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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Financial Disclosure Statement

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

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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 identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 16,200 leads about potential topics has resulted in identification and tracking of about 1,900 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 500 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 a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

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

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 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 38 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 October 27, 2013, in this priority area; *and* (3) we received six to nine sets of comments from experts between April 9, 2012, and October 29, 2013. (A total of 184 topics in this priority area were being tracked in the system as of October 29, 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 14 summaries on 17 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 (Tomtovok) for treatment of nonsmall cell lung cancer	No high-impact potential at this time
3. * Automated breast ultrasound for breast cancer screening of patients with dense breast tissue	Moderately high
4. Cologuard fecal DNA test for colorectal cancer screening	No high-impact potential at this time
5. Computer-assisted system (Sedasys) for automated propofol sedation during gastrointestinal endoscopy	No high-impact potential at this time
6. Doxepin oral rinse for the treatment of radiation therapy-associated oral mucositis	No high-impact potential at this time
7. * Enzalutamide (Xtandi) for treatment of metastatic castration-resistant prostate cancer	Moderately high
8. * Everolimus (Afinitor) for treatment of advanced estrogen receptor–positive breast cancer	Moderately high
9. Everolimus (Afinitor) for treatment of renal angiomyolipoma	No high-impact potential at this time

Topics	High-Impact Potential
10. High-intensity focused ultrasound (Ablatherm) for treatment of localized prostate cancer	No high-impact potential at this time
11. High-intensity focused ultrasound (Sonablate) for treatment of localized prostate cancer	No high-impact potential at this time
12. * Ibrutinib (Imbruvica) for treatment of chronic lymphocytic leukemia	High
13. * Ibrutinib (Imbruvica) for treatment of mantle cell lymphoma	High
14. Immature PSA ([-2]proPSA) assay as a decision aid regarding prostate cancer biopsy	No high-impact potential at this time
15. * Irreversible electroporation (NanoKnife) for treatment of hepatocellular carcinoma	Lower end of the high-impact-potential range
16. * Irreversible electroporation (NanoKnife) for treatment of pancreatic cancer	Lower end of the high-impact-potential range
17. Liposome-encapsulated vincristine (Marqibo) for treatment of acute lymphoblastic leukemia	No high-impact potential at this time
18. Magnetic resonance imaging–guided focused ultrasound therapy (ExAblate) for treatment of pain from bone metastases	No high-impact potential at this time
19. * Magnetic resonance imaging–ultrasound image fusion for image-guided prostate biopsy	Lower end of the high-impact-potential range
20. * MarginProbe System for intraoperatively identifying positive margins during breast cancer lumpectomy	Moderately high
21. * Methylated Septin 9 blood test for colorectal cancer screening	Lower end of the high-impact-potential range
22. Nab-paclitaxel (Abraxane) for treatment of pancreatic cancer	No high-impact potential at this time
23. Omacetaxine mepesuccinate (Synribo) for treatment of tyrosine kinase inhibitor-resistant chronic myelogenous leukemia	No high-impact potential at this time
24. Oncolytic reovirus (Reolysin) for treatment of head and neck cancer	No high-impact potential at this time
25. * Ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer therapy	High
26. * Pertuzumab (Perjeta) for treatment of advanced HER2-positive breast cancer	Moderately high
27. Pomalidomide (Pomalyst) for treatment-refractory multiple myeloma	No high-impact potential at this time
28. Ponatinib (Iclusig) for treatment of chronic myelogenous leukemia or chromosome–positive acute lymphoblastic leukemia	No high-impact potential at this time
29. * Radium-223 dichloride (Xofigo) for treatment of solid tumor bone metastases	Moderately high
30. Ramucirumab for treatment of gastric cancer	No high-impact potential at this time
31. Regorafenib (Stivarga) for treatment of colorectal cancer	No high-impact potential at this time
32. Regorafenib (Stivarga) for treatment of gastrointestinal stromal tumors	No high-impact potential at this time
33. * Sorafenib (Nexavar) for treatment of differentiated thyroid cancer	Lower end of the high-impact potential range
34. * Specialized care model for adolescents and young adults with cancer	Lower end of the high-impact-potential range
35. Talimogene laherparepvec for treatment of advanced melanoma	No high-impact potential at this time
36. Trametinib (Mekinist) for treatment of advanced melanoma with activated BRAF mutation	No high-impact potential at this time
37. Trebananib for treatment of ovarian cancer	No high-impact potential at this time
38. * Vismodegib (Erivedge) for treatment of advanced basal cell carcinoma	Moderately high

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, a specialized care delivery program for adolescents and young adult oncology patients, and a procedure intended to preserve fertility in female cancer patients. The conditions that these interventions addressed include both solid tumors (advanced basal cell carcinomas, breast cancer, colorectal cancer [CRC], prostate cancer, and thyroid cancer) and hematologic malignancies (chronic lymphocytic leukemia, mantle cell lymphoma).

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 a monoclonal antibody and an antibody-drug conjugate (ADC) targeting tumor-associated surface antigens. As such, they are considered to be "personalized medicines." 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 adolescent and young adult (AYA) patients (aged 13–30 years). 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 and 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 and the U.S.-based Teen Cancer America provides an example of a comprehensive AYA-specialized inpatient oncology program that may address the many unmet needs of these patients. These charitable organizations partner with hospitals to develop fully dedicated AYA oncology units with tailored clinical and social space. Specially trained staff include doctors, nurses, and other support staff with a specialty in common AYA cancers and care issues and extensive knowledge of clinical trial opportunities for AYAs. Primary goals of these programs include enhanced treatment adherence, improved patient satisfaction, improved health outcomes, better quality of life, and higher enrollment rates in clinical trials to enable 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 educational and social schedules of AYA patients and to 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. 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 and maintains 26 dedicated units in hospitals and cancer centers throughout the U.K., and the ongoing Brightlight Study is assessing this care model's impact on health outcomes. 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 the approach of AYA units, 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 it 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. The U.S. Food and Drug Administration (FDA) approved the somo•v® ABUS• (automated breast ultrasound) system (GE Healthcare division of General Electric Co., Fairfield, CT) in September 2012. The approved indication is "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." The approval was based on results of a reader study that demonstrated increased sensitivity over mammography alone for breast cancer in women with dense breasts when x-ray mammography was followed by ABUS. 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 [CI], 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% CI, -7.7% to 4.3%; $p=0.518$). Larger studies of the system in a screening population are ongoing. A search of 11 representative, private,

third-party payers that publish their coverage policies online identified only 1 payer with a specific policy regarding use of ABUS for breast cancer screening, and this payer considered it experimental or investigational and thus, dos not cover it.

- **Key Expert Comments:** Experts commenting on this topic suggested that a significant unmet need exists to improve breast cancer detection in women with dense breast tissue 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. Current lack of reimbursement for its use as a screening tool could be a barrier to adoption.
- **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. Given the central role that the mTOR pathway plays in fundamental cellular processes related to tumorigenesis and mTOR inhibitors' demonstrated efficacy in treating various cancers, researchers are studying mTOR inhibitors in a large number of clinical trials 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). Researchers reported results of a 724-patient trial, indicating that adding everolimus to exemestane resulted in 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 been reported. 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. A May 2013 query of a U.S.-based, online aggregator of prescription-drug prices identified a retail price of about $9,100 per month for everolimus. Many third-party payer formularies cover everolimus when prescribed for FDA-approved indications. Coverage typically requires preauthorization and is subject to quantity limits. Further study of everolimus in treating breast cancer is under way. Studies are looking for biomarkers that could predict response to everolimus in endocrine therapy-resistant, hormone receptor-positive disease, studies examining use of everolimus in the adjuvant setting for hormone receptor-positive disease, and studies examining use of everolimus to overcome resistance to therapy in other breast cancer subtypes (e.g., HER2-positive breast cancer).
- **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. Additionally, experts thought clinician and patient acceptance would be high, given the limited options for this patient population.

As an orally administered drug, experts thought everolimus would have minimal impact on health care staffing or infrastructure and be easily adopted into patient care.

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

MarginProbe System for Intraoperatively Identifying Positive Margins During Breast Cancer Lumpectomy

- **Key Facts:** Breast-conserving surgery (lumpectomy) followed by radiation therapy for early-stage breast cancer can achieve low recurrence rates equivalent to those achieved with total mastectomy. Achieving optimal outcomes requires that the tissue margins excised during surgery be cancer free. If subsequent pathologic analysis reveals tissue margins are not cancer free, patients typically need to undergo a second surgery to remove additional tissue. Therefore, techniques for identifying cancer-free 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 "unclean" 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. RF spectroscopy is said to 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. It provides a binary (yes/no) answer as to whether the assessed margin is clean. In results from a 664-patient trial, 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 surgeons identified positive surgical margins and removed additional tissue to achieve clean surgical margins (72% for MarginProbe; 22% for standard assessment, $p<0.0001$). In January 2013, FDA approved the MarginProbe for marketing, and the company reported installing the first U.S.-based system in March 2013. Several more have been installed. The system cost, as reported to ECRI Institute's PricePaid database by hospitals acquiring the device, is $39,995. 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. Eleven third-party payers whose policies we searched either have no specific coverage policies or if they have a policy, consider the system experimental or investigational at this time, and thus do not provide coverage. *The Wall Street Journal* reported in July 2013 that the per-surgery cost of adding use of the system during a breast resection was quoted by several hospitals as $995 additional per surgery; other reports have stated that the procedure adds about $2,000 to the surgery cost.
- **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 a need for such 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 [Kadcyla]; 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. Compounds with improved efficacy and/or efficacy against resistant disease are greatly needed.

  Two novel targeted therapies were recently FDA approved: ado-trastuzumab emtansine (Kadcyla™, F. Hoffmann-La Roche, Ltd., Basel, Switzerland) and pertuzumab (Perjeta®, also by Roche). Both are given as intravenous (IV) 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 antibody binding to the HER2 receptor, is emtansine released and activated. In this way, its cytotoxic activity targets cells expressing the HER2 receptor, potentially sparing many normal tissues from the drug's toxic effects. Ado-trastuzumab emtansine is in several phase III trials for treating metastatic breast cancer. The manufacturer recently announced that one of these trials (EMILIA), testing the therapy against a 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 monotherapy as second-line treatment of HER-2 positive metastatic breast cancer. The biologic is given at a dosage of 3.6 mg/kg, administered by intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. The drug is provided in 100 mg vials. A U.S.-based online aggregator of pharmacy pricing listed costs (as of December 2013) of about $2,934 to $3,053 per 100 mg vial. This pricing required use of a discount coupon. Thus, a 70 kg (154 lb) person would require about 252 mg, or 2.5 vials at a cost of about $7,500 per infusion cycle.

  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 purportedly 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 early stage or metastatic HER2-positive breast cancer. 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. FDA has approved marketing of pertuzumab for two HER2-positive breast cancer indications: (1) first-line treatment (in combination with trastuzumab and docetaxel) of metastatic disease and (2) neoadjuvant treatment (as a part of a complete treatment regimen) of locally advanced, inflammatory, or early stage disease. The drug is provided in 420 mg/14 mL vials, which constitutes one cycle. An online aggregator of pharmacy pricing has listed costs from various pharmacies in December 2013

of about $4,309 to $4,428 for one vial. This pricing required use of a discount coupon. FDA approval of the metastatic indication was based on data from the phase III CLEOPATRA trial, which demonstrated that adding pertuzumab to trastuzumab and docetaxel increased the duration of progression-free survival by about 6 months. FDA approval of the neoadjuvant indication was based on data from the phase II NeoSphere trial, which demonstrated adding pertuzumab to trastuzumab and docetaxel increased the pathologic complete response rate (a potential surrogate marker for disease-free and overall survival) to 39% in pertuzumab-treated patients, compared with 21% in patients who received only trastuzumab and docetaxel.

Both ado-trastuzumab emtansine and pertuzumab are typically covered by insurance and require preauthorization 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 could have significant impacts on patient management. The costs of ado-trastuzumab emtansine and pertuzumab will add to costs of patient care, experts thought, although costs of these agents are comparable to monthly costs of other targeted cancer therapies.
- **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, shown to be present specifically in the blood of individuals with CRC, is 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 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 and an FDA advisory committee meeting has been scheduled to review the premarket approval application on March 25, 2014.

- **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 somewhat 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

Fertility Issues Associated with Gonadotoxic Cancer Therapy

Ovarian Tissue Cryopreservation for Fertility Preservation in Women Undergoing Gonadotoxic Cancer Therapy

- **Key Facts:** For pediatric and reproductive-age female patients, cancer treatments can negatively and often permanently affect fertility (i.e., gonadotoxicity). As cancer survivorship continues to grow because of improved cancer diagnosis and treatment, fertility preservation has become an increasingly important concern for women with cancer who wish to conceive at some future time after undergoing gonadotoxic therapy. In vitro fertilization and embryo cryopreservation are the only standard options that are not considered to be experimental at this time. These methods are available to reproductive-age women who wish to be able to have children upon remission of cancer. A new option to preserve fertility after cancer treatment involves ovarian tissue harvesting and cryopreservation. The tissue is reimplanted into the patient when she completes cancer treatment and receives confirmation of disease remission. This option is available to prepubertal girls and reproductive-age women and does not require the ovarian stimulation or cancer treatment delays associated with fertility treatments (e.g., hormonal therapy to mature ovarian follicles for retrieval). Ovarian tissue collection is typically performed as a same-day outpatient surgical procedure. The patient is given general anesthesia and the surgeon retrieves tissue either laparoscopically or through an open laparotomy. Harvested ovarian tissue is prepared for cryopreservation through either slow freezing or vitrification (i.e., rapid cooling). Once the patient completes treatment, the cryopreserved ovarian tissue, or autograft, is reimplanted with the intent of restoring ovarian function and fertility. Depending on the patient, the autograft may be placed at an orthotopic site near the original location of the ovary, or at a heterotopic location such as the forearm or abdomen. This intervention remains in the early stages of development with larger studies under way to assess the safety and efficacy of ovarian tissue cryopreservation and tissue autotransplantation. To date, several case series have reported successful restoration of ovarian function after transplantation of cryopreserved ovarian tissues, as well as several successful pregnancies. High costs are anticipated for this specialized procedure, and it is unclear whether payers would provide coverage.
- **Key Expert Comments:** Experts offered very different perspectives on the significance of the unmet need and the intervention's potential to improve health outcomes. Some experts viewed the unmet need as very important and anticipated that patients and clinicians would

readily welcome a new approach for fertility preservation in cancer patients. Others did not view fertility preservation as a critical concern or unmet need for this patient population. Some of the views appeared to reflect personal value judgments of individual experts about patients' ability or need to procreate after having cancer. The majority of experts commented on the high costs and resource burden associated with this intervention. Most experts commented on the controversy surrounding this intervention, and saw it has having significant potential for disruption of patient management.

- **Potential for High Impact:** High

Hematologic Malignancies

Ibrutinib for Treatment of Non-Hodgkin's Lymphomas

- **Key Facts:** B-cell non-Hodgkin's lymphomas such as chronic lymphocytic leukemia and mantle cell lymphoma often respond well to first-line therapy; however, patients with these diseases frequently experience recurrence. In this situation, available therapies have limited or no efficacy. Additionally, certain molecularly defined subtypes, such as chronic lymphocytic leukemia harboring a deletion in the short arm of chromosome 17, have poor response to standard therapies. New agents to treat these conditions are highly desired. Recent research has identified the non-receptor tyrosine kinase Btk as a potential target in treating B-cell malignancies. Researchers have identified two potential roles for Btk in the biology of B-cell malignancies: (1) Btk promotes malignant B-cell proliferation and survival and (2) Btk promotes malignant B-cell homing to and retention in lymph nodes. Ibrutinib (Imbruvica™) is an oral, first-in-class inhibitor of Btk that is under study for treating a wide range of B-cell malignancies. In single-arm phase II studies in patients with mantle cell lymphoma or chronic lymphocytic leukemia, ibrutinib demonstrated substantial activity with reported response rates between 66% and 71%. FDA granted ibrutinib breakthrough therapy designation for several indications with high unmet needs including chronic lymphocytic leukemia harboring a chromosome 17 deletion and relapsed/refractory mantle cell lymphoma. FDA approved the drug for mantle cell lymphoma in November 2013. The recommended dosage on the labeling is 560 mg taken orally once daily (four 140 mg capsules once daily). A separate new drug application has been submitted for the chronic lymphocytic leukemia indication and is under FDA review. The company stated that the list price of ibrutinib would be about $10,900 (about $91 per capsule) per patient, per month, or about $130,000 per year.
- **Key Expert Comments:** Overall, experts opined that a significant need exists for novel treatments for chronic lymphocytic leukemia and mantle cell lymphoma and that the response rates observed in initial trials of ibrutinib indicated that it has significant potential to improve patient outcomes. Although reviewers suggested that further study was needed to confirm this early promise (particularly studies comparing ibrutinib to alternative treatments), the relatively benign side-effect profile of the drug and its potential to be used in treating several B-cell malignancies place ibrutinib at the high end of the high-impact-potential range. At the time of expert commenting, the pricing of the drug was not known.
- **Potential for High Impact:** 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. It improved survival in some patients. Since then, the armamentarium for treatment has increased with FDA approval of the chemotherapeutic agent cabazitaxel (Jevtana®); the therapeutic vaccine, sipuleucel-T (Provenge®); the androgen synthesis inhibitor abiraterone (Zytiga®); and the bone metastasis-targeting radiopharmaceutical radium-223 dichloride (Xofigo®). 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 is an oral medication that was initially studied in patients with CRPC who had previously undergone treatment with docetaxel. Patients treated with enzalutamide exhibited a 4- to 5-month increase in median overall survival compared with patients receiving placebo. More recently, results were reported from a trial studying enzalutamide in patients with CRPC who had not undergone prior docetaxel chemotherapy. In this trial, patients exhibited a significant decrease in the risk of both progression-free survival and overall survival. Significant changes in managing 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 steady diffusion of enzalutamide. Enzalutamide is administered at a dosage 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) is just over $8,000. The drug is considered a specialty pharmaceutical; insurers and Medicare Part D require preauthorization and impose quantity limits on each prescription.
- **Key Expert Comments:** Overall, experts commenting on this intervention expressed enthusiasm regarding enzalutamide's potential to improve both quality and survival time with mCRPC. However, experts pointed out that the demonstrated improvement in survival duration is only a few months in patients whose disease has not responded to first-line chemotherapy and suggested that enzalutamide may have a larger impact when used earlier in treatment. Experts suggested that study of the proper sequential and/or combined use of enzalutamide and the comparative effectiveness of 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 systematic 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 sometimes do not contain cancer cells; identification of 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 purportedly addresses 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 commonly used ultrasound platforms. Newly purchased systems for prostate biopsy may include software with fusion capability. Case studies report use 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. Data from studies examining MRI-TRUS image fusion-guided prostate biopsy platforms suggest that this approach may improve cancer detection rates and identify more high-grade cancers than standard TRUS-guided biopsy methods. After device clearance, image fusion-guided targeted biopsy platforms have been gradually diffusing nationwide.

Although MRI-TRUS image fusion-guided biopsies represent a cost increase over standard TRUS-guided biopsy, this approach is believed to be substantially less costly than in-bore MRI-guided biopsy. Implementing this biopsy approach would require patients who previously might have had only standard TRUS-guided biopsy to undergo an MRI procedure. Additionally, widespread implementation will require coordination between radiologists who read the images 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 obtaining prostate biopsy specimens and may enhance detection of clinically meaningful prostate cancers. Implementing this approach may significantly increase costs, they noted, as it would require adding MRI to the procedure. Experts agreed that the availability of coverage and reimbursement would determine whether it achieved 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 survival of 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; the May 2013 approval came 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 six treatment cycles. Radium-223 dichloride's reported cost is $69,000 for a complete cycle of treatment. Third-party payers generally require preauthorization, and for Medicare beneficiaries, if authorization is granted, the treatment is covered under Part B benefits. The company CEO reported at an August 2013 new conference that the launch was "on track."

- **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 has 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

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 response duration 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 with disease that 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 use of 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. FDA cleared the system for soft tissue ablation only and has not granted marketing approval for treating cancer or any specific disease or condition. In fact, FDA issued warnings to the company about promoting the system for cancer treatment without having marketing approval for those indications. The company ceased promotion on its Web site 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 actively investigating IRE for two cancer indications, pancreatic cancer and 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 controlled trials on efficacy should be conducted before wider adoption.
- **Potential for High Impact:** Lower end of the high-impact-potential range

Thyroid Cancer

Sorafenib (Nexavar) for treatment of differentiated thyroid cancer

- **Key Facts:** The majority of diagnosed thyroid cancers are the differentiated subtype, which is typically amenable to treatment with radioactive iodine; however, a subset of differentiated thyroid cancers will develop resistance. Treatment options for patients with these cancers are limited, and the prognosis for these patients is poor. Researchers have been investigating the use of targeted therapies, which are thought to regulate cancer-related processes such as cell growth, cell proliferation, cell survival, and angiogenesis. The targeted therapy that has been most extensively studied to date is the orally administered, multikinase inhibitor sorafenib (Nexavar®). In results from a recent phase III clinical trial comparing sorafenib to placebo in patients with progressive radioactive iodine-refractory differentiated thyroid cancer, sorafenib extended progression-free survival by approximately 86% (10.8 months vs. 5.8 months). Based on these data, a new drug application was submitted to FDA for use of sorafenib in treating thyroid cancer. Following a priority review, it became the first treatment approved for treating radioactive, iodine-refractory, thyroid cancer. Sorafenib had earlier been approved by FDA for use in treating patients with advanced renal cell carcinoma and advanced hepatocellular carcinoma, and some off-label prescribing of sorafenib for treating thyroid cancer had taken place before the November 2013 approval for this indication. Several third-party payers already had policies in place that covered off-label use of the drug in treating thyroid cancer. Coverage is anticipated to expand in the wake of the recent FDA approval.
- **Key Expert Comments:** Overall, experts concurred that sorafenib would fill an unmet need for patients with radioactive iodine–refractory thyroid cancer especially given that no other therapies had been approved by FDA for this indication and given the promising results regarding progression-free survival in recent data from a phase III clinical trial. The magnitude of sorafenib's impact was lessened by the relatively small patient population that would be a candidate for the treatment and sorafenib's oral route of administration, which limited any potential impact on health care staffing or infrastructure.
- **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; rough age range, 13–30 years) with cancer 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: Recently, the Institute of Medicine partnered with the Livestrong Foundation to host a workshop for health care providers, researchers, and health advocates to raise awareness and discuss solutions for the unique issues surrounding AYA oncology and patient care.[8] A new care model that presents a potential solution to shortcomings in AYA cancer care involves creating dedicated oncology programs with staff that offer comprehensive, specialized clinical and supportive care services. Several institutions have established AYA-directed oncology programs or support systems.[8-10] 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.[9,10] 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.[11] 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.[12] 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.[13]

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.[11] Individual rooms and common areas are outfitted with personal computers, gaming systems, televisions, and so on.[11] 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.[14] Efforts to bolster clinical-trial enrollment and participation may require additional clinical staff and research 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.[5,15] Preliminary data demonstrated improved clinical trial enrollment among patients treated in an AYA oncology program.[6] An ongoing, large-scale study called BRIGHTLIGHT was initiated in 2012 to gather qualitative and quantitative data from AYA oncology patients who received treatment on standard pediatric or adult units or AYA-specialized units.[16] As of November 2013, the study had enrolled 523 AYA patients with recent cancer diagnoses.[17] 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)[10] is a nonprofit organization established in 2011 as the U.S. extension of Teenage Cancer Trust, a U.K. charity organization based in England.[9] These organizations form partnerships with hospitals and cancer centers to design and implement AYA cancer units.[18] 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.[9,10] These efforts are sponsored by British musicians Roger Daltrey and Pete Townshend 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.

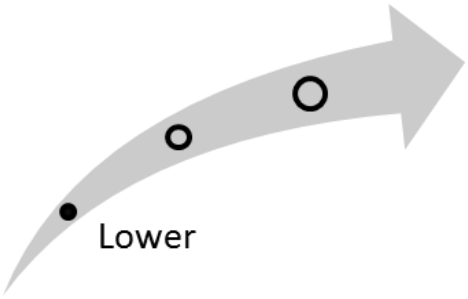
Diffusion: Since 1990, the Teenage Cancer Trust has funded 26 dedicated AYA oncology units throughout the United Kingdom, with another 9 in development.[19] The U.S. arm of the organization, Teen Cancer America, was launched in December 2011.[20] In collaboration with University of California, Los Angeles (UCLA), Medical Center, Teen Cancer America established the UCLA Daltrey/Townshend Teen & Young Adult Cancer Program (Santa Monica, CA) in 2011, which in November 2012 opened the first exclusively AYA-dedicated oncology unit in the United States.[21] 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.[10,22]

Although Teen Cancer America has pioneered the first fully dedicated AYA oncology unit and staffing care model, numerous cancer centers throughout the United Stated 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, AYA 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, career support) to AYA patients, and facilities are incorporating dedicated social space for AYAs on many pediatric units. Other centers are offering supportive services specifically geared to AYAs with cancer to address some of the specific needs of this patient population.[8]

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, their 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.[23-28] 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 who have 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 to discern potential health impacts of AYA units. The program has moderate potential to improve AYA patient outcomes, experts thought.

Acceptance and adoption: Most clinicians would be likely to welcome these specialized treatment programs, the experts generally indicated, 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 might 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.[29] 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%.[30] 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.[31,32]

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.[33] An automated breast ultrasound (ABUS) system could incorporate US imaging into routine breast cancer screening as an adjunct to mammography for women who have dense breasts. The somo•v® ABUS™ system was developed to address this need.

Intervention: Dense breast tissue and breast tumors both generate positive signals in x-ray images, and dense breast tissue can obscure tumors. In contrast, dense breast tissue reflects a high percentage of US waves (i.e., is hyperechogenic) and can generate a strong signal for imaging, whereas malignant breast tumors reflect a low percentage of US waves (i.e., is hypoechogenic). This difference in echogenicity produces a strong contrast between dense breast tissue and tumors in US images, potentially making tumors more readily detectable. Breast density is determined by radiologists who apply the BI-RADS breast density classification system. BI-RADs 1 density indicates that the breast is almost entirely fat. BI-RADS 2 density indicates 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 indicates that the breast tissue is dense and spread throughout the breast tissue with more areas of fibrous and glandular tissue (51% to 75%), making it difficult 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.[29]

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 technician reviews the images prior to radiologist interpretation.[34] With the patient in a supine position on a standard examination table, the technician images the breast using a convex transducer placed in direct contact with the breast. Each scan takes up to 350, two-dimensional (2-D) images that, when combined, 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 three-dimensional (3-D) reconstructions of the breast in multiple orientations.

Clinical trials: Investigators tested the somo•v ABUS system in a simulated screening model in a retrospective reader study. In this study, 164 women (133 noncancer and 31 biopsy-proven cancers) with dense breast tissue were imaged by digital x-ray mammography (XRM) and ABUS. Dense tissue was defined as more than 50% parenchymal breast density. 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 plus 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 plus ABUS (a difference of -2.0%; 95% CI, -7.7% to 4.3%; p=0.518).[35]

A larger trial of ABUS in the screening setting (the SOMO•INSIGHT study) is ongoing.[36] 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 2014.[37] Two smaller screening studies studying the addition of automated US imaging to standard mammographic screening have reported increases in cancer detection rates among women with dense breast tissue.[33,38]

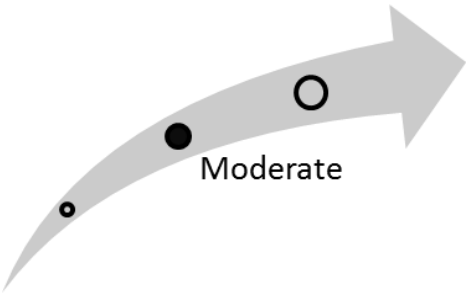
Manufacturer and regulatory status: The somo•v ABUS system was developed by U-Systems, Inc., a unit of General Electric Co. (Fairfield, CT). The company submitted a premarket approval (PMA) application for the system to the U.S. Food and Drug Administration (FDA), basing it on data from the reader study 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."[39] Although 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,[40,41] 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 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 only a single payer (Humana) with a policy for using ABUS for breast cancer screening. This payer considers ABUS to be experimental/investigational and thus does not cover it.[42] U-Systems has indicated that the results of its SOMO•INSIGHT study may improve the reimbursement climate.[37]

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).[43,44] Women in whom an abnormality is identified typically undergo additional diagnostic imaging (e.g., diagnostic mammography, US, 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.[43] ABUS has the potential to supplement mammographic screening for women with dense breasts. Its developer has proposed using 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 after ABUS would then be referred for additional diagnostic imaging.[45]

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. 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 sizeable 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.[46-51] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet of 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 saw the unmet need as very important because of the shortcomings of other adjunctive imaging methods (e.g., high cost of MRI, 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. 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 (Giger et al 2012)[35] 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 because of its potential to improve breast cancer detection rates for 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, including 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.

Adopting ABUS would not affect patient management substantially, the majority of experts thought; but one clinical expert suggested that these changes would represent a large disruption in how patients are managed because it adds a step to screening. 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 the therapy.[52] Multiple mechanisms of resistance to endocrine therapy have been identified, including signaling through the mammalian target of rapamycin (mTOR)/phosphatidylinositol-3 kinase (PI3K) pathway.[53]

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, mTOR-pathway molecules have been shown to be aberrantly expressed and/or mutated in various cancers, suggesting that agents inhibiting 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.[54] Rapamycin-like mTOR inhibitors have been approved for treating cancers, including everolimus (Afinitor®) for treating renal cell carcinoma, subependymal giant cell astrocytoma and angiomyolipoma associated with tuberous sclerosis, and pancreatic neuroendocrine tumors;[55] and temsirolimus (Torisel®) for treating renal cell carcinoma.[56]

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.[57] Everolimus is an oral medication administered at a dose of 10 mg, once daily.[58]

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).[57] Results from a randomized, double-blind, placebo-controlled trial of 724 patients (BOLERO-2) were published in 2012.[59] 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; $p<0.0001$).[59]

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.[60]

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.[58] In BOLERO-2, the most common grade 3 or 4 adverse events were stomatitis (8% in the combination-therapy group vs. 1% in the exemestane-alone group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). mTOR inhibition is also associated with renal failure, elevated blood glucose and lipids, and immunosuppression, which can lead to increased risk of infections.[56,58]

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.[61]

Diffusion: A May 2013 query of a U.S.-based, online aggregator of prescription-drug prices identified a retail price of about $9,100 per month for everolimus.[62] 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 5 payers with policies regarding everolimus.[63-67] These payers considered everolimus to be medically necessary when prescribed for FDA-approved indications. Formularies of representative plans typically classify everolimus as a specialty pharmaceutical that requires prior authorization and is subject to quantity limits.

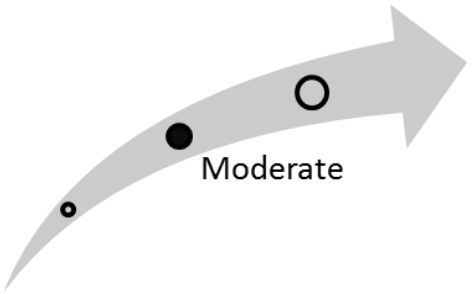
Expanded indications are the subject of ongoing investigations. Two phase III clinical trials are assessing everolimus used in combination with endocrine therapy in patients at high risk of recurrence following treatment of early-stage breast cancer.[68,69] Recent trial data suggest HER2-positive breast cancer that has progressed following treatment with trastuzumab is another potential indication for everolimus.[70]

Also, several investigational drugs are under study as adjuncts to endocrine therapy in metastatic hormone receptor–positive 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 for patients who have not previously undergone hormone therapy for metastatic disease[71] and the PI3K inhibitor BKM120 in combination with the anti-estrogen agent fulvestrant for patients who have undergone prior endocrine therapy for metastatic disease.[72]

Clinical Pathway at Point of This Intervention

Patients with locally advanced/metastatic hormone receptor–positive breast cancer are typically treated with endocrine therapy using aromatase inhibitors or antiestrogens; they 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.[73] Everolimus may be used 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).[57]

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. Additionally, experts thought clinician and patient acceptance would be high,

given the limited options for this patient population. However, as an orally administered drug, everolimus was seen as having minimal impact on health care staffing or infrastructure. 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 everolimus for treating ER+ breast cancer.[74-79] We have 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 is 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, experts noted that these patients have a poor prognosis and few treatment options aside from cytotoxic chemotherapy, which is typically highly toxic and of limited benefit in extending patient survival.

Health outcomes have some potential to improve with everolimus, the majority of experts believe. Experts who envisioned everolimus as having substantial potential to improve patient health noted the significant extension of progression-free survival observed in the BOLERO-2 trial. Conversely, one commenter with a research perspective suggested that the existing data left unclear the speed with which metastatic disease would develop resistance to everolimus. Multiple commenters noted that adding everolimus to exemestane resulted in additional toxicity, in particular stomatitis. One expert with a clinical perspective suggested that this could present a substantial issue for patients, particularly if everolimus came to be used in earlier stages of ER+ breast cancer treatment where it likely would be administered over long periods of time.

Acceptance and adoption: Both physicians and patients would be likely to adopt everolimus, the experts suggested, because of its oral route of administration and potential to increase progression-free survival. Additionally, one expert with a clinical perspective suggested that oncologists are familiar with the use of everolimus, which could hasten clinician adoption. Everolimus' side effect profile was mentioned as both a positive and negative for adoption by expert commenters. Some experts cited everolimus' relatively benign safety profile relative to cytotoxic chemotherapy as a reason for patient adoption while others suggested that the toxicity associated with the addition of everolimus to exemestane would dissuade some patients for opting for everolimus treatment.

The majority of experts suggested that, as an added option, everolimus would lead to a moderate increase in treatment costs for this patient population. Several experts noted that the upfront increase in pharmaceutical costs could be offset to some extent by delaying or obviating the need for cytotoxic chemotherapy. One expert with a clinical perspective noted that patients would likely have higher out-of-pocket costs for everolimus compared with those for infusion-based chemotherapy.

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. One expert with a clinical perspective suggested that widespread use of everolimus could place added demands on health care facility staffers who are responsible for processing prior authorization requests.

Health disparities: Everolimus would not have a significant impact on health disparities, the experts thought. Some experts suggested that the high cost of everolimus could exacerbate any existing disparities between under-insured and insured patient populations.

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 be free of cancer. Yet, many patients who undergo a breast-conserving lumpectomy require a second surgery when postsurgical histopathologic 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 identified an overall reexcision rate of 22.9% and noted that earlier studies had reported reexcision rates ranging from 30% to 60%.[80] This represents a significant problem with associated costs and additional anxiety and risks for patients having to undergo second procedures.

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 the lumpectomy procedure.[81] Investigators have also begun to test a version of the device for margin assessment in patients undergoing prostatectomy to treat prostate cancer.[82]

The system uses radiofrequency (RF) spectroscopy, in which tissue is subjected to an electromagnetic field, measuring its response to stimulation.[83] Research findings have indicated that RF spectroscopy can differentiate between normal and cancerous tissue based on their bioelectric profiles.[84] These differences may be due, in part, to changes in the cellular and tissue structure of cancerous tissue, including cell membrane depolarization, altered cell nucleus morphology, increased vascularity, and loss of cell-cell adhesion.[83] 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.[84]

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.[85] 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.[86] 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.[81] In results presented as an abstract at the 2011 San Antonio Breast Cancer Symposium (SABCS), the reported 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], $p<0.0001$). Investigators reported the volume of tissue dissected in each trial arm was similar (93 cc MarginProbe arm; 85 cc control arm).[86] A main goal of intraoperative screening is to reduce the re-operation rate. However, despite an improvement in intraoperative identification and resection of positive margins, use of the MarginProbe device did not lead to a statistically significant decrease in re-operation rate in the overall patient population (20.8% in the MarginProbe arm vs. 25.8% in the control arm, $p=0.3177$).[87]

Manufacturer and regulatory status: Dune Medical Devices, of Caesarea, Israel, makes the MarginProbe system. In January 2013, FDA approved MarginProbe.[88] 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."[87] The labeling indicates that the manufacturer provides training in the form of onsite, in-service orientation for surgical and operating room staff.[87]

Diffusion: In March 2013, Dune Medical announced that the first MarginProbe System had been installed in the United States.[89] The system cost, as reported in ECRI Institute's PricePaid database by hospitals acquiring the device during the fourth quarter of 2013, is $39,995.[90] Although specific costs for the MarginProbe System console and probes have not been released, one report placed the per-patient cost at approximately $2,000.[91] *The Wall Street Journal* reported in July 2013 that the per-surgery cost of adding use of the system during a breast resection was quoted by several hospitals as $995 additional per surgery.[92]

Few coverage determinations have been made regarding the MarginProbe system. In August 2013, the Blue Cross Blue Shield Technology Evaluation Center released a technology assessment concluding that the data available at the time did not demonstrate that the technology improved net health outcomes or demonstrate that the technology produced equivalent benefit to established alternatives.[93] MarginProbe will be used in the context of inpatient surgery for tumor removal; thus, its use may be considered integral to the primary procedure and be reimbursed under the primary procedure code. Alternatively, a separate code for intraoperative margin assessment could be established.

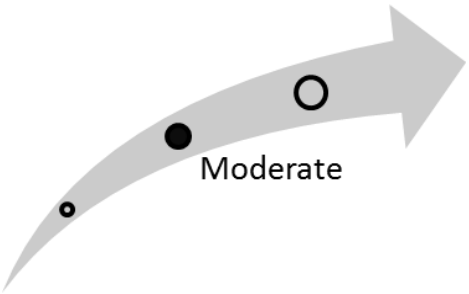
At least two other spectroscopy devices are under study in early-phase clinical trials for intraoperatively assessing lumpectomy margins.[94,95]

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.[73] 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 can rapidly and objectively identify positive margins during breast-conserving surgery, which could significantly reduce the morbidity and costs associated with performing second operations 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.[96-102] We have 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 associated adverse health and emotional effects for patients.

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.

Acceptance and adoption: The system could be easily adopted, the experts thought. They did not think that use of the system would have a significant impact on patient management, other than reducing the number of second operations, 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 second surgery procedures.

Health system infrastructure and staffing: Because the system could be easily adopted, according to experts, it would have minimal impact on health care system staffing and infrastructure. Potential changes—such as system acquisition and a slight shift in operating room demand caused by a small increase in the time needed for lumpectomy procedures and a reduction in the number of second operations—were seen as incremental, but not disruptive changes.

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 (HER2+) 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 has also provided a clearly defined molecular target.[103] Indeed, HER2+ breast cancer treatment outcomes have 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 are highly desired.[104]

Intervention: Two novel biologic therapies were recently FDA-approved for treating HER2+ breast cancer: ado-trastuzumab emtansine (Kadcyla™) and pertuzumab (Perjeta®).

Ado-trastuzumab emtansine (formerly called trastuzumab-DM1),[105] an antibody-drug conjugate (ADC), couples the HER2-specific monoclonal antibody (trastuzumab) to a potent chemotherapeutic agent, the microtubule assembly inhibitor emtansine (DM1).[106] 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.[106] In this way, emtansine is targeted to cells expressing the HER2 receptor, preferentially targeting tumor cells (which express high levels of HER2) and sparing many normal tissues from the 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).[104] 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.[107]

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; therefore, it may act synergistically with trastuzumab.[108] 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.[109] 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.[110]

Clinical trials: Ado-trastuzumab emtansine is being studied in a number of trials in patients with metastatic disease. Results are available from the phase III EMILIA trial, which compared treatment with ado-trastuzumab emtansine to standard therapy (lapatinib plus capecitabine) in patients with metastatic HER2+ breast cancer previously exposed to trastuzumab. Investigators reported improved progression-free and overall survival in patients receiving ado-trastuzumab emtansine compared with patients receiving lapatinib plus capecitabine (median progression-free survival 9.6 months and 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 and 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 in the lapatinib plus capecitabine arm experienced grade 3 or 4 adverse events (41% and 57%, respectively).[111] Recent results are available from the phase III trial of ado-trastuzumab emtansine for treating patients with metastatic disease who have undergone multiple prior therapies including trastuzumab and lapatinib. As compared with treatment of physician's choice, ado-trastuzumab emtansine increased progression-free survival in this patient population from 3.3 to 6.2 months while simultaneously reducing the overall incidence of grade 3 or higher adverse events.[112]

Pertuzumab is also under study in multiple trials for treating HER2+ disease. Results are available from the phase III CLEOPATRA trial, which demonstrated that adding pertuzumab to standard first-line therapy for metastatic disease consisting of trastuzumab and docetaxel 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) when used as a first-line therapy for patients with HER2+ metastatic breast cancer.[108,113] Analysis of overall survival at a median followup of 30 months indicated that adding pertuzumab to this regimen decreased the risk of death by 38% (HR, 0.62; 95% CI, 0.51 to 0.75; $p<0.0001$).[113]

Besides these studies in patients with metastatic disease, both pertuzumab and ado-trastuzumab emtansine are under study for treating nonmetastatic breast cancer both as neoadjuvant (presurgery) and adjuvant (postsurgery) treatment options. The indication with the most available data is the use of pertuzumab in the neoadjuvant setting. In the phase II NeoSphere trial, adding pertuzumab to the trastuzumab and docetaxel regimen increased the pathologic complete response rate from 29.0% to 45.8% ($p=0.0141$; FDA employs a more strict definition of pathologic complete response and reports these figures as 21.5% and 39.3%, respectively).[114,115]

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

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."[116,117] 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.[117]

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."[118]

In September 2013, FDA granted pertuzumab accelerated approval "as a part of a complete treatment regimen for patients with early stage breast cancer before surgery."[119] This represented the first drug to receive formal FDA approval for use in the neodjuvant setting. A confirmatory trial studying the use of pertuzumab in the adjuvant setting is ongoing.[119]

Diffusion: Roche announced pricing of ado-trastuzumab emtansine at $9,800 per month of treatment.[120] However, discount coupons have been available. The biologic is given at a dosage of 3.6 mg/kg every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. Thus, a 70 kg (154 lb) person would require about 252 mg. The drug is provided in 100 mg vials. An online aggregator of pharmacy pricing has listed costs from various pharmacies in December 2013 of about $2,934 to $3,053 for one 100 mg vial. This pricing required use of a discount coupon. If one 70 kg patient required about 2.5 vials, the cost would be about $7,500 per infusion cycle.[121]Ado-trastuzumab emtansine became available shortly after approval, and Roche has reported strong uptake of the drug in 2013.[122,123]

Pertuzumab became available in August 2012 and by late October of that year was reportedly being used in approximately 30% of eligible patients.[124,125] 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 used of pertuzumab included "concerns over cardiotoxicities, lack of

finalized overall survival data, and increased cost."[124] The drug is provided in 420 mg/14 mL vials, which constitutes one cycle. An online aggregator of pharmacy pricing has listed costs from various pharmacies in December 2013 of about $4,309 to $4,428 for one vial. This pricing required use of a discount coupon.[126] However, the on-label use of pertuzumab in combination with trastuzumab could push the cost of a typical course of treatment in the metastatic setting to approximately $187,000.[127]

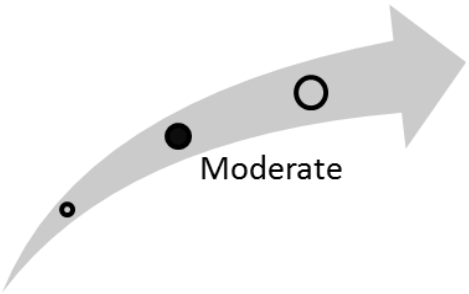
A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 3 payers with policies regarding ado-trastuzumab emtansine.[128-130] 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 eight with policies for pertuzumab.[131-138] These payers considered pertuzumab to be medically necessary when prescribed according to FDA-approved indications (i.e., part of a complete, neoadjuvant treatment regimen for patients with early stage breast cancer). Some plans require 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.[73] 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,[139-145] and six experts, with similar backgrounds, offered perspectives on pertuzumab for treating breast cancer;[146-151] of these groups, three experts commented on both interventions. We have 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 shortcomings of existing HER2-targeted agents (e.g., trastuzumab, lapatinib).

Regarding ado-trastuzumab emtansine's potential to improve patient health outcomes, most commenters rated it as minimal to moderate. Experts viewing ado-trastuzumab emtansine's potential to improve patient health more favorably cited the significant extension in progression-free and overall survival and decrease in adverse events for patients treated with ado-trastuzumab emtansine versus patients treated with lapatinib plus capecitabine in the EMILIA trial, which suggested that the drug could improve both the quantity and quality of life relative to current treatments. However, one expert with a health systems perspective suggested that the survival benefit was incremental to existing HER2-targeted therapies and suggested that further study was needed to clarify any potential health benefit of the drug.

Pertuzumab's potential to improve patient health was considered moderate by most experts, who cited the significant increase in progression-free survival observed in the CLEOPATRA trial. However, one expert with a research perspective suggested that the potential for improvement in patient health was incremental. Conversely, one expert with a clinical perspective suggested that the pertuzumab's potential to improve patient health was significant, citing the recent approval of pertuzumab in the neoadjuvant setting, which would allow it to be used in treating a larger number of patients than in the metastatic setting.

Acceptance and adoption: Both ado-trastuzumab emtansine and pertuzumab would be readily adopted by physicians and patients according to expert commenters. Factors promoting adoption included their potential to increase survival and their relatively good safety profiles. But the anticipated high cost of ado-trastuzumab emtansine and pertuzumab was one potential obstacle raised by the experts, particularly for pertuzumab, which is currently indicated for use in combination with trastuzumab.**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.

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. 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.[152] 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.[153] Also, elevated levels of certain methylated DNA species have been found in the blood of patients with CRC, which could serve as a readily accessible marker for cancer screening.[153]

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.[153] 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.[154]

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.[155,156] 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, measured against CRC detection by colonoscopy, the Septin 9 test had a sensitivity of 68% and a specificity of 80%.[156] 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.[157] 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.

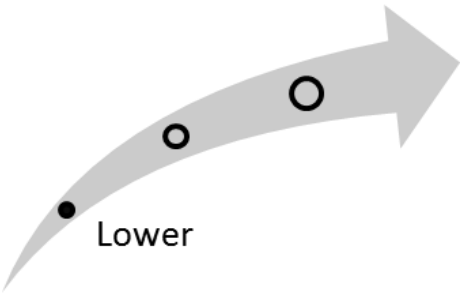
Manufacturer and regulatory status: The Epi proColon 2.0 methylated Septin 9 DNA blood test was developed by Epigenomics AG, of Berlin, Germany. As of April 2013, Epigenomics had completed its PMA submission to FDA for the Epi proColon test. FDA granted the submission priority review status in February 2013,[158] and an FDA advisory committee has been scheduled to review the PMA on March 25, 2014.[159]

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.[160] For noncolonoscopy tests, positive results require a subsequent colonoscopy to confirm the result and perform any required biopsy of suspicious polyps.[160] Septin 9 blood testing would be another routine screening option that also would require followup colonoscopy for confirming positive results and excising lesions.[154] 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.[161]

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, 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.[162-168] We have 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.

Acceptance and adoption: Experts stated that the septin 9 test 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.

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. 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 obtains a fecal sample collected in the home setting and returns it for processing.

Fertility Issues Associated with Gonadotoxic Cancer Therapy

Ovarian Tissue Cryopreservation for Fertility Preservation in Women Undergoing Gonadotoxic Cancer Therapy

Unmet need: Because cancer treatments have improved patients' long-term survival, procedures for maintaining long-term quality of life are of great interest. Many cancer therapy regimens (i.e., chemotherapy or radiation therapy) are highly gonadotoxic and can permanently impair fertility.[169,170] Prepubertal girls and reproductive age women who require gonadotoxic cancer treatments often express a desire to preserve fertility. Currently, in vitro fertilization and embryo cryopreservation is the only standard option that is available to women who wish to be able to have children after cancer remission.[171] However, this option requires weeks of ovarian stimulation with hormones to mature the follicles/oocytes. The ovarian stimulation process may be contraindicated for women who must urgently begin treatment or for those whose cancers may be worsened by hormone treatments.[172] A new option to preserve fertility involves ovarian tissue cryopreservation and, upon remission, reimplantation of the tissue to the patient after she achieves cancer remission. This option is available to prepubertal girls and reproductive-age women and requires no ovarian stimulation or treatment delay.[173]

Intervention: Ovarian tissue cryopreservation is a procedure under study in prepubertal and reproductive-age female patients who require gonadotoxic cancer therapies that may impair future fertility.[173] Before gonadotoxic cancer therapies are started, ovarian tissues are retrieved and carefully cryopreserved. At a later date, after cancer treatment has been completed, the ovarian tissue can be reimplanted with the intent of restoring ovarian function and fertility. Surgical techniques and cryopreservation protocols vary between institutions; in this report, we provide a general overview of the process.

Ovarian tissue collection is typically performed as a same-day outpatient surgical procedure in which the patient is placed under general anesthesia, and the procedure is performed laparoscopically or by laparotomy.[171] The tissue harvesting procedure can coincide with oophorectomy and an ovarian biopsy specimen may be sent for histopathological analysis to rule out the presence of malignant cells.[174] Typically, the cortex from at least one ovary is sectioned (about 1.0–1.5 mm thick, to ensure inclusion of the primordial follicles) and treated to withstand the freezing process. Tissues are prepared for cryopreservation through slow freezing or vitrification (i.e., rapid cooling). Cryopreservation is often performed at the site of tissue storage and may occur at off-site laboratories of tissue banks.[175]

Once the patient completes treatment, reimplantation of the cryopreserved ovarian tissue is performed with the intent of restoring ovarian function and fertility. The ovarian tissue transplant, or "autograft," may be placed orthotopically (i.e., in the same, or original, anatomical site) or heterotopically (i.e., at an alternative anatomical location). This surgical procedure can be performed by laparoscopy and typically takes place in the outpatient setting.[171,175] Orthotopic autotransplantation involves reimplanting the ovarian tissue into the pelvic cavity, either onto the existing ovary or within the uterine environment. When it is medically feasible, this orthotopic placement is preferred and provides a chance of natural pregnancy when the fallopian tubes are intact. If an ovary remains, surgeons will often decorticate this structure to expose the vascular bed and affix the ovarian tissue autograft onto this surface. When both ovaries have been removed, the surgeon may create a peritoneal pouch on the surface of the broad ligament and affix the autograft in place.[175]

As an alternative, surgeons can also place the autograph in a heterotopic location such as the abdominal wall, forearm, or rectus muscle,[171,174,175] an approach used in patients for whom

orthotopic transplantation is not feasible. Reports have demonstrated restored endocrine function with this approach, and mature follicles can be retrieved for in vitro fertilization.[174-176]

Clinical trials: Multiple nonrandomized trials are ongoing to examine ovarian tissue cryopreservation in adult females who require gonadotoxic therapies to treat a variety of malignant conditions.[177-182] The endpoints of these trials assess the safety and efficacy of ovarian tissue harvesting and reimplantation, successful restoration of ovarian function/hormonal cycling, and the rate of successful pregnancy after reimplantation. Due to the nature of this intervention, large randomized, controlled trials have not been carried out.

Clinical trial data have been reported in several case studies. Six case studies reported restoration of fertility and successful pregnancy in women who underwent ovarian tissue harvesting and reimplantation.[183-188] Puberty was successfully initiated via reimplantation of cryopreserved ovarian tissue in a 13-year-old girl with Ewing sarcoma several years prior.[189] In 2011, data were reported from a study of 12 women who underwent ovarian tissue harvesting before gonadotoxic therapy. After reimplantation of the ovarian tissue, the authors reported, all 12 women regained ovarian function, and 10 participants underwent in vitro fertilization, resulting in 6 pregnancies.[190] A 2013 study of 11 women who underwent reimplantation of cryopreserved ovarian tissue reported 5 live births and 1 ongoing pregnancy.[191] The data revealed that the duration of endocrine function varied after grafting; the mean duration was between 4 and 5 years, with reports of grafts functioning for longer than 7 years.[174,175] However, investigators are also closely evaluating the risk of reseeding malignant cells after reimplantation, and additional data are required to determine the risks associated with various malignancies.[192]

Manufacturer and regulatory status: A number of medical institutions in the United States offer ovarian tissue cryopreservation as a service for female patients with cancer who wish to preserve their fertility.[193] Additionally, several academic medical centers are conducting clinical trials to investigate reimplantation of cryopreserved ovarian tissue for restoring fertility. The following institutions are sponsoring ongoing clinical trials:

- Abramson Cancer Center of the University of Pennsylvania, Philadelphia[180]
- Boston IVF, Boston, MA[181]
- Hadassah Medical Center, Jerusalem, Israel[177]
- Oregon Health & Science University, Portland[182]
- University of Kansas Medical Center Research Institute, Kansas City[178]
- Weill Medical College of Cornell University, New York, NY[179]

Additionally, the Oncofertility Consortium® at Northwestern University (Chicago, IL) is a nationwide network that coordinates fertility preservation research and services for patients with cancer; these services include ovarian tissue cryopreservation and reimplantation.[194]

Diffusion: Initial uptake of ovarian tissue cryopreservation could be limited by lack of third-party coverage. The U.S. Centers for Medicare & Medicaid Services has no national coverage determination for ovarian tissue cryopreservation for preserving fertility. Thus, coverage decisions are left to the discretion of local Medicare carriers. 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 5 payers that consider ovarian tissue cryopreservation to be experimental and do not provide coverage (i.e., Anthem, Blue Cross/Blue Shield Massachusetts, CIGNA, Humana, United Healthcare).[195-199] No specific policies were identified for the other six payers.

Although official policies generally to do not establish coverage for ovarian tissue cryopreservation, survey results published in 2010 reported that health insurance companies did indeed cover the costs for oncology patients who had undergone these procedures.[200]

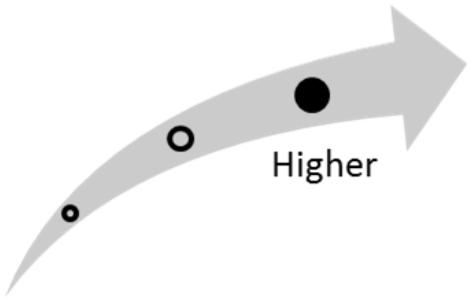
Clinical Pathway at Point of This Intervention

Embryo cryopreservation is the standard of care for fertility preservation in reproductive-age women undergoing gonadotoxic cancer therapy. After hormonal stimulation to mature ovarian follicle(s), mature oocytes are retrieved and the oocytes are then fertilized in vitro. Resulting embryos are cryopreserved until a later date for intrauterine embryo transfer.[201]

For patients who require radiation therapy that may affect the ovaries, several techniques exist to minimize damaging radiation exposure. Ovarian transposition is a surgical technique used to reposition the ovaries away from the radiation treatment zone to minimize damage. This technique can alter blood flow to the ovaries, compromising their function, and does not provide protection from chemotherapy effects.[170,171] Gonadal shields can also be used to minimize radiation exposure to the ovaries, but this technique requires care to ensure that shielding does not prevent adequate radiation dosing to targeted malignant areas.[171]

Besides ovarian tissue cryopreservation, several additional investigational approaches exist for fertility preservation: oocyte cryopreservation, oocyte in vitro maturation, and pharmacological ovarian suppression.[172] With the exception of gonadal shielding and ovarian transposition to prevent radiation exposure, these fertility preservation options are limited to reproductive-age females.

Figure 7. Overall high impact potential: ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer therapy



Experts commenting on this topic were often divided in their assessment of this intervention, which is reflective of the controversial nature of fertility preservation for female oncology patients and of fertility therapy as a whole. Some experts stated that this intervention filled an extremely important unmet need for female cancer patients, while others indicated that fertility preservation was not a critical unmet health care need. Overall, experts anticipated strong clinician and patient acceptance and adoption of this intervention, but several noted that cost and coverage issues could limit access and diffusion. Experts commented on the highly specialized nature of this technique and acknowledged the controversy surrounding this type of intervention. Based on the polarizing nature of this intervention and expert comments surrounding its disruptive potential, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered perspectives on ovarian tissue cryopreservation for fertility preservation in women undergoing gonadotoxic cancer

therapy.[202-207] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Experts were divided on the significance of the unmet need of fertility preservation in females undergoing gonadotoxic cancer treatments. Several experts, including two with a clinical background, felt that this issue presented a significant unmet need. Among their reasons, they stated the lack of any fertility preservation options for pre-pubertal girls and the significance of this issue for the patient population. However, a few experts rated the unmet need as having minimal to no significance, indicating that this issue does not directly improve patient health and that reproductive capacity may not be an essential need. Additionally, experts with a health devices and research background noted the potential risk of re-seeding the cancer or passing genetic predisposition for malignancy to offspring.

Acceptance and adoption: Experts anticipated widespread clinician and patient acceptance of this intervention. Clinicians would welcome an option to address an important patient need, experts thought. But substantial cost could hinder patient acceptance, a few experts opined. Additionally, another expert wondered whether younger women would struggle with this decision when faced with the obstacles of cancer therapy. However, the majority of experts thought that patients and clinicians would readily accept a fairly simple, low-risk procedure, particularly in the absence of other viable options.

Health care delivery infrastructure and patient management: The procedure would require ovarian tissue harvesting via laparoscopy, which would only slightly alter patient management, experts thought. Most experts anticipated that highly trained and specialized clinicians would continue to provide this intervention and predicted minimal disruption of existing infrastructure. If this approach were to become more widespread, infrastructure related to specialized staffing and storage facilities at fertility centers could be affected.

Health disparities: Because this procedure is likely to be associated with substantial cost and coverage may be unlikely, experts concurred that this option would likely be available only to economically advantaged patients. This may further increase health disparities for women and families who cannot afford fertility preservation. A few experts felt that this intervention would not be cost-effective or a worthwhile investment of resources for the population at large.

Hematologic Malignancy Interventions

Ibrutinib (Imbruvica) for Treatment of Non-Hodgkin's Lymphomas

Unmet need: Non-Hodgkin's lymphoma (NHL) comprises a set of malignancies that arise from lymphocytes of the immune system. Both B-cell-derived and T-cell-derived NHLs exist; however, the majority are malignant B-cells. Treatment of B-cell NHLs has improved in recent years with optimization of chemotherapy regimens and the introduction of the CD20 antibody rituximab. However, many patients with NHL experience disease recurrence, particularly patients with certain NHL subtypes such as chronic lymphocytic leukemia and mantle cell lymphoma. For patients with these conditions whose disease has recurred and who exhibit resistance to rituximab, few treatment options exist. Moreover, some forms of chronic lymphocytic leukemia, such as that harboring a deletion on the short arm of chromosome 17, have a poor prognosis when treated with current therapies.

Intervention: Ibrutinib (Imbruvica™) is a first-in-class, orally administered, small-molecule inhibitor of Bruton's tyrosine kinase (Btk), a nonreceptor tyrosine kinase that plays multiple roles in the regulation of B lymphocytes.[208]

Proliferation and survival of malignant B cells may be driven by chronic signaling through the B-cell receptor, which activates multiple molecular pathways regulating these processes (e.g., Akt, Extracellular Signal-Regulated Kinase, NF-κB). Btk is essential for the B-cell receptor–mediated activation of these pathways; therefore, Btk inhibition may inactivate these pathways, potentially depriving malignant B-cells of signals driving proliferation and survival.[208]

Besides Btk's role in regulating proliferation and survival downstream of the B-cell receptor, Btk may also play a role in regulating the trafficking and retention of malignant B cells in the lymph nodes. Lymph nodes may represent privileged sites within the body that play a role in the pathogenesis of B-cell malignancies. Btk has been shown to regulate both integrin-mediated adhesion downstream of the B-cell receptor and chemokine-mediated trafficking downstream of various chemokine receptors. Pharmacologic inhibition of Btk with ibrutinib results in an egress of malignant B cells from the lymph nodes into the peripheral blood, which is thought be caused by the inhibition of these pathways.[209,210]

Clinical trials: Investigators have reported results from phase II trials of ibrutinib in treating chronic lymphocytic leukemia and mantle cell lymphoma.

From a single-arm, open-label trial of ibrutinib (420 or 840 mg once daily) in patients (n=85) with chronic lymphocytic leukemia who had undergone at least two prior treatments, Byrd and colleagues in 2013 reported an overall response rate (according to the International Workshop on Chronic Lymphocytic Leukemia [IWCLL] criteria) of 71%. As noted above, ibrutinib's mechanism of action may lead to egress of B cells from the lymph nodes, leading to an increase in absolute lymphocyte count (i.e., lymphocytosis) in a substantial subset of patients. An additional 18% of patients met all IWCLL criteria for partial response except for the absolute lymphocyte count.[211]

In a separate single-arm, open-label trial of ibrutinib (420 mg once daily) in 53 patients with high-risk chronic lymphocytic leukemia (risk factors: 17p deletion [n=29], aged 65 years or older [n=24]), Farooqui and colleagues reported an overall response rate of 66% with an additional 28% of patients exhibiting partial response with lymphocytosis.[212] Importantly, both ibrutinib trials in patients with chronic lymphocytic leukemia demonstrated equivalent response rates in patients with and without a 17p deletion.[211,212]

From a single-arm, open-label trial of ibrutinib (560 mg once daily) in patients (n=111) with relapsed or refractory mantle cell lymphoma, Wang and colleagues reported an overall response rate of 68% (21% complete response, 47% partial response).[213]

Manufacturer and regulatory status: Ibrutinib was developed by Pharmacyclics, Inc., of Sunnyvale, CA, in collaboration with the Janssen Biotech unit of Johnson & Johnson of New Brunswick, NJ. FDA has granted ibrutinib breakthrough status for three indications: (1) chronic lymphocytic leukemia harboring a 17p deletion, (2) relapsed/refractory mantle cell lymphoma, and (3) Waldenstrom's macroglobulinemia.[214] New drug applications have been submitted for use of ibrutinib in treating chronic lymphocytic leukemia and mantle cell lymphoma. In November 2013, FDA granted accelerated approval for use of the drug in treating patients with mantle cell lymphoma who have received at least one prior therapy.[215] A decision on the new drug application for the chronic lymphocytic leukemia indication is pending.

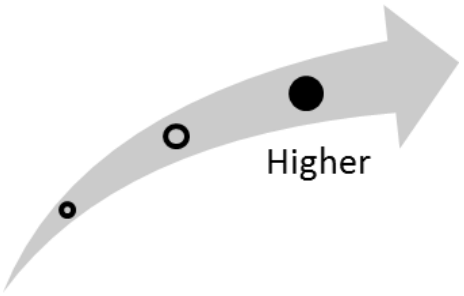
Diffusion: Having only recently been approved, little information on the diffusion of ibrutinib is available at this time. Pharmacyclics and Janssen have reportedly priced the drug at about $91 per 140 mg capsule, which translates to a monthly cost of about $10,920 per patient per month.[216]

Several additional novel agents are also in late-stage clinical trials for treating B-cell NHLs, in particular chronic lymphocytic leukemia. FDA recently approved obinutuzumab (Gazya®), a next-generation anti-CD20 antibody for treating chronic lymphocytic leukemia and positive results have been reported for the phosphoinositide 3-kinase inhibitor idelalisib in treating chronic lymphocytic leukemia and indolent NHLs.[217,218] Additional studies will be needed to optimize the combinatorial use and/or sequencing of these novel agents in treating NHLs.

Clinical Pathway at Point of This Intervention

Treatment of B-cell NHLs is highly individualized, based on the subtype of NHK diagnosed in the patient, the patient's overall condition, and his or her response to any earlier lines of therapy. Treatments for chronic lymphocytic leukemia and mantle cell lymphoma include various combinations of cytotoxic agents typically in combination with the monoclonal antibody rituximab. Other agents used in the treatment of NHLs include bortezomib and lenalidomide for mantle cell lymphoma and alemtuzumab, lenalidomide, and ofatumumab for chronic lymphocytic leukemia.[219] Based on the completed phase II clinical trials, ibrutinib would represent another treatment option for patients with relapsed B-cell NHL or certain high-risk patients with previously untreated NHL (e.g., patients with chronic lymphocytic leukemia harboring a chromosome 17 deletion).

Figure 8. Overall high-impact potential: ibrutinib (Imbruvica) for treating non-Hodgkin's lymphomas



Overall, experts opined that a significant need exists for novel treatments of chronic lymphocytic leukemia and mantle cell lymphoma and that the response rates observed in initial trials of the ibrutinib indicated that it has significant potential to improve patient outcomes. Although reviewers suggested that further study is needed to confirm this early promise (particularly studies comparing ibrutinib to alternative treatments), the relatively benign side-effect profile of the drug and its potential to be used in treating several B-cell malignancies place ibrutinib at the high 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 ibrutinib for treating chronic lymphocytic leukemia,[220-225] and six experts, with similar backgrounds, offered perspectives on the topic of ibrutinib for treating mantle cell lymphoma;[226-231] of these groups, four experts offered comment on both indications. It should be noted that experts offered perspectives on these topics before the recent FDA approval of ibrutinib for treating mantle cell lymphoma. We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: A moderate to high unmet need for new treatments for chronic lymphocytic leukemia and mantle cell lymphoma was seen by expert commenters. They cited the propensity of these malignancies to recur and the lack of effective treatment options for patients with relapsed disease.

Ibrutinib's potential to improve health was also considered moderate to high by commenters, who noted the high response rates reported from phase II trials and the relatively tolerable adverse event profile of the treatment. Commenters who rated ibrutinib's potential to improve patient health as only moderate suggested that randomized controlled trials and longer-term outcomes would be needed to fully assess ibrutinib's impact on patient health. One expert with a clinical perspective who rated ibrutinib's potential to improve patient health as high noted the significant unmet need presented by high-risk patients whose disease harbors a chromosome 17 deletion and the preliminary evidence of ibrutinib's efficacy in this patient population.

Acceptance and adoption: Both clinicians and patients were seen by commenters as highly likely adopt the use of ibrutinib. Factors encouraging adoption included the limited treatment options for patients with relapsed disease, ibrutinib's encouraging signs of efficacy and limited toxicity, and its ease of administration. Conversely, several commenters suggested that the cost of ibrutinib could be a factor that dissuades some patients from opting for the treatment.

Health system infrastructure and staffing: Ibrutinib is an orally administered medication and, therefore, most reviewers did not see its adoption as having a substantial impact on health care staffing or infrastructure. Some potential for change was envisioned if patients who might have received cytotoxic chemotherapy administered by infusion were instead treated with ibrutinib. Commenters noted that this would cause a shift in care setting and suggested that the mild side-effect profile observed thus far for ibrutinib could lessen the demand on health care providers to manage adverse events.

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.[232] 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 in treatment.[232] 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.[233]

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 purportedly inhibits androgen receptor signaling by blocking multiple steps required for androgen receptor activity, including androgen binding, androgen receptor nuclear translocation, and androgen receptor DNA binding.[234] Unlike currently available androgen receptor antagonists, enzalutamide purportedly exhibits no androgen-receptor agonist activity.

Enzalutamide is an oral medication that is administered at a dose of 160 mg (4 capsules), once daily. Unlike the recently FDA-approved androgen synthesis inhibitor abiraterone, enzalutamide does not require co-administration of low-dose prednisone.[235,236]

Clinical trials: Enzalutamide has been studied in the following two phase III, placebo-controlled clinical trials:

- The AFFIRM trial in patients with castration-resistant prostate cancer (CRPC) who had undergone prior treatment with docetaxel
- The PREVAIL trial in patients with CRPC who were chemotherapy naïve

In the AFFIRM trial, 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; $p<0.001$).[237] In the PREVAIL trial, enzalutamide improved progression-free survival and overall survival compared with those outcomes with placebo; risk of disease progression or death were decreased by 81% and 30%, respectively.[238] 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.[237]

Manufacturer and regulatory status: Medivation, Inc., of San Francisco, CA, and Astellas Pharma, Inc., of Tokyo, Japan, jointly developed and market 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.[239] The companies have indicated that meetings with regulators regarding a label expansion to include use in patients who have not received prior treatment with docetaxel will likely take place in early 2014.[238]

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

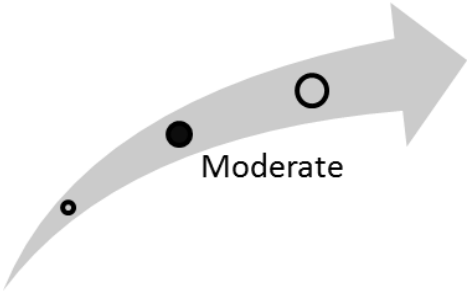
to expanded indications in chemotherapy-naïve mCRPC and nonmetastatic CRPC, promoting further diffusion.[240] A query of a U.S.–based, online aggregator of prescription-drug pricing identified a retail price of about $8,100 for a 1-month supply of enzalutamide, or $97,200 per year of treatment.[241]

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 4 payers with policies for enzalutamide.[242-245] These payers considered enzalutamide to be medically necessary when prescribed according to FDA-approved indications for mCRPC; coverage may be contingent upon failure or intolerance of other therapies (i.e., abiraterone plus prednisone and/or docetaxel); however, none of these policies have been updated since the release of the PREVAIL data in chemotherapy-naïve patients. 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. 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. For patients with more advanced, symptomatic mCRPC, the standard first-line treatment is systemic chemotherapy with the taxane docetaxel. Lastly, for patients whose disease progresses after treatment with docetaxel, treatment may consist of the androgen-synthesis inhibitor abiraterone, the radiopharmaceutical radium-223, or the taxane cabazitaxel.[246] In its FDA-approved indication, enzalutamide represents a potential treatment alternative in the postdocetaxel setting and based on the recently released data in chemotherapy-naïve patients, may move into this setting as well.

Figure 9. 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, they 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.[247-255] We have 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 purportedly addresses 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. Results of the phase III trial in the prechemotherapy setting were not available in time to collect new expert comments reflecting this data.

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 because of potential long-term use starting in earlier stages of treatment.

Magnetic Resonance Imaging–Ultrasound Image Fusion to Guide Prostate Biopsy

Unmet need: Substantial variability exists in prostate cancer diagnostic methods. Prostate biopsy methods used in arriving at a diagnosis can differ among practitioners and often provide results of varying consistency and predictive value.[256,257] 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 MRI-guided biopsy. Although effective, MRI-guided biopsy is more expensive than TRUS-guided prostate biopsy and requires highly specialized equipment and staff training.[256,258] 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.[259-261] The urologist then performs a real-time, three-dimensional, TRUS-guided biopsy on the patient in the office setting. Image-fusion technology superimposes the 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.[256,258] 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.[256,258] 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. These data could be used for a variety of purposes, including repeat biopsy or targeted focal therapy to specific biopsy sites.[256,258,262,263]

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 who 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.[259]

Data were released from a second study using the PercuNav image fusion and navigation technology (Royal Philips Electronics, Amsterdam, the Netherlands, in collaboration with the National Cancer Institute, Bethesda, MD). In this study, 582 patients underwent both standard 12-core biopsy and targeted biopsy using MRI-TRUS image fusion. Compared with 12-core biopsy, MRI-TRUS fusion targeted biopsy preferentially identified prostate cancer with more aggressive histology: it detected more cases of Gleason score 4+3 or higher than biopsy and fewer cases of Gleason score 3+4 or lower, "thus mitigating the detection of lower-grade disease."[264]

Gleason scores 4+3 and 3+4 indicate patterns of disease, and in a study published in 2009 of 693 prostatectomy and 119 biopsy specimens, Stark and colleagues found that the 4+3 pattern was associated with higher mortality than the 3+4 pattern.[265]

Lastly, 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 systematic biopsy cores and successfully identified more high Gleason-grade cancers.[266]

An ongoing clinical trial of the PercuNav image fusion and navigation technology has been undertaken by Philips in collaboration with the National Cancer Institute. 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.[267] 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.[268]

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 Bx, Eigen[269]
- BioJet™ 3D MR-TRUS Fusion Prostate Biopsy System, Geo Scan Medical, LLC, of Lakewood Ranch, FL[270]
- BiopSee Advanced Image Guided Prostate Biopsy System, MedCom[271]
- HI VISION Ascendus Platform with real-time virtual sonography, Hitachi Medical Corp. of Tokyo, Japan[272]
- PercuNav image fusion and navigation technology, Philips[273]
- UroNav Fusion Biopsy System, Invivo Corp., a Philips subsidiary[274]
- UroStation, Koelis[275,276]

These devices have received 510(k) device clearance from FDA.[269,273,277-281]

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.[276,277,279] Many newly purchased systems for prostate biopsy include software with this capability.[270,272]

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.

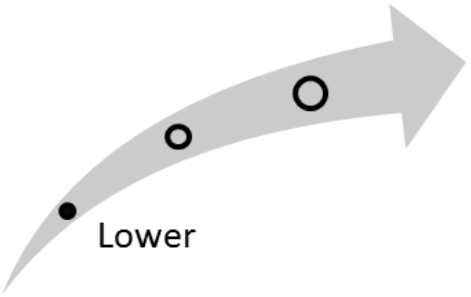
MRI cost and potential lack of procedure coverage are potential barriers to adoption. A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, 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-by-case basis. 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.[282-287] 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.[288] Abnormal findings on these tests or other suspicions of prostate cancer often warrant a prostate biopsy.[288,289] 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.[256] 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 identify clinically significant lesions.[256,258] Multiparametric MRI has been explored as an imaging modality with the potential to identify suspicious areas and obtain targeted biopsies.[258] Besides the purported improvement in prostate cancer detection, MRI may enable physicians to distinguish small, indolent lesions from higher-grade, more clinically significant lesions.[290,291] However, in-bore MRI-guided biopsy is expensive, cumbersome, and must be performed in a specialized setting.[258] 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.[292]

Figure 10. 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.[293-298] We have 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. Although the experts generally anticipated patient acceptance of more effective biopsy procedure with the potential to improve outcomes, some 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: Although a few experts commented that training requirements and implementation of image fusion software would not disrupt existing health care delivery infrastructure, 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.[299] 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.[299] 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, enabling palliation of only one symptom.[300]

Intervention: Radium-223 dichloride (Xofigo®) 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.[301] This may both reduce the side effects of treatment relative to current radionuclide treatments and improve patient outcomes.[301] Radium-223 dichloride is administered intravenously at a dosage of 50 kilobecquerel (1.35 microcurie)/kg, once every 4 weeks, for up to six treatment cycles.[302]

Clinical trials: In June 2012, results were presented from a double-blind, randomized controlled trial of the radiopharmaceutical versus placebo in 921 patients with castration-resistant prostate cancer (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). This represents the first time a radiopharmaceutical agent intended to treat prostate cancer bone metastases has demonstrated an increase in overall survival. Radium-223 dichloride treatment also prolonged the time to first skeletal-related event by 5.8 months more than placebo (15.6 months vs. 9.8 months; HR=0.658; p=0.00037).[303]

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.[303] Other commonly reported adverse events were similar between groups (bone pain, constipation, diarrhea, nausea, and vomiting).[304] 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.[305]

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.[306] Bayer submitted a new drug application to FDA for this indication in December 2012, and FDA granted priority review status in February 2013.[307] FDA approved radium-223 dichloride in May

2013, three months ahead of the expected decision date. It is indicated for treating patients with CRPC, symptomatic bone metastases, and no known visceral metastatic disease.[302,308]

Diffusion: The wholesale cost of radium-223 dichloride is reportedly $11,500 per injection ($69,000 for a full course of 6 injections).[309] The U.S. Nuclear Regulatory Commission has cleared distribution of radium-223 dichloride; individual sites must be licensed to administer the drug.[309] Sales of the drug in the United States have begun, with Bayer reporting substantial sales in the third quarter of 2013.[310]

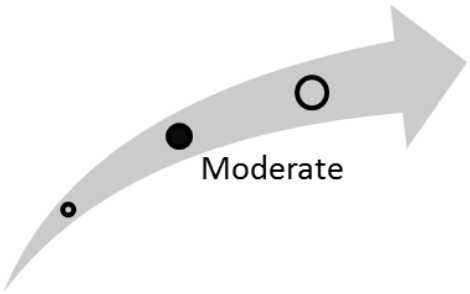
A search of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield Alabama, Blue Cross/Blue Shield Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 5 payers with policies for radium-223 dichloride.[311-315] All policies identified provide coverage for using radium-223 dichloride in patients with bone metastases from CRPC. Most policies require prior authorization and may require that the patients' bone metastases be symptomatic and that the patient have no known visceral metastases.

Radium-223 dichloride is also under investigation for treating osteosarcoma and breast cancers with bone metastases[316,317] An additional agent in development that has shown promise in treating prostate cancer bone metastases is the MET/RET/VEFGR2 kinase inhibitor cabozantinib; phase III clinical trials of this compound in treating metastatic prostate cancer are ongoing.[318]

Clinical Pathway at Point of This Intervention

Patients with cancer that has metastasized to bone are typically treated with a combination of locoregional treatment of bone metastases, systemic therapies, and pain medications.[299] Palliative local treatments for bone metastases include external beam radiation therapy and surgical resection of the lesion.[319] 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.[320] 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.[299] 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 11. 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.[321-327] We have 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., lessening 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 it would be widely adopted. 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

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.[328] 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.[329]

Intervention: Vismodegib is a small-molecule antagonist of the hedgehog pathway. Vismodegib inhibits a protein (called "Smoothened") that is essential for transducing hedgehog pathway activity. In basal cell carcinomas, mutations may occur that activate the hedgehog pathway.[330] 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.[331]

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.[332] 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.[333]

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.[334]

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).[329] 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.[335] 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. According to a May 2013 search of a U.S.-based online aggregator of prescription-drug prices a 10-month treatment course of this drug would total about $92,000.[336]

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

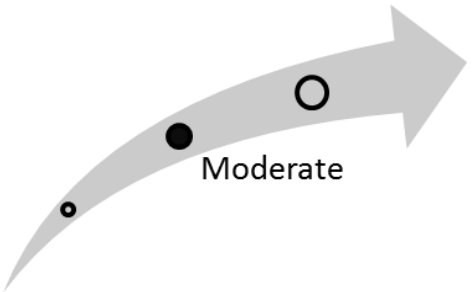
Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark), identified 5 payers with policies that specified coverage of vismodegib for FDA-approved indications.[337-341] Formularies of representative plans typically consider vismodegib to be a specialty pharmaceutical, 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.[342]

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.[343,344] Additionally, investigators recently began a phase IIb trial to determine vismodegib's efficacy in various histologic subtypes of basal cell carcinoma.[345] 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 acute myeloid leukemia and medulloblastoma.[123,346]

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.[328,347] 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. 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. Treatments include radiation therapy and various systemic chemotherapy options, typically platinum-based cytotoxic regimens.[347] Vismodegib provides a new pharmacotherapy option for patients with inoperable/metastatic basal cell carcinomas.[348,349] 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.[343,344]

Figure 12. 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.[350-356] We have 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 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. Therefore, novel nonthermal ablation methods could be useful to reduce morbidity associated with thermal ablation and allow treatment of tumors ineligible for thermal ablation.[357,358]

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.[359] The pulses purportedly disrupt cellular membranes, leading to a form of cell death in the treatment zone. Unlike thermal ablation methods, IRE is purportedly unaffected by 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.[359,360]

An interventional radiologist or surgeon performs IRE procedures using a percutaneous, laparoscopic, or open surgical approach.[360] Neuromuscular stimulation by the electric field produced during IRE treatment can cause uncontrolled movement and pain; therefore, IRE requires general anesthesia and muscle blockade.[359] 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.[359,361] A single ablation purportedly takes only a minute, and IRE electrodes can be repositioned to allow for multiple ablations.[362] 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 recently published.[363-366] In June 2013, 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.[363]

Cannon and coworkers in April 2013 reported on 44 patients with hepatic tumors in proximity to vital structures. The investigators reported that initial ablation was successful in 100% of procedures and that local recurrence-free survival at 3, 6, and 12 months was 97.4%, 94.6%, and 59.5%, respectively. A trend towards increased recurrence rate was observed for patients with tumors of more than 4 cm in size.[367]

In December 2012, 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.[364]

Martin and coworkers in November 2012 reported on 54 patients with locally advanced pancreatic adenocarcinoma. Patients were treated with IRE alone (n=35) or in combination with surgical resection (n=19). A comparison to historical controls indicated that IRE may have a positive effect on progression-free survival and overall survival.[368]

Kingham and colleagues in September 2012 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.[365]

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.[363-366] One patient death was reported in one study's 90-day morbidity followup.[366]

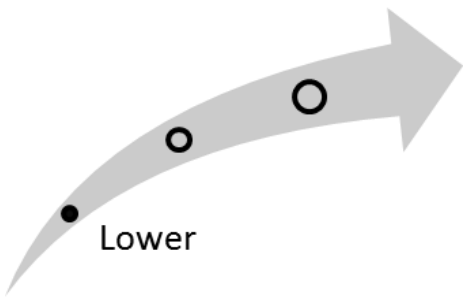
Manufacturer and regulatory status: AngioDynamics, of Latham, NY, is the sole company that produces an IRE system. The device has been FDA cleared for surgical "ablation of soft tissue;" however, FDA has not approved the system for use in treating cancer or any other specific disease or condition.[369] While much of the recently published literature on IRE addresses its use in treating unresectable hepatic or pancreatic tumors,[370] the manufacturer has recently received approval from FDA to conduct a trial using IRE for the treatment of focal prostate cancer.[371]

Diffusion: Several dozen cancer centers in the United States have acquired IRE systems and advertise use of the system for treating various cancers.[359] As of January 2012 (the last date for which data were released), AngioDynamics reported that more than 1,000 patients had undergone IRE treatment worldwide.[372] 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 2 payers (Aetna and Anthem) with policies that denied coverage for use of IRE to ablate tissue.[373,374] Other payers have no policies addressing use of NanoKnife.

Clinical Pathway at Point of This Intervention

In treating 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 clinicians for use in combination with or in place of other oncologic treatment methods such as chemotherapy, radiation therapy, surgery, and transcatheter arterial therapy.[358]

Figure 13. 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,[375-381] and six experts with similar backgrounds, offered perspectives on IRE for treating hepatocellular carcinoma;[382-387] of these groups, one expert commented on both indications. We have 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 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.

Thyroid Cancer Intervention

Sorafenib (Nexavar) for Treatment of Differentiated Thyroid Cancer

Unmet need: Differentiated thyroid cancer (i.e., follicular and papillary thyroid cancers) accounts for approximately 94% of thyroid cancer diagnoses.[388] While most patients with differentiated thyroid cancer will be cured by treatment with radioactive iodine, surgery, and thyroid-stimulating hormone suppression, approximately 15% of patients will develop recurrent disease. Recurrent disease, particularly metastatic disease, is frequently less responsive to radioactive iodine and patients have poor prognoses and limited treatment options.[388,389]

Intervention: Sorafenib (Nexavar®) is an orally administered, small-molecule tyrosine kinase inhibitor with activity against multiple kinases, including vascular endothelial growth factor receptor (VEGFR) 2, VEGFR3, RET, and B-RAF.[390] In recent years, so-called targeted therapies such as sorafenib have been used increasingly to treat a number of malignancies. The tyrosine kinases targeted by these inhibitors purportedly regulate multiple cellular processes related to tumor growth and angiogenesis; therefore, inhibiting these kinases may be of clinical benefit to patients. In particular, sorafenib's activity against RET and B-RAF may be of particular importance in treating thyroid cancer, because activating mutations in the genes encoding these kinases have been observed in differentiated thyroid cancers, suggesting that these kinases may play a role in the pathogenesis of the diseaes.[388]

Clinical trials: Investigators have reported promising results from phase II trials of various tyrosine kinase inhibitors (e.g., axitinib, cabozantinib, lenvatinib, motesanib, pazopanib, sorafenib, sunitinib) in treating radioactive iodine–refractory thyroid cancer; however, data from randomized control trials has been lacking.[388] Therefore, researchers undertook the phase III DECISION trial to assess the utility of sorafenib compared to placebo in patients with progressive, radioactive iodine–refractory, differentiated thyroid cancer. In this trial, patients (n=417) were randomly assigned to treatment with sorafenib (400 mg, twice daily) or placebo.[391]

At the 2013 American Society of Clinical Oncology Annual Meeting, Brose and colleagues reported that patients in the sorafenib arm of the DECISION trial demonstrated a significant increase the primary endpoint of progression-free survival (10.8 months vs. 5.8 months; hazard ratio 0.58; $p<0.0001$).[392] Median overall survival had not been reached at the time of data presentation, and 70% of patients in the placebo arm crossed over to sorafenib per the study protocol, which could obscure any overall survival benefit. Adverse events associated with sorafenib treatment were consistent with the known safety profile of the drug and included hand-foot skin reactions, diarrhea, alopecia, rash/desquamation, fatigue, weight loss, and hypertension.[392,393] Two deaths during the trial, one in each study arm, were attributed to the study drug.[394]

Manufacturer and regulatory status: Sorafenib was developed by Bayer AG (Leverkusen, Germany) in collaboration with Onyx Pharmaceuticals, Inc., now a subsidiary of Amgen, Inc. (Thousand Oaks, CA). In November 2013, FDA approved sorafenib for treating "locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment."[393,395] According to a U.S.-based, online aggregator of prescription-drug prices, a 1 month supply of sorafenib (at 400 mg, twice daily) costs approximately $10,500.[396]

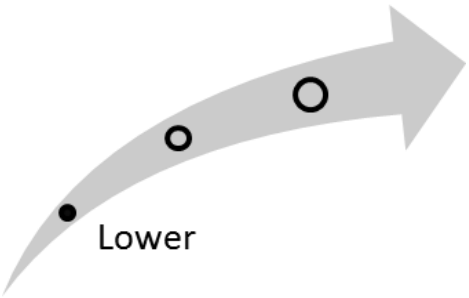
Diffusion: Although sorafenib has only recently been approved by FDA for treating patients with radioactive iodine-refractory thyroid cancer, the drug has been approved by FDA for use in treating renal cell carcinoma since 2005 and for treating hepatocellular carcinoma since 2007.[393] Several third-party payers had established coverage policies for off-label use of sorafenib in treating differentiated thyroid cancer. Among 11 representative, private, third-party payers that publish their coverage policies online, 4 had policies specific to use of sorafenib for treating differentiated

thyroid cancer.[63,397-399] Three policies stated that this indication was covered while one stated that this indication was considered investigational. Coverage for this indication will likely be expanded following the recent FDA approval.

Clinical Pathway at Point of This Intervention

Several systemic therapies have been studied for treating patients with differentiated thyroid cancer that is not amenable to surgery and is not responsive to radioactive iodine. Differentiated thyroid cancer does not typically respond well to treatment with cytotoxic chemotherapy (e.g., doxorubicin). Other treatment options that have been investigated for treating this patient population include several tyrosine kinase inhibitors, such as pazopanib, sorafenib, and sunitinib. The recent FDA approval of sorafenib marks the first time a systemic agent has been approved for patients with radioactive iodine–refractory differentiated thyroid cancer.[388,400]

Figure 14. Overall high-impact potential: sorafenib (Nexavar) for treatment of differentiated thyroid cancer



Overall, experts concurred that sorafenib would fill an unmet need for patients with radioactive iodine-refractory thyroid cancer especially given that no other therapies had been approved by FDA for this indication and given the promising results regarding progression-free survival in recent data from a phase III clinical trial. The magnitude of sorafenib's impact was lessened by the relatively small patient population that would be a candidate for the treatment and sorafenib's oral route of administration, which limited any potential impact on health care staffing or infrastructure. Therefore our overall assessment is that sorafenib for treating differentiated thyroid cancer is at 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 sorafenib for treating differentiated thyroid cancer.[401-406] We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: The unmet need in differentiated thyroid cancer purportedly addressed by sorafenib was seen as having moderate importance by expert commenters. Experts noted the relative absence of therapeutic options for radioactive iodine–refractory disease. But several experts noted that the relatively small patient population of patients with radioactive iodine–refractory thyroid cancer limited the importance of the unmet need to some extent. Experts suggested that sorafenib has a moderate potential to benefit health outcomes in these patients, noting the significant improvement in progression-free survival observed in the DECISION trial.

Acceptance and adoption: Moderate to wide clinician acceptance of this agent was anticipated by the commenters, who noted that many clinicians were likely to be familiar with this drug and that even before approval some third-party payers had policies in place that reimbursed for using

sorafenib in this patient population. Most experts predicted moderate patient acceptance of this new treatment option, with adverse effects and cost being potential barriers to more widespread acceptance. However, in the absence of other therapeutic alternatives, experts suggested that many patients would opt for sorafenib treatment.

Health system infrastructure and patient management: Little to no impact on health care delivery infrastructure and patient management was envisioned by experts regarding the adoption of sorafenib for use in this patient population. Expert commenters cited the oral route of administration and the familiarity of medical oncologists with using the drug as factors mitigating its impact on health care staffing and infrastructure. Among the small shifts to staffing and infrastructure that experts suggested may occur included potential changes to patient management to address drug-related toxicity, noted by one expert with a research background; a second expert with a research perspective highlighted the potential shift from infusion-based cytotoxic chemotherapy to self-administered sorafenib; and an expert with a clinical perspective suggested that the health care provider could change if some endocrinologists as opposed to medical oncologists were to prescribe sorafenib. Several experts anticipated that treatment paradigms would be modified to include the use of this agent following its approval.

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