AHRQ Healthcare Horizon Scanning System – Potential High Impact Interventions Report

Priority Area 02: Cancer

Potential High Impact Interventions Report

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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. HHSA29020100006C). 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 closer to diffusion into practice in the United States. Drafts of 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 those interventions that experts deem, 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 six 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 the horizon scanning, assessing the leads for topics, or provide opinions regarding potential impact of interventions.

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

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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 target technologies and innovations in health care and to create an inventory of target technologies 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 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 the analysis of 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 utilization 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 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 e-mail to effectivehealthcare@ahrq.hhs.gov.

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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 7 years out on the horizon and then to follow them for up to 2 years after initial entry into the health care system. Since that implementation, more than 7,000 leads about topics have resulted in identification and tracking of more than 900 topics across the 14 AHRQ priority areas.

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 twice annually. Topics eligible for inclusion are those interventions expected to be within 0 to 4 years of potential diffusion (e.g., in phase III trials for pharmaceuticals or biotechnologies or in phase II or a trial with some preliminary efficacy data on the target population for devices and programs) 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 a profile on topics and issuing topic profile 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 350 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 (COI). 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 seven or 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 high impact potential designation. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the potential high impact 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 potential high impact is expected to change over time. This report is being 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 the 40 topics for which (1) preliminary phase III data for drugs, phase II data for devices or procedures, or pilot programs were available; (2) information was compiled and sent for expert comment before November 1, 2011 in this priority area; *and* (3) we received six to eight sets of comments from experts between February 2011 and November 1, 2011. (A total of 205 topics in this priority area were being tracked in the system as of November 2011.) For purposes of the Potential High Impact Interventions Report, we aggregated related topics for summary and discussion (e.g., individual drugs into a class). Topics in this Executive Summary and report are organized alphabetically by class of therapy, and then by individual topic within each class. We present 20 summaries on a total of 22 topics (indicated by an asterisk) that emerged as higher impact on the basis of expert comments and assessment of potential impact.

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1.	*Abiraterone (Zytiga) for treatment of castration-resistant prostate cancer
2.	Autologous vascularized lymph node transfer for treatment of mastectomy-associated lymphedema
3.	Biophotonic system (LightTouch Scanner) for cervical cancer screening
4.	*Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory anaplastic large cell lymphoma
5.	*Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin's lymphoma
6.	*Cologuard fecal DNA test for colorectal cancer screening
7.	*Concomitant colorectal cancer screening and annual influenza vaccine (FLU-FOBT) program
8.	*Crizotinib (Xalkori) ALK inhibitor for treatment of nonsmall cell lung cancer
9.	Denosumab (Xgeva) for prevention of cancer-related bone injury
10.	*Digital, 3-D breast tomosynthesis for breast cancer screening
11.	Electrical impedance scanner (SciBase III Electrical Impedance Spectrometer) for melanoma diagnosis

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12.	*Hedgehog pathway inhibitor (vismodegib) for treatment of basal cell carcinoma
13.	HER2 dimerization inhibitor (pertuzumab) for treatment of metastatic breast cancer
14.	HistoScanning for diagnosis of ovarian masses
15.	*Hypofractionated whole-breast radiation therapy for breast cancer
16.	Integrated imaging system (Biograph mMR) for cancer indications
17.	*Ipilimumab (Yervoy) for treatment of metastatic melanoma
18.	Levonorgestrel-release intrauterine device for treatment of endometrial precancers and carcinoma
19.	Liver chemosaturation drug/device combination (melphalan/Chemosat) for treatment of melanoma metastases to the liver
20.	*MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy
21.	*MelaFind multispectral dermoscope for detection of melanoma in suspicious skin lesions
22.	*Methylated Septin 9 blood test for colorectal cancer screening
23.	*mTOR inhibitor (everolimus) for treatment of estrogen receptor-positive breast cancer
24.	*mTOR inhibitor (ridaforolimus) for treatment of soft tissue and bone sarcomas
25.	Multikinase inhibitor (afatinib) for treatment of nonsmall cell lung cancer
26.	Multikinase inhibitor (pazopanib, Votrient) for treatment of soft tissue sarcomas
27.	*Multikinase inhibitor (vandetanib) for treatment of metastatic, medullary thyroid cancer
28.	Mycobacterial cell wall-DNA complex (Urocidin) for treatment of nonmuscle-invasive bladder cancer
29.	Off-label metformin for treatment of breast cancer
30.	Off-label zoledronic acid (Zometa) for primary treatment of multiple myeloma
31.	PCA3 assay as a triage test to inform biopsy decision making for suspected prostate cancer
32.	Proteasome inhibitor (carfilzomib) for treatment of multiple myeloma
33.	*Radium-223 (Alpharadin) for treatment of bone metastases associated with solid tumors
34.	*Sedasys computer-assisted sedation system for automated administration of propofol
35.	Therapeutic cancer vaccine (BiovaxID) for indolent follicular non-Hodgkin's lymphoma
36.	*Transoral robotic surgery (TORS) for treatment of mouth and throat tumors
37.	*Trastuzumab emtansine antibody-drug conjugate for treatment of breast cancer
38.	*Tumor-treating fields therapy (NovoTTF-100A System) for brain cancer
39.	Vascular endothelial growth factor trap (aflibercept) for treatment of metastatic colorectal cancer
40.	*Vemurafenib (Zelboraf) B-RAF inhibitor for treatment of metastatic melanoma

Discussion

Topics in this Executive Summary and report are organized in alphabetical order by intervention type, such as device-related procedures, hormonal therapies, immunotherapies, etc. Overall, topics that emerged as potential high impact on the basis of experts' comments included novel drugs and biologics for treatment, novel screening and diagnostic tests, novel procedures including surgeries, or

devices used during procedures, and a screening program. Therapeutic areas included the most common, as well as, difficult-to-treat solid tumors (advanced basal cell carcinomas, breast cancer, glioblastomas, gliomas, medullary thyroid cancer, melanoma, mouth and throat tumors, nonsmall cell lung cancer, and prostate cancer) and hematologic malignancies (anaplastic large cell lymphoma (ALCL), Hodgkin's lymphoma (HL).

The group of therapeutic agents includes both small-molecule and biologic drugs. The majority of the small-molecule drugs have a well-defined mechanism of action and target a specific signaling pathway. Large-molecule drugs include antibody-drug conjugates directed to tumor-associated surface antigens and an immune stimulator. Diagnostic topics offered potentially simpler or improved solutions to existing technologies. Finally, novel surgical treatments that emerged as potential high impact included a new application of robotic-assisted surgery and a new anesthesia administration tool. Classes of interventions are summarized below.

Device-Related Procedures

Sedasys Computer-assisted Sedation System for Automated Administration of Propofol

- **Key facts**: Sedasys® (Ethicon Endo-Surgery, a unit of Johnson & Johnson, Inc., New Brunswick, NJ) is an anesthesia management system developed for propofol-mediated sedation during same-day procedures. The system is primarily intended for use during colonoscopy or other upper gastrointestinal (GI) endoscopic procedures. The majority of conscious sedation in the U.S. is performed using a combination of benzodiazepine and an opiate. However, propofol has the purported advantage of a more rapid onset and a more rapid termination of the sedative effect, leading to faster patient recovery from sedation. This anesthetic is known to have higher potency than benzodiazepines/opiates and, therefore, carries an increased potential for the unintended induction of general anesthesia and/or hemodynamic and respiratory depression. Additionally, while pharmacologic antagonists can reverse the effects of benzodiazepines and opiates, no such antagonist is available for propofol. Therefore, the current labeling approved by the U.S. Food and Drug Administration (FDA) for propofol states that propofol "should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure." The system could change that if approved for marketing by enabling clinicians untrained in general anesthesia administration to administer propofol for patient sedation during same-day GI procedures. The system is intended to deliver both propofol and oxygen to a patient in an automated fashion to achieve the desired level of mild to moderate sedation. By continuously adjusting the rates of propofol infusion and oxygen flow in response to patient vital signs and responsiveness, the system purports to avoid too much or too little sedation. The system's marketing approval was denied by FDA and the company appealed the decision. The appeal was to be heard by an FDA advisory committee in mid-December 2011, but about two weeks before the hearing, Johnson & Johnson announced that it had reached an agreement with FDA to reopen its premarket approval application for the system for endoscopy.
- **Key Expert Comments**: Overall, experts commenting on the intervention thought that the system has significant potential to disrupt the current methods of delivering propofol-mediated sedation, which could also have a big impact on the way colonoscopy centers operate. However, experts thought adoption might be hindered by concerns about potential

risk of oversedation of patients in a setting without an anesthesiologist present. If adopted, use of the system could significantly change costs associated with anesthesiologist-administered sedation. Experts expected considerable controversy over implementation of this system if it is approved for marketing.

- **Potential for High Impact**: High

Transoral Robotic Surgery for Mouth and Throat Cancers

- **Key facts**: Many general surgeries and cancer-related surgeries now employ the da Vinci® robotic surgery system (Intuitive Surgical, Inc., Sunnyvale, CA) to offer patients minimally invasive options with the promise of shorter recovery time and less pain. A relatively new application is use of the system to perform transoral robotic surgery (TORS) for resection of tumors located in an anatomical area with vitally important and vulnerable structures, such as the mouth and throat. Open surgery for this area typically requires an ear-to-ear incision with long recovery time, much pain, and elevated risk of infection. The question is whether the purported benefits of TORS actually result in equivalent or improved patient outcomes in terms of survival and adverse events.
- **Key Expert Comments**: Overall, the experts providing comments on this procedure thought that as a minimally invasive option, TORS offered better visualization and tissue manipulation than conventional transoral surgical techniques. Clinical experts asserted that this might lead to improved patient outcomes including reduced recovery time and blood loss, improved function, and improved cosmesis and quality of life after surgery. However, experts indicated that adoption of TORS could be hindered by significant equipment acquisition and maintenance costs, staffing and training costs that are not reimbursed beyond the standard reimbursement for the surgery, and/or the potential for operating room scheduling issues that can arise from longer procedure times than for open surgery.
- **Potential for High Impact**: High

Hormone Therapies

Abiraterone (Zytiga) for Treatment of Metastatic Castration-Resistant Prostate Cancer

- **Key facts**: Until 2010, patients with a form of prostate cancer that had become resistant to first-line hormone therapy (castration-resistant prostate cancer [CRPC]) had only the chemotherapeutic agent docetaxel as an option that improved survival in some patients. The armamentarium for treatment grew in 2010 with FDA approval of the chemotherapeutic agent cabazitaxel (Jevtana®, Sanofi-Aventis, Paris, France) and the therapeutic cancer vaccine sipuleucel-T (Provenge®, Dendreon Corp., Seattle, WA). The latest addition to treatment options for metastatic, castration-resistant prostate cancer (mCRPC) came in April 2011 with approval of abiraterone (Zytiga®, Johnson & Johnson, Inc., New Brunswick, NY). Abiraterone is intended to improve on current methods available to reduce androgen signaling, which is known to promote prostate cancer growth. Abiraterone has expanded the use of androgen inhibitors to a later stage of prostate cancer previously thought to be independent of androgen signaling. Experts commenting on abiraterone thought significant changes in the management

of mCRPC would be seen as physicians incorporate new therapies such as abiraterone, cabazitaxel, and sipuleucel-T into practice guidelines.

- **Key Expert Comments**: Overall, experts thought abiraterone has high potential to improve both quality and quantity of life for patients with mCRPC; however, some experts pointed out that the demonstrated improvement in survival duration is only a few months in patients whose disease has not responded to first-line chemotherapy. They also noted that results from a study of abiraterone for earlier stage CRPC are highly anticipated.
- **Potential for High Impact**: Moderately high

Immunotherapy

Ipilimumab (Yervoy) for Treatment of Metastatic Melanoma

- **Key Facts:** According to the American Academy of Dermatology, more than half of all new cases of melanoma are invasive at the time of diagnosis. Until recently, no clearly optimal treatments for metastatic melanoma were available. The monoclonal antibody ipilimumab (Yervoy™, Bristol-Myers Squibb, New York, NY) is an immunotherapy that attempts to modulate an existing immune response to leverage that response. Ipilimumab confronts the problem of immune tolerance (i.e., lack of an immune response) to many cancers, in particular melanoma. The recent approval of ipilimumab and the B-RAF inhibitor vemurafenib (Zelboraf®, developed by the Genentech unit of F. Hoffmann-La Roche, Ltd., Basel, Switzerland) represent the first therapies to demonstrate an improvement in overall survival by an average of about four months for patients with metastatic melanoma. Based on these results, FDA granted marketing approval in March 2011 for ipilimumab as a second-line therapy for advanced melanoma. The drug's estimated per patient cost is $120,000 for a full course (4 infusions). The company initiated a program to assist patients in paying so that patient out-of-pocket costs do not exceed $5,000 per year. More recently, data were published on ipilimumab as first-line therapy for metastatic melanoma in combination with the chemotherapeutic agent dacarbazine. Researchers reported a statistically significant improvement in overall survival of about 2 months for the ipilimumab group over the placebo group. Ipilimumab has a black box warning regarding the development of fatal immune-mediated adverse reactions due to T-cell activation and proliferation, which may involve any organ system; however, the most common reactions include dermatitis, endocrinopathy, enterocolitis, hepatitis, and neuropathy.
- **Key Expert Comments:** Experts commented that although ipilimumab was capable of extending overall survival in some patients with advanced melanoma, the 2-to 4-month increase in survival time demonstrated in trials represented a moderate impact on health outcomes. Nonetheless, experts noted that this is one of only two therapies in recent years that has demonstrated any survival benefit in this patient population. Experts thought that clinical enthusiasm for this therapy might be tempered by the possibility of fatal immune reactions in patients and the high cost of the therapy.
- **Potential for High Impact**: Moderately high

Radiation Therapy

Hypofractionated Whole-Breast Radiation Therapy for Breast Cancer

- **Key Facts:** Patient adherence to a full course of radiation therapy for early stage breast cancer presents a challenge because of the duration of the treatment course. Consequently, only about 30% of the women prescribed radiation therapy for breast cancer complete the entire recommended course. Hypofractionated external beam radiotherapy (HERT) is an abbreviated treatment regimen for early-stage breast cancer that is completed within about 3 weeks, rather than 6 weeks of conventional radiotherapy, and thus, experts believe, it has potential to improve patient adherence. The question is whether it can achieve the same health outcomes as the conventional course of external beam radiation therapy. In 2010, researchers reported 10-year local recurrence rates from a randomized controlled trial of 1,234 patients performed by the Ontario Clinical Oncology Group comparing a HERT treatment protocol (42.5 Gy in 16 fractions over 22 days) to conventional external beam radiation therapy (EBRT) (50 Gy in 25 fractions over 35 days). They reported that HERT and EBRT exhibited similar 10-year local recurrence rates of 6.7% and 6.2%, respectively.
- **Key Expert Comments:** Overall, experts commenting on this topic saw significant potential for HERT to improve health outcomes in patients with early stage breast cancer by improving adherence to the recommended radiation therapy regimen, which can be curative for early stage breast cancer if patients complete the full therapy course. However, experts expected that physicians would want to see longer-term efficacy and safety data before HERT would be widely adopted, given the known efficacy for current standard radiation therapy regimens among women who complete the regimens. Some experts opined, however, that for women in whom conventional EBRT regimens are not feasible because of transportation issues, lost time from work, or other barriers, HERT might provide an option worth considering even in the absence of longer-term data.
- **Potential for High Impact**: High

Tumor-Treating Fields Therapy (NovoTTF-100A System) for Brain Cancer

- **Key Facts:** Tumor-treating fields therapy (NovoTTF-100A™, Novocure Ltd., Haifa, Israel) is a novel treatment modality in which a patient's tumor is exposed to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis. Tumor-treating fields are delivered by a battery-powered portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's skin around the site of the tumor. The device is used by the patient at home on a continuous basis. The delivery device was approved for treatment-refractory glioblastoma in April 2011, and represents both a novel cancer treatment modality and a salvage therapy option that appears to have few adverse effects. The approval was based on results of a 237-patient randomized, controlled trial comparing tumor-treating fields to the clinician's chemotherapy of choice. Researchers reported that patients in the tumor-treating fields arm of the trial exhibited similar overall survival times to patients in the chemotherapy arm; median 7.8 months (n = 120) versus median 6.1 months (n = 117), respectively. Additionally, researchers reported that patients in the tumor-treating fields arm reported fewer side effects and improved quality of life compared with patients in the chemotherapy arm. The

therapy is undergoing study as a treatment for newly diagnosed glioblastoma multiforme in combination with temozolomide. An alternate version of the device is under study as second-line treatment in combination with pemetrexed for advanced nonsmall cell lung cancer (NSCLC).

- **Key Expert Comments:** Although experts were generally enthusiastic about the idea of a therapy with a novel mechanism of action and a seemingly low side-effect profile, experts cautioned that the data suggest the therapy exhibits marginal, if any, survival benefit over alternative salvage therapies and that patients and clinicians may be unlikely to adopt an unorthodox therapy administered at home without more data demonstrating its efficacy, unless it represents the only available treatment option.
- **Potential for High Impact**: Lower range of high impact

Screening and Diagnostics

Two diagnostic test kits intended to improve upon current options for CRC screening emerged as potentially high impact in this report: the Cologuard fecal-based test and the Methylated Septin 9 blood test. In addition, a program intended to encourage patients to obtain CRC screening was also considered to have the potential for high impact. New technologies for screening mammography, ensuring clear margins when resecting breast tumors, and detecting suspect skin lesions that warrant biopsy were also considered as having potential for high impact by experts commenting on these topics.

Cologuard Fecal DNA Testing for Colorectal Cancer

- **Key Facts:** The Cologuard® test (Exact Sciences Corp., Madison, WI) is a next-generation stool DNA-based CRC screening assay that analyzes a patient's stool to test for markers indicative of colon cancer or precancer (e.g., adenomatous polyps). It tests for three types of markers: multiple methylated DNA species, a mutated form of an oncogene, and the blood marker hemoglobin. This test is intended to replace the currently available ColoSure™ test, which examines only one marker (a methylated DNA species also included in the Cologuard test). Like the methylated Septin 9 CRC screening test discussed below, the updated version of the Cologuard test is currently undergoing testing in a large clinical trial.
- **Key Expert Comments:** Overall, the majority of experts commenting on this topic thought that improved noninvasive CRC screening methods that could improve CRC screening by simplifying sample collection or reducing the frequency at which patients need to be screened. However, experts noted that complete data on the updated versions of these tests would need to show improvement upon the detection abilities of prior versions of the tests for this to be the case. Pending the final outcomes on efficacy from clinical trials, experts believe that the blood-based screening test could have a larger potential impact, suggesting that such a test could transform screening practices by allowing integration of CRC screening into routine blood testing and avoiding the need to handle stool samples, which may dissuade some patients from using other noninvasive tests. However, experts also believe that the limited ability of a blood test to detect noninvasive precancerous lesions could dissuade some physicians and patients from opting for the test.
- **Potential for High Impact:** Lower range of high impact

Concomitant Colorectal Cancer Screening and Annual Influenza Vaccine (FLU-FOBT) Program

- **Key Facts:** While adherence to colorectal cancer (CRC) screening guidelines has been demonstrated to reduce CRC-related mortality, only a minority of the population adheres to CRC screening guidelines and about 50% of CRCs diagnosed in the U.S. are diagnosed at late disease stages. Therefore, innovations that have the potential to improve CRC screening rates are highly sought. The FLU-FOBT (fecal occult blood test) program is an initiative that seeks to target the provision of CRC information and noninvasive FOBT kits to patients accessing the health care system to receive annual influenza vaccines. Influenza vaccination and CRC screening are in some ways natural partners because both are targeted to elderly patients and it is recommended that both influenza vaccination and fecal occult blood testing be performed annually. Pilot programs run in various care settings (e.g., hospital-based/managed-care based influenza vaccine clinics, pharmacy-based influenza vaccination campaigns, community health care clinics, primary care centers) by researchers at the University of California San Francisco, demonstrated improved rates of FOBT completion and overall rates of CRC screening among patients who were part of FLU-FOBT-like programs compared with patients who only received an influenza vaccination.
- **Key Expert Comments:** Experts who commented on this intervention believe that it is an interesting approach to increasing CRC screening rates that has significant potential to improve screening adherence in certain settings. However, experts questioned whether such a program could be implemented on a large scale, thereby limiting its overall impact.
- **Potential for High Impact:** Lower range of high impact

Digital Breast Tomosynthesis for Mammography Screening

- **Key Facts:** A limitation of two-dimensional (2-D) conventional mammography is that the x-ray images capture information from all tissue constituents along the path from the x-ray source to the detector. Therefore, features of the breast may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest. Digital breast tomosynthesis is an x-ray imaging modality that purports to overcome this potential pitfall by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. For example, rather than taking a single image in the craniocaudal view as in conventional 2-D mammography, digital breast tomosynthesis involves taking 10 to 20 images in the craniocaudal view with the angle of the x-ray beam shifted by approximately 1 degree in each image. Breast tissue features that may obscure each other in one angle will be shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, digital breast tomosynthesis can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in reduced number of recalls for inconclusive results, reduced number of biopsies, and increased cancer detection. The first digital breast tomosynthesis system, the Selenia® Dimensions® 3D System (Hologic, Inc., Bedford, MA) received marketing approval from FDA in February 2011 based on results from two clinical trials of the system. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system.

- **Key Expert Comments:** Experts providing comments on this technology thought it had potential to bring incremental improvements in breast cancer screening by potentially improving breast cancer detection and reducing false-positive results. Such reductions, they noted, could obviate need for unnecessary followup imaging and biopsy, which could save costs and reduce patient anxiety created with false-positive results. Experts thought that given the likelihood that patients and clinicians would want to use this technology and the large changes in health care system costs and resources that its use would cause, digital breast tomosynthesis has potential high impact.
- **Potential for High Impact:** High

MarginProbe System for Intraoperative Identification of Positive Margins During Breast Cancer Lumpectomy

- **Key Facts:** Breast-conserving surgery followed by radiation therapy early stage breast cancer can achieve outcomes with regard to recurrence equivalent to those achieved with mastectomy; however, to achieve optimal outcomes with this technique the margins of the tissue excised during surgery must be free of cancer cells. If subsequent pathologic analysis reveals that surgical margins were not clear of cancer, patients may need to undergo a second surgical procedure to remove additional tissue. Therefore, techniques to identify positive margins during surgery are highly sought. While several techniques have been developed (e.g., frozen sections, touch-prep cytology) the reported rate of secondary surgeries for unclean margins continues to be around 30%. The MarginProbe™ System (Dune Medical Devices, Ltd., Caesarea, Israel) purports to provide an objective means of rapidly assessing surgical margins intraoperatively using a technology called radiofrequency (RF) spectroscopy, which may be able to differentiate between normal tissue and cancerous tissue based on bioelectric differences between the two tissue types. The MarginProbe algorithm is based on a training set of a large number of comparisons between RF spectroscopy readings and pathology results and provides a binary answer indicating whether the assessed margin is clean. In results announced by Dune Medical Devices from a 664-patient trial of the device, use of the MarginProbe System in combination with standard intraoperative assessment compared with standard intraoperative assessment alone increased the rate at which positive surgical margins were both identified and led to sufficient removal of additional tissue to achieve clean surgical margins (72% for MarginProbe vs. 22% for standard assessment, $p < 0.0001$). Based on this data, a premarket approval (PMA) application was submitted to FDA and has been granted priority review by the agency.
- **Key Expert Comments:** Experts providing comments thought this technology has potential to fill a significant unmet need for rapidly assessing surgical margins. Experts suggested that such a technology could significantly improve patient health outcomes by avoiding the need to perform secondary surgeries in a large number of women undergoing breast-conservation surgery. However, experts expressed a desire to see more data that definitively determined whether the system actually improved the rate of positive-margin detection and adequate excision of additional tissue for most patients.
- **Potential for High Impact:** Moderately high

MelaFind Multispectral Dermoscope for Detection of Melanoma in Suspicious Skin Lesions

- **Key Facts:** The gold standard for melanoma diagnosis is biopsy followed by histopathologic analysis; however, accurately identifying which lesions should be biopsied remains difficult. Current screening methods involve clinical visual examination with the naked eye, a dermoscope, or both. Both methods involve subjective decisions that require the user to be highly trained to discriminate between benign and potentially melanotic lesions, and research studies have estimated that up to 50 biopsies are performed for every one melanoma detected. The MelaFind® system (MELA Sciences, Inc., Irvington, NY) is a computer-based system intended to aid the clinician in determining whether a clinically atypical, cutaneous, pigmented lesion should be biopsied. It uses a hand-held probe to capture images of the lesion using multiple light wavelengths ranging from blue to near infrared. Because different light wavelengths penetrate skin to different depths, the wide spectrum of light sources used to image the lesion is intended to enable assessment of lesion properties that are not visible to the human eye, including subsurface portions of the lesion. In an automated fashion, the MelaFind system provides the user with either a positive or negative result, indicating that the system has determined that the lesion should or should not be biopsied, respectively. MELA Sciences submitted a PMA application to FDA in June 2009 and after feedback from an FDA advisory panel, submitted an amended PMA in 2011 that included a labeling change limiting use of the MelaFind to dermatologists. On November 2, 2011, the MelaFind device was granted marketing approval by FDA.
- **Key Expert Comments:** Overall, experts were enthusiastic about the MelaFind device's potential to modestly decrease the percentage of suspicious lesions that would otherwise need to be biopsied. However, experts expressed concerns regarding cost, reimbursement, and the care setting in which the device might be used, which they thought could limit its diffusion and potential impact.
- **Potential for High Impact:** Moderately high

Methylated Septin 9 Blood Test for Detection of Colorectal Cancer

- **Key Facts:** Research has demonstrated that cells undergo a range of epigenetic modifications (e.g., DNA methylation) during transformation to cancerous cells. In particular, elevated levels of certain methylated DNA species have been observed in the blood of patients with CRC, which could serve as a readily accessible marker for cancer screening. One such marker that has been shown to be present specifically in the blood of individuals with CRC is a methylated DNA derived from the S*eptin 9* gene, detection of which is being studied as a potential colon cancer screening test. Like other noninvasive colon cancer tests (e.g., FOBT), a positive result from the methylated Septin 9 test would require that the patient undergo a colonoscopy to confirm the result and biopsy and/or resect any suspect lesions. The methylated Septin 9 test is being developed by Epigenomics AG (Berlin, Germany), in collaboration with Abbott Laboratories (Abbott Park, IL). In 2010, Epigenomics reported data from its PRESEPT trial in which 7,940 patients undergoing colonoscopy screening were also tested with the Epigenomics' first-generation Septin 9 test. The company reported that, compared to colonoscopy, the Septin 9 test had a sensitivity of 66.7% and a specificity of 88.4%. Data on the test's ability to detect precancerous, adenomatous polyps were not presented. Epigenomics

and Abbott are currently developing a second-generation Septin 9 test that uses affinity purification of DNA to enrich samples for testing, potentially improving detection rates. Epigenomics initiated clinical trials of the new test in September 2011, and stated that it may submit a PMA to FDA by the end of 2011.

- **Key Expert Comments:** Overall, most experts commenting on this intervention thought that an accurate blood-based CRC screening test obtained through venipuncture (rather than testing a stool sample) could fundamentally change CRC screening practices by increasing the percentage of patients willing to be screened for CRC. However, experts noted that further data, especially on the second-generation test, would be needed before its full impact could be assessed, because the first-generation test did not have sufficiently high sensitivity and specificity.
- **Potential for High Impact:** High

Targeted Therapies

Antibody-Drug Conjugate: Brentuximab-Vedotin (Adcetris) for Treatment of Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma

- **Key Facts:** Antibody-drug conjugates (ADCs) represent a class of cancer treatments in which highly toxic chemotherapy agents are coupled to monoclonal antibodies specific for molecules present on the surface of cancer cells. These targeted therapeutic agents are intended to deliver high doses of cytotoxic therapy to tumor cells while simultaneously reducing systemic side effects associated with untargeted chemotherapy. CD30-positive malignancies such as HL and ALCL are rare, with only approximately 8,500 of HL and 2,250 cases of ALCL diagnosed annually in the U.S. However, patients with HL and ALCL often experience relapse, and in many cases the disease becomes resistant to first-line treatments. This has resulted in increased demand for new therapeutic options that can prevent or inhibit the growth of recurring tumors. Brentuximab-vedotin (Adcetris®, Seattle Genetics, Inc., Bothell, WA, in collaboration with the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd., Osaka, Japan) is an ADC that consists of a monoclonal antibody covalently attached to a potent, chemotherapeutic agent. It is intended to target CD30-expressing tumor cells and contains a novel linking system designed to allow it to remain stable in the bloodstream and only release its cytotoxic drug upon penetration of CD30-positive cells. Common adverse effects reported in trials included nausea, fatigue, peripheral neuropathy, pyrexia, diarrhea, and neutropenia, which were characterized as "manageable." Rare, but serious adverse events reported were progressive multifocal leukoencephalopathy (PML), a brain infection that can result in death. On August 19, 2011, FDA approved brentuximab-vedotin for patients with HL that has failed to respond to an autologous stem cell transplant or whose disease has progressed after at least two prior multi-agent chemotherapy regimens and who are not autologous stem cell transplant candidates and for patients with ALCL after failure of at least one prior multi-agent chemotherapy. The initial drug pricing was set at about $4,500 per vial with about 3 vials used per treatment and 7 to 9 cycles of treatment given per patient bringing the total cost for a complete regiment to a range of $108,000 to $121,000.

- **Key Expert Comments:** Overall, experts concurred that recurrent or refractory HL presents an important unmet need and that an ADC might prove to be safer and more efficacious than current chemotherapeutic approaches, and that CD30 represents a theoretically sound target for HL treatment. All but one expert, who represented an independent research perspective, were encouraged by available data suggesting that brentuximab vedotin may improve health outcomes of HL patients. For treating ACLS, experts were unanimous in their opinion that both physicians and patients would be highly likely to adopt the use of brentuximab vedotin, citing the lack of alternatives demonstrating efficacy in refractory ALCL and the encouraging response rates to treatment reported in clinical trials thus far. Additional factors noted by experts as influencing adoption included the routine and familiar (intravenous) route of administration and the relatively benign side-effect profile. While several experts mentioned the concerns regarding the unknown duration of responses to brentuximab vedotin, they did not believe that this would significantly impact adoption.
- **Potential for High Impact:** High

Antibody-Drug Conjugate: Trastuzumab Emtansine for Treatment of HER2-Positive Breast Cancer

- **Key Facts:** HER2-positive breast cancer is a subclass of invasive breast cancer characterized by the expression of high levels of the epidermal growth factor receptor (EGFR) family member HER2 and comprises approximately 20% of breast cancer cases. Historically, this cancer has been associated with more aggressive disease and poor outcomes. While the treatment of HER*2*-positive breast cancer has improved with the availability of HER2-targeted therapies such as trastuzumab (Herceptin®, Roche) and lapatinib (Tykerb®, GlaxoSmithKline, Middlesex, UK), many patients' cancers still progress on these treatments, and compounds with improved efficacy and/or efficacy against resistant disease are highly desired. Trastuzumab emtansine (Roche), formerly known as trastuzumab-DM1, is an ADC that couples a HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1). They are coupled in such a way that emtansine is held in a stable inactive form outside of the cell; only upon cellular uptake of the drug conjugate mediated by binding of the antibody to the HER2 receptor is emtansine released and activated. In this way, the cytotoxic activity of emtansine is targeted to cells expressing the HER2 receptor, potentially sparing many normal tissues from the toxic effects of the drug. Trastuzumab emtansine is currently in two phase III clinical trials: (1) versus trastuzumab and a taxane as a first-line treatment for metastatic disease; and (2) versus lapatinib and capecitabine as a second-line treatment for metastatic disease that has progressed after treatment with trastuzumab. In 2010, FDA turned down a request by Roche for accelerated approval of trastuzumab emtansine based on the phase II data in the third-line setting. Roche estimated that a regulatory filing for trastuzumab emtansine in the second-line setting could occur as early as 2012; however, a regulatory filing for the drug as first-line therapy is not anticipated until 2014.
- **Key Expert Comments**: Overall, experts believe that trastuzumab emtansine has significant potential to improve on existing HER2-positive metastatic breast cancer treatments, the shortcomings of which they thought represented a significant unmet need. Experts also thought that the drug's potential to displace current standard of care treatments for HER2-positive

metastatic breast cancer and likely high cost could have significant impacts on the management of these patients.

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

ALK Inhibitor Crizotinib (Xalkori) for Treatment of Nonsmall Cell Lung Cancer

- **Key Facts:** Current chemotherapy options for patients with advanced NSCLC yield a relatively low response rate (25% to 30%) and 2-year survival rates of only 10% to 15%. Therefore, the need for new treatments is significant. In recent years it has become clear that like other cancers, NSCLC is not a single disease, but rather a collection of related diseases with different molecular underpinnings. In particular, 2% to 7% of NSCLC tumors harbor genetic alterations that result in a fusion of the *ALK* gene with a second gene (often *EML4).* These gene fusions can result in production of an constitutively active ALK protein that can drive carcinogenesis. Targeted inhibition of activated ALK is seen by experts as a promising therapeutic target for these individuals. Crizotinib (Xalkori®, Pfizer, Inc., New York, NY) is a small molecule inhibitor of ALK kinase activity taken orally once daily. Two phase III trials of crizotinib in the first- and second-line treatment setting are under way. On August 30, 2011, FDA approved the drug for treatment of patients with locally advanced or metastatic NSCLC that is *ALK*-positive as detected by an FDA-approved companion diagnostic test, the Vysis ALK Break Apart FISH Probe Kit. The drug cost is about $115,000 per patient per year ($9,600 per months) and the test costs about $1,500. Pfizer introduced a plan to help reduce patient out-of-pocket costs and copays for some patients to $100 per prescription for an annual maximum savings of $24,000.
- **Key Expert Comments:** Experts commenting on this topic thought that the availability of an ALK inhibitor and its companion diagnostic test to identify patients who would be more likely to benefit from this treatment represents a significant advance in the treatment options for this patient population. Additionally, experts suggested that the drug's availability would likely necessitate genetic profiling for most or all patients with NSCLC, potentially altering patient management and increasing costs associated with diagnosis and treatment decisions. However, experts noted that the small percentage of patients with NSCLC who are *ALK* mutation-positive would limit overall health impact for all patients with NSCLC.
- **Potential for High Impact:** Moderately high

B-RAF Inhibitor Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

- **Key Facts**: B-RAF inhibitors belong to a growing class of personalized cancer treatments. Use of these treatments is intended for patients whose tumors harbor specific genetic changes that are targeted by the therapies and, therefore, are likely to respond. Identifying the appropriate patients for these therapies requires testing all patients with the cancer to identify the subset of patients for whom such personalized therapy may be appropriate. B-RAF plays a central role in the RAS/MAP kinase signal transduction pathway, which regulates cell growth and cell proliferation. Misregulation of this pathway has been demonstrated to be involved in multiple cancers. In particular, mutant versions of the *B-RAF* gene that encode a constitutively active B-RAF protein (e.g., B-RAF^{V600E}) have been identified in more than half of melanomas analyzed. Activated B-RAF is proposed to lead to hyperactivation of the downstream ERK/MEK/MAP kinase pathway, upon which melanomas may be dependent for growth and survival. Therefore,

the specific inhibition of B-RAF kinase activity is a promising pharmacologic target. Two orally administered small molecule inhibitors of B-RAF kinase activity were considered by experts to have high potential impact: vemurafenib (Zelboraf, Genentech unit of Roche) and dabrafenib (GlaxoSmithKline). Researchers reported that vemurafenib increased overall survival and progression-free survival relative to treatment with dacarbazine. On August 17, 2011, FDA approved vemurafenib for the treatment of patients with unresectable or metastatic melanoma harboring a *B-RAF* mutation as detected by an FDA-approved companion diagnostic test, the cobas 4800 *B-RAF V600* Mutation Test. The cost is about $9,400 per patient per month and the company estimates a treatment course of about 6 months for a total of about $56,400 per patient. Genentech introduced the Zelboraf Access Solutions program to help some patients cover out-of-pocket costs using a special company-issued co-pay card. therapy. The card provides eligible patients with up to $4,000 or $1,500 in co-pay assistance per year. Dabrafenib is currently being studied in a 200-patient, phase III trial with results anticipated by June 2012.

- **Key Expert Comments:** Experts commenting on this topic thought that the availability of B-RAF inhibitors had potential to fundamentally change treatment paradigms for metastatic melanoma because they will split a single syndrome into *B-RAF* mutation-positive and *B-RAF* mutation-negative disease. This will necessitate testing of all patients to determine their *B-RAF* status. Experts opined that while the potential of B-RAF inhibitors is limited by the fact that the vast majority of patients will eventually develop resistance to the therapy, these inhibitors are expected to be a central focus of melanoma treatment and clinical study in coming years. Experts noted that the cost impact is expected to be high because not only will the drug be new, but now all patients with melanoma are expected to be tested to determine their *B-RAF* status.
- **Potential for High Impact:** High

Hedgehog Pathway Inhibitor: Vismodegib

- **Key Facts:** No systemic therapy is approved for basal cell carcinomas that are not suitable for surgery. A potential pharmacologic target for this condition is a signaling pathway known as the Hedgehog pathway, the aberrant regulation of which has been implicated in a number of cancers. In particular, elevated levels Hedgehog pathway activity have been observed in the majority of basal cell carcinomas and preclinical data suggest that inhibition of this pathway could have an antitumor effect. While no Hedgehog pathway inhibitor is available, several are under study in clinical trials, the most advanced of which is vismodegib (Genentech unit of Roche). Vismodegib is an orally available, small-molecule antagonist of a protein (called Smoothened) that is essential for transducing Hedgehog pathway activity. Based on data on 104 patients in a phase II trial showing a 43% response rate for locally advanced disease, 30% response rate for metastatic disease, and 9.5 months progression-free survival, Genentech submitted to FDA an NDA for vismodegib for the treatment of advanced basal cell carcinoma. The agency formally accepted the application and granted it priority review status in November 2011. The most common adverse events reported in the trial included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea. In addition, serious adverse events were observed in 26 patients of which 4 (blocked bile flow from the liver, dehydration with loss of consciousness, pneumonia accompanied by cardiac failure, and pulmonary embolism) were considered vismodegib-related. A decision is expected in March 2012.

- **Key Expert Comments:** Experts commenting on this topic thought that vismodegib had significant potential as a first-in-class agent to affect treatment of basal cell carcinoma. Experts cited the compelling response rates in reported data thus far and a patient population lacking a systemic treatment option as the main factors signaling the potential importance of this drug; however, they wanted to see longer term data and survival data. Experts thought that vismodegib's potential impact on the health system as a whole would be limited by the limited number of patients targeted by this therapy.
- **Potential for High Impact:** Lower range of high impact

mTOR Inhibitors Ridaforolimus and Everolimus for Treatment of Various Cancers

- **Key Facts:** Inhibitors of the mammalian target of rapamycin (mTOR) have been approved for the treatment of various cancers such as renal cell carcinoma, subependymal giant cell astrocytomas associated with tuberous sclerosis, and pancreatic neuroendocrine tumors. Given their demonstrated efficacy in these cancers and the central role that the mTOR pathway plays in fundamental cellular processes related to tumorigenesis, researchers have undertaken a large number of clinical trials involving the use of mTOR inhibitors in the treatment of a wide variety of cancers. Two potential mTOR indications currently under study recently reported results from late stage clinical trials: (1) ridaforolimus (Merck & Co., Inc. Whitehouse Station, NJ, licensed from ARIAD Pharmaceuticals, Inc., Cambridge, MA) for the treatment of soft tissue and bone sarcomas; and (2) everolimus (Afinitor®, Novartis AG, Basel, Switzerland) for the treatment of estrogen receptor (ER)-positive breast cancer.

  In reporting preliminary results on 711 patient trial of ridaforolimus for treatment of soft tissue compared with placebo, researchers indicated achieving a statistically significant 3-week improvement in progression-free survival; results for overall survival were pending at the time this report was compiled. Merck submitted an NDA to FDA for the use of ridaforolimus in the treatment of soft tissue and bone sarcomas in August 2011.

  The clinical trial of everolimus for treatment of ER-positive metastatic breast cancer studied the drug in combination with the steroidal aromatase inhibitor exemestane in patients whose disease had progressed after treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole). In preliminary results from a 705-patient trial, researchers reported that adding everolimus to exemestane resulted in a statistically significant improvement in progression-free survival of about 4 months. Novartis announced plans to submit an NDA by the end of 2011 to FDA for the use of everolimus for treatment of breast cancer. As a drug class, mTOR inhibitors are relatively well tolerated. Commonly reported adverse events included stomatitis/mucositis, rash, and fatigue; however, serious side effects have also been reported such as renal failure, elevated levels of blood glucose and lipids, and immunosuppression (which can lead to increased risk of infections).
- **Key Expert Comments**: Experts commenting on these interventions suggested that the results for progression-free survival were promising for conditions lacking effective treatment options such as advanced soft tissue and bone sarcomas and endocrine therapy-resistant metastatic breast cancer. While experts were optimistic that the observed improvements in progression-free survival might translate to improvements in overall survival, they were eager to see mature overall survival data before claiming that mTOR inhibitors can have a large impact on patient outcomes.

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

Multikinase Inhibitors Vandetanib (Caprelsa) and Cabozantinib for Treatment of Medullary Thyroid Cancer

- **Key Facts:** Medullary thyroid cancer is a rare form of thyroid cancer for which few effective treatment options exist for advanced stages of the disease not amenable to surgical resection. In April 2011, vandetanib (Caprelsa®, AstraZeneca, London, UK) was approved by FDA as the first, and thus far only, medication specifically indicated for treatment of medullary thyroid cancer. Vandetanib is a small-molecule kinase inhibitor with activity against multiple tyrosine kinases that control multiple cancer-related cellular processes. Among vandetanib's targets is the RET (Rearranged during transfection) receptor tyrosine kinase, mutations in which have been linked with both sporadic and familial forms of medullary thyroid cancer. Researchers reported results from a 231-patient trial stating that progression-free survival was longer for patients receiving the drug than for patients in the placebo arm. The prescribing information for vandetanib carries a black box warning regarding the risks of heart rhythm abnormalities (QT prolongation, torsades de pointes) and sudden death. Only prescribers and pharmacies certified through the manufacturer's Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, are able to prescribe and dispense vandetanib. Studies of additional tyrosine kinase inhibitors with anti-RET activity are also under way for the treatment of medullary thyroid cancer, and results from a late-stage clinical trial of cabozantinib (Exelixis, South San Francisco, CA) were recently reported. The developer recently announced that cabozantinib had met its primary endpoint of improving progression-free survival compared with placebo. An NDA was expected to be completed in the first half of 2012.
- **Key Expert Comments:** Experts commenting on these inhibitors thought that the availability of vandetanib for the treatment of metastatic medullary thyroid cancer represented a significant improvement in available treatment options for this condition. However, experts believe that the small patient population eligible for this treatment and the routine nature of its administration would limit vandetanib's overall impact.
- **Potential for High Impact:** Lower range of high impact

Radium 223 (Alpharadin) for Treatment of Bone Metastasis

- **Key Facts:** Many cancers, in particular breast, prostate, and lung cancer, metastasize to bone, causing complications such as chronic pain and skeletal-related events (e.g., fractures) that adversely affect both patient quality of life and survival. Among the current treatment options for bone metastases are radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases. Preferential accumulation of the radioactive compound purportedly functions to concentrate the radiation dose at the target bone metastases. While currently available radionuclides have shown efficacy in the palliation of bone pain, the type of radiation that they emit penetrates tissues deeply enough to negatively affect the bone marrow, which limits the deliverable dose and restricts their use to one of symptom palliation. Alpharadin® (a preparation of radium-223 developed by Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany) is a novel bone metastasis-targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than the radiation generated by currently available radiopharmaceuticals, potentially reducing the side

effect profile of treatment and more effectively targeting bone metastases. Recent results reported by the developers from a randomized, double-blind trial of 900 patients with CRPC with skeletal metastases who were ineligible for initial treatment or further treatment with docetaxel indicated overall increased survival of almost 3 months in the Alpharadin group compared to placebo. An independent committee recommended that the trial be stopped early because of the positive results. Treatment with Alpharadin was also reported to have improved secondary endpoints such as the time to first skeletal-related event, percentage of patients achieving normalized total alkaline phosphatase levels, and time to biochemical disease progression. Side effects were reported as benign, suggesting that it could potentially be used in combination with other prostate cancer treatments. Alpharadin was granted fast track status by FDA for the treatment of CRPC with bone metastases. The developers expect to submit an NDA for this indication sometime in 2012. Alpharadin is also in phase II study for the treatment of breast cancer-related bone metastases.

- **Key Expert Comments:** Experts commenting on this topic thought that Alpharadin had significant potential to improve on current treatments for bone metastases, particularly for patients with prostate cancer. While experts thought Alpharadin would likely be widely adopted for this indication, the highly similar nature of Alpharadin to existing treatments suggested to experts that its adoption would have limited impact on health care system infrastructure and practices.
- **Potential for High Impact:** Moderately high

Device/Procedure Interventions

Intervention

Sedasys computer-assisted sedation system for automated administration of propofol

The majority of conscious sedation in the United States is performed using a combination of benzodiazepine and an opiate.[1] However, compared with benzodiazepine/opiate-mediated sedation, propofol has the advantage of having a more rapid onset and a more rapid termination of the sedative effect, leading to faster patient recovery from sedation.[2] It is often used during short procedures such as colonoscopy. Propofol also has higher potency than benzodiazepines/opiates and, therefore, carries an increased potential for the unintended induction of general anesthesia and/or hemodynamic and respiratory depression.[1] In addition, while pharmacologic antagonists can reverse the effects of benzodiazepines and opiates, no such antagonist is available for propofol.[1] Therefore, the current labeling approved by the U.S. Food and Drug Administration (FDA) for propofol states that propofol "should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure."[3]

The Sedasys® computer-assisted personalized sedation system (Ethicon Endo-Surgery, a unit of Johnson & Johnson, Inc., New Brunswick, NJ) is intended to allow clinicians untrained in general anesthesia administration to administer propofol for patient sedation during colonoscopy and esophagogastroduodenoscopy procedures.[4] Sedasys is intended to deliver both propofol and oxygen to a patient in an automated fashion to achieve the desired level of mild to moderate sedation.[4] By continuously adjusting the rates of propofol infusion and oxygen flow in response to patient vital signs and responsiveness, the Sedasys system purports to avoid too much or too little sedation.[2]

Results from a clinical trial comparing patients sedated with propofol delivered by Sedasys (n = 496) to patients sedated with current standard of care, benzodiazepine/opioid (n = 504), during routine colonoscopy or esophagogastroduodenoscopy procedures were published in 2010.[5] The trial compared area under the curve (AUC) of oxygen desaturation, patient satisfaction, clinician satisfaction, sedation level, and patient recovery time between the two arms. Researchers reported that AUC of oxygen desaturation was significantly lower in the Sedasys arm than the standard-of-care arm (23.6 s.% vs. 88.0 s.%; $p = 0.028$). Researchers also reported that both patient and clinician satisfaction were rated as higher in the Sedasys arm than the standard-of-care arm ($p = 0.007$ and $p < 0.001$, respectively). Lastly, researchers reported that patients in the Sedasys arm recovered more quickly from sedation than patients in the standard-of-care arm ($p < 0.001$). While the majority of patients in both arms achieved mild to moderate sedation, researchers reported that a higher percentage of patients receiving Sedasys-administered propofol sedation experienced deep sedation/general anesthesia (3%) compared with patients receiving benzodiazepine/opiate sedation (1%).[4]

Based on these results, Ethicon submitted a premarket approval (PMA) application to FDA in March 2008. In February 2010, FDA denied Ethicon's PMA application because of concerns regarding the following:[6]

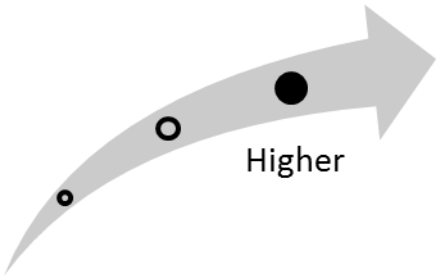
- The increased incidence of deeper-than-intended sedation and general anesthesia observed for patients sedated with the Sedasys system in the system's pivotal clinical trial.
- The Sedasys system's pivotal trial compared Sedasys-based propofol sedation with the current standard of care for benzodiazepine/opioid sedation rather than the standard of care for propofol delivery and, therefore, did not address the relative safety of the Sedasys system for its proposed indication of propofol delivery.

Ethicon appealed the denial of its PMA application, and this request was granted by FDA in November 2010.[7] The FDA Medical Devices Dispute Resolution Panel was scheduled to meet December 14, 2011[8] about the appeal, but the company and FDA reached agreement about two weeks before that meeting to reopen the PMA application.

Clinical Pathway at Point of This Intervention

During endoscopy procedures, patients are often sedated to ensure their comfort and the success of the procedure.[1] Diagnostic and uncomplicated endoscopic procedures (e.g., colonoscopies) are usually performed with the patient under moderate sedation (previously known as conscious sedation), in which the patient retains the ability to make purposeful responses to tactile or verbal stimuli and retains normal cardiovascular function and spontaneous ventilation.[1] Most endoscopic sedation procedures are performed by endoscopists and endoscopy nurses and use either benzodiazepine alone (e.g., midazolam, diazepam) or benzodiazepine in combination with an opiate (e.g., meperidine, fentanyl) to induce moderate sedation.[1] Approximately 25% of endoscopies performed in the U.S. use propofol; however, the current propofol labeling requires that it be administered by physicians trained in the administration of general anesthesia.[9] The Sedasys system could potentially allow administration of propofol by physicians or nurses who are not trained in the administration of general anesthesia.

Figure 1. Overall High Impact Potential: Sedasys computer-assisted sedation system for automated administration of propofol



Overall, experts commenting on this intervention believe that the Sedasys system has significant potential for controversy in that it would disrupt the current methods of delivering propofol-mediated sedation, which could also have a big impact on the way colonoscopy centers operate. However, experts were unsure whether the potential benefits of wider access to propofol-mediated sedation were significant enough to offset the concern about potential oversedation of patients in a setting without an anesthesiologist present, and thus adoption might be hindered by these concerns. If adopted, use of the system could significantly change costs associated with anesthesiologist-administered sedation. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Nine experts, with clinical, research, and health systems backgrounds, provided perspectives on this topic.[10-18] Experts were divided on whether the Sedasys system addressed a significant unmet need. The majority of experts did not think that there was a significant unmet need, citing the ability of anesthesiologists and nurse anesthetists to administer propofol-mediated sedation and relegating the unmet need to one of cost savings and improved throughput. However, two experts speaking from a clinical perspective suggested that the inability of clinicians untrained in the administration of general anesthesia to administer propofol-mediated sedation was a significant impediment to offering patients comfortable anesthesia for short procedures. One of these experts cited the lack of a sufficient number of anesthesiologists or nurse anesthetists to offer propofol sedation to all patients.

Irrespective of their opinions on the need for such a device, the majority of experts were cautious regarding the device's efficacy. Multiple experts seconded the concern raised by FDA that Sedasys-based propofol sedation should have been compared with standard-of-care delivery of propofol sedation rather than standard-of-care delivery of benzodiazepine/opiate sedation in clinical trials.

Additionally, multiple experts noted the increased potential for oversedation when using propofol, and one clinical expert suggested that the 3% over-sedation rate reported in the Sedasys clinical trial was too high to allow widespread use of the device. These concerns over the risk profile associated with automated administration of propofol highlight the fact that the debate over replacement of a trained anesthesiologist with the automated Sedasys system has significant potential for controversy.

Multiple experts suggested that gastroenterologists would likely be very enthusiastic about adopting use of the Sedasys system provided that per-patient costs were significantly less than having an anesthesiologist present. These same experts believe that anesthesiologists would likely claim that only clinicians trained in the administration of general anesthesia can safely administer propofol and, therefore, would resist adoption of the Sedasys system. These experts questioned whether a single physician could handle both the endoscopic intervention and attend to any anesthesia complications at the same time. Additional potential barriers to adoption of the Sedasys system, such as the requirement for training of staff in airway management and the upfront capital equipment costs of obtaining the system, were mentioned by experts but not seen as a significant impediment to adoption.

While experts' concerns regarding the method of propofol administration persist, their consensus is that patients prefer propofol-mediated sedation to benzodiazepine/opiate-mediated sedation because of increased comfort during the procedure, reduced recovery time, and less of a hangover effect from sedation. Therefore, a device such as Sedasys, which has the potential to increase access to propofol-mediated sedation by increasing the diversity of facilities that provide this sedation option and/or reducing the cost of the procedure, could improve patient satisfaction. Some experts suggested that this increased patient satisfaction could improve screening rates for conditions such as colorectal cancer by increasing the likelihood that a patient would be willing to undergo endoscopy. Conversely, multiple experts cautioned that Sedasys-mediated propofol sedation may be viewed as less safe than anesthesiologist-mediated propofol sedation, potentially limiting patient acceptance. However, other experts noted that patients may not appreciate the difference between the delivery methods.

Intervention

Transoral robotic surgery (TORS) for treatment of mouth and throat tumors

Patients presenting with early stage (T1 or T2) mouth or throat cancer are typically treated with surgical resection of the tumor. Adjuvant radiation therapy (external or brachytherapy) may also be prescribed as indicated. Conventional open surgery has been the standard approach to treating many head and neck cancers. However, open surgery is associated with significant pain, trauma, possible disfigurement, a long recovery, and damage to surrounding organs and nerves.[19] Conventional open surgery often requires an ear-to-ear incision across the throat or splitting of the jaw, either of which can lead to speech and/or swallowing difficulties in patients who undergo the procedures.[19] Other treatment options include transoral laser microsurgery, which may be limited by line-of-sight issues, poor tissue manipulation, and the inability to reconstruct or close the surgical area, and conventional transoral endoscopic surgery.

Minimally invasive TORS using the da Vinci® robotic surgical system is intended to enable the surgeon to access the surgical site through the mouth.[19] This site of entry requires no large incision to perform throat cancer surgery, a category of conditions that includes tonsil cancer, laryngeal cancer, pharyngeal cancer, and tongue cancer.[20]

The da Vinci system consists of a surgeon console, a computerized control system, a patient side cart with two or three instrument arms, and an endoscope with a fiber-optic camera.[21] One arm holds the endoscope. The other arms hold various interchangeable, proprietary surgical tools that perform grasping or cutting functions. The surgeon sits at a control console in the operating room several feet away from the patient table and views the patient in real time on a monitor that shows the surgical field through a video camera mounted on one of the robotic arms.[21] Computer digitization allows filtering of hand movements to eliminate minute tremor and scaling of larger movements to a microscopic level, thereby improving precision and making microsurgery with endoscopic instruments possible.[21] The latest models feature a three-dimensional (3-D), high-definition vision system with up to 10 times magnification, digital zoom, adjusted aspect ratios for more viewing area, an integrated fourth robotic arm, and a motorized patient cart. Potential benefits of this approach include a definitive treatment option with no ear-to-ear incision, less pain, a shorter hospital stay, less risk of infection, less blood loss and need for transfusion, less scarring, faster recovery, and a quicker return to normal daily activities.[22]

Investigators publishing results of a number of small clinical studies that evaluated TORS for the treatment of head and neck cancers suggested that TORS might improve health outcomes, including surgical excision of head and neck tumors with negative margins, in addition to minimizing blood loss and postoperative complications, preserving swallowing function, and minimizing decannulation time.[23-30]

In December 2010, FDA granted clearance to market the da Vinci Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA) for use in TORS procedures for benign as well as malignant T1 and T2 tumors.[31] Contraindications for the TORS procedure include any and all factors that would make any type of surgery unadvisable.[32]

The manufacturer cautions that TORS procedures should be performed only by surgeons who have received manufacturer-specific training and additional proctored training in the operating room during TORS cases.[32] Surgeons must also be trained in open surgery for head and neck cancers in the event

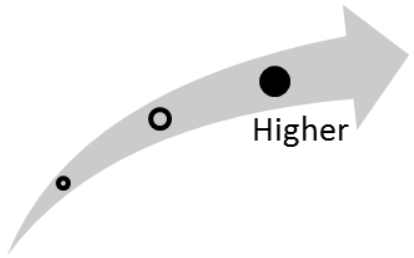
that an ongoing TORS procedure must be converted to open surgery. Members of the surgical team assisting during the procedure also require specialized training on use of the system.

No specific safety concerns for the TORS procedures have been reported in results of early studies. However, physician skill in performing the procedure is believed to be a key factor to successful outcomes from TORS.

Clinical Pathway at Point of This Intervention

According to guidelines from the National Comprehensive Cancer Network, a patient in whom early stage (T1 or T2) mouth or throat cancer has been diagnosed is typically treated with surgical excision of the tumor. Adjuvant radiation therapy (external or brachytherapy) may also be prescribed as indicated.[33] One of several surgical approaches may be used—open surgery, transoral laser microsurgery, or conventional transoral endoscopic surgery. TORS using the da Vinci robotic surgery system is an emerging surgical option for resection of mouth and throat tumors.

Figure 2. Overall High Impact Potential: Transoral robotic surgery (TORS) for treatment of mouth and throat tumors



Overall, the experts providing comments on this procedure believe that TORS is a minimally invasive option that offers better visualization and tissue manipulation than conventional transoral surgical techniques. Experts asserted that this might lead to improved patient outcomes including reduced recovery time and blood loss, improved function, and improved cosmesis and quality of life after surgery. However, experts indicated that adoption of TORS could be hindered by significant equipment acquisition and maintenance costs, staffing and training costs that are not reimbursed beyond the standard reimbursement for the surgery, and the potential for operating room scheduling issues that can arise from longer procedure times than for open surgery. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Six sets of comments from experts were received for this intervention.[34-39] Experts offered perspectives from clinical, research, health systems, and health administration backgrounds.

Overall, experts concurred that many cases of head and neck cancer present an important unmet need for new minimally invasive surgical treatment options to reduce recovery time and improve function and quality of life after surgery. All experts except one generally agreed that TORS might provide a less invasive and more precise alternative to conventional head and neck surgical procedures; thus, it has the potential to improve health outcomes after surgery. One expert with an independent research perspective remained unconvinced that TORS could significantly improve clinical outcomes compared with conventional endoscopic surgery. Two clinical experts had experience performing TORS procedures and believe that TORS offered benefits in terms of surgical field visualization, tissue manipulation, and ability to reconstruct or close the surgical area compared with other currently available minimally invasive treatment options (e.g., transoral laser microsurgery).

Most experts believe that adoption of TORS would not result in a significant change in our understanding of the disease or condition. However one health systems expert stated that during TORS, the da Vinci system maintains complete video, related imaging, and instrument movement from surgeries. Such information could be decoded and made available to the research community to increase the understanding of management of head and neck tumors. Overall the experts commented

that TORS would lead to mild disruptions in treatment and management paradigms. These disruptions would were mitigated by factors that included limited diffusion of the procedure and the fact that surgical resection of head and neck tumors is already an integral part of disease management.

Experts were split regarding the potential time it could take for surgeons to become proficient in TORS. All but one of the experts stated that the da Vinci system has been well documented as having a steep learning curve, especially if the surgeon has not performed other procedures on the system. Highly trained surgical teams are also required. However, the one outlier, a clinical expert, stated that surgeons familiar with transoral laser microsurgery would be able to learn the procedure quickly.

Many of the experts also identified high costs of the robotic system and need for larger surgical suites as issues that present a potentially high impact on infrastructure and process, which may pose barriers to diffusion or increase costs. However, one clinical expert agreed that although those factors might pose a barrier to the diffusion of the new surgical systems, TORS is a relatively rare procedure, and the procedure itself would not justify the purchase of a new surgical system. The expert stated that TORS procedures should be limited to facilities that already perform robot-assisted surgery for other cancers, so the equipment could be shared among specialties. Physicians and surgical teams could be cross-trained on TORS, which would minimize many barriers to diffusion at certain health care facilities. Additionally, the expert stated that some of the costs associated with the procedure would be offset by shorter hospital stays and fewer complications after surgery.

Overall, experts thought that TORS offered better visualization and tissue manipulation than conventional transoral surgical techniques and might lead to improved patient outcomes including reduced recovery time and blood loss, improved function, and improved quality of life following surgery. However, adoption of TORS could be hindered by controversies related to significant equipment acquisition, maintenance, staffing, and training costs that will not be reimbursed, and the potential for operating room scheduling issues because of decreased patient throughput and competition among specialties for use of the robotic system.

Hormone Intervention

Intervention

Abiraterone (Zytiga) for treatment of metastatic castration-resistant prostate cancer

Men with metastatic prostate cancer that is insensitive to androgen withdrawal have few treatment options and poor prognosis; recently reported survival time for this patient population treated with current therapies is approximately 22 months.[40] Therefore, novel treatments for this stage of prostate cancer are highly desired, especially for patients who have progressed following treatment with the first-line metastatic, castration-resistant prostate cancer (mCRPC) treatment, docetaxel.

mCRPC can progress in presence of castration-level androgens and, therefore, appears to be independent of androgen signaling, which is the primary driver of prostate tumor growth. However, recent research suggests that these cancers may still depend on androgen receptor signaling, which may be activated by residual androgens produced in the prostate tissue of patients who have been surgically or medically castrated.[40] Therefore, further inhibition of androgen signaling may have activity as an mCRPC treatment. One compound intended to function by reducing levels of residual androgens is abiraterone (Zytiga®, Centocor Ortho Biotech, Inc., which has been acquired by Janssen Biotech, Inc., a unit of Johnson & Johnson Inc., New Brunswick, NJ). Abiraterone is an orally administered pregnenolone analog that acts as an inhibitor of the enzyme CYP17, a rate-limiting enzyme involved in androgen biosynthesis.[40] Abiraterone has been under study for both the treatment of symptomatic mCRPC that has progressed after treatment with docetaxel (NCT00638690) and the treatment of asymptomatic or mildly symptomatic mCRPC that is systemic-chemotherapy naïve (NCT00887198).

On April 28, 2011, Centocor Ortho Biotech announced that FDA approved abiraterone (in combination with prednisone) for the treatment of mCRPC that had previously been treated with docetaxel.[41] This approval was based on results from a phase III, randomized, placebo-controlled trial that showed that overall survival in the abiraterone plus prednisone arm was 15.8 months versus 11.2 months in the placebo plus prednisone arm (hazard ratio [HR] 0.74).[41] Researchers reported that common adverse events associated with abiraterone treatment were hypertension, hypokalemia, and edema, which they reported to be manageable through treatment.[40] Results for trial NCT00887198 studying abiraterone in the treatment of asymptomatic mCRPC were not expected to be finalized until 2014.

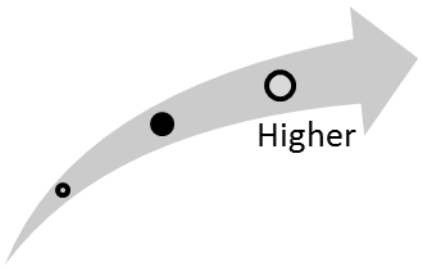
Additional compounds that target androgen signaling in mCRPC are currently in development, including a second CYP17 inhibitor (Orteronel [TAK-700], Millennium Pharmaceuticals unit of Takeda Pharmaceutical Co., Ltd., Osaka, Japan) and a novel androgen receptor signaling inhibitor (MDV3100, Medivation, Inc., San Francisco, CA).[42,43] Both compounds are currently in phase III clinical trials for both chemotherapy-naïve and postchemotherapy mCRPC. Medivation recently reported preliminary results from a 1,199-patient phase III trial in the postdocetaxel setting. Compared to patients treated with placebo, patients treated with MDV3100 were reported as exhibiting a 4.8-month increase in duration of overall survival (18.4 months vs. 13.6 months (HR 0.631).[44]

Clinical Pathway at Point of This Intervention

Traditionally, androgen deprivation therapy either by bilateral orchiectomy (surgical castration) or luteinizing hormone-releasing hormone agonist (medical castration) has been used to treat advanced prostate cancer when surgery and/or radiation are not indicated.[45] Yet, few options are available for patients whose cancer becomes resistant to androgen deprivation and progresses to mCRPC. mCRPC that is not symptomatic or only mildly symptomatic may be treated with the autologous cancer vaccine sipuleucel-T (Provenge®, Dendreon Corp., Seattle, WA).[45] For patients with more advanced,

symptomatic mCRPC the standard first-line treatment is systemic chemotherapy with the taxane docetaxel.[45] Lastly, for patients whose disease progresses after treatment with docetaxel, treatment with the recently approved taxane cabazitaxel in combination with prednisone may be used.[45] Abiraterone represents a potential treatment alternative to cabazitaxel in the postdocetaxel setting and could be used as an alternative to or in sequence with the immunotherapy sipuleucel-T in the predocetaxel/chemotherapy setting.

Figure 3. Overall High Impact Potential: Abiraterone (Zytiga) for treatment of metastatic castration-resistant prostate cancer



Overall, experts commenting on this intervention were quite positive regarding abiraterone's potential to improve both quality and quantity of life for patients diagnosed with mCRPC; however, some experts pointed out that the demonstrated improvement in survival duration is marginal (a few months) in patients whose disease has not responded to first-line chemotherapy. They noted that results from a study of patients with earlier stages of mCRPC are highly anticipated. Based on this input, our overall assessment is that this intervention is in the moderate range of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[46-52] Experts uniformly indicated a high unmet need for effective treatments for mCRPC, a need that abiraterone proposes to address. The need is high because few treatment options are available to these patients, and survival rates are low and of short duration. In particular, one clinical expert pointed to a significant need for therapies such as abiraterone in asymptomatic mCRPC for which current treatments are currently difficult to administer and/or expensive. Similarly, experts also concurred that the scientific rationale behind limiting residual androgen production in mCRPC seemed to be valid. One clinical expert suggested that the success of interfering with androgen signaling in mCRPC could lead to a shift in the understanding of disease progression.

Experts commented that they did not expect abiraterone use to cause a significant change to prostate cancer care; rather, it would be used in place of or after current therapies. One clinical expert noted that the androgen receptor antagonist, ketoconazole, though never approved for a prostate cancer indication, has been used in a similar manner to that proposed for abiraterone. Additionally, experts did not believe that abiraterone would cause a significant shift in care setting, health care staffing, or health care facility infrastructure requirements because of its nature as an orally administered medication. They did believe that it would increase costs of care by adding an option after other options had been exhausted. The estimated cost of treatment is about $40,000 per patient per year, which some experts thought was not a tremendous increase compared with sipuleucel-T's cost of $93,000 per year and cabazitaxel, which costs more than abiraterone but not as much as Provenge. Sipuleucel-T is labeled for use in a different patient population; however, physicians are already employing off-label use of abiraterone before chemotherapy as an alternative to sipuleucel-T or in sequence with it.[53]

While several experts noted that treatment with abiraterone resulted in only a modest increase in survival, experts agreed that it would likely be adopted by patients and physicians because of its ease of use and low side effect profile relative to chemotherapy. One clinical expert noted that the potential for adverse events associated with adrenal androgen production may dissuade some physicians and patients from use.

Overall, experts were quite positive regarding the potential for abiraterone to improve both quality and quantity of life for patients with mCRPC; however, the demonstrated improvement in survival duration is marginal in patients whose disease has failed to respond to first-line chemotherapy. The results from a study of patients at earlier stages of mCRPC are highly anticipated.

Immunotherapy Intervention

Intervention

Ipilimumab (Yervoy) for treatment of metastatic melanoma

According to the American Academy of Dermatology, more than half of all new cases of melanoma in the United States in 2010 were invasive at the time of diagnosis.[54] Until recently, guidelines from the National Comprehensive Cancer Network indicated that no clearly optimal treatments for metastatic melanoma were available, and there was little consensus on standard therapy.[55] The recent approval of ipilimumab (Yervoy™, Bristol-Myers Squibb, New York, NY) and vemurafenib for treatment of metastatic melanoma have provided the first treatments that generate any improved survival for this patient population; the improvement is, on average, 2 to 4 months.

Ipilimumab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody intended for treatment of unresectable or metastatic melanoma. Ipilimumab is a fully human, monoclonal antibody that is purported to exert its effects by enhancing T-cell antitumor responses by targeting CTLA-4, an antigen that downregulates T-cell replication and activation by binding to CD80 and CD86 antigens on the surface of T cells, preventing them from receiving stimulatory signals. By inhibiting the action of CTLA-4, ipilimumab is believed to increase T-cell activity, resulting in increased antitumor responses generated by the patient's immune system.[56,57]

In a clinical trial, patients with unresectable stage III or IV melanoma (n = 676) whose disease had progressed during therapy were randomly assigned to receive ipilimumab plus an experimental peptide vaccine gp100 (n = 403), ipilimumab alone (n = 137), or gp100 alone (n = 136). Ipilimumab, at a dose of 3 mg/kg of body weight, was administered with or without gp100 every 3 weeks for up to four treatments (induction). The median overall survival was 10.0 months among patients receiving ipilimumab plus gp100, compared with 6.4 months among patients receiving gp100 alone (hazard ratio [HR] for death 0.68; p <0.001). The median overall survival with ipilimumab alone was 10.1 months (HR for death compared with gp100 alone 0.66, p = 0.003).[58] In March 2011, FDA granted Bristol-Myers Squibb marketing approval of ipilimumab for treatment of advanced melanoma as a second-line therapy.[59]

Ipilimumab is also under study in treatment-naïve metastatic melanoma.[60] A 502-patient phase III clinical trial is investigating the efficacy of ipilimumab in combination with the standard first-line chemotherapy agent dacarbazine compared with dacarbazine plus placebo in treating metastatic melanoma. Results published in June 2011 indicated that treatment with ipilimumab plus dacarbazine exhibited a small but statistically significant improvement in the duration of overall survival compared with dacarbazine alone (11.2 months vs. 9.1 months).[60] Estimated survival rates of the ipilimumab-dacarbazine and dacarbazine-placebo groups were 47.3% and 36.3% at 1 year, 28, 5% and 17.9% at 2 years, and 20.8% and 12.2% at 3 years (HR for death with ipilimumab-dacarbazine 0.72, p <0.001).[60]

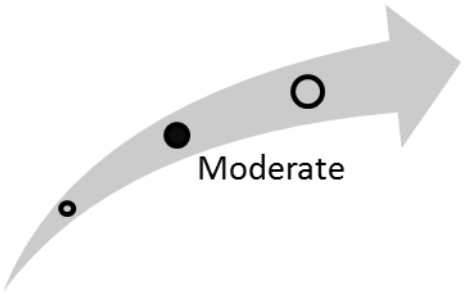
The drug's estimated per patient cost is $120,000 for a full course (4 infusions). The company initiated a program to assist patients in paying so that patient out-of-pocket costs do not exceed $5,000 per year. Ipilimumab has a black box warning regarding the development of fatal immune-mediated adverse reactions due to T-cell activation and proliferation, which may involve any organ system; however, the most common reactions include dermatitis, endocrinopathy, enterocolitis, hepatitis, and neuropathy.[61]

Clinical Pathway at Point of This Intervention

Patients in whom disseminated/unresectable metastatic melanoma has been diagnosed are typically treated with one of a number of systemic therapies and/or radiation therapy.[62] Standard systemic therapies include ipilimumab, vemurafenib (for patients whose melanoma harbors an activating mutation in the *B-RAF* gene), dacarbazine, temozolomide, high-dose interleukin-2, or paclitaxel with

or without cisplatin or carboplatin.[62] Patients maintaining sufficiently good health to undergo additional treatments may be treated sequentially with additional treatments.[62] Ipilimumab, along with vemurafenib, have become standard first-line options in the treatment of disseminated metastatic melanoma.[62]

Figure 4. Overall High Impact Potential: Ipilimumab (Yervoy) for treatment of metastatic melanoma



Experts commenting on this intervention noted that although ipilimumab was capable of extending overall survival in some advanced melanoma patients; the increase in survival time demonstrated in trials was an average of 4 months. Thus, the impact on health outcomes is moderate. Nonetheless, experts noted that this is one of few therapies that has demonstrated any survival benefit in this patient population. Clinical experts' enthusiasm for this therapy might be tempered by the possibility of fatal immune reactions in patients and the high cost of the therapy. In terms of cost and adverse events, the potential impact in this patient population could be high. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered comments on this intervention.[63-69] All experts concurred that advanced melanoma had no standard treatment option that improved overall survival until the development of ipilimumab (and the B-RAF inhibitor vemurafenib), and that ipilimumab fills an important unmet need for new therapies. Experts also agreed that the underlying theory behind ipilimumab is sound. However, they were cautious about the ability of ipilimumab to significantly improve health outcomes. Although ipilimumab was the first agent to demonstrate an improvement in overall survival of patients in whom metastatic melanoma has been diagnosed, experts noted that the treatment added only a median of 4 months to patients' lives and that the potential for biologic-induced, life-threatening autoimmune reactions in some patients is a concern.

In general, experts agreed that, as a new therapeutic option, ipilimumab might alter treatment and management models for patients with advanced melanoma. In particular, one clinical expert expected many aspects of management and treatment of patients with melanoma to change with the availability of ipilimumab. This expert stated that ipilimumab has the potential to induce durable, though low response rates, which will change how oncologists view response rates and how clinicians evaluate patients to determine whether a treatment is working. Additionally, clinical experts stated that physicians outside academic settings might use ipilimumab as first-line therapy, even though it is approved for use only as second-line therapy, because clinicians were previously limited to chemotherapy or referral to a melanoma center for interferon-based treatment or clinical trials. However, one of these clinical experts also suggested that because ipilimumab appeared to benefit only a subset of patients, it is unlikely that the treatment would become standard of care for all patients with metastatic melanoma. This expert noted that efforts are ongoing to identify patient subgroups most likely to benefit from ipilimumab, as are efforts to investigate ipilimumab administered in combination with other agents (e.g., B-RAF inhibitors). One clinical expert also expected patient interest in ipilimumab to be high, because many patients were requesting it prior to its approval because of news articles they read that reported a survival benefit. This expert also stated that oncologists are not accustomed to seeing the severe immune adverse events associated with ipilimumab therapy and that patients will need to be educated to report seemingly mild adverse events to their physicians. Multiple

experts noted that the manufacturer has provided a significant amount of information on managing the potential adverse events to physicians and patients.

The experts agreed that ipilimumab would likely add to the cost of care. Some experts also stated that the cost-benefit ratio combined with the potential for life-threatening adverse events may lead to controversy regarding the drug and barriers to its acceptance. Nevertheless, because of limited treatment options, ipilimumab is expected to be widely accepted by many patients and physicians.

Radiation Therapy Interventions

Intervention

Hypofractionated whole-breast radiation therapy for breast cancer

Standard treatment for early-stage breast cancer consists of breast conservation through surgical lumpectomy (removal of the breast tumor and affected regional lymph nodes) followed by 5 to 7 weeks of daily external beam radiation therapy (EBRT) of the entire breast to destroy any remaining tumor cells.[70] While EBRT is the current standard of care, only about 30% of women currently complete the full 5- to 7-week prescribed course of EBRT. Convenience, travel, and required time commitment are reasons given for nonadherence.[70]

Researchers have begun to examine whether the same dose of radiation typically administered in EBRT can be delivered over a shorter period with similar outcomes. This abbreviated treatment schedule is called hypofractionated external beam radiotherapy (HERT), also known as accelerated whole-breast irradiation therapy. By shortening the duration of treatment and/or number of treatments, HERT has the potential to improve patient adherence to the treatment regimen.[70]

A typical course of conventional EBRT comprises low-dose radiotherapy of 2 Gray (Gy) per fraction for 25 fractions (total dose 50 Gy) delivered over 5 to 7 weeks.[70] Current studies of whole-breast HERT use doses of 2.5 Gy to 3 Gy per fraction for 13 to 16 fractions delivered over 3 weeks. Large, ongoing clinical studies are testing incrementally higher doses of up to 6 Gy per fraction in 5 to 10 fractions (total dose 60 Gy).[70]

In 2010, results from a randomized, controlled trial of 1,234 patients performed by the Ontario Clinical Oncology Group comparing a HERT treatment protocol (42.5 Gy in 16 fractions over 22 days) to conventional EBRT (50 Gy in 25 fractions over 35 days) were published.[71] Researchers reported that HERT and EBRT exhibited similar 10-year local recurrence rates (6.7% and 6.2%, respectively). Long-term studies of morbidity of the skin, soft tissue, and heart beyond 10 years after treatment are ongoing in this patient population.[72] Additional trials performed by the United Kingdom's Standardisation of Breast Radiotherapy (START) trial group were published in 2008. Researchers reported that in the START trial A, conventional ERBT, a HERT protocol of 41.6 Gy in 13 fractions over 35 days, and a HERT protocol of 39 Gy in 13 fractions over 35 days exhibited 5-year recurrence rates of 3.6% (n = 749), 3.5% (n = 750), and 5.2% (n = 737), respectively. They reported that in the START trial B, conventional ERBT and a HERT protocol of 40 Gy in 15 fractions over 21 days exhibited 6-year recurrence rates of 3.3% (n = 1,105) and 2.2% (n = 750), respectively.

Based on the results from these and other trials, the American Society for Radiation Oncology formed a task force to generate guidelines for whole-breast irradiation fractionation.[73] The task force concluded that data were sufficient to support the use of HERT in patients meeting the following characteristics:

- 50 years of age or older at time of diagnosis.
- Diagnosed with stage T1-T2 N0 breast cancer (tumors less than 50 mm in greatest dimension, exhibiting no evidence of regional lymph node metastasis) treated with breast conservation surgery.
- Have not been treated with systemic chemotherapy.

The task force also concluded that the HERT dosage should be delivered as follows:

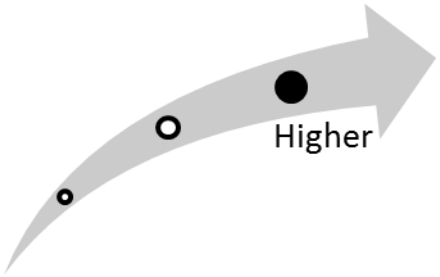
> Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (+/-7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).[73]

While the task force determined that sufficient evidence did not currently exist to recommend the use of HERT in patients who do not satisfy these criteria, the task force did not explicitly prohibit or oppose the use of HERT for these patients.[73] Additional and ongoing studies may clarify the utility of HERT in these patients.

Clinical Pathway at Point of This Intervention

Patients who undergo lumpectomy (breast conservation surgery) for treatment of early stage breast cancer require treatment with radiation therapy following surgery to achieve equivalent outcomes to patients undergoing mastectomy.[74] After surgery, the patient may undergo daily whole breast EBRT over the course of 5 to 7 weeks.[74] Alternatively, some patients with early stage breast cancer may be eligible for a different form of radiation therapy called accelerated partial breast irradiation (APBI) in which the tumor excision site is irradiated using one of a number of mechanisms (e.g., interstitial brachytherapy, intraoperative low-energy x-rays, intraoperative electrons, balloon brachytherapy, external-beam conformal radiation therapy).[74] HERT represents an emerging third radiotherapy alternative for this patient population.[73,74]

Figure 5. Overall High Impact Potential: Hypofractionated whole-breast radiation therapy for breast cancer



Overall, experts commenting on this intervention saw significant potential for HERT to improve health outcomes in patients with early stage breast cancer by improving adherence to the recommended radiation therapy regimen, which can be curative if patients complete the full therapy course. However, experts wanted long-term efficacy and safety data (10-year data or longer) to demonstrate equivalency to EBRT before widely adopting HERT, given the efficacy known for current standard radiation therapy regimens among women who complete the regimens. That said, some experts opined that for women in whom EBRT regimens are not feasible because of transportation issues, lost time from work, or other barriers to full adherence to a prescribed EBRT regimen, HERT might provide an option worth considering even in the absence of long-term data. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[75-81] Experts agreed that given the low levels of adherence to the recommended duration of conventional EBRT, the unmet need is significant for alternative breast-cancer radiation regimens that could improve adherence and health outcomes by reducing the time and effort required to undergo treatment. The abbreviated HERT regimen was generally viewed by experts as a valid approach to meeting this unmet need. However, one expert with a research perspective was unsure whether patients were likely to comply even with a shortened 3-week regimen. One clinical expert also noted that while APBI may be able to meet this need for some patients, HERT could potentially address an unmet need for an accelerated treatment program in patients ineligible for treatment with APBI.

While the concept of HERT appeared sound to experts, the majority noted that, in spite of promising initial data, more and longer-term, followup data on efficacy outcomes and adverse events will likely be needed before HERT would supplant standard EBRT. Two clinical experts noted that the long-term survival of many patients with early stage breast cancer will necessitate followup data that

may take 15 to 20 years to collect. However, another clinical expert suggested that the current level of evidence may be acceptable to some physicians, especially for patients who are unlikely to comply with lengthy standard EBRT regimens.

Multiple experts observed that few barriers to the implementation of HERT exist because it would be administered using technology currently used to administer conventional EBRT. In a similar vein, experts noted that adoption of HERT would not be likely to cause significant shifts in care setting, infrastructure, or staffing because of its similarity to EBRT. However, one clinical expert and one expert with a research background noted that HERT could allow more patients to be seen in a given radiation therapy center and, therefore, could place an increased burden on staff required for treatment planning and patient scheduling. On the other hand, higher patient throughput could result in process and system efficiencies and reduced wait times for patients needing radiation therapy.

Experts unanimously saw the potential for HERT to reduce overall health care costs relative to EBRT because of the reduced number of visits for treatment. Multiple experts also noted that HERT could reduce the direct financial burden on treated patients through reduced travel costs and less time missed from work, which could also improve adherence rates.

Intervention

Tumor-treating fields therapy (NovoTTF-100A) for glioblastoma multiforme

In many patients with cancer, the cancer is not adequately controlled using current therapies; therefore, an urgent unmet need exists for new treatment modalities. In particular, patients in whom glioblastoma multiforme (the most common form of brain cancer) has been diagnosed have very poor prognosis and patient quality of life is low during the course of currently employed treatments.[82] Tumor-treating fields (NovoTTF-100A™, Novocure, Ltd., Haifa, Israel) is a new technology that is intended to treat solid tumors using electrical fields. The technology, under study for the treatment of glioblastoma multiforme and NSCLC, was approved by the U.S. Food and Drug Administration (FDA) for the glioblastoma indication in April 2011.

Tumor-treating fields therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively inhibit tumor growth and reduce tumor angiogenesis.[83] Tumor-treating fields are proposed to inhibit rapidly dividing tumor cells by two mechanisms[84]:

- During formation of the mitotic spindle, which is necessary for proper chromosome segregation and progression through mitosis, highly polarized subunits (tubulin monomers) that make up the mitotic spindle become aligned with the electric field, inhibiting their incorporation into the growing spindle.[84]
- During cell division (cytokinesis), the formation of the cleavage furrow results in a nonuniform, electric field in the cell, which causes charged and polar molecules to aggregate at the cleavage furrow. This aggregation can lead to disruption of cell division and cell death.

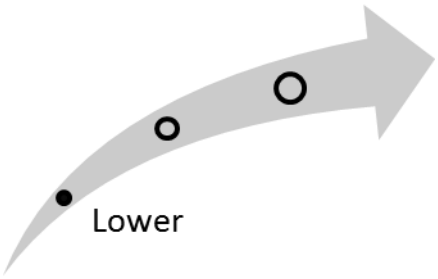
Tumor-treating fields are delivered by a battery-powered portable device that generates the fields via disposable electrodes that are noninvasively attached to the patient's skin around the site of the tumor. The device is used by the patient at home on a continuous basis (from 20 to 24 hours per day) for the duration of treatment, which can last for several months.[84,85]

In April 2011, the NovoTTF-100A device was approved by FDA as a monotherapy for recurrent glioblastoma multiforme.[82] This approval was based on results of a 237-patient randomized, controlled trial comparing tumor-treating fields to the clinician's chemotherapy of choice. Patients in the tumor-treating fields arm of the trial exhibited similar overall survival times to patients in the chemotherapy arm; median 7.8 months (n = 120) versus median 6.1 months (n = 117), respectively.[82] Additionally, patients in the tumor-treating fields arm reported fewer side effects and improved quality of life compared with patients in the chemotherapy arm.[82] Tumor-treating fields therapy continues to undergo study as a treatment for newly diagnosed glioblastoma multiforme in combination with temozolomide.[86] A second version of the device based on the same technology is under study as a second-line treatment in combination with pemetrexed for advanced nonsmall cell lung cancer.[87]

Clinical Pathway at Point of This Intervention

After receiving a diagnosis of high-grade glioblastoma multiforme, patients typically undergo debulking surgery to remove as much of the tumor as possible,[88] followed by radiation therapy and chemotherapy with the alkylating agent temozolomide to try to kill as many residual tumor cells as possible.[89] In many cases glioblastoma multiforme recurs, and patients typically undergo a second round of surgery, radiation therapy, and one of many chemotherapy options (e.g., bevacizumab; erlotinib; imatinib, irinotecan; nitrosoureas; procarbazine; procarbazine, CCNU, and vincristine combination; temozolomide).[85,89]

Figure 6. Overall High Impact Potential: Tumor-treating fields therapy (NovoTTF-100A) for glioblastoma multiforme



Although experts commenting on this intervention were generally enthusiastic about the idea of a therapy with a novel mechanism of action for this type of cancer, and they liked its seemingly low side-effect profile, experts cautioned that the data suggest the therapy exhibits a marginal, if any, survival benefit. They speculated that patients and clinicians might be unlikely to adopt an unorthodox therapy administered at home without more data demonstrating its efficacy, unless it is the only treatment option left for the patient. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on the use of tumor-treating fields for treatment of glioblastoma multiforme.[90-96] While experts agreed that a significant unmet need exists for novel treatments for patients with recurrent glioblastoma multiforme because of their poor prognosis and quality of life with current treatments, experts were less certain that tumor-treating fields therapy could meet that unmet need. Experts believe that the underlying scientific theory behind tumor-treating fields therapy seemed plausible, but noted that current data suggest that the therapy has only marginal survival benefits, if any. One clinical expert noted that the therapies used in the active comparator arm of the clinical trial in the recurrent disease setting had previously demonstrated little to no efficacy and suggested that data from the ongoing trial of tumor-treating fields versus placebo as an adjunct to standard chemotherapy might provide a better assessment of treatment efficacy. One expert with a clinical background noted that a therapy such as tumor-treating fields that has minimal side effects relative to conventional chemotherapy could significantly improve patient quality of life; however, an expert with a research background suggested that further data demonstrating that the therapy does not exert adverse effects on normal tissue are needed. While experts had some doubts about the efficacy of tumor-treating fields, an expert with a research background noted that demonstration of the efficacy of alternating electrical fields in the inhibition of tumor growth could represent a significant shift in our understanding of the disease and potential treatments.

However, even if the therapy is proven to be efficacious, experts believe, some significant barriers exist for clinician and patient adoption. Multiple experts noted that clinicians and patients alike could be reluctant to adopt the use of such a novel, unorthodox technology. Conversely, one expert with a clinical background suggested that patients would be willing to try a treatment that promises to reduce side effect profiles relative to another round of chemotherapy. Lastly, multiple experts noted that at-home treatment would require significant effort on the part of the patient to comply, citing the need to continuously shave electrode attachment sites and maintain device operability for 20 to 24 hours per day.

Screening and Diagnostic Interventions

Intervention

Cologuard fecal DNA test for colorectal cancer screening

Colorectal cancer (CRC) is currently the third most common cancer diagnosed in the United States.[97] CRC tends to be slow to develop, and precancerous lesions and early stage CRCs can typically be treated successfully by surgical resection. Therefore, successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition. However, with current screening options, only a minority of the population adheres to CRC screening guidelines, and approximately 50% of CRCs diagnosed in the U.S. are diagnosed at late disease stages.[97] Therefore, new screening methodologies that could increase the percentage of the population that undergoes recommended CRC screening are highly sought.

The Cologuard® test (Exact Sciences Corp., Madison, WI) is a CRC screening assay that analyzes the stool of patients for the presence of markers indicative of colon cancer or precancer (e.g., adenomatous polyps).[98] Patients provide a stool sample of approximately 8 g, which is analyzed for the presence or absence of three types of markers associated with CRC and precancerous lesions: methylated genes, mutated genes, and hemoglobin.[99,100] This test is the next generation of the currently available ColoSure™ test, which examines only one marker.

The DNA-based markers analyzed in the test are DNA from cells that are sloughed off the colon walls during stool passage and excreted along with the stool.[101] While epigenetic modifications and genetic mutations may occur sporadically in noncancerous cells, only changes that become clonally expanded in a precancerous or cancerous lesion accumulate to a level detectable by molecular assays; therefore, the detection of these epigenetic or genetic changes indicates the potential presence of such a lesion.[102] The genetic changes detected by the Cologuard assay included methylated *NDRG4*, methylated *BMP2*, methylated *vimentin*, methylated *TFP12*, and mutated *KRAS*.[100]

The presence of hemoglobin in stool is indicative of bleeding in the walls of the colon. Because precancerous and cancerous lesions sporadically bleed, detection of hemoglobin in the patient's stool may indicate the presence of a lesion in a manner similar to currently employed fecal occult blood tests (FOBTs).[101]

Exact Sciences had partnered with Laboratory Corp. of America (Burlington, NC) to make an earlier version of its stool DNA test (PreGen-Plus) commercially available as a laboratory-developed test.[103] The test was available in the U.S. beginning in 2003 until its withdrawal from the market in 2008 following U.S. Food and Drug Administration (FDA) reclassification of the test as a medical device, which has different requirements for marketing approval from a laboratory-developed test.[103] A single-marker (methylated vimentin) version of the Exact Sciences fecal DNA assay is currently available as a laboratory-developed test (ColoSure).[97] If the company obtains marketing approval for the Cologuard test, it is anticipated that the ColoSure test will no longer be offered.

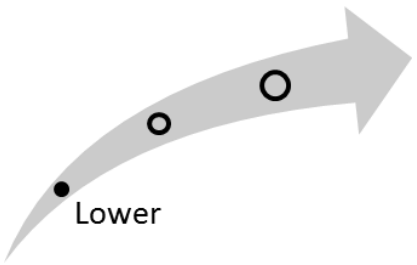
A clinical trial comparing the Cologuard test to colonoscopy began enrolling an anticipated 10,000 patients in July 2011.[104,105] Pilot results for Cologuard were presented in October 2010 for a validation study performed on more than 1,000 stored fecal samples from patients with known positive and negative results for CRC.[105] Researchers reported that Cologuard correctly identified 63.8% of samples from patients with precancerous polyps larger than 1 cm and 85% of samples from patients with CRCs when the assay cutoffs were set to achieve a specificity of 90%.[100]

Clinical Pathway at Point of This Intervention

Several options are currently used for routine CRC screening in the general population of patients with an average risk of developing CRC. These include annual FOBTs, sigmoidoscopy every 5 years,

double-contrast barium enema every 5 years, computed tomography (CT) colonography every 5 years, or colonoscopy every 10 years.[98,103] For the noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps.[98] The Cologuard stool DNA test would be another routine screening option that would require a followup colonoscopy for result confirmation and lesion excision.[98]

Figure 7. Overall High Impact Potential: Cologuard fecal DNA test for colorectal cancer screening



Overall, experts commenting on this intervention saw significant potential for a definitive noninvasive test to improve CRC screening rates. However, experts thought that the Cologuard test currently lacks the data to support a claim that it would deliver a significant improvement over currently available, noninvasive, fecal-based screening tests. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[106-112] Expert perspectives on this technology were highly divergent. Generally, expert comments could be divided into two camps: (1) three experts with research backgrounds and one expert with a health systems background who thought the Cologuard test would offer incremental improvement and potential replacement for current fecal-based CRC screens (e.g., FOBTs, fecal immunochemical tests); and (2) one clinical expert, one health systems expert, and another expert with a research background who thought the Cologuard test would be a potential replacement for colonoscopy as a first-line screening modality.

Experts who viewed the Cologuard test as a potential improvement on current fecal-based testing generally thought the unmet need would be low, citing the existence of multiple noninvasive tests and preliminary data indicating that Cologuard would provide only a modest improvement in accuracy. In particular, one expert with a research background questioned whether potential users who are currently unscreened would be likely to use the Cologuard test, given their reluctance to use the currently available ColoSure fecal DNA test. Conversely, experts who viewed the Cologuard test as a potential replacement for first-line colonoscopy screening generally thought the unmet need would be high, contrasting the colonoscopy procedure's invasive nature, inconvenience, and lack of availability in underserved (e.g., rural) areas as barriers to screening that could be overcome by the Cologuard test. In particular, one clinical expert cited the convenience and user-friendly nature of the stool DNA test.

These two groups were also split on potential impacts of the Cologuard test on cost and patient acceptance. If Cologuard simply replaces existing fecal-based tests, experts suggested that Cologuard would slightly increase the cost of care, because it would likely be priced higher than existing fecal-based tests. Conversely, if Cologuard came to replace colonoscopy as a preferred first-line screening tool, it would likely reduce costs by reserving the use of the more expensive colonoscopy procedure for confirmatory diagnosis and treatment. In a similar manner, experts expected that patients would prefer an effective stool DNA test to colonoscopy; however, experts did not see a reason why patients would prefer Cologuard to other fecal-based tests, unless a significant improvement in detection rates was demonstrated.

Most experts were enthusiastic about the potential for the inclusion of genetic markers in stool-based testing to improve testing accuracy. However, one expert with a research background cautioned

that while certain genetic markers have been clearly associated with CRC, their association with precancerous lesions is less certain. All experts cautioned that the available data on the latest version of the Cologuard test are only preliminary. They thought that further testing would be needed to establish the test's sensitivity, specificity, and recommended screening frequency, let alone its impact on health outcomes, all of which would significantly impact the likelihood of Cologuard's adoption by physicians, patients, and payers.

Intervention Abstract

Concomitant colorectal cancer screening and annual influenza vaccine (FLU-FOBT) program

CRC is currently the third most common cancer diagnosed in the U.S.[97] CRC tends to be slow to develop, and precancerous lesions and early stage CRCs can typically be treated successfully by surgical resection. Therefore, successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition. However, with current screening options, only a minority of the population adheres to CRC screening guidelines and about half of CRCs diagnosed in the U.S. are diagnosed at late disease stages.[97,113] Therefore, programs, such as FLU-FOBT, that have the potential to improve CRC screening rates are highly sought.

Multiple barriers to CRC screening have been cited, including patient-specific barriers and health care system barriers.[114] Patient-specific barriers include lack of patient awareness of the screening benefits/recommendations; embarrassment regarding the nature of screening methods; anxiety regarding screening; and cost of screening, especially for patients lacking health insurance coverage.[115] Health care system barriers include the lack of time to address all aspects of a patient's health during primary care appointments, a lack of reminders that a patient is due for screening, an inability to track down dates of prior screening, and long delays in colonoscopy scheduling and/or lack or direct access to colonoscopy.[116]

One proposed solution to the problem of finding a method to provide timely and routinized CRC screening is the pairing of FOBT or fecal immunochemical testing (FIT) with annual influenza immunization.[114] Influenza immunization and FOBT/FIT share several attributes that could make them highly complementary: both are recommended to be performed annually and both are, at least in part, targeted to elderly patients. The University of California San Francisco (UCSF) has implemented multiple versions of this program within various settings, including influenza vaccine clinics (both hospital-based and managed-care-based), pharmacy-based influenza vaccination campaigns, community health care clinics, and primary care centers.[114,117-120]

Hallmarks of the UCSF studies included the following: provision of home FOBT/FIT kits to patients whose medical records indicated that they were due for CRC screening, provision of a multilingual information pamphlet on the benefits of CRC screening, training of health care workers in culturally sensitive discussion of CRC screening, and followup telephone calls to patients who had received FOBT/FIT test kits, but not returned samples.[114]

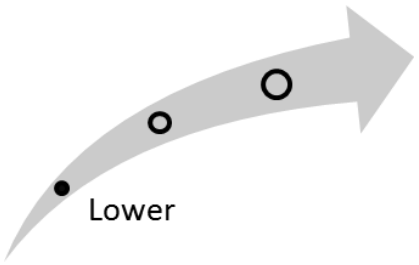
In the largest test of the concept to date, patients obtaining influenza vaccinations at a high-volume influenza clinic run by a managed care organization, were randomly assigned to receive either the influenza vaccination alone (n = 4,653) or the influenza vaccine as well as an FIT test kit (n = 2,182). Within three months of their visit to the influenza clinic, 13.7% of patients in the influenza vaccine-only cohort completed a FIT test compared to 30.3% of patients in the influenza vaccine plus FIT test kit cohort. The percentage of patients adhering to CRC screening recommendations went from 51.5% to 56.3% in the influenza-only group compared with 49.2% to 63.2% in the influenza vaccine plus FIT test kit cohort ($p < 0.0001$ for the change difference between cohorts).[117]

Current Approach to Care

Several options are currently used for routine CRC screening in the general population of patients with an average risk of developing CRC. These include annual FOBTs, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, CT colonography every 5 years, or colonoscopy every 10

years.[98,103] Patients typically engage the health care system during primary care visits, during which caregivers can advise patients of the potential benefits of CRC screening.[114] Additionally, national campaigns such as the U.S. Centers for Disease Control and Prevention's Screen for Life program disseminate information on CRC that may influence an individual's decision to seek CRC screening.[113]

Figure 8. Overall Potential Impact: Concomitant colorectal cancer screening and annual influenza vaccine (FLU-FOBT) program



Experts who commented on this topic believe that it has an interesting approach to increasing CRC screening rates that has significant potential to improve screening adherence in certain settings. However, experts questioned whether such a program would be able to be implemented on a large scale, thereby limiting its overall impact. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.[121-127] Experts were of the opinion that programs linking routine CRC screening with the annual administration of influenza vaccines have the potential to address a moderately to very important unmet need, citing low adherence rates to CRC screening guidelines in spite of evidence of their ability to reduce CRC-associated mortality. However, several experts noted that the ability of such a program to reach unscreened patients could be limited by the extent to which patients who are not compliant with CRC screening seek annual influenza vaccination. In this vein, experts noted that patients seeking prophylactic vaccination for influenza might be more likely than the average patient to already be adhering to preventive screening measures such as CRC screening. However, to the extent that patients who were not up to date with CRC screening were reached by such a program, it has significant potential to improve CRC screening rates and, therefore, improve patient health, experts thought.

Experts were divided on the issue of whether the FLU-FOBT program has the potential to improve health disparities. Those who thought the program has potential cited the emphasis placed on cultural sensitivity in the pilot programs, which could influence patients in certain underserved populations who previously resisted discussing or undergoing CRC screening to do so. These experts also noted the diversity of settings in which the program was offered (e.g., managed care clinics, pharmacies, community health care clinics), which could reach some underserved patients who do not routinely see a primary care physician. Conversely, experts who did not think the FLU-FOBT program would have a significant impact on health disparities questioned whether patients normally resistant to CRC screening could be convinced to undergo screening and suggested that fewer patients in traditionally underserved populations would routinely seek vaccination against influenza.

While implementation of the FLU-FOBT program would cause a shift in the care setting for disseminating information about CRC screening and would necessitate some training of health care facility staff, it would not have a significant impact on health care infrastructure or patient management, experts believe. However, multiple experts noted the need to ensure followup with patients receiving positive results from noninvasive tests, which could represent a significant shift in the way patients are otherwise managed, especially for FLU-FOBT programs implemented in settings that are not associated with a gastroenterologist (e.g., pharmacies).

Experts were highly divided on the issue of whether health care workers would accept and adopt the implementation of a FLU-FOBT program. While some experts suggested that clinicians would welcome an innovation that is purported to increase CRC screening rates, other experts suggested that clinicians may not want to spend the time providing information about CRC screening in what are presumably high-volume settings. Additionally, multiple experts noted that patients often fail to return FOBT test kits and health care systems might not want to allocate time and resources to follow up with patients to encourage them to return the kits.

Intervention

Digital breast tomosynthesis for breast cancer screening

Conventional mammography uses x-rays to capture two-dimensional images of breast tissue.[128] A limitation of conventional mammography is that the x-ray images capture information from all tissue constituents along the path from the x-ray source to the detector.[129] Therefore, features of the breast may be obscured by tissues that are in line with the x-ray path and above or below the feature of interest.

Digital breast tomosynthesis is a new x-ray imaging modality that purports to overcome this potential pitfall by imaging stabilized breast tissue in multiple angles for a given view by rotating the x-ray source in an arc around the target tissue. For example, rather than taking a single image in the craniocaudal view as in conventional two-dimensional (2-D) mammography, digital breast tomosynthesis involves taking 10 to 20 images in the craniocaudal view with the angle of the x-ray beam shifted by approximately 1 degree in each image.[129] Breast tissue features that may obscure each other in one angle will be shifted relative to one another in other angles. By combining the information from each beam angle at the point where it crosses a given depth in the breast under examination, digital breast tomosynthesis can reconstruct images that represent serial slices through the breast. Developers propose that this imaging technology will improve mammographic imaging, potentially resulting in the following:[129]

- A reduction in the number of women who have to be recalled because of inconclusive mammography results
- A reduction in the number of biopsies
- Increased cancer detection

The first digital breast tomosynthesis system, the Selenia® Dimensions® 3D System manufactured by Hologic, Inc. (Bedford, MA), received marketing approval from FDA in February 2011 based on results from two clinical trials of the system. This system is a software and hardware upgrade to the existing Selenia Dimensions 2D full-field digital mammography system.[130,131]

In the first trial, 312 cases (of which 48 were biopsy-confirmed breast cancer) were imaged using conventional 2-D mammography and three dimensional (3-D) digital tomosynthesis.[132] Twelve radiologists who had received training in the interpretation of 3-D digital tomosynthesis images then interpreted the cases based on the 2-D data alone and based on a combination of the 2-D data and the 3-D tomosynthesis data. The study measured the area under the receiver operating characteristic (ROC) curve and the recall rate of noncancer cases. Researchers reported that interpretation of 2-D plus 3-D tomosynthesis data showed an improved area under the curve relative to interpretation of 2-D data alone for all experts (average increase in area of 0.071 for the breast imaging reporting and data system [BIRADS] ROC analysis [$p = 0.0004$] and 0.072 for the probability of malignancy ROC analysis [$p = 0.0001$]).[132] They also reported that interpretation of 2-D plus 3-D tomosynthesis data exhibited a reduction in the recall rate for noncancer cases relative to interpretation of 2-D data alone with a reduction in the average recall rate from 51.5% to 12.9%.[132]

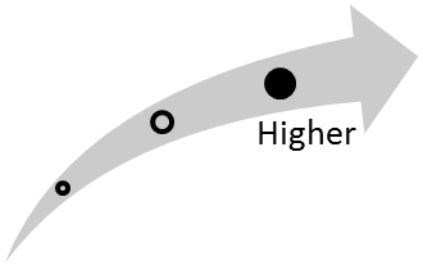
In the second study, 310 cases (of which 51 were biopsy-confirmed breast cancer) were imaged using conventional 2-D mammography and 3-D digital tomosynthesis.[132] Fifteen radiologists who had received training in the interpretation of 3-D digital tomosynthesis images then interpreted the cases based on the following: (1) 2-D data alone; (2) a combination of 2-D data and 3-D tomosynthesis data from only the mediolateral oblique (MLO) view; and (3) a combination of 2-D data and 3-D

tomosynthesis data from both the MLO view and the craniocaudal view. The study measured the area under the ROC curve and the recall rate of noncancer cases. Researchers reported that interpretation of 2-D plus 3-D tomosynthesis data in both views exhibited significant improvement in the area under the ROC curve compared with both 2-D data alone and 2-D data in combination with 3-D tomosynthesis MLO data.[132] They reported that recall rates for noncancer cases were 48.8% for 2-D data alone, 32.7% for 2-D plus 3-D MLO data, and 30.1% for 2-D plus full 3-D tomosynthesis data.[132]

Clinical Pathway at Point of This Intervention

Primary breast cancer screening is typically performed using 2-D digital or film x-ray mammography.[133] After identification of an abnormality on screening mammography, patients typically undergo additional diagnostic imaging (e.g., diagnostic mammography, ultrasound, magnetic resonance imaging) and a physical examination. If these studies suggest the abnormality is cancerous, biopsy material may be obtained by fine-needle aspiration, core-needle biopsy, or open surgical biopsy.[133] The Selenia Dimensions 3D tomosynthesis system would be used in place of conventional 2-D x-ray mammography for breast cancer screening and followup diagnostic imaging of suspicious lesions.[132]

Figure 9. Overall High Impact Potential: Digital breast tomosynthesis for breast cancer screening



Overall, experts providing comments on this technology thought that it has potential to bring incremental improvements in breast cancer screening by potentially improving breast cancer detection and reducing false-positive results. Such reductions, they opined, could obviate need for unnecessary followup imaging and biopsy, which could save costs and reduce patient anxiety created with false-positive results. Experts thought that, given the likelihood that patients and clinicians would want to use this technology and the large changes in health care system costs and resources that its use would cause, digital breast tomosynthesis has potential high impact. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, provided perspectives on this topic.[134-140] The consensus among experts was that digital tomosynthesis has the potential to address two significant unmet needs in breast cancer screening: (1) finding cancers that conventional screening mammography misses, particularly in women with dense breasts or at high risk of breast cancer for whom conventional mammography has poor sensitivity; and (2) reducing the high rate of inconclusive or false-positive results seen with conventional mammography, which leads to many unnecessary recalls for followup imaging and biopsies.

While experts agreed that digital breast tomosynthesis has the potential to improve sensitivity and specificity relative to conventional mammography, they were less certain on how large an impact digital tomosynthesis would have on these unmet needs. Multiple experts noted the incremental nature of the improvement in sensitivity and specificity. In addition, one clinical expert questioned whether data from a retrospective study of a case series enriched with cancer cases should be generalized to the screening population, where breast cancer rates would be much lower. This expert suggested that digital tomosynthesis might initially be best used by being reserved for high-risk patients and/or patients with dense breast tissue. In addition, multiple experts questioned whether the readers used in

the study, who were trained in interpretation of digital tomosynthesis by the manufacturer, would be representative of radiologists in general. Lastly, one expert with a clinical background noted that in addition to its purported benefits, digital breast tomosynthesis could add to the problem of breast cancer over-diagnosis, in which slow-growing noninvasive carcinomas that might not have impacted patient health are detected and treated. An expert with both a research and health systems perspective believes it has a high likelihood of becoming a replacement screening tool over time as hospitals upgrade their screening mammography technology, based on the assumption that it can potentially improve cancer detection, lower recall rates, and lower the proportion of biopsies that turn out to be negative because of a false-positive result from the prior screening.

Even if digital tomosynthesis provides only marginal improvements in sensitivity and specificity, experts thought, patients would be eager to receive screening with this technology, because it is the most advanced breast screening technology available. However, some experts noted that patients may fear the increase in radiation dose incurred during digital breast tomosynthesis compared with conventional mammography.

Multiple experts noted that adoption of digital breast tomosynthesis as a screening tool would have significant impacts on health care facility infrastructure and staffing. They pointed out that facilities wishing to offer it would not only need to acquire the imaging system itself, but also increase digital bandwidth, data storage capacity, and the number of viewing workstations to accommodate the increased data generated by a tomosynthesis system. Furthermore, radiologists would need to be trained in the acquisition and interpretation of the data and the large amount of data generated would significantly increase the amount of time radiologists need to spend analyzing the data. Several experts suggested that the cost-benefit ratio of digital breast tomosynthesis may reduce the willingness of clinicians to adopt this technology. It may also affect payer decisions to reimburse the use of the technology.

Intervention

MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy

Successful breast-conserving surgery for treatment of early-stage breast cancer requires that the margins of tissue excised by lumpectomy have cancer-free margins. Up to 30% of patients who undergo such procedures need to undergo a second surgical procedure because the tissue excised during lumpectomy is demonstrated by histologic analysis to have margins that are not cancer free.[141] The MarginProbe™ System (Dune Medical Devices, Ltd.,Caesarea, Israel)is intended to be used in intraoperative assessment of lumpectomy margins, which could allow breast cancer surgeons to resect additional tissue from unclean margins during the lumpectomy procedure rather than having to perform a second procedure at a later date.

The system uses a technology called radiofrequency (RF) spectroscopy, in which tissue is subjected to an electromagnetic field, and the response of the tissue to stimulation is measured.[142] Research findings suggest that RF spectroscopy can differentiate between normal tissue and cancerous tissue based on bioelectric differences between the two tissues.[143] These differences may be due in part to changes in the cellular and tissue structure of cancer, including cell membrane depolarization, altered cell nucleus morphology, increased vascularity, and loss of cell-cell adhesion.[144] Because RF spectroscopy detects only tissue response to the electromagnetic field near the surface of the sample, it is considered appropriate for detecting clean margins, often defined as having a depth of normal (noncancerous) tissue of at least 1 or 2 mm.[143] The system incorporates a diagnostic algorithm, based on a large number of comparisons between RF spectroscopy readings and pathology results, to differentiate between cancerous and noncancerous tissue.[145] The system provides a binary answer indicating whether the assessed margin is clean or not.

In a late-phase, clinical trial, the system was used to assess tissue excised from 664 women undergoing a lumpectomy procedure to treat nonpalpable malignant lesions that required image-guided localization.[141] Patients were randomly assigned to receive standard of care intraoperative assessment of whether to resect additional tissue or standard of care assessment plus assessment using the system.[141] The primary endpoint for the trial was the rate of complete surgical resection (CSR) defined as intraoperative identification of all positive margins and resection of such margins during the lumpectomy procedure.[141] Preliminary trial results reported by the manufacturer indicated that the rate of CSR was significantly improved in the MarginProbe arm of the study compared with the control arm (72% [117/163] vs. 22% [33/147], $p < 0.0001$).[141] Additionally, the volume of tissue dissected in each arm was comparable; 93 cc in the MarginProbe arm compared to 85 cc in the control arm.[141]

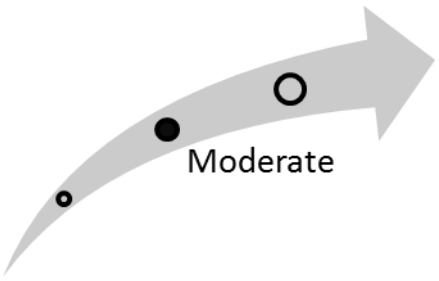
In May 2011, Dune Medical announced that FDA had formally accepted the company's premarket approval (PMA) application for the system based on the above trial results.[146] Given that no device is currently FDA approved for intraoperative assessment of lumpectomy margins, FDA granted the MarginProbe System priority review, but a decision date had not been announced as of November 2011.[146]

Clinical Pathway at Point of This Intervention

The primary treatment for patients in whom early stage breast cancer (e.g., ductal carcinoma in situ, stage I or II invasive carcinoma of the breast) has been diagnosed is surgical resection of the cancerous tissue. Depending on the stage and level of lymph node involvement, patients may undergo breast-conserving surgery (e.g., lumpectomy) or mastectomy.[74] Alternatively, patients who meet all

criteria for breast-conserving surgery except for the fact that their tumor is too large may undergo neoadjuvant chemotherapy to reduce tumor size.[74] Following surgical resection, histologic analysis of the resected tissue is performed to assess characteristics of the tumor that may influence subsequent treatment. In particular, lumpectomy samples are tested to assess whether the margins of resected tissue are cancer free.[74] Patients with cancer-positive margins may undergo a subsequent surgical resection to remove additional tissue and establish cancer-free margins. Following lumpectomy, patients are typically treated with radiation therapy or adjuvant systemic therapy (e.g., hormone therapy, chemotherapy) in an attempt to eradicate remaining cancer cells.[74] If approved, the MarginProbe System would be used during lumpectomy to assess whether lumpectomy margins are cancer free, potentially reducing the need for subsequent surgical procedures.

Figure 10. Overall Potential Impact: MarginProbe System for intraoperative identification of positive margins during breast cancer lumpectomy



Overall, experts commenting on this intervention believe that a significant unmet need exists for a technology that could rapidly and objectively identify positive margins during breast-conserving surgery, which could significantly reduce the morbidity and costs associated with the need to perform secondary surgeries in this patient population. While initial results for the MarginProbe system were viewed as promising with limited potential to negatively affect patient outcomes, most experts believe that additional data would be needed before widespread adoption. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[147-153] The majority of experts agreed that a significant unmet need exists for a technology or methodology that can rapidly assess the margins of excised breast tissue to determine whether further tissue resection is necessary. Experts cited the large number of patients who require a second surgery following the identification of positive margins during post-surgical histological analysis and the adverse health effects associated with undergoing a second surgical procedure.

While experts suggested that filling this unmet need could moderately improve health outcomes for patients by reducing the complications and stress associated with the need to undergo a second lumpectomy or mastectomy, experts were less certain regarding the potential for the MarginProbe System to influence long-term survival outcomes for patients with breast cancer. In addition, experts questioned whether the evidence base for the MarginProbe System was sufficient to suggest that it could meet the unmet need. One expert with a clinical background questioned whether the approximately 70% sensitivity and specificity was sufficient to significantly improve re-excision rates.

The majority of experts did not think that adoption of the MarginProbe system would have a significant impact on health disparities. However, one expert with a research perspective suggested that the MarginProbe might create a slight increase in health disparities if it were to be offered exclusively at more specialized breast cancer centers. Conversely, an expert with a clinical perspective suggested that the system could modestly decrease disparities if it allowed less specialized surgeons to perform breast-conserving surgery in undeserved regions of the country.

Experts agreed that adoption of the MarginProbe system would have minimal impact on health care system staffing and infrastructure, suggesting that changes such as the need to acquire the

MarginProbe system itself and a slight shift in operating room demand due to a slight increase in the duration of breast-conservation surgery procedures and a potentially reduced number of second surgeries. Additionally, experts did not think that use of the MarginProbe system would have a significant impact on patient management because patients would follow the same clinical pathway with or without the intraoperative screening with the device.

The majority of experts believe that if final results from the most recent clinical trial of the MarginProbe system demonstrate a clear improvement in the intraoperative detection of positive margins, physicians and patients would rapidly adopt its use. In terms of physician adoption, experts noted the purported minimal training required in the use of the device and potential to improve patient outcomes by avoiding complications of a second surgical procedure. Conversely, one expert with a research perspective suggested that physicians would be reluctant to adopt a new technology over existing margin detection techniques with which they were already familiar (e.g., frozen sections, touch-prep cytology, ultrasound analysis). In terms of patient adoption, experts noted the potential to avoid second surgeries and the lack of side effects aside from the potential for the unnecessary removal of additional breast tissue in the event of a false-positive result. However, multiple experts questioned whether the majority of patients would be aware of the technology employed during intraoperative margin assessment.

The majority of experts suggested that the MarginProbe system could have a significant impact by reducing costs associated with breast-conserving surgery. While initial acquisition of the system and intraoperative use of the system would likely increase costs, experts suggested that this increase could be outweighed by a reduction in secondary surgery procedures.

Intervention

MelaFind multispectral dermoscope for detection of melanoma in suspect skin lesions

The gold standard for melanoma diagnosis is biopsy followed by histopathologic analysis; however, accurately identifying which lesions should be biopsied remains difficult.[154] Current screening methods involve clinical examination using visual examination with the naked eye, a dermoscope, or both. Both methods involve subjective decisions that require the user to be highly trained to discriminate between benign and potentially melanotic lesions.[154] The positive predictive value of a decision to biopsy is relatively low; an estimated 50 biopsies are performed for every one melanoma detected.[155]

The MelaFind® system (MELA Sciences, Inc., Irvington, NY) is a computer-based system intended to aid the clinician in determining whether a clinically atypical cutaneous pigmented lesion should be biopsied.[156] The MelaFind system uses a hand-held probe to capture images of the lesion using multiple light wavelengths ranging from blue to near infrared. Because different light wavelengths penetrate skin to different depths, the wide spectrum of light sources used to image the lesion is intended to enable assessment of lesion properties that are not visible to the human eye, including subsurface portions of the lesion.[154] In an automated fashion, the MelaFind system provides the user with either a positive or negative result, indicating that the system has determined that the lesion should or should not be biopsied, respectively.[156]

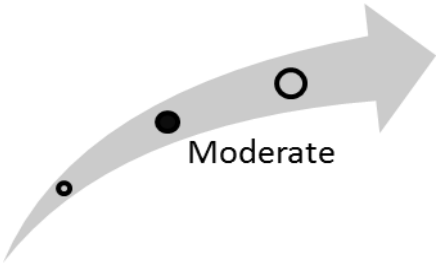
Results of a clinical trial of the MelaFind device published in 2010. In that trial, 1,632 clinically atypical lesions were tested using the MelaFind system and by biopsy.[157] Researchers reported that biopsy revealed that 127 of the test lesions were in fact melanoma. They reported that of the 127 melanotic lesions, MelaFind recommended biopsy for 125 (98.4% with a 95% lower confidence bound at 95.6%). Further, researchers reported that MelaFind exhibited a ratio of 10.8 biopsy recommendations per actual melanoma. As an assessment of the sensitivity of dermatologists, images of 25 representative melanomas and 25 representative nonmelanomas from the clinically atypical lesion set were submitted to examination by a panel of 39 independent dermatologists. Dermatologists were asked whether they would recommend biopsy of each imaged lesion. Researchers reported that the average sensitivity of the dermatologists in this reader study was 78%.

Based on these study results, MELA Sciences submitted a PMA application to FDA in June 2009, and the device was considered at a November 2010 FDA advisory panel meeting. In February 2011, MELA Sciences submitted an amended PMA to FDA based on input from that advisory panel meeting that included a labeling change limiting use of the MelaFind to dermatologists. On November 2, 2011, the MelaFind device was granted marketing approval by FDA.[158] The company has indicated that the MelaFind device will initially be installed in a small number of high-volume dermatologic clinics in the northeastern United States.[158]

Clinical Pathway at Point of This Intervention

A suspicious pigmented lesion is identified during a patient self-examination or during an annual clinical examination. After visual assessment of the lesion for risk of melanoma by a clinician, the lesion is biopsied and sent for histopathologic examination to make a definitive melanoma diagnosis.[55] The MelaFind device would be used after physician identification of a suspicious pigmented lesion to assist the physician in making the decision of whether to biopsy the lesion.[156]

Figure 11. Overall High Impact Potential: MelaFind multispectral dermoscope for detection of melanoma in suspect skin lesions



Overall, experts commenting on this intervention were enthusiastic about the MelaFind device's potential to modestly decrease the percentage of suspicious lesions that would otherwise need to be biopsied. However, experts expressed concerns regarding cost, reimbursement, and the care setting in which the device might be used, which they thought could limit its potential impact. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[159-164] The majority of these experts believe that the MelaFind device has the potential to address a significant unmet need, citing the high number of biopsies performed on nonmelanotic lesions to rule out melanoma, the difficulty in subjectively classifying lesions, and the lack of an objective, noninvasive tool for assessing melanoma. However, one expert with a research perspective stated that the MelaFind device would only be substituting for a function that physicians or dermatologists perform currently.

The majority of experts thought the theory behind the device and the evidence in support of its efficacy are sound. In particular, one expert with a research perspective noted the high sensitivity for melanoma reported in a large clinical trial (n = 1,632 lesions).[157] However, two experts with research perspectives noted that devices such as MelaFind that base their decisions on comparison against a database of positive and negative specimens often suffer from poor specificity and that melanoma is known to manifest with a significant level of variability. One of these experts also noted that while the MelaFind device appeared to achieve a high level of sensitivity in the published clinical trial, it suffered from a lack of specificity. However, one expert thought the study data seemed to indicate that the MelaFind system's specificity may be better than that of physicians.[157]

Comments from an expert with a research perspective and an expert with a health systems perspective indicated that the MelaFind device may have potential to disrupt the care setting from a dermatologic specialist to a primary care physician setting. The recent modification of MELA Sciences' PMA application to specify use of the device only by dermatologists may inhibit this care-setting shift. However, one expert noted that even within the dermatology clinic, the device could have a significant impact by increasing patient throughput. These experts also noted that the biggest worry surrounding this technology may be the potential for false-negative test results. If caregivers, especially nondermatologic specialists, come to depend on the device for biopsy decisions, treatment of melanoma could be delayed in the event of incorrect results.

Experts noted that the cost of the MelaFind system and the potential reimbursement are unknown at this time, and those factors could have a significant impact on the diffusion of this technology. Two experts noted that once the upfront costs of acquiring the system are absorbed, the system might actually reduce costs per patient based on a reduction in the number of biopsies performed. This potential for a reducing the number of biopsies was also cited as an improvement in patient health outcomes by avoiding the potential complications of biopsies and alleviating the stress associated with waiting for biopsy results.

Overall, experts were enthusiastic about the MelaFind device's potential to modestly decrease the percentage of suspicious lesions that would otherwise need to be biopsied; however, they thought that

variables such as cost, reimbursement, and the care setting in which the device might be used could limit its impact.

Intervention

Methylated Septin 9 blood test for colorectal cancer screening

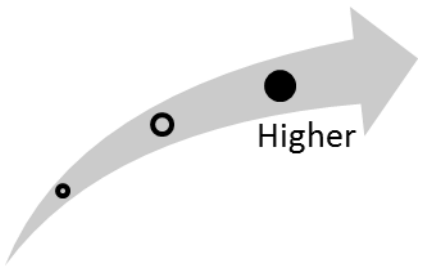
New screening methodologies that could increase the percentage of the population that undergoes recommended CRC screening are highly sought. Research has demonstrated that cells undergo a range of epigenetic modifications (e.g., DNA methylation) during transformation to cancerous cells.[165] Additionally, elevated levels of methylated DNA have been found in the blood of patients with CRC, and that could serve as a readily accessible marker for cancer screening.[165] One methylated DNA species that has been shown to be present specifically in the blood of individuals with CRC is a methylated form of the *Septin 9* gene, detection of which is being studied as a potential colon cancer screening test.[165] Like other noninvasive colon cancer tests (e.g., fecal occult blood testing), a positive result from the methylated Septin 9 test would require that the patient undergo a colonoscopy to confirm the result and resect any precancerous or cancerous lesions.[166]

A methylated Septin 9 DNA blood test is being developed by Epigenomics AG (Berlin, Germany), in collaboration with Abbott Laboratories (Abbott Park, IL). In 2010, Epigenomics presented data from its PRESEPT trial in which 7,940 patients undergoing colonoscopy screening were also tested with the Epigenomics first-generation Septin 9 test.[167] Preliminary results indicated that, compared with CRC detection by colonoscopy, the Septin 9 test had a sensitivity of 66.7% and a specificity of 88.4%.[167] Data on the test's ability to detect precancerous adematous polyps were not presented. Epigenomics and Abbott are developing a second-generation Septin 9 test that uses affinity purification of DNA to enrich samples for testing, potentially improving detection rates.[168] The companies planned to initiate clinical trials of the new test in the second half of 2011, and they stated that they planned to submit a PMA to FDA by the end of 2011.[168]

Clinical Pathway at Point of This Intervention

Several options are available for routine CRC screening in patients with an average risk of developing colon cancer, including annual FOBTs, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, CT colonography every 5 years, or colonoscopy every 10 years.[98,103] For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps.[98] Septin 9 blood testing would be another routine screening option that, like other noncolonoscopic methods, would require a followup colonoscopy for positive result confirmation and lesion excision.[166] Current information on the test states that it is not intended to substitute for colonoscopy; however, it might be useful as a complement to colonoscopy or for use in individuals unwilling or unable to undergo colonoscopy.[169] It might also be useful screening for individuals also unwilling or unable to undergo colonography.

Figure 12. Overall High Impact Potential: Methylated Septin 9 blood test for colorectal cancer screening



Overall, most experts commenting on this intervention thought that an accurate blood-based CRC screening test obtained through venipuncture (rather than testing a stool sample) could fundamentally change CRC screening practices by increasing the percentage of patients willing to be screened for CRC. However, experts noted that further data, especially on the second-generation test, would be needed before its full impact could be assessed, because the first-generation test did not have sufficiently high sensitivity and specificity. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.[170-175] The majority of experts thought that a blood-based screening technology has the potential to address a significant unmet need, citing the current lack of a blood-based screening test and the low rate of adherence to currently recommended screening—fecal sample testing, colonoscopy, and colonography. One researcher saw a limited unmet need, stating that there are already multiple noninvasive tests available for CRC and that the Septin 9 test would only provide another such option. Other experts saw more significance in the blood-based nature of the test, stating that it would likely be more acceptable to patients than current noninvasive fecal-based tests and that patients who had not been willing to undergo screening might do so.

While experts generally agreed that the scientific rationale of detecting methylated Septin 9 DNA as a marker for CRC is sound, they were less convinced of the potential for a blood-based test to detect CRC at a sufficiently early stage to allow highly effective treatment. In particular, one clinical expert noted that tumors might need to become invasive before large amounts of a DNA marker would be present in blood and, therefore, a blood-based test would need to demonstrate the ability to detect CRC at early noninvasive stages when it is still highly curable by surgical resection. It should be noted that following submission of expert perspectives, Epigenomics announced pilot data on its second-generation Septin 9 test that suggest the test could detect at least some early-stage CRCs.[168] However, the clinical expert cautioned that even a shift from detection of precancerous polyps (possible with colonoscopy or fecal immunochemistry testing) to detection of cancer at early stages could prove controversial.

Many experts noted the highly preliminary nature of the data thus far and said further demonstration of the test's efficacy would be needed before adoption. However, most experts believe that a blood test of sufficient sensitivity and specificity would be very rapidly adopted by patients and physicians alike because it would be very convenient. One clinical expert noted that periodic blood tests are routinely performed on the majority of the population recommended for CRC screening and that the Septin 9 test could easily be incorporated into a patient's testing regimen. In addition, several experts cited test convenience as having a potential impact on health disparities and access to care by allowing routine blood draws to replace the need for access to GI specialists. However, many experts noted that the cost per test and the frequency with which the test would need to be administered, both of which could significantly affect adoption and availability to underserved populations, are unknown at this time.

Targeted Therapy Interventions

Intervention

B-RAF kinase inhibitors vemurafenib (Zelboraf) for treatment of metastatic melanoma

According to the American Academy of Dermatology, more than half of all new cases of melanoma in the United States in 2010 were invasive at the time of diagnosis.[54] Until recently, guidelines from the National Comprehensive Cancer Network indicated that no clearly optimal treatments for metastatic melanoma were available, and there was little consensus on standard therapy.[55] The recent approval of ipilimumab and vemurafenib for treatment of metastatic melanoma have provided the first treatments that generate a clear improvement in survival for this patient population.

Small-molecule inhibitors of the protein kinase B-RAF represent a recent addition to the metastatic melanoma treatment armamentarium.[176] B-RAF plays a central role in the RAS/MAP kinase signal transduction pathway, which regulates cell growth and cell proliferation. Misregulation of this pathway has been demonstrated to be involved in multiple cancers. In particular, *B-RAF* gene mutations (e.g., *B-RAF*^{V600E}) encoding a constitutively active B-RAF protein have been identified in approximately 7% of cancers.[177] While only a small fraction of all human tumors harbor an activating *B-RAF* mutation, more than half of melanomas analyzed have been shown to bear such an allele.[177] Activated B-RAF is proposed to lead to hyperactivation of the downstream ERK/MEK/MAP kinase pathway, upon which melanomas may be dependent for growth and survival.[178] Therefore, the specific inhibition of B-RAF kinase activity is a promising pharmacologic target. Preclinical studies demonstrated that B-RAF inhibitors were able to inhibit signaling in the downstream MAP kinase pathway only in cells containing the activating *B-RAF*^{V600E} mutation.[177] Therefore, most studies have focused on patients whose cancers have been confirmed to contain this mutant form of *B-RAF*.

Two orally administered, small-molecule inhibitors of B-RAF kinase activity are in development for treatment of metastatic melanoma: vemurafenib (Zelboraf®, PLX4032, RG7204), codeveloped by the Genentech unit of F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Plexxikon (now owned by Daiichi Sankyo Co., Ltd., Tokyo, Japan),[179,180] and dabrafenib (GSK2118436), developed by GlaxoSmithKline (Middlesex, UK).[181]

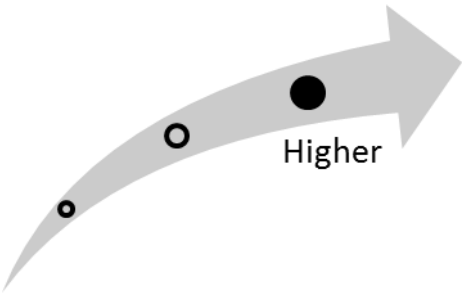
In May 2011, Genentech announced that it had submitted a new drug application (NDA) to the U.S. Food and Drug Administration (FDA) for vemurafenib for treatment of newly diagnosed *B-RAF*^{V600E}-positive metastatic melanoma.[182] This submission was based on results from the phase III BRIM3 study in which patients with metastatic melanoma (n = 675) were randomly assigned to receive either vemurafenib or dacarbazine.[183] In this study, vemurafenib was reported to have met its two primary endpoints of increasing overall survival and increasing progression-free survival relative to treatment with dacarbazine.[183] Researchers reported that treatment with vemurafenib versus dacarbazine was associated with a 63% reduction in the chance of death and a 74% reduction in the chance of either death or disease progression ($p < 0.001$ for both analyses).[183] A companion diagnostic test that will allow determination of *B-RAF*^{V600} status has been developed in tandem with vemurafenib.[182] On August 17, 2011, FDA approved vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the *B-RAF*^{V600E} mutation as detected by an FDA-approved test, the cobas 4800 *B-RAF V600* Mutation Test.[180,184] The cost is about $9,400 per patient per month and the company estimates a treatment course of about 6 months for a total of about $56,400 per patient. Genentech introduced its Zelboraf Access Solutions program to help some patients cover out-of-pocket costs using a special company-issued co-pay card. The card provides eligible patients with up to $4,000 or $1,500 in co-pay assistance per year.

Another B-RAF inhibitor is in earlier phase development for melanoma also. Dabrafenib (GlaxoSmithKline) is described by the developer as highly potent and selective with more than100-times selectivity for mutant *B-RAF*.[185] The drug is purported to display dose-dependent inhibition of MEK and ERK phosphorylation in mutated *B-RAF* cell lines and to achieve tumor regression. It is currently being studied in a 200-patient, phase III trial for metastatic melanoma with results anticipated by June 2012.[185]

Clinical Pathway at Point of This Intervention

Patients in whom disseminated/unresectable, metastatic melanoma has been diagnosed are typically treated with one of a number of systemic therapies and/or radiation therapy.[62] Standard systemic therapies include dacarbazine, high-dose interleukin-2, ipilimumab, temozolomide, vemurafenib (for patients whose melanoma harbors an activating mutation in the *B-RAF* gene), or paclitaxel with or without cisplatin or carboplatin.[62] Patients maintaining sufficiently good health to undergo additional treatments may be treated sequentially with additional treatments.[62] Vemurafenib, along with ipilimumab, have become standard first-line options in the treatment of disseminated metastatic melanoma.[62]

Figure 13. Overall High Impact Potential: B-RAF kinase inhibitors vemurafenib (Zelboraf) for treatment of metastatic melanoma



Overall, experts commenting on this drug class believe the availability of B-RAF inhibitors has potential to fundamentally change treatment paradigms for metastatic melanoma as they will split a single syndrome into *B-RAF* mutation-positive and *B-RAF* mutation-negative disease. This will necessitate testing of all patients to determine their *B-RAF* status. Experts opined that while the potential of B-RAF inhibitors is limited by the fact that it is unlikely to be a curative treatment and the vast majority of patients will eventually develop resistance to the therapy, these inhibitors are expected to be a central focus of melanoma treatment and clinical study in coming years. Experts noted that the cost impact is expected to be high because not only will the drug be new, but now all patients with melanoma will likely be tested to determine their *B-RAF* status. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration perspectives, offered comments on vemurafenib[186-192] and seven experts with clinical, research , health systems, and health administration perspectives offered comments on dabrafenib.[193-199]

Experts were unanimous in their opinion that B-RAF kinase inhibitors have potential to address an important unmet need, citing the poor prognosis and limited treatment options for patients with metastatic melanoma and the lack of other therapies targeting oncogenic *B-RAF*. Experts also believe that the scientific basis for targeting B-RAF kinase activity in patients with tumors expressing oncogenic *B-RAF* is sound. However, one clinical expert noted that while preliminary data indicate a significant increase in the response rate, duration of progression-free survival, and duration of overall survival, nearly all patients will eventually become refractory to this treatment and their disease will progress despite treatment with this therapy. Still, multiple experts believe that B-RAF inhibitors will quickly become the standard first-line therapy for patients with $B\text{-}RAF^{V600E}$-positive advanced

melanoma and that determination of *B-RAF* mutational status will be a standard component of pretreatment diagnosis.

Given the likelihood of patients to develop resistance to this therapy, experts noted, clinicians would want to investigate the mechanisms of B-RAF-inhibitor resistance and pursue combination therapies that may target resistance mechanisms. Multiple experts believe that the biology of B-RAF inhibition will be a focus of much future melanoma research and noted that clinical trials of B-RAF inhibitors in combination with other targeted therapies are already under way in an attempt to address the problem of B-RAF inhibitor resistance.

As an orally administered medication with a clear target patient population, B-RAF inhibitors are not likely to encounter many obstacles to adoption, experts believe. Several experts noted that while B-RAF inhibitors have a generally mild side-effect profile, significant side effects have been reported. In particular, the development of squamous cell carcinomas has been associated with B-RAF inhibitor treatment and would require that patients be monitored by a dermatologist. However, experts believe that side effects were typically manageable and, given the paucity of treatment options and the potential benefits of the treatment, the potential side effects would not dissuade significant numbers of patients or physicians from opting for B-RAF inhibitor treatment.

Several experts noted that the availability of an orally administered medication could shift the care setting, especially for patients who would otherwise be treated with interleukin-2 therapy, which is typically administered at regional cancer centers. In this way, the availability of B-RAF inhibitors could shift the first-line care setting from specialty centers to general oncologists.

Intervention

Brentuximab-vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin's lymphoma or anaplastic large cell lymphoma

CD30 is a defining marker of Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL).[200] Both HL and ALCL are rare, with only about 8,500 cases of HL and 2,250 cases of ALCL diagnosed annually in the United States.[201,202] While many patients will achieve complete remission following standard treatments for HL and ALCL, a significant fraction of patients will either be refractory to standard therapies or experience disease recurrence. Current treatments for recurrent or refractory HL and ALCL are of little benefit to affected patients, and no consensus exists on optimal treatment of these patients.[202]

Brentuximab-vedotin is an antibody-drug conjugate (ADC) targeted to CD30 that has been developed for the treatment of patients with recurrent or refractory HL or ALCL.[200,202] The biologic compound consists of a CD30-specific monoclonal antibody chemically conjugated to a potent, chemotherapeutic agent, monomethy auristatin E (MMAE).[200] Brentuximab-vedotin is intended to exclusively target CD30-expressing cells and contains a novel peptide-based linking system designed to allow it to remain stable in the bloodstream and only release the cytotoxic MMAE upon ADC internalization by CD30-positive cells.[200] By targeting the cytotoxic molecule to CD30-expressing tumor cells, brentuximab vedotin is purported to minimize systemic toxicity while focusing cytotoxic effects on the target tumor.

Researchers have reported results from two open-label, single-group assignment, phase II clinical trials; one trial in relapsed or refractory HL and one trial in relapsed or refractory ALCL. In the clinical trial of the agent in patients with relapsed or treatment-refractory HL (n = 102), the overall response rate as assessed by an independent review facility was 75%, and 34% of patients achieved complete remission.[203] The median response duration was 29 weeks as assessed by independent central review and 47 weeks as assessed by investigators.[204] Among patients achieving a complete remission, the median response duration had not yet been reached at median followup of approximately 1 year.[204] In the clinical trial of the agent in patients with relapsed or treatment-refractory ALCL (n = 58), the overall response rate as assessed by an independent review facility was 86%, and 53% of patients achieved complete remission.[205] The median response duration had not been reached when results were given and ranged from 0.3 to 45.3 weeks.[205]

Treatment with brentuximab vedotin consists of an intravenous infusion of 1.8 mg/kg of body weight every 3 weeks for up to 16 total doses.[200] Common adverse effects reported in trials included diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy, and pyrexia, which were characterized as "manageable." [204,206] Since the time of these trials, rare, but serious adverse events reported were progressive multifocal leukoencephalopathy, a brain infection that can result in death.

Seattle Genetics, Inc. (Bothell, WA), in collaboration with the Millennium Pharmaceuticals subsidiary of Takeda Pharmaceutical Co., Ltd. (Osaka, Japan), developed the agent. Seattle Genetics has commercialization rights in the U.S. and Canada. FDA granted the agent orphan drug designation in 2007 and fast track status in 2009. On August 19, 2011, FDA approved Adcetris® for treatment of both HL and ALCL.[207] The approved indications are for patients with HL who have failed to respond to an autologous stem cell transplant or whose disease has progressed after at least two prior multiagent chemotherapy regimens and who are not autologous stem cell transplant candidates and for patients with ALCL after failure of at least one prior multiagent chemotherapy.[207,208]

In addition to the FDA-approved indications in relapsed or refractory disease, early-phase, clinical trials incorporating brentuximab vedotin into first-line chemotherapy regimens for treatment of HL and ALCL are ongoing.[209,210] The initial drug pricing was set at about $4,500 per vial with about 3 vials

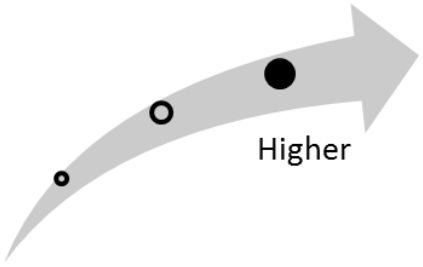
used per treatment and 7 to 9 cycles of treatment given per patient bringing the total cost for a complete regiment to a range of $108,000 to $121,000.

Clinical Pathway at Point of This Intervention

Standard treatment for HL consists of chemotherapy, involved-field radiation therapy, extended-field radiation therapy, and combined modality treatment; common chemotherapies used in combined modality treatment include AVBD (adriamycin [doxorubicin], vinblastine, bleomycin, and dacarbazine) and Stanford V (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, and prednisone).[201] Patients whose disease progresses following first-line therapy may undergo subsequent treatment(s) with radiation therapy, high-dose chemotherapy coupled with autologous stem cell transplant, or one of a range of salvage chemotherapy regimens.[201]

Patients in whom ALCL has been diagnosed typically undergo first-line therapy with an anthracycline-based chemotherapy combination, most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).[211] Some patients, in particular patients in whom anaplastic lymphoma kinase (ALK)-negative disease has been diagnosed, may undergo consolidation chemotherapy consisting of a high-dose chemotherapy regimen with stem cell rescue.[211] No consensus treatment has been established in patients who do not respond to first-line therapy or have recurrent disease following first-line treatment; however, patients are typically treated with a new chemotherapy regimen, including EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), ESHAP (etoposide, methylprednisone, cytarabine, cisplatin), or ICE (ifosfamide, carboplatin, etoposide).[202,211]

Figure 14. Overall High Impact Potential: Brentuximab-vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin's lymphoma or anaplastic large cell lymphoma



Overall, experts commenting on this intervention believe that the potential impact of brentuximab vedotin is high as a novel ADC that may have the potential to effectively treat CD30-positive malignancies that are refractory to standard therapies and have few treatment options. Based on this input, our overall assessment is that this intervention is in the higher end of the high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on use of brentuximab vedotin for the treatment of HL.[212-217] Overall, experts concurred that recurrent or refractory HL presents an important unmet need for new treatment options. They also generally agreed that an ADC might prove to be safer and more efficacious than current chemotherapeutic approaches, and that CD30 represents a theoretically sound target for HL treatment. All but one expert, who represented an independent research perspective, were encouraged by available data suggesting that brentuximab vedotin may improve health outcomes of HL patients. The one outlier was not impressed by available data thus far.

Two experts with a health systems perspective and one clinical expert thought that as an ADC, brentuximab vedotin may increase our understanding of how to treat cancers that continue to have poor treatment outcomes. The two experts with a health systems perspective identified side effects and lack of larger studies as potential barriers to patient and clinician acceptance; however, the other experts thought that brentuximab vedotin would be widely accepted by patients and clinicians because of the

lack of effective treatment options for patients with HL. All experts agreed that brentuximab vedotin would increase the cost of care because it would be additive to current combined modalities.

Overall, all but one expert, who represented a research perspective, thought that brentuximab vedotin has potential to offer an effective option to some patients with HL who are refractory to first-line treatment, while minimizing treatment-associated adverse events.

Seven experts, with clinical, research, and health systems backgrounds, offered comments on the use of brentuximab vedotin for the treatment of ALCL.[218-224] Experts were unanimous in their opinion that patients with ALCL who have failed to be cured by first-line chemotherapy (and in some cases, stem cell transplant) have few effective treatment options and poor prognosis and, therefore, this disease setting represents a significant unmet need. However, the majority of experts also noted that ALCL is a rare condition, which would limit potential impact of this therapy on the overall health system.

The majority of experts believe that the high response rates demonstrated in the phase II trial in patients with treatment-refractory ALCL suggests that brentuximab vedotin has significant potential to improve patient health outcomes. However, multiple experts noted that longer term, followup data are needed to determine whether these responses are durable. Additionally, several experts suggested that the lack of a control arm in the trial made it difficult to assess the response rates. With those data limitations in mind, one expert with a research background suggested that brentuximab-vedotin has only minimal potential to improve patient health outcomes.

Experts did not think that an intravenously administered chemotherapy drug that would be used in a patient population that has likely already undergone prior rounds of intravenous therapy would necessitate significant changes in health care facility staffing or infrastructure or the manner in which patients with ALCL are managed. However, one expert with a clinical background suggested that brentuximab could alter the continuum of care for ALCL if it is shown to be safe and effective in the first-line treatment of the disease.

Experts were unanimous in their opinion that both physicians and patients would be highly likely to adopt the use of brentuximab vedotin for treatment of ALCL, citing the lack of alternatives demonstrating efficacy in refractory ALCL and the encouraging response rates to treatment reported in the clinical trial. Additional factors noted by experts as influencing adoption included the routine and familiar route of administration and the relatively benign side-effect profile. While several experts mentioned the concerns regarding the unknown duration of responses to brentuximab vedotin, they did not believe that this would significantly impact adoption.

While all experts noted the high cost of brentuximab vedotin treatment per patient, many suggested that the impact on overall health care system costs would be limited by the small number of patients with ALCL who would receive the treatment.

Intervention

Crizotinib (Xalkori) for treatment of nonsmall cell lung cancer

Current chemotherapy options for patients in whom advanced nonsmall cell lung cancer (NSCLC) has been diagnosed have a relatively low response rate to current therapies (25% to 30%) and result in 2-year survival rates of only 10% to 15%[225]; therefore, the need is significant for new treatments for this condition. In recent years it has been shown that NSCLC is not a single disease, but rather a collection of related diseases with different molecular underpinnings. In particular, it has been shown that 2% to 7% of NSCLC tumors harbor genetic alterations that result in a fusion of the *ALK* gene with a second gene (e.g., *EML4*).[226] The *ALK* gene encodes a receptor tyrosine kinase that regulates multiple cellular processes, and gene fusions can result in production of an ALK protein product that is constitutively active, which can drive carcinogenesis.[226] Targeted inhibition of ALK kinase activity is a promising therapeutic alternative for these individuals.

Crizotinib (Xalkori®, Pfizer, Inc., New York, NY) is an oral chemotherapy drug that functions as an inhibitor of both ALK and hepatocyte growth factor receptor tyrosine kinase (MET).[227] Early clinical trials of crizotinib demonstrated a tumor response in a subset of patients whose tumors harbored an activating *ALK* mutation, and subsequent studies of crizotinib have focused on tumors containing similar *ALK* mutations.[227] A genetic test on a tumor sample is required to identify patients who may benefit from crizotinib therapy.[226]

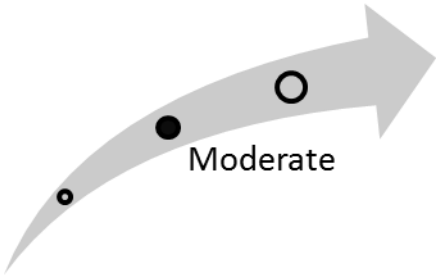
In a single-arm, phase II study published in 2010, Kwak and colleagues reported on 82 patients with *ALK*-mutation positive NSCLC who were treated using crizotinib monotherapy.[226] They reported that 57% of patients in the trial had a tumor response based on Response Evaluation Criteria in Solid Tumors criteria (46 partial responses and 1 complete response), and 33% of patients exhibited stable disease after a median treatment duration of 6.4 months. The twice-daily dose of 250 mg used in the trial was generally well tolerated; frequently reported adverse effects included grade 1 or 2 gastrointestinal side effects. Two phase III trials of crizotinib in the first- and second-line treatment setting are under way.[228,229]

On August 30, 2011, FDA approved the drug on the basis of two single-arm trials showing a response rate. The approval was for patients with locally advanced or metastatic NSCLC that is *ALK*-positive as detected by the FDA-approved test, Vysis ALK Break Apart FISH Probe Kit. [230] The drug cost is about $115,000 per patient per year ($9,600 per months) and the test costs about $1,500. Pfizer introduced a plan to help reduce patient out-of-pocket costs for copays for some patients to $100 per prescription for an annual maximum savings of $24,000.

Clinical Pathway at Point of This Intervention

The initial treatment of NSCLC typically involves surgery to remove the diseased portion of the lung. However, if the tumor is large and/or has spread to adjacent lymph nodes, neoadjuvant chemotherapy and radiation therapy is sometimes used before surgery to reduce the size of the tumor. Following surgery, patients may undergo sequential radiation therapy and chemotherapy or combined chemoradiation treatment. Multiple first- and second-line chemotherapy agents are currently available for the treatment of lung cancer.[231] The choice of one chemotherapy option over the others depends in part on the characteristics of the tumor (e.g., tumor histology, presence of specific genetic changes).[231] Crizotinib represents another first- or second-line chemotherapy option for patients with cancers bearing a specific genetic change at the ALK locus.[227]

Figure 15. Overall High Impact Potential: Crizotinib (Xalkori) for treatment of nonsmall cell lung cancer



Overall, experts commenting on this intervention (comments were submitted before the FDA approval news) thought that if late-stage trials exhibit results similar to preliminary studies, this intervention would be readily adopted by physicians and patients and has potential to significantly improve health outcomes for the small (*ALK*-positive) metastatic NSCLC patient population targeted by this drug. Use of the drug requires a test for eligibility, which experts indicated would change the care pathway and add to costs. Its use could also change the care setting because it might supplant infused chemotherapy options with an at-home oral medication. However, experts thought that the small subset of patients who would be eligible for this treatment might limit its overall impact on all patients with NSCLC. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.[232-237] While the proportion of patients with NSCLC who would be eligible for this targeted treatment is relatively small, the experts all agreed that the scientific rationale for the use of crizotinib in the appropriate patient population is sound. One clinical expert stated that, based on preliminary results, crizotinib would represent a significant improvement in efficacy and adverse event profile compared with currently available treatments for these patients. Multiple experts noted the significance of the use of a diagnostic test to determine whether patients would likely respond to crizotinib treatment, with one clinical expert stating that crizotinib represented a "poster child" for the use of molecular diagnostics and personalized medicine in treatment decisions. However, experts cautioned that this optimism was based on results from a single, mid-stage trial and that further data from controlled studies would be needed. Furthermore, clinical experts stated that crizotinib would not represent a cure for NSCLC and would only delay disease progression, albeit possibly extending survival.

The majority of experts did not view this treatment as disrupting current care models, because crizotinib would represent another treatment option in an expanding set of potential treatments for advanced NSCLC. However, multiple experts noted that orally administered crizotinib has the potential to displace chemotherapy administered by infusion as a first-line therapy in this patient population, which could shift the care setting from the infusion center setting to home care. Additionally, multiple experts noted that the requirement for a diagnostic test to identify eligible patients would need to be incorporated into pretreatment workup for all newly diagnosed NSCLC cases. While an expert with a health systems perspective observed that the incorporation of a genetic test into the treatment model should not present much difficulty, one clinical expert suggested that logistical hurdles in coordinating testing with treatment initiation could require physician training and that the requirement for this test could impede diffusion, especially to underserved populations, because genetic testing would likely be adopted most readily in large, academic, medical centers.

Intervention

Hedgehog pathway inhibitor (vismodegib) for treatment of basal cell carcinoma

Aberrant activation of the Hedgehog signaling pathway drives the development and survival of several tumor types, most prominently basal cell carcinoma, of which the large majority exhibit elevated levels of Hedgehog pathway activity.[238] While pharmacologic inhibition of the Hedgehog pathway would likely be of significant benefit to these patients for whom no consensus systemic treatment exists, no Hedgehog pathway inhibitor is currently available. Vismodegib is an inhibitor of the Hedgehog pathway, and is one of several Hedgehog pathway inhibitors in clinical trials.[238]

Vismodegib (Genentech subsidiary of F. Hoffmann-La Roche, Ltd. [Basel, Switzerland]) is an orally available, small-molecule antagonist of a protein (called Smoothened) that is essential for transducing Hedgehog pathway activity.[239] In basal cell carcinomas, mutations may occur that cause constitutive activation of the Hedgehog pathway.[239] If these mutations affect the Hedgehog pathway at or above the level of Smoothened, vismodegib may be able to reduce the aberrant levels of Hedgehog pathway activity and inhibit tumor growth and/or survival.

A single-arm phase II clinical trial (ERIVANCE BCC) was recently completed for the use of vismodegib (150 mg once daily) in the treatment of 104 patients in whom locally advanced and/or metastatic basal cell carcinoma inappropriate for surgical resection had been diagnosed. The overall response rate, as assessed by independent review, was 43% in patients with locally advanced disease and 30% in patients with metastatic disease. In addition, the median progression-free survival for both patient groups was 9.5 months.[240]

The most common adverse events reported in the trial included muscle spasms, hair loss, altered taste sensation, weight loss, fatigue, nausea, decreased appetite, and diarrhea. Additionally, serious adverse events were observed in 26 patients (25%) of which 4 (representing 4% of patients) were considered vismodegib-related.[240] These serious adverse events included one case each of: blocked bile flow from the liver (cholestasis), dehydration with loss of consciousness (syncope), pneumonia accompanied by an inability of the heart to pump enough blood (cardiac failure), and a sudden arterial blockage in the lung (pulmonary embolism).[240]

Based on the data from this clinical trial, Genentech has submitted to FDA an NDA for vismodegib for the treatment of advanced basal cell carcinoma, and the agency formally accepted the application and granted it priority review status in November 2011.[241]

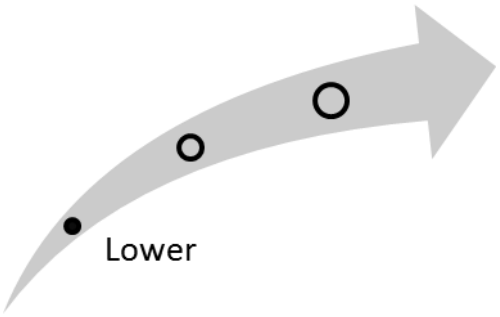
Additional evidence for the activity of vismodegib in basal cell carcinoma comes from an investigator-sponsored trial in patients with basal cell nevus syndrome, a genetic condition in which a hereditary defect leads to the formation of large numbers of basal cell carcinomas that each require surgical extirpation.[242] In this 41-patient trial, treatment with vismodegib (150 mg, once daily) was compared to treatment with placebo for its ability to prevent the formation of new basal cell carcinomas. An interim analysis indicated that patients treated with vismodegib developed 0.07 new basal cell carcinomas per month compared to 1.74 basal cell carcinomas in patients receiving placebo ($p < 0.0001$).[242] In addition, vismodegib was reported as leading to a significant reduction in the size of existing basal cell carcinomas.[242]

Vismodegib and other Hedgehog pathway inhibitors are under study in a wide range of cancers besides basal cell carcinoma.

Clinical Pathway at Point of This Intervention

Most basal cell carcinomas are identified as superficial skin lesions and can typically be treated by surgical resection.[238,243] An alternative primary treatment for these lesions is radiation therapy; however, this treatment is typically reserved for patients over 60 years of age because of concerns about the potential for collateral tissue damage.[243] Lastly, superficial treatments (e.g., photodynamic therapy, cryotherapy, topical chemotherapy) with lower reported cure rates than surgery or radiation therapy might be an option for patients unwilling or unable to undergo surgery or radiation therapy.[243] For basal cell carcinomas that become locally advanced and inoperable or become metastatic, there is no clear consensus on treatment options.[243] Treatments include radiation therapy and various systemic chemotherapy options, typically platinum-based cytotoxic regimens.[243] If approved, vismodegib would provide a new pharmacotherapy option for patients with inoperable/metastatic basal cell carcinomas.[244,245]

Figure 16. Overall Potential Impact: Hedgehog pathway inhibitor (vismodegib) for treatment of basal cell carcinoma



Overall experts commenting on this intervention believe that vismodegib has significant potential to affect the treatment of basal cell carcinoma as a first-in-class agent that has demonstrated compelling response rates in a patient population lacking a systemic treatment option. However, experts were cautious regarding vismodegib's potential to improve patient health outcomes because of the lack of long-term followup data. Additionally, experts believe that vismodegib's impact on the health system as a whole would be limited by the small target patient population. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[246-252] Experts thought the unmet need that vismodegib could address is moderately or very important, citing both the lack of effective systemic treatments for advanced/metastatic basal cell carcinoma and the fact that, if approved, vismodegib would represent a first-in-class inhibitor of the Hedgehog signaling pathway.

Experts also rated the potential for vismodegib to improve patient health outcomes as moderate to large, citing the relatively high response rates to vismodegib therapy reported in the clinical trial for a patient population with few treatment options. One expert with a clinical perspective observed that vismodegib could be used to down-stage large basal cell carcinomas for which surgery would cause significant morbidity and noted that currently no effective neoadjuvant therapy is available. Experts suggested that vismodegib would be readily adopted by physicians and patients alike, citing the lack of viable treatment alternatives for patients with unresectable basal cell carcinoma. While experts were enthusiastic regarding the preliminary data on vismodegib's antitumor activity, several experts noted the preliminary nature of these findings, especially with regard to potential long-term side effects of vismodegib treatment. One expert with a clinical perspective suggested that, based on the currently available data, vismodegib would most appropriately be used in a clinical trial setting until further data are available.

The majority of experts did not think vismodegib would have a significant impact on health disparities. One expert with a clinical perspective suggested that patients presenting with advanced or unresectable basal cell carcinomas tend to be underserved by the health care system and that vismodegib, which is likely to be an expensive treatment and potentially unavailable to some underserved patients, could worsen this disparity.

Because vismodegib is an orally administered drug that would be taken in the outpatient setting, it would not have significant impacts on health care delivery infrastructure or staffing, the majority of experts thought. However, several experts noted that the way in which patients are managed could be changed slightly in that some patients would be referred to medical oncologists if vismodegib became a viable systemic treatment option.

While experts thought that adoption of vismodegib for the treatment of basal cell carcinoma would likely increase the cost of treating these patients, the system-level effect of these costs was seen as minimal because of the relatively small number of patients who are diagnosed with unresectable basal cell carcinoma each year.

Intervention

mTOR inhibitors (ridaforolimus and everolimus) for treatment of various cancers

The mammalian target of rapamycin (mTOR) plays a central role in a cell-signaling pathway regulating multiple cancer-related processes such as cell growth, proliferation, survival, and migration.[253] In addition, multiple mTOR pathway molecules have been shown to be aberrantly expressed and/or mutated in various cancers, suggesting that mTOR inhibitors could function as anticancer agents.[253] Based on this observation, a class of drugs that inhibit mTOR via a mechanism of action similar to that of the naturally occurring macrolide antibiotic rapamycin (also known as sirolimus) has been developed.[253] Rapamycin-like mTOR inhibitors have been approved for the treatment of various cancers, including temsirolimus (Torisel®, Pfizer) for the treatment of renal cell carcinoma[254] and everolimus (Afinitor®, Novartis AG, Basel, Switzerland) for the treatment of renal cell carcinoma, subependymal giant cell astrocytoma associated with tuberous sclerosis, and pancreatic neuroendocrine tumors.[255]

Given mTOR's central role in multiple cancer-related cellular processes, mTOR inhibition may represent a viable treatment modality in a wide range of tumor types and many clinical trials are ongoing in various cancer indications. Potential mTOR inhibitor indications that have reached late stages of development include the treatment of soft tissue sarcomas and the treatment of breast cancer.[256,257]

Patients with advanced soft tissue or bone sarcoma that is unable to be treated by surgical resection have few treatment options and poor prognosis.[258] Front-line systemic chemotherapy options for this condition are largely palliative, and the disease often recurs in patients whose tumors initially respond to chemotherapy.[258] A novel rapamycin-like mTOR inhibitor (ridaforolimus, Merck & Co., Inc. Whitehouse Station, NJ, licensed from ARIAD Pharmaceuticals, Inc., Cambridge, MA) is currently under study as a maintenance therapy to control the growth of metastatic soft tissue or bone sarcomas that have responded to systemic chemotherapy.[256,259] Preliminary results from a randomized, double-blind, placebo-controlled clinical trial of 711 patients (SUCCEED) were presented at the 2011 American Society of Clinical Oncology Annual Meeting.[260] Ridaforolimus (40 mg, daily on a 5 days on/2 days off schedule) met its primary endpoint of improving progression-free survival (17.7 weeks vs. 14.6 weeks, hazard ratio [HR] 0.72, p = 0.0001).[260] While followup for overall survival is ongoing, a preliminary analysis indicated a trend in favor of improved overall survival in the ridaforolimus arm of the trial (88.0 weeks vs. 78.7 weeks, HR 0.92).[260]

Estrogen-receptor (ER)-positive metastatic breast cancer often responds to treatment with endocrine therapy; however, most patients' cancers will develop resistance to front-line endocrine therapy.[261] Multiple mechanisms of developing resistance to endocrine therapy have been identified, including signaling through the mTOR/phosphatidylinositol-3 kinase (PI3K) pathway.[262] Everolimus is currently being tested as an adjunct to the steroidal aromatase inhibitor exemestane in the treatment of patients whose disease has progressed following treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).[257] Preliminary results from a randomized, double-blind, placebo-controlled clinical trial of 705 patients (BOLERO-2) were recently announced by Novartis.[263] Everolimus (10 mg, daily) met its primary endpoint of improving progression-free survival as determined by investigator assessment (6.9 months vs. 2.8 months, HR 0.43, p <0.0001).[263] Additional late-phase studies of everolimus for use in other breast cancer indications are ongoing.[264,265] An earlier study investigating a combination of another mTOR inhibitor (temsirolimus, Pfizer) and letrozole for

first-line treatment of ER-positive metastatic breast cancer was discontinued after an interim analysis showed that adding temsirolimus to letrozole was unlikely to improve efficacy, demonstrating that even within cancer types, subgroups of patients who do or do not respond to a class of therapy exist.[266]

As a drug class, rapamycin-like mTOR inhibitors have been relatively well tolerated. The prescribing information for currently approved compounds lists the most common side effects as anorexia, asthenia, edema, rash, mucositis, and nausea for temsirolimus and abdominal pain, diarrhea, edema, fatigue, fever, headache, nausea, rash, and stomatitis for everolimus.[254,255] mTOR inhibition is also associated with renal failure, elevated blood glucose and lipids, and immunosuppression, which can lead to increased risk of infections.[254,255]

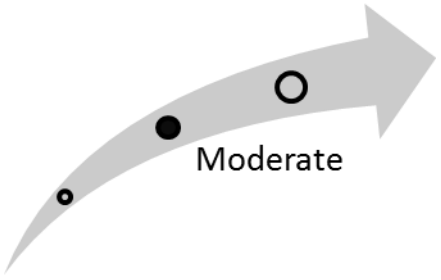
In August 2011, an NDA was submitted to FDA seeking approval for the use of ridaforolimus as a maintenance therapy in metastatic bone and soft tissue sarcomas.[267] Regulatory filings for the use of everolimus in ER-positive breast cancer were expected to be submitted to FDA by the end of 2011.[261]

Clinical Pathway at Point of This Intervention

Soft tissue and bone sarcomas encompass a large number of histologically distinct diseases, and standard of care varies among the different conditions.[268] Generally, patients in whom a localized sarcoma has been diagnosed are treated with some combination of radiation therapy and surgery.[268] Some patients are treated with chemotherapy as a neoadjuvant to reduce tumor size before surgical resection or as an adjuvant targeting tumor cells remaining after surgery.[268] Treatment of metastatic bone sarcomas (e.g., osteosarcoma, Ewing's sarcoma) typically consists of neoadjuvant chemotherapy followed by surgical resection of residual disease.[268] Treatment of metastatic soft tissue sarcomas typically consists of various chemotherapy regimens, which include combinations of multiple drugs, including dacarbazine, doxorubicin, gemcitabine, ifosfamide, platinum agents, and taxanes.[268] Ridaforolimus would potentially be used as a maintenance therapy to control the growth of metastatic soft tissue or bone sarcomas that have responded to systemic chemotherapy.[256]

Patients in whom locally advanced/metastatic ER-positive breast cancer has been diagnosed are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens and may undergo multiple rounds of endocrine therapy.[74] However, a subset of patients with symptomatic disease may be considered for initial treatment with cytotoxic chemotherapy.[74] Patients in whom HER2-negative disease is deemed to have become refractory to endocrine therapy are typically treated with one of several cytotoxic chemotherapy regimens.[74] Everolimus is being tested as an adjunct to the steroidal aromatase inhibitor exemestane in the treatment of patients whose disease has progressed following treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).[257]

Figure 17. Overall Potential Impact: mTOR inhibitors (ridaforolimus and everolimus) for treatment of various cancers



Experts commenting on these interventions suggested that results for progression-free survival were promising in conditions with few treatment options, e.g., advanced soft tissue and bone sarcomas and endocrine-therapy-resistant metastatic breast cancer. Experts were anxious to see data showing that the observed improvements in progression-free survival translated to improved overall survival, before claiming that mTOR inhibitors would have a large impact on patient outcomes. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on the use of ridaforolimus for treatment of soft tissue sarcomas.[269-275] The majority of experts saw the unmet need for improved treatments for soft tissue and bone sarcomas as very important, citing the fact that 40% of patients diagnosed with soft tissue and bone sarcomas die from the disease. In addition, multiple experts noted that currently no treatment is indicated for use as a maintenance therapy following response to chemotherapy; therefore, ridaforolimus purports to fill a novel therapeutic window for this condition.

While experts concurred that preliminary results from a phase III trial demonstrate a statistically significant improvement in the duration of progression-free survival and a trend towards improvement in the duration of overall survival, they were divided on whether the magnitude of this improvement represented a significant improvement in patient health outcomes. One expert with a clinical perspective suggested that future analysis of final data from the clinical trial might identify subtypes of soft tissue and bone sarcomas from among this heterogeneous patient population who derived the greatest benefit from treatment with mTOR inhibitors.

Experts held the unanimous opinion that ridaforolimus would be moderately to widely used by physicians in the treatment of soft tissue and bone sarcomas. Experts thought widespread use of the drug believe the risk-benefit ratio presented in data for ridaforolimus sided in favor of its use as a maintenance therapy. However, the majority of experts thought there would be only moderate adoption by physicians, noting the relatively small improvement reported thus far for both progression-free survival and overall survival. Conversely, the majority of experts believe that patients would be highly likely to opt for maintenance therapy with ridaforolimus, suggesting that patients would be likely to undergo treatment with an orally administered medication that has the potential to increase survival as long as the side effects were manageable.

Given that maintenance therapy with ridaforolimus would be an expensive additional therapy that would likely only delay disease progression, experts thought that use of ridaforolimus would increase the overall costs of treating this condition.

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of everolimus for the treatment of ER-positive breast cancer.[276-282] Experts viewed the unmet need for improved treatments for ER-positive breast cancer resistant to first-line endocrine therapy as moderately to very important, citing the fact that the majority of breast cancers are ER-positive and that most patients with metastatic disease will eventually develop resistance to hormone therapy. Additionally, experts noted that patients with ER-positive metastatic breast cancer resistant to endocrine therapy have a poor prognosis and few treatment options aside from cytotoxic chemotherapy.

The majority of experts believe that everolimus has minimal to moderate potential to improve patient health outcomes. While experts believe that the progression-free survival benefit demonstrated in the BOLERO-2 trial is significant and suggested that the treatment would likely improve overall survival, experts believe that any extension of overall survival would likely be small in duration. One expert with a clinical perspective noted that the toxicity of the addition of everolimus to endocrine therapy is not insignificant, citing the 5 times higher rate of treatment discontinuation reported in the everolimus arm of the BOLERO-2 trial. This clinical expert also noted that this positive result for use of an mTOR inhibitor in breast cancer would need to be balanced against the prior negative result for temsirolimus, but left open the possibility that patients with hormone-refractory disease represent a subpopulation likely to respond to mTOR inhibition.

Experts suggested that both physicians and patients would likely adopt the use everolimus in treating endocrine therapy-resistant breast cancer because of its potential to increase progression-free survival, oral route of administration, and manageable side effect profile relative to the alternative of cytotoxic chemotherapy. However, several experts noted that the use of everolimus in this setting has not demonstrated an overall survival benefit, which some physicians and patients would like to see before adopting treatment.

The majority of experts suggested that use of everolimus to treat endocrine therapy-resistant breast cancer would lead to a moderate increase in the costs of treating this condition. One expert with a clinical perspective noted that if combined treatment with everolimus and exemestane is effective in delaying disease progression, a relatively large population of patients with slowly progressing endocrine therapy-resistant breast cancer could undergo extended treatment with the combination. Two experts with clinical and research perspectives suggested that some controversy regarding cost of this therapy could arise if it ultimately fails to demonstrate a significant improvement in overall survival.

Experts did not think that the use of ridaforolimus or everolimus would have a significant impact on health disparities. However, multiple experts suggested that their oral route of administration could allow a minor reduction in health disparities if patients located in remote locations could avoid the need to travel to cancer centers to receive chemotherapy infusions.

As orally administered medications, ridaforolimus and everolimus were not anticipated by experts to cause significant shifts in health care staffing or infrastructure or require significant changes to the management of patients who would already be closely monitored for disease progression.

Intervention

Multikinase inhibitors (vandetanib and cabozantinib) for treatment of metastatic medullary thyroid cancer

Medullary thyroid cancer is a rare form of thyroid cancer arising from the calcitonin-producing parafollicular (C cells) of the thyroid.[283] Only about 1,500 cases of medullary thyroid cancer are diagnosed per year in the U.S., representing approximately 3% of thyroid malignancies; however, approximately 13% of thyroid-cancer-related deaths are caused by medullary thyroid cancer reflecting the paucity of effective treatment options for this condition.[284,285] In April 2011, vandetanib (Caprelsa®) was approved by FDA as the first, and thus far only, medication specifically indicated for treatment of medullary thyroid cancer.

Vandetanib is a small-molecule, tyrosine kinase inhibitor developed by AstraZeneca (London, UK). The drug has activity against multiple receptor tyrosine kinases, including RET (Rearranged during transfection), vascular endothelial growth factor receptor 2 (VEGFR2), and the epidermal growth factor receptor (EGFR).[286] Each of these receptor tyrosine kinases has been shown to regulate pathways controlling cell growth and proliferation; angiogenesis; and/or cell survival, and their inhibition has demonstrated antineoplastic activity in the treatment of various cancers.[285] With regard to medullary thyroid cancer, aberrant RET signaling has been directly implicated in the pathogenesis of the disease; mutant versions of the RET gene encoding activated forms of the receptor tyrosine kinase have been identified in both hereditary and sporadic forms of the disease and correlations have been made between the type of RET mutation present in an individual and the severity of thyroid tumors occuring in hereditary forms of the disease.[283,285] Therefore, tyrosine kinase inhibitors with activity against RET (e.g., vandetanib, sorafenib, sunitinib, motesanib, cabozantinib) represent promising treatment options for medullary thyroid cancer.[285]

In October 2011, results were published from a double-blind, placebo-controlled study of vandetanib in the treatment of 331 patients in whom locally advanced or metastatic medullary thyroid cancer had been diagnosed.[287] At a median followup of 24 months, patients in the vandetanib arm (n = 231) demonstrated a significant improvement in the duration of progression-free survival compared with patients in the placebo arm (n = 100) (HR 0.46; 95% confidence interval [CI], 0.31 to 0.69).[287] While, researchers attempted to correlate RET mutational status with treatment efficacy, the prescribing information for vandetanib states that no evidence exists of a relationship between RET mutational status and efficacy of treatment.[283,288] No significant difference in the duration of overall survival had been observed at the time of publication, and while overall survival will continue to be monitored, the result may be obscured by crossover of patients from the placebo arm to treatment with vandetanib.[283]

The prescribing information for vandetanib carries a black box warning regarding the risks of heart rhythm abnormalities (QT prolongation, torsades de pointes)and sudden death.[288] Only prescribers and pharmacies certified through the manufacturer's Risk Evaluation and Mitigation Strategy (REMS) program, a restricted distribution program, are able to prescribe and dispense vandetanib.[289] Additional commonly reported adverse events included diarrhea, hypertension, headache, nausea, and rash.[287] As tyrosine kinase inhibitors might be taken over an extended period of time during disease management, adverse events will need to be monitored and managed carefully.

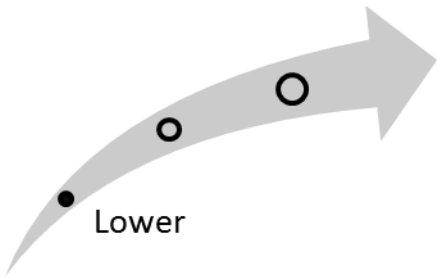
A second tyrosine kinase inhibitor, cabozantinib (Exelixis, South San Francisco, CA), which has activity against RET, VEGFR2, and MET receptor tyrosine kinases has also reached late stages of development.[290] The developer recently announced that cabozantinib had met its primary endpoint of

improving progression-free survival compared with placebo (HR 0.28; 95% CI, 0.19 to 0.40).[290] An NDA application with FDA for cabozantinib was expected to be completed in the first half of 2012.[290]

Clinical Pathway at Point of This Intervention

Patients in whom locally advanced unresectable or metastatic medullary thyroid cancer has been diagnosed have few treatment options. Patients may undergo palliative locoregional treatments such as external beam radiation therapy, radiofrequency ablation, or embolization. Alternatively, patients may undergo treatment with vandetanib, especially in cases of symptomatic or progressive disease.[291] Patients who present with or progress to disseminated symptomatic disease may undergo treatment with vandetanib or, in the case of unavailability of vandetanib or disease progression on vandetanib, other small-molecule, kinase inhibitors (e.g., sorafenib, sunitinib) or dacarbazine-based cytotoxic chemotherapy.[291]

Figure 18. Overall Potential Impact: Multikinase inhibitors (vandetanib and cabozantinib) for treatment of metastatic medullary thyroid cancer



Overall, experts commenting on this intervention thought that the availability of vandetanib for the treatment of metastatic medullary thyroid cancer represents a significant improvement in the available treatment options for this patient population, given the prior lack of effective systemic therapy options. However, experts believe that the small patient population eligible for this treatment and the routine nature of its administration would limit vandetanib's impact on the health care system as a whole. Based on this input, our overall assessment is that this intervention is in the lower end of the high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of vandetanib for treatment of medullary thyroid cancer.[292-298] Preliminary phase III data on the topic of cabozantinib for treatment of medullary thyroid cancer was not available in time for expert comments to be collected on the topic.

From the perspective of the unmet need for systemic treatments for metastatic medullary thyroid cancer, experts agreed that before vandetanib was approved, a significant unmet need existed, citing the lack of efficacious systemic treatments for this condition. However, several experts noted the small number of patients diagnosed with medullary thyroid cancer and suggested that a treatment for this condition would have limited impact on the health care system as a whole.

While one expert with a clinical perspective rated vandetanib's potential to improve patients health as large, other experts viewed vandetanib's potential to improve patient health as only minimal to moderate. While all experts pointed to vandetanib's reported effect of increasing the duration of progression-free survival, experts viewing vandetanib's potential more skeptically noted the significant side effects associated with treatment and questioned whether the demonstrated increase in progression-free survival would translate to a significant increase in the duration of overall survival.

Generally, experts did not think that the availability of vandetanib would have a large impact on health disparities. Experts who thought there would be a shift believe that the high cost and limited availability of the drug through the REMS program could worsen health disparities by further limiting access to treatment for underserved patient populations.

Vandetanib is the first systemic treatment to demonstrate a clear benefit in this patient population; experts anticipated that both patients and physicians would readily adopt its use in spite of the potential for significant adverse events. Experts did not anticipate that patient treatment with vandetanib, an orally administered medication, would require significant changes to the health care delivery infrastructure or the manner in which patients are managed.

As a novel medication that would likely be administered over a significant period of time, vandetanib has a moderate to large potential to increase the cost of care for patients with medullary thyroid cancer, the majority of experts thought. However, experts also noted that the small number of patients presenting with metastatic medullary thyroid cancer each year would limit the impact of these costs on the health care system as a whole.

Intervention

Radium-223 (Alpharadin) for treatment of solid tumor bone metastases

Many cancers, in particular cancers of the breast, prostate, and lung, metastasize to bone, where they can cause complications such as chronic pain and skeletal-related events (e.g., fractures) that can adversely affect both patient quality of life and survival.[299] Current treatments targeting bone metastases are largely palliative in nature, providing relief from pain or delaying skeletal-related events without having significant effects on overall disease progression or patient survival. Alpharadin® has the potential to be the first bone metastasis-targeted agent that has effects on both bone metastasis symptoms and patient survival.

Among the current treatment options for bone metastases are the radionuclides strontium-89 and samarium-153-EDTMP, radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases.[299] Preferential accumulation of the radioactive compound purportedly functions to concentrate the radiation dose at the target bone metastases. While currently available radionuclides have shown efficacy in the palliation of bone pain, the type of radiation that they emit penetrates tissues deeply enough to negatively impact the bone marrow, which limits the deliverable dose and restricts their use to one of symptom palliation.[300] Alpharadin (a preparation of radium-223) is a novel bone metastasis-targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than the radiation generated by currently available radiopharmaceuticals.[301] This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes.[301]

The developers of Alpharadin (Algeta ASA, Oslo, Norway, and Bayer AG, Leverkusen, Germany) recently announced preliminary results from a randomized, double-blind, clinical trial of Alpharadin versus placebo in the treatment of 900 patients with castration-resistant prostate cancer with skeletal metastases who were ineligible for initial treatment or further treatment with docetaxel.[302] An independent committee recommended that the trial be stopped following an interim analysis that demonstrated treatment with Alpharadin improved overall survival relative to placebo (median overall survival 14.0 vs. 11.2 months, two-sided p-value = 0.0022, HR 0.699).[302] Treatment with Alpharadin was also reported to have demonstrated improvement in secondary endpoints such as the time to first skeletal-related event, percentage of patients achieving normalized total alkaline phosphatase levels, and time to prostate-specific antigen progression.[302] Commonly reported adverse events included anemia, bone pain, constipation, diarrhea, nausea, and vomiting; however, rates of adverse events were similar in the Alpharadin and placebo arms of the trial.[302] The relatively benign adverse event profile of Alpharadin treatment may allow its use in combination with existing cancer treatments. An early-phase, clinical trial is currently under way testing the combination of Alpharadin with the standard chemotherapy agent docetaxel in the treatment of castration-resistant prostate cancer.[303]

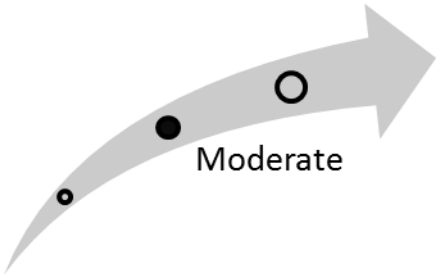
Alpharadin has been granted fast track status by FDA for the treatment of castrate-resistant prostate cancer with bone metastases.[304] A new drug application for this indication is anticipated to be filed sometime in 2012.[299] Alpharadin is also under study for the treatment of patients diagnosed with breast cancer with skeletal metastases; however, these trials are currently only at the phase II stage.[299]

An additional developmental agent that has exhibited promise in the treatment of prostate cancer bone metastases is the MET/RET/VEFGR2 kinase inhibitor cabozantinib (Exelixis); phase III clinical trials of this compound in the treatment of prostate cancer have been initiated.[305]

Clinical Pathway at Point of This Intervention

Patients with systemic cancer that has metastasized to bone are typically treated with a combination of locoregional treatment of bone metastases, systemic therapies, and pain medications.[306] Palliative local treatments for bone metastases include external beam radiation therapy and surgical resection of the lesion.[299] Systemic treatments include antineoplastic therapies such as chemotherapy and hormone therapy as well as agents that modulate bone remodeling such as bisphosphonates and the RANKL antibody denosumab.[299] Additional systemic agents that are targeted to bone include radiopharmaceuticals such as strontium-89 and samarium-153-EDTMP (ethylenediamine tetra [methylene phosphonic acid]), which preferentially accumulate in sites of bone metastasis and expose the cancer cells to beta and/or gamma radiation.[306] Radium-223 would represent a novel systemic radionuclide treatment for bone metastases that would be the first alpha-particle-emitting radionuclide indicated for treatment of this condition.

Figure 19. Overall Potential Impact: Radium-223 (Alpharadin) for treatment of solid tumor bone metastases



Overall, experts suggested that Alpharadin has significant potential to improve on current treatments for bone metastases, particularly for patients with prostate cancer bone metastases. While experts thought there is significant potential for Alpharadin to be widely adopted for treatment of bone metastases, the highly similar nature of Alpharadin to existing treatments suggested to experts that adoption of Alpharadin use would have limited impact on health care system infrastructure and practices. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[307-313] The majority of experts rated the need for improved treatments for bone metastases as having moderate importance, citing the high prevalence of bone metastases in advanced cancers and the significant impact that these metastases can have on patient quality of life and survival. Experts rating the unmet need addressed by Alpharadin as high suggested that the compound's purported improved safety profile relative to existing radiopharmaceutical treatments for bone metastases represents a significant improvement. However, one expert with a health systems perspective who rated the unmet need addressed by Alpharadin as minimal suggested that the compound represents an incremental improvement on existing radiopharmaceuticals.

All experts believe that Alpharadin has moderate to large potential to improve patient health, citing the increased duration of overall survival demonstrated in the recently completed phase III, clinical trial and the fact that the toxicity profile for Alpharadin appears to be relatively benign. In addition, several experts noted the ability of Alpharadin to affect skeletal-related symptoms (e.g., pain) in addition to its effects on survival and disease progression.

Generally, experts did not think Alpharadin would cause a significant shift in health disparities. A few experts noted that the likely premium price of Alpharadin relative to existing palliative treatments might place the treatment out of reach for some patients, potentially worsening health disparities. Conversely, one expert with a research perspective suggested that underserved populations might

present with more advanced disease and, therefore, Alpharadin might have a larger impact in these underserved populations.

Experts also did not think that Alpharadin would require significant changes to health care delivery and infrastructure or the manner in which patients are managed, noting the similarity between Alpharadin treatment methods and those used for currently employed radiopharmaceuticals.

In line with their view that Alpharadin has significant potential to improve health outcomes, all experts suggested that Alpharadin would likely be adopted by physicians and patients alike. Experts cited Alpharadin's reported efficacy in treating prostate cancer bone metastases, ease of use, and routine administration as factors influencing physician adoption and Alpharadin's relatively benign safety profile and potential to improve both severity of bone pain and duration of survival as factors influencing patient adoption. One expert with a research perspective suggested that some patients might be reluctant to opt for a treatment involving infusion of a radioactive isotope; however, this expert still believes that Alpharadin has moderate potential to be adopted by patients.

Experts suggested that Alpharadin would likely be priced at a premium relative to current radiotherapy options and, therefore, the majority of experts indicated that Alpharadin would increase the overall cost of care.

Intervention

Trastuzumab emtansine for treatment of breast cancer

HER2-positive breast cancer is a subclass of invasive breast cancer characterized by the expression of high levels of the EGFR family member HER2 and comprises approximately 20% of breast cancer cases.[314] Historically, HER2-positive breast cancer has been associated with more aggressive disease and poor outcomes.[314] While the treatment of HER2-positive breast cancer has improved with the availability of HER2-targeted therapies such as the HER2-specific monoclonal antibody trastuzumab (Herceptin®, Genentech) and the HER2 kinase inhibitor lapatinib (Tykerb®, GlaxoSmithKline), many patients' cancers still progress on these treatments and compounds with improved efficacy and/or efficacy against resistant disease are highly desired.[315]

Trastuzumab emtansine (formerly called trastuzumab-DM1), an ADC, is an investigational new biologic that couples a HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1).[316] The antibody and drug are coupled in such a way that emtansine is held in a stable inactive form outside of the cell; only upon cellular uptake of the drug conjugate mediated by binding of the antibody to the HER2 receptor is emtansine released and activated.[316] In this way, the cytotoxic activity of emtansine is targeted to cells expressing the HER2 receptor, preferentially targeting tumor cells (which express high levels of HER2) and sparing many normal tissues from the toxic effects of the drug. Preclinical studies have demonstrated that trastuzumab emtansine retains the antiproliferative activity of trastuzumab, and the cytotoxic activity of emtansine may endow the compound with additional antitumor properties even in tumors that have become independent of HER2 signaling (a hallmark of some tumors that have become resistant to trastuzumab and/or lapatinib).[315]

Preliminary evidence for the activity of trastuzumab emtansine came from a phase II trial treating patients with metastatic HER2-positive breast cancer that had progressed following treatment with trastuzumab-based and lapatinib-based chemotherapy regimens.[317] In this single arm trial of 100 heavily pretreated patients, trastuzumab emtansine resulted in an objective tumor response in 33% of patients.[317] In addition, it was recently announced that a second phase II trial of 120 patients in the first-line treatment of metastatic disease demonstrated that trastuzumab emtansine as compared with trastuzumab plus docetaxel resulted a significant increase in the duration of progression-free survival (14.2 months vs. 9.2 months, HR 0.59).[318] In addition, Roche reported that fewer severe adverse events were reported in the trastuzumab emtansine arm than the trastuzumab plus docetaxel arm; grade 3 or higher adverse events were reported by 46.4% of patients and 89.4% of patients in the trastuzumab emtansine and trastuzumab plus docetaxel arms, respectively.[318] Trastuzumab emtansine is currently under study in two phase III clinical trials: (1) versus trastuzumab and a taxane as a first-line treatment for metastatic disease,[319] and (2) versus lapatinib and capecitabine as a second-line treatment for metastatic disease that has progressed following treatment with trastuzumab.[320]

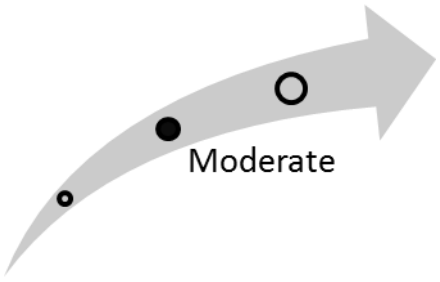
Trastuzumab emtansine is currently being developed by Roche.[321] In 2010, Roche submitted a biologic license application to FDA for use of trastuzumab emtansine as third-line treatment based on results from the initial phase II trial.[322] FDA issued a refuse to file letter to Roche, stating that the trial did not meet the standards for accelerated approval because all potential available treatment options had not been exhausted in the patient population under study.[322] Assuming that trastuzumab emtansine exhibits efficacy in the currently ongoing phase III trial, Roche estimated that a regulatory filing for trastuzumab emtansine in the second-line setting could occur as early as 2012.[321] A regulatory filing for trastuzumab emtansine in the first-line setting was not anticipated until 2014.[321]

An additional HER2-targeted therapy in development is the monoclonal antibody pertuzumab (Roche).[323] Pertuzumab is purported to inhibit HER2 activity through a mechanism of action different from that of trastuzumab and may act synergistically with trastuzumab treatment.[324] The developer recently announced positive results from the phase III CLEOPATRA study, which demonstrated that a combination of trastuzumab, docetaxel, and pertuzumab extended progression-free survival compared with trastuzumab, docetaxel, and placebo in chemotherapy-naïve patients diagnosed with metastatic breast cancer.[324]

Clinical Pathway at Point of This Intervention

Patients with HER2-positive breast cancer that has become metastatic or locally advanced and untreatable by surgical resection are typically treated using a series of HER2-targeted therapies. Standard first-line therapy typically includes treatment with trastuzumab plus a single cytotoxic chemotherapy agent (e.g., capecitabine, docetaxel, paclitaxel, vinorelbine).[74] Patients whose disease progresses following first-line therapy are typically treated with a second HER2-targeted therapy, typically lapatinib plus capecitabine.[74] Alternative second-line chemotherapy options include trastuzumab plus a cytotoxic agent that was not used in first-line treatment or trastuzumab plus lapatinib.[74] Trastuzumab emtansine is currently under study as a first- and second-line treatment option that could displace the use of current treatments. An additional HER2-targeted therapy that has the potential to be used as an adjunct to current metastatic HER2-positive breast cancer treatments is the monoclonal antibody pertuzumab, which binds HER2 in a different manner from trastuzumab and is purported to inhibit HER2 dimerization/activation.[315]

Figure 20. Overall High Impact Potential: Trastuzumab emtansine for treatment of breast cancer



Overall experts commenting on this intervention believe that trastuzumab emtansine has significant potential to provide an incremental improvement upon existing HER2-positive metastatic breast cancer treatments, the shortcomings of which they thought represented a significant unmet need. Experts also thought that trastuzumab emtansine's potential to displace current standard of care treatments for HER2-positive metastatic breast cancer and likely high cost could have significant impacts on the management of these patients. Based on this input, our overall assessment is that this intervention is in the moderate high potential impact range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.[325-331] Experts agreed that treatment of metastatic breast cancer represents a significant unmet need. The majority of experts also believe that the rationale behind the mechanism of action of trastuzumab emtansine is sound, citing the established anti-HER2 activity of trastuzumab that could be harnessed to target a cytotoxic agent. While several experts noted the potential to move away from treatment regimens containing systemic cytotoxic chemotherapy agents, experts believe that the improvements relative to the efficacy of current treatments for HER2-positive metastatic disease would likely be incremental, especially in the third-line refractory disease setting. Multiple experts noted that if trastuzumab emtansine were shown to improve outcomes in the first-line metastatic disease or adjuvant setting, it could have a more significant impact on HER2-positive disease treatment models.

Because health care workers would administer the drug in the same manner as existing HER2-targeted therapies (e.g., trastuzumab), experts did not think that adoption of trastuzumab emtansine would require significant changes in health care facility staffing or infrastructure. Similarly, experts did not think there would be a significant learning curve for clinicians administering trastuzumab emtansine. As such, experts saw few obstacles to patients or physicians adopting the use of trastuzumab emtansine, provided that it demonstrates improved outcomes in late-phase clinical trials. One potential obstacle raised by experts was the likely high cost of trastuzumab emtansine, which could affect patient out-of-pocket costs. Additionally, experts noted that the likely high cost of trastuzumab emtansine had the potential to be controversial in terms of the cost-benefit ratio and has the potential to increase health disparities.

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