

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

Priority Area 02: Cancer

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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. HHSA290201000006C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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Preface

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

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

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

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

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identifying 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 4 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,000 leads about potential topics has resulted in identification and tracking of about 1,800 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 600 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice annually. Topics eligible for inclusion are those interventions expected to be within 0–4 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 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

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the 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 designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received, and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is 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 50 topics for which (1) preliminary data from a trial intended to support regulatory approval for drugs (i.e., phase III data for most drugs and phase II data for accelerated, fast-track, or orphan drugs), phase II or III data for devices or procedures, or data from pilot programs were available; (2) information was compiled and sent for expert comment before May 16, 2013, in this priority area; *and* (3) we received five to nine sets of comments from experts between October 25, 2011, and May 8, 2013. (A total of 176 topics in this priority area were being tracked in the system as of May 18, 2013.) For purposes of this report, we aggregated related topics for summary and discussion (i.e., by drug class). Topics in this Executive Summary and report are organized alphabetically by disease state and by intervention within that disease state. We present 16 summaries on 19 topics (indicated by an asterisk) that emerged as having higher-impact potential on the basis of expert comments and assessment of potential impact.

Priority Area 02: Cancer

Topics	High-Impact Potential
1. *Ado-trastuzumab emtansine (Kadcyla) antibody-drug conjugate for treatment of advanced HER2-positive breast cancer	Moderately high
2. Afatinib (Tamtovok) for treatment of nonsmall cell lung cancer	No high-impact potential at this time
3. Anti-GD2 monoclonal antibody (ch14.18) for treatment of neuroblastoma	No high-impact potential at this time
4. *Automated breast ultrasound for breast cancer screening of patients with dense breast tissue	Moderately high
5. Axillary reverse mapping–guided breast cancer treatment for prevention of lymphedema	No high-impact potential at this time
6. *Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory anaplastic large cell lymphoma	Moderately high
7. *Brentuximab vedotin (Adcetris) for recurrent or treatment-refractory Hodgkin’s lymphoma	Moderately high
8. Bruton’s tyrosine kinase inhibitor (ibrutinib) for treatment of mantle cell lymphoma	No high-impact potential at this time
9. Carfilzomib (Kyprolis) for treatment of multiple myeloma	No high-impact potential at this time

Topics	High-Impact Potential
10. CD34-positive cell selection system (CliniMACS) for treatment of acute myeloid leukemia	No high-impact potential at this time
11. Cologuard fecal DNA test for colorectal cancer screening	No high-impact potential at this time
12. Computer-assisted system (Sedasys) for automated propofol sedation during gastrointestinal endoscopy	No high-impact potential at this time
13. *Crizotinib (Xalkori) for treatment of advanced nonsmall cell lung cancer	Moderately high
14. Dabrafenib (Tafinlar) for treatment of metastatic melanoma	No high-impact potential at this time
15. *Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Moderately high
16. *Everolimus (Afinitor) for treatment of advanced estrogen receptor–positive breast cancer	Moderately high
17. Everolimus (Afinitor) for treatment of renal angiomyolipoma	No high-impact potential at this time
18. High-intensity focused ultrasound (Ablatherm) for treatment of localized prostate cancer	No high-impact potential at this time
19. High-intensity focused ultrasound (Sonablate) for treatment of localized prostate cancer	No high-impact potential at this time
20. I-124 girentuximab (Redectane) positron emission tomography for detection of clear cell renal cell carcinoma	No high-impact potential at this time
21. Immature PSA ([–2]proPSA) assay as a decision aid regarding prostate cancer biopsy	No high-impact potential at this time
22. *Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Lower end of the high-impact-potential range
23. *Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Lower end of the high-impact-potential range
24. Liposome encapsulated vincristine (Marqibo) for treatment of acute lymphoblastic leukemia	No high-impact potential at this time
25. Magnetic resonance imaging–guided focused ultrasound therapy (ExAblate) for treatment of pain from bone metastases	No high-impact potential at this time
26. *Magnetic resonance imaging–ultrasound image fusion for image-guided prostate biopsy	Lower end of the high-impact-potential range
27. *MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy	Moderately high
28. *Methylated Septin 9 blood test for colorectal cancer screening	Lower end of the high-impact-potential range
29. Nab-paclitaxel (Abraxane) for treatment of pancreatic cancer	No high-impact potential at this time
30. Off-label maraviroc (Selzentry) for prevention of graft-versus-host disease	No high-impact potential at this time
31. Off-label metformin for treatment of breast cancer	No high-impact potential at this time
32. Omacetaxine mepesuccinate (Synribo) for treatment of tyrosine kinase inhibitor-resistant chronic myelogenous leukemia	No high-impact potential at this time
33. Pazopanib (Votrient) for treatment of soft tissue sarcomas	No high-impact potential at this time
34. *Pertuzumab (Perjeta) for treatment of advanced HER2-positive breast cancer	Moderately high
35. Polydisperse oligonucleotide (defibrotide) for treatment of chemotherapy-induced severe veno-occlusive disease	No high-impact potential at this time
36. Pomalidomide (Pomalyst) for treatment-refractory multiple myeloma	No high-impact potential at this time
37. *Ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or chromosome–positive acute lymphoblastic leukemia	Lower end of the high-impact-potential range
38. *Radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases	Moderately high
39. Ramucirumab for treatment of gastric cancer	No high-impact potential at this time
40. Regorafenib (Stivarga) for treatment of colorectal cancer	No high-impact potential at this time

Topics	High-Impact Potential
41. Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors	No high-impact potential at this time
42. Remestemcel-L (Prochymal) for treatment of acute graft-versus-host disease	No high-impact potential at this time
43. *Ruxolitinib (Jakafi) for treatment of myelofibrosis	Lower end of the high-impact-potential range
44. Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	No high-impact potential at this time
45. *Specialized care model for adolescents and young adults with cancer	Lower end of the high-impact-potential range
46. Tilmanocept (Lymphoseek) for sentinel lymph node detection	No high-impact potential at this time
47. Trametinib (Mekinist) for treatment of advanced melanoma with activated BRAF mutation	No high-impact potential at this time
48. *Vemurafenib (Zelboraf) for treatment of metastatic melanoma	High
49. *Vismodegib (Erivedge) for treatment of advanced basal cell carcinoma	Moderately high
50. Ziv-aflibercept (Zaltrap) for treatment of metastatic colorectal cancer	No high-impact potential at this time

Discussion

Topics that emerged as having potential for high impact in the cancer area included novel drugs, biologics, and devices for treatment; novel screening and diagnostic tests; a device used during surgical procedures, and a specialized care delivery program for adolescents and young adult oncology patients. The conditions that these interventions addressed are solid tumors (advanced basal cell carcinomas, breast cancer, colorectal cancer (CRC), melanoma, nonsmall cell lung cancer (NSCLC), prostate cancer, and solid tumor bone metastases) and hematologic malignancies (anaplastic large cell lymphoma [ALCL], chronic myelogenous leukemia [CML], Hodgkin's lymphoma [HL], myelofibrosis, and chromosome-positive acute lymphoblastic leukemia [Ph+ ALL]).

The group of therapeutic agents includes both small-molecule and biologic drugs. Most small-molecule drugs have a well-defined mechanism of action and target a specific signaling pathway. Large-molecule drugs include antibody-drug conjugates (ADCs) directed to tumor-associated surface antigens. Diagnostic topics offer potentially simpler or purportedly improved solutions to existing technologies.

Adolescent and Young Adult Oncology

Specialized Care Model for Adolescents and Young Adults with Cancer

- **Key Facts:** The improved health outcomes resulting from recent advancements in pediatric and older adult cancer care have not been realized by adolescents and young adult (AYA) patients (aged 13–30 years) with cancer. Several reasons have been given for this. AYAs represent a distinct patient population with unique clinical and supportive care needs, but many receive care on pediatric or adult units where they have little in common with those patient groups in clinical concerns/issues, and psychological, emotional, educational, and financial needs. Often, treatment adherence can pose a problem in the AYA population because of life circumstances (e.g., school, lack of experience navigating the health system, limited financial resources, desire to maintain independence, concerns about appearance, concerns about maintaining peer relationships). In recognition of the unique needs of AYAs, along with the observation that pediatric cancer outcomes improved after pediatric-specific oncology care models were adopted decades ago, some institutions have begun to develop

specialized AYA cancer care models. One care model pioneered by the Teenage Cancer Trust of the United Kingdom in collaboration with the U.S.-based Teen Cancer America provides an example of a comprehensive AYA-specialized oncology program that may address the many unmet needs of these patients. These charitable organizations are partnering with hospitals to develop fully dedicated AYA oncology units with AYA-tailored clinical and social space. Staff on these units receive special training on AYA-specific clinical and psychosocial needs and provide tailored programming and supportive care services. Primary goals of these programs include enhanced treatment adherence, improved patient satisfaction and quality of life, as well as better clinical trial enrollment rates enabling robust testing of new therapies in this patient population. For example, AYA units may offer modified schedules for treatment (e.g., late afternoon and evening) to prevent excess disruption to the daily schedules of AYA patients and promote treatment adherence. Clinical spaces are designed to mimic a home environment with dedicated space for education and peer social activities. Family and psychosocial therapy are often provided. Specially trained staff include doctors and nurses with a specialty in common AYA cancers and care issues and extensive knowledge of clinical trial opportunities for AYAs. Additionally, the units offer youth support coordinators who are trained to address the psychosocial and supportive care needs that arise during treatment and help to ease patients' transition back into school or work. Efforts are ongoing to establish metrics to assess the health impact of these dedicated units and specialized programs. Teenage Cancer Trust has established more than 20 dedicated units in hospitals and cancer centers throughout the U.K.; Teen Cancer America, following the U.K. model, recently established its first AYA unit in the United States, and plans for several additional centers are ongoing.

- **Key Expert Comments:** Experts commenting on this intervention saw significant potential for this approach to improve health outcomes for AYAs with cancer. They anticipated widespread adoption and acceptance among both clinicians and patients, but noted the substantial resources required to establish fully dedicated AYA oncology units. The experts provided an overall positive assessment of this program, while expressing the need for additional outcomes data to determine the potential magnitude of impact on patient health.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Breast Cancer

Automated Breast Ultrasound for Breast Cancer Screening of Patients with Dense Breast Tissue

- **Key Facts:** Screening mammography has increased the breast cancer detection rate among screened women, but misses a significant number of breast cancers, especially in the 40% of women with dense breasts. Ultrasound (US) imaging may be of particular use in this patient population because of its ability to provide high contrast between most breast cancers and dense breast tissue. However, US is not routinely used to screen asymptomatic women in the United States, in part because of the time-intensive nature and interoperator variability of manual US screening methods. By addressing some of these issues, automated breast ultrasound systems may allow incorporation of US into routine breast cancer screening as an adjunct to mammography for women with dense breasts. One automated breast ultrasound (ABUS) system, the sono.v ABUS (GE Healthcare division of General Electric Co., Fairfield, CT), was recently approved for use in breast cancer screening. The approval was

based on results of a reader study that demonstrated increased sensitivity for breast cancer in women with dense breasts when x-ray mammography was followed by ABUS compared with the sensitivity of mammography alone. Breast density is typically classified by radiologists who apply the American College of Radiology BI-RADS® breast density scale, which is a subjective assessment of breast density to categorize a patient's breast tissue as 1 (least dense) to 4 (most dense). Sensitivity for breast cancer across all readers was 38.8% for mammography alone compared with 63.1% for mammography plus ABUS (a difference of 24.3%, 95% confidence interval 10.7% to 37.9%, $p < 0.002$). Specificity for breast cancer across all readers was 78% for mammography alone compared with 76% for the addition of ABUS (a difference of -2.0%, 95% confidence interval -7.7% to 4.3%, $p = 0.518$). Larger studies of the system in a screening population are ongoing. A search of 14 representative, private, third-party payers that publish their coverage policies online identified none with a specific policy regarding use of ABUS for breast cancer screening; thus, lack of reimbursement for its use as a screening tool could be a barrier to adoption.

- **Key Expert Comments:** Experts commenting on this topic suggested that a significant unmet need exists to improve breast cancer detection in women with dense breasts and commented positively on the theoretical potential of ABUS to address this need in the screening setting. However, experts suggested that further study demonstrating an impact on long-term patient outcomes would be needed before widespread adoption is likely in the screening setting.
- **Potential for High Impact:** Moderately high

Everolimus (Afinitor) for Treatment of Advanced Estrogen Receptor–Positive Breast Cancer

- **Key Facts:** Pharmacologic inhibitors of the mammalian target of rapamycin (mTOR) have been approved for treating various cancers, such as renal cell carcinoma 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 using mTOR inhibitors for treating a wide variety of cancers. Researchers recently reported results of a study of the mTOR inhibitor everolimus (Afinitor®, Novartis International AG, Basel, Switzerland) for treating estrogen receptor–positive breast cancer. This trial 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 reporting results of a 724-patient trial, researchers noted that adding everolimus to exemestane yielded a statistically significant improvement in progression-free survival of about 4 months. As a drug class, mTOR inhibitors are relatively well tolerated. The most common adverse events included stomatitis/mucositis, infections, rash, and fatigue; however, serious side effects such as renal failure, elevated levels of blood glucose and lipids, and immunosuppression (which can lead to increased risk of infections) have also been reported. In July 2012, the U.S. Food and Drug Administration (FDA) approved everolimus used combination with exemestane to treat postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole. Recent data from late-stage everolimus trials in patients with HER2-positive breast cancer suggest that this agent may also be effective for treating HER2-positive disease.

- **Key Expert Comments:** Experts commenting on this intervention suggested that results for progression-free survival in endocrine therapy-resistant, metastatic breast cancer were promising for a condition with few treatment options. Experts hope data will eventually show that the observed improvement in progression-free survival translates to increased overall survival, which they believe would have a large impact on patient care and treatment options.
- **Potential for High Impact:** Moderately high

MarginProbe System for Intraoperatively Identifying Positive Margins During Breast Cancer Lumpectomy

- **Key Facts:** Breast-conserving surgery followed by radiation therapy for early-stage breast cancer can achieve low recurrence rates equivalent to those achieved with total mastectomy. Achieving optimal outcomes with this technique, however, requires that the margins of the tissue excised during surgery be cancer free. If subsequent pathologic analysis reveals surgical margins are not cancer free, patients typically need to undergo a second surgery to remove additional tissue. Therefore, techniques for identifying clean tissue margins during the initial surgery are highly sought. Although several techniques have been developed (e.g., frozen sections, touch-prep cytology), the reported rate of secondary surgeries for unclear margins remains about 30%. The MarginProbe™ System (Dune Medical Devices, Caesarea, Israel) purportedly provides an objective means of rapidly assessing surgical margins intraoperatively using radiofrequency (RF) spectroscopy, which may be able to differentiate between normal and cancerous tissue based on bioelectric differences between the two tissue types. The MarginProbe algorithm is based on a training set of many comparisons between RF spectroscopy readings and pathology results and provides a binary (yes/no) answer as to whether the assessed margin is clean. In results from a 664-patient trial of the device, the MarginProbe System used in combination with standard intraoperative assessment was compared with standard intraoperative assessment alone. MarginProbe use reportedly increased the rates at which positive surgical margins were identified and additional tissue was removed to achieve clean surgical margins (72% for MarginProbe; 22% for standard assessment, $p < 0.0001$). This led to an approximate 50% reduction in the number of patients who needed to undergo a reexcision procedure. In January 2013, FDA approved the MarginProbe for marketing and the first U.S. system was installed in March 2013. With regard to reimbursement and coverage, the device is used in the context of inpatient surgery for tumor removal, and thus its use may be considered integral to the primary procedure and covered under the primary procedure code.
- **Key Expert Comments:** Experts commenting thought this technology has potential to fill a significant unmet need for rapidly assessing surgical margins to ensure clean margins and obviate the need for a second surgery. Experts suggested that such a technology could significantly improve patient health outcomes by avoiding the need to perform second surgeries in a large number of women undergoing breast-conservation surgery. However, experts expressed a desire to see more data that definitively determine whether the system actually improves the rate of positive-margin detection and adequate excision of additional tissue for most patients.
- **Potential for High Impact:** Moderately high

Novel Targeted Therapies (Ado-Trastuzumab Emtansine; Pertuzumab [Perjeta]) for Advanced HER2-Positive Breast Cancer

- **Key Facts:** HER2-positive breast cancer is a subclass of invasive breast cancer characterized by expression of high levels of epidermal growth factor receptor family member HER2. This subtype comprises about 20% of breast cancer cases and is associated with more aggressive disease and poorer outcomes. Although treatment of HER2-positive breast cancer improved with the advent of HER2-targeted therapies such as trastuzumab (Herceptin®) and lapatinib (Tykerb®), many patients' cancers still progress with these treatments, and compounds with improved efficacy and/or efficacy against resistant disease are greatly needed.

Two novel targeted therapies were recently approved: ado-trastuzumab emtansine (Kadcyla™, F. Hoffmann-La Roche, Ltd., Basel, Switzerland) and pertuzumab (Perjeta®, also being developed by Roche). Both are given as intravenous infusions in an outpatient infusion center setting. Ado-trastuzumab emtansine, formerly known as trastuzumab-DM1, is an ADC that couples an 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 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 drug's toxic effects. Ado-trastuzumab emtansine is in many phase III trials for metastatic breast cancer. The manufacturer recently announced that one of these trials (EMILIA) testing the therapy against standard second-line therapy of lapatinib and capecitabine had demonstrated increased progression-free and overall survival, as well as reducing the overall rate of severe adverse events. In February 2013, FDA approved ado-trastuzumab emtansine for second-line treatment of HER-2 positive metastatic breast cancer for use as a monotherapy. The biologic is given at a dosage of 3.6 mg/kg, given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The reported wholesale cost per patient is about \$9,800 per month.

Pertuzumab is a novel HER2-specific monoclonal antibody that binds to a different site on the HER2 receptor than the available HER2-targeting monoclonal antibody trastuzumab. Mechanistically, pertuzumab is purported to prevent HER2 from interacting with other HER family receptors, which is required for their activation and function in breast cancer pathogenesis. Because pertuzumab functions through a mechanism of action distinct from that of trastuzumab, combining these two HER2-specific antibodies has the potential to improve outcomes. Like trastuzumab-emtansine, pertuzumab is in several phase III trials for treating localized breast cancer after surgery and for treating metastatic breast cancer. The most advanced trial of pertuzumab studied adding pertuzumab to a standard first-line treatment for metastatic breast cancer (trastuzumab plus docetaxel). Pertuzumab extended progression-free survival by about 6 months in this patient population. Pertuzumab is administered intravenously at an initial dose of 840 mg over a 60-minute infusion followed every 3 weeks by a 420 mg dose given over 30–60 minutes. In June 2012, FDA approved pertuzumab for first-line treatment of HER-2 positive metastatic breast cancer in combination with trastuzumab and docetaxel. The reported wholesale cost per patient is about \$5,900 per month.

Both of these therapies are typically covered by insurance after prior authorization for outpatient infusion therapy that is consistent with the labeled indications.

- **Key Expert Comments:** Overall, experts commenting on these interventions believe that ado-trastuzumab emtansine and pertuzumab have significant potential to incrementally improve outcomes for patients with HER2-positive metastatic breast cancer. They thought that the shortcomings of the previous therapies represented a significant unmet need. Experts also thought that ado-trastuzumab emtansine's potential to displace current standard of care for HER2-positive metastatic breast cancer and the anticipated high cost of ado-trastuzumab emtansine and pertuzumab could have significant impacts on managing disease in these patients.
- **Potential for High Impact:** Moderately high

Colorectal Cancer

Methylated Septin 9 Blood Test for Colorectal Cancer Screening

- **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 Septin 9 gene, the detection of which is being studied as a potential colon cancer screening test. Like other noninvasive colon cancer tests (e.g., fecal occult blood testing [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 2011, Epigenomics reported data from a trial in which a subset of 7,940 patients undergoing colonoscopy screening were also tested with the current version of the company's Septin 9 test (Epi proColon 2.0). The company reported that, compared with colonoscopy, the Septin 9 test had a sensitivity of 68% and a specificity of 80% for colorectal cancer. In December 2012, Epigenomics released top-line data from a second trial that compared Epi proColon 2.0 and fecal immunochemical testing (FIT). Epi proColon demonstrated statistically significant noninferiority of sensitivity for CRC, and specificity was reported as 81% (versus 98% for FIT). Data on the test's ability to detect precancerous, adenomatous polyps were not presented. In February 2013, Epigenomics submitted a premarket approval submission to FDA for the Epi proColon test; FDA granted the submission priority review.
- **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 screened for CRC. However, regarding the Epi proColon 2.0 test specifically, experts were more cautious, questioning whether the reported sensitivity and specificity of the test were high enough and whether the high cost they anticipated for the test relative to other noninvasive options such as FOBT would prevent its widespread adoption.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Hematologic Malignancies

Brentuximab Vedotin (Adcetris) for Recurrent or Treatment-Refractory Hodgkin's Lymphoma and Anaplastic Large Cell Lymphoma

- **Key Facts:** ADCs represent a class of cancer treatments in which highly toxic chemotherapy agents are coupled to monoclonal antibodies for molecules present on the surface of cancer cells. When delivering the highly cytotoxic drugs to tumor cells, but not to healthy cells, the ADC is expected to reduce systemic side effects associated with untargeted chemotherapy. CD30-positive malignancies such as HL and ALCL are rare, with only about 8,500 HL cases and 2,250 ALCL cases diagnosed annually in the United States. Although initial treatments for these conditions, in particular HL, are effective, patients often experience recurrence, and in many cases the disease becomes resistant to available therapies. This has resulted in a need for new therapeutic options for recurrent or refractory disease. 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 is infused intravenously. It consists of a CD30-specific 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 release its cytotoxic drug only when internalized by cells. Common adverse effects reported in trials included nausea, fatigue, peripheral neuropathy, pyrexia, diarrhea, and neutropenia, which were characterized as “manageable.” A rare but serious adverse event reported was progressive multifocal leukoencephalopathy, a potentially fatal brain infection. In August 2011, FDA approved brentuximab vedotin for HL that has failed to respond to an autologous stem cell transplantation or that has progressed after at least two multiagent chemotherapy regimens in patients who are not autologous stem cell transplant candidates. FDA also approved the drug for treating ALCL after failure of at least one multi-agent chemotherapy. The initial drug pricing was set at about \$4,500 per vial; about three vials are used per treatment and 7–9 cycles of treatment given per patient, bringing the total cost for a regimen to a range of \$94,000–\$121,000. Brentuximab vedotin has significant potential to expand beyond the FDA-approved indications, both earlier in the treatment pathway for HL and ALCL and also for other hematologic malignancies. This agent is under investigation for treating T-cell lymphoma in two late-stage trials. Also, in April 2013, Seattle Genetics reported that FDA had accepted a supplemental biologics license application for using brentuximab vedotin for retreatment and extended duration beyond the currently approved 16 cycles. The therapy is typically covered by insurance after prior authorization for outpatient infusion therapy that is consistent with the labeled indications.
- **Key Expert Comments:** Overall, experts concurred that a significant unmet need exists for efficacious treatments for recurrent or treatment-refractory HL and ALCL. Given the lack of effective alternatives and the promising response rates reported in initial clinical trials, experts believe that wide adoption of brentuximab vedotin by physicians and patients is likely. However, the routine method of administration and the relatively small patient population that would be eligible for treatment with the drug would limit its overall impact on the health system.
- **Potential for High Impact:** Moderately high

Ruxolitinib (Jakafi) for Treatment of Myelofibrosis

- **Key Facts:** Myelofibrosis is a relatively rare myeloproliferative neoplasm characterized by bone marrow fibrosis, progressive anemia, and hematopoiesis that occurs outside the bone marrow and typically results in an enlarged spleen. Until FDA approval of ruxolitinib in November 2011, the agency had not approved any pharmacotherapy for treating myelofibrosis. Ruxolitinib is an orally administered medication, a small-molecule inhibitor of two tyrosine kinases (i.e., JAK1, JAK2) that function in the JAK/STAT pathway. Active JAK/STAT signaling promotes two important aspects of myelofibrosis disease pathogenesis: (1) clonal myeloproliferation (many cases of myelofibrosis harbor genetic mutations that lead to JAK/STAT pathway activation, in particular an activating mutation in JAK2) and (2) a proinflammatory state mediated by overexpression of cytokines. In two phase III trials, ruxolitinib was reported to have led to significant improvements in spleen size and constitutional symptoms (e.g., fatigue). Additionally, preliminary analyses from these trials indicate that ruxolitinib may improve survival. However, treating patients with ruxolitinib has the potential to exacerbate the anemia symptoms of myelofibrosis. Ruxolitinib was developed by Incyte Corp., of Wilmington, DE, which reportedly priced the drug at \$7,000 per month, although as of June 2013, an online aggregator of pharmacies supplying the drug showed pricing of \$4,100 to just under \$4,200 with use of a coupon from the company. The drug is considered a specialty pharmaceutical and insurers and Medicare Part D typically require preauthorization and impose quantity limits on each prescription.
- **Key Expert Comments:** Overall, experts believe that ruxolitinib addresses a significant unmet need for novel treatments for myelofibrosis. Although experts believe that it would likely be adopted by physicians and patients on the basis of encouraging data regarding spleen size, experts were cautious, given the lack of a clear impact on patient survival and disease progression. Lastly, experts did not envision an oral medication used in a relatively small patient population as having significant impacts on the health care system infrastructure or patient management.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Ponatinib (Iclusig) for Treatment of Chronic Myelogenous Leukemia and Chromosome–Positive Acute Lymphoblastic Leukemia

- **Key Facts:** CML typically is a slowly progressing disease that represents 20% of adult leukemias. Commonly diagnosed in middle age, CML progresses through chronic, accelerated, and blast phases characterized by increasing numbers of immature blood cells (i.e., myoblasts or blasts) in the blood and bone marrow. Unlike CML, ALL is more commonly diagnosed in children younger than age 5 years; only about one in three ALL cases occurs in adults. Both CML and Ph+ ALL are characterized by the presence of the *BCR-ABL* oncogene, which generates a gene fusion product with constitutively active kinase activity that leads to the overproliferation of immature myoblasts. Tyrosine kinase inhibitors (TKIs) targeting oncogenic *BCR-ABL* are the current front-line therapies for CML and Ph+ ALL. Although patients initially typically respond well to existing TKIs, such as dasatinib, imatinib, and nilotinib, the disease in many patients develops resistance to these *BCR-ABL* inhibitors. In particular, patients with CML who are harboring the T315I mutation in *BCR-ABL* are refractory to all current therapies targeting *BCR-ABL*. Ponatinib (ARIAD Pharmaceuticals, Inc., Cambridge, MA) is a novel TKI that inhibits TKI-resistant forms of

BCR-ABL, including T315I as well as SRC, LYN, c-KIT, and members of the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor families. Phase II trials have shown positive results for ponatinib monotherapy using surrogate endpoints in patients whose disease is resistant to existing TKIs. Ongoing phase II and III trials are investigating ponatinib in the first-line treatment setting. FDA granted priority review status to ponatinib, and in December 2012, this agent received accelerated approval 3 months ahead of its scheduled decision date. Approval was granted for patients with chronic-, accelerated-, or blast-phase CML or Ph+ ALL that was resistant to or intolerant of existing TKIs. The existing data suggest that ponatinib may offer favorable response rates compared with the recently approved agent omacetaxine mepesuccinate (Synribo®), which is also indicated for treating CML that is resistant to or intolerant of two or more TKIs. Ponatinib is an oral medication that is administered at a dose of 45 mg, once daily. A May 2013 query of an online aggregator of pharmacy pricing showed pricing of \$10,300–\$10,400 per month (thirty 45 mg tablets). The drug is considered a specialty pharmaceutical and insurers and Medicare Part D typically require preauthorization and impose quantity limits on each prescription.

- **Key Expert Comments:** Overall, experts were encouraged by results from phase II trials of ponatinib, citing a significant unmet need and potential health benefit for those with CML or Ph+ ALL that is resistant to existing TKIs. Clinical experts were particularly enthusiastic about the potential for ponatinib as a first-line treatment option, either as a monotherapy or in combination with other therapies. Although easy adoption and acceptance of this orally administered agent is predicted for both clinicians and patients, high costs remained a concern for experts, and several agreed that additional data are needed to determine ponatinib's long-term impact potential.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Lung Cancer

Crizotinib (Xalkori) for Treatment of Advanced Nonsmall Cell Lung Cancer

- **Key Facts:** 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, as with other cancers, NSCLC is recognized as not being a single disease, but rather related diseases with different molecular underpinnings that respond differently to treatment. In particular, 2% to 7% of NSCLC tumors are believed to harbor genetic alterations that result in a fusion of the *ALK* gene with a second gene (often *EML4*). These gene fusions can produce a constitutively active ALK protein that drives carcinogenesis. Inhibiting this carcinogenic activity is seen by experts as a promising therapeutic target for individuals with this *ALK* gene rearrangement. Crizotinib (Xalkori®, Pfizer, Inc., New York, NY) is an oral, small-molecule inhibitor of *ALK* kinase activity taken once daily. In August 2011, FDA granted the drug accelerated approval on the basis of two single-arm, phase II clinical trials that exhibited a high rate of response to crizotinib therapy. More recently, in results from a phase III trial that compared crizotinib with standard second-line chemotherapies, investigators reported improved progression-free survival in *ALK*-mutation-positive patients with NSCLC. In this trial, crizotinib also decreased patient-reported lung cancer–related symptoms and improved health-related

quality of life measures. Crizotinib is administered orally twice daily, 200 or 250 mg per dose. It is indicated for 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. A query in June 2013 of an online aggregator of pharmacy drug pricing showed pricing of about \$11,250 per patient per month with a manufacturer-provided coupon. The drug is considered a specialty pharmaceutical and insurers and Medicare Part D require preauthorization (with confirmation of a positive test for the mutation) and impose quantity limits on each prescription. The list price of the companion diagnostic test is about \$225 per test; however, the full cost of the test also includes a fee for performing the test. In additional ongoing late-stage trials in early treatment settings for NSCLC, the manufacturer is also examining crizotinib use for treating other types of *ALK* mutation–positive tumors.

- **Key Expert Comments:** Experts commenting on this topic thought that the availability of an *ALK* inhibitor and its companion diagnostic test to identify appropriate patients for this treatment represents a significant advance in 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. 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

Prostate Cancer

Enzalutamide (Xtandi) for Treatment of Metastatic Castration-Resistant Prostate Cancer

- **Key Facts:** Until 2010, patients with 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. Since then, the armamentarium for treatment has increased with FDA approval of the chemotherapeutic agent cabazitaxel (Jevtana[®]), the therapeutic cancer vaccine sipuleucel-T (Provenge[®]), the androgen synthesis inhibitor abiraterone (Zytiga[®]), and radium-223 dichloride (Xofigo[®]), a novel bone metastasis-targeting radiopharmaceutical for metastatic prostate cancer that emits alpha particles. Another treatment option for metastatic castration-resistant prostate cancer (mCRPC) was approved in August 2012, the androgen signaling inhibitor enzalutamide (Xtandi[®], Medivation, Inc., San Francisco, CA). Enzalutamide was initially studied in patients with CRPC that had previously undergone treatment with docetaxel. Patients treated with enzalutamide exhibited a 4- to 5-month increase in median overall survival compared such survival in patients receiving placebo. This drug is also under study in patients who have chemotherapy-naïve mCRPC. Significant changes in the management of mCRPC will likely occur as physicians further elucidate which patients are best served by which interventions and incorporate abiraterone, cabazitaxel, enzalutamide, radium-223 dichloride, and sipuleucel-T into practice guidelines. The manufacturer has reported a steady uptake of enzalutamide. Enzalutamide is an oral medication that is administered at a dose of 160 mg (4 capsules), once daily. A June 2013 inquiry of an online aggregator of pharmacy pricing showed a retail cost for 1 month of treatment (120 capsules)

with enzalutamide is just over \$8,000. The drug is considered a specialty pharmaceutical and insurers and Medicare Part D require preauthorization and impose quantity limits on each prescription.

- **Key Expert Comments:** Overall, experts commenting on this intervention were quite positive regarding the potential of enzalutamide to improve both quality and quantity of life for patients with mCRPC. However, 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 and suggested that enzalutamide may have a larger impact when used earlier in treatment. Experts suggested that significant study of the proper sequential and/or combined use of enzalutamide and other recently approved prostate cancer treatments are needed.
- **Potential for High Impact:** Moderately high

Magnetic Resonance Imaging–Ultrasound Image Fusion to Guide Prostate Biopsy

- **Key Facts:** Standard prostate biopsy involves the systemic collection of tissue core biopsy samples obtained from various anatomical zones under guidance by transrectal ultrasound (TRUS) of the prostate. Limitations of this approach include missed cancer diagnoses because core samples did not contain cancer cells; identification of indolent, clinically insignificant cancers; and lack of consistent biopsy methods. Also, poor anatomical resolution on ultrasound makes it difficult for urologists to accurately identify and target suspicious lesions for biopsy. Magnetic resonance imaging (MRI) is known to provide superior anatomical resolution, enabling radiologists to discern between potentially high-grade cancers and clinically insignificant lesions. However, MRI-guided biopsy approaches during which samples are collected from the patient while in the MRI machine (in-bore sample collection) are expensive and cumbersome. MRI-TRUS image fusion–guided biopsy purports to address these issues by enabling targeted biopsy sampling from lesions identified using a previously obtained MRI. Using image-fusion software, the urologist overlays a graded MRI image onto real-time ultrasound imaging to enable targeting of suspicious lesions identified by the radiologist to obtain the biopsy sample.

Multiple manufacturers have developed software modules and platforms to enable image fusion–guided prostate biopsy; these systems were cleared through FDA’s 510(k) process. Many of these software packages are designed for integration with many commonly used ultrasound platforms. Newly purchased systems for prostate biopsy may include software with this capability. Case studies report experience with this technology in patients undergoing primary prostate biopsy when prostate cancer is suspected, as well as in patients who had a negative standard TRUS-guided biopsy but have persistently elevated prostate-specific antigen levels. According to case study data, MRI-TRUS image fusion–guided prostate biopsy may improve cancer detection rates and identify more high-grade cancers than standard TRUS-guided biopsy methods. Following device clearance, image fusion–guided targeted biopsy platforms have gradually diffused nationwide.

While MRI-TRUS image fusion–guided biopsies represent a cost increase over standard TRUS-guided biopsy, this approach is believed to be substantially less expensive than in-bore MRI-guided biopsy. Implementation of this biopsy approach would require patients who previously might have had only standard TRUS-guided biopsy to undergo an MRI procedure. Additionally, widespread implementation of this approach will require

coordination between radiologists who read the MRI and urologists who perform image fusion–guided biopsy procedures. Ongoing trials are examining various image-fusion platforms and may provide further evidence on the clinical application of this diagnostic method.

- **Key Expert Comments:** Experts commenting on this technology concurred that it has the potential to improve the methodologic consistency of prostate biopsies and may enhance the detection of clinically meaningful prostate cancers. Implementing this approach may significantly increase costs, they noted, as an additional imaging procedure (MRI) would be required. Experts agreed that the availability of coverage and reimbursement would be primary determinants of widespread adoption.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Radium 223 Dichloride (Xofigo) for Treatment of Solid Tumor Bone Metastases

- **Key Facts:** Many solid tumors, in particular breast, prostate, and lung cancer, metastasize to bone, causing chronic pain and skeletal-related events (e.g., fractures) that adversely affect patient quality of life and survival. Among the 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 concentrates the radiation dose at the target bone metastases. Although available radionuclides have shown efficacy in palliating 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. Radium-223 dichloride (Xofigo[®], 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 radiation generated by available radiopharmaceuticals, potentially reducing the side-effect profile of treatment and more effectively targeting bone metastases. Results reported by the developers from a double-blind, randomized controlled trial of 921 patients with mCRPC and skeletal metastases who were ineligible for treatment with docetaxel indicated increased overall survival of 3.6 months in patients treated with radium-223 dichloride compared with patients treated with placebo. An independent committee recommended that the trial be stopped early because of the positive results. Investigators reported that, besides improving overall survival, treatment with radium-223 dichloride 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 being relatively benign, suggesting that it could potentially be used in combination with other prostate cancer treatments. After priority review, FDA approved radium-223 dichloride for treating bone metastases in patients with mCRPC in May 2013, 3 months ahead of the anticipated decision date. Bayer initiated a phase III trial to collect additional long-term safety data, and an early-phase trial is examining the agent in combination with docetaxel for treating CRPC bone metastases. This agent is also under investigation for treating osteosarcoma and breast cancer with bone metastases. Radium-223 dichloride is administered intravenously at a dose of 50 kilobecquerel (1.35 microcurie)/kg, once every 4 weeks, for up to 6 treatment cycles.
- **Key Expert Comments:** Experts commenting on this topic thought that radium-223 dichloride has significant potential to improve current treatments for bone metastases,

particularly for patients with prostate cancer. Although experts thought radium-223 dichloride would likely be widely adopted for this indication, they thought it had similarities to other existing treatments that would limit its degree of impact on health care system infrastructure and practices.

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

Skin Cancer

Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

- **Key Facts:** Vemurafenib (Zelboraf[®], Genentech unit of Roche) is a BRAF inhibitor; BRAF inhibitors belong to a growing class of personalized cancer treatments intended for patients whose tumors harbor specific genetic changes that can serve as therapeutic targets. 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. The drug target BRAF 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 *BRAF* gene that encode a constitutively active BRAF protein (e.g., BRAF^{V600E}) have been identified in more than half of melanomas analyzed. Activated BRAF 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 BRAF kinase activity is a promising pharmacologic target. Researchers reported that vemurafenib increased overall survival and progression-free survival relative to treatment with dacarbazine in a phase III clinical trial. In August 2011, FDA approved vemurafenib for treating patients with unresectable or metastatic melanoma harboring a BRAF mutation as detected by an FDA-approved companion diagnostic test, the cobas 4800 *B-RAF V600* Mutation Test. The cost of vemurafenib is about \$11,670 per patient per month, and the company estimates a treatment course of about 6 months for a total of about \$70,000 per patient. FDA recently approved monotherapy with a second *BRAF* inhibitor, dabrafenib (GlaxoSmithKline, Middlesex, UK); this agent is also being examined as part of a combination therapy regimen with the *MEK*-inhibitor, trametinib. Ongoing trials are investigating combination therapy with *BRAF* and *MEK* inhibitors.
- **Key Expert Comments:** An orally administered, small-molecule inhibitor of *BRAF* kinase activity was considered by experts to have potential for high impact. Experts commenting on this topic thought that *BRAF* inhibitors could fundamentally change treatment paradigms for metastatic melanoma because they will split a single syndrome into *BRAF* mutation–positive and mutation-negative disease. This will necessitate testing all patients to determine their *BRAF* status. Experts opined that although the potential of BRAF inhibitors is limited because 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.
- **Potential for High Impact:** High

Vismodegib (Erivedge) for Treatment of Advanced Basal Cell Carcinoma

- **Key Facts:** Until FDA approved vismodegib (Erivedge[®], Genentech subsidiary of Roche), no systemic therapy was available for inoperable basal cell carcinomas. Vismodegib is an oral, small-molecule drug that inhibits a signaling pathway known as the hedgehog pathway. The aberrant regulation of this pathway has been implicated in a number of cancers. In particular, elevated activity in the hedgehog pathway has been observed in the majority of basal cell carcinomas, and preclinical data suggested that inhibiting this pathway could have an antitumor effect. In the primary analysis of a single-arm, phase II trial (n=104), patients with locally advanced or metastatic basal cell carcinoma who received vismodegib showed a 43% response rate for locally advanced disease, a 30% response rate for metastatic disease, and mean progression-free survival of 9.5 months, according to investigators. An 18-month update after the primary analysis showed an overall response rate of 60.3% in patients with locally advanced disease and 48.5% in patients with metastatic disease. The median duration of response was 20.3 months for locally advanced disease and 14.7 months for metastatic disease. Investigators further reported in an interim analysis of 300 patients with advanced basal cell carcinoma that the following common adverse events occurred: muscle spasm (59.3%), alopecia (49.3%), and dysgeusia (41.0%). Among patients with tumor assessments available (n=251), 17.5% achieved complete response, 39.8% achieved partial response, 39% had stable disease, and 2.8% had progressive disease. FDA approved the drug in January 2012 for treating inoperable basal cell carcinomas. Ongoing studies are also examining potential vismodegib indications for treating patients with operable basal cell carcinomas. An online aggregator of pharmacy pricing reported pricing between \$9,000 and \$9,200 for thirty 150 mg capsules (a month's supply), and the estimated treatment duration is 10 months.
- **Key Expert Comments:** Experts commenting on this topic thought that vismodegib has significant potential as a first-in-class agent for treating 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 mitigated by the relatively small number of patients who would be targeted by this therapy.
- **Potential for High Impact:** Moderately high

Solid Tumor Ablation

Irreversible Electroporation (NanoKnife) for Ablation of Solid Tumors

- **Key Facts:** Irreversible electroporation (IRE) using the NanoKnife system (AngioDynamics, Latham, NY) is a nonthermal tissue ablation technique that uses a rapid series of short-duration, high-voltage electrical pulses to purportedly induce irreversible permeabilization of cell membranes. These membrane defects are believed to lead to programmed cell death within an ablation zone defined by the placement of IRE-delivering electrodes. IRE procedures can be performed using percutaneous, laparoscopic, or surgical approaches. Purported benefits of IRE include its nonthermal nature, which may permit ablation of tumors at or near vital structures, and the elimination of heat-sink effects, which are thought to hinder using thermal technologies to ablate tumors located close to large blood vessels because of inadequate heating/cooling of perivascular tumor. Potential

drawbacks of the system include potential for electrical pulses to stimulate muscle contraction, which requires that the patient undergo general anesthesia and paralytic induction. Additionally, to reduce the risk of cardiac arrhythmias, IRE pulses must be precisely timed with the patient's heart rhythm using a compatible cardiac synchronization system. The NanoKnife IRE System is the only commercially available IRE system, and it was FDA cleared for soft tissue ablation only and has not received marketing approval for treating cancer or any specific disease or condition. In fact, FDA issued warnings to the company about promotion of the system for cancer treatment without having marketing approval for those indications. The company ceased promotion on its Website for cancer indications; however, numerous oncology centers throughout the United States have recently advertised acquisition of the NanoKnife system and are promoting its use for cancer treatment. Several case studies of IRE treatment have been published that focus mostly on pancreatic cancer, primary liver cancer, and liver metastases. The manufacturer is conducting two trials of IRE for cancer indications, one for treating pancreatic cancer and the other for treating prostate cancer.

- **Key Expert Comments:** As a novel nonthermal tumor ablation technique, IRE was viewed by experts as a potentially important addition to cancer treatment options. It could be particularly useful in pancreatic cancer, for which experts noted a large unmet need and for which IRE could significantly shift the way in which patients are managed. However, experts indicated that only limited data from case series are available on IRE for cancer indications and additional studies on efficacy should be conducted in a controlled clinical trial setting before wider adoption.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Adolescent and Young Adult Oncology Intervention

Specialized Care Model for Adolescents and Young Adults with Cancer

Unmet need: Despite significant improvements in survival rates for pediatric and adult cancer patients during the past several decades, outcomes for adolescent and young adults (AYAs) with cancer (i.e., roughly aged 13–30 years) have not improved, and some believe that care settings may be a contributing factor.¹⁻³ AYAs with cancer are often placed in pediatric units with much younger children or in adult cancer centers among much older patients. Standard care settings often fail to adapt to the life circumstances of AYAs, including demands of ongoing education, developing careers, and relationships and emotional and financial vulnerability.⁴ The relative dearth of AYA oncologic clinicians and clinical trials targeted to these age groups presents further challenges for delivering effective care for these patients.⁵⁻⁷

Intervention: A new care model presents a potential solution that involves creating AYA-dedicated oncology programs with staff that offer comprehensive, specialized clinical and supportive care services. Authors from several institutions have described models for such AYA oncology programs.^{8,9} Although approaches to AYA-focused oncology programs vary, one model pioneered by the U.K. Teenage Cancer Trust and Teen Cancer America illustrates the interventions that a comprehensive AYA-focused oncology program may entail.^{8,9} Teen Cancer America is the first U.S. program to develop inpatient and outpatient AYA oncology units with fully dedicated clinical staff, clinical and social spaces, and resources.

AYA specialized units may offer inpatient and outpatient therapies on a modified schedule (i.e., chemotherapy sessions or medical procedures in the afternoon or evenings) to prevent excess disruption to the daily schedule of their AYA patients and promote treatment adherence.¹⁰ Clinical spaces are designed to mimic the home environment, and dedicated spaces for education, peer social activities, family, and psychosocial therapy are often provided. Specially trained staff on Teen Cancer America/Teenage Cancer Trust AYA units include doctors and nurses with a specialty in common AYA cancers and care issues and extensive knowledge of clinical trial opportunities for AYAs. Additionally, the units offer youth support coordinators who are trained to address the psychosocial and supportive care needs of AYA patients that arise during treatment and help to ease patients' transition back into school or work.¹¹ Because AYAs are more likely to be uninsured or underinsured than younger children or older adults, financial counseling is a critical aspect of the services offered to patients and their families.¹²

The resources required to establish an AYA oncology unit vary, but begin with dedicated physical space distinct from pediatric or adult oncology wings. Resources are required to renovate or build units to create a home-like environment with clinical functionality. Structural modifications may include the creation of social, kitchen and dining, education, and recreation zones and tailored construction to conceal medical equipment.¹⁰ Individual rooms and common areas are outfitted with personal computers, gaming systems, televisions, and so on.¹⁰ Hospitals may need to recruit or train staff to provide AYA-specific clinical and supportive care needs. Care-team staffing requirements include clinical nurse specialists, youth support coordinators, and oncologists with experience in AYA malignancies and treatment.¹³ Efforts to bolster clinical-trial enrollment and participation may require additional research and clinical staff resources.

Clinical trials: With the recent establishment and rapid growth of AYA programs, researchers, clinicians, and patients have begun to work collaboratively to establish metrics by which to collect data and assess health outcomes of patients treated in such programs or on AYA-dedicated oncology units.^{5,14} Preliminary data demonstrated improved clinical trial enrollment among patients

treated in an AYA oncology program.⁶ An ongoing, large-scale study called BRIGHTLIGHT will gather qualitative and quantitative data from AYA oncology patients who received treatment on standard pediatric or adult units and AYA-specialized units.¹⁵ Data from this study should enable the first multicenter investigation of the impacts of AYA oncology units on patients, clinical trial programs, and the health care system.

Program developers and funding: Teen Cancer America (Bala Cynwyd, PA),⁹ is a nonprofit organization established in 2011 as the U.S. extension of Teenage Cancer Trust, a United Kingdom charity organization based in England.⁸ These organizations form partnerships with various hospitals and cancer centers to design and implement AYA cancer units.¹⁶ Unit establishment requires the collaborative efforts and support of the hospital, Teen Cancer America/Teenage Cancer Trust, and health care providers. As charitable organizations, Teen Cancer America and Teenage Cancer Trust coordinate and assume the fundraising and financial responsibilities for construction and operation of AYA units. Hospitals or cancer centers may also share financial costs, which run an estimated \$3 million to \$5 million to establish and outfit each AYA unit.^{8,9} These efforts are sponsored by British musicians Roger Daltrey and Pete Townshend, members of the rock band The Who, through their organization “Who Cares,” which provides the primary financial and fundraising support to Teen Cancer America and the Teenage Cancer Trust.

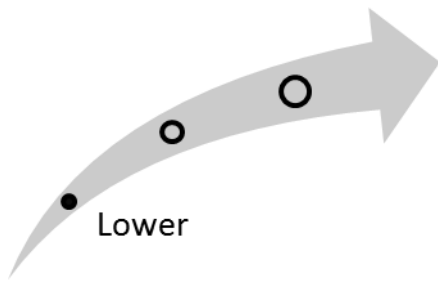
Diffusion: Since 1990, the Teenage Cancer Trust has funded 25 dedicated AYA oncology units throughout the United Kingdom, with another 9 in development.¹⁶ The U.S. arm of the organization, Teen Cancer America, was launched in December 2011.¹⁷ In collaboration with University of California, Los Angeles (UCLA) Medical Center, Teen Cancer America established the UCLA Daltrey/Townshend Teen & Young Adult Cancer Program (Santa Monica, CA) in 2011, which opened the first exclusively AYA-dedicated oncology unit in the United States in November 2012.¹⁸ Teen Cancer America recently began to raise funds for new AYA-dedicated units at Memorial Sloan-Kettering Cancer Center (New York, NY) and Yale-New Haven Children’s Hospital (New Haven, CT), and the organization plans to open AYA oncology units in strategic locations throughout the United States.^{9,19}

Although Teen Cancer America has pioneered the first fully dedicated AYA oncology unit and staffing care model, numerous cancer centers throughout the United States have established AYA oncology programs that provide dedicated services, programming, and/or space for AYA patients. This care model is rapidly diffusing nationwide, with more than 30 programs in place.

Current Approach to Care

Upon diagnosis of cancer, adolescent and young adult patients often receive treatment on established pediatric or adult cancer units. Care providers typically have a specialty in pediatric or adult oncology. Care settings and supportive services may be tailored to the predominant age range of patients who receive care at a given facility. Recently, some cancer centers have begun to offer tailored supportive care services (i.e., psychosocial, educational and career support) to AYA patients, and facilities are incorporating dedicated social space for AYAs on many pediatric units.

Figure 1. Overall high-impact potential: specialized care model for adolescents and young adults with cancer



Most experts commenting on this intervention agreed that AYA-focused oncology care represents an important unmet need, that this model might improve outcomes in the target population, and that this innovation could dramatically affect hospital infrastructure and the environment in which patients are managed. However, expert enthusiasm for the model was tempered by the speculative nature of the potential impact on health outcomes. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of specialized care models for AYA oncology patients.²⁰⁻²⁵ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Standard care settings may not adequately address the needs of AYAs with cancer, the experts acknowledged, noting that a moderately significant unmet need for improvement exists for this patient population. Multiple experts expressed the need for more concrete outcomes data in order to discern potential health impacts of AYA units. The program has moderate potential to improve AYA patient outcomes, experts thought.

Acceptance and adoption: Experts generally indicated that most clinicians would be likely to welcome these specialized treatment programs, citing the potential to provide patient-centered care for AYAs. Scarce resources and additional training requirements were noted as potential barriers to clinical acceptance by two experts with a health care research background. The majority of experts predicted widespread patient acceptance of this model, although one expert speculated that older AYAs might prefer to receive treatment on an adult unit.

Health care delivery infrastructure and patient management: Developing and implementing specialized AYA oncology units would be moderately disruptive to health care delivery infrastructure and patient management, experts thought. They cited the development or renovation of dedicated physical space and staffing and training requirements as the predominant disruptive forces. Experts differed on anticipated disruptions to patient management. A few experts noted that the majority of treatment regimens would remain largely unchanged, while others felt that expanded patient services, specialized treatment settings and schedules, and care by specially trained staff would result in positive disruptions to existing patient management practices.

Health disparities: Experts believe that this intervention is likely to have a moderate impact on health disparities, but differed in their reasoning. Two experts highlighted the central tenet of this intervention, addressing age-based health disparities. But three experts anticipated that these units may be concentrated within specialized cancer centers that may not be equally accessible to all AYAs. Looking beyond age parameters, a clinical expert suggested that this program would have a minimal impact on racial, ethnic, and socioeconomic disparities.

Breast Cancer Interventions

Automated Breast Ultrasound (Somo.v System) for Breast Cancer Screening of Patients with Dense Breast Tissue

Unmet need: Screening mammography has increased the breast cancer detection rate among screened women, but misses a significant number of breast cancers, particularly in women deemed to have dense breasts, as classified according to the American College of Radiology BI-RADS® breast density scale. This density scale is a subjective assessment of breast density used by radiologists; 1 represents least dense and 4 is most dense.²⁶ About 40% of women undergoing routine screening have dense breasts, and the sensitivity of screening mammography for breast cancer in these women is reported to be as low as 30% to 48%.²⁷ Recognizing the shortcomings of x-ray mammography, several States have passed laws mandating that women be informed of high breast density and the potential need for screening with adjunctive imaging tests.^{28,29}

Ultrasound (US) is one potential adjunctive imaging technique. While US has been used for some time in breast imaging and may be particularly effective in identifying tumors in dense breasts, it is not routinely used in screening asymptomatic women in part because of its time-consuming nature and interoperator variability.³⁰ Automated breast ultrasound (ABUS) systems would incorporate ultrasound imaging into routine breast cancer screening as an adjunct to mammography for women who have dense breasts.

Intervention: Mammography is limited in dense breast tissue because dense tissue and tumors both generate positive signals in x-ray images, so dense breast tissue can obscure tumors. In contrast, US may perform better because dense breast tissue reflects a high percentage of the ultrasound waves, generating a strong signal in US images, known as hyperechogenicity, and malignant breast tumors do not, known as hypoechogenicity. This difference in echogenicity—a strong contrast between dense breast tissue and tumors in ultrasound images—potentially makes tumors more readily detectable.

Breast density is determined by radiologists who apply the BI-RADS breast density classification system. BI-RADS 1 density means that the breast is almost entirely fat. BI-RADS 2 density means that fibroglandular densities are scattered throughout the breast tissue, and fibrous and glandular tissue makes up 25% to 50% of the breast. BI-RADS 3 classification means the breast tissue is dense and spread throughout the breast tissue with more areas of fibrous and glandular tissue (51% to 75%) making it hard to find small masses. BI-RADS 4 classification means that the breast tissue is extremely dense and made up of more than 75% fibrous and glandular tissue, which can lead to missing some cancers.²⁶

The somo.v ABUS system consists of two components: the somo.v scan station, which generates the ultrasound images and the somo.Viewer™ workstation, on which a health care worker reviews the images generated by the scan station.³¹ While lying in a supine position on a standard examination table, the patient's breast is imaged using a convex transducer that is placed in direct contact with the breast. Each scan takes up to 350, 2-dimensional (2-D) images that capture a volume of 15.4 by 17 by 5 cm. Each scan takes about 60 seconds, and 2–3 scans must be taken for each breast, depending on breast size. Image sets are then transferred to the somo.Viewer workstation, on which physicians can view 3-dimensional (3-D) reconstructions of the breast in multiple orientations.

Clinical trials: Investigators tested the somo.v ABUS system in a simulated screening setting in a retrospective reader study. In this study, 164 women (133 noncancer and 31 biopsy proven cancers) with dense breast tissue (defined as more than 50% parenchymal breast density) were imaged by digital x-ray mammography (XRM) and ABUS. Seventeen Mammography Quality

Standards Act (MQSA)-qualified radiologists analyzed the images, first considering the XRM data alone and subsequently considering both XRM and ABUS data. Sensitivity for breast cancer across all readers was 38.8% for XRM alone compared with 63.1% for XRM+ABUS (a difference of 24.3%; 95% confidence interval [CI], 10.7% to 37.9%, $p<0.002$). Specificity for breast cancer across all readers was 78% for XRM alone compared with 76% for XRM+ABUS (a difference of -2.0%, 95% CI, -7.7% to 4.3%, $p=0.518$).³²

A larger trial of ABUS in the screening setting (the SOMO•INSIGHT study) is ongoing.³³ The somo.v ABUS manufacturer reports that more than 15,000 women have been recruited and that trial results may be available some time in 2013.³⁴ Two smaller screening studies studying the addition of automated ultrasound imaging to standard mammographic screening have reported increases in cancer detection rates among women with dense breast tissue.^{30,35}

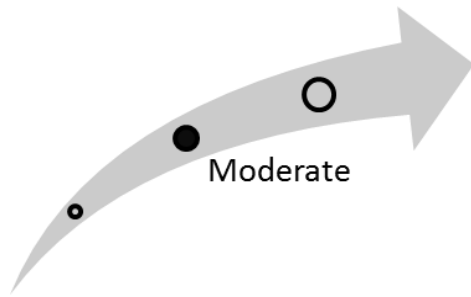
Manufacturer and regulatory status: The somo.v ABUS system was developed by U-Systems, Inc., a unit of General Electric Co. (Fairfield, CT). The company submitted a premarket approval (PMA) application for the system to the U.S. Food and Drug Administration (FDA), basing it on data from the reader study described above. In September 2012, FDA approved the somo.v ABUS system for use “as an adjunct to mammography for breast cancer screening in asymptomatic women for whom screening mammography findings are normal or benign (BI-RADS Assessment Category 1 or 2), with dense breast parenchyma (BI-RADS Composition/Density 3 or 4), and have not had previous clinical breast intervention.”³⁶ Other manufacturers market similar systems, including the SonoCiné® Automated Whole Breast Ultrasound system (SonoCiné, Inc., Reno, NV) and the ACUSON S2000 Automated Breast Volume System (Siemens AG, Munich, Germany).^{37,38} However, these systems have not been FDA approved for use in breast cancer screening.

Diffusion: Initial uptake of ABUS in the screening setting could be limited by lack of reimbursement. A search of 14 representative, private, third-party payers that publish their coverage policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) identified no payers with a policy for using ABUS for breast cancer screening. U-Systems has indicated that the results of the SOMO•INSIGHT study may influence reimbursement policies for ABUS.³⁴

Clinical Pathway at Point of This Intervention

Primary breast cancer screening is typically performed using x-ray-based mammography (2-D film, 2-D digital, or digital breast tomosynthesis).^{39,40} Women in whom an abnormality is identified typically undergo additional diagnostic imaging (e.g., diagnostic mammography, ultrasound, magnetic resonance imaging [MRI]) and a physical examination. If these imaging studies show an abnormality interpreted to be cancerous, a biopsy may be performed by fine-needle aspiration, core-needle biopsy, or open surgery.³⁹ ABUS has the potential to supplement mammographic screening for women with dense breasts. Its developer has proposed use of the system in women with dense breasts who have received a negative mammographic screening result to confirm the negative result (i.e., that they do not have a suspicious lesion). When used in this way, women who are identified as having an abnormality would then be referred for additional diagnostic imaging.⁴¹

Figure 2. Overall high impact potential: automated breast ultrasound (Somo.v System) for breast cancer screening of patients with dense breast tissue



Experts commenting on this topic suggested that a significant unmet need exists to improve breast cancer detection in women with dense breasts and commented positively on the theoretical potential of ABUS to address this need in the screening setting. Experts suggested that further study demonstrating the technology's impact on long-term patient outcomes would be needed to support widespread adoption, but that clinician and patient acceptance would likely be high given the unmet need. Experts thought the procedure could moderately disrupt patient management and infrastructure because of the proportion of women with dense breasts, the additional coordination needed for carrying out ABUS exams after mammography, and the additional patient visits that might be required. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of automated breast ultrasound for breast cancer screening.⁴²⁻⁴⁷ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need of improved breast cancer screening methods in women with dense breasts is moderately important, the majority of experts thought. They cited the significant percentage of women with high breast density and the relatively low sensitivity of standard mammographic screening for this patient population. Going further, an expert with a research perspective suggested the unmet need is very important, because of the shortcomings of other adjunctive imaging methods (e.g., high cost of magnetic resonance imaging, radiation exposure of breast-specific gamma imaging) in women with dense breasts and their elevated breast cancer risks.

As for patient health outcomes, adding ABUS to standard mammography for women with dense breast tissue has a moderate to large potential to improve outcomes, suggested the experts. However, they cautioned that the observed increase in the breast cancer detection rate and lack of an observed increase in the false-positive rate reported in the reader study would need to be confirmed in future trials. In particular, the sensitivity and specificity results reported for ABUS in the reader study may shift when tested in a screening population, which would contain a significantly smaller percentage of individuals with breast cancer compared with the reader study, one expert with a clinical perspective indicated. This expert also suggested that additional breast cancers identified by ABUS would likely represent a mixture of potentially beneficial early detection and potentially harmful overdiagnosis of breast tumors that would not substantially affect patient health if left untreated. Multiple experts suggested that long-term studies would be needed to demonstrate whether incorporating ABUS into breast cancer screening leads to improvements in breast cancer-related patient outcomes.

Acceptance and adoption: Likelihood of clinician and patient acceptance of ABUS into breast cancer screening was seen as moderate to high by most experts. Reasons for favoring adoption included ABUS' potential to improve breast cancer detection rates in women with dense breasts and the safety of the imaging procedure itself. However, experts also noted several barriers to adoption, including increased reading time for radiologists, potential of needing a second patient appointment if breast density results are not immediately available, a significant learning curve for adopting clinicians, the lack of trials assessing long-term patient outcomes, and the potential for lack of reimbursement for the procedure in the near term.

The recent State mandates requiring notification would likely generate demand for adjunctive imaging techniques to perform additional screening in women identified as having dense breasts, noted one expert with a clinical perspective.

Health care delivery infrastructure and patient management: The majority of experts did not envision a substantial impact of ABUS on health care infrastructure. However, one clinical expert thought widespread adoption would require significant radiologist training in interpreting ABUS-generated images. The experts mentioned other potential shifts in health care infrastructure and staffing included acquisition, installation, and maintenance costs for the ABUS system and increased time for radiologists to read more images for this patient population, which could increase radiologist staffing needs.

Although the majority of experts did not believe that adopting ABUS would affect patient management substantially, one clinical expert suggested that these changes would represent a large disruption in how patients are managed. All of the experts thought it would affect case flow and throughput because of the need to identify women with dense breasts at the time of mammography, the increased time required for screening visits and followup, and the need for additional patient visits to health care facilities if x-ray mammography and ABUS are not efficiently coordinated.

Everolimus (Afinitor) for Treatment of Advanced Estrogen Receptor–Positive Breast Cancer

Unmet need: Estrogen receptor–positive (ER+) metastatic breast cancer often responds to treatment with endocrine therapy; however, most patients' cancers eventually develop resistance to endocrine therapy.⁴⁸ Multiple mechanisms of resistance to endocrine therapy have been identified, including signaling through the mammalian target of rapamycin (mTOR)/phosphatidylinositol-3 kinase (PI3K) pathway.⁴⁹

Intervention: mTOR plays a central role in a cell-signaling pathway that regulates multiple cancer-related processes, such as cell growth, proliferation, survival, and migration. Additionally, multiple mTOR-pathway molecules have been shown to be aberrantly expressed and/or mutated in various cancers, suggesting that any agents that could inhibit mTOR pathway molecules could function as anticancer agents. 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.⁵⁰ Rapamycin-like mTOR inhibitors have been approved for treating cancers, including temsirolimus (Torisel®) for treating renal cell carcinoma⁵¹ and everolimus (Afinitor®) for treating renal cell carcinoma, subependymal giant cell astrocytoma and angiomyolipoma associated with tuberous sclerosis, and pancreatic neuroendocrine tumors.⁵²

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 cancer indications. One potential mTOR inhibitor indication that has reached late stages of development is everolimus for treating ER+ breast cancer.⁵³ Everolimus is an oral medication administered at a dose of 10 mg, once daily.⁵⁴

Clinical trials: Everolimus is being tested as an adjunct to the steroidal aromatase inhibitor exemestane in treating patients whose disease has progressed after treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).⁵³ Results from a randomized, double-blind, placebo-controlled trial of 724 patients (BOLERO-2) were published in 2012.⁵⁵ Everolimus (10 mg daily) met its primary endpoint of improving progression-free survival as determined by investigator assessment (6.9 months with everolimus plus exemestane vs. 2.8 months with placebo plus exemestane; hazard ratio, 0.43; $p < 0.0001$).⁵⁵

Although results reported from the BOLERO-2 study were promising, it should be noted that an earlier study investigating a combination of the mTOR inhibitor temsirolimus and the aromatase inhibitor letrozole in the first-line treatment of ER+ metastatic breast cancer was discontinued after an interim analysis showed that adding temsirolimus to letrozole was unlikely to improve efficacy.⁵⁶

Additional late-phase studies of everolimus used in other breast cancer indications are ongoing.⁵⁷⁻⁶¹ In recently reported results from the BOLERO-3 study, everolimus significantly increased progression-free survival in patients whose HER2-positive disease was resistant to trastuzumab and who had received prior taxane chemotherapy.^{62,63} This trial compared trastuzumab, vinorelbine, and everolimus combination therapy with treatment using trastuzumab, vinorelbine, and placebo.

As a drug class, rapamycin-like mTOR inhibitors have been relatively well tolerated by patients. Everolimus prescribing information lists the most common side effects observed in patients with breast cancer as follows (in decreasing order of all-grade incidence): stomatitis, infections, rash, fatigue, diarrhea, decreased appetite, nausea, cough, headache, edema, and asthenia.⁵⁴ mTOR inhibition is also associated with renal failure, elevated blood glucose and lipids, and immunosuppression, which can lead to increased risk of infections.^{51,54}

Manufacturer and regulatory status: Novartis International AG, of Basel, Switzerland, makes everolimus. In July 2012, FDA approved everolimus for use in combination with exemestane to treat postmenopausal women with advanced hormone receptor–positive, HER2-negative breast cancer after treatment failure with letrozole or anastrozole.⁶⁴

Diffusion: A May 2013 query of an online aggregator of U.S. pharmacy pricing identified a retail price of about \$9,100 per month for everolimus.⁶⁵ A search of representative, private, third-party payers that publish their coverage policies online (Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 5 payers with policies regarding everolimus.⁶⁶⁻⁷⁰ These payers considered everolimus to be medically necessary when prescribed for FDA-approved indications. Formularies of representative plans, including Medicare Part D, typically classify everolimus as a specialty pharmaceutical that requires prior authorization and is subject to quantity limits.

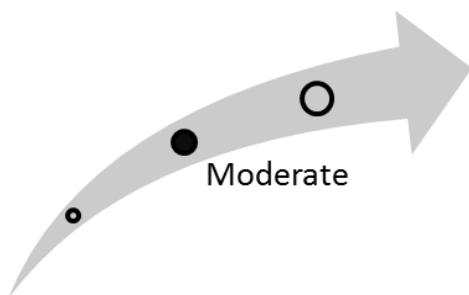
Expanded indications are the subject of ongoing investigations. A large phase III trial is investigating the addition of everolimus to adjuvant therapy (i.e., endocrine therapy) in patients who had ER+, HER2-negative breast cancer and have been disease-free for 3 years after adjuvant endocrine therapy.⁷¹ Based on recent trial data, HER2-positive breast cancer is another potential indication for everolimus.

Also, several investigational drugs are under study as adjuncts to endocrine therapy in metastatic ER+ breast cancer and could complement or compete with everolimus in this patient population. Drugs in phase III trials include the cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole in the first-line setting⁷² and the PI3K inhibitor, BKM120, in combination with the anti-estrogen agent fulvestrant in the second-line setting.⁷³

Clinical Pathway at Point of This Intervention

Patients with locally advanced/metastatic ER+ breast cancer are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens and may undergo multiple rounds of endocrine therapy. However, a subset of patients with symptomatic disease may be considered for initial treatment with cytotoxic chemotherapy. Patients with HER2-negative disease that is refractory to endocrine therapy are typically treated with one of several cytotoxic chemotherapy regimens.⁷⁴ Everolimus may be used as an adjunct to the steroidal aromatase inhibitor exemestane in treating patients whose disease has progressed following treatment with a nonsteroidal aromatase inhibitor (e.g., anastrozole, letrozole).⁵³

Figure 3. Overall high-impact potential: everolimus (Afinitor) for treatment of advanced estrogen receptor–positive breast cancer



Experts commenting on this intervention suggested that results for progression-free survival in endocrine therapy–resistant, metastatic breast cancer were promising for a condition with few

treatment options. Experts were eager to see data showing that the observed improvement in progression-free survival translates to improved overall survival before claiming that mTOR inhibitors would have a large impact on patient outcomes. They thought clinician and patient acceptance would be high, given the limited options for this patient population. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of everolimus for treating ER+ breast cancer.⁷⁵⁻⁸¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for improved treatments for ER+ breast cancer that is resistant to first-line endocrine therapy as moderately to very important, the experts thought. They stated that the majority of breast cancers are ER+ and that metastatic disease in most patients eventually develops resistance to hormone therapy. Additionally, these patients have a poor prognosis and few treatment options aside from cytotoxic chemotherapy, the experts noted.

Health outcomes have some potential to improve with everolimus, the majority of experts believe. Although the progression-free survival benefit demonstrated in the BOLERO-2 trial is significant and treatment might also improve overall survival, the experts thought, they tempered this belief by noting that any extension of overall survival would likely be of short duration. One clinical expert noted that the toxicity of adding everolimus to endocrine therapy can be significant, citing the five-times-higher rate of treatment discontinuation reported in the everolimus arm of the BOLERO-2 trial than in the placebo plus exemestane arm. This clinical expert also noted that this positive result 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 inhibitors.

Acceptance and adoption: Both physicians and patients would probably adopt everolimus, the experts suggested, because it is taken orally, has a manageable side-effect profile relative to cytotoxic chemotherapy, and has potential to increase progression-free survival. However, an overall survival benefit has not been demonstrated yet, several experts noted, and they thought that some physicians and patients would like to see such a benefit before adopting treatment, given the possible side effects.

The majority of experts suggested that everolimus would lead to a moderate increase in treatment costs for this patient population, as an added option. 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, one clinical expert noted. A clinical expert and a research expert both suggested that if the therapy ultimately fails to show significant improvement in overall survival, some controversy could arise over its cost.

Health care delivery infrastructure and patient management: As an orally administered medication, everolimus was not anticipated by experts to significantly shift health care staffing or infrastructure or require significant changes in managing patients, who would already be closely monitored for disease progression.

Health disparities: Everolimus would not have a significant impact on health disparities, the experts thought. However, several experts suggested that an oral route of administration could allow a minor reduction in health disparities by making adherence to treatment easier if patients who live in remote locations could avoid traveling to cancer centers for chemotherapy infusions.

MarginProbe System for Intraoperatively Identifying Positive Margins During Breast Cancer Lumpectomy

Unmet need: Successful breast-conserving surgery for early-stage breast cancer requires that the margins around the tumor excised during lumpectomy have cancer-free margins. Yet, many patients who undergo a breast-conserving lumpectomy require a second surgery when postsurgical histopathology examination of the tumor identifies surgical margins with cancer cells present or when cancer-free surgical margins are not deep enough. A recent observational study of reexcision rates after breast conservation surgery at four institutions calculated an overall reexcision rate of 22.9% and noted that earlier studies had reported reexcision rates ranging from 30% to 60%.⁸² Thus, this is a significant problem with associated costs and additional anxiety and risks for patients having to undergo second surgeries.

Intervention: The MarginProbe™ System is intended to reduce the need for second surgeries by providing intraoperative assessment of lumpectomy margins to enable breast cancer surgeons to resect additional tissue from positive margins during lumpectomy.⁸³ Investigators have also begun to test the device for margin assessment in patients undergoing prostatectomy to treat prostate cancer.⁸⁴

The system uses radiofrequency (RF) spectroscopy, in which tissue is subjected to an electromagnetic field to measure its response to stimulation.⁸⁵ Research findings have indicated that RF spectroscopy differentiates between normal and cancerous tissue based on their bioelectric profiles.⁸⁶ 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.⁸⁵ Because RF spectroscopy detects tissue response to the electromagnetic field only near the surface of the sample, it is considered appropriate for detecting clean margins, often defined as a depth of normal (noncancerous) tissue of at least 1–2 mm.⁸⁶

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.⁸⁷ The system provides a binary (yes/no) answer indicating whether the assessed margin is clean.

Clinical trials: In a late-phase trial, MarginProbe was used to assess tissue excised from 664 women undergoing lumpectomy procedures to treat nonpalpable malignant lesions that required image-guided localization. Patients were randomly assigned to receive standard intraoperative assessment to inform decisions about resecting additional tissue or standard assessment plus use of the MarginProbe system.⁸⁸ The primary endpoint was the rate of complete surgical resection (CSR), defined as intraoperative identification of all positive margins and resection of such margins during lumpectomy.⁸³ Results reported by the manufacturer indicated that the CSR rate was more than three times as high in the MarginProbe arm as in the control arm (72% [117/163] vs. 22% [33/147], $p < 0.0001$). This increase was reported to have reduced the reexcision rate by about half (5.6% reexcision rate in the MarginProbe arm; 12.7% in the standard of care arm). Also, the volume of tissue dissected in each arm was similar (93 cc MarginProbe arm; 85 cc control arm).⁸⁸

Manufacturer and regulatory status: Dune Medical Devices, Caesarea, Israel, makes the MarginProbe system. In January 2013, FDA approved MarginProbe.⁸⁹ The product labeling describes the system as “an adjunctive diagnostic tool for identification of cancerous tissue at the margins (≤ 1 mm) of the main ex-vivo lumpectomy specimen following primary excision and is indicated for intraoperative use, in conjunction with standard methods (such as intraoperative imaging and palpation) in patients undergoing breast lumpectomy surgery for previously diagnosed

breast cancer.”⁹⁰ The labeling indicates that the manufacturer provides training in the form of onsite, in-service orientation for surgical and operating room staff.⁹⁰

Diffusion: In March 2013, Dune Medical announced that the first MarginProbe System had been installed in the United States.⁹¹ MarginProbe will be used in the context of inpatient surgery for tumor removal, and thus its use may be considered integral to the primary procedure and be covered under the primary procedure code. While specific costs for the MarginProbe System console and probes have not been released, one report placed the cost per patient at approximately \$2,000.⁹²

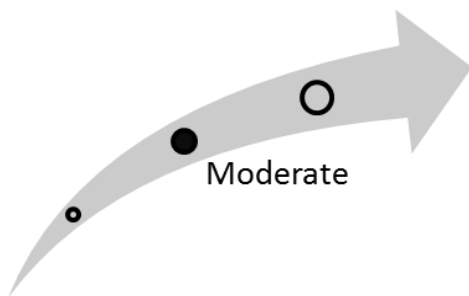
At least two additional RF spectroscopy and optical spectroscopy devices are under study in early-phase clinical trials for intraoperatively assessing lumpectomy margins.^{93,94}

Clinical Pathway at Point of This Intervention

The primary treatment for patients with early-stage breast cancer (e.g., ductal carcinoma in situ, stage I or II invasive carcinoma of the breast) is surgical resection of the cancerous tissue. Depending on the stage and degree of lymph node involvement, patients undergo breast-conserving surgery (e.g., lumpectomy) or mastectomy. Patients who meet all criteria for breast-conserving surgery except for having a large tumor may undergo neoadjuvant chemotherapy to reduce tumor size prior to surgery. After surgery, histologic analysis of the tumor is performed to assess tumor characteristics that may affect subsequent treatment. In particular, lumpectomy samples are tested to assess whether the margins of resected tissue are cancer free. Patients with cancer-positive margins typically undergo a second surgery to remove additional tissue and establish cancer-free margins.

After 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 MarginProbe can be used during lumpectomy to assess whether tumor margins are cancer free, potentially reducing the need for second surgeries.

Figure 4. Overall high-impact potential: MarginProbe System for intraoperatively identifying 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 performing secondary surgeries in this patient population. Although initial results for MarginProbe were viewed as promising, with limited potential to negatively affect patient outcomes, most experts wanted to see additional data and thought adoption would be limited until then. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁹⁵⁻¹⁰¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for a technology or methodology that can rapidly assess the margins of excised breast tissue during a first surgery to determine whether further tissue resection is necessary, the experts agreed. They cited as reasons the large number of patients who require a second surgery after postsurgical histologic analysis and the adverse health and emotional effects associated with having to undergo a second surgery.

Filling this unmet need could moderately improve health outcomes for patients, the experts suggested; but they were less certain about the MarginProbe System's potential to improve long-term survival for patients with breast cancer. Additionally, they questioned whether the evidence base for the MarginProbe System was sufficient at this time to conclude that it could meet the unmet need. One expert with a research background questioned whether the device's sensitivity and specificity were sufficient to significantly improve reexcision rates.

Health system infrastructure and staffing: The system could be easily adopted, according to experts, thereby having minimal impact on health care system staffing and infrastructure. Potential changes—such as system acquisition and a slight shift in operating room demand from a small increase in the time needed for lumpectomy procedures and a reduction in the number of second surgeries—were seen as incremental, but not disruptive changes. Additionally, experts did not think that use of the system would have a significant impact on patient management, other than reducing the number of second surgeries, because patients would follow the same clinical pathway with or without the intraoperative screening with the device.

The majority of experts suggested that the system could significantly reduce costs associated with breast-conserving surgery, even considering the initial costs of acquiring the system, and the cost it would add to each operation. Experts expected that this increase would be outweighed by a reduced number of secondary surgery procedures.

Health disparities: Adoption of the MarginProbe system would not have a significant impact on health disparities, the majority of experts thought. One clinical expert suggested that the system might create a slight increase in health disparities if it were to be offered exclusively at large, high-volume breast cancer centers and not in community or rural hospital settings. Conversely, another clinical expert suggested that the system could modestly decrease disparities if it allows less-specialized surgeons to perform breast-conserving surgery with greater confidence in obtaining clean margins at facilities in underserved regions of the country.

Novel Targeted Therapies: Ado-Trastuzumab Emtansine (Kadcyla); Pertuzumab (Perjeta) for Advanced HER2-Positive Breast Cancer

Unmet need: HER2-positive (HER+) 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 it comprises approximately 20% of breast cancer cases. Historically, HER2+ breast cancer has been associated with more aggressive disease and poor outcomes; however, the dependence of HER2+ breast cancers on HER2 activity for continued proliferation and survival has also provided a clearly defined molecular target.¹⁰² Indeed, the treatment of HER2+ breast cancer has improved with the availability of targeted therapies such as the HER2-specific monoclonal antibody trastuzumab (Herceptin[®]) and the HER2 kinase inhibitor lapatinib (Tykerb[®]). However, many patients' cancers still progress during these treatments and compounds with improved efficacy and efficacy against resistant disease are highly desired.¹⁰³

Intervention: Two recently FDA-approved novel biologic therapies also continue to be studied in late-stage clinical trials for treating HER2+ breast cancer: ado-trastuzumab emtansine (Kadcyla[™]) and pertuzumab (Perjeta[®]).

Ado-trastuzumab emtansine (formerly called trastuzumab-DM1),¹⁰⁴ an antibody-drug conjugate (ADC), couples the HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1).¹⁰⁵ The antibody and drug are coupled such that emtansine is held in a stable inactive form outside the cell. Emtansine is released and activated only upon cellular uptake of the drug conjugate mediated by the antibody's binding to the HER2 receptor.¹⁰⁵ In this way, emtansine targets cells expressing the HER2 receptor, preferentially targeting tumor cells (which express high levels of HER2) and spares many normal tissues from the drug's toxic effects. Preclinical studies demonstrated that ado-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 are independent of HER2 signaling (a hallmark of some tumors that have become resistant to trastuzumab and/or lapatinib).¹⁰³ Ado-trastuzumab emtansine is an intravenous medication that is administered at dose of 3.6 mg/kg, once every 3 weeks, until disease progression or unacceptable toxicity.¹⁰⁶

Like trastuzumab, pertuzumab is a monoclonal antibody specific for the HER2 protein; however, it purportedly inhibits HER2 activity through a different mechanism of action than trastuzumab, and it may act synergistically with trastuzumab.¹⁰⁷ Pertuzumab is intended to block the dimerization of HER2 with HER family receptor tyrosine kinases (e.g., homodimerization with HER2, heterodimerization with HER3), which is required for receptor tyrosine kinase activation.¹⁰⁸ Pertuzumab is administered intravenously at an initial dose of 840 mg over a 60-minute infusion; initial dosing is followed by a 420 mg dose over 30–60 minutes, once every 3 weeks.¹⁰⁹

Clinical trials: Ado-trastuzumab emtansine is being studied in a number of trials in patients with metastatic disease and patients undergoing adjuvant (postsurgical) chemotherapy. Results were recently reported from the phase III EMILIA trial, which compared treatment with trastuzumab emtansine to standard therapy (lapatinib plus capecitabine) as second-line therapy patients with metastatic HER2+ breast cancer. Investigators reported improved progression-free and overall survival in patients given ado-trastuzumab emtansine compared with lapatinib plus capecitabine arm (median progression-free survival 9.6 months versus 6.4 months, respectively; hazard ratio [HR]=0.65; 95% CI, 0.55 to 0.77; p<0.001; overall survival at second interim analysis 30.9 months

versus 25.1 months, respectively; HR=0.68; 95% CI, 0.55 to 0.85, $p<0.001$). Fewer patients in the ado-trastuzumab-emtansine arm than lapatinib plus capecitabine arm experienced grade 3 or 4 adverse events (41% vs. 57%, respectively).¹¹⁰ Additional phase III trials in the first- and third-line settings are ongoing.

Pertuzumab is under study for treating several stages of breast cancer, including localized disease (adjuvant therapy) and metastatic disease (first-line therapy). In 2011, pertuzumab's manufacturer announced positive results from the phase III CLEOPATRA trial, which demonstrated that a combination of trastuzumab, docetaxel, and pertuzumab extended progression-free survival by an average of 6.1 months (18.5 months in the pertuzumab group vs. 12.4 months in the control group) as first-line therapy for metastatic breast cancer.^{107,111} Analysis of overall survival at a median followup of 30 months indicated that pertuzumab added to standard first-line therapy decreased the risk of death by 38% (HR, 0.62; 95% CI, 0.51 to 0.75, $p<0.0001$).¹¹¹

Manufacturer and regulatory status: Both ado-trastuzumab emtansine and pertuzumab were developed by F. Hoffmann-La Roche, Ltd., of Basel, Switzerland.

The EMILIA study provided the basis for Roche's ado-trastuzumab emtansine biologic license application (BLA) to FDA, which was granted priority review status in November 2012.¹¹² In February 2013, FDA approved ado-trastuzumab emtansine for "the treatment of patients with HER2-positive (HER2+), metastatic breast cancer (MBC) who previously received trastuzumab and a taxane, separately or in combination."^{113,114} The prescribing information notes that patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.¹¹⁴

Roche used the results of the CLEOPATRA study for the basis of its pertuzumab BLA submission to FDA, which was granted priority review status in February 2012.¹¹⁵ In June 2012, FDA approved pertuzumab "for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease."¹¹⁶

Diffusion: Roche reportedly has priced ado-trastuzumab emtansine at \$9,800 per month of treatment.¹¹⁷ Ado-trastuzumab emtansine became available shortly after approval, and Roche reported significant sales of the drug in the first quarter of 2013.¹¹⁸

Pertuzumab became available in August 2012, and by late October of that year was reportedly being used in approximately 30% of eligible patients.^{119,120} Although about 40% of oncologists were reported as having prescribed pertuzumab at least once, a survey of 74 oncologists indicated that key barriers to increased use of pertuzumab included "concerns over cardiotoxicities, lack of finalized overall survival data, and increased cost."¹¹⁹ The reported wholesale acquisition cost for one patient for a month of pertuzumab is \$5,900, similar to other recently approved anticancer agents. However, the on-label use of pertuzumab in combination with trastuzumab could push the cost of a typical course of treatment to approximately \$187,000.¹²¹

A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 3 payers with policies regarding ado-trastuzumab emtansine.¹²²⁻¹²⁴ These payers considered this agent to be medically necessary when prescribed according to FDA-approved indications (HER2-positive, metastatic breast cancer in patients who previously received trastuzumab and a taxane, separately or in combination). As an intravenous medication administered in the health care setting, ado-trastuzumab emtansine may be covered under Medicare Part B benefits.

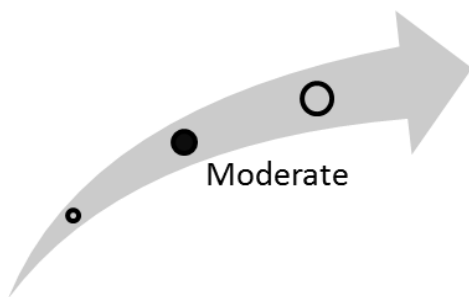
A search of these payers also found 7 with policies for pertuzumab.¹²⁵⁻¹³¹ These payers considered pertuzumab to be medically necessary when prescribed according to FDA-approved

indications (for treating HER2-positive, metastatic breast cancer in patients who have not received prior HER2 therapy; used in combination with trastuzumab and chemotherapy). Some plans requires prior authorization and impose quantity limits. Similar to ado-trastuzumab emtansine, as an intravenous medication administered in the health care setting, pertuzumab may be covered under Medicare Part B benefits.

Clinical Pathway at Point of This Intervention

Patients with HER2-positive breast cancer that is locally advanced or has become metastatic and is 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). Patients whose disease progresses after first-line therapy are typically treated with a second HER2-targeted therapy, typically lapatinib plus capecitabine. Alternative second-line chemotherapy options include trastuzumab plus a cytotoxic agent that was not used in first-line treatment or trastuzumab plus lapatinib.⁷⁴ The recent approvals of pertuzumab in the first-line setting and ado-trastuzumab emtansine in the second-line setting provide new treatment options for patients with metastatic breast cancer.

Figure 5. Overall high-impact potential: novel targeted therapies (ado-trastuzumab emtansine [Kadcyla]; pertuzumab [Perjeta]) for advanced HER2-positive breast cancer



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

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on ado-trastuzumab emtansine for treating breast cancer.¹³²⁻¹³⁸ Seven experts, with similar backgrounds, offered perspectives on pertuzumab for treating breast cancer.¹³⁹⁻¹⁴⁵

Please note that experts provided comments on these interventions before the very recent release of phase III data. At the time of review, Roche had not yet announced that the phase III trial of ado-trastuzumab emtansine in second-line treatment of metastatic breast cancer had met its primary endpoint. Similarly, although Roche had announced that the phase III trial of pertuzumab in first-line treatment of metastatic breast cancer had met its primary endpoint, the magnitude of the improvement in progression-free survival had not yet been released. New expert comments

regarding this new information will be sought for a future “Potential High-Impact Interventions” report.

We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for improved treatments of HER2+ metastatic breast cancer, the majority of experts agreed, citing the fact that many patients have disease that is refractory to therapies approved earlier than these new therapies. Although experts believe the overall unmet need addressed by these new therapies is large, they were cautious about the potential of these novel agents in salvage treatment settings.

Basing their opinions on the results of the phase II trials, the majority of experts thought that ado-trastuzumab emtansine has moderate to high potential to improve patient health. Experts thought that the phase II trial results suggested that ado-trastuzumab emtansine might improve on both the efficacy (i.e., ability to improve progression-free survival) and safety of current HER2-targeted therapies. However, experts seemed to believe that the improvements relative to other treatments for HER2+ metastatic disease would be incremental, especially as third-line treatment after disease progression. Several experts noted that if ado-trastuzumab emtansine were shown to improve outcomes in the first-line metastatic disease or adjuvant setting, its impact on HER2+ disease treatment models would be more significant.

Similarly, pertuzumab was thought by experts to have moderate to high potential to improve patient health. They cited the preliminary signals of activity in the neoadjuvant setting (i.e., presurgical treatment of localized disease) and in heavily pretreated patients. But two experts, both with a research perspective, thought that pertuzumab has only minimal potential to improve patient health, suggesting the potential for improvement was incremental. The potential for cardiac toxicity known to be associated with trastuzumab treatment was mentioned by multiple experts and they suggested that further study would need to rule out the possibility of cumulative heart damage arising from multiple antibodies simultaneously targeting HER2 or prolonged duration of anti-HER2 therapy.

Health care delivery infrastructure and patient management: Because health care workers would administer ado-trastuzumab emtansine and pertuzumab in the same manner as existing HER2-targeted therapies (e.g., trastuzumab), experts did not think that adoption of the drugs would require significant changes in health care facility staffing or infrastructure.

Health disparities: The anticipated high cost of ado-trastuzumab emtansine and pertuzumab was one potential obstacle raised by the experts, who noted it would be added to current regimens. Additionally, experts noted that the cost of these drugs has potential to create controversy over the cost-benefit ratio, with potential to increase health disparities between those who can afford the treatment and those who cannot.

Colorectal Cancer Intervention

Methylated Septin 9 Blood Test for Colorectal Cancer Screening

Unmet need: Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States. CRC tends to be slow to develop, and precancerous lesions and early stage CRCs can typically be successfully treated 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 50% of CRCs diagnosed in the United States are diagnosed at late disease stages.¹⁴⁶ Therefore, new screening methodologies are highly desired that could increase the percentage of the population that undergoes recommended CRC screening.

Intervention: Research has demonstrated that cells undergo a range of epigenetic modifications (e.g., DNA methylation) during their transformation to cancerous cells.¹⁴⁷ Also, elevated levels of methylated DNA have been found in the blood of patients with CRC, which could serve as a readily accessible marker for cancer screening.¹⁴⁷

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. Its detection using the Epi proColon 2.0 methylated Septin 9 DNA blood test is being studied as a potential CRC screening test.¹⁴⁷ Like other noninvasive colon cancer tests (e.g., fecal occult blood test [FOBT], fecal immunochemical test [FIT]), a positive result from the methylated Septin 9 test would require that the patient undergo colonoscopy to confirm findings and resect any precancerous or cancerous lesions.¹⁴⁸

Clinical trials: In December 2011, the Epi proColon 2.0 test's manufacturer released initial data from a trial in which a subset of 7,940 patients undergoing colonoscopy screening were also tested with its Septin 9 test.^{149,150} Blood samples were collected from all patients who subsequently underwent colonoscopy for determining CRC status. A subset of these samples was tested using the Epi proColon 2.0 blood test. Tested samples included those from all 50 patients with CRC, all 650 patients with advanced adenomas, a random subset of 450 patients with small polyps, and a random subset of 450 patients with no evidence of CRC. Preliminary results indicated that, compared with CRC detection by colonoscopy, the Septin 9 test had a sensitivity of 68% and a specificity of 80%.¹⁵⁰ Data on the test's ability to detect precancerous adenomatous polyps were not presented.

In December 2012, the manufacturer released top-line data from a second trial that compared Epi proColon 2.0 and FIT.¹⁵¹ In this trial, 103 patients with CRC and 195 individuals without CRC were tested with both Epi proColon 2.0 and FIT. Sensitivity was reported as 71% for Epi proColon and 67% for FIT, which company investigators reported as a statistically significant result of noninferiority regarding sensitivity for CRC. Specificity was reported as 81% for Epi proColon and 98% for FIT.

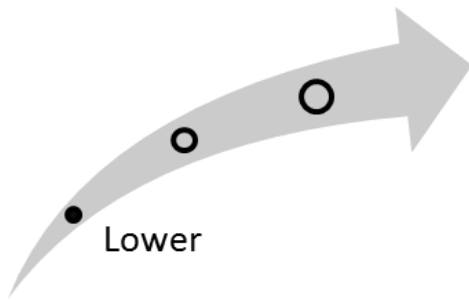
Manufacturer and regulatory status: The Epi proColon 2.0 methylated Septin 9 DNA blood test was developed by Epigenomics AG, of Berlin, Germany. As of April 2013, Epigenomics had completed its PMA submission to FDA for the Epi proColon test. FDA granted the submission priority review status in February 2013.¹⁵²

Clinical Pathway at Point of This Intervention

Several options are available for routine CRC screening in patients with an average risk of developing CRC, including annual FOBTs, sigmoidoscopy every 5 years, double-contrast barium enema every 5 years, computed tomography colonography every 5 years, or colonoscopy every 10 years.¹⁵³ For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the

result and perform any required biopsy of suspicious polyps.¹⁵³ Septin 9 blood testing would be another routine screening option that also would require followup colonoscopy for confirming positive results and excising lesions.¹⁴⁸ Test information states that it is not intended to substitute for colonoscopy, but might be useful as a complement to colonoscopy or for use in individuals unwilling or unable to undergo colonoscopy.¹⁵⁴

Figure 6. 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 in which venipuncture is used to collect a blood sample rather than testing a stool sample, could fundamentally change CRC screening practices by increasing the percentage of patients screened for CRC. However, regarding the Epi proColon 2.0 test specifically, experts were cautious about its potential use because of the relatively low reported sensitivity and specificity of the test thus far and they wondered whether the likely high cost of the test relative to other noninvasive options such as FOBTs would prevent widespread adoption, should it become available. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.¹⁵⁵⁻¹⁶¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A blood-based screening technology could have potential to address the unmet need for CRC screening, the majority of experts thought. They cited the low rate of adherence to recommended screening (i.e., fecal sample testing, colonoscopy, colonography), and speculated that it may be due in part to dislike of current test preparation and test methods. However, one researcher saw the unmet need as small, stating that multiple noninvasive tests are already available for CRC and that the Septin 9 test would only add to that mix.

Health outcomes might be significantly improved with the septin 9 screening test, the experts thought, basing their opinions on the belief that a blood-based test might increase screening rates among individuals who are not undergoing any screening at this time. However, multiple experts expressed concern about the relatively low reported sensitivity and specificity of the Epi proColon test and noted that false-negative results could lead to significant disease progression before detection. False-negative results could be most relevant if some patients opt for the convenience of an available blood test over colonoscopy, one expert noted.

Health care delivery infrastructure and patient management: Patient management in the diagnostic pathway could potentially shift somewhat with use of the septin 9 blood test, the experts

thought. Experts stated that it would probably be more acceptable to patients as a blood test than the current noninvasive, fecal-based tests, and that patients who had not been willing to undergo screening before might do so with the septin 9 blood test. Additionally, the test could be incorporated into primary care office visits during which blood samples are collected for other routine blood tests (e.g., cholesterol screening), multiple experts noted. In this way, experts envisioned that the septin 9 blood test could enable primary care physicians to incorporate a noninvasive CRC blood test into routine care and know that the test was carried out with a result reported to the primary care clinician rather than giving an FOBT to a patient with hopes that the patient will obtain a fecal sample collected in the home setting and return it for processing.

Hematologic Malignancy Interventions

Brentuximab Vedotin (Adcetris) for Recurrent or Treatment-Refractory Hodgkin's Lymphoma or Anaplastic Large Cell Lymphoma

Unmet need: CD30 is a defining marker of Hodgkin's lymphoma (HL) and anaplastic, large cell lymphoma (ALCL).¹⁶² Both diseases are rare, with about 8,500 cases of HL and 2,250 cases of ALCL diagnosed annually in the United States.^{162,163} Although many patients achieve complete remission following standard treatments for HL and ALCL, a significant proportion has disease that is refractory to standard therapies or recurs after first-line treatment. Available treatments for recurrent or refractory HL and ALCL provide little benefit to affected patients, and no consensus exists on optimal treatment of these patients.¹⁶²

Intervention: Brentuximab vedotin (Adcetris®) is an ADC targeted to CD30 that has been developed for treating recurrent or refractory HL or ALCL.¹⁶² The biologic compound consists of a CD30-specific monoclonal antibody chemically conjugated to a potent, chemotherapeutic agent, monomethyl auristatin E (MMAE).¹⁶⁴ Brentuximab vedotin is intended to 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 cells.¹⁶⁵ By targeting the cytotoxic molecule to CD30-expressing tumor cells, brentuximab vedotin is purported to minimize systemic toxicity while focusing its effects on the target tumor. Brentuximab vedotin is an intravenous (IV) medication that is administered at a dose of 1.8 mg/kg, over 30 minutes, once every 3 weeks.

Clinical trials: Researchers have reported results from two open-label, single-group assignment, phase II trials: one trial in patients with relapsed or refractory HL and the other in patients with relapsed or refractory ALCL. Treatment consisted of an IV infusion of 1.8 mg/kg every 3 weeks for up to 16 total doses.¹⁶⁶

In the HL trial (n=102), the overall response rate, as assessed by an independent review facility, was 75%, and 34% of patients achieved complete remission. The median response duration was 5.6 months as assessed by independent central review, and among patients achieving a complete remission, the median response duration was reported to be 20.5 months.¹⁶⁵

In the ALCL clinical trial (n=58), the overall response rate, as assessed by an independent review facility, was 86%, and 53% of patients achieved complete remission. The median response duration had not been reached when results were released and ranged from 0.3 to 45.3 weeks.¹⁶⁷

Common adverse effects reported in trials included diarrhea, fatigue, nausea, neutropenia, peripheral neuropathy, and pyrexia, which were characterized as "manageable."^{168,169} Since the trials, three cases of progressive multifocal leukoencephalopathy, a brain infection that can result in death, have been reported in patients who were undergoing brentuximab vedotin treatment.¹⁷⁰

Manufacturer and regulatory status: The agent was developed by Seattle Genetics, Inc., of Bothell, WA, in collaboration with Millennium Pharmaceuticals, a subsidiary of Takeda Pharmaceutical Co., Ltd., of Osaka, Japan; Seattle Genetics owns commercialization rights in the United States and Canada.

FDA granted the drug accelerated approval in August 2011 for treating both HL and ALCL.¹⁷¹ The approved indications are for patients with HL whose disease has not responded to an autologous stem cell transplantation or whose disease has progressed after at least two combination chemotherapy regimens, and who are not autologous stem cell transplant candidates.^{171,172} It is also indicated for patients with ALCL whose disease has not responded to one prior combination chemotherapy regimen.^{171,172} Labeling indicates that treatment is continued until disease progression or unacceptable toxicity, for up to a maximum of 16 treatment cycles.¹⁷³ Seattle

Genetics has submitted a supplemental BLA to expand the use of brentuximab vedotin beyond 16 cycles.¹⁷⁴

Also, a late-phase clinical trial incorporating brentuximab vedotin into first-line chemotherapy regimens for treating HL is ongoing, as well as mid-stage trials for first-line treatment of ALCL.^{175,176}

Diffusion: The initial drug pricing was set at about \$4,500 per vial with about three vials used per treatment and 7–9 cycles of treatment given per patient, bringing the total cost for a complete regimen to \$94,500 to \$121,500.¹⁷⁷ In July 2012, the company announced a 3.5% price increase.¹⁷⁸ Reports on the preliminary diffusion of brentuximab vedotin indicate that physicians are prescribing the drug as a bridge to stem cell transplant in patients with HL in addition to its FDA-approved indication (i.e., posttransplant or transplant-ineligible HL).¹⁷⁹

A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), identified 6 payers with policies that cover brentuximab vedotin for the FDA-approved indications in HL and ALCL.^{180–185} Some policies require prior authorization for coverage of this medication.

As an intravenous medication administered in the health care setting, brentuximab vedotin may be covered under Medicare Part B benefits. Since the launch of brentuximab vedotin, Seattle Genetics has reported that it is not aware of any refusals to reimburse an on-label use of the drug.¹⁷⁹ Seattle Genetics has a patient assistance program that may provide assistance to both uninsured and underinsured patients as well as assistance with insurance copayments.¹⁸⁶

Brentuximab vedotin is also being studied in phase III trials to treat other CD30-positive malignancies (e.g., CD30-positive cutaneous T-cell lymphoma).^{187,188}

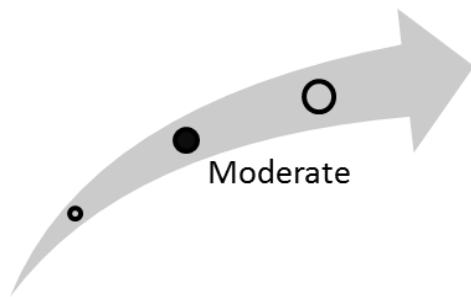
Clinical Pathway at Point of This Intervention

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 ABVD (adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) and Stanford V (mechlorethamine, doxorubicin, etoposide, vinblastine, vincristine, bleomycin, and prednisone).¹⁶³ Patients whose disease progresses after first-line therapy may undergo subsequent treatment with radiation therapy, high-dose chemotherapy coupled with autologous stem cell transplantation, or one of a range of salvage chemotherapy regimens.¹⁶³

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).¹⁸⁹ Some patients, in particular patients with anaplastic lymphoma kinase (ALK)-negative disease, may undergo consolidation chemotherapy consisting of a high-dose chemotherapy regimen with stem cell rescue.¹⁸⁹

No consensus treatment has been established in patients with ALCL whose disease does not respond to first-line therapy or recurs after first-line treatment; however, patients are typically treated with a new chemotherapy regimen, including EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), or ICE (ifosfamide, carboplatin, etoposide).^{162,189}

Figure 7. 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 its potential is high as a novel ADC that could treat CD30-positive malignancies that are refractory to standard therapies, especially for patients with few treatment options. However, the overall impact on the health care system would be limited by the routine manner of administration and the relatively small patient population affected by these conditions. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on use of brentuximab vedotin.¹⁹⁰⁻¹⁹⁵ Additionally, six experts, with clinical, research, and health systems backgrounds, offered comments on using brentuximab vedotin to treat ALCL.¹⁹⁶⁻²⁰¹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A lack of efficacious treatments for these cancers represents an important unmet need for new treatment options, the experts concurred.

For patients with HL, all but one expert thought that the available data suggested that brentuximab vedotin has significant potential to improve health outcomes, citing the high response rate observed in the clinical trial and the fact that no other therapy has shown a significant benefit in this patient population. However, several experts noted that the completed trials were single-arm clinical trials that reported only a response rate, and so a clear survival benefit had not yet been demonstrated.

For patients with ALCL, experts were unanimous in their opinion that patients whose cancer was not cured by first-line chemotherapy (and in some cases, stem cell transplantation) have few effective treatment options and a poor prognosis; 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.

Brentuximab vedotin has significant potential to improve patient health outcomes as evidenced by the high response rates demonstrated in the phase II trial of patients with treatment-refractory ALCL, most experts thought. However, several 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 response rates. With those data limitations in mind, one research expert suggested that brentuximab vedotin has some, but minimal potential to improve patient health outcomes, compared with salvage therapy options.

Acceptance and adoption: For patients with HL, despite the preliminary nature of the data, the majority experts thought that brentuximab vedotin would be widely accepted by both patients and clinicians because of the lack of effective treatment options and the high response rate reported in trials. Multiple experts also cited brentuximab vedotin's relatively benign adverse event profile for

the common events as another factor influencing physician and patient adoption; however, a few experts thought that the reports of high rates of peripheral neuropathy and rare cases of progressive multifocal leukoencephalopathy might discourage physicians and patients from opting for the treatments.

In the ALCL setting, both physicians and patients would be highly likely to adopt use of brentuximab vedotin, the experts unanimously opined, citing the lack of effective alternatives in refractory ALCL and the encouraging response rates 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. However, like the experts commenting on the use of brentuximab vedotin for treating HL, these experts suggested that reports of high rates of peripheral neuropathy and sporadic, though uncommon reports of progressive multifocal leukoencephalopathy could discourage some patients from opting for brentuximab vedotin treatment.

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

Health care delivery infrastructure and patient management: In the ALCL setting, the delivery mode would not necessitate significant changes in health care facility staffing or infrastructure, experts thought, or in the manner in which patients are managed. However, one expert with a clinical background suggested that brentuximab vedotin could alter the continuum of care for ALCL if it is shown to be safe and effective as first-line treatment.

Health disparities: In the HL setting, brentuximab vedotin use would increase the cost of care because it is additive to the current clinical pathway, the experts agreed. Several experts suggested that the high cost of brentuximab vedotin might make the drug inaccessible to underserved patients, possibly worsening existing health disparities. Although all experts indicated that they believe brentuximab vedotin would increase costs, some suggested that further studies might lead to use earlier in the treatment pathway and, if it improves long-term response rates, it could limit downstream costs associated with expensive second-line therapies such as autologous stem cell transplantation.

Ruxolitinib (Jakafi) for Treatment of Myelofibrosis

Unmet need: Myelofibrosis is one of three closely related disorders (i.e., myelofibrosis, polycythemia vera, essential thrombocytosis) caused by abnormalities in the myeloid hematopoietic lineage that lead to clonal expansion of a myeloid progenitor cell. One of the primary symptoms of myelofibrosis is splenomegaly (i.e., enlarged spleen) caused by abnormal myeloid cells accumulating in the spleen.²⁰² Current treatments for myelofibrosis are largely palliative, and effective treatments are needed.

Intervention: One molecular target that may be amenable to drug therapy for myelofibrosis is the JAK/STAT pathway. JAK/STAT activity has been implicated in the clonal proliferation of myeloid progenitor cells that lead to myelofibrosis. In particular, genetic mutations that lead to JAK/STAT pathway activation (e.g., activating mutations in JAK2, a tyrosine kinase that functions in the JAK/STAT pathway) have been identified in about two-thirds of myelofibrosis cases.^{203,204}

Besides playing a potential role in driving clonal proliferation, JAK/STAT signaling may also play a role in the elevated levels of proinflammatory cytokines observed in myelofibrosis and that probably contribute to disease symptoms.²⁰⁵ JAK/STAT signaling is known to be involved in both producing proinflammatory cytokines and mediating the effects of cytokines in target cells; therefore, inhibition of JAK kinases also has the potential to improve myelofibrosis symptoms by limiting inflammation.²⁰⁵

Ruxolitinib (Jakafi®) is an orally administered small-molecule kinase inhibitor that has activity against both JAK1 and JAK2 tyrosine kinases and represents the first JAK/STAT pathway inhibitor for treating myelofibrosis.²⁰⁶ Ruxolitinib labeling indicates that the drug should be given as follows:

- At a starting dosage of 20 mg, twice daily, for patients with a platelet count greater than $200 \times 10^9/L$
- At a dosage of 15 mg, twice daily, for patients with a platelet count between $100 \times 10^9/L$ and $200 \times 10^9/L$
- At a dosage of 5 mg, twice daily, for patients with a platelet count between $50 \times 10^9/L$ and $100 \times 10^9/L$.

As platelet counts allow, the dose may be increased up to 25 mg, twice daily, for patients with initial platelet counts greater than $100 \times 10^9/L$ and up to 10 mg, twice daily, for patients with initial platelet counts between $50 \times 10^9/L$ and $100 \times 10^9/L$.²⁰⁷

Clinical trials: Ruxolitinib has been studied in two phase III trials (COMFORT-I and COMFORT-II). In COMFORT-I, its safety and efficacy for treating myelofibrosis (n=155) was compared with placebo (n=154).²⁰⁸ In 2012, investigators reported that 41.9% of patients in the ruxolitinib arm achieved a 35% or more reduction in spleen size at 24 weeks compared with 0.7% of patients in the placebo arm ($p < 0.001$).²⁰⁸ In COMFORT-II, ruxolitinib (n=146) was compared with best alternative therapy (another agent) or no treatment (n=73).²⁰⁹ In 2012, researchers reported 28% of patients receiving ruxolitinib exhibited a 35% or greater reduction in spleen size at 48 weeks versus 0% of patients in the best alternative therapy arm ($p < 0.001$).²⁰⁹ In updated results at a median followup of 112 weeks, investigators reported death rates of 14% in the ruxolitinib-arm and 22% in the best alternative therapy-arm (HR = 0.52; 95% CI, 0.27-1.00).²¹⁰

Adverse events were reported as more common in the ruxolitinib arms than the placebo or best alternative therapy arms.^{208,209} The most common adverse events included anemia, diarrhea, peripheral edema, and thrombocytopenia. Grade 3 or 4 adverse events were observed in fewer than 10% of patients treated with ruxolitinib and included anemia and thrombocytopenia, which may require blood transfusions.²¹¹ Besides adverse events observed during treatment, instances of

serious adverse events (e.g., acute relapse of symptoms, rapid and painful spleen enlargement, acute hemodynamic decompensation) were reported after discontinuing ruxolitinib.²⁰⁵

Manufacturer and regulatory status: The drug was developed by Incyte Corp., of Wilmington, DE, in cooperation with Novartis International AG, of Basel, Switzerland, which holds rights to the compound outside the United States.²¹² In November 2011, FDA approved ruxolitinib for treating intermediate- or high-risk myelofibrosis (including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis).^{207,213}

Diffusion: Incyte set the retail price of ruxolitinib at \$7,000 for 1 month of treatment.²¹⁴ The initial uptake of ruxolitinib for treating patients with myelofibrosis has been reported as rapid, which has been attributed to “high physician awareness, limited reimbursement pushback, and strong patient demand.”²¹⁵ As of mid-June 2013, an online aggregator of pharmacy pricing showed costs of \$4,100 to just under \$4,200 across the United States with use of a coupon from the company.²¹⁶

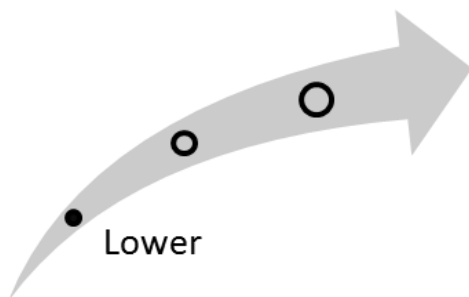
Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), identified 4 payers with policies that generally cover ruxolitinib for the FDA-approved indications in myelofibrosis.²¹⁷⁻²²⁰ Most policies and formularies of representative plans consider this agent a specialty pharmaceutical and require prior authorization for coverage of this medication. For Medicare beneficiaries with prescription drug coverage, the medication is covered under Medicare Part D, depending on the level of coverage a beneficiary has.

Ruxolitinib is also under study in a phase III trial for treating polycythemia vera as well as phase I and II trials for other hematologic malignancies.²²¹

Clinical Pathway at Point of This Intervention

After diagnosis of a myelofibrosis disorder, symptomatic patients may undergo palliative treatments such as blood transfusions or androgen therapy (for anemia), hydroxyurea chemotherapy, radiation therapy, combination thalidomide and prednisone treatment, or splenectomy.²²² Patients may also undergo allogeneic stem cell transplantation to attempt to cure the condition.²²² Ruxolitinib represents an additional treatment option for patients with myelofibrosis.

Figure 8. Overall high-impact potential: ruxolitinib (Jakafi) for treatment of myelofibrosis



Overall, experts believe that ruxolitinib addresses a significant unmet need for novel treatments for myelofibrosis. Although experts thought its adoption by physicians and patients would be high because of encouraging data regarding spleen size; but they were cautious in their optimism, given the lack of a clear impact on patient survival and disease progression. Lastly, experts did not envision an oral medication intended for use in a relatively small patient population as having significant impacts on the health care system infrastructure or patient management. Based on this

input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this topic.²²³⁻²²⁸ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for myelofibrosis treatment, experts concurred, citing the lack of FDA-approved therapies before the approval of ruxolitinib and the inadequacy of current treatments in addressing disease progression. One expert with a clinical perspective noted that while allogeneic hematopoietic stem cell transplant may provide a curative option for some patients with myelofibrosis, very few patients are eligible for this treatment. The available data on ruxolitinib's effectiveness was positively noted by experts, citing the clear effects of treatment on organomegaly. However, multiple experts noted that the long-term effects of ruxolitinib treatment on patient survival and disease progression were unknown and, therefore, suggested that ruxolitinib might be considered another palliative treatment for myelofibrosis. However, it should be noted that at the time of expert comment the results from extended followup that have shown a trend towards improved overall survival were not available. Thus, given the latest data, opinions might be even more positive.

Acceptance and adoption: The majority of experts suggested that patients and physicians alike would be highly likely to adopt ruxolitinib, citing the lack of effective options and the ease and convenience of prescribing and taking an oral medication. However, one expert with a health systems perspective suggested that the potential for uptake was only minimal, citing the unclear benefits of ruxolitinib on disease progression and its high cost, which could mean substantial out-of-pocket costs for patients.

Health care delivery infrastructure and patient management: As an oral medication that would be used to treat a relatively uncommon disease, experts did not expect ruxolitinib to have a significant impact on health care staffing or infrastructure, or to significantly shift health care processes.

Ponatinib (Iclusig) for Treatment of Chronic Myelogenous Leukemia or Chromosome–Positive Acute Lymphoblastic Leukemia

Unmet need: Chronic myelogenous leukemia (CML) is a myeloproliferative disorder that typically progresses through three phases—chronic, accelerated, and blast—characterized by increasing numbers of immature blood cells (i.e., myoblasts or blasts) in the blood and bone marrow.^{229,230} Although patients with chronic-phase CML typically have mild symptoms (e.g., fever, poor appetite, weight loss) and their disease often responds to treatment, patients in more advanced phases typically have more pronounced symptoms and their disease responds less well to treatment. CML in blast crisis behaves more like an acute leukemia than a chronic leukemia and requires aggressive treatment. The majority (85%) of patients receive the diagnosis of CML when they are in the chronic phase.²³¹

CML's defining feature is a specific genetic mutation, a genetic fusion between the breakpoint cluster region (*BCR*) of chromosome 22 and the Abelson kinase (*ABL*) oncogene on chromosome 9.²³¹ The majority of *BCR-ABL* gene fusions result from a reciprocal translocation between the long arm of chromosome 22 and the long arm of chromosome 9, a cytogenic abnormality known as the chromosome.²³⁰ The protein kinase expressed by the *BCR-ABL* gene is constitutively active and drives the pathogenesis of CML.²³⁰ About 25% of cases of another type of leukemia, acute lymphoblastic leukemia (ALL) also involve the *BCR-ABL* oncogene.²³² ALL typically progresses rapidly and can be lethal within months in the absence of aggressive treatment. Historically, chromosome-positive ALL (Ph+ ALL) has been associated with a worse prognosis than Philadelphia chromosome–negative ALL.²³³

The availability of tyrosine kinase inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib that target the oncogenic BCR-ABL kinase has significantly improved the prognosis for patients with CML.²³⁴ However, although many patients have long-term responses to ongoing TKI treatment, no treatment options are available for patients who fail to respond to available TKIs or develop resistance to them. In particular, CML with the threonine 315 to isoleucine (T315I) mutation in the BCR-ABL kinase is resistant to all previously available TKIs.²³⁴

Intervention: Ponatinib (IclusigTM) is a novel orally administered BCR-ABL inhibitor that has demonstrated activity against resistant forms of CML, including CML harboring the T315I mutation.²³⁵ Besides its activity against BCR-ABL, ponatinib has also demonstrated inhibition of other tyrosine kinases, including SRC, LYN, and c-KIT as well as members of the vascular endothelial growth factor receptor, fibroblast growth factor receptor, and platelet-derived growth factor receptor families.²³⁵ Based on these activities, ponatinib has the potential to improve outcomes for patients with CML and/or other malignancies harboring the *BCR-ABL* oncogene (e.g., Ph+ ALL). Ponatinib is an oral medication that is administered at a dosage of 45 mg, once daily.²³⁶

Clinical trials: Data from the phase II PACE study of ponatinib for treating patients with TKI-refractory CML or Ph+ ALL demonstrated that treatment with ponatinib resulted in the following:²³⁷

- A major cytogenic response rate of 49% for patients with chronic-phase CML
- A major hematologic response rate of 67% for patients with accelerated-phase CML
- A major hematologic response rate of 37% for patients with Ph+ ALL

Manufacturer and regulatory status: Ponatinib is being developed by ARIAD Pharmaceuticals, Inc., of Cambridge, MA. Based on data from the PACE study, ARIAD submitted a new drug application to FDA seeking accelerated approval of ponatinib. In December 2012, FDA approved ponatinib for the “treatment of adult patients with chronic phase, accelerated phase, or

blast phase CML that is resistant or intolerant to prior tyrosine kinase inhibitor therapy or Ph+ ALL that is resistant or intolerant to prior tyrosine kinase inhibitor therapy.”^{236,238}

This accelerated approval was based on response rate only, and the prescribing information for ponatinib indicates that no clinical trials have yet verified improved disease-related symptoms or overall survival.²³⁶ Ponatinib’s prescribing information carries a black box warning regarding the potential for arterial thrombosis and hepatotoxicity.²³⁶

Diffusion: A May 2013 query of an online aggregator of pharmacy pricing identified a retail price of about \$10,305 for a one-month supply of ponatinib 45 mg dose,²³⁹ which represents a significant premium over the price of previously approved TKIs for treating CML.^{236,240} Initial reports from ARIAD indicate that more than 325 patients began treatment with ponatinib in the first 12 weeks of commercial distribution.²⁴¹

A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 3 payers with policies regarding ponatinib.²⁴²⁻²⁴⁴ These payers may cover ponatinib when prescribed according to FDA-approved indications, but require prior authorization and impose quantity limits. Ponatinib is eligible for coverage under Medicare Part D benefits, depending on the plan selected by a beneficiary.

Potential exists for ponatinib to be used in earlier stages of CML treatment. In June 2012, ARIAD began a phase III, randomized, open-label trial of ponatinib versus imatinib in patients with treatment-naïve chronic phase CML (the EPIC trial).²⁴⁵

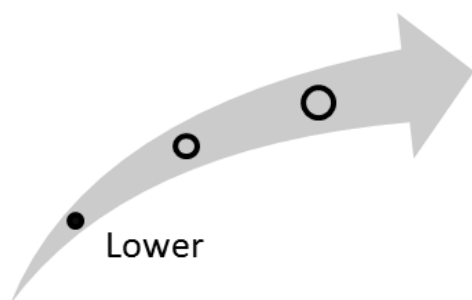
Clinical Pathway at Point of This Intervention

Treatment options for patients with CML depend on the disease phase. Initial treatment of chronic phase CML typically consists of TKI monotherapy with dasatinib, imatinib, or nilotinib. Patients whose disease shows an incomplete response or recurs during this monotherapy may be switched to a higher dose of the initial inhibitor or switched to a second inhibitor. Treatment of accelerated phase CML often consists of monotherapy with dasatinib or nilotinib, particularly if the patient has not been previously treated with these agents.²⁴⁶ Additionally, FDA recently approved an additional TKI (bosutinib) and omacetaxine mepesuccinate for treating CML with resistance or intolerance to prior therapy.²⁴⁷ Some patients in chronic- or accelerated-phase CML may be considered for treatment with hematopoietic stem cell transplant.

Patients in whom CML is initially diagnosed in blast crisis may be treated with TKI therapy followed by hematopoietic stem cell therapy.²⁴⁶ Patients whose disease has progressed to blast crisis during TKI therapy are typically treated with regimens usually reserved for acute leukemias (e.g., ALL, acute myeloid leukemia). These treatments typically consist of multiagent chemotherapy regimens that in the case of Ph+ ALL are supplemented with a TKI targeting *BCR-ABL*.^{248,249} When possible, these chemotherapy regimens are followed by hematopoietic stem cell transplant.^{248,249} Alternatively, patients with Ph+ disease may undergo maintenance therapy using TKIs.^{246,248}

Patients whose disease does not achieve remission or recurs following hematopoietic stem cell transplantation may resume TKI treatment, undergo donor lymphocyte infusion, or undergo interferon treatment.²⁴⁶

Figure 9. Overall high-impact potential: ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia



Overall, experts highlighted the critical role of ponatinib as a therapeutic agent for patients with CML or Ph+ ALL that is resistant to other available TKIs. Several experts noted the importance of data from the ongoing phase III trial in the first-line treatment setting as a determining factor in long-term impact potential. Clinical experts were enthusiastic about the potential for ponatinib's use as a monotherapy or as part of combination therapy in first-line treatment settings. Experts predicted minimal disruption to existing health care infrastructure and patient management based on the oral administration route and familiar mechanism of action and safety profile. Based on the above, our overall assessment is that this intervention is in the lower end of the high-potential-impact range.

Results and Discussion of Comments

Eight experts, with clinical, research, and health systems backgrounds, commented on ponatinib.²⁵⁰⁻²⁵⁷ It should be noted that omacetaxine mepesuccinate (Synribo™) was not yet available at the time we received expert comments. We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts were unanimous about the significant unmet need for patients with CML or Ph+ ALL that is resistant or intolerant to the available TKI therapies, particularly for those with the T315I mutation in *BCR-ABL*. Preliminary data for surrogate endpoints (i.e., major cytogenic response rate, major hematologic response rate) are encouraging, a majority of experts noted, acknowledging significant potential to improve patient health should ongoing trials corroborate initial efficacy data. Several experts also commented on the potential for benefit for ponatinib use in the first-line setting, possibly in combination with other treatments.

Acceptance and adoption: Clinicians and patients would widely adopt and accept ponatinib because it addresses an important gap in care, experts with clinical and health systems perspectives believe.

Health care delivery infrastructure and patient management: Because ponatinib is an oral medication with a similar or improved safety profile as with existing TKIs, clinical experts anticipated little disruption to health care infrastructure and patient management as a result of its use. One clinical expert noted the potential for increased testing for the T315I mutation that confers resistance to other TKIs.

Health disparities: Given ponatinib's cost and potential to be used as part of combination therapy during earlier disease phases, experts anticipated slight to moderate cost increases with its use. Among this relatively small patient population, experts suggested, cost could deter use by those without sufficient insurance coverage, but experts thought overall effects on health disparities would be minimal. Experts noted that potential cost increases might be offset by postponing or obviating need for bone marrow transplantation and by preserving quality of life and the patient's

ability to work. A clinical expert also noted that ponatinib may enhance competition with existing TKIs, potentially decreasing the cost of existing first- and second-line treatments.

Lung Cancer Intervention

Crizotinib (Xalkori) for Treatment of Advanced Nonsmall Cell Lung Cancer

Unmet need: Patients with advanced nonsmall cell lung cancer (NSCLC) have a relatively low response rate to current therapies (25% to 30%) and result in 2-year survival rates of only 10% to 15%;²⁵⁸ therefore, the need is significant for new treatments for this condition.

Intervention: 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*). The *ALK* gene encodes a receptor tyrosine kinase that regulates multiple cellular processes, and gene fusions can result in production of an ALK protein that is constitutively active, which can drive carcinogenesis.²⁵⁹ Targeted inhibition of ALK kinase activity is a promising therapeutic alternative for these individuals.

Crizotinib (Xalkori[®]) is a twice-daily oral chemotherapy drug that inhibits both ALK and hepatocyte growth factor receptor tyrosine kinase (MET).²⁶⁰ It is given at a dosage of 200 mg twice daily or 250 mg once daily, depending on the patient's tolerance.²⁶¹ 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. A genetic test on a tumor sample is required to identify patients who may benefit from crizotinib therapy.²⁵⁹

Clinical trials: Data from the pivotal phase II study were published in 2010; Kwak and colleagues reported on 82 patients with *ALK* mutation–positive NSCLC who were treated using crizotinib monotherapy.²⁵⁹ 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.

Two phase III trials of crizotinib in the first- and second-line treatment setting followed up on the phase II trial findings.^{262,263} In September 2012, initial results were presented for the trial of crizotinib in the second-line setting.²⁶⁴ In this trial, patients with *ALK*-mutation-positive disease who had previously undergone treatment with one platinum drug–containing regimen were randomly assigned to treatment with either crizotinib or cytotoxic chemotherapy (either pemetrexed or docetaxel). Patients in the crizotinib arm demonstrated improved progression-free survival (median 7.7 vs. 3.0 months, HR 0.49; 95% CI, 0.37 to 0.64; $p < 0.0001$); however, overall survival data were immature at that time.²⁶⁴ Investigators reported that compared with standard cytotoxic chemotherapy, crizotinib significantly reduced key patient-reported lung cancer symptoms and improved quality-of-life ratings.²⁶⁵

Crizotinib prescribing information states that the most commonly reported adverse reactions occurring in more than 25% of patients were the following (in decreasing order of all-grades incidence): vision disorder, nausea, diarrhea, vomiting, edema, and constipation.²⁶⁶ The prescribing information also carries warnings regarding the potential for hepatotoxicity, pneumonitis, and QT interval prolongation.

Manufacturer and regulatory status: Pfizer, Inc., of New York, NY, makes crizotinib. FDA approved crizotinib through its accelerated approval program in August 2011 on the basis of two single-arm, phase II trials involving 136 and 119 patients with *ALK*-mutation-positive NSCLC, in whom crizotinib treatment generated an overall objective response rate of 50% and 61%, respectively.²⁶⁶ The approval was for treating patients who have locally advanced or metastatic

NSCLC that is *ALK*-positive as detected by the FDA-approved test, Vysis *ALK* Break Apart FISH Probe Kit.²⁶⁷

Diffusion: Pfizer has indicated that adoption of crizotinib for treating patients with *ALK*-mutation-positive NSCLC has been slower than anticipated.²⁶⁸ This may be due, in part, to complications related to testing for presence of the *ALK* mutation in a patient population for whom tumor tissue quantity may be limiting and physicians may want to test for other targetable genetic mutations (e.g., EGFR mutations).²⁶⁸

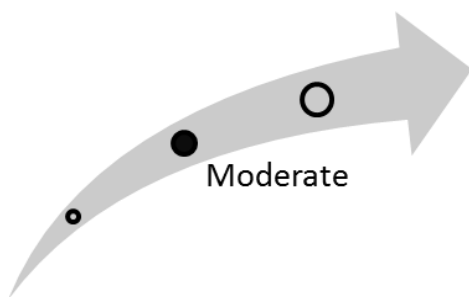
A June 2013 query of a U.S.-based, online aggregator of pharmacy drug pricing identified a retail cost of about \$135,000 per patient per year (\$11,250 per month) with use of a company-provided coupon.²⁶⁹ The list price of the companion diagnostic test is approximately \$225 per test, but the full cost of the test will also include a fee for performing the test.²⁷⁰

A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 4 payers with policies regarding crizotinib.²⁷¹⁻²⁷⁴ These payers considered crizotinib to be medically necessary when prescribed according to FDA-approved indications for NSCLC and require prior authorization. Formularies of representative plans typically classify crizotinib as a specialty tier pharmaceutical that requires prior authorization and may impose quantity limits. Crizotinib may be eligible for coverage under Medicare Part D benefits. Pfizer has a plan that helps reduce patient out-of-pocket costs to \$100 per prescription for copayments for some patients for an annual maximum savings of \$24,000.²⁷⁵ Besides the ongoing phase III trials in the first- and second-line treatment setting for NSCLC, early stage trials are also ongoing to test crizotinib for treating other types of *ALK* mutation-positive tumors.²⁷⁶

Clinical Pathway at Point of This Intervention

The initial treatment of early stage 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 are sometimes used before surgery to reduce tumor size. After surgery, patients may undergo sequential radiation therapy and chemotherapy or combined chemoradiation treatment. Multiple first- and second-line chemotherapy agents are available for treating lung cancer. 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).²⁷⁷ Crizotinib represents another first- or second-line chemotherapy option for patients with cancers bearing a specific genetic change at the *ALK* locus.

Figure 10. Overall high-impact potential: crizotinib (Xalkori) for treatment of advanced nonsmall cell lung cancer



Overall, experts commenting on this intervention thought that it 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. Crizotinib 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 limited number 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-impact-potential range.

Results and Discussion of Comments

Eight experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on this intervention.²⁷⁸⁻²⁸⁵ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A significant unmet need exists for novel therapies for NSCLC, all of the experts agreed, citing the short duration of survival for patients with advanced NSCLC when treated with available therapies. However, several experts noted limited significance of the unmet need purportedly addressed by crizotinib because treatment is targeted to only a small subset of patients with NSCLC that harbors an *ALK* mutation. However, for this select patient population, the majority of experts indicated, the available data suggested that crizotinib has significant potential to improve patient health; the experts cited the high response rate and an indication that crizotinib may improve patient survival. Several experts noted that a clearer picture of the benefits of crizotinib would be generated after completion of ongoing randomized controlled trials comparing crizotinib with standard treatment options.

Acceptance and adoption: Physicians and patients alike would readily adopt crizotinib, all experts thought. They cited the few viable alternatives, the drug's activity, and the drug's relatively well-tolerated safety profile. Additionally, multiple experts suggested that patients would prefer to take an orally administered medication at home rather than traveling to infusion centers for treatment. However, multiple experts noted the potential for patients to be burdened with a large copayment for crizotinib, which could limit adoption by some patients.

Health care delivery infrastructure and patient management: One expert with a clinical perspective suggested that drugs like crizotinib that are intended for a select, targeted patient population with a high rate of response to the therapy should serve as a paradigm for future cancer-drug development. Still, the majority of experts did not think that crizotinib would require significant shifts in patient management. Although multiple experts noted that identifying the small number of patients eligible for crizotinib would require screening a large number of patients with NSCLC, some experts noted that because molecular testing (e.g., EGFR mutation status) is already routinely performed on biopsy samples from NSCLC patients, this intervention's screening need may not lead to a major shift in patient management. Two experts with clinical perspectives suggested that some patients might have to undergo multiple biopsies if insufficient tumor tissue is recovered to perform all necessary molecular diagnostic tests. Besides the additional testing requirements, another reviewer with a clinical perspective suggested, the shift from intravenous chemotherapy agents to an orally administered agent such as crizotinib would require a shift in the way patients are observed for adverse effects of the therapy.

Health disparities: Multiple experts, in noting the potential for a large drug copayment, thought using crizotinib could worsen health disparities for certain underserved patient populations.

Prostate Cancer Interventions

Enzalutamide (Xtandi) for Metastatic Castration-Resistant Prostate Cancer

Unmet need: Men with metastatic castration-resistant prostate cancer (mCRPC; i.e., cancer that is insensitive to androgen withdrawal) have few treatment options and a poor prognosis. Recently reported survival time for this patient population when treated using cytotoxic chemotherapy is about 22 months.²⁸⁶ Novel treatments for this stage of prostate cancer are highly desired, especially for patients whose disease has progressed after first-line treatment with docetaxel.

Intervention: 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 has suggested that these cancers may still depend on androgen receptor signaling; therefore, further inhibition of androgen signaling may have efficacy as an mCRPC treatment.²⁸⁶ This hypothesis was affirmed by the demonstration that further inhibition of androgen synthesis with the androgen synthesis inhibitor abiraterone improved outcomes in this patient population.²⁸⁷

Enzalutamide (Xtandi®) is a second pharmacologic approach to targeting residual androgen signaling in this patient population. In contrast to abiraterone's inhibition of androgen synthesis, enzalutamide is purported to inhibit androgen receptor signaling by blocking multiple steps required for androgen receptor activity, including androgen binding, androgen receptor nuclear translocation, and androgen receptor DNA binding.²⁸⁸ Unlike currently available androgen receptor antagonists, enzalutamide purportedly exhibits no androgen receptor agonist activity.

Clinical trials: A phase III, randomized, placebo-controlled trial (the AFFIRM trial) of patients with castration-resistant prostate cancer (CRPC) who had undergone prior treatment with docetaxel showed that overall survival in the enzalutamide arm was 18.4 months versus 13.6 months in the placebo arm (HR 0.63; 95% CI, 0.53 to 0.75; $p < 0.001$).²⁸⁹ Researchers reported that adverse events associated with enzalutamide treatment included fatigue, diarrhea, and hot flashes. Additionally, seizures (a known side effect of high-affinity antiandrogens) were reported in 0.6% of patients taking enzalutamide.²⁸⁹

Enzalutamide is also undergoing study in earlier lines of prostate cancer treatment; a 1,680-patient, phase III trial of enzalutamide for treating patients with chemotherapy-naïve mCRPC completed enrollment in June 2012.²⁹⁰

Manufacturer and regulatory status: Medivation, Inc., of San Francisco, CA, makes enzalutamide. Based on the AFFIRM trial data, FDA approved enzalutamide in August 2012 for treating mCRPC in patients who have previously received treatment with docetaxel.²⁹¹ Enzalutamide is an oral medication that is administered at a dose of 160 mg (4 capsules), once daily.²⁹²

Diffusion: In the U.S. market, enzalutamide has been available since September 2012. Initial adoption of enzalutamide has been relatively rapid; sales in the first quarter of 2013 were up more than 30% compared with the previous quarter. Positive data from ongoing phase III trials may lead to expanded indications in chemotherapy-naïve mCRPC and nonmetastatic CRPC, promoting further diffusion.²⁹³ A query of an online, U.S.-based aggregator of pharmacy pricing identified a retail price of about \$8,100 for a 1-month supply of enzalutamide, or \$97,200 per year of treatment.²⁹⁴

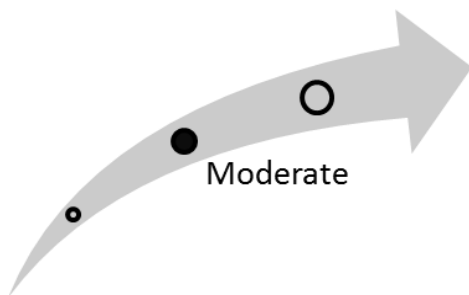
A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 3 payers with policies for enzalutamide.²⁹⁵⁻²⁹⁷ These payers considered enzalutamide to be medically

necessary when prescribed according to FDA-approved indications for mCRPC; coverage may be contingent upon failure of prior therapy (i.e., abiraterone and/or docetaxel). Formularies of representative plans classify enzalutamide as a specialty tier pharmaceutical and some formularies require prior authorization and impose quantity limits. Enzalutamide may be eligible for coverage under Medicare Part D benefits.

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.²⁹⁸ Yet, few options are available for patients whose cancer becomes resistant to androgen deprivation and progresses to mCRPC; such disease that is not symptomatic or only mildly symptomatic may be treated with the autologous cancer vaccine sipuleucel-T or the androgen synthesis inhibitor abiraterone.²⁹⁸ For patients with more advanced, symptomatic mCRPC, the standard first-line treatment is systemic chemotherapy with the taxane docetaxel.²⁹⁸ Lastly, for patients whose disease progresses after treatment with docetaxel, treatment may consist of the androgen-synthesis inhibitor abiraterone or the taxane cabazitaxel.²⁹⁸ In its FDA-approved indication, enzalutamide represents a potential treatment alternative to abiraterone and cabazitaxel in the postdocetaxel setting.

Figure 11. Overall high-impact potential: enzalutamide (Xtandi) for metastatic castration-resistant prostate cancer



Overall, experts commenting on this intervention were enthusiastic about its potential to improve both quality and quantity of life for patients with mCRPC. However, 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 and suggested that enzalutamide may have a larger impact when used in earlier in the treatment pathway. Experts suggested that study of the proper sequential and/or combinatorial use of abiraterone, enzalutamide, and other recently approved drugs for prostate cancer is needed. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Nine experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on enzalutamide for treating prostate cancer.²⁹⁹⁻³⁰⁷ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A high unmet need exists for effective treatments for mCRPC, the experts uniformly indicated; enzalutamide purports to address this need. They cited the few treatment options available to these patients and survival rates of short duration using current therapies. In particular, a significant need exists for therapies in treating asymptomatic mCRPC.

Because of the availability of abiraterone in this setting, some experts commenting on enzalutamide concluded that the unmet need was not large; however, multiple experts suggested that enzalutamide might complement abiraterone or offer an incremental improvement in efficacy and safety compared with abiraterone.

Acceptance and adoption: Although several experts noted that treatment with enzalutamide results in only a modest increase in survival, experts agreed that the drug would likely be adopted by both patients and physicians. The experts cited the promising efficacy results reported in the phase III trial in the postchemotherapy setting, the drug's ease of use, and its low side-effect profile relative to chemotherapy.

Health care delivery infrastructure and patient management: Enzalutamide will not likely cause a shift in health care staffing or health care facility infrastructure requirements, according to the experts, because it is orally administered. Several experts suggested that its use in earlier stages of treatment could shift the care setting for certain patients from infusion therapy to self-administered therapy. All experts suggested that enzalutamide would increase costs of care as an add-on treatment or potential long-term use starting in earlier stages of treatment.

Magnetic Resonance Imaging–Ultrasound Image Fusion to Guide Prostate Biopsy

Unmet need: Despite the widespread occurrence of prostate cancer, significant variability exists in prostate cancer diagnostic methods.^{308,309} Prostate biopsy methods used in arriving at a diagnosis can differ among practitioners and often provide results of varying consistency and predictive value.^{308,309} The standard of care, transrectal ultrasound (TRUS)-guided prostate biopsy, provides a convenient and cost-efficient approach, but may lack the diagnostic sensitivity and accuracy of magnetic resonance imaging (MRI)-guided biopsy.^{308,310} Although effective, MRI-guided biopsy is more expensive than TRUS-guided prostate biopsy and requires highly specialized equipment and staff training.^{308,310} A more convenient, cost-efficient, and reliable solution for lesion-targeted prostate biopsy is needed.

Intervention: Image fusion–guided prostate biopsy combines the anatomical resolution and sensitivity of multiparametric MRI with the relatively low cost and convenience of TRUS performed in the urology suite. A multiparametric MRI scan of the prostate obtained at an MRI facility is sent to a radiologist to identify and grade any suspicious prostate lesions.³¹¹⁻³¹³ The urologist then performs a real-time three-dimensional (3-D) TRUS-guided biopsy on the patient in the office setting. Image-fusion technology superimposes real-time TRUS images onto the previously obtained MRI of the prostate, enabling the urologist to obtain targeted biopsy samples from suspicious lesions, typically in addition to the conventional 12-core biopsy.^{308,310} MRI-TRUS fusion-guided biopsy requires coordination between the radiologist who grades the MRI and the urologist who performs the TRUS and uses the fused images to guide the biopsy.

A central feature of MRI-TRUS image fusion is the incorporation of algorithms to adjust for patient movement and prostate deformation due to pressure from the ultrasound probe.^{308,310} Besides improving the precision of targeted biopsies, many MRI-TRUS image-fusion platforms also incorporate technology to track the specific location of biopsy sites for each patient.^{308,310,314,315} These data could be used for a variety of purposes, including repeat biopsy or targeted focal therapy to specific biopsy sites.^{308,310,314,315}

Clinical trials: Imaging software systems for MRI-TRUS image fusion have been developed by several manufacturers for lesion-targeted prostate biopsy. We summarize published results of three of the largest recent trials; each study used a different system.

One study used the Artemis with the ProFuse Bx (Eigen, Grass Valley, CA) system. In 171 patients with either had persistent elevated prostate-specific antigen (PSA) levels but prior negative standard biopsy or were under active surveillance and subject to a yearly biopsy protocol, targeted biopsy using this platform yielded significantly more positive biopsies and identified more high Gleason grade samples than standard, nontargeted biopsy.³¹¹

Other data were released from the second study, a recent study on the PercuNav image fusion and navigation technology (Royal Philips Electronics, Amsterdam, the Netherlands, in collaboration with the National Cancer Institute, Bethesda, MD) in 195 patients with elevated PSA but prior negative standard biopsy. Image fusion–guided biopsy, in combination with standard biopsy, identified prostate cancer in 37% of these men, 11% of whom had high-grade cancer. Standard TRUS-guided biopsy missed 55% of these high-grade cancers, and pathological upgrading occurred in 38.9% of participants as a result of the image fusion–guided approach.³¹⁶

Finally, investigators recently published data from use of the BiopSee Advanced Image Guided Prostate Biopsy System (MedCom GmbH, Darmstadt, Germany) in patients with previous negative TRUS-guided biopsy (n=170) or patients undergoing primary biopsy (n=177). Targeted biopsy

cores revealed significantly more cancers than systemic biopsy cores and successfully identified more high Gleason grade cancers.³¹⁷

An ongoing clinical trial of PercuNav image fusion and navigation technology is under way by Philips in collaboration with the National Cancer Institute (Bethesda, MD). This trial is comparing MRI-TRUS fusion-guided prostate biopsy with standard TRUS-guided biopsy in about 980 patients with elevated PSA levels or abnormal digital rectal examination findings.³¹⁸ Another trial is testing the Urostation image-fusion platform, developed by Koelis (Grenoble, France). This trial is comparing positive biopsy rates between standard TRUS-guided biopsy and MRI-TRUS fusion-guided biopsy in 300 patients with suspected prostate cancer and no prior prostate biopsy history.³¹⁹

Manufacturer and regulatory status: Several imaging and software systems for MRI-TRUS image fusion are available for conducting lesion-targeted prostate biopsies. Available systems include the following:

- Artemis with ProFuse Bx³²⁰
- BioJet™ 3D MR-TRUS Fusion Prostate Biopsy System, Geo Scan Medical, LLC, of Lakewood Ranch, FL³²¹
- BiopSee Advanced Image Guided Prostate Biopsy System³²²
- HI VISION Ascendus Platform with real-time virtual sonography, Hitachi Medical Corp., of Tokyo, Japan³²³
- PercuNav image fusion and navigation technology³²⁴
- UroNav Fusion Biopsy System, Invivo Corp., a Philips subsidiary³²⁵
- UroStation^{326,327}

These devices have received 510(k) device clearance from FDA.^{320,328-333}

Diffusion: Image-fusion, prostate-biopsy software platforms are gradually diffusing throughout the United States. MRI-TRUS image fusion software is designed to integrate with many commonly used ultrasound platforms. Several types of image fusion modules are available for installation onto existing prostate biopsy-TRUS workstations.^{327,328,330} Many newly purchased systems for prostate biopsy include software with this capability.^{321,323}

MRI-TRUS image fusion-guided biopsies are likely to be more expensive than standard TRUS-guided biopsy. However, MRI-TRUS image fusion-guided biopsy is likely to be substantially less expensive than in-bore MRI-guided biopsy.

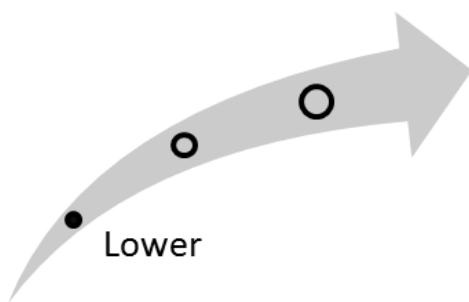
MRI cost and potential lack of procedure coverage are potential barriers to adoption. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found no payers with specific policies regarding MRI-TRUS image fusion-guided biopsy, and coverage might be determined on a case basis or coded for under existing codes. Some payers consider other nonstandard approaches to prostate cancer staging or diagnosis (e.g., magnetic resonance spectroscopy, MRI, or saturation biopsy) to be investigational and therefore ineligible for coverage.³³⁴⁻³³⁹ Ongoing trials of image fusion platforms may support future diffusion.

Clinical Pathway at Point of This Intervention

Primary screening for prostate cancer often begins around the age of 50 years and may include digital rectal exams and PSA-level tests, although recommendations for PSA testing have recently changed.³⁴⁰ Abnormal findings on these tests or other suspicions of prostate cancer often warrant a prostate biopsy.^{340,341} The standard-of-care, TRUS-guided prostate biopsy, uses a random sampling of the prostate gland, with clinicians collecting about 12 tissue cores from medial and lateral aspects

of the base, mid-zone, and apex of each side of the prostate gland.³⁰⁸ Conventional TRUS-guided biopsy is relatively inexpensive and is easily performed in the urologist's office, but procedural shortcomings include high false-negative rates and a limited ability to target clinically significant lesions identified by imaging studies.^{308,310} Multiparametric MRI has been explored to identify suspicious areas and obtain targeted biopsies in real time.³¹⁰ Besides improving prostate cancer detection, MRI enables physicians to distinguish small, indolent lesions from higher-grade, more clinically significant lesions.^{342,343} However, in-bore MRI-guided biopsy is expensive and must be performed in a specialized setting.³¹⁰ Image fusion-guided prostate biopsy overlays previously obtained MRIs onto real-time ultrasound imaging to enable improved lesion-targeted biopsy in the urologist's office.

Figure 12. Overall high-impact potential: magnetic resonance imaging–ultrasound image fusion for image-guided prostate biopsy



Overall, experts commenting on this intervention believe that a significant unmet need exists for a low-cost, safe, and accurate prostate biopsy approach that could significantly reduce the number of false-negative biopsies and help urologists distinguish high-risk from clinically insignificant prostate cancers. The image fusion approach to prostate biopsy requires an MRI scan and timely coordination between the radiologist and urologist. Experts anticipated that widespread adoption would depend in part on imaging and procedure costs and payer coverage policies. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on the topic of MRI-US image fusion-guidance for prostate biopsy.³⁴⁴⁻³⁴⁹ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need for improved biopsy methods is moderately to very important, the experts thought, citing limitations of standard biopsy approaches and the large degree of interprovider variability in biopsy protocols and accuracy. They generally agreed that this intervention could ensure greater methodologic consistency and enhance detection of clinically important prostate lesions. Experts were unanimous in their opinion that MR-TRUS image fusion-guided biopsy methods could likely improve patient outcomes.

Acceptance and adoption: Most clinicians would readily welcome a more accurate and consistent biopsy method, the experts generally agreed. But the cost of acquiring the image fusion interface and the requirement for a compatible ultrasound platform could be deterrents to clinical acceptance and adoption, noted one clinical expert. Looking at cost a different way, another expert highlighted the reduced cost of MRI-TRUS-guided biopsy compared with in-bore MRI-guided procedures. While experts generally anticipated patient acceptance of more effective biopsy

procedure with the potential to improve outcomes, others noted that the need for an additional MRI imaging procedure and potential added costs might affect patient adoption if insurers do not provide coverage.

Health care delivery infrastructure and patient management: A few experts commented that training requirements and implementation of image fusion software would not disrupt existing health care delivery infrastructure, while others thought the requirements for an additional imaging procedure and/or imaging equipment would moderately disrupt infrastructure and patient management.

Health disparities: The majority of experts were concerned that MRI-related expenses associated with this biopsy approach might increase health disparities among economically disadvantaged patients. However, one expert with a clinical background believes this intervention could improve health disparities by providing improved detection of a disease that has a greater incidence among black men than white men. Most experts agreed that coverage for this procedure would be an important determinant of the potential impact on health disparities.

Radium-223 Dichloride (Xofigo) for Treatment of Solid Tumor Bone Metastases

Unmet need: Many cancers, in particular breast, prostate, and lung cancers, metastasize to bone, where they can cause chronic pain and skeletal-related events (e.g., fractures) that can adversely affect both patient quality of life and survival.³⁵⁰ Current treatments targeting bone metastases are largely palliative, providing pain relief or delaying skeletal-related events without having significant effects on overall disease progression or patient survival.

These treatment options include the radionuclides strontium-89 and samarium-153-EDTMP (ethylenediamine tetra [methylene phosphonic acid]), radioactive molecules that have a natural affinity for sites of bone remodeling, which occurs at bone metastases.³⁵⁰ Preferential accumulation of the radioactive compound purportedly concentrates the radiation dose at the target bone metastases. Although available radionuclides have shown some efficacy in relieving bone pain, the type of radiation that they emit penetrates tissues deeply enough to negatively affect bone marrow, which limits the deliverable dose thereby enabling palliation of only one symptom.³⁵¹

Intervention: Radium-223 dichloride (Xofigo[®]) has the potential to be the first bone metastasis-targeted agent that affects both bone metastasis symptoms and patient survival. Radium-223 dichloride is a novel bone metastasis-targeting radiopharmaceutical that emits alpha particles, which have higher energies and more localized activity than the radiation generated by available radiopharmaceuticals indicated for treating bone metastases.³⁵² This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes.³⁵² Radium-223 dichloride is administered intravenously at a dosage of 50 kilobecquerel (1.35 microcurie)/kg, once every 4 weeks, for up to 6 treatment cycles.³⁵³

Clinical trials: In June 2012, results were presented from a double-blind, randomized controlled trial of the radiopharmaceutical versus placebo in 921 patients with CRPC and skeletal metastases who were ineligible for initial or further treatment with docetaxel. In this trial, radium-223 dichloride was reported to have increased overall survival by 3.6 months compared with survival with placebo, representing a 30.5% reduction in the risk of death compared with placebo (two-sided $p=0.00007$). Radium-223 dichloride treatment also prolonged the time to first skeletal-related event by 5.8 months compared with placebo (15.6 months vs. 9.8 months; $p=0.00037$; $HR=0.658$).³⁵⁴

Radium-223 dichloride treatment was reported as being well tolerated by patients; the most significant adverse event was myelosuppression. Rates of grade 3 or 4 neutropenia were 2.2% in the radium-223 dichloride arm and 0.7% in the placebo arm, and rates of grade 3 or 4 thrombocytopenia were 6.3% in the radium-223 dichloride arm and 2% in the placebo arm.³⁵⁴ Other commonly reported adverse events were similar between groups (bone pain, constipation, diarrhea, nausea, and vomiting).³⁵⁵ The relatively benign adverse-event profile of radium-223 dichloride treatment may allow its use in combination with other cancer treatments. An early phase, clinical trial is under way testing the combination of radium-223 dichloride with docetaxel for CRPC.³⁵⁶

Manufacturer and regulatory status: Algeta ASA, of Oslo, Norway, and Bayer AG, of Leverkusen, Germany, make radium-223 dichloride.

FDA granted radium-223 dichloride fast track status for treating CRPC with bone metastases.³⁵⁷ Bayer submitted a new drug application to FDA for this indication in December 2012, and FDA granted priority review status in February 2013.³⁵⁸ FDA approved radium-223 dichloride in May 2013, 3 months ahead of the expected decision date. It is indicated for treating patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease.^{353,359}

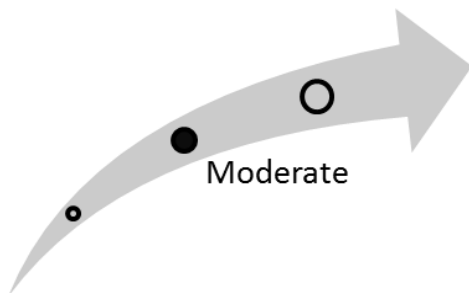
Diffusion: The wholesale cost of radium-223 dichloride is reportedly \$11,500 per injection (\$69,000 for a full course of 6 injections).³⁶⁰ The U.S. Nuclear Regulatory Commission has cleared distribution of radium-223 dichloride; individual sites must be licensed to administer the drug.³⁶⁰

Radium-223 dichloride is also under investigation for treating osteosarcoma and breast cancers with bone metastases.^{361,362} An additional agent in development that has shown promise in treating prostate cancer bone metastases is the MET/RET/VEGFR2 kinase inhibitor cabozantinib; phase III clinical trials of this compound in treating metastatic prostate cancer have begun.³⁶³

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.³⁵⁰ Palliative local treatments for bone metastases include external beam radiation therapy and surgical resection of the lesion.³⁶⁴ Systemic treatments include antineoplastic treatments, such as chemotherapy and hormone therapy, as well as agents that modulate bone remodeling such as bisphosphonates and the RANKL antibody denosumab.³⁶⁵ Additional systemic agents that are targeted to bone include radiopharmaceuticals such as strontium-89 and samarium-153-EDTMP, which preferentially accumulate in sites of bone metastasis and expose the cancer cells to beta and/or gamma radiation.³⁵⁰ Radium-223 dichloride represents a novel, systemic radionuclide treatment for bone metastases that is the first alpha particle–emitting radionuclide indicated for treating this condition.

Figure 13. Overall high-impact potential: radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases



Overall, experts thought that radium-223 dichloride has significant potential to improve current treatments for bone metastases, particularly for patients with prostate cancer bone metastases. Although experts saw significant potential for wide adoption, the highly similar nature of this agent to existing treatments suggested to experts that radium-223 dichloride 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-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.³⁶⁶⁻³⁷² We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The need for improved treatments for bone metastases is moderately or very important, the experts thought, citing the high prevalence of bone metastases in many advanced cancers and the significant impact that metastases have on patient quality of life and survival. Most experts 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 research perspective who thought the unmet need addressed by radium-223 dichloride was small suggested that the compound represents only an incremental improvement.

Radium-223 dichloride has moderate to large potential to improve patient health, the experts all suggested, citing the increased overall survival time reported in the recently completed phase III trial and the relatively benign toxicity profile thus far. Several experts noted the ability of radium-223 dichloride to affect patient quality of life (e.g., pain) in addition to its effects on survival and disease progression.

One clinical expert expressed caution regarding the potential for long-term sequelae of radium-223 dichloride, noting that use of another radium isotope (radium-224) in treating ankylosing spondylitis had led to an increase in leukemia incidence in treated patients. However, the expert also noted that the two radium isotopes have differing decay patterns (which could alter the systemic radiation exposure) and that such long-term sequelae may not be as relevant to patient populations with metastatic disease whose long-term prognosis is relatively poor.

Acceptance and adoption: In line with their view that radium-223 dichloride has significant potential to improve health outcomes, most of the experts thought widespread adoption would occur. Experts cited radium-223 dichloride's reported efficacy, safety, relatively benign adverse-event profile, ease of use, and routine administration as factors that would enhance adoption. One expert with a research perspective suggested that a small proportion of patients might hesitate to accept treatment involving a radioactive isotope; however, this expert thought that overall, radium-223 dichloride is likely to be widely accepted by patients.

Radium-223 dichloride would likely be priced at a premium to other radiotherapy options, the experts suggested, and a majority indicated that it would increase the overall cost of care. This could limit patient adoption, multiple experts suggested, adding that payers might require a stepped therapy approach.

Health care delivery infrastructure and patient management: Experts did not think that using radium-223 dichloride would require significant changes to health care delivery and infrastructure or patient management, noting the similarity between radium-223 dichloride treatment methods and radiopharmaceuticals now used.

Health disparities: Generally, experts did not think radium-223 dichloride would significantly shift health disparities. A few experts noted that the cost relative to existing palliative treatments might make the treatment prohibitive for patients without insurance, potentially worsening health disparities. Conversely, one expert with a clinical perspective suggested that underserved populations might present with more advanced disease and therefore, radium-223 dichloride might have a larger impact in an underserved population.

Skin Cancer Interventions

Vemurafenib (Zelboraf) for Treatment of Metastatic Melanoma

Unmet need: More than half of all new cases of melanoma in the United States in 2010 were invasive at the time of diagnosis, according to the American Academy of Dermatology.³⁷³ 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.³⁷⁴ The recent approvals of ipilimumab (YervoyTM) and vemurafenib (ZelborafTM) for treating metastatic melanoma have provided the first treatments that generated improved survival for many in this patient population.

Intervention: Vemurafenib is a small molecule BRAF protein kinase inhibitor and belongs to a drug class that represents a recent addition to the metastatic melanoma treatment armamentarium.³⁷⁵ BRAF plays a central role in the RAS/MAP kinase signal transduction pathway, which regulates cell growth and cell proliferation. Misregulation of this pathway is involved in multiple cancers and *BRAF* mutations (e.g., *BRAF*^{V600E}) encoding a constitutively active BRAF protein have been identified in about 7% of cancers.³⁷⁶ Although only a small fraction of all human tumors harbor an activating *BRAF* mutation, more than half of melanomas analyzed have been shown to bear such an allele.³⁷⁶ Activated BRAF is proposed to lead to hyperactivation of the downstream ERK/MEK/MAP kinase pathway, upon which melanomas depend growth and survival.³⁷⁷ Therefore, inhibiting BRAF kinase activity is thought to be a promising pharmacologic target. Preclinical studies demonstrated that BRAF inhibitors could inhibit signaling in the downstream MAP kinase pathway only in cells containing the activating *BRAF*^{V600E} mutation.³⁷⁶ Therefore, most studies have focused on patients whose cancers have been confirmed to contain this mutant form of *BRAF*. Vemurafenib is an oral medication that is administered at a dosage of 960 mg (four 240 mg tablets), twice daily, about 12 hours apart.³⁷⁸

Clinical trials: In the phase III BRIM3 study, in which patients with metastatic melanoma (n=675) were randomly assigned to receive either vemurafenib or dacarbazine, investigators reported that vemurafenib increased overall and progression-free survival relative to treatment with dacarbazine. Researchers reported that vemurafenib 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) compared with those outcomes with dacarbazine. Commonly reported adverse events associated with vemurafenib treatment included alopecia, arthralgia, diarrhea, fatigue, keratoacanthoma or squamous-cell carcinoma, nausea, photosensitivity, and rash.³⁷⁹ A companion diagnostic test (cobas[®] 4800 B-RAF V600 Mutation Test) that allows determination of *BRAF*^{V600} status was developed in tandem with vemurafenib.³⁸⁰ An early-stage trial to examine combination therapy with vemurafenib and ipilimumab was terminated early because of liver toxicity in several trial participants with metastatic melanoma.³⁸¹

Manufacturer and regulatory status: Vemurafenib is manufactured by the Genentech subsidiary of F. Hoffmann-La Roche, Ltd., of Basel, Switzerland. In August 2011, FDA approved vemurafenib for treating patients with unresectable or metastatic melanoma with the *BRAF*^{V600E} mutation as detected by an FDA-approved test.^{382,383}

Diffusion: A query of a U.S.-based online aggregator of pharmacy pricing identified a retail price of \$11,670 for a 1-month supply of the drug, and a treatment course of about 6 months would cost about \$70,000 per patient.³⁸⁴ Initial uptake of vemurafenib has been relatively rapid. Roche estimates that 85% of eligible patients receive first-line treatment with vemurafenib.³⁸⁵ *BRAF* gene mutation testing has also become relatively routine in patients with metastatic melanoma; surveys have indicated that a majority of physicians test at least half their patients for the presence of an activating *BRAF* mutation.²⁶⁸

A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), identified 4 payers with policies specifying coverage for the FDA-approved indication.³⁸⁶⁻³⁸⁹ At least two other major, third-party payers had specific policies that provide coverage for *BRAF*^{V600} mutation analysis in individuals with unresectable or metastatic melanoma who are being considered for treatment with vemurafenib.^{390,391} Insurance plans treat the drug as a specialty pharmaceutical, require prior authorization, and impose quantity limits. Vemurafenib may be eligible for coverage under Medicare Part D benefits, depending on the plan selected by the beneficiary. Genentech offers a savings card to reduce patients' out-of-pocket costs for those with commercial health insurance, and the Genentech Access to Care Foundation may offer assistance to uninsured individuals who cannot afford their prescriptions.^{392,393}

A second *BRAF* inhibitor, dabrafenib (Tafinlar[®]), was FDA approved in May 2013 and is expected to compete with vemurafenib.³⁹⁴ Investigators reported that results of a phase III trial comparing dabrafenib with dacarbazine in patients with previously untreated *BRAF* mutation–positive, metastatic melanoma showed median progression-free survival of 5.1 months for the dabrafenib arm compared with 2.7 months for the dacarbazine arm (HR 0.30; 95% CI, 0.18 to 0.51, $p < 0.0001$).³⁹⁵

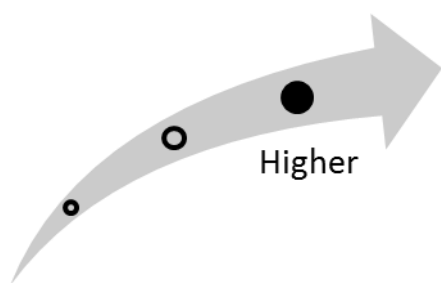
Recent data suggest that continued treatment with vemurafenib or dabrafenib even after disease progression while taking these agents may have survival benefits. Patients who continued *BRAF* inhibitor treatment after progression had longer median overall survival from start of therapy than those who discontinued treatment (15.0 months vs. 6.5 months, $p < 0.001$), as well as improved overall survival from time of disease progression (7.4 months vs. 1.9 months; $p = 0.001$; HR, 0.32; $p = 0.012$).³⁹⁶ These data may promote extended use of these agents in patients with progressing disease.

One shortcoming of *BRAF* inhibitors is the relatively rapid development of resistance to therapy. To address this issue, researchers are investigating drug combinations that may block certain resistance pathways. Recently, encouraging results were reported for the combination of a *BRAF* and MEK inhibitor;³⁹⁷ and several companies are investigating similar approaches in late-stage clinical trials.^{398,399} The success of such combination could lead to new competing or complementary regimens, potentially expanding vemurafenib use.

Clinical Pathway at Point of This Intervention

Patients with metastatic melanoma are typically treated with one of several systemic therapies and/or radiation therapy. Standard systemic therapies include dacarbazine, high-dose interleukin-2, ipilimumab, temozolomide, vemurafenib (for patients whose melanoma harbors an activating mutation in the *BRAF* gene), or paclitaxel with or without cisplatin or carboplatin. Patients maintaining sufficiently good health to undergo additional treatments may receive sequential additional treatments. Vemurafenib and ipilimumab have become standard first-line options for treating disseminated metastatic melanoma.³⁷⁵ In May 2013, dabrafenib and trametinib were added to the armamentarium of pharmacotherapeutic options for treating *BRAF* mutation–positive advanced melanoma.^{394,400}

Figure 14. Overall high-impact potential: vemurafenib (Zelboraf) for treatment of metastatic melanoma



Overall, experts commenting on this drug class believe that BRAF inhibitors have potential to fundamentally change treatment paradigms for metastatic melanoma because they will split a single syndrome into those with and without *BRAF* mutations. This will necessitate testing of all melanoma patients to determine *BRAF* status. Experts opined that although the potential of BRAF inhibitors is limited because 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. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, health systems, and health administration backgrounds, offered perspectives on vemurafenib.⁴⁰¹⁻⁴⁰⁷ Please note that these comments were received before the FDA approval of two other BRAF inhibitors in this class. We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Vemurafenib could address an important unmet need, the experts unanimously thought, citing the poor prognosis and limited treatment options for patients with metastatic melanoma before the availability of therapies targeting oncogenic BRAF. Experts cited data from clinical trials showing that vemurafenib improved patient outcomes, showing a significant increase in response rate and duration of progression-free and overall survival. They noted, however, that nearly all patients with the mutation will have disease that eventually becomes refractory and progresses. One clinical expert stated that vemurafenib was the only melanoma therapy that frequently generated a rapid tumor response and, therefore, had potential to provide symptomatic relief to patients.

As an orally administered medication with a clear target patient population, vemurafenib is not likely to encounter many obstacles to adoption, experts believe. Several experts noted that although vemurafenib has a generally mild side-effect profile, significant side effects have been reported. In particular, the development of squamous cell carcinomas has been associated with BRAF 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 a significant number of patients or physicians from opting for vemurafenib treatment. Indeed, one expert with a clinical perspective suggested that vemurafenib has already been adopted widely by patients and physicians.

Health care delivery infrastructure and patient management: Adding vemurafenib to the clinical pathway for treating *BRAF*-positive melanoma would lead to a moderate increase in the cost of care for this patient population, the majority of experts suggested. Additionally, they suggested

that the need to screen patients with melanoma for *BRAF* status would add to the cost of treating this condition.

Health disparities: Experts did not think that the availability of vemurafenib would affect disparities much. One expert with a clinical perspective suggested that an orally administered medication could enable local oncologists to offer a treatment to patients unable to easily travel to an infusion center for intravenous treatment (e.g., high-dose interleukin-2, ipilimumab) and so might reach some previously underserved patients. Conversely, an expert with a health administration background suggested that the high cost of vemurafenib and required *BRAF* mutation testing could make this treatment unavailable to underserved patients lacking insurance coverage and/or the money for treatment.

Vismodegib (Erivedge) for Treatment of Advanced Basal Cell Carcinoma

Unmet need: 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.⁴⁰⁸ Although pharmacologic inhibition of this pathway would likely benefit patients for whom no consensus exists for optimal systemic treatment, no hedgehog pathway inhibitor was available until the recent FDA approval of vismodegib.⁴⁰⁹

Intervention: Vismodegib is a small-molecule antagonist of the hedgehog pathway. Vismodegib functions by inhibiting a protein (called “Smoothened”) that is essential for transducing hedgehog pathway activity. In basal cell carcinomas, mutations may occur that activate the hedgehog pathway.⁴¹⁰ If these mutations affect the 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. Vismodegib is an oral medication administered at a dosage of 150 mg, once daily.⁴¹¹

Clinical trials: The ERIVANCE BCC trial studied vismodegib (150 mg, once daily) in 104 patients with locally advanced and/or metastatic basal cell carcinoma that could not be treated surgically. The overall response rate, as assessed by independent review, was 43% ($p=0.001$) in patients with locally advanced disease and 30% ($p=0.001$) in patients with metastatic disease. A complete response was achieved in 21% of patients. The median progression-free survival for both patient groups was 9.5 months.⁴¹² At 18 months after primary analysis, overall response rate was 60.3% in patients with locally advanced disease and 48.5% in patients with metastatic disease. The median duration of response was 20.3 months for locally advanced disease and 14.7 months for metastatic disease. Adverse events remained consistent with earlier findings.⁴¹³

A third interim analysis of the STEVIE study, an ongoing analysis of safety of the drug, presented safety and efficacy data from 300 patients with locally advanced and/or metastatic basal cell carcinoma. Common treatment-emergent adverse events (typically grade 2 or less) included muscle spasm (59.3%), alopecia (49.3%), and dysgeusia (41.0%). Serious events occurred in 53 patients (17.7%), and 35 patients stopped participating in the study because of treatment-related adverse events. Preliminary data on overall response in patients with available tumor assessments ($n=251$) revealed 17.5% of patients had complete response, 39.8% had partial response, 39.0% had stable disease, and 2.8% had progressive disease.⁴¹⁴

Manufacturer and regulatory status: Genentech, a subsidiary of Roche, makes vismodegib. FDA approved vismodegib in January 2012 on the basis of data from a single-arm, phase II clinical trial (ERIVANCE BCC).⁴⁰⁹ The prescribing information indicates that the drug is intended for “the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.”

Diffusion: Genentech announced that vismodegib’s average wholesale cost is \$7,500 per month per patient, and the estimated treatment duration is 10 months.⁴¹⁵ A query of a U.S.-based online aggregator of pharmacy pricing identified retail costs of between \$9,000 and \$9,200 for a 1-month supply (thirty 150 mg capsules) of vismodegib. For a 10-month treatment course, costs for this drug would total about \$92,000.⁴¹⁶ In a mid-year 2012 update, Roche’s partner in developing vismodegib, Curis, Inc., of Lexington, MA, reported a “consistent increase in prescription on a monthly basis over the period since vismodegib launch in February 2012.”⁴¹⁷

A search of representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), identified 4 payers with policies that specified coverage of vismodegib for FDA-approved indications.⁴¹⁸⁻⁴²¹ Formularies of representative plans typically consider vismodegib to be a specialty pharmaceutical, require prior authorization, and impose quantity limits. Vismodegib may be eligible for coverage under Medicare Part D benefits, depending on a beneficiary's plan.

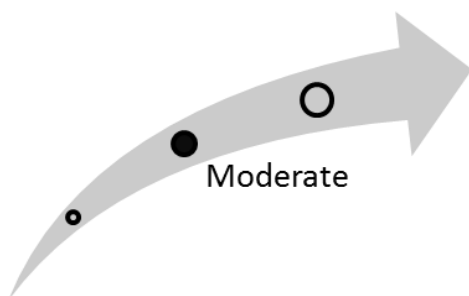
Genentech's Access Solutions program facilitates access, including for patients who cannot afford the drug because of large copayments or lack of prescription drug insurance.⁴²²

Future applications of vismodegib may include treatment of operable basal cell carcinomas: ongoing phase II clinical trials are examining the safety and efficacy of vismodegib in patients with such disease.^{423,424} Additionally, investigators recently began a phase IIb trial to determine vismodegib's efficacy in various histologic subtypes of basal cell carcinoma.⁴²⁵ In the future, these data may help clinicians tailor treatment based on the histologic nature of an individual's basal cell carcinoma. Vismodegib and other hedgehog pathway inhibitors are also under study in a wide range of cancers, including ovarian and colorectal cancers.^{426,427}

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.^{408,428} An alternative primary treatment for these lesions is radiation therapy; however, this treatment is typically reserved for patients older than 60 years of age because of concerns about the potential for collateral tissue damage.⁴²⁸ 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. For basal cell carcinomas that become locally advanced and inoperable or become metastatic, no clear consensus exists on treatment options.⁴²⁸ Treatments include radiation therapy and various systemic chemotherapy options, typically platinum-based cytotoxic regimens.⁴²⁸ Vismodegib provides a new pharmacotherapy option for patients with inoperable/metastatic basal cell carcinomas.^{429,430} Future indications may include the use of vismodegib for operable basal cell carcinomas. Studies are under way to examine the potential benefit as an adjuvant therapy to surgical resection.^{423,424}

Figure 15. Overall high-impact potential: vismodegib (Erivedge) for treatment of advanced basal cell carcinoma



Overall, experts providing comments thought that vismodegib has significant potential to become a first-in-class agent and found the response rates reported in trials to be compelling 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 moderate high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on this intervention.⁴³¹⁻⁴³⁷ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need that vismodegib could address is moderately or very important, the experts thought, because of the lack of effective systemic treatments and the fact that vismodegib is a first-in-class hedgehog inhibitor.

The drug's potential to improve patient health outcomes was viewed as moderate to large by these experts, who cited the relatively high response rates 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 downstage large basal cell carcinomas for which surgery would cause significant morbidity and noted that no effective neoadjuvant therapy is available.

Acceptance and adoption: Experts thought that vismodegib would be readily adopted by physicians and patients alike because of the lack of viable treatments for unresectable basal cell carcinoma. However, two experts suggested that some patients may hesitate to opt for a therapy with such a high rate of side effects, citing the discontinuation rate in the clinical trials. Although experts were enthusiastic about the preliminary data on vismodegib's antitumor activity, several noted the preliminary nature of these findings, especially on side effects.

Health care delivery infrastructure and patient management: Because vismodegib is orally self-administered by the patient, it would not have significant impacts on health care delivery infrastructure or staffing, the majority of experts thought. However, several experts noted that patient management could change, with some patients being referred to medical oncologists (rather than surgeons), which would not have occurred before the drug's availability, given the lack of systemic therapy options.

Although experts thought that vismodegib would likely increase per-patient costs, they thought the health system-level effect of these costs would be minimal because of the relatively small number of patients in whom unresectable basal cell carcinoma is diagnosed each year.

Health disparities: The majority of experts did not think vismodegib would have a significant impact on health disparities. But one expert with a clinical perspective suggested that patients 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.

Solid Tumor Ablation Intervention

Irreversible Electroporation (NanoKnife) for Ablation of Solid Tumors

Unmet need: Ablation of tumors using various forms of energy has become a standard component of cancer treatments. Available ablation methods include RF, cryotherapy, and microwaves, which all rely on thermal ablation to destroy tumors by heating or cooling tissue. Thermal ablation can also lead to collateral damage in adjacent tissues and associated adverse events during and after treatment. The inability to precisely control the affected zones during ablative procedures renders some tumors close to fragile structures (e.g., critical blood vessels) ineligible for thermal ablation. Also, thermal ablation methods may be subject to heat-sink effects in which blood flow through large blood vessels adjacent to tumors prevents adequate heating and cooling of perivascular tumors. This can lead to inadequate ablation of the tumor target and possible damage to vessels. Therefore, novel nonthermal ablation methods could be useful to reduce morbidity associated with thermal ablation and allow treatment of tumors ineligible for thermal ablation.^{438,439}

Intervention: Irreversible electroporation (IRE) is a nonthermal ablation technique in which target tissue is exposed to a precisely aimed, rapid series of short-duration, high-voltage electrical pulses.⁴⁴⁰ The pulses purportedly disrupt cellular membranes, leading to a form of cell death in the treatment zone. Unlike thermal ablation methods, IRE purportedly does not cause heat sink effects and can leave intact the acellular portion of tissues, such as blood vessels, ducts, and nerves, potentially allowing ablation of tumors next to these structures while retaining their patency.^{440,441}

An interventional radiologist or surgeon performs IRE procedures using a percutaneous, laparoscopic, or open surgical approach.⁴⁴¹ Neuromuscular stimulation by the electric field produced during IRE treatment can cause uncontrolled movement and pain; therefore, IRE requires general anesthesia and muscle blockade.⁴⁴⁰ Also, to reduce the risk of inducing cardiac arrhythmias, an electrocardiogram synchronization device coupled to the IRE system is intended to precisely time the energy pulse to occur during (or just before) the ventricular refractory period.^{440,442} A single ablation purportedly takes only a minute, and IRE electrodes can be repositioned to allow for multiple ablations.⁴⁴³ An entire IRE procedure, including set-up time and postprocedure imaging, takes an estimated 2–3 hours. Patients undergoing percutaneous IRE procedures may be released from the hospital the same day or after an overnight stay.

Clinical trials: Although no randomized controlled trials of IRE for treating solid tumors have been reported, data from multiple case studies have been published recently.⁴⁴⁴⁻⁴⁴⁷ Cheung and colleagues reported on 11 patients with 18 hepatocellular carcinoma lesions that were unamenable to surgical resection and RF ablation because they were near organs (e.g., the bowel) or large blood vessels that could sustain thermal damage. All patients underwent IRE using a percutaneous approach, and 13 of 18 lesions were completely ablated. After a mean followup of 18 months (range 14–24 months), the local disease-free period was 18 ± 4 months and the distant recurrence-free period was 14 ± 6 months.⁴⁴⁴

Narayanan and coworkers reported on 14 patients with unresectable, locally advanced or metastatic pancreatic adenocarcinoma whose cancer remained unresectable after standard therapy (e.g., chemotherapy, radiation therapy) or who were intolerant of standard therapy. All patients underwent percutaneous IRE. In two patients, cancer was successfully downstaged to the point of being operable, and these patients underwent surgery 4–5 months after IRE.⁴⁴⁵

Kingham and colleagues reported on 28 patients with 65 perivascular hepatic malignant tumors that were considered unresectable or were located in regions not amenable to thermal ablation.

Patients were treated with IRE using an open (79%) or percutaneous (21%) approach. At median followup of 6 months, one treated lesion persisted and three treated lesions had recurred locally.⁴⁴⁶

Martin and coworkers reported on 27 patients with locally advanced pancreatic adenocarcinoma. Patients were treated with IRE alone (n=19) or in combination with surgical resection (n=8). At 90-day followup, researchers observed a 100% ablation success rate.⁴⁴⁷

IRE-related adverse events reported in these case series included three instances of blood vessel thrombosis; two instances of duodenal leak; and one instance each of abdominal pain/pancreatitis, cardiac arrhythmia, spontaneous pneumothorax, and subcutaneous hematoma.⁴⁴⁴⁻⁴⁴⁷ One patient death was reported in one study's 90-day morbidity followup.⁴⁴⁷

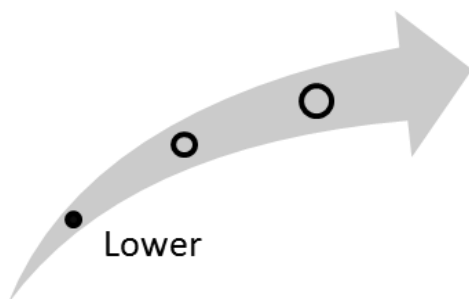
Manufacturer and regulatory status: AngioDynamics, of Latham, NY, is the sole company that produces an IRE system. The device has been FDA cleared for surgical “ablation of soft tissue”; however, FDA has not cleared the system for use in treating cancer or any other specific disease or condition.⁴⁴⁸ The company has submitted investigation device exemption applications to FDA to enable use of the device in clinical trials of patients with pancreatic cancer and prostate cancer.⁴⁴⁹

Diffusion: Several dozen cancer centers in the United States have acquired IRE systems and advertise use of the system for treating various cancers.⁴⁴⁰ As of January 2012 (the last date for which these data were released), AngioDynamics reported that more than 1,000 patients had undergone IRE treatment worldwide.⁴⁵⁰ Searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, Wellmark, United Healthcare) identified two payers (Aetna and Anthem) with policies that denied coverage for use of IRE to ablate tissue.^{451,452} Other payers have no policies addressing use of NanoKnife.

Clinical Pathway at Point of This Intervention

In the treatment of focal malignancies, IRE may compete with other radiofrequency ablation, laser ablation, cryoablation, microwave ablations, and chemical ablation. Additionally, IRE is an option proposed by some for use in combination with or in place of other oncologic treatment methods such as chemotherapy, radiation therapy, surgery, and transcatheter arterial therapy.⁴³⁹

Figure 16. Overall high-impact potential: irreversible electroporation (NanoKnife) for treatment of solid tumors



Because IRE is a novel, nonthermal ablation technique, experts viewed it as a potential addition to cancer treatment options for tumors not treatable by other means. Particularly in regards to pancreatic cancer, experts noted a large unmet need and thought IRE could significantly shift the way in which patients are managed. However, expert comments expressed concern about the availability of a technology being used in cancer treatment outside the context of clinical trials, given the limited data available and risks of treatment reported in the small studies conducted thus

far. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Comments from expert reviewers were collected on the use of IRE for treating pancreatic cancer or hepatocellular carcinoma, which were the original indications for trials listed in the clinicaltrials.gov registry. Seven experts, with clinical, research, and health systems backgrounds, offered perspectives on IRE for treating pancreatic cancer,⁴⁵³⁻⁴⁵⁹ and six experts with clinical, research, and health systems backgrounds, offered perspectives on IRE for treating hepatocellular carcinoma.⁴⁶⁰⁻⁴⁶⁵ We organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need that IRE purportedly addresses in unresectable pancreatic cancer was seen as moderately or very important by the experts commenting. Experts cited the substantial proportion of pancreatic cancers that are diagnosed at advanced stages and the poor prognosis for these patients. But in hepatocellular carcinoma, the unmet need that IRE purports to address was seen as less important by experts. While the experts indicated that improving outcomes for patients with hepatocellular carcinoma represents an important unmet need, the availability of several other ablation techniques for hepatocellular carcinoma was seen as limiting the scope of the unmet need that IRE could address.

The majority of experts suggested that IRE's potential to improve health outcomes for patients with either pancreatic cancer or hepatocellular carcinoma is only minimal, as indicated by the limited available data. Although a few experts expressed enthusiasm about the initial ablation success rate, most noted that the small number of patients treated in published IRE studies, the very short followup of patients, and the lack of control arms in these studies made IRE's potential to improve patient health difficult to assess. Additionally, multiple experts noted that IRE is a complex procedure that carries substantial risk of adverse events, which could affect patient health outcomes.

Acceptance and adoption: The likelihood of widespread IRE adoption was seen as small by the majority of experts; additionally, they expressed concerns that the technology is being used outside of clinical trials that would collect the necessary data to determine safety and efficacy for pancreatic cancer. Other barriers to adoption included the newness of the technology to physicians, the high expense of IRE equipment, and the potential lack of reimbursement. Despite these barriers, experts suggested that select centers would still adopt the technology, noting that some centers are currently using the system off label, which may give them a marketing edge to attract patients with cancers that cannot otherwise be treated. The experts who viewed the adoption of IRE by clinicians more favorably suggested that additional evidence of the safety and efficacy could increase adoption.

The potential for patient adoption was viewed as more likely by experts, with the majority indicating that wide acceptance by patients is likely. Experts suggested that patients with cancers that carry a poor prognosis and few treatment options will often readily accept treatments that lack sufficient data on safety and efficacy. Conversely, some experts thought the adverse event profile of IRE treatment and its potentially high cost and limited availability would curtail patient acceptance and adoption in some areas.

Health care delivery infrastructure and patient management: Expert comments on the impacts of IRE use on health care delivery infrastructure and patient management differed between use of IRE in treating pancreatic cancer and use in treating hepatocellular carcinoma. For pancreatic cancer, in which focal ablation is not routinely used, experts suggested that shifting patients from outpatient radiation therapy or chemotherapy to an inpatient IRE procedure or shifting patients from

an open surgical procedure to a percutaneous IRE procedure would represent significant changes to the way in which pancreatic cancer patients are managed and the infrastructure resources needed to treat those patients. Conversely, for hepatocellular carcinoma, in which several focal ablation therapies are available, experts suggested that IRE would be used in similar settings by similar clinicians who use other focal ablation therapies.

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