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

Cross-Cutting Interventions and Programs

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA290-2010-00006-C

Prepared by:
ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2015

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.

Disclaimer Regarding 508-Compliance

Individuals using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.gov.

Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Cross-Cutting Interventions and Programs. (Prepared by ECRI Institute under Contract No. HHSA290-2010-00006-C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2015. http://effectivehealthcare.ahrq.gov/index.cfm/

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, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Contents

Executive Summary ES-1

Background ES-1

Methods ES-1

Results ES-2

Discussion ES-2

Cross-Cutting Interventions and Programs 1

Digital Medicines (Proteus Digital Health Feedback System) for Chronic Conditions Requiring Long-Term Drug Therapy 2

Patient-Based 3-D Printed Biomodels to Aid Surgical Planning 6

Patient Training and Risk Assessment Program (MSHOP) for Major Abdominal Surgery Preparation 9

References 12

Figures

Figure 1. Overall high-impact potential: digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy 4

Figure 2. Overall high-impact potential: patient-based 3-D printed biomodels to aid surgical planning 7

Figure 3. Overall high-impact potential: patient training and risk assessment program (MSHOP) for major abdominal surgery preparation 10

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 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system at this time.

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 195 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 four topics for which (1) preliminary phase III data for drugs were available; (2) phase II data for devices were available; (3) any type of outcomes data were available for programs; (4) information was compiled and sent for expert comment by November 6, 2015; and (5) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Eight topics in this priority area were being tracked in the system as of November 6, 2015.) We present summaries on three topics (designated by an asterisk in the table below) that were deemed to have high-impact potential on the basis of expert comments. The material in this 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. * Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy	Lower end of the high-impact-potential range
2. * Patient-based 3-D printed biomodels to aid surgical planning	High
3. * Patient training and risk assessment program (MSHOP) for major abdominal surgery preparation	Moderately high
4. Mobile platform (Triton Fluid Management System) to monitor blood loss during surgery	No high-impact potential at this time; archived on the basis of experts' comments

Discussion

We created this priority area to capture 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 potential for high impact are technologies and care-delivery innovations that might shift providers' roles or settings.

Eligible Topics Not Deemed High Impact

- **Mobile platform (Triton Fluid Management System) to monitor blood loss during surgery:** The Triton Fluid Management System (Gauss Surgical, Inc., Palo Alto, CA) is a

mobile medical platform intended to help clinicians estimate the amount of blood a patient loses during surgery to inform blood transfusion decisions. This topic has been tracked in the system for more than 3 years and was approved in May 2014 by the U.S. Food and Drug Administration (FDA). Overall, experts commenting in mid-2015 on this topic expressed views that the Triton system is an adjunct to, not a replacement for, other blood-loss estimation techniques and that available data were insufficient to demonstrate it improved patient management and outcomes. The Triton system cannot capture total blood loss and does not address other factors that affect blood transfusion decisionmaking, experts thought. Because of these reasons, experts thought this system had little potential for high impact. As a result, we archived this topic in the horizon scanning system in November 2015.

Potential High-Impact Interventions

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

- **Key Facts:** The World Health Organization has estimated that medication adherence is 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) embedded in 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 and colleagues (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 through the 510(k) process for the monitoring device in March 2010 and for the ingestible sensor in July 2012, but no medications embedded with the sensor had been approved for marketing. Now, Proteus is collaborating with Otsuka Pharmaceuticals Co., Ltd. (Tokyo, Japan), to integrate sensors into aripiprazole (Abilify®) tablets, and they jointly submitted a new drug application to FDA in September 2015. Proteus has also formed a partnership with the Oracle Health Sciences division of Oracle Corp. (Redwood Shores, CA), 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. Whether this will add to overall costs or offset costs of nonadherence to medication regimens is not known.

- **Key Expert Comments:** This technology could significantly affect several health system parameters if adopted, experts commented. The additional variables that affect 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 other experts also thought technologically savvy patients might embrace it. Experts thought clinician acceptance could vary because it could offer more insight into patient behavior, but demand more time for data review that 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. Preoperative imaging may provide insufficient planning that is limited by two-dimensional (2-D) or three-dimensional (3-D) virtual displays. A new technique may overcome these deficiencies in surgical planning by enabling surgeons to create actual patient-specific 3-D printed biomodels. Such models are intended to reduce surgical time, avoid surgical complications, and cut costs. This approach uses images from a patient to manufacture patient-specific anatomic models to plan surgical steps and techniques for that patient. Termed additive manufacturing, 3-D printing used in this 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. Computer-aided design software guides the model creation; the modeling 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 with imaging only. Surgeons can plan incisions, resections, or implant placement using such biomodels, and the models can serve as a reference during surgery. They can serve as templates for building customized instruments, cutting guides, and implants or as test models to practice potentially complex repairs or techniques. This modeling technique can be used for any surgical procedure, but is most often used for cardiovascular, orthopedic, maxillofacial, and neurosurgeries.

  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), Children's Hospital of Philadelphia (PA), Phoenix Children's Hospital with Arizona State University, Rush University Medical Center (Chicago, IL), 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, Valverde et al. (2015) reported that surgeons using the models rated satisfaction with model use 8.5 out of 10, thought models could 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 to patient images.

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. Third-party reimbursement is unavailable for 3-D printing biomodels.

- **Key Expert Comments:** Experts commenting on this intervention agreed that tools are needed to aid complex surgical planning and reduce surgical complications. Experts thought that patient health might improve if use of models could reduce surgical time and enable personalized surgical 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, the survey reported by Valverde suggests clinicians are likely to adopt 3-D printed biomodels, the experts suggested.
- **High-Impact Potential:** High

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

- **Key Facts:** Several prevalent risk factors increase complications during and after major abdominal 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 risks before major abdominal surgery and targeting interventions before surgery to reduce 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. Under the 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. 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.

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 chronologic age. According to the University of Michigan, an ongoing prospective cohort study (n=12,500) is assessing program efficacy in improving surgical outcomes, reducing cost of care, and predicting surgical risk. MSHOP was implemented there in early 2013 and is expected to expand to 40 Michigan hospitals through 2016. 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 mm^2 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 technology's manufacturer 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, and 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 into 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 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. Proteus is collaborating with Otsuka Pharmaceuticals Co., Ltd., (Tokyo, Japan) to integrate sensors into aripiprazole (Abilify®) tablets; they jointly submitted a new drug application in September 2015.[14]

In August 2010, the company received CE mark to market the complete system in the European Union.[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 medical 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, 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

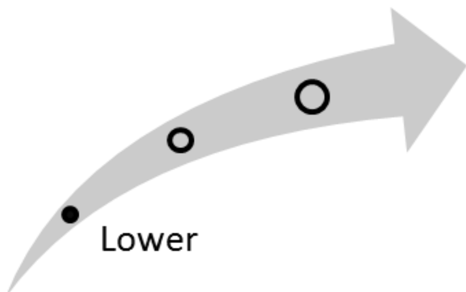
The company states that tablets can be delivered to patients in one of three ways, depending on the pharmacy's capabilities and the physician's prescription:[17,18]

- 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 to 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, the 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. Three experts thought the greatest utility may be for clinical trials or diseases that affect public health (e.g., tuberculosis).[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 acceptance. However, clinicians and patients comfortable with this type of 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 using the technology, an expert with a health systems 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 patient outcomes. Although various imaging techniques allow surgeons to visualize their patients' anatomy before surgery, benefits are sometimes limited by two-dimensional (2-D) displays and three-dimensional (3-D) virtual models. A new technique creates patient-specific 3-D printed biomodels that can be manipulated and viewed from all angles, giving surgeons the opportunity to plan and practice techniques before surgery. Surgeons can create the individualized models to aid surgical planning by using patient images taken with computed tomography (CT) or magnetic resonance imaging (MRI) that are edited on a computer with modeling software and then printed by additive manufacturing.

Intervention: Surgical planning using patient-specific, 3-D–printed biomodels is intended to shorten surgical time, reduce complications, improve patient outcomes, and cut costs.[28] 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]

Computer-aided design (CAD) 3-D modeling software guides the model creation. In medical applications, data in the CAD file originate from the CT and MRI images. The 2-D 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. Then the patient-specific biomodels is printed.[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 fiber.[31]

The biomodel may reveal anatomic abnormalities that were not apparent in imaging.[32] Surgeons can use the model to plan incisions, resections, and implant placement. These models can also 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. They can also 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]

Three-dimensional biomodels can be used in any surgery case, but are used most often for cardiovascular, orthopedic, maxillofacial, and neurosurgeries.[33] After imaging manipulation is complete, biomodels can be printed in a few hours, depending on size and complexity. For institutions with in-house printers, the entire process from imaging to printing can take about 2 days.[35] When biomodels are printed by an outside manufacturer, turnaround times may be weeks to months.[35,36]

Clinical trials: A conference abstract (n=8) by Valverde and colleagues of 3-D printed cardiovascular models reported that surgeons gave an overall satisfaction level of 8.5 out 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), Children's

Hospital of Philadelphia (PA), Phoenix Children's Hospital with Arizona State University, Rush University Medical Center (Chicago, IL), and Texas Children's Hospital (Houston).[31,32,34,40,41]

Surgeons may commission manufacturers to create 3-D printed 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 are met (e.g., resolution, field of view, artifacts, file format).[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 used, 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] Third-party reimbursement is unavailable for 3-D printing biomodels.[32] Coverage decisions are likely to depend on whether biomodels are medically necessary for surgical planning.

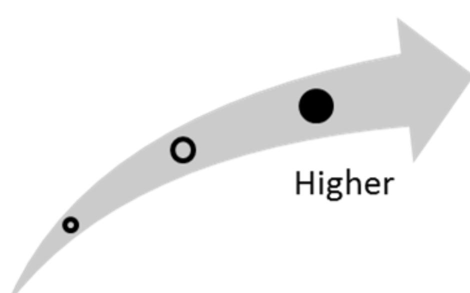
Diffusion: Multiple institutions have published case reports of 3-D printed biomodels used in surgical planning. Boston Children's Hospital has one of the most established programs and, in October 2015, reported that it had printed more than 300 biomodels in 16 specialties since July of 2013.[45]

Current Approach to Care

In surgical planning, collaborative teams composed of surgeons, radiologists, anesthesiologists, or others use one or more imaging techniques—CT, MRI, ultrasound—combined with other patient information to plan surgical steps, technique, and resource use. 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 and provide another tool for visualizing the patient's anatomy. Additional imaging may be necessary to make the 3-D printed biomodels meet specifications.

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 important, especially for complex cases. Hospitals that 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.[46-51] 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 images 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.[51] However, an expert with a research perspective doubted that the absence of 3-D printed biomodels prevented surgeries from progressing or caused injury or death, indicating the effect on patient health outcomes would be minimal.[48]

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 that the clinician survey reported by Valverde found high acceptance and willingness to recommend 3-D models to colleagues.[48,50] 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 affected by additional imaging needed and the potential of the process to delay surgery, experts suggested. Costs to hospitals 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 if model use reduces surgical times and complications, experts speculated.

Health disparities: Although the experts agreed that health disparities could increase because of costs and access to the technology, they disagreed over the magnitude of the impact. Early adoption may be restricted to large teaching hospitals, two experts said, which may provide access only to patients who live nearby.[46,51]

Patient Training and Risk Assessment Program (MSHOP) for Major Abdominal 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).[52] 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.[52,53] 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.[54]

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:[53]

- 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 day[55]
- 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[56,57]
- 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).[58]

The second component of MSHOP 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 or a more conservative approach is appropriate.[59]

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).[60,61] Patients who are elderly or frail may particularly benefit from the program.[54]

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."[54,62] A retrospective study of analytic morphomics 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.[63] 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.[54,61]

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).[54] The MSHOP collaborative is funded by a 3-year grant of $6.4 million from the U.S. Centers for Medicare & Medicaid Services (CMS).[61]

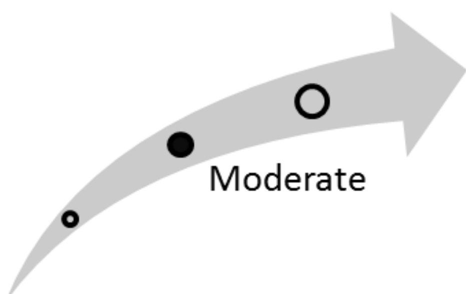
MSHOP costs include program coordinators to support and track patient progress, pedometers and incentive spirometers for each patient, and maintenance of the online portal and tracking logs. Cost savings may be realized if MSHOP reduces the length of patients' hospital stays, avoids surgical complications, and reduces readmissions.[54]

Diffusion: MSHOP was implemented in early 2013 at the University of Michigan Health System.[59] 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.[54]

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.[64-66] Some prehabilitation efforts focus on muscle groups affected directly by surgery;[65,66] others focus on overall health.[64] 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.[66] 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 major abdominal 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.[67-72] 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.[68]

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 concern about limited available data on patient training and risk assessment methods, other experts countered.[68,71] 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.[67,68]

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, the program may reduce the length of hospital stays, complications, and postoperative 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.[70] 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.[72]

References

1. World Health Organization (WHO). Adherence to long-term therapies. Geneva (Switzerland): World Health Organization (WHO); 2003. 211 p. Also available: http://www.who.int/chp/knowledge/publications/adherence_report/en/.

2. Au-Yeung KY, Moon GD, Robertson TL, et al. Early clinical experience with networked system for promoting patient self-management. Am J Manag Care. 2011;17(7):e277-87. PMID: 21819175.

3. Proteus Digital Health completes $62.5 million financing. [internet]. Redwood City (CA): Proteus Digital Health, Inc.; 2013 May 01 [accessed 2013 Nov 18]. [2 p]. Available: http://www.proteus.com/proteus-digital-health-completes-62-5-million-financing/.

4. Proteus announces issuance of U.S. patent for ingestible digital devices. [internet]. Redwood City (CA): Proteus Biomedical, Inc.; 2011 Jul 14 [accessed 2012 Apr 03]. [2 p]. Available: http://www.proteus.com/proteus-announces-issuance-of-u-s-patent-for-ingestible-digital-devices/.

5. Proteus Digital Health announces FDA clearance of ingestible sensor. [internet]. Redwood City (CA): Proteus Digital Health; 2012 Jul 30 [accessed 2012 Aug 06]. [2 p]. Available: http://proteusdigitalhealth.com/proteus-digital-health-announces-fda-clearance-of-ingestible-sensor/.

6. The chips that are good for your health. Pharmacy to sell edible microchips that will alert doctors if patients are not taking right medicines. [internet]. London: The Independent; 2012 Jan 17 [accessed 2012 Apr 03]. [8 p]. Available: http://www.independent.co.uk/news/science/the-chips-that-are-good-for-your-health-6290700.html.

7. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLoS ONE. 2013;8(1):e53373; Epub 2013 Jan 7. Also available: http://dx.doi.org/10.1371/journal.pone.0053373. PMID: 23308203.

8. Oracle invests in Proteus Digital Health and its FDA-approved ingestible sensor platform. [internet]. Redwood Shores (CA): Oracle; 2013 May 01 [accessed 2013 Nov 18]. [3 p]. Available: http://www.oracle.com/us/corporate/press/1941306.

9. Foley J. Ingestible sensors signal new era of digital medicine. [internet]. New York (NY): Forbes; 2013 Aug 30 [accessed 2013 Nov 18]. [8 p]. Available: http://www.forbes.com/sites/oracle/2013/08/30/ingestible-sensors-signal-new-era-of-digital-medicine/.

10. mHealth UCSD. Wirelessly observed therapy in comparison to directly observed therapy for the treatment of tuberculosis. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2014 Nov 21]. [5 p]. Available: http://clinicaltrials.gov/ct2/show/NCT01960257 NLM Identifier: NCT01960257.

11. U.S. Food and Drug Administration (FDA). 510(k) summary for Raisin personal monitor [K093976]. [internet]. Washington (DC): U.S. Food and Drug Administration (FDA); 2010 Mar 25 [accessed 2010 Dec 27]. [10 p]. Available: http://www.fda.gov.

12. Mezo I. The FDA lowers the regulatory bar for ingestible event markers, downgrading them from Class II to Class III devices. [internet]. Boston (MA): MassDevice; 2013 May 17 [accessed 2013 May 23]. [3 p]. Available: http://www.massdevice.com/news/fda-lowers-regulatory-bar-ingestible-sensors?page=show.

13. Evaluation of automatic class III designation (De Novo) for proteus personal monitor including ingestion event marker. K113070. Rockville (MD): U.S. Food and Drug Administration (FDA); 2012 May 14. 10 p. Also available: http://www.accessdata.fda.gov/cdrh_docs/reviews/K113070.pdf.

14. U.S. FDA accepts first digital medicine New Drug Application for Otsuka and Proteus Digital Health. [internet]. Redwood Shores (CA): Proteus Digital Health; 2015 Sep 10 [accessed 2015 Nov 17]. [9 p]. Available: http://www.proteus.com/press-releases/u-s-fda-accepts-first-digital-medicine-new-drug-application-for-otsuka-and-proteus-digital-health/.

15. Proteus Biomedical announces European CE mark approval of ingestible sensor and monitor system. [internet]. Redwood City (CA): Proteus Biomedical, Inc.; 2010 Aug 13 [accessed 2010 Dec 29]. [2 p]. Available: http://www.proteus.com/proteus-biomedical-announces-european-ce-mark-approval-of-ingestible-sensor-and-monitor-system/.

16. Proteus aims to change the shape of healthcare delivery. London (UK): EP Vantage; 2014 Aug 18. 3 p.

17. Helius prescribing information. Redwood City (CA): Proteus Digital Health; 2013 Jun 21. 2 p. Also available: http://www.proteusdigitalhealth.com/wp-content/themes/proteus/images/prescriber_information.pdf.

18. Helius frequently asked questions. [internet]. Redwood City (CA): Proteus Digital Health [accessed 2013 Aug 09]. [3 p]. Available: http://www.proteusdigitalhealth.com/todays-products/helius-faq/.

19. Miners Z. Proteus promotes medication adherence using ingestible sensors. Gray Sheet. 2012 Aug 6.

20. Technology. [internet]. Redwood (CA): Proteus Biomedical, Inc. [accessed 2010 Dec 27]. [1 p]. Available: http://www.proteusbiomed.com/technology/.

21. Expert Commenter 712. (External, Clinical). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 9 [review date].

22. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 10 [review date].

23. Expert Commenter 1489. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 13 [review date].

24. Expert Commenter 1026. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Mar 13 [review date].

25. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 12 [review date].

26. Expert Commenter 1261. (External, Research/Scientific/Technical). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 26 [review date].

27. Expert Commenter 533. (External, Health Systems/Administration). Horizon Scanning Structured Comment Form. HS262 - Digital medicines (Proteus Digital Health Feedback System) for chronic conditions requiring long-term drug therapy. 2015 Feb 27 [review date].

28. 3-D printer helps doctors prep for complex surgeries. [internet]. Boston (MA): Boston Globe; 2015 Jan 18 [accessed 2015 Mar 27]. [10 p]. Available: http://www.bostonglobe.com/business/2015/01/18/with-printer-doctors-get-help-prepping-for-complex-surgeries/Wf4GVpGMHapbG6sWGYlEYP/story.html.

29. Winder J, Bibb R. Medical rapid prototyping technologies: state of the art and current limitations for application in oral and maxillofacial surgery. J Oral Maxillofac Surg. 2005 Jul;63(7):1006-15. PMID: 16003630.

30. Rybicki F. RSNA 2014 3D printing (hands-on) training guide. Boston (MA): Applied Imaging Science Lab; 20 p.

31. Surgeons get 'dress rehearsals' with 3D-printed body parts. [internet]. Boston (MA): Boston Children's Hospital [accessed 2015 Mar 27]. [6 p]. Available: http://simpeds.org/simpeds3d-print/.

32. Knight M. 3-D printing is revolutionizing surgery. [internet]. Chicago (IL): Crain's Chicago Business; 2014 Mar 22 [accessed 2015 Mar 13]. [4 p]. Available: http://www.chicagobusiness.com/article/20140322/ISSUE01/140229904/3-d-printing-is-revolutionizing-surgery.

33. 3D printing revolutionizing healthcare. In: eHealth Magazine [internet]. Noida (India): Elets Technomedia Pvt. Ltd.; 2015 Jan [accessed 2015 Mar 27]. [6 p]. Available: http://ehealth.eletsonline.com/2015/01/3d-printing-revolutionizing-healthcare/.

34. Kim M. Using 3-D printing to treat children's heart defects. [internet]. Philadelphia (PA): Philadelphia Inquirer; 2014 Feb 10 [accessed 2015 Mar 27]. [4 p]. Available: http://articles.philly.com/2014-02-10/news/47171542_1_heart-defects-3-d-printer-phoenix-children.

35. 3D printing puts patients in surgeons' hands. Literally. [internet]. Boston (MA): Boston Children's Hospital [accessed 2015 Mar 09]. [4 p]. Available: http://simpeds.org/news/3d-printing-puts-patients-in-surgeons-hands-literally/.

36. OsteoView anatomical models. [internet]. Golden (CO): Medical Modeling Inc. [accessed 2015 Mar 09]. [1 p]. Available: http://www.medicalmodeling.com/solutions-for-surgeons/tactile-medical-imaging/osteoview-sup-sup-anatomical-models[3/.

37. Valverde I, Gomez G, Suarez-Mejias C, et al. 3D printed cardiovascular models for surgical planning in complexcongenital heart diseases. J Cardiovasc Magn Reson. 2015;17(suppl 1).

38. Wu XB, Wang JQ, Zhao CP, et al. Printed three-dimensional anatomic templates for virtual preoperative planning before reconstruction of old pelvic injuries: Initial results. Chin Med J. 2015;128(4):477-82. Also available: http://dx.doi.org/10.4103/0366-6999.151088.

39. Emory University. Surgical planning for reconstruction of complex heart defects. In: ClinicalTrials.gov [internet]. Bethesda (MD): U.S. National Library of Medicine (NLM); 2000- [accessed 2015 May 27]. [3 p]. Available: https://www.clinicaltrials.gov/ct2/show/NCT00972608 NLM Identifier: NCT00972608.

40. Weintraub K. Off the 3-D printer, practice parts for the surgeon. [internet]. New York (NY): New York Times; 2015 Jan 26 [accessed 2015 Mar 27]. [10 p]. Available: http://www.nytimes.com/2015/01/27/science/off-the-3-d-printer-practice-parts-for-the-surgeon.html?_r=0.

41. Hassan A. 3-D printer moving into medicine. [internet]. Houston (TX): Houston Chronicle; 2013 Aug 2 [accessed 2015 Mar 27]. [7 p]. Available: http://www.houstonchronicle.com/news/article/3-D-printer-moving-into-medicine-4704392.php.

42. Orthopedic CT scanning protocol. Golden (CO): 3D Systems, Inc.; 2014. 1 p.

43. Materialise's HeartPrint now listed as a class 1 medical device. [internet]. Leuven (Belgium): Materialise NV; 2014 Oct 9 [accessed 2015 Mar 09]. [3 p]. Available: http://www.materialise.com/press/materialise-s-heartprint-now-listed-as-a-class-1-medical-device.

44. FDA 510(k) clearances: January 2014. Gray Sheet. 2014 Mar 10:Article # 01140310015. Also available: https://www.pharmamedtechbi.com/.

45. Fliesler N. Surgical 3-D printing: 300 prints, 16 specialties and counting. [internet]. Boston (MA): Boston Children's Hospital; 2015 Oct 2 [accessed 2015 Nov 18]. [9 p]. Available: http://vector.childrenshospital.org/2015/10/surgical-3-d-printing-300-prints-16-specialties-and-counting/.

46. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 Apr 13 [review date].

47. Expert Commenter 347. (External, Clinical). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 Apr 13 [review date].

48. Expert Commenter 1192. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 Apr 17 [review date].

49. Expert Commenter 394. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 Apr 17 [review date].

50. Expert Commenter 1243. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 Apr 21 [review date].

51. Expert Commenter 1216. (External, Clinical). Horizon Scanning Structured Comment Form. HS2226 - Patient-based 3-D printed biomodels to aid surgical planning. 2015 May 4 [review date].

52. Cabilan CJ, Hines S, Munday J. Prehabilitation for surgical patients: a systematic review protocol. JBI Database Syst Rev Implement Rep. 2013;11(5):112-22.

53. What is MSHOP? [internet]. Ann Arbor (MI): University of Michigan Department of Surgery; [accessed 2015 Mar 09]. [3 p]. Available: http://www.med.umich.edu/surgery/mshop/about.html.

54. Helping patients train for surgery earns $6.4M Health Care Innovation award. [internet]. Ann Arbor (MI): University of Michigan; 2014 Jun 5 [accessed 2015 Feb 20]. [5 p]. Available: http://www.uofmhealth.org/news/archive/201406/helping-patients-train-surgery-earns-64m-health-care.

55. Move: activities before your surgery. [internet]. Ann Arbor (MI): University of Michigan Department of Surgery [accessed 2015 Feb 20]. [2 p]. Available: http://www.med.umich.edu/surgery/mshop/move.html.

56. Breathe. [internet]. Ann Arbor (MI): University of Michigan Department of Surgery [accessed 2015 Feb 20]. [2 p]. Available: http://www.med.umich.edu/surgery/mshop/breathe.html.

57. Breathe: exercise your lungs. [internet]. Ann Arbor (MI): University of Michigan Department of Surgery [accessed 2015 Feb 20]. [2 p]. Available: http://www.med.umich.edu/surgery/mshop/b_is_lungs.html.

58. Get in shape for surgery. [internet]. Ann Arbor (MI): University of Michigan; 2014 Jul 10 [accessed 2015 Feb 20]. [3 p]. Available: https://www.umhsheadlines.org/2014/07/get-in-shape-for-surgery/.

59. Mophonic Analysis Group. Analytic Morphomics part of UM's $6.4M Health Care Innovation award. [internet]. Ann Arbor (MI): University of Michigan; 2014 Jul 1 [accessed 2015 Mar 09]. [2 p]. Available: http://www.morphomicanalysisgroup.org/content/analytic-morphomics-part-ums-64m-health-care-innovation-award.

60. Bendall I. U-M Health System expands pre/post-surgery 'boot camp'. [internet]. Detroit (MI): DBusiness Magazine; 2014 Jun 11 [accessed 2015 Mar 02]. [4 p]. Available: http://www.dbusiness.com/daily-news/Annual-2014/U-M-Health-System-Expands-Pre-Post-Surgery-Boot-Camp/.

61. Affordable Care Act brings half billion dollars to Michigan for infrastructure, access to health care. [internet]. Ann Arbor (MI): University of Michigan; 2015 Feb 3 [accessed 2015 Mar 09]. [3 p]. Available: https://www.umhsheadlines.org/2015/02/affordable-care-act-brings-half-billion-dollars-to-michigan-for-infrastructure-access-to-health-care/.

62. Kerr E. Pre-surgery University program awarded $6.3 million. [internet]. Ann Arbor (MI): The Michigan Daily; 2014 Jun 11 [accessed 2015 Mar 09]. [2 p]. Available: http://www.michigandaily.com/news/mshop-award.

63. Englesbe MJ, Terjimanian MN, Lee JS, et al. Morphometric age and surgical risk. J Am Coll Surg. 2013 May;216(5):976-85. Also available: http://dx.doi.org/10.1016/j.jamcollsurg.2013.01.052. PMID: 23522786.

64. Pouwels S, Willigendael EM, Van Sambeek MR, et al. Beneficial effects of pre-operative exercise therapy in patients with an abdominal aortic aneurysm: a systematic review. Eur J Vasc Endovasc Surg. 2015 Jan 1;49(1):66-76. Also available: http://dx.doi.org/10.1016/j.ejvs.2014.10.008.

65. Valkenet K, Trappenburg JCA, Gosselink R, et al. Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection (PREPARE study): Study protocol for a randomized controlled trial. Trials. 2014 Apr 27;15(1):144. Also available: http://dx.doi.org/10.1186/1745-6215-15-144.

66. Hirschhorn AD, Kolt GS, Brooks AJ. A multicomponent theory-based intervention improves uptake of pelvic floor muscle training before radical prostatectomy: a 'before and after' cohort study. BJU Int. 2014 Mar;113(3):383-92. Also available: http://dx.doi.org/10.1111/bju.12385. PMID: 24053154.

67. Expert Commenter 1170. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Mar 27 [review date].

68. Expert Commenter 1383. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Apr 6 [review date].

69. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Apr 16 [review date].

70. Expert Commenter 427. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Apr 3 [review date].

71. Expert Commenter 1264. (External, Clinical). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Apr 23 [review date].

72. Expert Commenter 64. (External, Clinical). Horizon Scanning Structured Comment Form. HS2268 - Patient training and risk assessment program (MSHOP) for surgery preparation. 2015 Apr 27 [review date].