

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Cross-Cutting Interventions and Programs

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 21,000 leads about potential topics has resulted in identification and tracking of about 2,250 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated semi-annually. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 170 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists five topics for which (1) preliminary phase III data for drugs were available; (2) information was compiled and sent for expert comment before May 8, 2015, in this priority area; and (3) we received five to seven sets of comments from experts between July 1, 2014, and May 18, 2015. (Nine topics in this priority area were being tracked in the system as of May 8, 2015.) We present summaries on three topics (designated by an asterisk in the table below), which were deemed to have high-impact potential at this time on the basis of expert comments. The material on interventions in this Executive Summary and report is organized alphabetically. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 15: Cross-Cutting Interventions and Programs

Topic	High-Impact Potential
1. Computer-assisted system (Sedasys) for propofol sedation during gastrointestinal endoscopy procedures	No high-impact potential at this time; archived on the basis of experts’ comments
2. * Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy	Lower end of the high-impact-potential range
3. * Patient-based 3-D printed biomodels to aid surgical planning	High
4. * Patient training and risk assessment program (MSHOP) for surgery preparation	Moderately high
5. Senior-specific emergency departments for treatment of elderly patients	Prior high impact topic (December 2014); archived because intervention is widely diffused

Discussion

We created this priority area to capture cross-cutting interventions that affect two or more of AHRQ’s 14 priority areas. Some of these interventions are health care technologies and others are programs, services, or care-delivery innovations. The topics that emerged as having potentially high impact are technologies and care-delivery innovations that might shift providers’ roles or settings. We also briefly discuss below topics from the previous Potential High-Impact Interventions report that have been archived from active tracking in the horizon scanning system.

Prior High Impact Topic Archived Since December 2014 Report

- **Senior-specific emergency departments (EDs) for treatment of elderly patients:** In the December 2014 report (and several prior reports), this topic was deemed by expert comments to have potential for high impact (in the moderate range of the high-impact-potential scale) because it could potentially reduce admissions, reduce length of stay, achieve more appropriate hospital admissions, improve safety for seniors in the ED and improve the diagnostic process. We have now identified scores of additional senior-specific EDs in planning or operation nationwide, and a multigroup task force has developed the Geriatric Emergency Department Guidelines for implementing new senior-specific EDs. Thus, we consider this mode of care delivery as having reached a tipping point of broad acceptance and diffusion. Whether these EDs have achieved all the desired outcomes remains unclear at this time because of the small number of studies published, but the availability of these EDs makes it possible to conduct more and larger studies. Thus, we archived the topic from the horizon scanning system in January 2015 because this infrastructure innovation and care delivery model appear to have wide acceptance and implementation.

Eligible Topics Not Deemed High Impact

One eligible topic, discussed here, was deemed by experts to lack potential for high impact.

- **Computer-assisted system (Sedasys) for propofol sedation during gastrointestinal endoscopy procedures:** Sedasys® (Ethicon Endo-Surgery, Inc., a unit of Johnson & Johnson, New Brunswick, NJ) is a computer-assisted personalized sedation system intended to aid clinicians in delivering propofol for minimal to moderate sedation during routine colonoscopy and esophagogastroduodenoscopy procedures. This topic has been tracked in the system for several years and has received several sets of comments at different points in its development and since its approval by the U.S. Food and Drug Administration (FDA) in May 2013. Although propofol may be preferred because of improved patient experience and faster recovery times, safety concerns complicate its use. The Sedasys sedation system is intended to allow teams led by physicians who are not anesthesiologists to administer propofol during routine endoscopy procedures (although an anesthesia professional needs to be available in case of emergency). The product launch did not occur until October 2014, more than a year after FDA approval, and its diffusion has been intentionally limited by the manufacturer since then because of concerns of anesthesia professionals and others about the system's use by nonanesthesiologist clinicians. Overall, in our latest round of expert comments (received in early 2015), experts commenting on this topic expressed views that the Sedasys system does not address a significant unmet need because alternative sedation methods (e.g., benzodiazepine/opioid, anesthesiologist-administered propofol) are readily available. Experts suggested adoption may remain limited because of safety concerns and resistance from anesthesiologists. Because of these reasons, experts thought the Sedasys system no longer has potential for high impact. As a result, we archived this topic in the horizon scanning system in May 2015.

Potential High-Impact Interventions

Below are three interventions that, according to experts' comments, have high-impact potential at this time. They are technologies and care-delivery innovations that incorporate technologic advances.

Digital Medicines (Proteus Digital Health Feedback System) for Chronic Conditions Requiring Long-Term Drug Therapy

- **Key Facts:** Medication adherence may be as low as 50% for patients with chronic diseases, which compromises patient health. The Proteus Digital Health™ Feedback System (Proteus Digital Health, Inc., Redwood City, CA), a form of “smart-pill” technology or “digital medicine,” has been developed for use with oral pill or capsule medications prescribed for chronic diseases and for use during clinical trials of new medications to track adherence to dosing schedules. The intention is to track medication adherence in patients, especially in those requiring ongoing daily medication use for conditions such as tuberculosis, diabetes, heart failure, HIV, hepatitis C virus infection, and mental health disorders. The technology consists of an ingestible sensor (made of silicon, copper, magnesium, and cellulose, which are commonly used food ingredients) taken with a medication, a personal monitor, and a Bluetooth-enabled data device such as a smartphone. The patient ingests the medication along with the sensor, and digestive fluids activate the sensor in the stomach. The activated sensor transmits its unique signature to the personal monitor, which records and timestamps the event and physiologic data. The personal monitor is a miniature, battery-operated, data-logging device in the form of a patch worn on the torso. It records heart rate, activity, sensor ingestion, and patient-logged events such as symptoms. The monitor transmits the data to the patient’s Bluetooth-enabled smartphone or other computerized device. Encrypted data are forwarded to a secure database that clinicians can access to review the patient’s status.

Au-Yeung et al. (2011) reported a study in which 111 patients ingested 7,144 monitored pills. The investigators found that the system’s positive and negative ingestible-marker detection accuracy was greater than 97%, and medication adherence was more than 85%. The most common adverse effect was mild skin rash from the monitor patch’s electrodes; no serious adverse events were reported. A phase IV trial is ongoing for patients with tuberculosis.

The company received FDA clearance for the monitoring device in March 2010 and for the ingestible sensor in July 2012. The company is working with selected pharmaceutical manufacturers to choose medications for sensor integration and has also partnered with the Oracle Health Sciences division of Oracle Corp., which conducts trials on behalf of many pharmaceutical companies, to embed the technology in medications for more complete results in clinical trials. Lack of patient adherence to medication regimens tested in clinical trials has been implicated as a significant reason that many phase II and III trials do not meet their endpoints.

Costs of using the technology have not been published, but the manufacturer stated intentions of setting “value-based pricing,” which may vary by indication and potential cost-savings. Costs would involve more than the device itself, because equipment and staffing for collecting, monitoring, and reviewing additional patient data would have costs. Thus, whether this will add to overall costs or offset costs of nonadherence to medication regimens is not known at this time.

- **Key Expert Comments:** This technology could significantly affect several health system parameters if adopted, experts commented. Variables affecting adherence (e.g., medication affordability, access, side effects) caused some skepticism among experts about this technology’s potential to improve adherence and health outcomes. Patient acceptance of the technology might be low, some experts thought, although some experts also thought technologically savvy patients may embrace it. Experts thought clinician acceptance could

vary because it could offer them more insight into patient behavior, but demand more time for data review and that time is not reimbursed.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Patient-Based 3-D Printed Biomodels to Aid Surgical Planning

- **Key Facts:** Surgery performed on or near vital organs and structures can increase the complexity of the surgery and risk of negative outcomes. Benefits of preoperative imaging are sometimes limited by two-dimensional (2-D) displays. A new technique creates patient-specific 3-D printed biomodels that are intended to reduce surgical time, avoid complications, and cut costs. This approach uses imaging from a patient to manufacture unique anatomical models for planning surgical steps and techniques for that patient. Termed additive manufacturing, 3-D printing used in this particular way builds objects by laying down successive layers of a material until the whole object forms. The 3-D printed objects are made from one or more materials (e.g., plastic, metal, nylon, sugar, ceramic) in varying colors and textures. The technique is guided by computer-aided design software, whose data originate from DICOM image files taken with computed tomography (CT) or magnetic resonance imaging scanners. The biomodel may reveal anatomical abnormalities to the surgeon or collaborative team that were not apparent in two-dimensional imaging. Surgeons may plan incisions, resections, or implant placement using such biomodels. The 3-D models can serve as a reference during surgery; as templates for building customized instruments, cutting guides, and implants; or as test models to practice potential repairs or techniques. Three-dimensional printed biomodels for surgical planning may be used in any procedure; but, are most commonly used in cardiovascular, orthopedic, maxillofacial, and neuro surgeries.

Institutions reporting use of in-house 3-D printers for such purposes include Boston Children's Hospital (MA), Brigham and Women's Hospital (Boston, MA), Children's Hospital of Illinois (Peoria), Rush University Medical Center (Chicago, IL), Children's Hospital of Philadelphia (PA), Phoenix Children's Hospital with Arizona State University, and Texas Children's Hospital (Houston). Manufacturers that print 3-D biomodels for surgical planning include Materialise NV (Leuven, Belgium) and Medical Modeling, a subsidiary of 3D Systems (Rock Hill, SC). FDA granted 510(k) clearances to two software programs for image editing and biomodel design, Mimics® Innovation Suite (Materialise) and the VSP® System (Medical Modeling). Materialise has listed its HeartPrint® cardiovascular models as Class I medical devices.

One observational study (n=80) is ongoing to evaluate the use of 3-D printed heart models for planning reconstruction of complex heart defects. In a study (n=8) of 3-D printed cardiovascular models published in 2015, Valverde et al. reported that surgeons gave an overall satisfaction level of 8.5 out of 10, agreed they may decrease complications, and would recommend them to colleagues. Valverde et al. and Wu et al. (2015) reported that 3-D printed biomodels were accurate within specifications compared with patient imaging.

Printers for 3-D biomodels range in price from \$40,000 to \$1 million, depending on resolution, materials it uses, and speed. Based on size and complexity, each model costs between \$50 and \$2,000 to print. No third-party reimbursement is available for 3-D printing biomodels.

- **Key Expert Comments:** Experts commenting on this intervention agreed that tools to reduce surgical complications are necessary, especially for complex cases. Experts thought that patient health may improve by reducing surgical time and personalizing tools and

techniques. Hospitals that establish 3-D printing departments will face significant equipment, space, personnel, and training needs, experts noted. Despite the large investment of time and money needed, clinicians are likely to adopt 3-D printed biomodels based on responses to a survey of surgeons who used them, the experts suggested.

- **High-Impact Potential:** High

Patient Training and Risk Assessment Program (MSHOP) for Surgery Preparation

- **Key Facts:** Several prevalent risk factors increase complications during and after surgery, including inactivity, poor diet, smoking or tobacco use, excess alcohol use, stress, and poor sleep quality. The Michigan Surgical Health and Optimization Program (MSHOP) is an example of an initiative aimed at improving surgical outcomes by assessing patient-specific risk before major abdominal surgery and improving overall health by targeting prevalent risk factors. MSHOP is a collaboration between the University of Michigan Health System (Ann Arbor), the Michigan Surgical Quality Collaborative (Ann Arbor, MI), and Blue Cross Blue Shield of Michigan (Detroit). The program consists of patient physical training, lifestyle modification, and risk assessment before surgery. Training focuses on a walking program, breathing exercises, smoking cessation, improved nutrition, and stress reduction. A program coordinator initiates the training and periodically contacts the patient by phone, text message, or email to track and encourage progress using personal and automated messages. The patient updates daily walking and lung exercise logs via text message. The second component is a risk-assessment smartphone app that uses analytic morphomics to predict surgical outcomes and complications based on patients' CT and x-ray scans. The software quantitatively calculates core (i.e., psoas) muscle size, subcutaneous fat, and aortic calcification from uploaded scans. It reportedly predicts surgical risk, characterizes overall health, and objectively measures frailty independent of age. Clinicians use the app with patients to decide whether surgery is recommended.

Under the MSHOP program, patients who are undergoing major abdominal surgery (e.g., cardiovascular surgery, cancer resection) and are at high risk for complications (e.g., elderly, frail) enroll about a month before surgery.

According to press releases, the University of Michigan Health System saved an average of \$2,518 per patient and reduced hospital stays by 30% with MSHOP. In a retrospective study of analytic morphomics for predicting surgical risk, Englesbe et al. (2013) reported that morphometric risk stratification predicted length of stay and mortality better than chronological age. According to press releases, an ongoing prospective cohort study (n=12,500) is assessing MSHOP's efficacy in improving surgical outcomes, reducing cost of care, and predicting surgical risk. MSHOP was implemented in early 2013 at the University of Michigan Health System and is expected to expand to 40 Michigan hospitals over 3 years. After completing the study, developers expect an optimized model suitable for nationwide implementation. MSHOP costs include program coordinators to support and track patient progress, pedometers and incentive spirometers for each patient, and maintenance of the online portal and tracking logs. Cost savings may be realized if MSHOP reduces the length of a patient's hospital stay, avoids surgical complications, and reduces readmissions.

- **Key Expert Comments:** Programs such as MSHOP may address an unmet need for reducing surgical risks and complications, most expert commenters on this intervention agreed. Some experts thought that clinicians would be likely to adopt a MSHOP-like program based on the potential to decrease risks and improve health outcomes despite

limited published data. However, one expert was skeptical of MSHOP's superiority over standard ad-hoc clinician advice. Potential cost savings for hospitals, payers, and patients may expand acceptance of this model. MSHOP's ultimate impact will depend on patient access and participation, experts said.

- **High-Impact Potential:** Moderately high

Cross-Cutting Interventions and Programs

Digital Medicines (Proteus Digital Health Feedback System) for Chronic Conditions Requiring Long-Term Drug Therapy

Unmet need: Effective medical therapy for many chronic diseases depends on patient adherence to prescribed medication doses at the correct times. According to the World Health Organization, however, the average medication adherence rate among patients with chronic diseases in developed nations is only 50%.¹ This suboptimal rate compromises treatment outcomes.² Therefore, an unmet need exists for technologies that assess, manage, and improve patient adherence to medication regimens for chronic diseases.

Intervention: The Proteus Digital Health Feedback System is a networked medication adherence-monitoring system—or digital medicine technology—intended “to confirm the ingestion of individual oral medications and doses, to integrate this adherence data with physiological parameters and wellness metrics, to offer patient-directed sharing of health information with caregivers and providers, and to incorporate individualized behavior support tools.”² Developers state that one benefit of the system is its ability to improve providers’ “knowledge of a patient’s adherence.”² With access to objective medication-adherence data, providers could determine whether their clinical management “should focus upon improving medication adherence, dose adjustment, drug substitution, or polypharmacy”² or other factors affecting adherence, such as cost or side effects.

Three main components comprise the system:³

1. Ingestible sensor (formerly known as Ingestible Event Marker or IEM): a 1 mm² microfabricated chip sensor that can be embedded in an inactive tablet swallowed by the patient with the medication or into the active medication itself.^{2,4,5} The company states that the sensor is made of “materials found in the food chain,” such as silicon, copper, magnesium, and cellulose. When swallowed, stomach fluids activate the sensor. Once activated, the sensor transmits digital information regarding the drug taken, its dose, and time of ingestion.^{2,4} The system’s wearable personal monitor captures the data, and after about 7 minutes of activation, the sensor becomes inactive and is subsequently excreted through fecal elimination.
2. Personal monitor: a wearable, adhesive, soft foam, skin-patch device (5 by 11 by 1 cm) that looks like an adhesive bandage and records information sent from the ingestible sensor. The monitor also records additional physiologic metrics, such as heart rate, respiration, activity, body position, and monitor-wearing compliance. The battery-operated monitor transmits this information via Bluetooth telemetry to a computing device and is designed to be worn for 7 days.^{2,6}
3. Smartphone or Web-based communication platform: a device used to view transmitted sensor data captured by the personal monitor. Encrypted data are sent securely to either a smartphone or Web-based platform for viewing by the patient and, with patient approval, by family members, caregivers, or health care providers.²

Clinical trials: Investigators reported results of a clinical trial of 111 subjects who ingested 7,144 ingestible markers.² They reported, “The system’s positive detection accuracy and negative detection accuracy in detecting ingested markers were 97.1% and 97.7%, respectively. It differentiated 100% of multiple drugs and doses taken simultaneously by type and by dose. Medication adherence was >85%. The most common adverse effect was mild skin rash from the monitor’s electrodes. No definitive marker-related adverse effects were reported.”² Another report from a clinical trial of 30 patients reported similar detection accuracy of the system.⁷ These

investigators reported four adverse events related to the device, of which three were skin rashes and one was nausea.⁷

The company also has entered a collaboration with Oracle Health Sciences (a division of Oracle Corp., Redwood Shores, CA) “to work together in clinical trials exclusively to provide clinical investigators worldwide the ability to measure information about medication ingestion, dose timing, and associated physiologic response continuously and precisely for patients enrolled in clinical trials.”⁸ According to a recent Forbes magazine article, Proteus expects this alliance to significantly influence the success of pharmaceutical trials because “patient adherence to prescribed drug regimens is often as low as 50 percent. That undermines the statistical analysis of trial results and makes it difficult to determine the ‘dose response curve,’ which represents the maximum tolerable dose and the minimal effective dose. Failure to determine these thresholds during Phase 2 is believed to be one of the main reasons for Phase 3 failures.”⁹

One phase IV clinical trial (NCT01960257) is ongoing to evaluate the cost and perception of the technology for monitoring medication adherence in patients with tuberculosis in comparison to standard of care direct observation therapy.¹⁰

Manufacturer and regulatory status: Proteus Digital Health, Inc., (Redwood City, CA) makes the system. The manufacturer worked with the U.S. Food and Drug Administration (FDA) to determine the regulatory pathway because its components are regulated separately.⁵ In March 2010, FDA cleared for marketing the Raisin Personal Monitor (an earlier name of the wearable monitor) to record heart rate, activity, and patient-logged events.¹¹ In July 2012, FDA granted a 510(k) de novo clearance for the Proteus Ingestible Event Marker.⁵ In May 2013, FDA reclassified the ingestible sensor as a Class II device subject to special controls.^{12,13} The entire system is now available for sale and use in the United States; however, each medication embedded with the sensor is expected to be subject to FDA clearance.

In August 2010, the company received CE mark to market the complete system in the European Union.¹⁴ The company announced collaborations with Novartis International AG (Basel, Switzerland) and Otsuka Holdings Co., Ltd., (Tokyo, Japan) to develop and commercialize digital medicines.¹⁵

Cost: The manufacturer intends to set “value-based” pricing, depending on the situation and potential cost savings to the health care system. In experiments with consumers, the manufacturer has asked patients to pay \$84 to \$167 per week for use with daily medication.¹⁶ The system will require use of technology to collect the data and will need staff to monitor, interpret, and act upon the data collected as appropriate to follow up with patients. Whether these added costs would offset costs of medication regimen nonadherence and whether patients or third-party payers would pay for this extra expense is unknown.

No information regarding potential coverage, coding, or payment for the system is available at this time, and it is not clear whether use of the system would be reimbursed separately from the medication. Third-party payers would require evidence that the system improves patient adherence and clinical outcomes before providing additional reimbursement (over medication cost) for the technology.

Clinical Pathway at Point of This Intervention

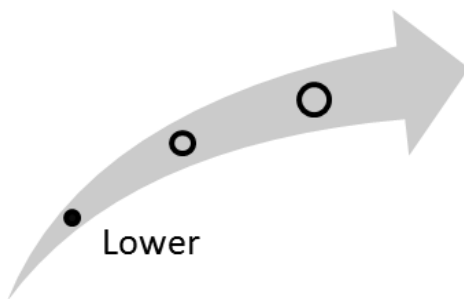
The company states that tablets can be delivered to patients in one of three ways, depending on the pharmacy’s capabilities and the physician’s prescription:^{17,18}

- Using stand-alone packaging, with patients directed to co-ingest one sensor-enabled inactive tablet each time they take their medication of interest.

- Co-packaged in specialty blister packets or sachets, with one sensor-enabled inactive tablet in the same compartment as one dose of the medication of interest.
- Packaged inside capsules that co-encapsulate a sensor-enabled inactive tablet and the medication of interest.

Patients can ingest up to 30 sensors per day.¹⁹ Patients take oral medications along with sensors as prescribed by a physician. Patients wear a monitoring patch on the skin and receive training on how to access transmitted information using a computer or smartphone. Clinicians can access objective, accurate, and timely data about patient adherence to monitor patients' physiologic parameters, understand more about medication response, and prescribe any necessary adjustments in the regimen.²⁰

Figure 1. Overall high-impact potential: digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy



Most experts who commented on this topic thought this intervention could have an impact on many health system parameters, although some experts were skeptical about its potential to improve patient medication adherence and health outcomes. Its ultimate impact may depend most on patient acceptance, cost, and third-party reimbursement. Experts are eager to see more clinical utility data to ascertain whether this technology can improve patient health outcomes. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.²¹⁻²⁷ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An important unmet need exists for improving patient adherence to medication regimens, experts agreed. However, the impact on patient health outcomes is unclear, the experts noted, because of a lack of data supporting improved adherence rates with digital medicines. They assumed that improved adherence improves health but also noted that other options (e.g., directly observed therapy, electronic bottle cap) are available. Patient access, acceptance, and their medical conditions may influence the overall impact of digital medicines, the experts said. The greatest utility may be for clinical trials or diseases that affect public health (e.g., tuberculosis), three experts thought.^{22,26,27}

Acceptance and adoption: Clinicians may be reluctant to prescribe digital medicines to patients because of the additional data monitoring needed, experts said, especially because simpler alternatives are available. Patients may view the technology as an invasion of privacy or feel uncomfortable using new technology, which experts thought may limit their acceptance. However, clinicians and patients who are more comfortable using technology may readily embrace this tool,

the experts agreed. Two experts noted that acceptance might be higher when used in clinical trials or in place of directly observed therapy.^{24,26}

Health care delivery infrastructure and patient management: Health care delivery infrastructure may be slightly affected by the additional data transfer and storage needs associated with digital medicines, some experts suggested. Time dedicated to patient management may increase when clinicians initially prescribe digital medicines because they will need to explain the technology and teach patients about its use, experts said. Ongoing data review and patient followup may continue to increase the time clinicians spend on patient management, experts speculated.

Patients and payers may be reluctant to take on additional medication costs without proof that digital medicines improve health outcomes, which experts said would limit the impact. However, experts expect a huge cost impact if payers provide coverage for digital medicines. Long-term cost savings may be realized if digital medicines increase adherence enough to improve patient health, experts thought.

Health disparities: Digital medicines add to the total medication cost, which may be unaffordable for some patients and negatively affect health disparities, experts agreed. Elderly patients may not be comfortable with using the technology, an expert with a research perspective speculated.²³ For patients who use digital medicines, health disparities may decrease, one expert with a research perspective said.²⁵

Patient-Based 3-D Printed Biomodels to Aid Surgical Planning

Unmet need: Surgery performed on or near vital organs and structures can increase the complexity of the procedure and the risk of negative outcomes. Although various imaging techniques allow a surgeon to visualize a patient's anatomy before surgery, benefits are sometimes limited by two-dimensional (2-D) displays. A new technique creates patient-specific three-dimensional (3-D) printed biomodels that can be manipulated and viewed from all angles, giving surgeons the opportunity to plan or practice techniques before surgery. The individualized models for aiding surgical planning are based on patient imaging, edited with specialized software, and printed by additive manufacturing.

Intervention: Surgical planning using patient-specific, 3-D-printed biomodels is intended to reduce surgical time, avoid complications, improve patient outcomes, and cut costs.²⁸ The biomodels have three distinct features as an innovation. They use (1) imaging of individual patients to (2) manufacture unique anatomical models for (3) planning surgical steps and techniques.

As an additive manufacturing process, 3-D printing builds objects by laying down successive layers of a material until the whole object forms. It contrasts with traditional subtractive manufacturing, which forms objects by carving or removing pieces from a whole until the object remains. The 3-D printed objects are made from one or more materials such as plastic, metal, nylon, sugar, and ceramic. They may be clear, opaque white, or multicolored. Multiple textures and different rigidities may be incorporated.²⁹

The technique is guided by 3-D-modeling computer-aided design (CAD) software. In medical applications, data in the CAD file originate from DICOM image files taken with computed tomography (CT) or magnetic resonance imaging (MRI) scanners. The 2-D DICOM image is segmented with software to identify and separate the target anatomy from the rest of the image and create a 3-D image. The selected voxels (volumes that make up the image) are further refined to obtain smooth surfaces, remove unwanted details, and add structural supports. Patient-specific biomodels are printed based on imaging of each patient's anatomy.^{28,30} The printer resolution is typically better than the imaging resolution and may be as good as 16 microns per layer.^{29,31} This means that each printed layer of the biomodel is about the width of a cotton filament.³¹

Surgeons and collaborative teams use the 3-D-printed biomodels for planning the surgery. The biomodel may reveal anatomical abnormalities that were not apparent in imaging.³² Surgeons can use them to plan incisions, resections, or implant placement. They may serve as a reference during surgery with steps mapped onto them (biomodels made of certain materials can be sterilized and brought into the sterile field). Biomodels may be used as templates for building customized instruments, cutting guides, and implants before surgery.³³ Surgeons may print multiple biomodels for one procedure to test potential repairs or techniques.³⁴

These biomodels may be used in any simple or complex surgery case but are most commonly used in cardiovascular, orthopedic, and maxillofacial surgeries.³³ After imaging manipulation is complete, biomodels may be printed in a few hours, depending on size and complexity. For institutions with in-house printers, the entire process from imaging to printing may take about 2 days.³⁵ When biomodels are printed by an outside manufacturer, turnaround time may be weeks to months.^{35,36}

Clinical trials: A published study (n=8) of 3-D printed cardiovascular models reported that surgeons gave an overall satisfaction level of 8.5 of 10 and agreed the models may decrease complications. These surgeons stated they would recommend biomodels to colleagues.³⁷ Two studies reported that 3-D printed biomodels were accurate within specifications compared to patient imaging.^{37,38} One observational study (n=80) is ongoing to evaluate the use of 3-D printed heart models for planning reconstruction of complex heart defects.³⁹

Manufacturer and regulatory status: Several research hospitals report using 3-D printed biomodels in surgical planning. These institutions include Boston Children’s Hospital (MA), Brigham and Women’s Hospital (Boston, MA), Children’s Hospital of Illinois (Peoria), Rush University Medical Center (Chicago, IL), Children’s Hospital of Philadelphia (PA), Phoenix Children’s Hospital with Arizona State University, and Texas Children’s Hospital (Houston).^{31,32,34,40,41}

Surgeons may commission manufacturers to create 3-D print biomodels. Manufacturers that print biomodels for surgical planning include Materialise NV (Leuven, Belgium) and Medical Modeling, a subsidiary of 3D Systems (Rock Hill, SC). Manufacturers provide guidelines for imaging done by the clinician to ensure specifications (e.g., resolution, field of view, artifacts, file format) are met.⁴² FDA granted 510(k) clearances to two software programs for image editing and biomodel design, the Mimics® Innovation Suite (Materialise) and the VSP® System (Medical Modeling).^{43,44} Materialise listed its HeartPrint® cardiovascular models as Class I medical devices.⁴³

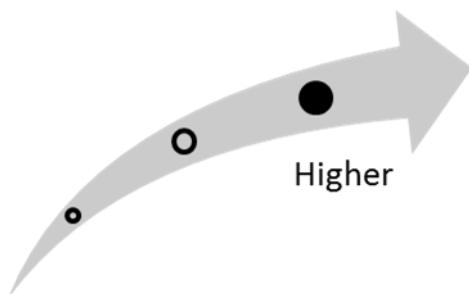
Cost: Printers for 3-D biomodels range in price from \$40,000 to \$1 million, depending on resolution, materials it uses, and speed.³² For example, Boston Children’s Hospital purchased a printer made by Stratasys, Ltd. (Minneapolis, MN, and Rehovot, Israel), for \$400,000 and has used it to make biomodels of brains, skulls, spines, rib cages, and blood vessels. Based on size and complexity, each model costs between \$50 and \$2,000 to print.²⁸ No third-party reimbursement is available for 3-D printing biomodels.³² Coverage decisions are likely to depend on whether biomodels are medically necessary for surgical planning.

Current Approach to Care

In surgical planning, collaborative teams composed of surgeons, radiologists, anesthesiologists, or others use imaging data and other patient information to plan surgical steps, technique, and resource use. The types of imaging available include CT, MRI, and ultrasound—the choice of imaging depends on tissue type and location of the region of interest. Patient factors such as the presence of a pacemaker may also influence the type of imaging chosen.

Advanced aids for surgical planning include virtual planning computer software for 3-D representation and simulation, which does not allow surgeons to practice with surgical tools as 3-D printed biomodels do.³³ Physical simulation on models or cadavers may be used during surgical planning. Three-dimensional printed biomodels complement this process because they are constructed from the images and provide another tool for visualizing the patient’s anatomy. Additional imaging may be necessary to make the 3-D printed biomodels because specifications must be met.

Figure 2. Overall high-impact potential: patient-based 3-D printed biomodels to aid surgical planning



Most experts commenting on this intervention agreed that tools to reduce surgical complications are necessary, especially for complex cases. Hospitals that choose to establish 3-D printing

departments will face significant equipment, personnel, space, and training needs, experts noted. Despite the large investment of time and money needed, experts suggested clinicians are likely to adopt 3-D printed biomodels to improve surgical planning. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health administration backgrounds, offered perspectives on this intervention.⁴⁵⁻⁵⁰ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: A large unmet need exists for surgical planning tools that provide better guidance than 2-D imaging and that enable surgeons to improve surgical outcomes, most experts agreed. Patient health outcomes may improve with 3-D printed biomodels by improving surgical skill, allowing for custom tool creation, and providing more information than 2-D imaging, experts thought. Patients may experience shorter surgical times and fewer complications, one clinical expert suggested.⁵⁰ However, an expert with a research perspective doubted that the lack of 3-D printed biomodels has stopped surgeries from progressing or has caused injury or death, indicating the effect on patient health outcomes would be minimal.⁴⁷

Acceptance and adoption: Clinicians may readily adopt 3-D printed biomodels, even though their use creates a need for increased training and collaboration, the experts said. Two experts noted a survey of clinicians reported high acceptance and willingness to recommend to colleagues.^{47,49} Patients may consider costs and additional imaging but will likely be guided by clinicians' recommendations of use of 3-D printed biomodels, the experts thought.

Infrastructure and staffing: Equipment, personnel, and space needed to establish 3-D printed biomodel departments in a hospital may significantly affect health care delivery infrastructure, the experts said. Patient management may be moderately impacted by additional imaging needed and its potential to delay surgery, experts suggested. Costs to hospitals may include capital equipment, consumables, maintenance, and staff, experts noted. A potential return on investment may be realized in hospitals that use 3-D printed biomodels and experience reduced surgical times and complications, experts speculated.

Health disparities: Although the experts agreed that health disparities may be affected by costs and access, they disagreed over the magnitude of the impact. Early adoption may be restricted to large teaching hospitals, two experts said, which may limit access to patients who live nearby.^{45,50}

Patient Training and Risk Assessment Program for Surgery Preparation

Unmet need: A decline in physical function is common after major surgery, potentially interfering with a patient's timely discharge from the hospital and ability to perform daily activities (e.g., dressing, walking, toileting).⁵¹ Several prevalent risk factors increase complications during and after surgery, including inactivity, poor diet, smoking or tobacco use, excess alcohol use, stress, and poor sleep quality.^{51,52} The Michigan Surgical Health and Optimization Program (MSHOP) is a model aimed at improving surgical outcomes by assessing patient-specific risk before surgery and improving overall health by targeting prevalent risk factors.⁵³

Intervention: MSHOP is designed to improve the health of patients before major abdominal surgery and provide tools for a faster recovery. The program consists of patient training and risk assessment before surgery. Patient training focuses on four steps to improve surgical outcomes, as follows:⁵²

- **Move:** A walking program with an online log for patients to incrementally increase their total daily steps with a goal of 10,000 steps (about 3 - 5 miles) a day⁵⁴
- **Breathe:** Lung exercises three times a day with a provided incentive spirometer to increase lung capacity and function; smoking or tobacco cessation aids, including a cigarette log to identify triggers^{55,56}
- **Eat:** Adequate nutrition advice, including recipes
- **Relax:** Stress-reduction techniques

A program coordinator initiates the patient training. The coordinator periodically contacts the patient by phone, text message, or email to track and encourage progress using personal and automated messages. The patient updates daily walking and lung exercise logs via text message. A Web portal provides patient access to updated logs and various resource links (e.g., recipes, free exercise classes, smoking cessation tips).⁵⁷

The second component of MSHOP is a risk-assessment smartphone app that uses analytic morphometrics to predict surgical outcomes and complications based on patients' CT and x-ray scans. The software quantitatively calculates core (i.e., psoas) muscle size, subcutaneous fat, and aortic calcification from uploaded scans. It reportedly predicts surgical risk, characterizes overall health, and objectively measures frailty independent of age. Clinicians use the app with patients to decide whether surgery is recommended or a more conservative approach is appropriate.⁵⁸

Patients who are at high risk for complications are enrolled in the program for about a month before major abdominal surgery (e.g., cardiovascular surgery, cancer resection).^{59,60} Patients who are elderly or frail may particularly benefit from the program.⁵³

Clinical trials: According to press releases detailing preliminary success with more than 300 patients, "...the U-M [University of Michigan Health System] has seen savings of \$2,518 a case, and has reduced time in the hospital after surgery by 30 percent."^{53,61} A retrospective study of analytic morphometrics for predicting surgical risk—the basis of the risk assessment app—reported that morphometric risk stratification predicted length of stay and mortality better than chronological age.⁶² Although no ongoing clinical trials are registered at the National Clinical Trials database, the developers are continuing to study MSHOP. According to press releases, an ongoing study has a planned enrollment of 12,500 patients. The prospective cohort study is assessing MSHOP's efficacy in improving surgical outcomes, reducing cost of care, and predicting surgical risk. The study is expected to expand to 40 hospitals in Michigan and complete in 2017.^{53,60}

Program developers and funding: MSHOP is a collaboration between the University of Michigan Health System (Ann Arbor), the Michigan Surgical Quality Collaborative (Ann Arbor,

MI), and Blue Cross Blue Shield of Michigan (Detroit).⁵³ The MSHOP collaborative is funded by a 3-year grant of \$6.4 million from the U.S. Centers for Medicare & Medicaid Services (CMS).⁶⁰

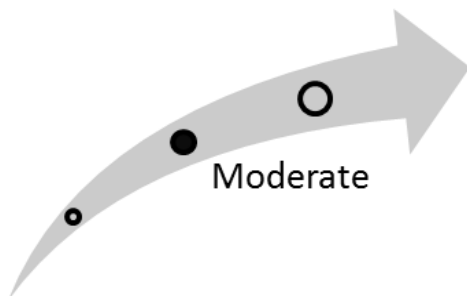
MSHOP costs include program coordinators to support and track patient progress, pedometers and incentive spirometers for each patient, and maintenance of the online portal and tracking logs. Cost savings may be realized if MSHOP reduces the length of a patient's hospital stay, avoids surgical complications, and reduces readmissions.⁵³

Diffusion: MSHOP was implemented in early 2013 at the University of Michigan Health System.⁵⁸ In 2014, CMS granted the MSHOP collaborative the \$6.4 million Health Care Innovation Award to expand the program to 40 hospitals in Michigan and enroll 12,500 patients. After completing it, developers expect an optimized model suitable for nationwide implementation.⁵³

Current Approach to Care

Prehabilitation—physical therapy that occurs before surgery—may be recommended for many types of surgery, including esophageal resection, prostatectomy, and abdominal aortic aneurysm repair.⁶³⁻⁶⁵ Some prehabilitation efforts focus on muscle groups affected directly by surgery;^{64,65} others focus on overall health.⁶³ Additional efforts include ad-hoc advice from clinicians and clinician-provided literature addressing exercise, nutrition, and other health issues. Patient participation in surgical preparation may be lacking when patients are not provided with enough information or support.⁶⁵ MSHOP addresses overall patient health and may be used in conjunction with programs that are tailored for specific surgeries. Alternatively, MSHOP may compete with other generalized prehabilitation programs.

Figure 3. Overall high-impact potential: patient training and risk assessment program (MSHOP) for surgery preparation



Most experts commenting on this intervention agreed that an unmet need exists for reducing surgical risks and complications and that MSHOP may address this need. Some experts thought that clinicians are likely to adopt MSHOP because of its potential to decrease risks and improve health outcomes despite limited published data. Potential cost savings for hospitals, payers, and patients may expand the program's acceptance, experts suggested. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health administration backgrounds, offered perspectives on this program.⁶⁶⁻⁷¹ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: An unmet need exists to decrease surgical risks and complications, the experts agreed. Published data from MSHOP indicates it reduces hospital stays after surgery by 30%, which may improve patient health, experts speculated. Additional data are

needed to project MSHOP's potential impact, experts agreed. However, a research expert stated that MSHOP "...is merely a reformatted version of standard advice for good health that all patients should follow" and does not address the biggest hurdle, which is patient compliance.⁶⁷

Acceptance and adoption: The potential to decrease risks, improve outcomes, and reduce costs may sway some clinicians into adopting MSHOP, some experts speculated. Other clinicians are likely to be reluctant to adopt MSHOP because of limited available data on patient training and risk assessment methods, other experts countered.^{67,70} Patients who are able to meet the exercise demands of MSHOP may readily accept it, experts thought. However, some patients may not want to make the extra effort to keep logs or be comfortable with increased monitoring, two experts suggested.^{66,67}

Infrastructure and staffing: Although minimal health care delivery infrastructure changes are expected, additional staff, tools, and time for patient engagement are needed for MSHOP, experts surmised. Experts were split on whether MSHOP will cost or save money for hospitals. Additional staff and training are needed to establish MSHOP, experts said. However, MSHOP may reduce the length of hospital stays, complications, and post-operative care, which may all save money, the experts said.

Health disparities: Health disparities may increase for patients who do not have reliable access to the Internet because of low economic status, the experts thought. An expert with a research perspective thought that access to the program may be limited by the number and type of hospitals that offer it, potentially increasing health disparities.⁶⁹ If MSHOP is targeted at patients of low socioeconomic status and access issues are addressed, health disparities may improve for this population, a clinical expert suggested.⁷¹

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