Horizon Scanning: Identifying and Estimating Future Impact of Emerging Innovations on US Health Care

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KEY POINTS . . .

The Agency for Healthcare Research and Quality (AHRQ) has developed the first publicly funded health care horizon scanning effort in the US

A protocol for identifying, analyzing, and tracking novel health care interventions governs the processes. The potential future impact of interventions is described in regularly updated reports.

A pilot effort to estimate potential 1-year cost of interventions with moderate to high potential future impact was carried out in late 2014.



Introduction

Healthcare Horizon Scanning is a systematic process used to identify novel health care interventions that address significant unmet medical needs. The Agency for Healthcare Research and Quality (AHRQ) established the first publicly funded Healthcare Horizon Scanning program in the US in the fall of 2010. While the original purpose of the program was to inform AHRQ's research priorities, wider applications of the findings to a variety of stakeholders were soon apparent.

The focus of the AHRQ Healthcare Horizon Scanning program is to identify novel interventions that address unmet needs related to any of AHRQ's priority conditions. AHRQ's 14 priority conditions include: arthritis and non-traumatic joint disease; cancer; cardiovascular disease; dementia (including Alzheimer's disease); depression and other mental health disorders; developmental delays, attentiondeficit hyperactivity disorder & autism; diabetes mellitus; functional limitations and disability; infectious disease, including HIV/AIDS; obesity; peptic ulcer disease and dyspepsia; pregnancy, including preterm birth; pulmonary disease/asthma; and substance abuse.

The AHRQ Healthcare Horizon Scanning System evaluates a variety of health care interventions, including drugs, biologics, devices, diagnostics, procedures, behavioral health services, and health care delivery innovations. Following the Horizon Scanning Protocol, we capture interventions that are likely to diffuse into clinical practice within the next 2 to 3 years, and track the diffusion of identified interventions for about 2 years after they become available for clinical practice. Thus, the interventions identified are typically in late-phase or pivotal trials. For interventions subject to US Food and Drug Administration (FDA) regulatory pathways, we also include interventions in earlier development if FDA has granted a special designation, such as orphan, breakthrough, accelerated approval, innovation pathway, or fast track status.

The basic steps in horizon scanning are described in a Systematic Review of Methods for Health Care Technology Horizon Scanning. They include broad scanning, lead selection, topic identification, topic development, impact assessment, and ongoing monitoring, updating and archiving. For AHRQ's purposes, an unmet need is any need arising from an important gap in effective ways to screen, diagnose, treat, monitor, manage, or provide or deliver care for a health condition or disease. The novelty criterion may be met by interventions with a new mechanism of action, or a system change that creates new access to an intervention. It may involve an existing intervention being applied to a novel use.

In fall 2014, AHRQ asked the project team to undertake a series of cost estimates for all the topics in two iterations of these Potential High Impact reports that had been designated as having moderate-to-high potential impact.

Since December 2010, the project team at ECRI Institute has identified more than 22,000 "leads" of possible interventions that are then researched further by analysts to determine if they meet criteria for proposing a topic for entry into the system. These leads have coalesced into over 2,300 topics that have traveled through the system since its inception.

Horizon Scanning Outputs

An inventory of the active topics in the horizon scanning system is published on the Effective Healthcare Web site as the <u>Horizon Scan Status Update</u> (see Table 1). Typically, about 600 topics are profiled in each update, organized by Priority Condition and tabled in a "PICO" (Patient/Population, Intervention, Comparators and Outcomes) format. These updates are published five times a year as new topics added since the prior edition are identified (Section 2 of the report), and topics to be archived, along with reasons for archiving, are provided (Section 3 of the report).

The <u>Potential High Impact Reports</u> are published twice a year (see Table 2). Of those topics meeting AHRQ's criteria, about 700 have been suitable for more in-depth investigation and vetting by experts for potential impact. Experts in various areas of health care are sent information about a topic and are asked to respond to a series of questions to elicit potential future impacts of interventions in development. The answers to these questions are used by horizon scanning analysts to identify those topics with the highest potential for impact on patient health, health disparities, the delivery system, patient management, and costs.

Payers have referenced AHRQ Healthcare Horizon Scanning reports in medical policy documents (Table 3).

Ultra Rapid Cost Analyses

In fall 2014, AHRQ asked the project team to undertake a series of cost estimates for all the topics in two iterations of these Potential High Impact reports that had been designated as having moderate-tohigh potential impact. Over a 4-month period, five horizon scanning analysts prepared cost analyses on 55 topics that met this criterion. These cost analyses focused on the projected 1-year spend for the interventions if they were to be implemented starting January 2015. The team prepared an overarching summary report with a discussion about observations and possible trends in various priority areas, intervention types, and disease states (See Rapid Cost Analyses of Selected Potential High-Impact Interventions).

Methods for Conducting Cost Analyses

Accurately estimating the potential costs of emerging health care technologies requires these key considerations:

• Accurate understanding of the disease or condition and the number of patients in the target population eligible for the new intervention. Often, emerging technologies are developed for subpopulations with a target condition. Reliable information on such subpopulations can be hard to find.

Actual or projected adoption of the

Table 1. Excerpt from an AHRQ Healthcare Horizon Scanning Status Update

Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Apremilast (Otezla) for treatment of ankylosing spondylitis	Patients in whom ankylosing spondylitis has been diagnosed	Investigators have not found a cure for ankylosing spondylitis. Treatments are intended to reduce inflammation and improve mobility but are not effective for all patients. Apremilast (Otezla [®]) purportedly inhibits phosphodiesterase type 4 (PDE-4). By inhibiting the PDE-4 enzyme, apremilast purportedly increases intracellular cAMP, which modulates multiple inflammatory mediators. When FDA approved the product for psoriatic arthritis, it became available in 10, 20, and 30 mg strengths for oral administration. In trials for ankylosing spondylitis, it is being administered in 20 or 30 mg doses. Celgene Corp., Summit, NJ Completed phase III trial failed to meet primary endpoint; company is deciding next steps; FDA approved Mar 2014 for treating adults who have active psoriatic arthritis	Corticosteroids Disease-modifying antirheumatic drugs Nonsteroidal anti- inflammatory drugs Physical therapy Sulfasalazine (Azulfidine) Tumor necrosis factor inhibitors	Reduced signs and symptoms Improved mobility Improved quality of life

AHRQ indicates Agency for Healthcare Research and Quality; FDA, US Food and Drug Administration.

Table 2. Sample topics in an AHRQ Healthcare Horizon Scanning Potential High Impact Chapter

Topics	High-Impact Potential			
*Ado-trastuzumab emtansine (Kadcyla) antibody-drug conjugate for treatment of advanced HER2-positive breast cancer	Moderately high			
Anastrozole (Arimidex) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	No high-impact potential; archived on basis of experts' comments			
Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Prior high-impact topic (June 2014); archived because it no longer meets criteria for tracking; FDA approved more than 2 years ago			
*Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High			
AHRO indicates Agency for Healthcare Research and Quality: EDA JIS Food and Drug				

AHRQ indicates Agency for Healthcare Research and Quality; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2.

Table 3. Sample medical policies citing AHRQ Healthcare Horizon Scanning reports

Topics	High-Impact Potential
*Ado-trastuzumab emtansine (Kadcyla) antibody-drug conjugate for treatment of advanced HER2-positive breast cancer	Moderately high
Anastrozole (Arimidex) for prevention of breast cancer in postmenopausal women at elevated risk of breast cancer	No high-impact potential; archived on basis of experts' comments
Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Prior high-impact topic (June 2014); archived because it no longer meets criteria for tracking; FDA approved more than 2 years ago
*Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High

GI indicates gastrointestinal; HIFU, high-intensity focused ultrasound.

intervention. Projections of anticipated market share published by drug/device manufacturers were used in the absence of reliable information on actual disease prevalence and adoption rates. These projections are typically optimistic and analysts considered them with a degree of skepticism, often downsizing them based on experience and knowledge of the landscape. When possible, multiple sources of disease prevalence data and market share projections were compared for gaps or discrepancies. Adoption estimates were also tempered with comments collected for the "Potential High-Impact Interventions" report.

• **Costs of implementing the intervention.** Reliable information is typically available for commercially available interventions. In other instances, cost projections were taken from investor resources. Also, to estimate costs of interventions not yet marketed,

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existing interventions were identified to serve as proxies. For novel pharmaceuticals or biotechnologies, appropriate benchmarking agents that entered the market within the past 2 to 3 years for the same or similar conditions were used. In some instances, costs of devices on the European market were used for general pricing guidance for industrialized nations.

For standard-of-care price benchmarking, we also sought to identify the costs of one or two similar competing interventions in the space, as well as the costs of one or two alternative interventions that could be used to treat the condition. We also sought to determine whether the new intervention would replace or add costs to the existing standard of care. The cost analyses performed did not consider effectiveness of interventions in any depth, as systematic effectiveness reviews are beyond the scope of Horizon Scanning.

To identify data for our cost analyses, ECRI Institute medical librarians performed topic-specific searches of the following: Embase®; Lexis-Nexis®; Pharma and MedTech Business Intelligence (Grey Sheet, Pink Sheet, In Vivo, Start-up, Medtech Insight); GoodRX (drugs); PriceGuide ECRI Database (searches for implant and disposable prices paid by hospitals); PricePaid ECRI Database (searches for capital equipment prices paid by hospitals); Health Technology Assessment Information Service ECRI Database (information on clinical, safety, cost, and reimbursement for health care interventions); Cochrane Database (cost studies); The Wall Street Journal; HCUP; Google; and NICE (if no US information found).

Analyses typically estimated the costs of interventions for 1 year of adoption and did not examine any cost offsets or other downstream effects that the interventions may provide. If available, published costeffectiveness models on topics of interest were used to inform our analyses and provide longer-term cost impact projections. See Figure 1 for 1-year cost estimates for 11 interventions estimated to average over \$1 billion each.

Below we present findings from two of the 55 cost analyses completed to illustrate our processes for evaluating the costs of emerging health care technologies and some challenges encountered with this activity.



Topic Overview: Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation is an investigational procedure for females undergoing cancer therapies that impair fertility [1]. Before treatment, ovarian tissue is surgically collected and cryopreserved [2]. After completing treatment, ovarian tissue is reimplanted to restore ovarian function and fertility [2,3].

Available data indicated that about 14.5 million people were cancer survivors in the US, of which 52% were female. Of these, 5.1% were aged 15-39 years. We estimated that about 384,540 female cancer survivors of reproductive age could be eligible for ovarian tissue cryopreservation, but assumed that only some would opt for this procedure [4]. To estimate adoption rate, we used results of an oncologist survey reporting that 58% of patients who consulted oncologists about fertility preservation underwent fertility treatment [5]. Embryo cryopreservation is the standard fertility procedure, but may not suit all patients. Some patients may prefer ovarian tissue cryopreservation [6]. Assuming 58% of patients seek fertility treatment, we estimated about 20%, or 44,600, might use ovarian tissue cryopreservation.

Available data indicated that ovarian tissue cryopreservation costs about \$27,000 [7]. Additional fees apply, such as an initial processing fee (\$2,000 to \$4,000) and monthly storage fees of \$16 to \$38 [8]. Other sources listed charges of \$350 to \$425 annually [9,10]. Processing and freezing an oocyte by ultrafast cooling costs about \$2,225; the pregnancy rate per oocyte ranges between 7.5% and 10%. Physicians recommend freezing 10-12 oocytes, bringing processing costs to \$22,250 to \$27,000 [11]. Also, the live birth rate (25% to 38%) should be considered for pricing; multiple treatment cycles may be required for conception [12,13], costing \$7,340 to \$8,410 per additional cycle [12].

If fully implemented, ovarian tissue cryopreservation could incur a health care expenditure of about \$1.2 billion (\$27,000 per procedure \times 44,600 patients). Adoption could increase if third-party payer coverage expands, but evidence on the procedure is limited at this time.

Challenges encountered during this analysis included gathering information to estimate adoption because no data were available on patient acceptance or ability to pay for the procedure. Few estimates exist on procedure costs, and we found no information on downstream cost impacts. Finally, psychosocial factors impacting fertility decision making unfold over years and are unique to each patient, so quantifying costs within a prescribed 1-year spend estimate is difficult.

Topic Overview: Interferon-Free Oral Therapies for Chronic Hepatitis C Infection

Chronic hepatitic C (HCV) infection is the leading cause for US liver transplants [14]. Sovaldi® was the first interferon (IFN)-free treatment approved in December 2013, followed by several approved and off-label options that have become available for treating all HCV genotypes. We determined drug costs using the pharmaceutical price aggregator, GoodRx.

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Guidance from liver disease professional associations (American Association for the Study of Liver Diseases and Infectious Diseases Society of America) was used to determine likely treatment options and comparators [15]. We used drug costs and guidance from March 2014. For example, for previously untreated patients with HCV genotype 1 or 4, 12 weeks of Sovaldi® and IFN/ribavirin (RBV) was recommended [15] costing about \$99,300 [16-18]. For the same patients who were unable to tolerate IFN, daily Sovaldi and Olysio®, with or without RBV for 12 weeks, was recommended [15], costing about \$160,600 or \$161,500, respectively [16,17,19]. We anticipated that when approved, Harvoni® and Viekira Pak™ would be preferred for genotype 1 infection. We expected 12 weeks of Harvoni and Viekira Pak to cost about \$94,500 and \$60,000, respectively [20,21]. Currently, 12 weeks of Harvoni and Viekira Pak cost about \$92,000 and \$85,000, respectively, without discounts [22,23].

In the third guarter of 2014, Sovaldi sales grossed \$8,55 billion [24]. We estimated sofosbuvir sales would remain constant, reaching \$11.4 billion in 2014-the cost of a 12-week regimen for 128,000 patients at \$88,500 per patient [16]. We assumed that when approved, Harvoni and Viekira Pak would increase treatment rates for genotype 1 infection by providing an IFN/RBV-free regimen [15]. Expecting approval of both drugs, we estimated by the end of 2014 about 160,000 patients (5% of US HCV infections) could be treated without IFN at costs exceeding \$13 billion. We estimated an additional 256,000 patients (about 8% of HCV infections) could be treated in 2015, considering fullyear availability of IFN-free regimens for genotype 1 infections and pricing discounts from manufacturers. Assuming discounts of 20% to 30%, we estimated about \$17 billion would be spent on IFN-free regimens in 2015.

We identified two barriers to diffusion: the number of clinicians available and financial resources needed (third-party payer pushback) to treat the large HCV population.

Challenges unique to this cost analysis included the changing landscape of HCV regimens, fluid regulatory environment, difficulty obtaining cost and reimbursement information, and evolving treatment guidance, all compounded by the growing number of competitors in the space.

Challenges in "Rapid Review" Cost Analysis of Emerging Technologies

The challenges of performing rapid cost analysis of new and emerging health care technologies occur across three broad dimensions. First is the novelty of the technologies. Novel technologies still in development, by definition, may have no analog with regard to the data needed to perform a robust cost analysis. A second challenge is the fragmented nature of the US health care system. With the multitude of payers, hospitals/providers, and increasing cost-sharing with patients, how does one choose which perspective to take for the rapid cost analysis? Even for a payer perspective, inputs and results can be very different depending on whether one chooses a private payer, Medicare, Medicaid, Veterans Health Administration, or integrated health system. A third challenge is the "rapid" review process itself, for which standard methods do not exist. In this case, the timeframe allotted to perform analyses was very short: 16 weeks to complete 55 analyses. A team of five analysts completed the work, an average of 3.4 analyses per week.

These three challenges arise for each step in performing the cost analyses: (1) how to identify the target population; (2) how to estimate the proportion of that population that might actually be prescribed and use the technology, and (3) how to estimate the costs associated with the technology. As mentioned earlier, hard data on such inputs are not often known for emerging technologies; and even if known, may vary widely by payer type and population. We know large differences exist in socioeconomic, demographic, and clinical profiles of insured populations, and that coverage, reimbursement, prices, rebates, and discounts vary by payer. The recent case of Sovaldi and Harvoni and other new HCV drug costs is an excellent case in point. The need for "rapid" review limits one's ability to analyze existing secondary data sources to generate more accurate estimates or perform numerous sensitivity analyses. Uncertainty surrounds many factors that may impact demand or actual technology utilization.

Among the issues that need further thought and examination regarding rapid cost

analyses are how much we care about the accuracy or precision of estimates. How close do these estimates need to be to offer useful information to prepare for adoption and implementation in the health care system? Part of the answer depends on the purpose and real-world application of the estimates. Part of the answer may also be that rapid, less complex cost analyses of emerging technologies can be updated more easily and frequently as new information becomes available early in the clinical diffusion curve. Perhaps the ability to perform rapid analyses on many topics can then feed into more careful decision making about which technologies merit indepth, more complex analysis that focus on cost offsets and/or cost-effectiveness.

Readers are encouraged to learn more about the AHRQ Healthcare Horizon Scanning System on the Effective Healthcare website: <u>http://</u> <u>effectivehealthcare.ahrq.gov/</u>.

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Additional information:

The preceding article is based the a workshop, "Horizon Scanning—Identifying and Estimating Future Impact of Emerging Innovations on US Health Care," given at the ISPOR 20th Annual International Meeting, May 16-20, 2015, Philadelphia, PA, USA.

To view the panel's presentation, go to: http://www.ispor.org/Event/ ReleasedPresentations/2015 Philadelphia#workshoppresentations

This topic will be presented at the ISPOR 21st Annual International Meeting in Washington, DC, USA, during Workshop 9: "Five Years Of Health Care Horizon Scanning For AHRQ – Results And Lessons Learned." See pages 30-31 for further meeting details.

A Real-World Research Perspective for Biosimilars

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KEY POINTS . . .

Real-world evidence is needed to support claims of safety, effectiveness, and value of biosimilars.

Methodological considerations will be affected by the evolving regulatory and policy landscape on issues such as non-harmonized naming conventions, interchangeability and automatic substitution, as well as decisions regarding reimbursement and physician adoption of biosimilars.

Accurate identification of the biosimilar from its originator is critically important to attribute safety and effectiveness outcomes to the correct product.

Introduction

Biologics are effective and lifealtering therapies used to treat cancer. rheumatologic diseases, diabetes, and other conditions. However, biologics may cost from \$15,000 to \$150,000 per year [1], far exceeding the cost of most smallmolecule drugs. Biologics represented 27% (€36 billion) of drug spending in Europe (EU) in 2011 [2] and 28% (\$92 billion) in the US in 2013 [3], yet they accounted for less than 1% of all prescriptions dispensed in the US in that year. While biosimilars are intended to be more affordable to patients than the originator, the cost savings are not as great as for small-molecule generics because of the complexity of synthesizing biosimilars using living organisms. In the EU, biosimilar prices are discounted by an average of at least 25% compared with the originator biologic [4]. The first US biosimilar is being marketed at a wholesale price 15% lower than its originator [5].

Biosimilars are similar or highly similar versions of an approved biologic (or originator) and hold the promise of reducing health care costs, increasing patient access, and promoting innovation [4]. The European Medicines Agency (EMA) has approved 21 biosimilars since the introduction of their *similar biological medicinal product* guidance in 2006, and currently 20 are marketed [6]. The US Food and Drug Administration (FDA) approved its first biosimilar under the 351(k) regulatory pathway [7] on 06 March 2015 and the first biosimilar hit the US market on 03 September 2015 [5]. An estimated 12 biologic patents will have expired by 2020; thus, the availability of biosimilars is expected to increase across the globe.

Biosimilars Considerations

Careful design and implementation of real-world studies are needed for highquality evidence generation to fully understand biosimilars. However, the lack of harmonization in naming conventions for biosimilars, the variability in regulations on interchangeability of biosimilars for originators and for automatic substitution, reimbursement decisions, and physician awareness and prescribing adoption must