designed to target molecular mechanisms of disease, based on knowledge of relevant variations between individuals with that disease, and by relevant molecular variations in the expression of that disease.
- **Personalized medicine intervention** – a diagnostic test or targeted therapy based on molecular analysis of genes.
- **Genomics** – study of the entire DNA contained in an organism or a cell: the entire genome of an organism.
- **Phenotype** – those traits that are observable in an organism such as hair color, skin color, height, or the presence or absence of a disease.
- **Pharmacogenomics** – study of the genetic basis for individual variation in drug response.
- **Return on Investment (ROI)** – the ratio of money gained or lost relative to the money invested. Generally reported on an annualized basis, or annual rate of return.

Figure 1: Scenarios Selected for ROI Framework



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The literature review included a number of clinical conditions for which personalized medicine interventions resulted in changes to conventional therapies and more efficacious treatment. Examples of these include: affecting the cost of care in HIV/AIDS; avoiding adverse events in anticoagulant therapy; decreasing adverse events due to individual responses to therapy; decreasing costs associated with life course of disease; and improving quality of care for cardiovascular disease. Several of these case studies are referenced and summarized in Figure 2 (next page), and may be considered as alternatives for use in an ROI framework.

The literature review suggested that newly diagnosed breast cancer would be an optimal condition to develop an ROI framework that might be generalized across other conditions. Breast cancer is highly studied, resulting in sufficient benefits and costs evidence for populating an economic framework.³ In addition, newly diagnosed breast cancer offers two examples of personalized medicine interventions that correspond to the two scenarios identified for the ROI of personalized medicine framework: 1) interventions that alter the standard course of therapy (e.g., with Oncotype DX[®] or 21Gene PCR: a low recurrence

³ Breast cancer is a disease with considerable societal impact. New breast cancer cases are estimated to affect 182,460 women and 1,990 men in the U.S. in 2008. National Cancer Institute. <http://www.seer.cancer.gov>, accessed 09/2008. Early breast cancer involves a localized lesion in the breast and is typically treated with a combination of surgery, radiation, hormonal therapy and/or chemotherapy.

Figure 2: Personalized Medicine Clinical Case Study Examples⁴

Literature Clinical Case Studies	Action	Costs	Outcomes
<p>Personalized Medicine Adverse Event Avoidance: Warfarin⁵</p> <p>An anticoagulant long used in treating blood-clotting problems in cardiovascular disease, cancer, and some surgical procedures. Difficult to dose due to great variation in individual responses to the drug (effective doses range from 0.5mg to 60 mg/day).</p>	<p>Prior to genetic testing, trial-and-error dosing was the norm, sometimes with serious consequences; under-dosing of Warfarin could lead to strokes, and over-dosing could lead to severe and even fatal hemorrhages.</p>	<p>Genetic testing to guide Warfarin dosing could avoid 85,000 serious bleeding events and 17,000 strokes annually in the U.S. Treatment cost estimates in 2006 were as follows:</p> <p>Cost per severe bleeding event is approximately \$13,500.</p> <p>Cost per stroke is \$39,500.</p>	<p>The estimated potential annual health care cost savings from individual dosing of Warfarin based on genetic testing are \$1.1 billion with a range of \$100 million – \$2 billion for the U.S. health care system.⁶</p>
<p>Personalized Medicine Decreases Costs Associated with the Life Course of a Disease – Gleevec (Imatinib)</p> <p>A molecularly targeted drug approved in 2001 for the treatment of chronic myeloid leukemia (CML). Each year, 4,500 Americans are diagnosed with CML.</p>	<p>Targets tumor protein in cancer cells, avoids damage to healthy tissue.</p>	<p>Treatment Cost of CML disease progression is as follows:</p> <p>Chronic phase inpatient: \$998/day.</p> <p>Accelerated phase inpatient: \$1,400/day.</p> <p>Blast crisis: \$1,433/day.⁷</p>	<p>Although long-term outcomes for control of CML are not known, Gleevec prevents progression of CML, prevents future treatment costs, and improves quality of life for affected individuals.</p>
<p>Personalized Medicine Impacts the Cost of Care: HIV/AIDS – Genotype Analysis Resistance Testing (GART)</p> <p>For individuals with HIV/AIDS, resistance to highly active antiretroviral therapy (HAART), the current standard of care for HIV, is associated with disease progression and death.</p>	<p>GART results allow physicians to determine the ideal regimen of therapy, based on an individual drug resistance profile. GART is a personalized medicine diagnostic that determines how an individual will respond to drugs used in HAART.</p>	<p>Cost of care (physician visits, diagnostic tests, treatments, and inpatient care) for individual with HIV is \$8,427/6 months; costs for an individual who has AIDS is \$10,893/6 months – a greater than \$2,000 savings over six months for every person with HIV whose disease does not progress to AIDS.⁸</p>	<p>Employing GART in HIV improves life expectancy, reduces the number of cases that progress to AIDS, and also increases life expectancy by nine months compared to HAART therapy without resistance testing.</p>

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⁴ There are many other examples, but only three are described here.

⁵ Reimbursement by health plans varies. Some health plans are still debating the clinical utility of genetic testing to guide Warfarin dosing. Payors need evidence of clinical utility to satisfy their coverage policies.

⁶ McWilliam A, Lutter R, Nardinelli C. *Health care savings from personalizing medicine using genetic testing: the case of Warfarin*. Working Paper 06-23. Nov 2006. AEI-Brookings Joint Center for Regulatory Studies. http://aei-brookings.org/admin/authorpdfs/redirect-safely.php?fname=../pdffiles/WP06-23_topost.pdf, accessed March 11, 2008.

⁷ Reed SD, Anstrom KJ, Ludmer JA, Glendenning GA, Schulman KA. "Cost-effectiveness of imatinib versus interferon- α plus low-dose cytarabine for patients with newly diagnosed chronic-phase chronic myeloid leukemia," *Cancer*, 2004;101:2574-83

⁸ Corzillus M, Mühlberger N, Sroczynski G, Jaeger H, Wasem J, Siebert U. "Cost effectiveness analysis of routine use of genotypic antiretroviral resistance testing after failure of antiretroviral treatment for HIV," *Antiviral Therapy*, 2004;9:27-36

score for early Stage I/II breast cancer with negative nodes and estrogen positivity indicates a low likelihood of recurrence, and thus no need for chemotherapy ((CMF⁹)/(MF¹⁰)) vs. a high recurrence score emphasizes the need for chemotherapy ((CMF⁹/MF¹⁰));¹¹ and 2) the introduction of a companion therapy after a personalized diagnostic (e.g., with Her-2 and Herceptin, a positive testing patient with early Stage I/II breast cancer with negative nodes and estrogen positivity indicates the need for confirmatory FISH¹² testing. If the FISH¹² tests positive, Herceptin should be added to the adjuvant chemotherapy regimen).¹³ In the first scenario, standard therapy for newly diagnosed breast cancer patients consists of a combination of surgery, radiation, hormonal therapy and/or chemotherapy. Oncotype DX[®] alters the standard therapy by identifying individuals who would not benefit from chemotherapy, and have little likelihood of tumor recurrence. In the second scenario, HER2 tests the responsiveness of the tumor to a specific chemotherapy agent, affecting the aggressiveness and growth of the tumor. In responsive cases, companion chemotherapy is introduced to standard treatment.

Framework Components

The ROI framework includes only additional costs and benefits above and beyond traditional approaches to treatment. Based on the literature review, five components were included in the development of the ROI framework: increase or reduction of adverse events, reduced costs of life course of disease, cost of the personalized medicine intervention, reduced non-medical costs, and non-economic benefits such as quality of life.¹⁴ Values included in the framework for each of these components were based on the literature review.

Calculating ROI

The framework for calculating return on investment is presented in Exhibit 1.

Exhibit 1: High-level ROI Framework

Net Value of a Personalized Medicine Intervention =
 Reduced Adverse Events + Reduced Life Course Costs +
 Reduced Non-medical Costs – Cost of Personalized
 Medicine Intervention + Non-economic Benefit
 (e.g., quality of life or longevity)

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⁹ cyclophosphamide plus methotrexate plus 5-fluorouracil

¹⁰ methotrexate plus 5-fluorouracil

¹¹ Oncotype DX[®] is a 21-gene panel test that predicts individual tumor responsiveness to chemotherapy. Genomic Health is the developer of Oncotype DX[®], used in the diagnosis for early-stage breast cancer patients. It is the “first and only multi-gene expression test commercially available that has clinical evidence validating its ability to predict the likelihood of chemotherapy benefit as well as recurrence in early-stage breast cancer.” (*Genomic Health*, 2008.) “The majority of women with early-stage, hormone receptor positive, node negative breast cancer are treated with chemotherapy, yet clinical studies have shown that it only improves survival rates in 4 out of 100 patients. (*Lancet* 1996 Apr 20 :347:1066-71.)

¹² Fluorescence *in situ* Hybridization

¹³ HER2 testing predicts responsiveness to trastuzumab (Herceptin), a breast cancer chemotherapy agent. The HER2 gene can affect breast tumor growth and aggressiveness of the disease. Each normal breast tissue cell has two copies of HER2; however in some breast cancers the cells have many more copies of HER2 and multiple HER2 receptors. The action of Herceptin is to interrupt the pathway of the HER2 genes and receptors.

¹⁴ Operational definitions: Adverse Events – those events associated with adjuvant chemotherapy treatment, such as nausea, neutropenia/thrombosis, and anemia; in the case of Herceptin, there is substantial risk of life-threatening cardiotoxicity. Literature values of probabilities and direct medical cost of treating these adverse events, e.g., drugs, physician visits and inpatient care, were included in the framework; Life Course of Disease Costs – the probabilities and costs of treating a breast cancer recurrence or metastatic event. Net value to patients and payors is based on the reduced probability of recurrence due to the personalized medicine intervention; non-medical costs – costs associated with receiving care and treatment, such as travel; non-economic benefits – improved quality of life and increased longevity due to PM intervention.

Net present value (NPV) is the metric used in the framework to quantify the economic costs and benefits. Using estimates cited in the literature, dollar amounts were converted to 2008 values, and non-economic benefits were converted to 2008 dollar values; obtaining an overall “net value” for each scenario.¹⁵ Two time dimensions were analyzed: product exclusivity and time to realize benefit. Product exclusivity is the time that the patent owner has exclusive rights to market and sell a therapeutic agent. Since a patent’s life is fixed at 20 years, the longer it takes to prepare a therapy for market (R&D), the less time there is available for a biotech/pharma company to benefit from a product’s market exclusivity. The framework assumes a seven-year period of market exclusivity, but an eight-year period was also modeled to determine the value of a potentially shortened R&D phase for a personalized medicine targeted therapy. Each scenario framework is based on a 12-year benefit timeline, assuming that will cover the period of avoided disease recurrence for most individuals. In addition to net present value, a breakeven point for a positive return on investment was also determined for each stakeholder.¹⁶

Industry Stakeholders

Personalized medicine, although referred to as an entity, is comprised of a complex series of R&D, market, and professional relationships among multiple stakeholders. For the purpose of this project, four major stakeholder groups were identified: consumers, diagnostic companies, pharmaceutical and biotechnology companies, and payors. Two other stakeholder groups, health care providers and employers, were not sufficiently represented in the literature case studies for inclusion in this framework.

However, some clear challenges for these two groups are discussed in stakeholder implications. The stakeholder groups selected for this framework contribute to personalized medicine in several ways. The focus and recipient of personalized medicine is the person – including but not limited to health care consumers, or patients. Diagnostic companies develop, manufacture, and distribute personalized medicine diagnostic tests that are based on advances in genetics. Pharmaceutical and biotechnology developers and manufacturers provide research, development, manufacture, and sales of personalized therapies. Those who make funding decisions about coverage for personalized health care expenditures include both public and private payors.

¹⁵ In abstracting estimates cited in the literature for framework variables, the cited figures were updated to U.S. dollars (if the published figures were in a foreign currency) and to 2008 figures (using a medical price index). It was assumed that consumers and payors would split direct medical costs such as pharmaceuticals using a 20/80 split, representative of a typical health plan benefit design. To calculate the appropriate value for biotech/pharma companies, it was assumed that 80 percent of societal values would accrue to them as gross margins on the pharmaceutical products. Finally, it was assumed that 73 percent of societal values would go to diagnostic firms as gross margins for the diagnostic tests sold to consumers and payors. These figures are consistent across both scenarios.

¹⁶ Readers may change these timeframes and discount rates in the framework to suit their particular scenario requirements.

The current evolution in the health insurance market adds to the importance of understanding ROI for stakeholders. The commercial market is transitioning from a group model to a retail model as employers stop providing health benefits and the cost of health care coverage is shifted to the end user – the employee/consumer – which will influence plans to customize a suite of individualized products and services. The CMS Medicare program is already an individual model, and is developing tools to both assess and access the personalized medicine market. As the SCHIP (pediatric and adolescent health) program and the federally subsidized adult program expand, there is increased likelihood that larger numbers of the uninsured will access these individual programs. The confluence of these market changes with the potential benefits of personalized medicine for improved population health is profound.

Procedure

Separate ROI calculations were generated for each of the stakeholder groups. Based on the two scenario case studies referenced above, the Net Present Value (NPV) and breakeven points were calculated for the four stakeholder groups. Where possible, personalized medicine conditions were identified where it would be advantageous for particular stakeholder groups to invest or reimburse interventions. Sensitivity analyses were conducted for each stakeholder group to show how the framework may be applied to other clinical situations/case studies. Costs and probabilities were varied to assess each impact on overall

Stakeholders

- **Consumers – people of all ages in all stages of health and disease, including but not limited to patients interacting with the health care system.**
- **Diagnostic companies – businesses that research, develop, manufacture, distribute, sell, and/or conduct molecular diagnostic tests. Tests may be used for early and continuing disease detection, diagnosis and treatment response monitoring.**
- **Biotech/pharmaceutical industry – companies that research, discover, develop, manufacture, market, and sell biotechnology and drug products used in preventing and treating both disease and symptoms of disease.**
- **Personalized medicine therapeutics companies – a subset of the pharmaceutical industry; businesses that manufacture, market and sell molecular-based therapies.**
- **Payors – funders of health care. Includes public programs such as CMS, VA; commercial funders such as private insurers.¹⁷**

¹⁷ 2005 National health expenditures distribution: private insurance – 35 percent; Medicare – 17 percent, Medicaid-16 percent; out-of-pocket – 13 percent, other public (e.g.VA, DoD) – 13 percent, other private sources – 7 percent. *2005 The Nation's Health Care Dollar: Where it Came From*. CMS Exhibit. <http://www.cms.hhs.gov/NationalHealthExpendData/downloads/PieChartSourcesExpenditures2005.pdf>. Accessed December 12, 2008.

NPV within the frameworks. The variables that were used in the sensitivity analysis include: 1) the proportion of patients adopting the personalized medicine intervention (PMI);^{18,19} 2) the costs of adverse events and the life course of the disease;²⁰ 3) the price of the PMI;²¹ 4) the R&D costs associated with the PMI.²²

Although framework components (e.g., adverse events, life course costs and personalized medical intervention costs) stay the same across stakeholders, the value of a particular component variable changes between positive and negative depending on who the stakeholder is and whether that variable is a “cost” or “benefit” to them. Annual totals were used to generate a breakeven graph for each stakeholder for both frameworks (Figure 3, next page).

¹⁸ Personalized Medicine Intervention (PMI) as discussed in this paper’s scenarios include targeted diagnostics that can change the clinical care plan and/or also result in the addition of companion therapy.

¹⁹ If more (or fewer) patients are affected by the personalized medicine intervention (PMI), one might expect that the overall net value will substantially increase (or decrease), as these additional patients will accrue all of the benefits (and costs) associated with the PMI. Sensitivity calculation is based on the number of adopters and responders.

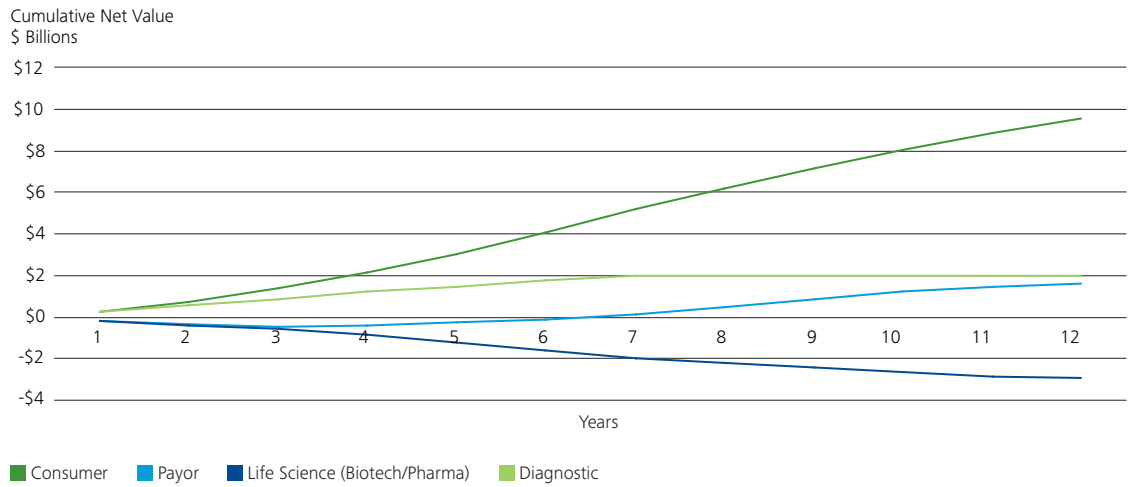
²⁰ As the cost of an adverse event increases, the overall net value is expected to increase if the PMI helps reduce the probability of an adverse event (as in the case of Scenario 1 for those patients who are taken off of chemotherapy treatment). As the cost of treating the disease’s life course increases, the overall net value is expected to increase if the PMI helps reduce the probability of disease progression (as in the case of Scenario 2 where patients undergoing Herceptin therapy experience a reduction in disease recurrence and metastases probabilities). Sensitivity calculation is based on a benefit for adverse events: +/-50 percent. Additional sensitivity calculation is based on the benefit for avoiding life course of disease costs: +/-50 percent.

²¹ If the price of the PMI diagnostic and/or therapeutic product increases, the overall net value is also expected to increase, particularly for the diagnostic and/or biotech/pharma firms that developed it. However, with these price increases, the overall net value for consumers and payors may decrease. The sensitivity analysis can show to what degree stakeholders experience change due to price variations of the PMI diagnostic and/or therapeutic products. Sensitivity calculation is based on 33 percent increase in price of diagnostic test.

²² The costs associated with R&D are decreased in the sensitivity analyses to reflect the potential differences between R&D for PMI therapies as compared to conventional diagnostics and therapeutics. The analyses assume that PMI may succeed in clinical trials with fewer numbers of patients required for statistically significant results and/or a shorter timeframe needed for PMI therapy development. Sensitivity calculation is based on decreased R&D costs of 25 percent. Additional sensitivity calculation is based on additional year of product life exclusivity.

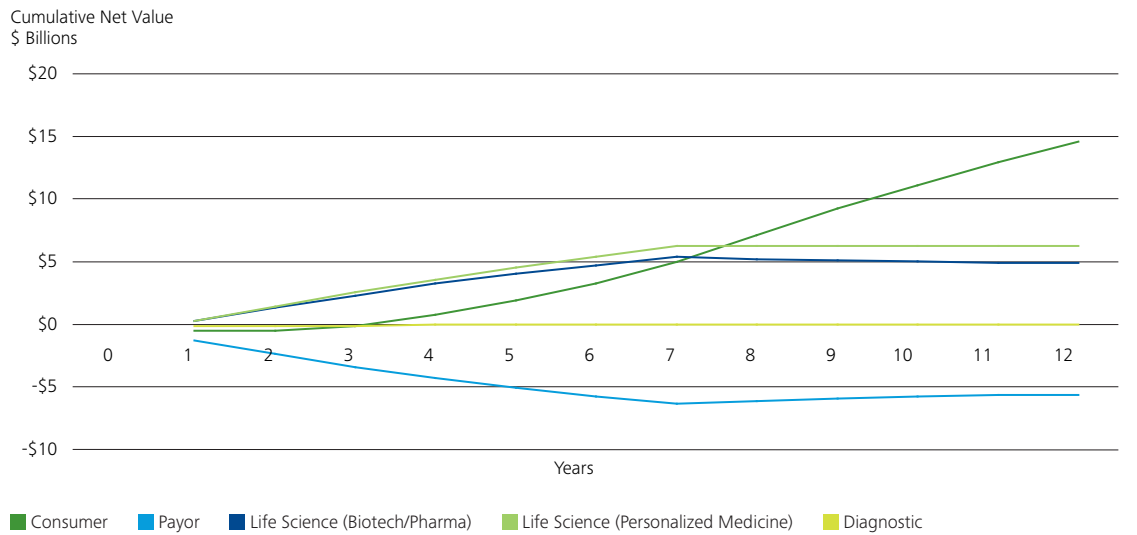
Figure 3: Breakeven Point for Both Scenarios

Breakeven Point for Scenario 1*



*Using data from the Oncotype DX Diagnostic Testing breast cancer case study

Breakeven Point for Scenario 2*



*Using data from the HER-2 Diagnostic Testing/Herceptin Therapy breast cancer case study

Results

Summary results are presented for each scenario, followed by a more detailed discussion for each stakeholder group by scenario. These results were created using reasonable assumptions and data from the breast cancer literature to populate this paper's ROI framework for breast cancer care. For example, in Scenario 1, we chose 21Gene PCR or Oncotype DX® risk scoring; in Scenario 2, we chose Her-2/Herceptin. These results are not intended to describe ROI for all scenarios, but to explain ROI for the breast cancer scenarios used in this paper. As a result, the reader is better able to understand each stakeholder's barriers/benefits for a productive personalized medicine business model.

Summary

Scenario 1:²³ Alterations to the Current Course of Care

- Consumers/patients experience a positive ROI within the first year, with increasing positive benefit over time due to the alteration of the current course of therapy, either because no therapy is required, or because they are better informed about a high risk of disease recurrence.
- Payors eventually achieve a positive ROI; realization of the ROI develops over a six-year period. This is a substantial financial challenge for commercial payors, given the annual turnover rate in member populations. Public payors can realize a positive ROI if their members' average tenure is greater than 6.35 years.
- Biotech/pharma companies consistently experience a negative ROI, due to the shrinking of the population-based blockbuster drug model to a narrower, more efficacious, targeted therapy subpopulation.
- Diagnostic testing companies consistently experience a positive ROI, as they make a sale for every consumer who is tested.

Scenario 2:²⁴ Personalized Medicine Intervention that Introduces a Targeted Therapy

- Consumers/patients achieve a positive ROI once the initial exposure to the expensive personalized medicine therapy exceeds initial adverse events, life-course costs, and quality-of-life year (QALY) impacts. In the long term, benefits of reducing the risk of recurrence greatly exceed the initial adverse events, life-course treatment costs, and negative quality-of-life issues.
- Although the framework shows the payors never achieving a positive ROI in this scenario, this is a framework limitation. The framework fails to reflect other benefits important to the payor, such as providing coverage for evidence-based treatment that is safer and more efficacious, and for increasing sales to personalized medicine candidates to increase throughput of patients and resulting benefits attributed to personalized medicine.
- Biotechnology/pharmaceutical companies experience a positive ROI due to the addition of the targeted therapy to the standard treatment, which produces new sales revenue. A key variable affecting the ROI is the extensive R&D investment cycle required to produce personalized medicine targeted therapies. If the cycle and expenses are decreased due to improved patient recruitment and safety processes, there is likelihood of increased ROI
- Diagnostic testing companies receive no benefit under most conditions of this scenario. Although every consumer who is tested generates a sale, the revenue is not sufficient to offset the substantial R&D investment required to develop the test. Decreasing the R&D cycle time would affect the investment required, as well as shorten the time to ROI benefit.

²³ Using data from the Oncotype DX Diagnostic Testing breast cancer case study

²⁴ Using data from the HER-2 Diagnostic Testing breast cancer case study.

Results by Stakeholder: Consumers²⁵

Scenario for Consumers	NPV	Break Even
1. Personalized Diagnostic Alters the Standard	\$11.4B	Always Positive
2. Personalized Diagnostic Introduces a Companion Therapy	\$18.7B	4.4 years

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- **Scenario 1: Consumers have a strong ROI** due to the decrease in adverse events from the avoidance of unnecessary treatment and the prevention of costly life-course-of-disease events such as recurrences and/or metastatic disease. In this scenario, high-risk individuals are identified by the personalized diagnostic test and treated pre-emptively. The consumer benefit is directly attributable to the personalized medicine diagnostic testing intervention, which indicates the degree of risk for disease recurrence.
- **Scenario 2: The consumer experiences a positive ROI after 4.4 years.** Paying for personalized medicine interventions by co-payment, deductibles, or self-pay are an initial cost for the consumer. Associated costs are the adverse events resulting from the addition of a companion therapy, however efficacious. However, effective personalized treatment which reduces the life-course-of-disease costs, due to reduced recurrences and metastases, and resulting in improved quality of life provide compelling returns on the initial investment. The profound value of decreased mortality represents a real value to consumers, and should be considered by the reader when evaluating benefits for the consumer stakeholder group.²⁶
- **Consumers benefit from improved safety and efficacy of personalized therapies.** Benefits for consumers are conceptualized as improved quality of life, and consumer costs are defined as out-of-pocket expenses. Concrete information about costs and expenses is more easily understood than the more abstract concepts of quality of life, and population calculations of treatment safety and efficacy. This theoretical value may not be as obvious to consumers, and thus require consumer outreach and education on the multiple benefits of personalized medicine. Additional and related consumer benefits, improved work presenteeism and reduced absenteeism, were not modeled in the framework, as direct financial benefits accrue to both employers and consumers. Although consumers are the primary beneficiaries of treatment, they are generally assisted in covering the costs of care by payors (often through employer-sponsored programs), who take on a substantial amount of the costs. Thus, consumers and their employers might want to consider approaches to work with payors to adopt beneficial personalized medicine therapies in circumstances where reimbursing these therapies creates negative ROI for payors. For example, payors might change benefit designs to increase member financial responsibility by increasing co-pay, co-insurance, deductibles, or adding riders for personalized medicine.

²⁵ These data are derived by using the Deloitte framework with reasonable assumptions from the personalized medicine literature for breast cancer care as described elsewhere in this paper. These are notional ROIs that are only applicable to the breast cancer scenarios studied here. These ROI values will differ for other personalized medicine modalities for breast cancer treatment and also for other diseases/conditions. This Deloitte framework can be applied to other diseases/conditions to determine their specific notional ROIs attributable to their respective personalized medicine interventions.

²⁶ An acknowledged limitation to the study: reduced mortality, as calculated by statistical life years, was considered by the study team, but not included in the framework calculations.

Results by Stakeholder: Payors²⁷

Scenario for Payors	NPV	Break Even	Sensitivity Analysis		
			NPV if Adverse Events +/- 50%	NPV if Life Course Events +/-50%	NPV if Price of PMI +/- 33%
1. Personalized Diagnostic Alters the Standard Course of Therapy	\$1.9B	6.35 Years	\$1.9B to \$1.8B	\$3.4B to \$0.4B	\$1.5B to 2.6B
2. Personalized Diagnostic Introduces a Companion Therapy	-\$5.5B	None	-\$5.5B to -\$5.5B	-\$4.4B to -\$6.6B	-\$7.9B to -\$3.0B

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- Scenario 1: Payors have a positive ROI after 6.35 years for breast cancer.** In this calculation, payors reimburse costly diagnostics for their member population. Although there are initial benefits due to reduction in treatment costs and adverse events because therapy is no longer indicated for a subset of the population, it is not sufficient to provide an early positive ROI. The delayed breakeven point of 6.35 years for breast cancer modeled in this scenario poses a financial challenge for commercial payors, as annual turnover in membership may severely limit payors' ability to recoup their investment on a subset of their member population. In contrast, public payors, whose average tenure for members is greater than 6.35 years, will be able to recoup the initial personalized medicine investment. It is important to note that our framework only focuses on the cost and benefits associated with breast cancer per-member per-month (PMPM) costs to the payor. Some genetic tests may have an immediate ROI, e.g., KRAS²⁸ in colorectal cancer, and some tests may never achieve ROI. This is a limitation of the Deloitte model since it is based on only the breast

cancer literature. Other conditions lack supporting clinical evidence (analytic/clinical/ and/or clinical utility). There are other benefits that motivate payor reimbursement decisions, but this approach highlights the unique challenge for commercial payors confronting high turnover rates in membership.

- Scenario 2: Payors do not achieve a positive ROI in terms of their per-member per-month (PMPM) costs in this scenario.** The high costs of personalized medicine targeted therapies make it difficult for payors to recoup their early reimbursement of a companion targeted therapy and its associated adverse events and risks. This scenario adds cost to standard therapy, and the change in life course costs is not sufficient to generate a positive ROI, based on a PMPM calculation. The PMPM calculus is only one aspect of determining benefit decisions; it does not include payor values of supporting more efficacious and safer treatments, and commitment to advancing personalized medicine applications that are supported by evidence and positive comparative effectiveness results.

²⁷ These data are derived by using the Deloitte framework with reasonable assumptions on the personalized medicine literature for breast cancer care as described elsewhere in this paper. These are notional ROIs that are only applicable to the breast cancer scenarios studied here. These ROI values will differ for other personalized medicine modalities for breast cancer treatment and also for other diseases/conditions. This Deloitte framework can be applied to other diseases/conditions to determine their specific notional ROIs attributable to their respective personalized medicine interventions.

²⁸ The KRAS gene is a biomarker for response to the personalized medicine, Erbitux, used in colorectal cancer treatment. Erbitux is a monoclonal antibody that blocks the effects of a protein called epidermal growth factor (EGFR) that fuels tumor growth. People with normal KRAS genes given Erbitux are less likely to have their cancer progress than those who have mutated KRAS genes.

- **Sensitivity Analysis:** Sensitivity analyses were conducted to demonstrate the change in payor ROI values when adverse events, life-course-event costs, and therapy prices change, which could occur in clinical conditions other than the breast cancer example illustrated in this document. For example, if a product were introduced at a lower price, the value of the avoided adverse or life course events significantly offset the cost of the product. In another example, if a targeted diagnostic altered the prevalence of positive test results for follow-on therapy, it might improve ROI for the payor. In the case of the breast cancer scenarios, results of the sensitivity analysis indicate that payors experience a positive ROI only in the first scenario. There are circumstances when decreased costs associated with the reduction of adverse events and poor outcomes may be more significant than in the breast cancer case studies.
- **Payors will require substantial evidence-based results of the safety, efficacy, and comparative effectiveness of personalized medicine interventions, for personalized medicine coverage decisions.** The high cost of personalized medicine interventions and the time delay for payors to receive some – if any – ROI create significant barriers for adoption of this innovation. Decreases in costs of therapies and diagnostics, and reduction in R&D cycles and investment, could potentially contribute to a positive and more timely ROI.

Results by Stakeholder: Diagnostic Companies²⁹

Scenario for Diagnostic Companies	NPV	Break Even	Sensitivity Analysis	
			NPV with Additional Year of Exclusivity	NPV if Price of Diagnostic Increases 33%
1. Personalized Diagnostic Alters the Standard Course of Therapy	\$2.0B	Always Positive	\$2.3B	\$2.7B
2. Personalized Diagnostic Introduces a Companion Therapy	-\$0.02B	None	\$0.01B	\$0.02B

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- Scenario 1: Diagnostic companies experience a consistently positive ROI throughout the twelve year scenario.** The one-time testing of all eligible consumers generates the ROI, based on a high price point for the diagnostic test. The relatively flat line of the positive ROI is due to one-time testing. Other clinical conditions, such as HIV/AIDS, require multiple diagnostic tests over time (due to mutating pathogens), and thus would be likely to show a continued growth trend in ROI.
- Scenario 2: Diagnostic companies experience a slightly negative ROI, with no demonstrated breakeven point.** Every consumer who has the condition will receive the personalized medicine diagnostic test. This represents significant sales revenue but is not sufficient to offset the large R&D expense to develop the test. It is important to note that the price diagnostic companies are able to charge for the HER2 test used in this scenario is less than the price for the Oncotype DX[®] test used in Scenario 1. As demonstrated in the sensitivity analysis, modest changes in assumptions for R&D expenditure and a price increase for the test contribute to a positive ROI for diagnostic companies.
- Sensitivity Analysis:** A sensitivity analysis was conducted for two alternatives: an additional year of test exclusivity and a diagnostic test price increase of 30 percent. An additional year of diagnostic test exclusivity could be obtained by a more rapid FDA approval cycle, or by a legislative approach similar to the Orphan Drug Act. Introducing a diagnostic test price increase of over 30 percent to the framework resulted in a modest gain in scenario one and a significant positive ROI in scenario two.
- Personalized medicine diagnostic companies most likely to experience positive and significant ROI are those that can command high prices per test and provide testing for clinical conditions that require repeated diagnostic testing.** In circumstances where a companion targeted therapy is introduced and products cannot command high prices, increased exclusivity may help companies generate a positive ROI. Personalized medicine diagnostics have considerable potential for disruption of current markets. When personalized diagnostics render current therapies obsolete (Scenario 1) and when additional personalized targeted therapies are added to current treatment (Scenario 2) the prevailing business models are challenged. Diagnostic companies may become increasingly attractive as investment targets to life sciences companies trying to diversify risk or launch personalized medicine therapeutics.

²⁹ These data are derived by using the Deloitte framework with reasonable assumptions on the personalized medicine literature for breast cancer care as described elsewhere in this paper. These are notional ROIs that are only applicable to the breast cancer scenarios studied here. These ROI values will differ for other personalized medicine modalities for breast cancer treatment and also for other diseases/conditions. This Deloitte framework can be applied to other diseases/conditions to determine their specific notional ROIs attributable to their respective personalized medicine interventions.

Results by Stakeholder: Pharmaceutical and Biotechnology Industry and Companies Developing Personalized Therapies³⁰

Scenario for Pharma/Biotech Industry and Companies Developing PM Products	NPV for Industry	Break Even for Industry	NPV for PM Companies	Sensitivity Analysis	
				Break Even for PM Companies	NPV of Additional Year of Exclusivity
1. Personalized Diagnostic Alters the Standard Course of Therapy	-\$3.1B	Always Negative	N/A	N/A	N/A
2. Personalized Diagnostic Introduces a Companion Therapy	\$4.8 B	Always Positive	\$6.3B	Always Positive	\$7.0B

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- **Scenario 1: Pharmaceutical and biotechnology developers and manufacturers experience a negative ROI.** Current practice includes adjuvant therapy for most consumers who are newly diagnosed with breast cancer. Personalized diagnostics enable the identification of individuals who will likely receive a benefit from chemotherapy treatment, which results in a shrinkage of the market for standard therapies. The decrease in the total number of individuals who receive adjuvant therapy in this scenario framework substantially reduces the sales revenue; the loss of this revenue compounds over time.
- **Scenario 2: Personalized therapeutic companies experience a positive ROI and are able to “pay off” R&D investments early.** In this scenario, the developer was able to charge a substantial price premium for targeted therapeutic compounds, despite smaller market sizes, resulting in a positive ROI. The ROI of the pharmaceutical and biotechnology developers and manufacturers is less than that of those companies producing personalized medicine

targeted therapeutics. The products developed by the latter group displace those of the former group, which reduces the market for “traditional” therapy products.

- **Sensitivity Analysis:** Sensitivity analysis was conducted to evaluate the ROI effect of an additional year of personalized therapy exclusivity. This does not affect the first scenario, as no therapy is introduced. However, in scenario 2, an additional year of exclusivity contributes significant ROI. There is initial evidence that the R&D cycle for producing personalized medicine therapies can be streamlined. Animal research models have identified biochemical pathways that indicate likelihood of responsiveness to therapy. By using these biomarkers in human clinical trials, there is the possibility of more clearly identifying the link between treatment and response, thus bringing a targeted therapy to market more quickly with additional years of exclusivity. Reduced R&D cycle time and costs may allow for products to be priced more competitively.

³⁰ These data are derived by using the Deloitte framework with reasonable assumptions on the personalized medicine literature for breast cancer care as described elsewhere in this paper. These are notional ROIs that are only applicable to the breast cancer scenarios studied here. These ROI values will differ for other personalized medicine modalities for breast cancer treatment and also for other diseases/conditions. This Deloitte framework can be applied to other diseases/conditions to determine their specific notional ROIs attributable to their respective personalized medicine interventions.

- **Personalized medicine will change the product paradigm from blockbuster treatments to “more therapies – smaller markets.”** Biotech/pharma and personalized medicine manufacturers who are early adopters of personalized medicine stand to receive significant ROI as highly effective targeted therapies displace traditional therapies. Those companies that are slower to develop personalized targeted therapies risk losing substantial market share, not only due to these newer therapies, but also in situations where diagnostic tests alter the course of care. Personalized diagnostics will segment the market into optimal responders and those that should not receive a particular treatment. New personalized therapies may be more efficacious than current treatment approaches, thus rendering current therapies obsolete. Diagnostic testing that targets patient cohorts for whom treatment is likely to be advantageous will lead to reduction in recurrence of disease and subsequent treatments, reduce adverse events and their treatments, and enhance quality of life. The reduction in volume of therapeutic interventions is disruptive to established markets. Being late to production and market may result in reduced market share for companies which are slower to adopt personalized medicine. Approaches to enhancing patient recruitment and scientific processes which streamline R&D processes may decrease R&D expenses. If companies can produce therapies more cost-effectively or if additional exclusivity is legislated, it is possible that savings may be passed on to payors and consumers in the form of lower prices. This highlights the opportunity for health informatics to leverage the secondary use of data to drive more value and perhaps even lower prices – i.e., the utility of data and its central role in executing a personalized medicine strategy.

Implications

Health care innovations that challenge the status quo are often adopted slowly by the scientific community and society. Personalized medicine is likely to experience a similar response because it is also a disruptive health care innovation. This paper has addressed a key barrier to adoption: personalized medicine's economic value proposition. By exploring the value proposition over multiple years and across stakeholders, we seek to increase stakeholders' understanding of the promise, sustainability, and value of adopting personalized medicine. The ROI results for these stakeholders indicate considerable variability in business challenges and opportunities for the adoption of personalized medicine.

Implications of this beginning work are suggested in the areas of policy, education and business processes.

Policy Affecting Science, Discovery, and Innovation

The health care industry has had limited success in documenting the clinical value of new technologies and treatments in economic terms. Personalized medicine will likely face the same, if not a greater, challenge given its expense and disruptive nature to current markets. Continued emphasis on empirical studies is critical to understanding the clinical and economic benefits of personalized medicine interventions. The more that is known about the incremental outcomes of treatment – not just arbitrary endpoints – the more likely it will be for policy interventions to address gaps between current medical practice and personalized medicine. However, policymakers considering support for personalized medicine will need information about the diversity of clinical scenarios relevant to personalized medicine, the value of developing new targeted therapies, and the benefit of personalized medicine to society as a whole.

Three federal agencies are critical to the success of personalized medicine: the National Institutes of Health (NIH), the Centers for Medicare and Medicaid Services (CMS), and the Food and Drug Administration (FDA). The policies and strategies of these three organizations and federal and state policy makers will be key to the adoption of personalized medicine.

- CMS, as the largest health care payor, should benefit from the potential of personalized medicine to reduce disease morbidity, recurrence, risk without benefit, and (in some cases) costs. CMS as policy maker has the potential to work across the industry to assist in rationalizing the investment in personalized medicine, particularly when the financial value is in conflict with obvious improvement in efficacy, clinical outcomes and costs.
- The FDA, with its pivotal role in the regulatory process for new drugs and medical technologies, should continue to study personalized medicine's clinical efficacy and seek methods that will facilitate the development and effectiveness of new molecular entities and genetic diagnostic technologies.
- The NIH should continue to prioritize the investment in biomarkers, genetically targeted diagnostics, and discoveries which can yield personalized targeted therapies.

Policy Affecting Business Processes

Disruptive innovations generally require disruptive business models for successful adoption. We suggest several categories for planning and action that may assist in altering current business models that do not support personalized medicine adoption.

Just as the Orphan Drug Act (ODA) of 1983 provided support for diseases that affect less than 200,000 people, so might legislators consider a similar act to develop and commercialize clinically effective and cost-effective therapies by providing special incentives for biotech/ pharmaceutical and diagnostic companies. Incentives and approaches could include:

- Tax benefits for companies that produce or research personalized therapeutics
- Protections beyond typical patent protection to prolong product exclusivity
- Subsidizing and funding clinical research
- Creating public-private companies that can manufacture products, particularly diagnostic tests, that might not initially have large markets
- Funding research collaboratives that help researchers take advantage of larger patient populations for their clinical trials to decrease the time and costs of patient recruitment
- Funding technologies such as grid services and health information exchanges to connect scientists and clinicians, thus increasing capacity to mine larger data sets and recruit patients from larger populations
- Developing innovative payment options for patent holders and inventors.

Consumer Education and Advocacy

Personalized medicine holds incredible value for consumers. As the framework analysis suggests, this group receives the largest marginal value gains across all stakeholders. However, this value may not be readily apparent to consumers. Because personalized medicine targeted therapies are more complex than standard therapies, consumers and their providers will need to be educated so they can make informed choices about a therapy, based on diagnostic testing results. Understanding both the benefits and limitations of personalized medicine is key to informed decision making. It will be important for industry stakeholders to inform consumers of personalized medicine's benefits via direct-to-consumer campaigns and other communication vehicles; however, this will be challenging due to a continually evolving scientific and regulatory climate. Despite consistent benefit for consumers, the more compelling question remains: Who will pay for it?

As consumerism in health care increases, consumers will gain knowledge and assume more financial accountability for the costs of care, including very expensive personalized targeted therapies. This responsibility is likely to affect consumers' preferences and choices of therapies. Both consumer benefit sponsors and consumer advocacy groups may be called on to provide programs for access to personalized medicine diagnostic tests and targeted therapies, including exerting pressure on payors to offer personalized medicine benefits.

Business Processes

Payors

If the business model for commercial payors continues to move to a retail (as opposed to employer-sponsored) model, lower member turnover rates may increase the potential for earlier ROI for personalized medicine. However, payors will need to rationalize formulary and benefit design to leverage personalized medicine, including developing new actuarial models to account for smaller risk classes. Coding systems, billing systems, and bundled reimbursement strategies may not accommodate rapidly advancing diagnostic technologies and represent procedural challenges for payors, both public and private. The move to a retail model will also prompt health plans to customize a suite of individualized products and services. This presents a powerful opportunity to include personalized medicine applications that have robust and generalizable evidence supporting their efficacy and safety, and clear guidelines for appropriate use. As depicted in Figure 4, several factors will influence coverage/reimbursement decisions for personalized diagnostic tests.

The information systems infrastructure for both public and private payors will need to expand substantially to support storage and analysis of individual clinical biomarker data.

The profound pattern of negative ROI for payors will likely influence payors' expectation for government subsidies, premium tax reductions and abatements to make coverage for personalized medicine profitable.

Although employers were not explicitly included in the economic framework, they are one of the subgroups directly involved in paying for health care. Large employers are experiencing increasing pressure on their bottom line from health care expenditures. Personalized medicine, because of its focus on prevention, early detection, and efficacious treatment, creates an incentive for early adoption by employers. Slowing the advance of conditions and diseases that, if left untreated result in more acute, expensive, and institutionalized care, may have a profound downstream effect on employer health costs.

Biotech/Pharmaceutical and Diagnostic Companies

As indicated in the framework analysis, there are profound ROI implications for biotech/pharmaceutical companies as the product paradigm shifts from "blockbuster" therapies to individual targeted therapies. To diversify their approach to personalized medicine, biotech/pharmaceutical companies may view personalized diagnostic companies as prime investment or acquisition targets. As depicted in Figure 5, several factors contribute to a positive investment scenario.

Figure 4: Factors Favoring Reimbursement of Personalized Medicine

Diagnostic test required once	Diagnostic test moderately priced	No new therapy added to standard treatment
Costs of the diagnostic test and companion therapy	Non-medical costs savings	Non-economic benefits
Number of patients whose clinical care is changed due to the diagnostic test	Value of adverse events or life course mitigated by the targeted therapy or diagnostic	Timing benefits realized
R&D costs are low	High likelihood of changing clinical protocols	Strong evidence base to support clinical efficacy

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Figure 5: Factors Favoring Investment in Personalized Diagnostic Companies

Test required multiple times	Test commands high price	Standard therapies are displaced
R&D costs are low	High likelihood of changing clinical protocols	Strong evidence base to support higher prices

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Pharmaceutical companies may focus on developing compounds whose improved profits and shorter development cycles could offset lower revenues from smaller, non-population-based therapies. In some cases, they may demand protection from generics to help fund product development. To support the patient recruitment and multi-center trial requirements for more targeted study populations, companies may begin to develop research and

information collaboratives with affiliates, academic medical centers and research organizations. This collaboration may also contribute to the generation of the evidence base that will demonstrate the efficacy of personalized medicine to policy makers and payors.

Figure 6 summarizes the stakeholder implications of personalized medicine.

Figure 6: Stakeholder Implications

Consumers	<ul style="list-style-type: none"> Personalized medicine will likely require an up-front cost for consumers/patients, as these therapies may be more expensive than conventional treatments. Long-term benefits of personalized medicine create an incentive to adopt these care modalities. Education regarding personalized medicine diagnostics and therapeutics will be required for consumers to make more informed treatment decisions with their health care providers. Consumers and their employers may exert pressure on health plans to promote the use of personalized medicine. Awareness and educational campaigns will be needed to clarify risks and benefits, including potential for improved health outcomes, available through access to personalized medicine.
Providers	<ul style="list-style-type: none"> Personalized medicine will offer new tools to improve patient care, which providers will need to understand and use with patients and with payors. They will need to provide evidence of treatment efficacy as demonstrated value to payors for reimbursement. As providers move to EHR/EMRs, new decision-support tools will facilitate rapid identification and dissemination of disease-specific standards of practice; improve provider management with real-time outcomes data; prioritize therapies based on potential drug interactions and patient clinical profiles; and identify at-risk patients for earlier intervention.
Payors	<ul style="list-style-type: none"> As the employer-provided group health insurance model moves toward a retail (individual) health insurance model, the issue of employee turnover should mitigate the hesitancy of insurers to adopt personalized medicine due to the lack of a near-term ROI. Employers, as a financier of health care, may benefit from early adoption of personalized medicine. This new care paradigm has the capacity to slow the advancement of conditions and diseases that, left untreated, result in more expensive acute interventions and institutionalized care. The evolution of the commercial insurance market to a retail market will also prompt the design of customized products and services, which provides opportunity for inclusion of personalized medicine products. When personalized medicine is used for specific patients, it may be a trigger for enrollment into other health plan quality initiatives including early detection initiatives, wellness programs, genetic counseling, disease management, etc. Payors will need to rationalize formulary and benefit design to leverage personal medicine appropriately. Members will need education to understand why a treatment is/is not required based upon diagnostic test results. New actuarial models will be needed to account for smaller risk classes. Health plans will need to balance the risk of adverse selection against the benefit of more patients receiving personalized medicine's positive impacts. Health plans will need to expand analytics to incorporate clinical biomarker data to refine patient risk segmentation. Payors may desire government subsidies, premium tax reductions and abatements to make coverage of personalized medicine more profitable.

Continued on page 22

<p>Policy Makers</p>	<ul style="list-style-type: none"> • The Centers for Medicare and Medicaid Services (CMS), as one of the nation’s largest insurers, can play a pivotal role in the adoption of personalized medicine and its marketplace acceptance. Medicare and Medicaid have already begun the transition to an individualized retail market and thus may provide leadership to commercial health plans who need assistance to understand the value of personalized therapies for individual health insurance. • Policy makers (and federal payors) will need to provide incentives for commercial health plans to adopt personalized medicine by leading by example – e.g., reimbursing these technologies. Many health plans make coverage decisions based upon CMS practices. • Policy makers may need to rationalize and leverage the linkage/opportunity of personalized medicine with the Orphan Drug Act • Policy makers should consider supporting R&D tax credits (or other strategies) to the biotech/pharma industry to encourage their personalized medicine development efforts. This can reduce R&D costs and thus price points, making the personalized therapy more affordable for patients and payors. Policy makers should consider subsidizing and funding clinical research in personalized medicine to advance the field and develop the evidence base to support clinical effectiveness. • Policy makers could grant competitive product windows before generics enter the market. They could time the exclusivity period to be coterminous with the ROI timing of the therapy. Policy makers could offer to take on more of the risk of personalized medicine from R&D to market release so that payors would be closer to breaking even. Government could offer prize funds, facilitate industry collaboration on R&D; and/or centralize knowledge on safety to “nationalize” the expense of personalized medicine against the overwhelmingly positive society benefit.
<p>Biotech/pharmaceutical and Diagnostic Companies</p>	<ul style="list-style-type: none"> • Biotech/pharmaceutical companies may need to consider more virtual R&D to address smaller markets with more targeted therapies. This could reduce R&D expenditures. • Biotech/pharmaceutical companies may view personalized diagnostic companies as prime investment or acquisition targets. Life sciences companies with limited capital may seek partnerships with more established and capitalized partners for investment, sales, and distribution support. • Biotech/pharmaceutical companies producing targeted therapies should start to consider strategies to integrate marketing, sales and distribution with companion diagnostics to improve the cost effectiveness of these activities. • Pharmaceutical companies may focus on developing compounds whose improved profits and shorter development cycles could offset lower revenues from smaller, non-population-based therapies. • Biotech/pharmaceutical companies may demand protection from generics to help fund product development. • Biotech/pharmaceutical companies will need to generate an evidence base to demonstrate the efficacy of personalized medicine to garner public policy and payor support. • Biotech/pharmaceutical companies may begin to develop research and information collaboratives with affiliates, academics medical centers, and research organizations to support the patient recruitment and multi-center trials required for more targeted study populations. This could also reduce R&D expenditures and lower price points for broader adoption.

Conclusions and Recommendations

Our aim in conducting this project was to explore two questions: 1) Does personalized medicine have a quantifiable ROI? 2) Is it possible to derive an economic framework from published case studies to demonstrate differences in ROI across significant stakeholders? We were able to extract sufficient case study data from the literature to formulate such a framework, and used that to calculate ROI for four stakeholder groups: consumers, payors, biotech/pharma companies and diagnostic companies. Framework economic components, suggested by case study data, included cost of the personalized medicine therapy, adverse events costs, life-course-of-disease costs, non-medical costs, and non-economic benefits such as quality of life and longevity. We were able to demonstrate through the use of two clinical scenarios that all stakeholder groups experienced a positive ROI under certain conditions, although payors received only a marginal benefit and that is after six years. The group that consistently experienced a positive ROI across all scenario conditions was the consumer.

Based on this initial work, and the awareness that personalized medicine is a dynamic innovation informed by continual new discovery in the genomic sciences, we encourage consideration of the following:

- Continue to refine the framework based on new study findings in current literature.
- Test the framework with additional scenarios and clinical conditions.
- Explore policy options for including elements of personalized medicine in health reform debates.
- Use these preliminary findings to generate discussion with stakeholder groups.
- Encourage exploration and evaluation of new business models that will support this disruptive and promising innovation.

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